Table of Contents

HIV treatment centres

Medisch Centrum Alkmaar (MCA), Alkmaar

Academisch Medisch Centrum bij de Universiteit van Amsterdam (AMC), Amsterdam

St. Medisch Centrum Jan van Goyen, Amsterdam

Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam

Slotervaart Ziekenhuis, Amsterdam

Sint Lucas Andreas Ziekenhuis, Amsterdam

VU Medisch Centrum, Amsterdam

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Haga Ziekenhuis, Den Haag, Locatie Leyenburg

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Universitair Medisch Centrum Groningen (UMCG), Groningen

Kennemer Gasthuis, Haarlem, Locatie EG

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Erasmus MC, Rotterdam

St. Elisabeth Ziekenhuis, Tilburg

Universitair Medisch Centrum Utrecht (UMC), Utrecht

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Paediatric HIV treatment centres

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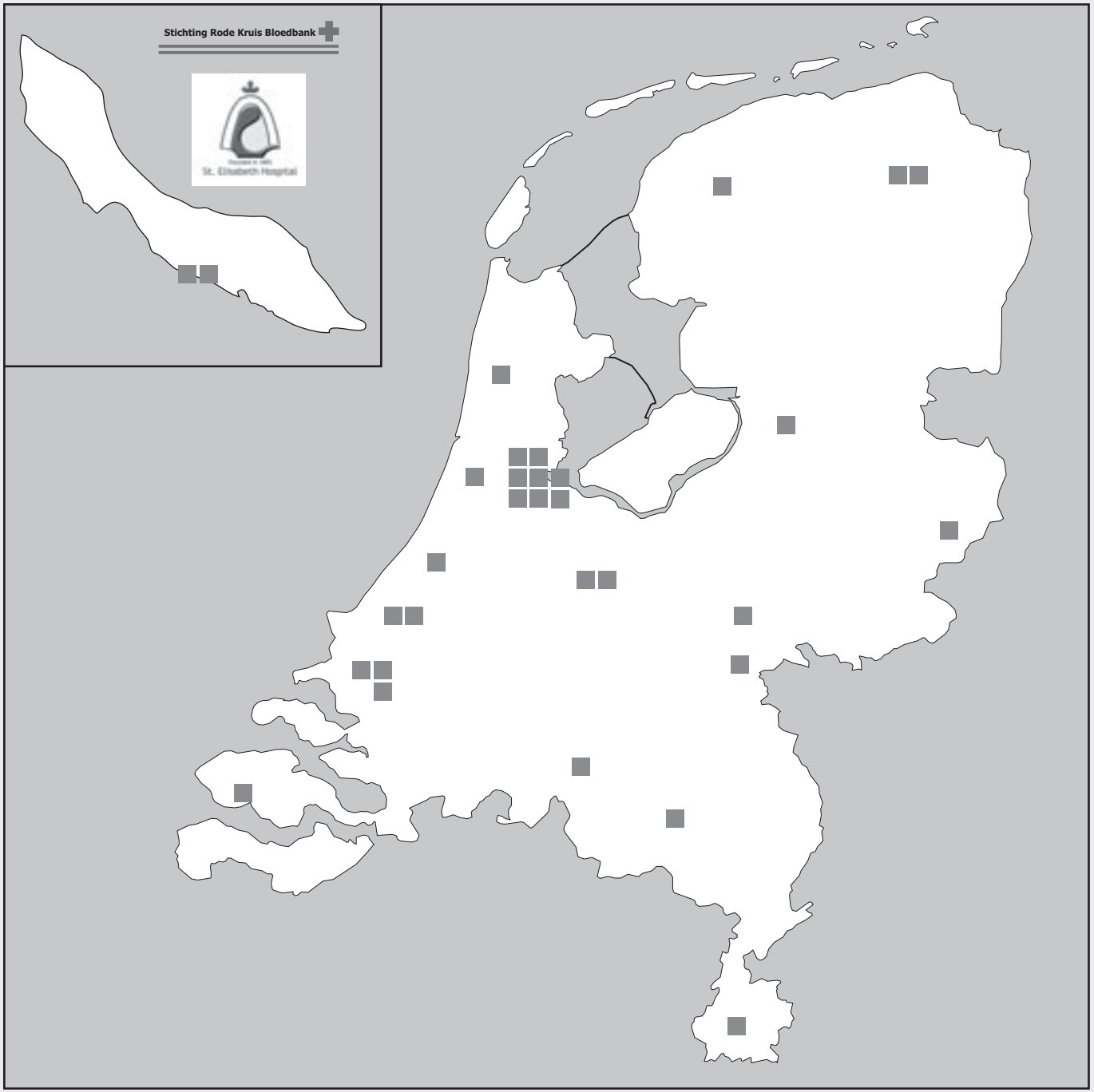

Stichting Rode Kruis Bloedbank
St. Elisabeth Hospital

1 Inleiding, Samenvatting & Aanbevelingen

Inleiding

De HIV epidemie onder met name homoseksuele mannen is niet onder controle (Bezemer 2007, ingediend voor publicatie). Weliswaar heeft de in 1996 geïntroduceerde, grootschalige antiretrovirale combinatietherapie (cART) een belangrijke rol gespeeld bij het beperken van HIV transmissie (overdracht), maar de geboekte winst weegt niet op tegen de toename van het transmissie-risico. Was dit niet gebeurd, dan zou de epidemie nu duidelijk afnemen. Netto wordt het transmissierisico grotendeels bepaald door het zich bewust zijn van de infectie en - daarmee samenhangend - door het besmettingsrisico-gedrag. Vooral diegenen die zich niet bewust zijn van hun infectie dragen substantieel bij aan de verspreiding van HIV. Het bekorten van de tijd tussen HIV infectie en diagnose en het op tijd starten met cART, zijn de uitdagingen waar we nog steeds voor staan als we de epidemie in Nederland terug willen dringen.

HIV-geïnfecteerde individuen sterven nog steeds aan hun infectie, hoewel minder vaak dan voor de introductie van cART. In de totale groep van 12.915 patiënten met 78.635 persoonsjaren follow-up werden sinds 1996 1.127 sterfgevallen geregistreerd. Dit aantal correspondeert met gemiddeld 1,43 (95% CI 1,35 – 1,52) sterfgevallen per 100 persoonsjaren. Het sterftecijfer nam de afgelopen tijd enigszins af van 1,95 (95% CI 1,55 – 2,41) in 1997 tot 1,23 (0,87 – 1,68) in 2007 (p=0,008). Het sterftecijfer voor 2007 is hoger dan voor 2006, hoewel de dataverzameling voor 2007 (en, voor enkele behandelcentra, ook voor 2006) nog niet is voltooid. Interessant is dat de doodsoorzaken in de meerderheid van de gevallen gedurende de eerste 7 jaren na de start met cART gerelateerd waren aan de HIV-infectie en AIDS; niet aan HIV gerelateerde oorzaken kwamen het meest voor in de periode daarna. Bij de met cART behandelde HIV-geïnfecteerde populatie was de sterfte aan kanker vijfmaal hoger dan bij de algemene Nederlandse bevolking (deze cijfers zijn gecorrigeerd voor leeftijd en geslacht). Niet aan AIDS gerelateerde kanker kwam tweemaal vaker voor.

Er is ruimte om de ziekte- en sterftecijfers te verbeteren door eerder met cART te beginnen. Het is bekend dat lage aantallen CD4 cellen of AIDS bij of voorafgaand aan het beginnen met cART samenhangt met een grotere kans op het ontwikkelen van AIDS of overlijden. Bovendien neemt de kans op overlijden verder af wanneer met cART wordt begonnen als het aantal CD4 cellen hoog of zelfs zeer hoog is; het risico op een nieuwe AIDS diagnose neemt bij aantallen hoger dan 300 CD4 cellen/mm^3 niet verder af. Ondanks het belang om met cART te beginnen wanneer het aantal CD4 cellen hoger is dan 200 /$mm^{3,}$ startte meer dan de helft van de patiënten beneden die drempelwaarde. Het aantal CD4 cellen bij de start van cART lag voor de hele bij de Stichting HIV Monitoring (SHM) geregistreerde populatie lager dan 200 cellen/mm^3, ofschoon 65% van de patiënten zich tijdig genoeg voor HIV-behandeling aandienden.

Het aantal HIV-geïnfecteerde personen, dat bij de Stichting HIV Monitoring (SHM) is geregistreerd en wordt gemonitord in het observationele AIDS Therapie Evaluatie Nederland (ATHENA) cohort, groeit nog steeds. Sinds vorig jaar is dat aantal toegenomen met 1.205 patiënten en de totale follow-up tijd met 17.218 jaar. In totaal zijn per 1 juni 2007 13.264 met HIV geïnfecteerde personen geregistreerd bij één van de 24 HIV behandelcentra of de 4 pediatrische HIV behandelcentra. De follow-up tijd is 97.982 persoonsjaren vanaf de HIV-diagnose. Van de geregistreerde patiënten zijn er 10.095 13 jaar of ouder en in actieve follow-up. Het werkelijke aantal in actieve follow-up is hoger, als gevolg van achterstanden in dataverzameling in enkele van de HIV behandelcentra. Ondanks meer dan tien jaar cART is de jaarlijkse groei van de HIV-geïnfecteerde populatie sinds 1996 alleen maar toegenomen. Deze toename is het meest merkbaar

geweest onder homoseksuele mannen, maar ook het jaarlijkse aantal diagnoses onder heteroseksuelen is over de tijd iets toegenomen. Het aantal CD4 cellen bij diagnose is gestegen over de tijd, wat er op duidt dat nieuwe gevallen nu in een vroeg stadium van de infectie worden gediagnosticeerd. Daarnaast is het aandeel van patiënten van wie een laatste HIV negatieve datum is geregistreerd eveneens toegenomen over de tijd. De feitelijke groei van de geregistreerde geïnfecteerde populatie bevestigt de uitkomst van ons model, dat de verspreiding van HIV in Nederland nog steeds epidemisch verloopt.

Het aantal patiënten in follow-up bij één van de behandelcentra in Nederland betreft, per definitie, die patiënten die weten dat zij met HIV geïnfecteerd zijn. Het totale aantal met HIV geïnfecteerde personen in Nederland in de leeftijd tussen 15 en 50 jaar – daarbij inbegrepen degenen die zich van hun infectie niet bewust zijn – wordt door ons geschat op 18.500 individuen[1]. Bij analyse van de omvang en leeftijdsdistributie van de door de SHM geregistreerde populatie bleken 6.944 patiënten in de data en 6.992 in het model tussen 15 en 50 jaar oud zijn. Dit zou betekenen dat meer dan 60% van de HIV-geïnfecteerde patiënten nog niet in follow-up zijn, en dus, naar alle waarschijnlijkheid, nog niet van hun HIV-infectie op de hoogte zijn.

De met HIV geïnfecteerde populatie in follow-up in 2015 is naar verwachting 3,3 keer groter dan die in 2000, of 2,0 keer groter dan die in 2005. Het aantal patiënten ouder dan 50 jaar zal dan zijn toegenomen met een factor 6,3, en het aantal patiënten onder de 30 jaar met een factor 1,5. De behandeling van HIV dreigt complexer te worden door de groeiende leeftijd van de met HIV geïnfecteerde patiënten. Bij oudere patiënten is de kans op herstel van het aantal CD4 cellen over het geheel genomen minder gunstig dan bij jongere patiënten[2-4] en leeftijdsgerelateerde en andere niet HIV-gerelateerde ziekten zullen de behandeling van HIV compliceren. Bovendien kunnen tolerantie en veiligheid van antiretrovirale middelen bij oudere HIV-geïnfecteerde patiënten minder zijn[5], en kunnen geneesmiddeleninteracties tussen antiretrovirale en andere (leeftijdgerelateerde) middelen optreden.

Men mag aannemen dat een HIV-geïnfecteerde populatie van tweemaal de omvang van de populatie die momenteel wordt gevolgd de HIV zorg in Nederland onder behoorlijke druk zal zetten. Eerder schatten wij dat een jaar behandelen van een HIV-geïnfecteerde persoon 12.500 euro kost[6]. Daarom zullen, wanneer de kosten per persoon en de populatiegrootte worden vermenigvuldigd, de jaarlijkse kosten van HIV-behandeling toenemen van 115 miljoen euro in 2005 tot 230 miljoen euro in 2015.

Dit zijn de belangrijkste bevindingen neergelegd in het wetenschappelijk verslag van 2007 over de monitoring van de infectie met het human immunodeficiency virus (HIV) in Nederland: de epidemie groeit, ondanks massale en effectieve antiretrovirale behandeling; de sterfte onder HIV-geïnfecteerde personen is nog altijd hoger dan onder de algemene bevolking, met een verschuiving naar niet aan HIV- en AIDS gerelateerde doodsoorzaken; er wordt bij een substantieel deel van de gediagnosticeerde en geregistreerde HIV-positieve populatie laat met cART gestart; niet alleen de geregistreerde populatie, maar ook de populatie die niet bekend is met zijn infectie groeit; de HIV-geïnfecteerde populatie vergrijst.

Naast de gunstige resultaten van behandelen met cART over de afgelopen 11 jaren, bespreekt het verslag ook de nu voor ons liggende uitdagingen. Andere onderwerpen die worden besproken zijn onder meer:

- De veranderingen die in de afgelopen jaren zijn opgetreden in de effectiviteit van eerstelijns cART, inclusief de verschillen tussen geneesmiddelenregimes
- De korte termijn virologische respons na wijziging van het initiële cART regime
- Resistentie van HIV-1 tijdens cART en overdracht van resistente stammen

- cART en de respons op de behandeling bij zwangere vrouwen
- De CD4 cel respons op cART bij HIV-geïnfecteerde kinderen
- De CD4 cel respons op de behandeling van co-infectie met het hepatitis C virus

Verder presenteren we dit jaar voor het eerst resultaten van de eerste evaluatie van de kwaliteit van HIV-zorg in Nederland en de invloed van late binnenkomst in de zorg. Tenslotte zijn er twee speciale hoofdstukken, één over de Amsterdam Cohort Studies naar HIV infectie en één dat verslag doet van HIV en AIDS op Curaçao en onder migrantenpopulaties in Nederland.

Om te beginnen rapporteert hoofdstuk 3 over de kwaliteit van data en de uitkomsten van een nieuwe aanpak voor de selectie van data items voor brondata-verificatie. Sinds begin 2002 heeft de SHM data verzameld van alle HIV-geïnfecteerde patiënten, ongeacht of zij werden behandeld, of regelmatig gezien door een HIV/AIDS behandelend arts in één van de huidige 24 HIV behandelcentra. De missie van SHM is het bestuderen van het natuurlijke beloop van HIV en de effecten van behandeling, evenals het bevorderen van de kennis en het begrip van de HIV epidemie en het verloop van HIV infectie zowel bij behandelde als bij onbehandelde patiënten. Bovendien houdt de SHM toezicht en draagt bij aan de kwaliteit van de HIV-zorg. Een belangrijke manier waarop de SHM haar missie tracht te verwezenlijken is door gegevens voor HIV/AIDS-gerelateerd onderzoek beschikbaar te stellen. Om aan dit gebruik tegemoet te komen is een nauwgezette en periodiek bijgewerkte beschrijving van de HIV-geïnfecteerde populatie waaraan de SHM haar gegevens ontleent van groot belang. Dit zesde jaarlijkse verslag biedt opnieuw zo'n uitvoerige beschrijving.

De SHM blijft deelnemen aan studies die worden verricht in het kader van de Antiretroviral Therapy Cohort Collaboration (ART-CC), die 16 cohorten in verschillende Europese landen, de Verenigde Staten en Canada omvat. Voor ART-CC worden alleen gegevens gebruikt van patiënten die starten met cART, zonder eerder antiretrovirale middelen te hebben gebruikt. Studies zijn verricht naar de veranderende levensverwachting, mogelijke associaties tussen specifieke AIDS diagnoses en verschillen in sterftecijfers, en de voorspellende waarde van het meest recente aantal CD4 cellen en van anemie, alsmede verschillen in het virologisch effect op korte termijn van verschillende cART regimes.

Naast ART-CC werd 2 jaar geleden een nieuwe Europese samenwerking tussen observationele cohorten opgezet. De Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) doet epidemiologisch onderzoek naar de prognose en uitkomst van HIV in de geïnfecteerde populatie en concentreert zich op wetenschappelijke vragen waarvan voor de beantwoording grote verzamelingen van patiëntengegevens nodig zijn. Het eerste onderzoeksproject naar het effect van leeftijd op cART uitkomsten is afgerond en andere projecten zijn van start gegaan.

De reeds lang bestaande samenwerking met het Department of Infectious Disease Epidemiology van de Medical Faculty of Imperial College London heeft geresulteerd in het eerder genoemde mathematische model voor de analyse van de invloed van grootschalige toediening van cART op de epidemie in Nederland. Dit jaar werd ook een model ontwikkeld voor het vergelijken van de kwaliteit van zorg in Nederland. In een andere studie is onderzoek gedaan naar de variatie in de concentratie HIV-1 RNA in plasma, wanneer het zogeheten set-point is bereikt tijdens de symptoomloze periode van de infectie. De hoogte van dit set-point correleert met de infectieusiteit en duur van de symptoomloze periode van de HIV-infectie. De studie laat zien dat er clusters zijn rond set-points, waardoor HIV een maximale kans krijgt te worden overgedragen. Voorts is na rapportage het afgelopen jaar van onze studie over viraemie tijdens cART, de

dataverzameling en de ontwikkeling van een mathematisch model voor het bepalen van de invloed van superinfectie van start gegaan.

De HIV/AIDS-internisten en de SHM dataverzamelaars in de 24 HIV behandelcentra in Nederland, zijn van cruciaal belang voor het werk van de SHM. Nadat gegevens aan de nationale monitoring database zijn toegevoegd controleren de SHM datamonitors de kwaliteit van de ingevoerde data. Databewerking en –analyse worden uitgevoerd door de medewerkers en assistent onderzoekers van de analysegroep van de SHM; deze groep is van essentieel belang voor de uitvoering van de SHM registratie en onderzoeksprogramma's en voor het ondersteunen van groepen die gegevens uit de ATHENA dataverzameling gebruiken. Ook in dit rapport geven wij weer een overzicht van de diverse publicaties en presentaties van 2007 die (deels) gebaseerd zijn op deze unieke verzameling gegevens over HIV en AIDS in Nederland.

Samenvatting

Data kwaliteit: Resultaten van op maat gesneden procedures voor kwaliteitsverbetering

Controle en verbetering van de kwaliteit van longitudinaal verkregen observationele klinische data is van overwegend belang, gegeven de minder gestructureerde wijze waarop deze data zijn verzameld. Onze verzameling van observationele gegevens van HIV-geïnfecteerde patiënten startte in 1996 in het kader van het ATHENA project[7], en van een groot aantal patiënten zijn de gegevens die sinds het begin van de tachtiger jaren zijn verkregen hierin opgenomen. De kwaliteit van data wordt doorgaans gecontroleerd met behulp van bron-data verificatie[8-12]. Maar 100% bron-data verificatie is gezien het grote aantal patiënten die jarenlang zijn gevolgd onhaalbaar. Tegelijkertijd blijkt brondata-verificatie van een willekeurige selectie van 10% data onvoldoende te zijn voor het verbeteren van datakwaliteit[13, 14]. Daarom hebben wij op maat gesneden procedures ingevoerd om de nauwkeurigheid van de ATHENA cohort data continu te kunnen volgen en, vervolgens, discrepanties te kunnen oplossen.

In het kort: de volgende twee gegevensitems werden voor de kwaliteitscontrole geselecteerd: 1) de datum van de eerste positieve HIV test en 2) specifieke HIV-gerelateerde events volgens de CDC classificatie[15]. Beide items hebben een duidelijke invloed op de gegevensanalyses. Brondata-verificatie van de eerste positieve testdatum geregistreerd als 'onbekend' bleek juist in slechts eenderde van de gevallen; in tweederde kon een datum worden gevonden in het patiëntendossier. Brondata-verificatie van ontbrekende of onjuist vastgelegde symptomatische HIV (CDC-B event) of AIDS (CDC-C event) werd uitgevoerd op een selectie van patiënten met een aantal CD4 cellen $<50/mm^3$, in de veronderstelling dat een dergelijk event vaker bij deze patiënten zou voorkomen. In de geselecteerde groep werden voornamelijk CDC-B events gemist of incorrect geregistreerd. Voorts werd de diagnostische (on)zekerheid van een CDC-B of –C event nagetrokken en gecorrigeerd in 39% van de events.

Onze conclusie is dat voor de primaire data-analyse de kwaliteit van de gegevens substantieel verbeterd kan worden door het gebruik van gerichte brondata-verificatie. Wanneer data direct in een observationele setting wordt verzameld, zullen klinische, diagnostische en organisatorische procedures een effect hebben op de toegankelijkheid van de data. Bijvoorbeeld, wanneer de verzameling van data direct na een bezoek van de patiënt aan het ziekenhuis wordt uitgevoerd, kan het gebeuren dat brondata pas op een later tijdstip aan het dossier worden toegevoegd, en zodoende kunnen die data tijdens invoer worden gemist.

Het eerste jaar van dataverzameling blijkt het meest complex om vast te leggen, met name wanneer patiënten worden gezien in een gevorderd stadium van HIV-infectie en hun medische dossier daarom de neerslag van een lange en gecompliceerde ziektegeschiedenis bevat. Resultaten van gespecialiseerde diagnostieken, zoals pathologie, radiologie of immunologie, zijn niet altijd duidelijk en direct gerelateerd aan het zekerheidsniveau van de CDC-B of -C diagnose.

Hoewel brondata-verificatie bewezen effectief is, is ze ook bewerkelijk. Door echter de brondata-verificatie specifiek te beperken tot alle end-points die essentieel zijn voor kerndata-analyse, kan ze zelfs worden ingezet voor datasets van grote aantallen patiënten. Bovendien zou de efficiëntie van brondata-verificatie kunnen worden verbeterd door haar te beperken tot het eerste jaar van dataverzameling.

De populatie van het ATHENA onderzoek

Op 1 juni 2007 had de Stichting HIV Monitoring data verzameld en in de ATHENA database opgeslagen van 13.264 HIV-geïnfecteerde personen, geregistreerd in één van de 24 HIV behandelcentra (HTC) in Nederland. De totale follow-up bedroeg 97.982 persoonsjaren sinds diagnose; 12.958 (97,7%) waren geïnfecteerd met HIV-1 en 78 (0,6%) met HIV-2. Bij 95 (0,7%) patiënten werd seroreactiviteit op zowel HIV-1 als HIV-2 vastgesteld, en bij 133 (1,0%) patiënten waren deze serologische resultaten onduidelijk of (nog) niet bekend. In 78% van de patiënten waarvan het HIV-1 subtype kon worden bepaald werd subtype B gevonden.

In totaal 10.095 (76,1%) patiënten waren op 1 juni 2007 actief in follow-up en 13 jaar of ouder. Dat aantal is waarschijnlijk te laag, omdat enkele HIV behandelcentra een achterstand in datavergaring hadden van meer dan een jaar.

Bijna 79% waren mannen uit Nederland (58,5%) en geïnfecteerd via homoseksueel contact (55,7%). In totaal waren 1.354 (13,4%) mannen en 1.954 (19,5%) vrouwen geïnfecteerd via heteroseksueel contact, terwijl 3,5% van de patiënten geïnfecteerd was via injecterend druggebruik. De mediane leeftijd van de populatie was 43,3 (Interquartile range 36,8 - 50,1) jaar, en mannen waren over het algemeen ouder dan vrouwen, d.w.z. 44,7 (38,7 – 51,3) jaar voor mannen, vergeleken met 37,8 (31,8 - 44,8) jaar voor vrouwen ($p<0,001$).

De mediane tijd sinds diagnose was 5,9 (IQR 3,0 – 9,9) jaar voor vrouwen en 6,7 (3,0 – 11,4) jaar voor mannen ($p<0,001$). In totaal werd bij 2.523 (25,0%) patiënten HIV gediagnosticeerd in de afgelopen 3 jaar, met een vergelijkbaar percentage van rond 25% voor mannen en vrouwen ($p=0,6$). Dat was 10 jaar geleden anders, toen bij een relatief groter aantal mannen (2.521, 32,1%) dan vrouwen (536, 24,1%) HIV werd gediagnosticeerd ($p<0,001$).

cART werd gegeven aan 8.115 (80,4%) patiënten, en 1.924 (19,1%) waren (nog) niet behandeld. Het aantal nog niet behandelde patiënten was hoger onder vrouwen dan onder mannen. Tenofovir plus lamivudine of emtrictabine en zidovudine plus lamivudine zijn de meest frequent gebruikte backbones in eerstelijns cART regimes, met nevirapine, efavirenz, lopinavir en atazanavir als de meest frequent gebruikte toevoegingen.

Bij mannen was het meest recent gemeten aantal CD4 cellen 480 (IQR 340 – 670) $\times 10^6$ cellen/l en bij vrouwen 490 (350 – 670). In 87,6% van de met cART behandelde populatie was de concentratie HIV RNA in plasma <500 kopieën/ml. Een of meerdere AIDS-diagnoses werden gesteld bij 25,9% van de totale populatie in follow-up, en bij ongeveer de helft werd deze diagnose binnen 4 weken na de HIV-diagnose gesteld.

In totaal 9.291 (92,0%) patiënten werden getest op hepatitis B surface (HBsAg) of envelope (HBeAg) antigen en 812 (8,7%) testten positief. Het Hepatitis B virus (HBV) kwam het meest voor onder met HIV geïnfecteerde injecterende druggebruikers (IDU) (11,6%). Van de homoseksuele mannen was 9,4% HBV positief en van de heteroseksueel met HIV geïnfecteerde patiënten 7,1%. In deze laatste groep was een hoger percentage mannen (9,1%) dan vrouwen (5,8%) HBV positief.

Infectie met hepatitis C virus (HCV) werd bepaald bij 8.581 (85,0%) patiënten en 926 (10,8%) van hen waren HCV-positief. Co-infectie met zowel HBV als HCV werd gevonden bij 95 patiënten. HCV was het meest prevalent onder IDU's (93,9%). De HCV prevalentie in de populatie die met HIV was geïnfecteerd via heteroseksueel contact was 6,8% bij mannen en 6,2% bij vrouwen. De HCV prevalentie onder homoseksuele mannen was vergelijkbaar (5,8%).

Trends in baseline-karakteristieken over de tijd

Sinds vorig jaar is de HIV-geïnfecteerde populatie in Nederland, geregistreerd door de Stichting HIV Monitoring, toegenomen met 1.205 patiënten[16], en de totale follow-up met 17.218 persoonsjaren.

De laatste jaren was 50% tot 60% van de gediagnosticeerde patiënten geïnfecteerd via homoseksueel contact, terwijl ongeveer 35% werd geïnfecteerd via heteroseksueel contact. Het aantal patiënten geïnfecteerd via injecterend druggebruik bedroeg ongeveer 10 personen per jaar. Het absolute aantal diagnoses onder homoseksuele mannen nam toe van 300 tot 400 per jaar in de tweede helft van de jaren negentig, tot meer dan 500 na 2004. In 2006 zijn tot dusverre 513 diagnoses onder homoseksuele mannen geregistreerd, maar vanwege de achterstand in de registratie valt het werkelijke aantal diagnoses in 2006 naar verwachting ongeveer 15% hoger uit.

Sinds 2002 is het aantal patiënten afkomstig uit Zuidelijk Afrika (sub-Sahara) afgenomen. Dit is consistent met het afnemende aantal mensen dat uit Afrika naar Nederland immigreert[16]. In 2007 werd echter een toename van het aandeel van Zuidelijk Afrikanen in de heteroseksuele populatie waargenomen. Aangezien deze toename statistisch niet significant is, kunnen hier vooralsnog geen conclusies aan worden verbonden.

Het aandeel homoseksuele mannen gediagnosticeerd met een recente infectie is toegenomen tot bijna 30% in de afgelopen twee jaar. Meer dan 50% van de geïnfecteerde homoseksuele mannen heeft ooit een negatieve test gehad. Dit is naar alle waarschijnlijkheid een afspiegeling van de toenemende testfrequentie[17]. In de afgelopen jaren is bij patiënten bij wie de HIV diagnose later wordt gesteld, de tijd tussen besmetting en diagnose afgenomen terwijl het aantal CD4 cellen bij diagnose toenam. Samen met de waarneming dat de mediane leeftijd bij diagnose is toegenomen, kan worden geconcludeerd dat homoseksuele mannen op steeds latere leeftijd geïnfecteerd raakten.

In de heteroseksuele geïnfecteerde populatie zijn het aandeel recente infecties en het aandeel patiënten met een eerder negatieve HIV test eveneens toegenomen over de tijd. De toename is meer uitgesproken in de vrouwelijke populatie, hetgeen mogelijk het gevolg is van de invoering in 2004 van de nationale prenatale screening van zwangere vrouwen[18].

Bijna de helft van alle behandelde patiënten gebruikt thans een cART regime dat tenofovir bevat in plaats van zidovudine, als gevolg van het minder gunstig toxiciteitprofiel van zidovudine ten opzichte van tenofovir[19]. Voorts gebruikt een groeiend deel van de patiënten emtricitabine in plaats van lamivudine, waarschijnlijk omdat emtricitabine beschikbaar is in een vaste dosering in combinatie met tenofovir.

Regimes die tenofovir bevatten werden voorgeschreven aan tweederde van de patiënten die met cART startten tussen 1 juni 2006 en 31 mei 2007; de helft van de patiënten startte met emtricitabine. In de totale behandelde populatie werden geen veranderingen waargenomen in de toediening van nevirapine en in de meest frequent gebruikte proteaseremmers, maar regimes met efavirenz wonnen aan populariteit. Ook in eerstelijns cART werden regimes met efavirenz vaker en regimes met lopinavir minder vaak gebruikt.

Het aantal CD4 cellen ten tijde van de HIV diagnose blijkt te zijn toegenomen over de tijd, wat betekent dat een groter deel van patiënten tijdig met cART kan beginnen. Sinds 2005 blijkt het aantal CD4 cellen bij de start van cART wel te zijn toegenomen bij de heteroseksuele, maar niet bij de homoseksuele populatie. Dat het CD4 cel aantal bij de start van cART onder homoseksuele mannen niet toeneemt komt voornamelijk omdat in deze groep het aantal cellen bij HIV diagnose hoger is dan de drempelwaarde, waarbij volgens de behandelrichtlijn met cART moet worden begonnen.

De prevalentie van co-infecties met HBV en HCV was, als gemeld, ongeveer 10% en veranderde niet ten opzichte van eerder gerapporteerde getallen in de ATHENA onderzoekspopulatie.

Ondanks een decennium van cART is de jaarlijkse groei van de HIV-geïnfecteerde populatie sinds 1996 alleen maar toegenomen. Deze toename is het meest merkbaar geweest in de risicogroep homoseksuele mannen, maar ook het jaarlijkse aantal diagnoses onder heteroseksuelen is in dat tijdsbestek licht gestegen. In de totale populatie was het mediane aantal CD4 cellen juist beneden 500×10^6 cellen/l, en cART resulteerde in onderdrukking van virusproductie tot beneden 500 HIV-RNA kopieën/ml bij de overgrote meerderheid van patiënten.

Veranderingen in de effectiviteit van eerstelijns cART in de tijd

Antiretrovirale combinatietherapie (cART) reduceert de HIV productie substantieel[20] en voor lange tijd[21]. Voorwaarde is dat cART tijdig wordt begonnen[22] en toegediend op een manier die therapietrouw van de patiënt bevordert[23, 24]. Daarbij is de korte termijn respons op eerstelijns cART een belangrijke prognostische indicatie voor ziekteprogressie[25]. In een subset van 7.655 antiretrovirale therapie naïeve volwassen patiënten die met eerstelijns cART begonnen tussen 1996 en 2006 werden de immuunrespons en het antivirale effect van diverse combinaties van klassen van antiretrovirale middelen die in het eerste cART regiem werden gebruikt vergeleken, en de tijd tot verandering van het initiële cART regime werd geanalyseerd.

Suppressie van virusproductie op korte termijn na starten va de behandeling met cART verbeterde in de afgelopen jaren onafhankelijk van het type cART-combinatie dat werd gebruikt. Er werden geen significante verschillen gevonden in het anti-virale effect op korte termijn tussen de tegenwoordig meest frequent gebruikte cART bestaande uit een non-nucleoside HIV reverse transcriptaseremmer (NNRTI) of een boosted HIV proteaseremmer (PI) in combinatie met een nucleotide reverse transcriptase (NRTI) backbone.

Dit duidt op vertekening van de analyse door variabelen waar niet voor wordt gecorrigeerd. De specifieke middelen die in de NRTI component van cART worden gebruikt kunnen mogelijk ook speciaal de werkzaamheid beïnvloeden. Zo wordt voor combinaties van tenofovir en lamivudine of emtricitabine[26] een betere virologische respons gerapporteerd. In latere kalenderjaren groeit het aandeel van patiënten die met cART starten waarin deze NRTI's zijn opgenomen, hetgeen de betere virologische uitkomst in recente jaren kan verklaren.

De toename in het aantal CD4 cellen, gemeten tussen de start van cART en bij 24 weken therapie was 31 cellen/mm^3 hoger bij patiënten die begonnen met een boosted PI vergeleken met diegenen die startten met een NNRTI.

De tijd tot verandering van het cART regime was bij patiënten die met een cART met een boosted PI begonnen korter. Er werd echter geen significant verschil gevonden in de kans op verandering van het regime door toxiciteit tussen patiënten die begonnen met een cART waarbij een NNRTI was inbegrepen versus een met een boosted PI.

Betere begeleiding van specifieke subgroepen is nodig om de therapietrouw en daarmee de virologische respons te verbeteren. Patiënten van niet-westerse oorsprong en jongere patiënten vertoonden een verminderde virologische respons na 24 weken cART. Bovendien hadden patiënten van niet-westerse origine kleinere toenames in het aantal CD4 cellen. Hoewel tegenstrijdige resultaten worden gemeld[27] bevestigen onze resultaten die van andere studies[21, 28-30] en zijn waarschijnlijk het beste te verklaren uit verschillen in therapietrouw. Patiënten die met cART beginnen wanneer het aantal CD4 cellen nog hoog is hebben een hoger risico op therapieverandering en een lagere virologische respons. Ook hier zou sprake kunnen zijn van beperkte therapietrouw, aangezien het gezond voelen een aanleiding is om de medicatie niet in te nemen[7, 31, 32].

Een hoger risico op een therapieverandering door toxiciteit werd gevonden bij patiënten, waaronder vrouwen, met een lager gewicht, na correctie voor gewicht. Observatie van geneesmiddelenspiegels in plasma ter begeleiding van het verlagen van de dosis van antiretrovirale middelen zou kunnen helpen bij patiënten met een hoger risico op geneesmiddelentoxiciteit[33].

Tenslotte hadden vrouwen die tijdens hun zwangerschap met cART begonnen een lagere kans op het bereiken van een HIV RNA plasma concentratie <50 kopieën/ml na 24 weken behandeling, hoewel een hogere toename in het aantal CD4 cellen werd gevonden. Waarschijnlijk komt dit door het starten met cART wanneer het aantal CD4 cellen nog hoog is en het vervolgens stoppen van de behandeling na de bevalling.

De virologische respons op cART als initiële behandeling is verbeterd sinds de introductie van cART in 1996. Een initieel regime met daarin een boosted PI of NNRTI heeft een superieure virologische werkzaamheid vergeleken met een unboosted PI of een combinatie met alleen NRTI's. Met de recent geïntroduceerde antiretrovirale middelen is er geen significant verschil meer in de kans op verandering van het regime door toxiciteit tussen patiënten die met ofwel een boosted PI, ofwel een NNRTI bevattend cART regime starten.

Korte termijn virologische respons na verandering van het initiële cART regime

Bij een groot deel van de patiënten wordt de initiële combinatie van antiretrovirale drugs veranderd om redenen die variëren van toxiciteit van één of meer geneesmiddelen tot virologisch falen, het niet in staat zijn trouw te blijven aan het voorgeschreven regime, of de versimpeling van het regime[34, 35]. In het geval dat het initiële regime wordt gewijzigd vanwege virologisch falen is het risico op een volgend virologisch falen bij een volgend regime hoog. Zo is het risico op een toxiciteit gerelateerde verandering van een nieuw regime ook hoger wanneer het initiële regime werd veranderd in verband met toxiciteit[36, 37].

In een studie naar het korte termijn virologische effect van een tweede cART regime na verandering van het eerste om redenen van falen of toxiciteit, werd nagegaan

of met het beschikbaar komen van nieuwe antivirale middelen het zich steeds herhalende patroon van oorzaken van regimeveranderingen doorbroken is.
Per eind december 2006 was bij 4.947 (64,6%) van de 7.655 patiënten met cART één of meer van de initieel in de combinatie voorgeschreven antiretrovirale middelen veranderd. De meest frequent geregistreerde redenen voor de wijziging waren toxiciteit bij 1.982 (40,1%), gevolgd door simplificatie van een nieuw regime bij 516 (10,4%), virologisch falen bij 446 (9,0%), en op verzoek van de patiënt zelf bij 412 (8,3%). Bij 53,9% van de 4.947 patiënten met een verandering werd de NRTI backbone van de combinatie gewijzigd, en dit was de enige wijziging bij 24,4%. Een wijziging van een combinatie met een NNRTI naar een met een PI werd geregistreerd bij 23,3%, van een unboosted naar een boosted PI bij 9,9%, en van een NNRTI naar een PI bij 7,8%. Bij 9,2% van de patiënten resulteerde de verandering in een nieuwe combinatie met alleen NRTI en bij 14% bleef de wijziging binnen dezelfde combinatie van geneesmiddelenklassen. cART met een NNRTI was de meest frequent gebruikte combinatie in de nieuwe cART (45,0%), gevolgd door cART met een boosted PI (25,5%) en cART met een unboosted PI (15,1%). De meeste patiënten (78,2%) gingen zonder onderbreking over van de initiële naar de nieuwe cART.

Van de 3.286 patiënten bij wie dat werd gemeten, daalde bij 2.781 (84,6%) na 24 weken nieuw cART regime de HIV-RNA plasma concentratie onder de detectiegrens van 50 kopieën/ml. Virologisch succes na 24 weken was het hoogst (94.6%) onder de patiënten bij wie om redenen van vereenvoudiging het initiële regime werd veranderd, gevolgd door diegenen bij wie toxiciteit (85,0%) of virologisch falen (70,4%) de reden was.

Het risico op onvoldoende HIV onderdrukking, 24 weken na het starten met een tweede cART regime was hoger onder patiënten uit regio's buiten Nederland. Patiënten die van regime wisselden vanwege virologisch falen hadden tevens een lagere kans op het bereiken van HIV RNA plasmaspiegels beneden 50 HIV RNA kopieën/ml dan patiënten die wisselden vanwege toxiciteit. In vergelijking met patiënten met een cART regime wijziging als gevolg van virologisch falen in of na 2003, hadden diegenen met een dergelijke cART regime wijziging voorafgaand aan 2003 een nog lagere kans op het bereiken van een afdoende onderdrukking van de HIV reproductie. Dit effect van kalendertijd op HIV onderdrukking werd niet gevonden bij de gevallen van wijziging van het cART regime door toxiciteit.

Net als bij de initiële cART regimes zijn ook de virologische resultaten van tweede regimes mettertijd verbeterd, hoogstwaarschijnlijk als gevolg van de introductie in recentere kalenderjaren van minder toxische geneesmiddelen met een eenvoudiger doseringsschema[38] en een hogere therapeutische werkzaamheid. Daarnaast hebben verandering van het cART regime op geleide van genotypische resistentiebepaling bij patiënten die virologisch falen en het monitoren van plasmaspiegels van antivirale middelen[40] in geval van toxiciteit, bijgedragen[39] aan de verbetering van het virologisch effect van cART in de tijd.

Resistentie

Tegenwoordig resulteert cART bij de meeste patiënten in langdurige onderdrukking van HIV productie (weergegeven in het onder de detectielimiet van de huidige tests blijven van de HIV RNA plasmaspiegel). Echter, de onderdrukking is onvolledig, en een laag niveau van HIV productie blijft bestaan[41, 42]. Suboptimale trouw aan het regime van antiretrovirale middelen dat in cART wordt gebruikt, kan leiden tot selectie van geneesmiddelresistent HIV[43, 44]. Vervolgens beperkt de aanwezigheid van resistente virusstammen de toekomstige therapieopties en dat kan leiden tot een verslechterde prognose[45]. De aanwezigheid van resistent virus bij patiënten die niet trouw zijn aan de therapie kan oplopen tot 80%[46-48].

Resistente virusstammen kunnen ook worden overgedragen op niet-geïnfecteerde patiënten. De laatste jaren schommelde de aanwezigheid van resistente virussen bij recent geïnfecteerde patiënten in Europa en Noord-Amerika tussen 5% en 25%. Na 1998 werd transmissie van resistente virusstammen waargenomen bij 6% van recent geïnfecteerde deelnemers aan de Nederlandse Amsterdam Cohort Studies[49].

Onze update van 2007 toont dat slechts 4,8% van de recent geïnfecteerde patiënten in Nederland resistent HIV bij zich draagt. Onder de recent gediagnosticeerde patiënten werd 8% resistentie aangetroffen. Deze percentages zijn vergelijkbaar met die percentages in andere Westerse landen zijn waargenomen, hoewel toenemende percentages van resistentie elders zijn gerapporteerd[50-54]. Wanneer resistente mutaties die werden aangetroffen werden vertaald naar een verwachte gevoeligheidscore was ongeveer 4% van de patiënten in beide groepen geïnfecteerd met een stam die een gemiddelde of hoge resistentie had tegen ten minste één antiretroviraal middel. Ook al is een belangrijke met resistentie geassocieerde mutatie aanwezig, dan is dit daarom nog niet noodzakelijk een teken van volledige resistentie.

Het grotere aandeel van recent gediagnosticeerde patiënten met aan resistentie gerelateerde mutaties, dan dat waargenomen bij recent geïnfecteerde patiënten bleek te worden veroorzaakt door een hoger percentage van patiënten met een M41L mutatie, hetzij als een enige mutatie in RT of in combinatie met een T215X mutatie. De M41L mutatie is stabiel aanwezig bij patiënten die zijn geïnfecteerd met een resistentie HIV stam[55] en hoogstwaarschijnlijk zijn deze patiënten in de jaren negentig geïnfecteerd, toen resistentie tegen zidovudine en stavudine het meest voorkwam.

Het stabiele en lage niveau van overdracht van resistent virus is enigszins verrassend, gegeven de toename van het aantal met cART behandelde patiënten sinds 1996. Eén verklaring is dat het aandeel van patiënten die falen in de therapie over de tijd is afgenomen en dat, dientengevolge, het reservoir aan mogelijk besmettelijke patiënten – degenen met HIV RNA niveaus boven 500 kopieën/ml – relatief klein is. Anderzijds bevestigt dit ook dat de meeste HIV besmettingen worden overgedragen door HIV-geïnfecteerde individuen die onbehandeld zijn of zelfs onwetend van hun infectie[56, 57].

Het jaarlijkse aandeel van patiënten die faalden met cART nam af van 60% in 1997 tot 19% in 2006 en 14% in 2007 onder diegenen die voor cART met antiretrovirale middelen waren behandeld en nam gedurende dezelfde periode langzaam toe van 10% tot 14% onder degenen die niet eerder met een antiretroviraal middel behandeld waren. Onder de falers werd resistentie tegen antiretrovirale geneesmiddelen aangetroffen bij 88,4% van eerder behandelde patiënten en bij 64% van therapie-naïeve patiënten. Zoals eerder werd opgemerkt, is de mate van voorkomen van resistentie tegen specifieke antiretrovirale geneesmiddelen veranderd over de tijd in correlatie met veranderingen in het antiretroviraal geneesmiddelgebruik[58].

Bij bijna 11% van de patiënten die in 2007 nog steeds werden gevolgd door de Stichting HIV Monitoring werden virusstammen gevonden met een hoog resistentie-niveau tegen ten minste één antiretroviraal geneesmiddel. Dit percentage is waarschijnlijk een te lage inschatting aangezien andere cohorten met meer frequente resistentietests een prevalentie van ongeveer 25% hebben gevonden[44, 59]. Echter, ook na correctie voor mogelijke vertekeningen bleef de door ons gevonden prevalentie gelijk.

Het effect van cART bij de behandeling van zwangere vrouwen

Teneinde de overdracht van moeder op kind (MTCT) te verminderen, worden met HIV geïnfecteerde vrouwen in Nederland sinds 1998 met cART behandeld. Die therapie, samen met een geplande keizersnede in het geval van

een meetbare maternale virale load en behandeling van pasgeborenen gedurende de eerste weken van hun leven, heeft geleid tot een afname van het risico op MTCT tot 2%[60]. Om dat risico verder te verkleinen is de nationale HIV zwangerschapsscreening[61] in gebruik sinds 2004, en een groter aandeel van de geïnfecteerde vrouwen is nu vroeg in de zwangerschap gediagnosticeerd. Bijgevolg zijn deze vrouwen veelal voor het eerst met cART begonnen tijdens hun zwangerschap.

Als gevolg van de zwangerschap treden veranderingen op in het aantal CD4 cellen. Hormonen die tijdens de zwangerschap worden geproduceerd verlagen de immuunrespons om afstoting van de foetus te voorkomen[62]. Een afname van het aantal CD4 cellen tijdens de zwangerschap zou gerelateerd kunnen zijn aan de zwangerschap zelf en niet aan de progressie van de HIV ziekte of aan een geringere respons op de behandeling, ofschoon het initiëren van cART tijdens de zwangerschap het aantal CD4 cellen kan doen toenemen. Om de virologische en immunologische werkzaamheid van cART gestart voor en tijdens de zwangerschap te bestuderen, werden data geselecteerd uit de populatie van 570 HIV-geïnfecteerde, zwangere vrouwen in ATHENA. Slechts eerste zwangerschappen tussen 1 januari 1998 en 1 juni 2007 en die vastgesteld werden nadat de moeder was gediagnosticeerd met HIV werden in de analyses opgenomen. In totaal bracht 85% van de vrouwen een kind ter wereld.

De meeste vrouwen bevielen terwijl de HIV RNA plasmaspiegel onmeetbaar was. Vrouwen die tijdens hun zwangerschap met cART begonnen hadden significant hogere HIV RNA plasmaspiegels tijdens de eerste twee trimesters van de zwangerschap dan vrouwen die met cART begonnen voordat zij zwanger werden, maar de HIV RNA plasmaspiegels bij beide groepen bereikte hetzelfde niveau ten tijde van de bevalling. Er werden geen verschillen waargenomen tussen Nederlandse en niet-Nederlandse vrouwen met betrekking tot HIV RNA plasmaspiegels bij het begin van of tijdens de zwangerschap.

Nederlandse vrouwen hadden hogere aantallen CD4 cellen tijdens de zwangerschap in vergelijking met vrouwen van niet-Nederlandse origine. De meerderheid van de niet-Nederlandse vrouwen was afkomstig uit Zuidelijk Afrika, en verschillen in aantallen CD4 cellen weerspiegelen waarschijnlijk etnische verschillen in aantallen CD4 cellen tussen vrouwen van Nederlandse en van Afrikaanse origine.

Het aantal CD4 cellen nam af tijdens de eerste twee trimesters van de zwangerschap, zowel bij de vrouwen die al onder behandeling waren als bij degenen die tijdens de zwangerschap met cART begonnen. Deze afname kan worden verklaard door hormonale veranderingen[62]. Blijkbaar veroorzaakt deze afname geen versnelde toename van HIV. Van de toename van het aantal CD4 cellen, die in het laatste trimester werd gevonden is aangetoond dat deze eveneens aan de zwangerschap gerelateerd is[63]. Echter, in ons onderzoek is de toename van het aantal CD4 cellen tussen week 20 en week 28 onder vrouwen die tijdens de zwangerschap met cART begonnen mogelijk ook een respons op de behandeling omdat bij de meeste vrouwen juist in die periode met cART werd gestart.

Zowel bij vrouwen die al met cART werden behandeld voordat zij zwanger werden, als bij vrouwen die tijdens de zwangerschap met cART begonnen, had een significante verlaging van de HIV RNA plasmaspiegel plaats. Aangezien de geldende richtlijnen het beginnen met cART tussen week 20 en week 28 aanbevelen, was de afname van de HIV RNA spiegels gedurende die periode het sterkst[64]. Een sterke afname van HIV RNA spiegels werd ook waargenomen bij vrouwen die al met cART werden behandeld voor de zwangerschap. Dit weerspiegelt waarschijnlijk een wijziging in het cART regime naar een meer effectieve of een meer verkieslijke combinatie tijdens de zwangerschap. Voorts onderbrak een deel van de vrouwen cART tijdelijk in het begin van de zwangerschap.

Combinaties die nelfinavir of nevirapine bevatten werden goed verdragen tijdens de zwangerschap[65]. Een combinatie met nelfinavir bleek het meest frequent gebruikte regime onder zwangere vrouwen in ATHENA.

Ondanks de sterke afname van HIV RNA plasma niveaus onder zwangere vrouwen die met cART werden behandeld, had 30% tot 36% nog steeds een meetbare virale load tijdens de bevalling. Het risico van MTCT is erg laag onder vrouwen die effectief worden behandeld met cART[66], maar een geplande keizersnede wordt aanbevolen in gevallen waarin de virale load bij de moeder >50 kopieën/ml bedraagt. In ATHENA onderging 60% van de vrouwen met een meetbare virale load een keizersnede.

Groeiend belang van andere doodsoorzaken dan die door AIDS bij langere duur van cART

In een significant deel van de HIV-geïnfecteerde met cART behandelde patiënten blijkt de doodsoorzaak niet-AIDS-gerelateerd[67, 68]. Door antiretrovirale therapie-naïeve groepen patiënten te vergelijken aan de hand van hun aantal CD4 cellen bij het starten met cART, werden verschillen in morbiditeit en mortaliteit bestudeerd en, in het bijzonder, doodsoorzaken binnen het tijdsbestek van 10 jaar volgend op het starten met cART.

Tussen 1 juli 1996 en 31 december 2006 begonnen 7.655 HIV-geïnfecteerde patiënten met cART. De mediane concentratie HIV RNA in plasma was 5,0 $\log_{10}$ kopieën/ml. Het mediane aantal CD4 cellen fluctueerde van 250 cellen/mm^3 in 1996 -1997 tot 190 in 1998 - 2000, 180 in 2001 - 2003, en 190 in 2004 - 2006 ($p<0.0001$). In 1997 startte 37,5% van de patiënten waarvan een pre-cART CD4 celaantal beschikbaar was met cART beneden de drempelwaarde van 200 CD4 cellen/mm^3, vergeleken met een gemiddelde van 52,9% in de periode 2000 – 2006 ($p<0,0001$).

Het risico van starten met cART met minder dan 200 CD4 cellen/mm^3 was lager voor vrouwen dan voor mannen en lager voor patiënten die met cART begonnen in 2006 dan voor hen die in 2000 begonnen. Het risico was hoger onder patiënten van niet-Nederlandse origine en voor patiënten met heteroseksuele contacten als HIV transmissieroute.

In totaal overleden 463 patiënten, en bij 212 (45,8%) was de doodsoorzaak gerelateerd aan HIV. De doodsoorzaak was niet aan HIV gerelateerd bij 190 (41,0%); aan therapie gerelateerd bij 5 (1,1%) en onbekend bij 56 (12,1%). De algehele mortaliteit, 10 jaar na het starten met cART was 10,6%, namelijk 3,7% HIV-gerelateerde oorzaken, 5,5% niet-HIV-gerelateerde oorzaken, 1,3% overlijden door onbekende oorzaken, en 0,1% antiretrovirale (ARV) therapiegerelateerde oorzaken. De belangrijkste doodsoorzaak tijdens de eerste 7 jaren na het starten met cART was HIV-gerelateerd; na die periode was niet-HIV-gerelateerde mortaliteit het belangrijkst.

Er was geen significant verschil in het aandeel van specifieke doodsoorzaken voor en na 1 januari 2004; alleen dood door cardiovasculaire complicaties en zelfmoord kwam vanaf begin 2004 vaker voor. De algehele incidentie van kankergerelateerd overlijden na het starten met cART was vijfmaal hoger dan de voor leeftijd en geslacht genormaliseerde incidentie in de algemene Nederlandse populatie, en de incidentie van niet-AIDS kanker was tweemaal hoger in de met HIV geïnfecteerde populatie.

Binnen 3 jaren nadat met cART was gestart overleden 269 patiënten. Patiënten die in de periode 2001 tot en met 2006 begonnen hadden een risico om te overlijden dat 1,7 keer hoger was dan het risico voor patiënten die begonnen in de periode 1998 tot en met 2000. De tijd tot overlijden bij patiënten die in de periode 2001 – 2006 begonnen verschilde niet significant van die van degenen die begonnen in 1996 – 1997. Injecterend druggebruik als de HIV transmissieroute werd geassocieerd met een kortere tijd tot overlijden.

Wanneer het aantal CD4 cellen voor de start van de cART behandeling lager was dan 100 cellen/mm^3, nam, naarmate het aantal CD4 cellen verder daalde, het overlijdensrisico snel toe. Wanneer het aantal hoger was dan 100 CD4 cellen/mm^3, nam de overlijdenskans lineair af naarmate het aantal CD4 cellen steeg. Er was geen effect van de HIV RNA plasmaspiegel bij aanvang van cART op de overlijdenskans binnen 3 jaar. Patiënten met symptomatische HIV hadden een tweemaal hogere kans op overlijden en degenen met AIDS hadden een 4 keer zo hoge kans. Patiënten met progressieve multifocale leukoencephalopathie of non-Hodgkin's lymfoom (met inbegrip van primair hersenlymfoom) hadden het hoogste risico om te overlijden, vergeleken met patiënten met andere AIDS diagnoses.

Een nieuwe AIDS diagnose werd geregistreerd bij 545 patiënten binnen 3 jaar na het beginnen met cART, en schattingen van AIDS morbiditeit bedroegen 8,6% (8,0 – 9,2) binnen 3 jaar en 18,9% (17,7 – 20,1) binnen 10 jaar.

De belangrijkste variabelen die onafhankelijk geassocieerd werden met een kortere tijd tot een nieuwe AIDS diagnose waren: een laag aantal CD4 cellen en een HIV RNA plasmaspiegel boven de 100.000 kopieën/ml bij het begin van cART, een AIDS diagnose voor de start van cART, en de regio van herkomst.

De kans op overlijden bleef dalen voor hogere aantallen CD4 cellen bij aanvang van cART, zelfs ook voor zeer hoge CD4 cel aantallen, terwijl het risico op een nieuw AIDS diagnose vergelijkbaar was bij CD4 waarden boven 300 cellen/mm^3 bij aanvang. Ondanks het belang om met cART te beginnen wanneer CD4 waarden nog boven 200 cellen/mm^3 liggen, begon meer dan de helft van de patiënten beneden die drempelwaarde. Dit duidt erop dat er ruimte is voor verbetering van mortaliteits- en morbiditeitsratio's door eerder in het beloop van de infectie te starten met de behandeling.

Niet-HIV-gerelateerde en niet-AIDS-gerelateerde doodsoorzaken (in het bijzonder overlijden door cardiovasculaire complicaties) werden belangrijker bij een langere duur van cART. Aangezien cART HIV heeft veranderd in een levenslange chronische infectie, valt te verwachten dat de doodsoorzaken bij met HIV geïnfecteerde patiënten een nauwere overeenkomst vertonen met die welke in de Nederlandse populatie worden waargenomen. De toename in het aandeel van niet-AIDS vormen van kanker die ook in andere cohorten wordt waargenomen[69] zou dit kunnen weerspiegelen.

Kanker-gerelateerde mortaliteit was bijna vijfmaal hoger dan die in de algemene Nederlandse bevolking. Mortaliteit tengevolge van niet-AIDS kanker was bijna even gangbaar als die tengevolge van AIDS-gerelateerde kanker, maar niet hoger, zoals elders werd gerapporteerd[70]. Overlijden door niet-AIDS kanker in de HIV-geïnfecteerde populatie was tweemaal zo hoog als in de algemene Nederlandse bevolking. Dit wijst erop dat immunodeficiëntie inderdaad verband kan houden met het risico op fatale niet-AIDS kanker, zoals door sommigen is verondersteld[70-72], maar door anderen niet gevonden[73-75].

De trend van een lager overlijdensrisico bij een hogere CD4 waarde bij aanvang van cART is ook waarneembaar bij hoge CD4 waarden. Dit suggereert dat het eerder starten met cART dan de huidige richtlijnen aanbevelen, gunstig kan zijn.

Immuunrespons van met HIV-1 geïnfecteerde kinderen op cART

De levensverwachting van met HIV geïnfecteerde kinderen is, net als bij volwassenen[76], dramatisch verbeterd sinds cART algemeen beschikbaar werd[77]. De virologische en immunologische respons op cART zijn uitgebreid bestudeerd bij volwassenen, maar minder vaak bij met HIV-1 geïnfecteerde kinderen. Kinderen zijn beter in staat om nieuwe CD4 cellen aan te

maken[78], wat in verband gebracht is met een hogere thymusfunctie. Bij toenemende leeftijd nemen de absolute aantallen CD4 cellen af en verandert de immuunrespons[79, 80]. Tezamen compliceren deze factoren de evaluatie van de immuunrespons van met HIV-1 geïnfecteerde kinderen op cART. De immunologische en virologische respons van met cART behandelde HIV-1 geïnfecteerde kinderen die werden gevolgd in één van de vier speciaal erkende pedriatische HIV behandelcentra in Nederland tussen 1 januari 1997 en 1 juni 2007 werd geëvalueerd.

Het mediane aantal CD4 cellen bij aanvang van cART bedroeg 1.058 × 10^6 cellen/l (442 –1.690) voor kinderen die 2 jaar of jonger waren ten tijde van het begin met cART en nam toe tot 1.710 × 10^6 cellen/l (1.090 - 2.425) na 24 weken cART. Kinderen die bij aanvang van cART ouder waren dan 2 jaar begonnen behandeling met 350 × 10^6 CD4 cellen/l (100 - 600) en dit aantal was na 24 weken toegenomen tot 650 × 10^6 cellen/l (390 - 920). Adolescenten hadden nog lagere aantallen CD4 cellen. Bij aanvang was het mediane aantal CD4 cellen 206 × 10^6 cellen/l (11 - 206), en dit nam toe tot 372 × 10^6 cellen/l (201 - 550) na 24 weken cART.

Veranderingen in CD4 cel percentages onder de met HIV-1 geïnfecteerde kinderen die met cART begonnen, lieten zien dat oudere kinderen (meer dan 2 jaar oud) significant hogere CD4 cel percentages hadden dan kinderen die 2 jaar of jonger waren toen zij met cART begonnen. In de eerste 12 weken met cART namen de CD4 cel percentages in beide groepen toe, maar de toename verliep significant sneller onder de kinderen die ten minste 2 jaar oud waren toen zij met cART begonnen. Vanaf 12 weken met cART namen de CD4 percentages nog steeds significant sneller toe onder deze oudere kinderen. Tijdens het eerste jaar met cART bleven de CD4 cel percentages hoger onder deze oudere kinderen vergeleken met de jongere kinderen.

Onder de kinderen die 2 jaar of jonger waren toen zij met cART begonnen, namen de mediane HIV RNA spiegels significant af van 5,8 $\log_{10}$/ml (5,3 – 6,0) bij aanvang tot 2,6 $\log_{10}$/ml (2,1 – 2,6) bij 24 weken cART. HIV RNA spiegels waren significant lager bij aanvang van cART bij de oudere kinderen en namen significant af van 4,9 $\log_{10}$/ml (4,3 – 5,6) tot 1,7 $\log_{10}$/ml (1,7 – 2,6) bij 24 weken cART. HIV RNA spiegels bij adolescenten namen eveneens significant af van 5,0 $\log_{10}$/ml (4,7 – 5,3) bij aanvang tot 1,7 $\log_{10}$/ml (1,7 – 2,6) bij week 24.

Leeftijdgerelateerde variatie in absolute aantallen CD4 cellen zijn eerder beschreven bij kinderen die niet geïnfecteerd zijn met HIV[80]. De absolute CD4 cel aantallen namen af bij toenemende leeftijd, hetgeen de significant hogere aantallen CD4 cellen bij jongere met HIV-1 geïnfecteerde kinderen verklaart. De CD4 cel percentages zijn waarschijnlijk een betere indicator voor het vergelijken van de immunologische respons na cART tussen kinderen van verschillende leeftijden. Kinderen die ten minste 2 jaar oud waren toen zij met cART begonnen, hadden significant hogere CD4 cel percentages, en het aandeel CD4 cellen nam sneller toe bij de oudere kinderen. Onderdrukking van de HIV RNA niveaus is nodig voor het herstel van de thymusfunctie en daarmee voor het terugkeren van CD4 cellen[81]. De kinderen die ten minste 2 jaar oud waren toen zij met cART begonnen, hadden een betere kans om een onmeetbare virale load te bereiken dan de jongere kinderen. Deze zwakkere virologische respons bij jongere met HIV-1 geïnfecteerde kinderen die cART kregen, is eerder beschreven[79]. In ons onderzoek hadden oudere kinderen lagere HIV RNA niveaus bij aanvang van cART en ook bij 24 weken na het begin van cART. Een hoger CD4 percentage als beginwaarde en gedurende het eerste jaar met cART is waarschijnlijk een resultaat van de betere virologische onderdrukking in de groep van de oudere kinderen.

De resultaten van deze studie wijzen uit dat de immunologische en virologische respons bij met HIV-1 geïnfecteerde kinderen met cART leeftijdafhankelijk is. Hoewel jongere kinderen hogere aantallen CD4 cellen hebben is de immuunrespons sterker bij oudere kinderen, zoals dat goed wordt weergegeven in de hogere CD4 percentages.

Immunologische respons op de behandeling van hepatitis C co-infectie

Co-infectie met hepatitis C (HCV) komt veel voor bij HIV geïnfecteerden, met prevalenties die variëren tussen 6% tot zelfs 82%, in het bijzonder bij injecterend druggebruik[82, 83]. Ziekteprogressie van met HCV geassocieerde leveraandoeningen verloopt sneller bij met HIV geïnfecteerde individuen, en omdat door cART de HIV-gerelateerde morbiditeit en mortaliteit significant en langdurig is gedaald, wordt nu een toename in leverziekten en daaraan gerelateerde sterfte zichtbaar[84, 85]. Als gevolg hiervan is de effectieve behandeling van HCV bij patiënten met een HIV co-infectie belangrijker geworden. Een combinatie van interferon (IFN) en ribavirine (RBV)[86] wordt gebruikt sinds 1998 bij de behandeling van HCV[87], maar recentelijk werd IFN vervangen door pegylated interferon (peg-IFN)[88]. Van de combinatie van IFN en (peg)-IFN is aangetoond dat deze effectiever is dan IFN plus RBV voor chronische HCV infectie bij tevens met HIV geïnfecteerde individuen, hoofdzakelijk bij patiënten geïnfecteerd met HCV genotypen 1 en 4[89].

Afname van het aantal CD4 cellen is waargenomen tijdens de behandeling van HCV[89]. Hoewel korte termijn complicaties zoals opportunistische infecties niet zijn gerapporteerd[89], is het onbekend of de afname van het aantal CD4 cellen een negatieve invloed heeft op het lange termijn effect van de HIV-behandeling[90]. Om deze afname te onderzoeken werd het beloop van het aantal CD4 cellen en van HIV RNA tijdens de HCV behandeling bij patiënten met een HIV/HCV co-infectie bestudeerd. De algehele mortaliteit werd vergeleken tussen patiënten met een HIV/HCV co-infectie met en zonder HCV behandeling, en individuen met alleen een HIV-infectie .

De HCV prevalentie in de totale geteste populatie was 9% en HCV RNA werd aangetoond bij 564 van de 1.013 patiënten die positief testten op HCV antilichamen. Bij de overige 449 patiënten kon HCV RNA niet worden aangetoond, of waren testresultaten nog niet gerapporteerd. HCV co-infectie kwam het meest voor (82%) onder injecterende druggebruikers.

Acht procent (83 uit 1.013) van de patiënten die positief testten op HCV antilichamen werd behandeld met IFN of (peg)-IFN; 69 daarvan werden al met cART behandeld voor HIV voordat zij (peg)-IFN kregen; 9 begonnen met cART na het afmaken van de behandeling met (peg)-IFN, en 5 werden niet behandeld voor hun HIV infectie. Plasmaspiegels HCV RNA werden bepaald bij 68 van de 83 patiënten, en bij 35 (51%) werden de spiegels onmeetbaar na het volgen van (mediaan) 37 weken (peg)-IFN behandeling. De mediane duur van de anti-HCV-behandeling onder de overige 33 patiënten bedroeg 22 weken.

Het aantal CD4 cellen nam af van 400×10^6 cellen/l (IQR: 270 - 610) bij aanvang met (peg)-IFN tot 240×10^6 cellen/l (140 - 460) na 24 weken behandeling met (peg)-IFN. De afname verliep in twee fasen, met een sterke en significante afname in de eerste 12 weken en een geringere, maar nog altijd significante, afname gedurende de volgende 12 weken. Na week 24, toen de meeste patiënten waren gestopt met hun (peg)-IFN behandeling, namen de aantallen CD4 cellen toe, hoewel niet significant. CD4 percentages bedroegen 25 bij de start van (peg)-IFN en 27% tussen week 20 en week 28.

Mediane HIV RNA spiegels vertoonden een niet-significante toename van 1,4 $\log_{10}$ kopieën/ml (1,4 – 2,9) bij aanvang van (peg)-IFN tot 1,7 $\log_{10}$ kopieën/ml (1,4 – 3,9) na 24 weken.

Achtentwintig procent van de alleen met HIV geïnfecteerde patiënten, 37% van de patiënten met een HIV/HCV- co-infectie die werden behandeld met (peg)-IFN, en 38% van de onbehandelde patiënten met een HIV/HCV co-infectie ontwikkelden AIDS. Patiënten met een HCV co-infectie werden vaker behandeld met cART, en de tijd van aanvang cART tot AIDS was niet geassocieerd met HCV co-infectie. De kans op progressie tot AIDS was niet-significant lager bij zowel HIV/HCV co-geïnfecteerde patiënten die (peg)-IFN kregen als bij patiënten die alleen met HIV geïnfecteerd waren, in vergelijking met HIV/HCV co-geïnfecteerde patiënten zonder anti-HCV behandeling.

Patiënten met een HCV co-infectie stierven significant sneller dan patiënten zonder co-infectie. Tijd tot overlijden verschilde niet significant tussen patiënten met een HCV co-infectie die (peg)-IFN kregen en degenen die dat niet kregen. Vijf jaar na aanvang cART was de overall mortaliteit 10% (95% CI 8 -12) onder de patiënten met een HIV/HCV co-infectie zonder (peg)-IFN behandeling, en 5% (3 - 14) onder de patiënten met HIV/HCV co-infectie die (peg)-IFN kregen. Van de alleen met HIV geïnfecteerde patiënten overleed 4% (3 - 4) na 5 jaar cART.

Aangezien slechts een klein deel van de patiënten met een HIV/HCV-co-infectie werd behandeld voor HCV[91] en de afname van CD4 cellen tijdens de (peg)-IFN behandeling geen effect leek te hebben op HIV-gerelateerde mortaliteit, zou er een verbeterde beschikbaarheid van de anti-HCV behandeling moeten komen om de hogere HCV-gerelateerde morbiditeit en mortaliteit bij HIV/HCV co-geïnfecteerde patiënten terug te dringen.

Dood en AIDS

HIV krijgt geleidelijk aan de kenmerken van een chronische, in plaats van een dodelijke ziekte. De HIV-gerelateerde mortaliteit en de incidentiecijfers van AIDS in Europa en Noord Amerika zijn substantieel gedaald bij met cART behandelde patiënten, vergeleken met die bij onbehandelde patiënten[67, 92-95]. Zodoende is de prognose voor met HIV geïnfecteerde patiënten verbeterd, en voor met succes behandelde patiënten is gebleken dat de mortaliteitscijfers die van niet-geïnfecteerde patiënten benaderen[25, 96-99].

Gebruikmakend van ons prognostisch model voor het voorspellen van overlevingskansen bij met HIV geïnfecteerde patiënten na diagnose met HIV in plaats van pas na aanvang van cART[16, 96], werd een update gedaan van de analyse van de jaarlijkse mortaliteitscijfers en de incidentie van AIDS, in zowel de totale HIV-geïnfecteerde als bij de met cART behandelde populatie in Nederland sinds 1996.

De algemene mortaliteitsratio in de met HIV geïnfecteerde populatie is sinds 1996 licht gedaald tot een niveau, net boven 1 dode per 100 persoonsjaren follow-up, wat lager was dan was gerapporteerd in een recente Deense studie[98]. Daarentegen zijn de mortaliteitsratio's in de met cART behandelde populatie in de tijd afgenomen tot een niveau dat vergelijkbaar is met die in de totale geïnfecteerde populatie. Echter, deze afname werd alleen waargenomen in de populatie die voor cART met antiretrovirale middelen was behandeld; aangezien de eerder behandelde populatie slechts 18% van de totale met HIV geïnfecteerde populatie uitmaakt, verklaart dit waarom het effect van cART in de totale populatie minimaal was. Op dit ogenblik is de mortaliteitsratio onder eerder behandelde patiënten nog altijd tweemaal zo hoog als die onder therapie-naïeve patiënten, hoewel de AIDS incidentie gelijk is in beide populaties.

Vorig jaar rapporteerden wij een mortaliteitsratio van 0,84 (95% CI 0,54 – 1,24) voor 2006, wat substantieel lager was dan hetgeen in 2005 was waargenomen[16]. In de huidige analyse nam de score voor 2006 toe tot 0,97 (95% 0,79 – 1,19), nog altijd een daling t.o.v. de

thans voor 2005 gerapporteerde score, 1,40 (1,18 – 1,66), maar een minder steile. De mortaliteitsratio die thans voor 2007 wordt gerapporteerd is hoger dan voor 2006, maar de dataverzameling van 2007 (en, voor sommige behandelcentra ook van 2006) is nog niet compleet.

Patiënten bij wie bij de HIV diagnose minder dan 200 $\times 10^6$ CD4 cellen/l werden gemeten, hadden een betere prognose wanneer die diagnose werd gesteld in of voor 2000, dan daarna. Hoogstwaarschijnlijk is dit resultaat het gevolg van een vertekening bij de indeling van patiënten. Voor 2001 registreerde de ATHENA studie alleen patiënten met cART. Sinds 2001 registreerde de Stichting HIV Monitoring (SHM) in essentie alle patiënten met HIV die ten tijde van de registratie in leven waren.

In de patiëntpopulatie die na 2000 werden gediagnosticeerd had het kalenderjaar, na correctie voor alle andere covariaten, geen effect meer op de overlijdenskans. Zelfs als de prognose van patiënten die na 2000 werden gediagnosticeerd minder gunstig zou zijn geweest dan voor hen die voor 2000 gediagnosticeerd werden, dan betekent dit in elk geval geen verslechtering van die prognose na 2000.

Een opnieuw groeiende HIV-1 epidemie onder homoseksuele mannen in Nederland

In het begin van de jaren tachtig werden de eerste gevallen van AIDS in Nederland gevonden bij homoseksuele mannen[100]. Vanaf 1996 is antiretrovirale combinatietherapie (cART) algemeen beschikbaar. Omdat cART de virale load in plasma en sperma dramatisch reduceert, en aangezien infectieusiteit gecorreleerd is met virale load, mag worden verwacht dat het wijdverbreide gebruik van cART het aantal gevallen van HIV infectie heeft verminderd[67, 101-107]. Paradoxaal genoeg neemt het jaarlijkse aantal diagnoses onder homoseksuele mannen juist toe, niet alleen in Nederland, maar ook in andere westerse landen[16, 108]. Tevens wordt toename van risicogedrag en van het aantal gevallen van syfilis en gonorroe gerapporteerd[17, 109, 110].

Mathematische modellen hebben laten zien dat een toename van transmissierisicogedrag het gunstige effect van cART teniet kan doen[111-118]. Wij evalueerden de afzonderlijke invloed van risicogedrag, HIV testgedrag en cART op de HIV epidemie bij homoseksuele mannen in Nederland met behulp van een mathematisch model waarvan de resultaten werden gefit op data van het ATHENA cohort en van de Amsterdam Cohort Studies.

Het aantal nieuwe infecties onder homoseksuele mannen in Nederland per jaar vertoonde een piek in 1983, met 802 nieuwe infecties, en dat aantal was ongeveer 250 in de 15 jaren daarna. Vervolgens steeg het aantal nieuwe infecties van 224 in 1999 tot 554 in 2004.

Tussen 1980 en 1983 bedroeg de schatting voor de reproductieratio, een maat voor het aantal nieuwe infecties dat een geïnfecteerde persoon veroorzaakt, $R(t)$ 2,39 (95% CI, 2,17 – 2,76), wat neerkomt op een zich uitbreidende epidemie. Tussen 1984 en 1995 nam de netto reproductieratio ten opzichte van de voorafgaande periode af met een factor 2,33 (2,03 – 2,83), hetgeen wees op grote reducties in risicogedrag. Het resultaat was dat de reproductieratio $R(t)$ omlaag ging tot 0,89 (0,85 – 0,93), minder dan één, en dus net onder de epidemische grenswaarde.

Na 1995, toen cART werd geïntroduceerd, nam het $R(t)$ verder af tot 0,76 (95% CI, 0,70 – 0,86). De afname had groter kunnen zijn als het HIV transmissierisico niet was toegenomen met 18% (3 – 34). Voor de periode 2000 tot 2004 werd het HIV transmissierisico zelfs nog hoger geschat, namelijk tot een niveau dat slechts 29% (22 – 72) lag onder het niveau tijdens de eerste periode van de epidemie tussen 1980 tot 1983. Een reductie in de geschatte gemiddelde tijd van HIV infectie tot

diagnose, die tussen 1984 en 1995 3,71 (3,49 – 3,97) jaar bedroeg en in de periode na 2000 2,90 (2,84 – 3,03) jaar, resulteerde in een veel lagere reproductieratio dan die in de eerste periode. Niettemin werd $R(t)$ voor die laatste periode geschat op 1,04 (0,98 – 1,09), dichtbij of boven de kritieke epidemische grenswaarde, hetgeen betekent dat HIV onder homoseksuele mannen in Nederland opnieuw epidemisch wordt verspreid.

De modelvoorspellingen werden op hun consistentie getoetst met behulp van gegevens uit de ATHENA database over het aantal thans in leven zijnde homoseksuele mannen. Op basis van het model werd geschat dat 24% van alle levende HIV-positieve homoseksuele mannen niet op de hoogte waren van hun positieve HIV-status begin 2005. Deze groep, die zich niet van zijn infectie bewust is, vormt de bron van 90% van de nieuwe infecties. Afgaand op het model zal in 2015 het aantal bekende, met HIV geïnfecteerde homoseksuele mannen 10.997 bedragen.

Een aantal hypothetische scenario's vanaf 1995 werd verkend. Zonder cART om de besmettelijkheid bij behandelde patiënten te beperken zou de epidemie onder huidige omstandigheden veel groter zijn, met naar schatting 7.609 infecties tussen 1995 en 2004, tegen de naar schatting 3.665 in het oorspronkelijke model. Als daarentegen cART was geïntroduceerd, maar zonder enige toenames in het transmissierisico, dan zou het aantal nieuwe infecties gedurende deze periode slechts 1.647 zijn geweest. Als cART was geïntroduceerd en als dezelfde toename in het transmissierisico had plaatsgevonden, maar zonder vermindering van de tijd tussen infectie en diagnose, dan zou het cumulatieve aantal nieuwe infecties 4.132 zijn geweest. Tenslotte, als er geen veranderingen waren opgetreden sinds 1995, dat wil zeggen geen cART en geen toename in risico- en testgedrag, dan zou dit aantal 2.984 zijn geweest. Conclusie is, dat cART een belangrijke rol heeft gespeeld bij het beperken van overdracht, maar dat de geboekte winst meer dan tenietgedaan is door een toename van het netto transmissierisico. Was deze toename er niet geweest in het cART tijdperk, dan zou de reproductieratio $R(t)$ zijn afgenomen tot 0,6 en zou de epidemie op overtuigende wijze aan het afnemen zijn.

Zoals blijkt uit het model heeft cART de HIV epidemie afgeremd, ofschoon het aantal voorkomen HIV infecties groter had kunnen zijn als het transmissierisico niet was toegenomen na 1995. Het model geeft aan dat de enige manier om de epidemische verspreiding substantieel terug te dringen en $R(t)$ ruim beneden 1 te brengen, ligt in het reduceren van het transmissierisico ten opzichte van de huidige niveaus. Dat betekent dat preventie gericht op het verminderen van risicogedrag van even cruciaal belang blijft als het voor het cART tijdperk was. Echter, een tijdige diagnose draagt ook bij aan het indammen van de epidemie, en meer frequent testen kan indirect tot veranderingen in risicogedrag leiden. Daarom dient het testen zich (opnieuw) te richten op die groepen die risicogedrag vertonen.

De met HIV geïnfecteerde populatie in de komende 10 jaar

Dankzij de grootschalige behandeling met cART neemt de mortaliteitsratio onder HIV geïnfecteerde patiënten af, met als gevolg dat de met HIV geïnfecteerde populatie in de Westerse wereld veroudert[16, 119, 120].

Met behulp van een mathematisch model werd een schatting gemaakt van de omvang en veroudering van de bekende met HIV geïnfecteerde populatie in Nederland in de komende jaren. Vervolgens werd de omvang en leeftijdsdistributie van de populatie in follow-up in 2015 voorspeld, op grond van de aanname dat vanaf 2006 de trends die worden waargenomen in de data tussen 2000 en 2005 zich zouden voortzetten. Voorts werden vier hypothetische scenario's verkend: (A) geen import van nieuwe met HIV geïnfecteerde patiënten uit Zuidelijk Afrika na 2006; (B) een op het niveau van 2006

gelijk blijvend aantal diagnoses onder homoseksuele mannen; (C) een 10% of 20% toename in het aantal diagnoses onder patiënten van niet-Nederlandse origine na 2006; en (D) het opnemen in het model van het aan de leeftijdsdistributie van homoseksuele mannen gefitte jaar van diagnose.

Op 1 januari 2000 waren 5.666 HIV geïnfecteerde personen in follow-up, waaronder 3.306 (58,3%) homoseksuele mannen, 1.407 (24,8%) via heteroseksueel contact geïnfecteerde mannen en vrouwen, en 953 (16,8%) personen die op een andere manier waren besmet. In totaal 672 (11,9%) patiënten waren jonger dan 30 jaar, 1.002 (17,7%) waren 50 jaar of ouder, en 4.660 (82,2%) tussen 15 en 50 jaar oud.

Wanneer een lineair model werd gebruikt, steeg het jaarlijkse aantal diagnoses onder homoseksuele mannen van 348 in 2000 tot 558 in 2005. In dezelfde periode nam het jaarlijks aantal diagnoses onder heteroseksuele mannen toe van 148 tot 182 en bij vrouwen van 221 tot 255. Er deden zich geen significante veranderingen in de tijd voor in het aantal diagnoses onder patiënten die op een andere manier werden geïnfecteerd, met een jaarlijks aantal diagnoses van 79 onder mannen en 15 onder vrouwen.

Tussen 2000 en 2005 daalde het percentage recent gediagnosticeerde patiënten afkomstig uit Zuidelijk Afrika in de heteroseksuele populatie van 52% tot 42%, terwijl het percentage Nederlandse patiënten steeg van 21% tot 31%.

Op grond van ons model zal de met HIV geïnfecteerde populatie in de follow-up in 2015 3,3 keer groter zijn dan in 2000 en 2,0 keer groter dan de populatie in 2005. Het aantal patiënten ouder dan 50 jaar zal toenemen met een factor 6,3, terwijl het aantal patiënten onder de 30 jaar naar verwachting zal toenemen met een factor 1,5.

Door het ouder worden van de met HIV geïnfecteerde populatie zal de behandeling gecompliceerder worden. Bij oudere patiënten verloopt het herstel van CD4 cellen over het algemeen minder goed dan bij jongere patiënten[2-4]. Bovendien kunnen leeftijdgerelateerde aandoeningen en andere niet HIV-gerelateerde ziekten de behandeling van HIV bemoeilijken. Ook is weinig bekend over de tolerantie en veiligheid van antiretrovirale geneesmiddelen bij oudere met HIV geïnfecteerde patiënten[5]. Bij oudere patiënten nemen de nier- en leverfuncties af, wat zou kunnen leiden tot een verminderde tolerantie vergeleken met die bij jongere patiënten. Tenslotte moet rekening worden gehouden met geneesmiddeleninteracties tussen antiretrovirale geneesmiddelen en medicatie die wordt gebruikt voor de behandeling van bijvoorbeeld leeftijdgerelateerde aandoeningen.

Het model geeft alleen een schatting van het aantal patiënten in de follow-up bij één van de HIV behandelcentra in Nederland die, per definitie, patiënten zijn die weten dat zij met HIV geïnfecteerd zijn. Onze eerdere schatting van de met HIV geïnfecteerde populatie met een leeftijd tussen 15 en 50 jaar in Nederland – inclusief degenen die niet weten dat zij geïnfecteerd zijn – kwam uit op 18.500 individuen[1]. Uit de nu gepresenteerde analyse blijkt dat op grond van de data 6.944 en op grond van het model 6.992 patiënten in dezelfde leeftijdscategorie zaten. Dit betekent dat meer dan 60% van de met HIV geïnfecteerde patiënten nog niet in de follow-up zitten, en zich dus waarschijnlijk nog niet bewust zijn van hun infectie.

Met behulp van het model werden een aantal scenario's verkend. Deze scenario's waren gebaseerd op de aanname dat alle andere factoren constant bleven. Meer dan 1.000 nieuwe HIV gevallen zouden worden vermeden als ofwel de infecties onder de populaties afkomstig uit Zuidelijk Afrika tot staan zou worden gebracht, ofwel het aantal diagnoses onder homoseksuele mannen op het niveau zou blijven van dat in 2006. Het eerste scenario

is echter moeilijk te realiseren, aangezien de meeste patiënten uit Zuidelijk Afrika daar ook geïnfecteerd raken[1]. Het verminderen van het aantal diagnoses zou dan alleen mogelijk zijn als de immigratie vanuit Zuidelijk Afrika afnam. Het tweede scenario zou mogelijk kunnen zijn als het risicogedrag onder homoseksuele mannen afneemt. Een toename in het jaarlijkse aantal diagnoses onder individuen van niet-Nederlandse origine voor alle transmissiecategorieën zou hoofdzakelijk de heteroseksuele populatie beïnvloeden.

Het laatste, minder hypothetische scenario hield rekening met de toenemende leeftijd bij diagnose onder homoseksuele mannen als gevolg van de toenemende leeftijd van de bron populatie, die gemiddeld meer dan 40 jaar bedroeg. De grootste winst bij het reduceren van het aantal nieuwe diagnoses onder homoseksuele mannen zou daarom worden verkregen door een reductie van het risicogedrag onder mannen van middelbare leeftijd.

Kwaliteit van HIV zorg in Nederland en de invloed van late presentatie in de kliniek

HIV- en AIDS-zorg en antiretrovirale behandeling wordt geboden door 24 gezondheidsinstellingen verspreid over Nederland. Elke instelling is als HIV behandelcentrum erkend door de Nederlandse Minister van Volksgezondheid, Welzijn en Sport, en elk is gehouden om de SHM te voorzien van gegevens over de diagnose, follow-up, en behandeling van alle met HIV geïnfecteerde patiënten in (poli)klinische zorg. De SHM rapporteert aan het Ministerie van Volksgezondheid, niet alleen over de HIV epidemie en de resultaten van anti-HIV-behandeling, maar ook over de kwaliteit van de geboden HIV- en AIDS-zorg.

Wanneer overleving wordt gezien als een cruciale indicator voor de kwaliteit van de zorg, dan zou, behalve verschillen in patiëntprofielen, presentatie van patiënten in een laat stadium van de infectie een belangrijke rol kunnen spelen. Patiënten die laat in zorg komen, kunnen een substantieel beslag leggen op de klinische capaciteit, en bij sommigen is het behandelingsperspectief slecht[121, 122]. In studies in het Verenigd Koninkrijk is eerder aangetoond dat met name Afrikaanse patiënten zich vaak in een laat stadium van de infectie aanmelden voor zorg, wanneer het aantal CD4 cellen laag is[122-124]. Een dergelijke late presentatie zou wellicht ook kunnen samenhangen met de demografische karakteristieken van een specifieke patiëntenpopulatie.

Voor ons rapport werd de overlevingskans na aanvang van cART tussen de verschillende HIV behandelcentra vergeleken, waarbij rekening werd gehouden met de verschillen in de patiëntenpopulatie en met de late aanmelding voor zorg.

Tussen 1 januari 1997 en 1 juni 2007 werden 8.616 patiënten gediagnosticeerd met HIV en voor het eerst aangemeld voor zorg in één van de HIV behandelcentra in Nederland. De meerderheid van de populatie was man en de helft van de patiënten was afkomstig uit Nederland. Echter, verschillen in de demografische kenmerken van de patiëntenpopulatie tussen ziekenhuizen komen voor. Het percentage patiënten dat afkomstig was uit het Caribisch gebied en Latijns-Amerika varieerde van 1% tot 30%, en het percentage patiënten dat afkomstig was uit Zuidelijk Afrika varieerde van 1% tot 40%.

Het mediane aantal CD4 cellen bij eerste aanmelding voor zorg bedroeg 308×10^6 cellen/l (IQR 120 - 510). Patiënten afkomstig uit Nederland en andere Westerse landen hebben een significant hoger aantal CD4 cellen dan zij die afkomstig zijn uit het Caribisch gebied/ Latijns-Amerika, Zuidelijk Afrika, en de overige regio's. Het aantal CD4 cellen bij eerste aanmelding verschilde significant tussen de HIV behandelcentra (HTC's); bij 6 centra was het aantal hoger dan de mediaan, terwijl bij

11 HTC's het mediane CD4 cel aantal lager was. Het aantal CD4 cellen bij aanvang van cART was 180 × 10^6 cellen/l (70 - 290). Het aantal CD4 cellen bij eerste aanmelding is sterk geassocieerd met het aantal bij aanvang van cART. Bij HTC's waar de meerderheid van de patiënten zich vroeg aanmeldden, was het aantal CD4 cellen bij aanvang van cART over het algemeen hoger dan het mediane aantal van alle HTC's bij elkaar.

Van alle patiënten presenteerde 35% zich voor zorg bij een HTC in een laat stadium van de HIV infectie, dat wil zeggen met een aantal CD4 cellen lager dan 200 × 10^6 cellen/l. Late presentatie was geassocieerd met hogere leeftijd; onbekend overdrachtsrisico; Zuidelijk Afrikaanse, Caribische, of Latijns-Amerikaanse origine; en ziekteverschijnselen van HIV bij het eerste bezoek. Met HIV geïnfecteerde patiënten in Nederland blijken zich overigens voor de eerste keer bij een HTC te presenteren met een CD4 cel aantal dat vergelijkbaar is met het aantal dat wordt gevonden bij mannen en vrouwen in West-Afrika bij de start van cART[125]. Dat is verassend, gegeven de ruimere mogelijkheden die in Nederland beschikbaar zijn voor testen en behandelen.

Een HIV diagnose tussen 2003 en 2007 bleek geassocieerd met een lagere kans op late presentatie. Echter, hoewel het aantal mensen dat laat in zorg komt in de afgelopen jaren kleiner is geworden, werd bij 26% van de patiënten waarbij recentelijk HIV werd gediagnosticeerd een CD4 cel aantal lager dan 200 × 10^6 cellen/l gevonden.

De huidige richtlijnen voor de behandeling bevelen aan om met cART te beginnen bij CD4 cel aantallen tussen 200 en 350 × 10^6 cellen/l[126]. Hoewel 65% van de patiënten zich vroeg genoeg voor zorg aanmeldden, lag het mediane CD4 cel aantal bij aanvang van cART in de totale populatie beneden de aanbevolen waarde. Negen procent van de patiënten die zich aanmeldden voor zorg met ten minste 200 × 10^6 CD4 cellen/l begonnen met cART op het moment dat dit aantal beneden 200 × 10^6 cellen/l was gedaald. Op grond hiervan kan worden geconcludeerd dat de gevonden late start niet geheel kan worden verklaard op grond van late presentatie.

Sterfte onder patiënten die zich presenteren wanneer het aantal CD4 cellen beneden de 200 is gedaald is significant hoger dan onder diegenen die zich presenteren met ten minste 200 × 10^6 cellen/l. In totaal stierven 403 van de patiënten met een HIV diagnose vanaf 1 januari 1997, waarvan 288 binnen 5 jaar na aanvang van cART. Mannelijk geslacht, latere leeftijd, HIV infectie door heteroseksueel contact, injecterend druggebruik, een onbekend of ander HIV transmissierisico, en kalenderjaar van de HIV diagnose waren geassocieerd met het risico van overlijden binnen 5 jaar na aanvang van cART.

Voor alle HTC's op twee na verschilde het overlijdensrisico binnen de eerste 3 jaar met cART niet significant van het nationaal gemiddelde. Twee HTC's vertoonden een hoger risico, ook na correctie voor geslacht, leeftijd, HIV risicogroep en klinische verschillen in de patiëntenpopulatie. Bij beide HTC's werd een significant lagere aantal CD4 cellen gevonden op het moment van de presentatie van patiënten bij deze HTC's. Ook na correctie voor aantallen CD4 cellen bij presentatie bleef het risico van overlijden significant hoger.

Aanbevelingen

Drie aanbevelingen worden gedaan.
Uit ons werk en dat van anderen, op het gebied van het modelleren van de epidemie en de invloed daarop van grootschalige behandeling met antiretrovirale middelen, blijkt dat gegevens nodig zijn over de

tijd tussen HIV besmetting en diagnose en de tijd tussen diagnose en het starten van zorg. Hiermee kan men een beter inzicht krijgen in de factoren die van cruciale invloed zijn op het overdrachtsrisico van HIV. Die kennis is nodig voor het ontwikkelen van een geconcentreerd, op het afremmen van de epidemie gericht HIV preventiebeleid. Daarbij is inbreng vanuit de sociale- en gedragswetenschappen van groot belang. Het Rijksinstituut voor Volksgezondheid en Milieu (RIVM) is, samen met de SHM, de HIV behandelcentra en de regionale GGD's, momenteel bezig met het opzetten van een onderzoeksproject om de variatie in de tijd tussen HIV diagnose en het binnenkomen in de zorg te onderzoeken.

De ziekte- en sterftecijfers in de met HIV geïnfecteerde populatie kunnen worden verbeterd door eerder met cART te beginnen dan op dit moment het geval is. Ook hier is betere kennis over met name late presentatie van patiënten bij de behandelcentra nodig, waaronder de redenen om het starten met HIV zorg uit te stellen. Daarnaast zijn echter strategieën nodig om de kwaliteit van HIV zorg te verbeteren, zodanig dat patiënten die wel op tijd binnenkomen in de zorg (dat wil zeggen wanneer de afweer van een patiënt nog voldoende is), ook op tijd met cART beginnen (namelijk op het moment of voordat het aantal CD4 cellen beneden de grenswaarde is gedaald). De HIV/AIDS behandelende artsen spelen in dit opzicht een cruciale rol.

Tot slot: het is duidelijk dat de met HIV geïnfecteerde populatie groeit en ouder wordt. De patronen van HIV overdracht en de demografische kenmerken van HIV risicogroepen zullen veranderen naarmate de bronpopulatie ouder wordt. De verschuiving in de leeftijd bij diagnose richting de 40 jaar bij homoseksuele mannen is een voorbeeld van zulke veranderingen. Bovendien kan de behandeling van HIV gecompliceerder worden met het toenemen van de leeftijd, en kan de HIV-behandeling minder succesvol worden. Speciale aandacht moet worden besteed aan studies van leeftijdgerelateerde complicaties van HIV, de invloed van HIV op het optreden van leeftijdgerelateerde ziekten, en de interactie van antiretrovirale geneesmiddelen en geneesmiddelen die worden gebruikt voor leeftijdgerelateerde en andere ziekten. Verder wordt aanbevolen om studies te verrichten naar de invloed van de groeiende en ouder wordende populatie op de kosten van de HIV zorg.

2 Introduction, Summary & Recommendations

Introduction

The HIV epidemic, especially amongst men having sex with men, is not under control (Bezemer, 2007, submitted). The recently introduced large-scale combination antiretroviral therapy (cART) has played an important role in limiting HIV transmission, but any gains made have been more than offset by an increase in the net transmission rate. Had this not occurred, the epidemic would have been in a convincing decline. The net transmission rate is largely determined by awareness of infection and transmission risk behaviour. Especially those who are unaware of their infection contribute substantially to the spread of HIV. Shortening the time period between infection and diagnosis of HIV, together with the timely start of cART, is the challenge we still face when aiming to contain the epidemic.

HIV-infected individuals still die of their infection, although less often than before the introduction of cART. In the total group of 12,915 patients with 78,635 person-years of follow-up since 1996, 1127 deaths were recorded. This number corresponded with an average mortality rate of 1.43 (95% confidence interval [CI] 1.35–1.52) deaths per 100 person-years. The mortality slightly decreased over time (p=0.008), from 1.95 (95% CI 1.55–2.41) in 1997 to 1.23 (0.87–1.68) in 2007. The mortality rate currently reported for 2007 is higher than for 2006, although the data collection for 2007 (and, for some treatment centres, also for 2006) has not yet been completed. Interestingly, the causes of death in the majority of cases were related to HIV infection and AIDS during the first 7 years after the start of cART; non-HIV-related causes were the most prevalent thereafter. In comparison to the age- and gender-standardized incidence in the general Dutch population, the overall incidence of cancer-related death after starting cART was five times higher and the incidence of non-AIDS-defining cancers was two times higher amongst the HIV-infected population.

There is room for improving mortality and morbidity rates by starting treatment earlier in the course of the infection. The association between low CD4 cell counts or AIDS at or prior to commencing cART and a higher probability of progression to AIDS and death thereafter is well known. Moreover, the probability of death continues to decrease with higher CD4 cell counts, and even for very high counts at the start of cART, although the risk of a new AIDS event remains similar across counts higher than 300 CD4 cells/mm^3 at the start of cART. Despite the importance of starting cART when CD4 counts are still above 200 cells/mm^3, more than half of patients started below that threshold. The median CD4 cell count in the whole AIDS Therapy Evaluation in the Netherlands (ATHENA) population at start of cART was below 200 cells/mm^3, although 65% of the patients presented early enough for HIV care.

The population of HIV-infected persons registered by the HIV Monitoring Foundation (HMF) and monitored in the ATHENA observational cohort is still growing. Since last year, the number increased by 1205 patients and the total follow-up time by 17,218 years. The total number of persons infected with HIV and registered by the 23 HIV treatment centres and 4 paediatric HIV treatment centres has reached 13,264 as of 1st of June 2007. The follow-up time is 97,982 person-years since HIV diagnosis. Of the registered patients, 10,095 patients were 13 years or older and in active follow-up, which is an underestimation because of the backlog in data collection in some of the HIV treatment centres. Despite a decade of cART, the annual growth of the HIV-infected population has only increased since 1996. This increase has been most noticeable in the population of men having sex with men (MSM), but the annual number of diagnoses amongst heterosexuals has increased slightly over time. The CD4 cell count at diagnosis has increased over time, indicating that nowadays new cases are diagnosed early in the infection. In addition, the proportion of patients for whom a last

seronegative date is recorded has increased over time, as well. The actual growth of the registered infected population confirms our model outcome that the spread of HIV in the Netherlands is still epidemic.

The estimated number of patients in follow-up in any of the HIV treatment centres in the Netherlands are, by definition, patients who know they are HIV-infected. Recently, we estimated that the HIV-infected population in the Netherlands aged between 15 and 50 years – including those unaware of their infection – amounted to 18,500 individuals[1]. In our analysis of the size and age distribution of our registered population, we found that 6944 patients in the data and 6992 in the model were aged between 15 and 50 years. This implies that more than 60% of the HIV-infected patients are not yet in follow-up, and thus, most likely, not yet aware of their HIV infection.

The HIV-infected population in follow-up in 2015 is expected to be 3.3 times larger than the population in 2000, or 2.0 times larger than the population in 2005. The number of patients more than 50 years of age is predicted to increase by a factor of 6.3, whereas the number of patients less than 30 years of age is expected to increase by a factor of 1.5. The treatment of the disease will be complicated by the increasing age of the HIV-infected population. In older patients, the potential for restoration of CD4 cells is generally less favourable than that in younger patients[2-4] and age-related diseases and other non-HIV-related illnesses will complicate the treatment of HIV. In addition, tolerability and safety of antiretroviral drugs in older HIV-infected patients may be less[5], and drug-drug interactions between antiretroviral drugs and other age-related medication may occur.

An HIV-infected population twice the size of the population currently being followed in the Netherlands might be expected to put a substantial strain on HIV health care. Previously, we estimated that one year of treatment for an HIV-infected individual costs 12,500 euro[6]. Hence, when the per capita costs and the population size are multiplied, the cost of HIV treatment will increase from 115 million euro annually in 2005 to 230 million euro in 2015.

The main findings described in the 2007 scientific report on the monitoring of human immunodeficiency virus (HIV) infection in the Netherlands are the following: the growing epidemic, despite massive and effective antiretroviral treatment; the still higher mortality rate amongst HIV-infected persons, with a shift towards non-HIV- and AIDS-related causes of death; the relatively late initiation of cART in a substantial proportion of the diagnosed and registered HIV-positive population; the growth not only in the registered population, who are therefore aware of their diagnosis, but also in the unaware population; and the phenomenon of aging in the HIV-infected population. This report shows the favourable results of cART intervention over the past 11 years, especially, the dramatic decline in HIV-related morbidity and mortality rates, but it also indicates the challenges ahead.

Other items that are addressed include:

- The changes in effectiveness of first-line cART over time, exploring the improvement achieved by various drug regimens
- The short-term virologic response after changing the initial cART regimen
- Resistance of HIV-1 during cART and transmission of resistant strains
- cART and the response to treatment in pregnant women
- The CD4 cell response to cART in HIV-infected children
- The CD4 cell response to treatment of hepatitis C virus co-infection

In addition, this year we present for the first time results of the first assessment of the quality of HIV care in the Netherlands and the impact of late presentation for care.

Finally, there are two special chapters, one regarding the Amsterdam Cohort Studies on HIV infection and one reporting on HIV and AIDS in Curacao and amongst migrant populations in the Netherlands.

To begin, however, we will report on the quality of data and the outcomes of a different approach of selecting data items for source data verification. Since the beginning of 2002, the HMF has collected data from all HIV-infected patients, whether or not they were being treated and seen regularly by an HIV/AIDS-treating physician in one of the current 23 HIV treatment centres. HMF's mission is to study the natural history of HIV and the effects of treatment, as well as to further knowledge and understanding of the HIV epidemic and the course of HIV infection in both treated and untreated patients. In addition, HMF monitors and contributes to the quality of HIV care.

One primary way the HMF seeks to accomplish its mission is through making data available for HIV/AIDS-related research. To support this use, an accurate and periodically updated description of the HIV-infected population from which HMF draws its data is of great importance. This sixth annual report provides such a comprehensive description. Since the population under study is not static, the report also addresses the dynamics of change in the course of the infection and in the epidemic that has resulted even after more than a decade of large-scale, lifetime treatment of HIV.

The HMF continues to participate in studies performed within the framework of the Antiretroviral Therapy Cohort Collaboration (ART-CC), which encompasses 16 cohorts from various European countries, the United States, and Canada. For ART-CC, the only data used are those obtained from patients starting cART without previous experience with antiretroviral drugs. Studies have been performed on the changing life expectancy, different mortality rates after various AIDS-defining events, and the prognostic importance of the most recent CD4 cell count and of anaemia, as well as differences in the short-term virologic effect of various cART regimens.

Besides ART-CC, a new European collaboration between observational cohorts was started 2 years ago. The Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) conducts epidemiologic research on the prognosis and outcome of HIV in the infected population and focuses on scientific questions that require large sample sizes of patients for the answers. The first research project on the effect of age on cART outcomes has been finalized, and other projects have been started.

The long-standing collaboration with the Department of Infectious Disease Epidemiology of the Medical Faculty of Imperial College London has resulted in a model analysing the impact of large-scale administration of cART on the epidemic in the Netherlands and, recently, in a model comparing quality of care in the Netherlands. Another study is examining the variation in HIV-1 plasma RNA set-points and the clustering around those set-points that maximise the transmission potential. In addition, after last year's report on transient viraemia during cART, the collection of data and development of a mathematical model assessing the impact of superinfection has been started.

The HIV/AIDS treating physicians, together with the HMF data collection staff in the HIV treatment centres throughout the Netherlands, are crucial for the work of the HMF. After transmission of data to the national HMF database, quality control is established by HMF's data monitors. Data preparation and analyses are performed by the staff and assistant researchers of the analysis unit of the HMF; this unit is essential for the execution of the registration and research programmes of the HMF and for the support of groups who have approval to use

data from the ATHENA dataset. In the final chapter, we list the various publications and presentations of 2007 that are (partly) based on this unique collection of data on HIV and AIDS in the Netherlands.

Summary

Data quality: Results of customized quality improvement procedures

Maintenance and improvement of the quality of longitudinally obtained observational clinical data is of main interest, given the less structured way these data are collected. Our collection of monitoring data from HIV-infected patients started in 1996 within the framework of the ATHENA project[7], and for a substantial number of patients, data obtained since the early 1980s are included. The quality of the data is usually controlled by source data verification[8–12], but since we deal with a vast number of patients followed for a long period, i.e., years, a 100% source data verification is not feasible. At the same time, source data verification of a random selection of 10% of data has been reported as insufficient for improving data quality[13, 14]. Therefore, we have implemented customized procedures for continuous monitoring of the accuracy of the ATHENA cohort data and, subsequently, for resolution of discrepancies.

In short, we selected the following data items for quality control: the date of the first positive HIV test and specific HIV-related events according to the CDC classification[15]. Both items have a marked influence on the data analyses. Source data verification of the first positive test date registered as 'unknown' was true in only one third of the cases; in two thirds, a date could be found in the patient file. Source data verification of missing or incorrectly recorded symptomatic HIV (CDC-B event) or AIDS (CDC-C event) was performed in a selection of patients with CD4 cells $<50/mm^3$, on the assumption that these patients were more prone to such a clinical event. In the verified population, especially CDC-B events were missed or incorrectly recorded. In addition, the diagnostic (un)certainty of a recorded CDC-B or -C event was verified and corrected in 39% of the events.

Our conclusion is that quality of data essential in primary data analyses can be improved substantially by using source data verification. When data is collected directly in an observational setting, clinical, diagnostic, and organisational procedures will have an effect on the accessibility of data. For instance, when data collection is carried out directly after a patient's visit to the hospital, source data may be added to the file at a later time point, and thereby those data are missed for entry.

The first year of data collection appears to be the most complex to record, especially when patients are seen in an advanced stage of HIV infection and thus have a substantial and complicated history reflected in their medical file. Results from specialized diagnostics, such as pathology, radiology, or immunology, are not always clearly related directly to the certainty level of the CDC-B or -C diagnosis.

Although source data verification has been shown effective, it is also laborious. However, by restricting source data verification pecifically to all end-points essential for key data analysis, it can be used even for data sets of large numbers of patients. In addition, the efficiency of source data verification might be improved by restricting it to the first year of data collection.

The ATHENA study population

By 1 June 2007, the HIV Monitoring Foundation had data collected and stored in the ATHENA database from 13,264 HIV-infected persons registered in one of the

23 HIV treatment centres (HTC) in the Netherlands. The total follow-up was 97,982 person-years since diagnosis; 12,958 (97.7%) were infected with HIV-1, and 78 (0.6%) with HIV-2. For 95 (0.7%) patients, seroreactivity to both HIV-1 and HIV-2 was found, and for 133 (1.0%) patients, these serologic results were inconclusive or not (yet) known. When measured, HIV-1 subtype B was found in a majority of 78%, more frequently in men than in women.

In total, 10,095 (76.1%) patients were 13 years or older and in follow-up as of 1 June 2007, which is probably an underestimation because some HIV treatment centres had a backlog in data collection of more than one year.

Almost 79% were men who originated from the Netherlands (58.5%) and were infected via homosexual contact (55.7%). In total, 1354 (13.4%) men and 1954 (19.5%) women were infected via heterosexual contact, whereas patients infected via injection drug use accounted for 3.5% of the population. The median age of the population was 43.3 (Interquartile range [IQR], 36.8-50.1) years, and men were generally older than women, that is, 44.7 (38.7-51.3) years of age for men compared to 37.8 (31.8-44.8) years for women ($p<0.001$).

The median time since diagnosis was 5.9 (IQR, 3.0-9.9) years for women and 6.7 (3.0-11.4) years for men ($p<0.001$). In total, 2523 (25.0%) patients were diagnosed in the previous 3 years; this proportion was similar for men and women ($p=0.6$). On the other hand, a larger proportion of men (2521, 32.1%) than women (536, 24.1%) received their HIV diagnosis more than 10 years ago ($p<0.001$).

cART was administered to 8115 (80.4%) patients, and 1924 (19.1%) were not (yet) treated. The number of patients not yet treated was higher amongst women than men. Tenofovir plus lamivudine or emtrictabine and zidovudine plus lamivudine are the most frequently used backbones in first-line cART regimens, with nevirapine, efavirenz, lopinavir and atazanavir as the most frequently used additions.

The most recently measured CD4 cell counts were 480 (IQR, 340-670) $\times$ 10^6 cells/l for the male population and 490 (350-670) for women. Plasma viral-load levels were <500 copies/ml in 87.6% of the cART-treated population. One or more AIDS-defining events were found in 25.9% of the total population in follow-up, and about half of those had an AIDS diagnosis at or within 4 weeks after an HIV diagnosis.

A total of 9291 (92.0%) patients were tested for hepatitis B surface (HBsAg) or envelope (HBeAg) antigen and 812 (8.7%) tested positive. Hepatitis B virus (HBV) was most prevalent amongst HIV-infected injection drug users (IDU) (11.6%). The HBV prevalence was 9.4% amongst homosexual men and 7.1% amongst the heterosexually HIV-infected patients and higher amongst men (9.1%) than amongst women (5.8%).

The hepatitis C virus (HCV) status was known for 8581 (85.0%) patients, and 926 (10.8%) were HCV-positive. Co-infection with both HBV and HCV was found in 95 patients. The HCV prevalence was highest amongst IDUs (93.9%). In the population infected via heterosexual contact, the HCV prevalence was 6.8% for men and 6.2% for women. The prevalence was similar amongst homosexual men (5.8%).

Trends in baseline characteristics over time

Since last year, the HIV-infected population in the Netherlands as registered by the HIV Monitoring Foundation has increased by 1205 patients[16], and the total number of person-years of follow-up increased by 17,218.

In recent years, 50% to 60% of the diagnosed patients were infected via homosexual contact, whereas approximately 35% were infected via heterosexual contact. The number of patients infected via injection drug use was approximately 10 persons per year. The absolute number of diagnoses amongst homosexual men increased from 300 to 400 per year in the second half of the 1990s to more than 500 after 2004. In 2006, 513 diagnoses amongst MSM have been registered so far, but because of the backlog in registration, the real number of 2006 diagnoses is expected to be approximately 15% higher.

Since 2002, the number of patients originating from sub-Saharan Africa has declined. This is consistent with the decreasing number of people immigrating from Africa to the Netherlands[16]. In 2007, however, an increase in the proportion of sub-Saharan Africans in the heterosexual population was observed. Because this increase is not statistically significant, no conclusions can be drawn from it as yet.

The proportion of homosexual men diagnosed with a recent infection has increased to nearly 30% in the past 2 years. More than 50% of the infected MSM ever had a negative test. This most likely reflects the increasing testing frequency[17]. In patients not diagnosed with a recent infection, the time between infection and diagnosis has decreased as the CD4 cell count at diagnosis has increased over calendar time. Taken together with the observation that the median age at diagnosis has increased, it can be concluded that that MSM are infected at an older age.

In the heterosexually infected population, the proportion of recent infections and proportion of patients with a negative test ever before have also increased over time. The increase is more pronounced in the female population, which may be attributable to the implementation of the national prenatal screening of pregnant women[18].

Almost half of all treated patients are now using a cART regimen containing tenofovir instead of zidovudine, which has a less favourable toxicity profile than tenofovir[19]. In addition, an increasing proportion of patients are using emtricitabine instead of lamivudine, probably because emtricitabine is available in a fixed-dose combination with tenofovir. Tenofovir-containing regimens were prescribed to two-thirds of the patients starting cART between 1 June 2006 and 31 May 2007; half of the patients started with emtricitabine. In the total treated population, no changes were observed in the administration of nevirapine and in the most frequently used protease inhibitors, but efavirenz-containing regimens gained in popularity. Also in first-line cART, efavirenz-containing regimens were more often used, whilst regimens containing lopinavir became less common.

CD4 cell counts at HIV diagnosis have appeared to increase over time, indicating that a larger proportion of patients can start cART in time. Since 2005, CD4 cell counts at the start of cART have appeared to increase in the heterosexual, but not in the homosexual, population. The CD4 counts in the homosexual population at diagnosis are already at or above the threshold region in which cART should be started.

The prevalence of hepatitis B and C co-infection reportedly was approximately 10% and did not change from previously reported figures in the ATHENA study population.

Despite a decade of cART, the annual growth of the HIV-infected population has only increased since 1996. This increase has been most noticeable in the MSM population, but the annual number of diagnoses amongst heterosexuals has increased slightly over time. In the total population, the median CD4 cell counts were just below 500×10^6 cells/l, and cART was able to suppress the viral load below 500 copies/ml in the vast majority of patients.

Changes in effectiveness of first-line cART over time

Combination antiretroviral therapy (cART) has been shown to be effective in reducing HIV production substantially[20] and for a long period of time[21], providing it is started in a timely manner[22] and administered in a way that encourages patient adherence[23, 24]. In addition, the short-term response to first-line cART is an important prognostic marker for further disease progression[25]. We compared various combinations of antiretroviral drug classes in first-line cART with respect to short-term immunologic and virologic outcomes and analysed differences in time to change of the initial cART regimen. For this study, we used a subset of 7655 antiretroviral therapy-naïve adult patients starting first-line cART between 1996 and 2006.

It appears that the short-term virologic outcome improved over calendar years independent of the type of cART combination used. When comparing the currently most frequently used cART with a non-nucleoside HIV reverse transcriptase inhibitor (NNRTI) or a boosted HIV protease inhibitor (PI) added to the nucleotide reverse transcriptase (NRTI) backbone, we found no significant differences in short-term virologic outcome.

This indicates that there is residual confounding through variables not adjusted for in the analysis. The specific drugs used in the NRTI component of cART may also especially affect efficacy. Improved virologic responses are reported for combinations of tenofovir and lamivudine or emtricitabine[26], and the increasing proportion of patients starting cART using these NRTIs in later calendar years might explain the better virologic outcome in recent years.

The increase in CD4 cell number measured between the start of cART and 24 weeks of therapy was 31 cells/mm^3 higher in patients starting with a boosted PI compared to those starting with an NNRTI.

Patients starting cART that included a boosted PI had a shorter time to change in the regimen for any reason, but no significant difference was found in the risk of a toxicity-related change between patients starting cART that included an NNRTI versus cART that included a boosted PI.

Closer follow-up of specific subgroups is needed, with the aim of improving the virologic response through better adherence. Patients of non-Western origin and younger patients showed a diminished virologic response after 24 weeks of cART. Moreover, patients of non-Western origin had smaller gains in CD4 cell count. Although contrasting results are reported[27], our results confirm studies by others[21, 28-30] and are probably best explained by differences in adherence. Patients starting cART when CD4 cell counts are still high have a higher risk of changing therapy and a lower virologic response. Again, this is probably due to limited adherence, since feeling healthy is a reason for not taking medication[7, 31, 32].

A higher risk of a toxicity-related change in therapy was found in patients, including women, with a lower weight and after adjustment for the weight. Therapeutic drug monitoring to guide the lowering of the dosage of antiretroviral drugs could be of benefit to patients considered at higher risk of drug toxicity[33].

Finally, women starting cART during pregnancy had a lower probability of achieving an HIV RNA plasma concentration <50 copies/ml after 24 weeks of treatment, although they experienced a higher increase in CD4 count. This is probably the result of starting cART with a high CD4 count and then stopping treatment after delivery.

Virologic responses to cART as the initial treatment have improved since the introduction of cART in 1996. Initial therapy including a boosted PI or NNRTI has superior virologic efficacy to an unboosted PI or a combination of

NRTIs only. With the recently introduced antiretroviral drugs, there is no significant difference in the risk of toxicity-related change in patients initiating cART with either a boosted PI or an NNRTI.

Short-term virologic response after changing the initial cART regimen

In a substantial proportion of patients, the initial combination of antiretroviral drugs is altered for reasons varying from toxic response to one or more of the drugs to virologic failure, the inability to adhere to the prescribed regimen, or the simplification of the regimen[34, 35]. In cases of changing the initial regimen because of virologic failure, the risk of another virologic failure with a subsequent regimen is high. Likewise, the risk of a toxicity-related change of a new regimen is higher when the initial regimen was changed because of toxicity[36, 37].

However, this repetition of events following changes in the combination of antiretroviral drugs used for effective suppression of HIV might have changed over time with the availability of new drugs and drug classes. We looked at short-term virologic efficacy of new antiretroviral drug combinations administered to patients after failure of their initial cART regimen, because of either toxicity or insufficient HIV suppression.

By the end of December 2006, 4947 (64.6%) of the 7655 patients who started combination antiretroviral therapy (cART) experienced a change of one or more of the initially prescribed antiretroviral drugs. The most frequently recorded reasons for the change in the initial cART were toxicity in 1982 patients (40.1%), followed by simplification of a new regimen in 516 (10.4%), virologic failure in 446 patients (9.0%), and patient‘s request in 412 (8.3%). In 53.9% of the 4947 patients with a change of regimen, the NRTI backbone of the combination was changed, and it was the only change in 24.4%. A change from a combination including a NNRTI to one with a PI was recorded for 23.3%, from an unboosted to a boosted PI for 9.9%, and from a NNRTI to a PI for 7.8%. In 9.2% of the patients, the change resulted in a new NRTI-only combination, and in 14% the change remained within the same combination of drug classes. cART that included an NNRTI was the most frequently used combination in the new cART (45.0%), followed by cART that included a boosted PI (25.5%) and cART that included an unboosted PI (15.1%). Most patients (78.2%) switched from first-line to the new cART without interruption.

Of the 3286 patients for whom the HIV RNA plasma concentration was measured by an assay with a detection limit of 50 copies/ml or less, 2781 (84.6%) had results below this limit after 24 weeks of new cART. The proportion of patients with <50 HIV-RNA copies/ml at week 24 was highest amongst those who switched because of simplification of the initial regimen (94.6%), followed by those who switched because of toxicity (85.0%), and then by patients who showed virologic failure on their initial regimen (70.4%).

The risk of insufficient HIV suppression 24 weeks after starting a second cART regimen was higher amongst patients from regions other than the Netherlands. Patients who switched regimen because of virologic failure also had a lower probability of reaching plasma HIV RNA plasma levels below 50 HIV RNA copies/ml than patients who switched due to toxicity. Compared to patients experiencing a cART regimen switch following virologic failure in or after 2003, those who switched the cART regimen after virologic failure prior to 2003 had an even lower probability of reaching sufficient suppression of HIV replication. This effect of calendar time on HIV suppression was not found in cases of toxicity-related change of the cART regimen.

In accordance with the improved results of initial cART regimens, results of a second regimen have also improved over time. As with first-line regimens, this

improvement most probably follows the introduction of less toxic drugs with a lower pill burden[38] and a higher therapeutic efficacy in more recent calendar years. In addition, genotypic resistance-guided HIV-treatment decisions in patients with plasma HIV concentrations >1000 copies/ml may contribute[39], whilst therapeutic drug monitoring[40] may be effective in decreasing toxicity-related changes in regimen.

Resistance

Nowadays, cART results in long-term suppression of HIV production, mimicked by HIV RNA plasma levels below the quantification level of current assays. However, suppression is incomplete, and low-level HIV production remains[41, 42]. Suboptimal adherence to antiretroviral drugs used in cART may lead to selection of drug-resistant HIV[43, 44]. In turn, the presence of resistant strains of virus limits future therapy options and may lead to a worsened prognosis[45]. The prevalence of resistant virus in patients who fail on therapy may be as high as 80%[46-48].

Resistant strains of virus may also be transmitted to uninfected patients. In recent years, the prevalence of drug-resistant viruses in newly infected patients in Europe and North America has varied between 5% and 25%. After 1998, transmission of resistant virus strains was observed in 6% of newly infected participants of the Dutch Amsterdam Cohort Studies[49].

Our 2007 update shows only 4.8% of the recently infected patients in the Netherlands having drug-resistant HIV. Amongst newly diagnosed patients, 8% resistance was found. These percentages are comparable to those observed in other Western countries, although increasing percentages of resistance have been reported elsewhere[50-54]. When resistance mutations that were found were translated into a predicted susceptibility score, approximately 4% of the patients in both groups were infected with a strain that carried intermediate or high-level resistance to at least one antiretroviral drug. Hence, although a major resistance-associated mutation is present, it is not necessarily a sign of full resistance.

The higher proportion of newly diagnosed patients with resistance-associated mutations than that seen in recently infected patients was found to be due to a higher percentage of patients with an M41L mutation, either as an only mutation in RT or in combination with a T215X mutation. The M41L mutation has been shown to be stable in patients infected with a resistance-carrying virus strain[55]. Most likely, the patients harbouring an M41L mutation were infected in the 1990s, when resistance to zidovudine and stavudine was most abundant.

The stable and low level of transmission of resistant virus strains is somewhat surprising, given the increase in the number of cART-treated patients since 1996. One explanation is that the proportion of patients failing therapy has decreased over time, and, as a consequence, the reservoir of possibly infectious patients – those having RNA levels above 500 copies/ml – is relatively small. On the other hand, it also confirms that most HIV infections are transmitted from HIV-infected individuals who are untreated or are not yet even aware of their infection[56, 57].

The annual proportion of patients who failed on cART declined from 60% in 1997 to 19% in 2006 and 14% in 2007 amongst those who were antiretroviral drug-experienced and increased slowly from 10 to 14% over the same period amongst those who were antiretroviral drug-naïve. Resistance to antiretroviral drugs was found in 88.4% of pre-treated patients and 64% of therapy-naïve patients. As observed previously, the prevalence of resistance to specific antiretroviral drugs has changed over time in correlation with changes in antiretroviral drug use[58].

Almost 11% of the patients who were still being followed by the HIV Monitoring Foundation in 2007harboured virus strains with high-level resistance to at least one antiretroviral drug. This percentage is probably an underestimation since other cohorts with more frequent sampling for resistance have found prevalences of approximately 25%[44, 59]. The estimation of prevalence of resistance amongst failing patients, however, seemed to be very accurate, since similar results were produced by taking into account testing bias.

cART and treatment response in pregnant women

To reduce mother-to-child transmission (MTCT), HIV-infected pregnant women in the Netherlands have been treated with cART since 1998, and that therapy, together with elective caesarean delivery in case of a detectable maternal viral load and treatment of newborns in their first weeks of life, has resulted in a decrease in risk of MTCT to 2%[60]. To further reduce that risk, national HIV pregnancy screening[61] has been in use since 2004, and a larger proportion of women have been diagnosed with HIV early in their pregnancy. As a result, these women have often started cART for the first time during their pregnancy.

CD4 cell count, an important prognostic marker in HIV infection, is affected by pregnancy. Hormones produced during the pregnancy downregulate the immune response to prevent rejection of the fetus[62]. A decline in CD4 cell counts during pregnancy might be associated with the pregnancy itself and not with HIV disease progression or a lower response to treatment, whilst initiation of cART during pregnancy might increase CD4 cell counts.

To study the virologic and immunologic efficacy of cART started before and during pregnancy, data were selected from the population of 570 HIV-infected pregnant women in ATHENA. Only first-time pregnancies between 1 January 1998 and 1 June 2007 occurring after the mother was diagnosed with HIV were included in the analyses. Overall, 85% of the women delivered a baby.

Most women delivered with undetectable HIV RNA plasma levels. Women who initiated cART during their pregnancy had significantly higher HIV RNA plasma levels in the first two trimesters of the pregnancy than women who initiated cART before they became pregnant, but the HIV RNA plasma levels in both groups reached the same level at the time of delivery. No differences were seen between Dutch and non-Dutch women with respect to HIV RNA plasma levels at the beginning of or during the pregnancy.

Dutch women had higher CD4 cell counts during the pregnancy compared to women of non-Dutch origin. The majority of non-Dutch women originated from sub-Saharan Africa, and differences in CD4 cell counts probably reflect ethnic differences in CD4 cell counts between women of Dutch and non-Dutch origin.

CD4 cell counts declined in the first two trimesters of the pregnancy amongst both the women who were already on treatment and those who initiated cART during pregnancy. This decline may be explained by hormonal changes as the immune system alters because of the immune suppressive reproductive hormones[62]. Apparently, this decline does not accelerate HIV. The increasing CD4 cell counts found in the last trimester have been shown to be pregnancy-related, as well[63]. However, in our study, the increase in CD4 cell count between weeks 20 and 28 amongst women who initiated cART during pregnancy is likely be to a response to treatment because most women initiated cART during that period.

In women already on cART before becoming pregnant as well as in women starting cART during pregnancy, a significant decline in plasma HIV RNA levels occurred.

Since current guidelines recommend the start of cART between weeks 20 and 28, the decline in HIV RNA levels was strongest during that period[64]. A sharp decline in HIV RNA levels was also seen amongst women who were already on cART. This probably reflects a change in cART regimen to a more effective or a more preferable combination in pregnancy. In addition, a portion of the women temporarily interrupted cART at the beginning of the pregnancy.

Combinations including nelfinavir or nevirapine were well tolerated during pregnancy[65]. A combination including nelfinavir appeared to be the most frequently used regimen amongst pregnant women in ATHENA.

Despite the strong decline in HIV RNA plasma levels among pregnant women receiving cART, 30% to 36% still had a detectable viral load during delivery. The risk of MTCT is very low among women who are effectively treated with cART[66], but an elective caesarean section is recommended in cases where the maternal viral load is >50 copies/ml. In ATHENA, 60% of the women with a detectable viral load underwent an elective caesarean section.

Increasing importance of non-AIDS-defining causes of death with increasing time on cART

In a significant proportion of HIV-infected patients treated with cART, the cause of death appears to be non-AIDS-related[67, 68]. By comparing antiretroviral therapy-naïve groups of patients according to their CD4 cell count at start of cART, we evaluated differences in morbidity and mortality and, especially, causes of death within the time frame of 10 years following the start of cART.

Between 1 July 1996 and 31 December 2006, 7655 HIV-infected patients started cART. The median HIV RNA concentration in plasma was 5.0 $\log_{10}$ copies/ml. The median CD4 count fluctuated from 250 cells/mm^3 in 1996-1997 to 190 in 1998-2000, 180 in 2001-2003, and 190 in 2004-2006 ($p<0.0001$). In 1997, 37.5% of the patients with a pre-cART CD4 cell count available started cART below the threshold of 200 CD4 cells/mm^3 compared to on average of 52.9% in the period 2000-2006 ($p<0.0001$).

The risk of starting cART below the 200 cells/mm^3 threshold was lower for women than for men and lower for patients starting cART in 2006 than for those starting in 2000. The risk was higher among patients of non-Dutch origin and for patients with heterosexual contacts as route of HIV transmission.

In total, 463 patients died, and the cause of death was related to HIV in 212 (45.8%); it was not related in 190 (41.0%); it was related to therapy in 5 (1.1%) and was unknown in 56 (12.1%). All-cause mortality 10 years after starting cART was 10.6%, being 3.7% for HIV-related causes, 5.5% for non-HIV-related causes, 1.3% for deaths of unknown cause, and 0.1% for antiretroviral (ARV) therapy-related causes. The major cause of death during the first 7 years after starting cART was HIV-related; after that period, non-HIV-related mortality was the major cause.

There was no significant difference in the proportion of specific causes of death before and after 1 January 2004, except for deaths related to cardiovascular complications and suicide, both of which were more frequent in or after 2004. The overall incidence of cancer-related death after starting cART was five times higher than the age- and gender-standardized incidence in the general Dutch population, and the incidence of non-AIDS-defining cancers was two times higher amongst the HIV-infected population.

Within 3 years of commencing cART, 269 patients died, and those starting in 2001 through 2006 had a risk of dying that was 1.7 times higher than the risk for patients starting in 1998 through 2000. Time to death in patients starting in 2001-2006 was not significantly different

from that of those starting in 1996-1997. Injecting drug use as the HIV transmission route was associated with a shorter time to death.

When CD4 counts were below 100 cells/mm^3 before start of cART, hazard ratios for death increased rapidly with lower counts. When the CD4 cell counts were above 100 cells/mm^3, a monotone trend was observed for a lower hazard of death with increasing counts at the start of cART. There was no effect of baseline HIV RNA levels on the hazard of death within 3 years of starting cART. Patients with symptomatic HIV had a hazard two times higher for death than those without AIDS, and those with AIDS had a hazard 4 times higher. Patients with progressive multifocal leucoencephalopathy or non-Hodgkin's lymphoma (including primary brain lymphoma) were at the highest risk of death compared to patients with other AIDS events.

A new AIDS event was registered in 545 within 3 years of starting cART, and estimates for AIDS morbidity were 8.6% (8.0-9.2) within 3 years and 18.9% (17.7-20.1) within 10 years.

The main variables independently associated with a shorter time to a new CDC-C event were: a low CD4 cell count and an HIV RNA plasma level above 100,000 copies/ml at the start of cART, an AIDS diagnosis before cART initiation, and the region of origin.

The probability of death continued to decrease with higher CD4 counts at the start of cART, even for very high CD4 counts, whereas the risk of a new AIDS event was similar across CD4 counts higher than 300 cells/mm^3 at the start. Despite the importance of starting cART when CD4 counts are still above 200 cells/mm^3, more than half of patients started below that threshold. This indicates that there is room for improving mortality and morbidity rates by starting treatment earlier in the course of the infection.

Non-HIV-related and non-AIDS-related causes of death (in particular, death because of cardiovascular complications) became more important with longer time on cART. Since cART has turned HIV into a lifelong chronic infection, causes of death in HIV-infected patients can be expected to resemble more closely those seen in the Dutch population. The increase in the proportion of non-AIDS cancers seen also in other cohorts[69] might reflect this.

Cancer-related mortality was nearly five times higher than that in the general Dutch population. Mortality due to non-AIDS-defining cancer was almost as common as that of AIDS-defining cancer, but not higher, as was reported elsewhere[70]. Death due to non-AIDS-defining cancer in the HIV-infected population was two times higher than in the general Dutch population. This indicates that immunodeficiency may be associated with the risk of fatal non-AIDS-defining malignancies as suggested by some[70-72], but not found by others[73-75].

The trend of a lower risk of death with higher CD4 count at the start of cART is also seen at high CD4 counts. This suggests that starting cART earlier than current guidelines recommend may be beneficial.

Immune response of HIV-1 infected children on cART

The life expectancy of HIV-infected children, as of adults[76], has been dramatically improved since cART became generally available[77]. The virologic and immunologic responses to cART have been extensively studied in adults, but less so in HIV-1-infected children. Children have a better capacity for CD4 cell reconstitution than adults[78], which has been linked to a higher thymus function. With age, the absolute CD4 cell counts decrease and the immune response varies[79, 80]. Together, these complicate evaluation of the immune response amongst HIV-1-infected children on cART. We studied the immunologic and virologic

response of HIV-1-infected children who were followed in one of the four specifically acknowledged paediatric HIV treatment centres in the Netherlands between 1 January 1997 and 1 June 2007.

The median CD4 cell counts at the start of cART were 1058×10^6 cells/l (442-1690) for those children who were 2 years or younger at the time of cART initiation and increased to 1710×10^6 cells/l (1090-2425) at 24 weeks after start of cART. Children who were older than 2 years at cART initiation had lower baseline CD4 cell counts of 350×10^6 cells/l (100-600) that increased to 650×10^6 cells/l (390-920) at 24 weeks after cART initiation. Adolescents had lower CD4 cell counts than the HIV-infected children. At the start, the median CD4 cell count was 206×10^6 cells/l (11-206), and it increased to 372×10^6 cells/l (201-550) after 24 weeks of cART.

Changes in CD4 cell percentages among the HIV-1-infected children who commenced cART showed that older children (more than 2 years of age) had significantly higher CD4 cell percentages than children who were 2 years of age or younger at time of cART initiation. In the first 12 weeks on cART, the CD4 cell percentages increased in both groups, but the increase became significant more rapidly amongst the children who were more than 2 years old at the time of cART initiation. From 12 weeks of cART onwards, the CD4 percentages still increased significantly faster among the older children. During the first year on cART, the CD4 cell percentages remained higher among the children who were more than 2 years of age compared to the children who were two years of age or younger at the time of cART initiation.

Among the children who were 2 years old or younger at time of cART initiation, median HIV RNA levels decreased significantly from 5.8 $\log_{10}$/ml (5.3-6.0) at start to 2.6 $\log_{10}$/ml (2.1-2.6) at 24 weeks of cART. HIV RNA levels were significantly lower at start of cART in the older children and decreased significantly from 4.9 $\log_{10}$/ml (4.3-5.6) to 1.7 $\log_{10}$/ml (1.7-2.6) at 24 weeks of cART. HIV RNA levels in adolescents decreased also significantly from 5.0 $\log_{10}$/ml (4.7-5.3) at start to 1.7 $\log_{10}$/ml (1.7-2.6) at week 24.

Age-related variation in the absolute numbers of CD4 cells have been described earlier in children uninfected with HIV[80]. The absolute CD4 cell counts decreased with increasing age, which explains the significantly higher CD4 cell counts among younger HIV-1 infected children. The CD4 cell percentages are probably a better marker for comparing the immunologic response after cART between children of different ages. Children who were more than 2 years of age at the time of cART initiation had significantly higher CD4 cell percentages, and the proportion of CD4 cells increased faster among the older children. Suppression of the HIV RNA levels is needed for the recovery of the thymic function and thus, for the return of CD4 cells[81]. The children who were more than 2 years of age when starting cART were more likely to achieve an undetectable viral load than the younger children. This poorer virologic response among younger HIV-1-infected children receiving cART has been described earlier[79]. In our study, older children had lower HIV RNA levels at start of cART initiation and also at 24 weeks after the start of cART. Higher CD4 percentage at baseline and during the first year on cART is likely to be a result of the higher virologic suppression in the group of older children.

The results of this study indicate that the immunologic and virological response among HIV-1-infected children on cART is age-dependent. Although younger children have higher CD4 cell counts, the immune response is stronger in older children, as reflected by the higher CD4 percentages.

Immunologic response to treatment of hepatitis C co-infection

Co-infection with hepatitis C (HCV) is common among HIV-infected individuals, with a prevalence ranging between 6% to as high as 82%, especially when a history

of injecting drug use is reported[82, 83]. Progression of HCV-associated liver disease is known to be accelerated in HIV-infected individuals, and following the significant and long-lasting decline of the HIV-related morbidity rate and death in patients on cART, an increase in liver-related deaths became apparent[84, 85]. Consequently, effective treatment of HCV in HIV co-infected patients has become more important. A combination of interferon (IFN) and ribavirine (RBV)[86] has been used for HCV treatment since 1998[87], but recently IFN was replaced by pegylated interferon ([peg]-IFN)[88]. The combination of IFN and (peg)-IFN has been shown to be more effective than IFN plus RBV for chronic HCV infection in HIV-co-infected individuals, mainly in patients infected with HCV genotypes 1 and 4[89].

Declines in CD4 cell count have been observed during HCV treatment[89]. Although, short-term complications such as opportunistic infections have not been reported[89], it is unknown whether these CD4 cell declines have a negative effect on the long-term effect of HIV treatment[90]. To study this decline, we examined CD4 cell count and HIV RNA trajectories during HCV treatment among HIV/HCV co-infected patients. All-cause mortality was compared between HIV/HCV co-infected patients with and without HCV treatment and individuals infected only with HIV.

A 9% HCV prevalence was found amongst the total population tested, and HCV RNA was present in 564 of the 1013 patients who tested positive for HCV antibody. In the remaining 449 patients, HCV RNA was not determined, or test results were not yet reported. HCV co-infection was most prevalent (82%) amongst injecting drug users.

Eight percent (83 out of 1013) of the patients who tested positive for HCV antibody were treated with IFN or (peg)-IFN; 69 of them were already on cART for HIV before receiving (peg)-IFN; 9 started cART after finishing (peg)-IFN, and 5 were not treated for their HIV infection. Plasma HCV RNA levels were determined in 68 of the 83 patients, and in 35 (51%) levels became undetectable following a median of 37 weeks of (peg)-IFN treatment. The median duration of anti-HCV treatment amongst the remaining 33 patients was 22 weeks.

The median CD4 cell count declined from 400×10^6 cells/l (IQR: 270-610) at time of (peg)-IFN initiation to 240×10^6 cells/l (140-460) after 24 weeks of treatment with (peg)-IFN. The decline was biphasic, with a strong and significant decline in the first 12 weeks and a lesser, but still significant, one in the following 12 weeks. After week 24, when most of the patients had discontinued their (peg)-IFN treatment, CD4 cell counts increased, although not significantly. CD4 percentages were 25 at the start of (peg)IFN and 27% between weeks 20 and 28.

Median HIV RNA levels showed a non-significant increase from 1.4 $\log_{10}$ copies/ml (1.4-2.9) at (peg)-IFN initiation to 1.7 $\log_{10}$ copies/ml (1.4-3.9) after 24 weeks.

Twenty-eight percent of the single HIV-infected patients, 37% of the HIV/HCV-co-infected patients treated with (peg)-IFN, and 38% of the untreated HIV/HCV-co-infected patients progressed to AIDS. HCV-co-infected patients were treated more often with cART, and the time from cART initiation to AIDS was not associated with HCV co-infection. The adjusted risk of progression to AIDS was non-significantly lower in both HIV/HCV-co-infected patients receiving (peg)-IFN and patients infected only with HIV as compared to HIV/HCV-co-infected patients without anti-HCV treatment.

HCV-co-infected patients died significantly more quickly than the non-co-infected patients. Time to death did not significantly differ between HCV co-infected patients receiving (peg)-IFN and those who were not. Five years after cART initiation, all-cause mortality was 10% (95%

CI 8-12) amongst those patients with a HIV/HCV-co-infection without (peg)-IFN treatment, and 5% (3-14) amongst the HIV/HCV co-infected patients receiving (PEG)-IFN. Of the single HIV-infected patients, 4% (3-4) died after 5 years of cART.

Since only a small proportion of the HIV/HCV-co-infected patients was treated for HCV[91] and the CD4 cell decrease during (peg)-IFN treatment seemed to have no effect on HIV-related mortality, there should be improved accessibility of anti-HCV treatment to reduce the higher HCV-related morbidity and mortality in HIV/HCV-co-infected patients.

Death and AIDS

HIV is gradually acquiring the characteristics of a chronic, rather than a lethal, disease. The HIV-related mortality and incidence rates of AIDS in Europe and North America have declined substantially in cART-treated patients compared to those in untreated patients[67, 92-95]. As a result, the prognosis for HIV-infected patients has improved, and for successfully treated patients, it has been shown that mortality rates approach those of uninfected patients[25, 96-99].

Using a prognostic model for predicting survival probabilities of HIV-infected patients after diagnosis with HIV instead of only after the start of cART[16, 96], we performed an updated analysis of annual mortality rates and the incidence of AIDS in both the total HIV-infected and cART-treated populations in the Netherlands since 1996.

The overall mortality rate in the HIV-infected population in the Netherlands has slightly declined since 1996 to a level just above 1 death per 100 person-years of follow-up, which was lower than reported in a recent Danish study[98]. In contrast, mortality rates in the cART-treated population have declined over time to a level similar to those in the total infected population. However, this decline was observed only in the pre-treated population; since the pre-treated population accounts for only 18% of the total HIV-infected population, this explains why the effect of cART in the total population was minimal. Presently, the mortality rate amongst pre-treated patients is still two times higher than that amongst therapy-naïve patients, although the incidence of AIDS events is the same in both populations.

Last year we reported a mortality rate of 0.84 (95% CI 0.54–1.24) for 2006, which was substantially lower than that observed for 2005[16]. In the current analysis, the rate for 2006 increased to 0.97 (95% 0.79-1.19), still lower than the currently reported value for 2005, 1.40 (1.18-1.66), but less sharp. The mortality rate currently reported for 2007 is higher than for 2006, but the data collection for 2007 (and, for some treatment centres, also for 2006) has not yet been completed.

Patients diagnosed with CD4 cell counts below 200 × 10^6 cells/l had a better prognosis when diagnosed in or before 2000 than thereafter. Most likely, this result is due to a bias in the inclusion of patients. Before 2001, the ATHENA study registered only patients on cART. Since 2001, the HIV Monitoring Foundation (HFM) registered essentially all patients with HIV who were alive at the time of registration.

In the population of patients diagnosed after 2000, calendar year had no effect on progression to death when adjusted for all the other covariates. This indicates that even if the prognosis of patients diagnosed after 2000 has been less favourable than it was for those diagnosed before 2000, at least, it is not becoming worse over time.

A resurgent HIV-1 epidemic amongst MSM in the Netherlands

In the beginning of the 1980's, the first AIDS cases in the Netherlands were found amongst men having sex with men[100]. From 1996 onwards, combination antiretroviral

therapy (cART) has become widely available. Because cART dramatically reduces plasma and seminal viral load and since infectivity is correlated with viral load, the widespread use of cART might thus be expected to have reduced the incidence of HIV infection[67, 101-107]. Paradoxically, the annual number of diagnoses amongst MSM is increasing not only in the Netherlands but also in other Western countries[16, 108]. Also, increases in risk behaviour and in diagnoses of syphilis and gonorrhoea have been reported[17, 109, 110].

Mathematical models have shown that an increase in risk behaviour can counterbalance the beneficial effect of cART[111-118]. We evaluated the separate impact of risk behaviour, HIV testing behaviour, and cART on the HIV epidemic in MSM in the Netherlands by means of a mathematical model fitted to data from the ATHENA cohort and from the Amsterdam Cohort Studies.

The number of new infections amongst MSM per year in the Netherlands peaked in 1983, with 802 new infections, and that number was approximately 250 in the 15 years thereafter. Subsequently, the number of new infections increased from 224 in 1999 to 554 in 2004.

Between 1980 and 1983, the estimate for the reproduction number $R(t)$ was 2.39 (95% CI, 2.17-2.76), indicating an expanding epidemic. Between 1984 and 1995, the net transmission rate declined by a factor of 2.33 (2.03-2.83) relative to the period before, thereby indicating large reductions in risk behaviour. As a result, the reproduction number $R(t)$ was reduced to 0.89 (0.85-0.93), which is below one, and thus, just below the epidemic threshold.

After 1995, when cART was introduced, the reproduction number declined further to 0.76 (95% CI, 0.70-0.86). The reduction could have been larger if the transmission rate had not increased by 18% (3-34). During the period 2000 to 2004, the net transmission rate was estimated to have increased even more, returning to a level only 29% (22-72) below the value in the initial period of 1980 to 1983. A reduction in the estimated mean time from infection to diagnosis, which was 3.71 (3.49-3.97) years between 1984 and 1995 and 2.90 (2.84-3.03) years in the period after 2000, resulted in a much lower reproduction number than that in the initial period. Still, for the last period, $R(t)$ was estimated to be 1.04 (0.98-1.09), near or above the critical epidemic threshold, thus indicating that HIV once again has been spreading epidemically amongst MSM in the Netherlands.

The model predictions were verified for consistency with data in the ATHENA database on the number of currently living MSM. From the model, it was estimated that 24% of all living HIV-positive MSM were unaware of their HIV-positive status at the start of 2005. These individuals accounted for 90% of the new infections. According to the model, by 2015 the number of known HIV-infected MSM will be 10,997.

A number of hypothetical scenarios from 1995 onwards were explored. Without cART to limit infectiousness in treated patients, the epidemic under current conditions would have been much larger, with an estimated 7609 infections arising between 1995 and 2004, instead of the estimated 3665 in the main model. If, on the other hand, cART had been introduced, but without any increases in the net transmission rate, the number of new infections during this period would have been only 1647. If cART had been introduced and if there had been the same increase in the net transmission rate, but with no increase in the rate of diagnosis, the cumulative number of new infections would have been 4132. Finally, if no changes had occurred since 1995, that is, no cART and no increase in risk and testing behaviour, this number would have been 2984. Thus, it can be concluded that cART has played an important role in limiting transmission, but any gains made have been more than offset by an increase in the net transmission rate. Had these increases not

occurred in the cART era, the reproduction number $R(t)$ would have declined to 0.6, and the epidemic would have been in a convincing decline.

According to the model, cART has slowed the HIV epidemic, although the number of prevented HIV infections could have been greater if the net transmission rate had not increased after 1995. The model suggests that the only way to substantially reverse the epidemic spread and reduce the $R(t)$ well below 1 is to reduce the net transmission rate from current levels. Hence, prevention focussing on reducing risk behaviour remains as crucial as it was previously in reducing the epidemic. However, a timely diagnosis also adds to the retraction of the epidemic, and more frequent testing may indirectly induce changes in risk behaviour. Therefore, in the Netherlands, testing should (again) focus on those groups who display high risk behaviour.

The HIV-infected population in the coming 10 years

As a result of the decreasing mortality and morbidity rates amongst HIV-infected patients due to the widespread treatment with combination antiretroviral therapy (cART), the HIV-infected population in the Western world is ageing[16, 119, 120].

Using a mathematical model, we estimated the size and ageing of the known HIV-infected population in the Netherlands in the coming years. Subsequently, the size and age distribution of the population in follow-up in 2015 was predicted on the assumption that from 2006 onwards, trends observed in the data between 2000 and 2005 would continue. In addition, four hypothetical scenarios were explored: (A) no new HIV-infected patients would originate from sub-Saharan Africa after 2006; (B) after 2006, the number of diagnoses amongst MSM would remain at the 2006 level; (C) a 10% or 20% increase would be expected in the number of diagnoses amongst patients of non-Dutch origin after 2006; and (D) the year of diagnosis that was fitted to the age distribution of MSM would be included in the model.

The total HIV-infected population in follow-up at 1 January 2000 consisted of 5666 individuals, of whom 3306 (58.3%) were MSM, 1407 (24.8%) were heterosexuals, and 953 (16.8%) were infected via other transmission routes. In total, 672 (11.9%) patients were younger than 30 years, 1002 (17.7%) were 50 years of age or older, and 4660 (82.2%) were between 15 and 50 years of age.

When a linear model was fit to the data, the annual number of diagnoses amongst homosexual men increased from 348 in 2000 to 558 in 2005. During the same period, the number of diagnoses amongst heterosexual men increased from 148 to 182 and increased in heterosexual women from 221 to 255. No significant changes over time were observed in the number of diagnoses amongst patients infected via other or unknown transmission routes. The annual number of diagnoses was 79 amongst men and 15 amongst women.

Between 2000 and 2005, the proportion of newly diagnosed sub-Saharan Africans in the heterosexual population decreased from 52% to 42%, whereas the proportion of Dutch patients increased from 21% to 31%.

According to our model, the HIV-infected population in follow-up in 2015 is expected to be 3.3 times larger than the population in 2000, or 2.0 times larger than the population in 2005. The number of patients more than 50 years of age is predicted to increase by a factor of 6.3, whereas the number of patients less than 30 years of age is expected to increase by a factor of 1.5.

The treatment of the disease will be complicated by the increasing age of the HIV-infected population. In older patients, the restoration of CD4 cells is generally less favourable than in younger patients[2-4]. Moreover,

the appearance of age-related diseases and other non-HIV-related illnesses could complicate the treatment of HIV. In addition, few studies have examined the tolerability and safety of antiretroviral drugs in older HIV-infected patients[5]. In older patients, renal and hepatic functions decrease, which could lead to a reduced tolerability compared to that in younger patients. Another complication could be drug-drug interactions between antiretroviral drugs and medication used for treatment of age-related morbidities.

Our model estimates only the number of patients in follow-up in any of the HIV treatment centres in the Netherlands who are, by definition, patients who know they are HIV-infected. Recently, we estimated that the HIV-infected population aged between 15 and 50 years of age in the Netherlands – including those unaware of their infection – amounted to 18,500 individuals[1]. In our analysis, we found that 6944 patients in the data and 6992 in the model were in the same age category. This implies that more than 60% of the HIV-infected patients are not yet in follow-up, and thus probably not yet aware of their HIV infection.

We explored a few hypothetical scenarios using the model. These scenarios were based on the assumption that all other factors remained constant. More than 1000 new cases would be avoided if either infections amongst sub-Saharan Africans would be halted or the number of diagnoses amongst homosexual men would remain at the level of those in 2006. The first of these two scenarios, however, would be hard to realise, since most patients of sub-Saharan African origin are infected in that region[16]. Reducing the number of diagnoses would then be possible only if immigration from sub-Saharan Africa declined. The second scenario might be possible if risk behaviour amongst MSM decreases. An increase in the annual number of diagnoses amongst individuals of non-Dutch origin for all transmission groups would mainly affect the heterosexual population.

The last, less hypothetical scenario took into account the increasing age at diagnosis amongst MSM as a result of the increasing age of the source population, which was on average more than 40 years. The largest gain in reducing the number of new diagnoses amongst MSM might therefore be obtained by a reduction in risk behaviour amongst middle-aged MSM.

Quality of HIV care in the Netherlands and the impact of late presentation at the clinic

HIV and AIDS care and antiretroviral treatment is provided by 23 health care institutes throughout the Netherlands. Each institute is acknowledged by the Dutch Minister of Health, Welfare and Sport as an HIV treatment centre, and each is obliged to provide the HMF with data on the diagnostics, follow-up, and treatment of all HIV-infected patients in care, including those in out-patient care. HMF reports to the Ministry of Health not only on the HIV epidemic and the results of anti-HIV treatment, but also on the quality of HIV and AIDS care provided.

When taking survival as a crucial indicator for quality of care, late presentation may play as important a role as patient profile differences per HIV treatment centre. Those who present at the hospital when already in a late stage of HIV-infection may make a substantial demand on clinical resources, and some will have a poor treatment outcome[121, 122]. Earlier studies in the United Kingdom have shown that, in particular, black African patients tended to present for care in a late stage of infection, as indicated by low CD4 cell counts[122-124]. Presenting for care with low CD4 cell counts might also depend on demographic characteristics of a specific patient population.

We compared the survival rates after the start of cART between the different HIV treatment centres, taking into account the differences in the patient population as well as the impact of late presentation for care.

Between 1 January 1997 and 1 June 2007, 8616 patients were diagnosed with HIV and presented for care in one of the HIV treatment centres in the Netherlands for the first time. The majority of patients were male, and half of the patients originated from the Netherlands. However, differences in the demographic characteristics of the patient population between hospitals occur. The percentage of patients originating from the Caribbean and Latin America ranges from 1 to 30%, and the percentage of patients originating from sub-Saharan Africa varies from 1 to 40%.

The median CD4 cell count at first presentation for care was 308 $\times$ 10^6 cells/l (IQR 120-510). Patients originating from the Netherlands and other Western countries have significantly higher CD4 cell counts than those originating from the Caribbean/Latin America, sub-Saharan Africa, and the regions designated as "other". CD4 cell count at first presentation differed significantly between HTCs; in 6 centres it exceeded the overall median, whilst in 11 HTCs the patient population arrived with lower CD4 cell counts. The median CD4 cell count at cART initiation was 180 $\times$ 10^6 cells/l (70-290). CD4 cell count at first presentation and at cART initiation are highly correlated. For HTCs where the majority of patients presented early, the median CD4 cell counts at cART initiation generally exceeded the overall median.

Of all patients presenting for care at one of the HTCs in the Netherlands, 35% were late presenters, with a CD4 cell count below 200 $\times$ 10^6 cells/l. Late presentation was independently associated with older age; unknown transmission risk; sub-Saharan African, Caribbean, or Latin American origin; and symptoms of HIV disease at first visit. Overall, HIV-infected patients in the Netherlands tended to first present at the HTC with almost the same CD4 cell counts as those of men and women in West Africa[125], which is surprising, given the greater opportunities for testing and treatment available in the Netherlands.

An HIV diagnosis between 2003 and 2007 was associated with a lower risk of late presentation. However, although the proportion of late presentation has become smaller in more recent years, 26% of the patients who were recently diagnosed with HIV still had CD4 cell counts below 200 $\times$ 10^6 cells/l at diagnosis.

Current treatment guidelines recommend initiating cART when a CD4 cell count value is between 200 and 350 $\times$ 10^6 cells/l[126]. Although 65% of the patients presented for care early enough, the median CD4 cells at cART initiation in the total population was below the number recommended. Nine percent of the patients who presented for care with at least 200 $\times$ 10^6 CD4 cells/l initiated cART when CD4 cell counts were below 200 $\times$ 10^6 cells/l. Therefore, we conclude that the late initiation of cART found in our study cannot be explained fully by late presentation.

Patients who presented with CD4 cell counts below 200 died significantly more rapidly than did those who presented with at least 200 $\times$ 10^6 cells/l. In total, 403 of the patients diagnosed with HIV from 1 January 1997 onwards died; amongst them, 288 died within 5 years after cART initiation. Male gender, older age, HIV infection through heterosexual contact, injecting drug use, unknown or other HIV transmission risk, and calendar year of HIV diagnosis were independently associated with the risk of dying within 5 years after the start of cART.

For all except two HTCs, the risk of death within the first 3 years on cART did not significantly differ from the national average. Two HTCs showed a higher risk, even after adjusting for gender, age, HIV transmission category, and clinical differences in the patient population. Both HTCs showed a significantly lower CD4 cell count in patients at presentation for care. After adjusting for CD4 cell count at presentation, the risk of dying remained significantly higher.

Recommendations

Three recommendations are made.
From our work, as well as that of others, of modelling the epidemic since the start of large-scale chemotherapeutic intervention, it appears that data needs to be available on the time between HIV infection (or transmission) and diagnosis and the time between diagnosis and entry into care to gain better insight into the factors that crucially impact the transmission rate of HIV. Knowledge of these factors will enable the development of a dedicated and focussed HIV prevention policy needed to contain the epidemic. The involvement of social and behavioural science is evidently needed. The National Institute for Public Heath and the Environment (RIVM), together with the HMF, the HIV Treatment Centres, and the Regional Public Health Centres, is currently in the process of setting up a research project to investigate variation in time between diagnosis and entry into care.

There is still room for improvement of morbidity and mortality rates amongst HIV-infected persons by an earlier start of cART than that which is currently accepted. Also, more extensive knowledge about late presentation is needed, and reasons for delaying entry into care should be studied. However, strategies need to be developed to improve the quality of care, such that patients entering care on time (i.e., with a sufficient immune status) start cART on time (i.e., at or before the CD4 cell threshold has been reached). The HIV/AIDS treating physicians play a crucial role in this respect.

Additionally, the HIV-infected population is clearly growing and ageing, and with the source population getting older, patterns of HIV transmission and demographics of risk groups for infection will change. The shift in age at diagnosis towards 40 years in MSM is an example of these changes. Moreover, the treatment of HIV may become more complicated with age, and the HIV treatment may become less successful. Special attention should be paid to studies of age-related complications of HIV, the influence of HIV on the appearance of age-related diseases, and the interaction of antiretroviral drugs and drugs used for age-related and other diseases. Finally, studies are recommended to investigate the impact of the growing and ageing population on the costs of HIV care.

Chapters 3-15

Data q

quality

Customized procedures for the improvement of data quality

Shula Grivell, Sima Zaheri

Introduction

Our collection of monitoring data obtained from HIV-infected patients started in 1996 within the framework of the AIDS Therapy Evaluation in the Netherlands (ATHENA) project[7]. Maintenance and improvement of the quality of this longitudinal clinical data set is of primary interest in view of its observational nature. Controlling the quality of data obtained from patients is crucial for all clinical research, irrespective of the setting in which the collection takes place,[8-12] and usually, source data verification is the tool of choice. However, given the large number of patients followed in our ATHENA cohort for a long period (i.e., over years), a 100% source data verification is not feasible, and the comparison of a random selection of 10% of data has been reported as insufficient for improvement of data quality[13, 14]. Therefore, customized procedures for continuous monitoring of the accuracy of the ATHENA cohort data and, subsequently, for resolution of discrepancies were implemented[7].

Data collection

Data for all HIV-infected patients who are registered and followed longitudinally in 1 of the 23 health care institutes encompassing 29 hospitals acknowledged by the Dutch Ministry of Health, Welfare, and Sport as HIV treatment centres are collected by the HIV Monitoring Foundation (HMF) (see Appendix 3.1). The HMF maintains the ATHENA cohort data set and processes data for subsequent analysis. Data are obtained directly from the patients' medical files and in part from case report forms. HMF data collectors, supervised by the HIV/AIDS treating physicians, enter the data online into the national ATHENA database after each patient's visit. This database is developed in Oracle Clinical® (OC), a system that is specifically designed for the data management of clinical trials and that complies with guidelines of the International Conference on Harmonisation-Good Clinical Practices and the U.S. Food and Drug Administration.

Data quality

The quality of data was verified and assessed by customized procedures[13]. In short, we selected data for quality control that had a marked influence on the data analyses. Since HIV diagnosis and disease progression to AIDS are considered important factors for data quality, the date of the first positive HIV test and specific HIV-related events, in accordance with the Centers for Disease Control and Prevention (CDC) classification[15], were chosen. Table 3.1. summarizes 3 data selection procedures for quality control by Source Data Verification (SDV).

Results

1. HIV infection without a registered date of first positive test

In total, we found 69 cases with a registered "unknown" date for the first positive HIV test. So, the date of HIV diagnosis was unknown in only a small portion of the total registered population (12,098 as of Dec 31st 2005). However, data obtained from patients with an unknown date of HIV diagnosis is unsuitable for analysis. Therefore, we questioned whether the dates of HIV diagnoses were truly unknown and hypothesized that source data had been added to the patient files after the initial data collection or that data in the patient files were misinterpreted.

Results of SDV of all 69 cases are summarized in Table 3.2. and show that a date for the first positive HIV test was registered in the patient file in 47 (68%) cases. In 20 (29%) cases, no date of diagnosis was found. Table 3.3. shows the reasons for the lack of a date of the first positive HIV test. The main reason appears to be missed or misinterpreted dates that were available in the patient file. In 11%, the HIV diagnosis date was truly unknown at the time of the data collection, since additional information, including the diagnosis date, subsequently became available from another HIV treatment centre. In the 20 cases that did not yield a more accurate test date, no test date was mentioned in the patient file. In addition to adding information to the patient file

after the collection of data, another problem was misinterpreting or overlooking data in the patient file. In half of the cases, the only date available was the year of HIV diagnosis.

In summary, in about 70% of the patients registered in the national HIV monitoring database as HIV-positive but without a date of diagnosis, the date could be found through SDV. A recommendation for improving the quality of the initial data at an earlier stage would be implementation of a data-check in the database, reminding data collectors to check any (newly) available source documents that might improve the accuracy of the date of the first positive test. Besides this step, interpretation of available data could be improved by fine-tuning existing data-entry protocols. In addition, certain support measures might prove useful, such as extending the frequently asked questions (FAQ) page and involving help desk support from data monitors at the Quality Control unit of the HMF.

Finally, to improve data, in cases with an inaccurate date, such as those with only an accurate year of diagnosis, we will apply the same approach as we suggest for cases with a missing date of HIV diagnosis.

2. Quality of CDC events registered when CD4 values are low

The onset of AIDS is often used as an end-point in HIV/AIDS studies. Therefore, the quality of data of clinical symptoms that are registered as related to HIV (i.e., CDC-B and CDC-C events) is highly important. Missing events can impact the results of data analysis. To assess the feasibility of source data verification of all CDC-B and CDC-C events, we studied the data collected from patients with initially low CD4 cell counts, assuming that they would have potentially more complex medical files with a higher incidence of events than patients diagnosed with HIV with higher CD4 levels (Table 3.1.). We selected data from patients with 2 consecutive initial CD4 measurements of <50 cells/mm^3. The selection yielded 840 patients, and 94 were randomly chosen for SDV. Of these patients, 87 were eventually verified; the patient files were not available for 5, and monitoring of the data entered was not completed for 2.

Data obtained from 87 patients showed 247 CDC-B/C events. SDV revealed 54 missed events, and 11 that were incorrectly recorded. Thus, 65 corrections were made that resulted in a total of 290 CDC-B/C events being noted after SDV. Because 47 of the missed or incorrectly recorded events were found in the first year of follow-up after entry in the database, substantial improvement of the quality of the data for CDC-B/C events can be achieved by SDV restricted to the first year of follow-up.

When CDC-B events (n=138) and CDC-C events (n=152) are considered, -B events are missed relatively more often than -C events (25% vs. 12%). This may be due to less explicit definitions of CDC-B events, in contrast to those of -C events, where criteria are more circumscriptive. Missing results of diagnostic procedures (such as histology or microbiology) appear to be important reasons for the underestimation of both CDC-B and -C events.

In conclusion, SDV restricted to CDC-B/C data obtained during the first year of data collection is sufficient for finding 72% of corrections. However, to implement long-term strategies for improving the quality of CDC-B/C data, reasons for missing data need to be further analysed.

3. Diagnostic certainty of CDC-B or -C events

We distinguish 3 levels of diagnostic certainty: possible, presumptive, and definitive. The more evidence, the higher the diagnostic certainty. The most uncertain diagnosis, where either little or no evidence or only a working hypothesis existed, is described as possible. A presumptive diagnosis usually has some circumstantial evidence, such as radiography (for *Pneumocystis carinii* pneumonia [PCP]) or a positive Ziehl–Nielsen stain (for mycobacterial infection). To reach the level of a definitive diagnosis, results of diagnostics such as histology (for Kaposi's sarcoma) or microbial culture (for tuberculosis) is needed.

We investigated whether SDV might yield a higher level

of diagnostic certainty. Since diagnostic procedures take time, source data that could change the level of the certainty of the diagnosis might be added to the patient file during the interval between the procedure and the reporting of the diagnosis in the patient file; that data could be easily missed at the time of the data collection. In addition, we wanted to determine whether diagnostic test results are understood well enough in combination with our protocol to ensure that the correct certainty level is recorded in the database.

From a total of 5682 CDC-B/C events recorded, 479 had a diagnostic certainty level of "possible," and we selected the following events: Kaposi's sarcoma, HIV-related neuropathy, oral hairy leukoplakia, thrombocytopenia, toxoplasmosis, and tuberculosis (pulmonary and extra-pulmonary) (Table 3.1).

Of the 208 cases, 119 (57%) were correctly recorded with a level of "possible" (Figure 3.1.). In 80 cases, the diagnostic certainty level was incorrectly recorded; after SDV, 51 (25%) cases were changed to a higher certainty level, and in 29 (14%) the event was deleted from the database. Missing descriptions of clinical signs and symptoms and missing results of diagnostic procedures (such as pathology, specific laboratory diagnostics) were the main reasons why certainty levels did not improve.

All together, 25% of the CDC-B/C events recorded as "possible" were corrected after SDV and moved to another certainty level, and 14% were deleted from the database. Data quality of CDC-B/C events could be improved by verifying the events with a diagnostic certainty level of "possible".

Conclusion

With source data verification, we have developed new procedures for improving the quality of data essential in primary data analyses. When data is collected directly in an observational setting, clinical, diagnostic, and organisational procedures will affect its accessibility. When data is collected directly after a patient's visit to the hospital, source data may be added to the patient's file later on, and, therefore, it will be missed at collection. The first year of data collection appears to be the most complex to record, especially when patients are seen in an advanced stage of HIV infection with a substantial, complicated medical history reflected in their medical file. Results from specialized diagnostics, such as pathology, radiology, and immunology, are not always directly and clearly related to the certainty level of the CDC-B/C diagnosis.

SDV has been shown effective in improving data quality, but it is laborious. To efficiently use SDV might be to restrict it to the first year of data collection, in combination with SDV of all end-points essential for analysis of key data. Besides SDV, incorporating data-checks into the database reminding data collectors to check for missing or inconsistent data in the database might also help in improving data quality. Finally, data collectors should be trained regularly in the use and understanding of diagnostic results.

Title	Sample selection date	Selection Procedure	Data to be verified
HIV infection without a registered date of first positive test	1-mar-06	Identify all cases with date of first positive HIV test recorded as (day-month-year): (nk-nk-nk) (nk=not known)	Initial data from HIV diagnosis
Quality of CDC events registered when CD4 values are low	16-feb-06	Identify all cases with 2 initial consecutive CD4 measurements with values <50 cells/mm^3	All CDC data retrospectively
Diagnosis certainty of CDC-B or CDC-C events	22-feb-06	Identify all uncertain cases of: Kaposi's sarcoma, HIV-related neuropathy, oral hairy leukoplakia, *P. carinii* pneumonia (PCP), thrombocytopenia, toxoplasmosis and tuberculosis (pulmonary/extra pulmonary)	CDC event with uncertain classification

Table 3.1. Summary of 3 data selection procedures for quality control by 'Source Data Verification' (SDV).

Results of source data verification	Number	Percentage of total (%)
Changed to more accurate date	47	68
Data unchanged	20	29
Data still to be monitored	2	3
Total no. of Patients in Query	**69**	**100**

Table 3.2. Results after source data verification of cases in selection: HIV infection without a registered date of first positive test.

Source	Number	Percentage of total (%)
Letter, diagnostic test or written part of the file	23	48
Interpretation of existing information	13	28
Information from other HIV treatment centre	5	11
Unknown	6	13
Total cases changed after review	**47**	**100**

Table 3.3. Reason for missing dates of first positive HIV test.

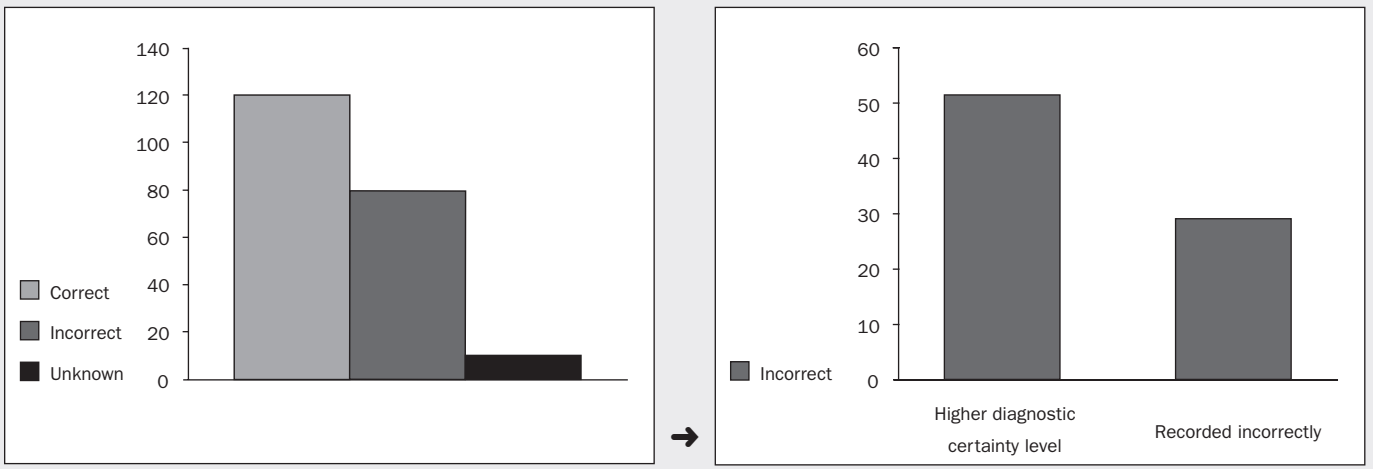


Figure 3.1. Results of selection: Diagnostic certainty of CDC-B or CDC-C events. 80 incorrect cases were either changed to a higher diagnostic certainty level or deleted, if recorded incorrectly.

Appendix 3.1: Data

Items collected upon initial enrolment for HIV-infected adults		
Demographic data	Date of birth, gender, first and second nationality, country of birth, height	
History of HIV infection	Date of the last negative HIV-1 and HIV-2 test	
	Date of the first positive HIV-1 and HIV-2 test	
	Was the patient diagnosed with a primary HIV infection? (yes, no, most likely)	
HIV transmission	The most likely transmission route: homosexual heterosexual injecting drug use (IDU) blood and blood products during pregnancy/partum via breastfeeding other and unknown	For sexual transmission, the most likely transmission route is entered: either a steady sexual partner or multiple sexual contacts
	Country where the patient became infected	
Additional data for HIV-infected children		
Demographic data	Nationality and country of birth of patient's parents	
Family data	HIV status of patient's mother, father, brothers and sisters	
Perinatal data	Pregnancy duration, way of birth, weight at birth, Apgar scores, congenital defects, perinatal exposure to antiretroviral (ARV) therapy and co-medication, antenatal complications	
Additional data for HIV-infected pregnant women		
Demographic data	Nationality and country of birth of patient's parents Patient's ethnicity (*'Asian', 'Caucasian', 'Black', 'other', or 'unknown'*)	
Screening	Was the patient found to be HIV-positive at the national pregnancy screening?	
Visits to the Gynecologist	Visit date, Blood pressure	
Obstetric data	Has there been a delivery/abortion? Date of delivery/abortion Sex of the baby Duration of pregnancy Child number Prophylactic antibiotics? Intra-uterine infection Duration of dilation Duration of expulsion	Duration of ruptured membranes Mode of delivery Caesarean section? Fetal scalp electrode Episiotomy or rupture Birth weight of the baby Apgar scores after 1 minute/5 minutes Duration of stay in the incubator Perinatal mortality Breast-feeding?
Complications during pregnancy	Complications during and/or after birth? Blood loss during the first half of pregnancy? Blood loss during second half of pregnancy? Intercurrent infection? Version (attempt) with breech presentation?	Intra-uterine retardation of growth (sonography<p5%)? PPROM (preterm premature rupture of outer membranes) at how many weeks? Abdominal trauma at how many weeks?

Items collected at every follow-up visit for HIV-infected adults		
Clinical examination	Weight, blood pressure	
CDC events *Start and stop date and the status of event at current visit (ongoing: yes or no).*	HIV-related events as classified by CDC. Definition of diagnosis (possible, presumptive or definitive) are recorded by standard protocol	
Adverse events *Start and stop date and the status of event at current visit (ongoing: yes or no).*	Every event that results in a change of antiretroviral treatment is collected. In addition, the following events are always recorded:	
	Peripheral neuropathy	Alcohol or drug abuse
	Myopathy	Non-CDC malignancies
	Lactate acidosis	Diabetes mellitus
	Hepatic cirrhosis	Myocardial infarction
	Osteopenia / Osteoporosis	Hypertension
	Hepatic steatosis	Arrhythmia
	Hepatic encephalopathy	Heart failure
	Pancreatitis	Cardiomyopathy
	Nephrolithiasis	Stroke
	Renal insufficiency and failure	Coronary artery by-pass grafting
	Lipodystrophy, fat loss in extremities	Coronary angioplasty / stenting
	Lipodystrophy, central fat accumulation	Carotid endarterectomy
	Rash	Pregnancy
	Sexual dysfunction (loss of libido, erectile dysfunction)	Hospital admission
Antiretroviral therapy *Start and stop date, dosage and units, route of admission, reason for stop and the status of medication at current visit (ongoing: yes or no)*	Standard stop reasons are as follows:	
	Virological failure	Newly available medication
	Immunological failure	As a precaution
	Patient's decision	Pregnancy wish
	Toxicity	Pregnancy
	New CDC-B and or CDC-C events	End of pregnancy
	Interaction with co-medication	Compliance problems
	Simplification of the regimen	Other
	Related to blood concentration of ARV	Unknown

Structured treatment interruption		
Co-medication	CDC events, prophylaxis	Anabolic steroids and appetite stimulants
Start and stop date and the medication	CDC events, treatment	Hepatitis B treatment
status at current visit (ongoing: yes or no)	Anti-epileptic agents	Hepatitis C treatment
	Anti-coagulant agents	Medication that interacts with antiretroviral therapy
	Platelet aggregation inhibitors	Miscellaneous: megestrol acetate, dranabinol and methadone
	Anti-hypertensive agents	
	Anti-arrhythmic agents	
	Lipid lowering agents	
	Anti-diabetic agents	
	Insulin and its derivatives	
Lab results	*HIV virology: RNA*	
	Value (copies/ml), laboratory, sample date, VL assay type, sample material, cut-off and undetectable: yes or no	
	Immunology: T-cell count	
	Value, units, laboratory and sample date for the following determinates: CD4 count, CD8 count,	
	CD4 percentage, CD8 percentage, CD4/CD8 ratio	
	Chemistry	
	Value, units, laboratory and sample date for the following determinates:	
	Glucose >N*	
	Amylase >250 mmol/l	
	ALAT/SGPT>3 x N*	
	ASAT/SGOT>3 x N*	
	Alkaline phosphatase >3 x N*	
	Gamma GT >3 x N*	
	Lactate>N*	
	Creatinin always collected	
	Triglycerides always collected	
	Cholesterol always collected	
	Cholesterol HDL always collected	
	* N is normal value; can vary for different laboratories.	
	Haematology	
	Value, units, laboratory and sample date for the following determinates:	
	Haemoglobin <5.5 mmol/l	
	Leukocytes <2.0 10e9/l	
	Thrombocytes <150 10e9/l	
	Other viral infections	
	Value (positive or negative), laboratory, sample date for the following determinates:	
	HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV-DNA,	
	HCV-Ab, HCV-RNA, CMV-IgG, CMV-IgM	
	ART drug concentrations	
	Plasma concentration, laboratory, sample data, time after drug intake, dosage and units of the medication	
Patient's participation in clinical trials	Trial name, start and stop date	

Additional data for HIV-infected children		
Clinical examination	Skull circumference, puberty stage	
Adverse events	Pathologic and traumatic fractures, abnormalities of psychological development, abnormalities of locomotion development, abnormalities of puberty development	
Additional treatment *Star and stop date,* status at current visit	Psychologist, pedagogue, psychiatrist, speech therapist, physiotherapist, rehabilitation worker, social worker	
Care and education	Care by:	Mother, father, parents, family, foster family, care institute, other and unknown
	Education:	Nursery school, playgroup, primary school, secondary school, other and unknown
Vaccinations date	DKTP1, DKTP2, DKTP3, DKTP4, HIB1, HIB2, HIB3, HIB4, BMR, BCG, PNCV, influenza, meningitis C, pneumovax, other	
Lab results	*HIV virology: DNA* Value (positive or negative), laboratory, sample date for the following determinates: HIV-1 DNA, HIV-2 DNA, HIV-1 antibodies, HIV-2 antibodies	
	Chemistry: The following determinates are always collected: Glucose, Amylase, ALAT/SGPT,ASAT/SGOT, Alkaline phosphatase, Gamma GT, Lactate, Triglycerides, Cholesterol, Cholesterol, HBA1c	
	Haematology: The following determinates are always collected: Haemoglobin, Leukocytes, Thrombocytes, MCV	

Baselines a

and trends

Baseline characteristics of the ATHENA population and trends over time

Ard van Sighem

Introduction

By 1 June 2007, the total HIV-infected population registered in the database of the HIV Monitoring Foundation was 13,556 patients. Of these patients, 292 were being followed in Willemstad in Curaçao, and they will be described in more detail in chapter 17. In this chapter, demographic and clinical characteristics of the population currently in follow-up are presented. In addition, the changes in these characteristics over calendar time are described at the time of diagnosis and at the time of the start of combination antiretroviral therapy (cART).

Study population and methods

In the analyses, two groups of patients were considered. The first group consisted of HIV-1-infected patients who were alive as of 1 June 2007, were 13 years of age or older, and were still in follow-up. A patient was considered as still in follow-up if data had been collected in the preceding year. The second population comprised all HIV-1-infected patients diagnosed at 13 years of age or older with a known year of HIV diagnosis. Infection with HIV was diagnosed in serum by an HIV-1/HIV-2 antibody assay in combination with an HIV-1 p24 antigen assay, followed by Western blot confirmation of an antibody response specific for HIV-1, HIV-2, or both.

Patients were classified according to their transmission risk category, including men who acquired their infection via homosexual contact (men having sex with men, MSM), via heterosexual contact, via injection drug use (IDU), via contact with infected blood or blood products, via vertical transmission, or via other or unknown transmission routes. Countries of origin were considered as 12 regions: the Netherlands, Western Europe excluding the Netherlands, Central Europe, Eastern Europe, South/Southeast Asia, North Africa and the Middle East, sub-Saharan Africa, North America, Latin America, the Caribbean, Australia and New Zealand, and the Pacific islands.

$CD4^+$ and $CD8^+$ T cell counts and plasma HIV RNA levels at diagnosis were taken closest to the time of diagnosis and prior to the start of therapy within the first 12 weeks after the diagnosis was made. CD4 and CD8 cell counts and viral load at start of cART were determined closest to the date at which cART was started, which was, at most, 12 weeks before and 1 week (0 weeks for RNA) after the start date. Measurements at 24 and 48 weeks after the start of cART were defined as the measurements closest to these time points within an interval of 12 weeks before or after the start date. cART was defined as a combination of at least three antiretroviral drugs from at least two different drug classes. Centers for Disease Control (CDC) status at a specific time point was defined as the most serious CDC event occurring, at most, one year before and 4 weeks after the time point. Hepatitis B (HBV) co-infection was defined as a positive HBV surface antigen (HBsAg) or a positive envelop antigen (HBeAg). Hepatitis C (HCV) infection was defined by a positive HCV-antibody test or a positive HCV RNA test result.

HIV-1 subtypes were determined using the nucleotide sequences of protease and reverse transcriptase (RT). Subtypes were determined separately for every genotypic sequence available for each patient. Sequences were compared pair-wise using the Kimura 2-parameter model for distances[127]. A representative set of reference sequences was obtained from the Los Alamos National Laboratory sequence database (http://www.hiv-web.lanl.gov) and was included in the distance calculations. Sequences were clustered by the neighbour-joining method; they were assigned a specific subtype when the bootstrap value of the cluster containing the sequences and a reference sequence exceeded 85%[128]. Sequences that could not be classified as a specific non-B subtype or a circulating recombinant form (CRF) were labelled "non-B". The circulating recombinant forms designated as CRF01_AE and CRF02_AG will be referred to, in brief, as AE and AG.

Changes over time were assessed by studying changes in the patient characteristics at diagnosis or at the start of cART. Proportions were compared by a chi square test or, if sample sizes were small, by Fisher's exact test. Differences in age, T cell counts, and RNA levels were tested with Wilcoxon-Mann-Whitney and chi square nonparametric tests. The significance of proportional changes over time was assessed with Poisson regression modelling linear in time. For continuous variables, medians were reported with the interquartile range (IQR); changes over time were studied using a linear median regression model. For changes over time, p values refer to the slope of the linear model.

Results

Total population

The total HIV-infected population consisted of 13,264 patients with a total follow-up of 97,982 person-years since diagnosis. Of these patients, 12,958 (97.7%) were infected with HIV-1, and 78 (0.6%) were infected with HIV-2. For 95 (0.7%) patients seroreactivity to both HIV-1 and HIV-2 were found, and for 133 (1.0%) patients serologic results were inconclusive or not (yet) known.

Population currently in follow-up

The majority of the 10,095 (76.1%) patients aged 13 years or older and in follow-up as of 1 June 2007 were men (77.9%) who originated from the Netherlands (58.5%) and were infected via homosexual contact (55.7%). In total, 1354 (13.4%) men and 1954 (19.5%) women were infected via heterosexual contact, whereas patients infected via injection drug use accounted for 3.5% of the population (Table 4.1). The majority of the patients, 7595 or 75.2%, were seen in the hospitals in the western part of the Netherlands – Rotterdam, Amsterdam, Den Haag and Leiden. The median age of the population was 43.3 (IQR, 36.8-50.1) years, and men were generally older than women, that is, 44.7 (38.7-51.3) years of age for men compared to 37.8 (31.8-44.8) years for women ($p<0.001$).

cART was administered to 8115 (80.4%) patients, whilst 56 (0.6%) patients used a non-cART regimen, and 1924 (19.1%) were not (yet) treated. The number of patients not yet treated was higher amongst women than men, being 1582 (20.1%) and 342 (15.4%), respectively ($p<0.001$).

The four most frequently used regimens as of 1 June 2007 were zidovudine+lamivudine+nevirapine (824 patients, 10.2%), tenofovir+emtricitabine+efavirenz (700 patients, 8.6%), tenofovir+lamivudine+nevirapine (587 patients, 7.2%), and tenofovir+lamivudine+efavirenz (586 patients, 7.2%), accounting for 33.2% of all regimens (Table 4.2). As of 1 June 2006, these regimens accounted for 31.8% of all regimens given. Between 1 June 2006 and 1 June 2007, the proportion of patients using tenofovir increased from 39.5% to 47.2% ($p<0.001$), and the proportion using emtricitabine increased from 7.5% to 19.7% ($p<0.001$). On the other hand, the use of lamivudine decreased from 78.6% to 69.3%, and zidovudine use decreased from 40.3% to 34.7% ($p<0.001$). As of 1 June 2007, the most frequently used additions to the backbone were nevirapine (30.7%, 2006: 31.4%, $p=0.2$), efavirenz (26.2%, 2006: 24.8%, $p=0.002$), lopinavir (17.0%, 2006: 16.6%, $p=0.2$), and atazanavir (11.0%, 2006: 10.4%, $p=0.06$).

The most recently measured CD4 cell counts were 480 (IQR, 340-670) $\times 10^6$ cells/l for the male population and 490 (350-670) for women ($p=0.1$). CD8 cell counts were 970 (IQR, 690-1330) $\times 10^6$ cells/l for men and 850 (620-1160) $\times 10^6$ cells/l for women ($p<0.001$). In the total population, 7287 (72.2%) patients had a plasma viral load <500 copies/ml, whereas the load was 7112 (87.6%) in the cART-treated population. One or more AIDS-defining events were found in 2608 (25.9%) patients. About half of those patients, 1362 (13.5%), had an AIDS diagnosis at or within four weeks after an HIV diagnosis.

For 2887 (28.6%) patients, including 2136 men and 571 women, the HIV-1 subtype could be determined. The majority, 2253 (78.0%), were infected with a subtype B

virus; this subtype was more frequently observed in men (2016, 94.4%) than in women (237, 41.5%). Other frequently observed subtypes were AG (184, 6.4%), C (148, 5.1%), A (81, 2.8%), and AE (79, 2.7%).

The median time since diagnosis was 5.9 (IQR, 3.0-9.9) years for women and 6.7 (3.0-11.4) years for men ($p<0.001$). In total, 2523 (25.0%) patients were diagnosed in the previous three years; this proportion was similar for men and women ($p=0.6$). On the other hand, a larger proportion of men (2521, 32.1%) than women (536, 24.1%) received their HIV diagnosis more than 10 years ago ($p<0.001$).

A total of 9291 (92.0%) patients were tested for hepatitis B surface (HBsAg) or envelop (HBeAg) antigen; 812 (8.7%) tested positive. HBV was most prevalent amongst injection drug users, of whom 37 (11.6% of the 318 tested) were co-infected. The HBV prevalence was 9.4% (489 positive of 5188 tested) amongst homosexual men ($p=0.1$ compared to IDU). Amongst heterosexually infected patients, the overall prevalence was 7.1%, significantly higher amongst men (9.1%) than amongst women (5.8%) ($p<0.001$).

The HCV status was known for 8581 (85.0%) patients, of whom 926 (10.8%) were HCV-positive. Co-infection with both HBV and HCV was found in 95 patients. The HCV prevalence was highest amongst IDUs, of whom 310 (93.9%) were co-infected with HCV. In the population infected via heterosexual contact, the HCV prevalence was 6.8% for men and 6.2% for women ($p=0.5$). The prevalence was similar amongst homosexual men ($p=0.3$), of whom 282 out of 4830 tested (5.8%) were HCV-positive. The HCV prevalence was higher amongst those infected by blood-blood contact (34%; 44% for men, 14% for women) ($p<0.001$) and amongst those for whom the route of transmission was unknown (21.8%; 15.6% for men, 49% for women ($p<0.001$).

Trends over time – diagnosis

Men having sex with men (MSM)

For 6843 (68.9%) of the 9929 men with an HIV-1 diagnosis, the reported mode of transmission was homosexual contact. The majority of these patients, 4762 (69.6%), were diagnosed in 1996 or later. The annual number of diagnoses amongst MSM was 364 in 1996; the number decreased to 314 in 1998 and then steadily increased to 513 in 2006 (Table 4.3). The proportion of MSM in the annual tally decreased from 57.9% in 1996 to a nadir of 44.3% in 2003. Thereafter, it increased to 56.0% in 2007 (Figure 4.1). Most MSM, 5016 (73.3%), were of Dutch origin, whereas 527 (7.7%) originated from other Western European countries, 439 (6.4%) from Latin America, 189 (2.8%) from the Caribbean, and 189 (2.8%) from South/Southeast Asia. These proportions did not change over time ($p=0.6$).

For patients diagnosed in or after 1996, median HIV-1 RNA plasma levels at diagnosis were 4.9 (IQR, 4.3-5.3) $\log_{10}$ copies/ml and CD4 and CD8 counts were 350 (150-540) and 910 (610-1322) $\times 10^6$ cells/l, respectively. Patients originating from the Netherlands had higher RNA levels than other patients, 4.9 (IQR, 4.3-5.3) $\log_{10}$ copies/ml for patients of Dutch origin and 4.7 (4.1-5.2) for the other patients ($p<0.001$), but CD4 ($p=0.03$) and CD8 counts ($p=0.09$) did not differ. Median CD4 cell counts increased from 260 (IQR, 96-430) $\times 10^6$ cells/l in 1996 to 420 (250-630) in 2007 ($p<0.001$).

The median age at diagnosis was 37.8 (IQR, 31.8-44.8) years; for patients of non-Dutch origin it was 33.9 (28.8-40.0) years, which was lower than that of patients originating from the Netherlands, for whom the median age was 39.1 (33.3-46.3) years ($p<0.001$). For Dutch patients, the median age at diagnosis increased from 37.0 (IQR, 31.7-45.5) years in 1996 to 42.6 (35.1-48.2) in 2007 ($p<0.001$), whereas it also increased for patients from other regions from 33.0 (29.8-39.4) years to 36.6 (30.4-43.1) ($p<0.001$). An AIDS-defining event at

diagnosis was found in 61 (10.8%) of the 565 patients diagnosed in 2005, whereas 460 (81.4%) were without any event.

In total, 845 (17.7%) patients diagnosed in 1996 or later had a negative HIV-1 test in the 18 months prior to diagnosis (classified as "recent infection"). Since 1996, there has been a steady increase in the proportion of MSM with a recent infection ($p<0.001$), rising from 32 out of 364 (8.8%) in 1996 to 146 out of 513 (28.5%) in 2006, and 34 out of 116 (29.3%) in 2007. There was no difference in the proportion of recent infections amongst patients of Dutch or non-Dutch origin ($p=0.07$). A recent infection was found in 481 out of 2416 (19.9%) patients who were 38 years of age or younger at diagnosis. In older patients, a recent infection was less common, specifically, 364 out of 2346 (15.5%) ($p<0.001$). For patients with a recent infection, median CD4 and CD8 counts at diagnosis were 510 (IQR, 360-690) $\times 10^6$ cells/l and 1025 (720-1480) and did not change over time ($p=1$). CD4 and CD8 counts were lower ($p<0.001$) for patients without recent infection, specifically 301 (IQR, 118-490) $\times 10^6$ cells/l and 892 (600-1290). However, for patients without recent infection, CD4 counts increased from 224 (IQR, 80-400) $\times 10^6$ cells/l in 1996 to 400 (200-560) in 2006 ($p<0.001$). The number of patients who ever had a negative HIV test increased from 79 (21.7%) in 1996 to 262 (51.1%) in 2006, and it was 63 (54.3%) in 2007.

For 4992 (73.0%) patients, the most likely country of infection was known. A majority, 4447 (89.1%), were infected in the Netherlands. The proportion of patients infected in the Netherlands increased from 232 out of 264 (87.9%) in 1996 to 381 out of 406 (93.8%) in 2006 ($p<0.001$). For 3802 (96.4%) of the 3941 Dutch patients for whom the country of infection was known, the country of infection was the Netherlands. The country of infection was known for 92 of 156 (59%) patients originating from the Netherlands Antilles or Aruba and for 117 of 192 (61%) patients from Suriname. Of the 92 from the Antilles, 18 (20%) were infected there, and 68 (74%) were infected in the Netherlands, whilst of the 117 patients from Suriname, 13 (11%) were infected in Suriname and 102 (87%) in the Netherlands.

The HIV-1 subtype could be determined for 2009 (29.4%) MSM. Of these, 1946 (96.9%) were infected with subtype B, and the proportion of patients infected with a subtype B strain did not change over time between 1996 and 2007 ($p=0.1$). Other subtypes found in homosexual men were AE (23 patients, 1.1%), AG (14 patients, 0.7%), C (13 patients), A (6 patients), G (4 patients), and other subtypes (3 patients).

Heterosexual men and women

Of the 4226 patients infected via heterosexual contact, 1776 (13.9% of the total population and 42.0% of the heterosexual group) were men, and 2450 (19.2% of the total population and 58.0% of heterosexuals) were women. The proportion of heterosexual men in the annual number of diagnosed patients varied slightly over time; it increased from 13.0% in 1996 to 17.9% between 2000 and 2003 and decreased thereafter to 14.5% in 2007 (Figure 4.1). For heterosexual women, a similar, although more pronounced, pattern was observed: 13.0% in 1996, 26.6% between 2000 and 2003, and a decrease to 19.3% in 2007. Between 2000 and 2005, the mean annual number of diagnoses was 165 for men and 238 for women, and for both sexes it increased on average by 6.7 diagnoses yearly ($p=0.002$). For 2006, 122 diagnoses amongst men and 154 amongst women have been reported so far.

The most frequently reported regions of origin for heterosexual men were the Netherlands (660 patients, 37.2%) and sub-Saharan Africa (622, 35.0%). Other regions were Latin America (182 patients, 10.3%), Europe excluding the Netherlands (127 patients, 7.2%), and the Caribbean (92 patients, 5.2%). Almost half of

the heterosexual women originated from sub-Saharan Africa (1200 patients, 49.0%), whilst 609 patients (24.9%) were from the Netherlands. The proportion of women originating from the Caribbean (148, 6.0%) and Latin America (221, 9.0%) was similar to that of men, whilst 138 (5.6%) female patients originated from South/ Southeast Asia and 96 (3.9%) from Europe excluding the Netherlands.

Between 1996 and 2002, the proportion of patients originating from sub-Saharan Africa increased from 33.5% to 57.5% ($p<0.001$). Thereafter, this proportion declined 38.8% (107 out of 276) in 2006, but again increased to 47% (33 out of 70) in 2007 ($p=0.2$). This pattern was counterbalanced by a decrease in the proportion of Dutch patients from 41.5% in 1996 to a nadir of 19.2% in 2001 ($p<0.001$), with a subsequent increase to 33.7% in 2006 (27.1% in 2007).

The median CD4 cell counts at diagnosis were 200 (IQR, 60-400) $\times 10^6$ cells/l for heterosexual men and 290 (130-490) for heterosexual women ($p<0.001$). Median CD8 cell counts were 800 (IQR, 500-114) $\times 10^6$ cells/l, and did not differ between men and women ($p=0.8$). Plasma viral load at diagnosis was 4.4 (IQR, 3.6-5.0) $\log_{10}$ copies/ml for women and was higher for men ($p<0.001$), being 4.9 (4.3-5.3). Women were younger at diagnosis than men ($p<0.001$), with a median age of 30.6 (IQR, 25.3-36.9) years, compared to 37.0 (31.4-44.5) years for men.

Age, viral load, and CD4 and CD8 cell counts of men and women did not differ between Dutch patients and patients from other European countries. On the other hand, men and women from sub-Saharan Africa were generally younger ($p<0.001$) and had lower CD4 cell counts ($p<0.001$) than their Dutch counterparts. The median age was 28.9 (IQR, 23.9-34.1) for women from sub-Saharan Africa and 33.9 (28.0-38.6) years for men from sub-Saharan Africa, whereas for Dutch women the median age was 40.8 (33.9-50.0) years and for Dutch men the median age was 34.6 (28.0-45.1) years. CD4 counts were 260 (IQR, 130-414) $\times 10^6$ cells/l for sub-Saharan African women and 170 (70-320) for sub-Saharan African men, whereas they were 450 (170-650) for heterosexual men from the Netherlands and 289 (70-500) for heterosexual women from the Netherlands. Patients from Latin America, the Caribbean, and South/ Southeast Asia likewise had lower CD4 counts than Dutch patients. CD8 cell counts and viral load were similar for patients from different regions, taking into account differences due to gender.

In general, no significant changes occurred in RNA levels and CD8 counts between 1996 and 2007. Median CD4 cell counts increased from 115 (IQR, 40-380) $\times 10^6$ cells/l in 1996 to 260 (130-460) in 2006 ($p<0.001$) in the male population. For women, CD4 counts were 260 (130-440) $\times 10^6$ cells/l in 1996 and 318 (165-520) in 2006, but this increase was not statistically significant ($p=0.3$). The median age at diagnosis of the entire heterosexual population increased from 33.2 (IQR, 27.4-38.5) years in 1996 to 35.3 (29.2-42.8) years in 2006 ($p<0.001$).

Between 1996 and 2007, 643 (17.9%) patients presented with an AIDS-defining event, whereas 218 (6.1%) patients had a CDC-B event. The proportion of patients with AIDS was different for men, being 22.9% (349 out of 1525), and for women, 14.2% (294 out of 2074, $p<0.001$). Proportions did not change over time ($p>0.1$).

Of the heterosexuals diagnosed between 1996 and 2007, 181 (5.0%) had a negative HIV test within 18 months prior to the diagnosis, whilst 544 (15.1%) ever had a negative test. This proportion was similar for men and women ($p=0.3$). Of the 1142 patients originating from the Netherlands and the rest of Europe, 254 (22.2%) ever had a negative test, and 94 (8.2%) had a negative test in the 18 months prior to diagnosis, whilst for the 2457 patients born outside Europe, 290 (11.8%) ever

had a negative test, and 87 (3.5%) had a recent infection. The proportion of patients with a recent diagnosis tended to increase over time (p=0.01) from 3.4% in 1996 to 6.9% in 2007. Likewise, the proportion of patients with a negative HIV test at any time before diagnosis increased (p<0.001) from 10.6% in 1996 to 20.0% in 2007.

The most likely country of infection was recorded for 3068 (72.6%) patients, including 1227 (69.1%) men and 1841 (75.1%) women (p<0.001). Of the 3068 patients, 1336 (43.6%) were infected in the Netherlands, and 1240 (40.4%) were infected in sub-Saharan Africa. The majority of the patients infected in the Netherlands (805, 60.3%) also originated from the Netherlands, whilst 155 (11.6%) originated from sub-Saharan Africa, 138 (10.3%) from Suriname, and 70 (5.2%) from the Netherlands Antilles and Aruba. Of the patients who were infected in sub-Saharan Africa, 1142 (92.1%) were also born in sub-Saharan Africa, whilst 85 (6.9%) originated from the Netherlands. Of the patients from the Netherlands Antilles and Aruba, 64 (46.4%) of 138 were infected in the home country, as were 57 (29%) of 200 from Suriname. More men than women of Dutch origin were infected abroad: 120 (11.4%) men compared to 39 (2.5%) women. Of these 120 men, 57 (48%) were infected in South/Southeast Asia, the majority (50) of them in Thailand.

Of the 1031 (24.4%) patients with a known HIV-1 subtype, 458 (44.4%) originated from sub-Saharan Africa and 573 (55.6%) from other regions. The most prevalent subtype amongst patients from other regions was B (414 patients, 72.3%). Other reported subtypes were AE (48 patients, 8.4%), AG (30, 5.2%), C (29, 5.1%), A (22, 3.8%), G (12, 2.1%), D (6, 1.0%), F (3, 0.5%) and other non-B subtypes (9, 1.6%). Subtype B was found in only 11 (2.4%) patients from sub-Saharan Africa. The most frequent subtypes other than B amongst sub-Saharan Africans were AG (154, 33.6%), C (119, 26.0%), A (57, 12.4%), G (33, 7.2%), D (30, 6.6%), and other non-B subtypes (41, 9.0%).

Injection drug users (IDU)

For 616 (4.8%) patients, including 450 (73.1%) men and 166 (26.9%) women, the reported mode of transmission was IDU. The majority of the patients, 382 (62.0%), were infected before 1996; only 99 (16.1%) patients were infected in or after 2000. The majority of the IDUs originated from the Netherlands (399 patients, 64.8%) as well as other Western European countries (108, 17.5%).

Of the 234 patients diagnosed in or after 1996, 82 (35.0%) were followed in a hospital in Amsterdam, 70 (29.9%) in another hospital in the Randstad, and 57 (24.4%) patients in the southern part of the Netherlands, in particular Maastricht (42, 18.0%). The median age at diagnosis was 37.7 (IQR, 32.1-42.7) years. Median CD4 counts, CD8 counts and viral load were 280 (IQR, 90-510) $\times 10^6$ cells/ml, 805 (470-1220) $\times 10^6$ cells/ml and 4.7 (4.0-5.2) $\log_{10}$ copies/ml. There were no differences between men and women and between patients of Dutch origin and patients originating from outside the Netherlands. However, patients from outside the Netherlands were younger than those of Dutch origin: the age of non-Dutch patients was 33.7 (IQR, 28.6-40.5) compared to 38.8 (35.0-43.0) years for those of Dutch origin (p<0.001). An AIDS event was found in 28 (12.0%) of the IDUs, whilst 186 (79.5%) were asymptomatic at diagnosis.

The most likely country of infection was reported for 508 (82.5%). The majority, 442 (87.0%), were infected in the Netherlands, whilst 36 (7.1%) patients were infected in other Western European countries. Of the IDUs diagnosed from 1996 onwards, 12 (5.1%) patients had a recent infection, whereas 41 (17.5%) patients ever had a negative HIV test. Subtype B was the most frequently reported HIV subtype; 129 (92.8%) of the 139 with a known subtype were infected with this strain.

Trends over time – start of cART

Amongst the 12,739 patients with a known year of HIV-1 diagnosis, 10,126 (79.5%) started cART. Of these patients, 2293 (22.6%) had been treated with mono or dual antiretroviral therapy before starting cART, whilst 7833 (77.4%) started cART as therapy-naïve patients. For the total population, the median age at the start of cART was 37.8 (IQR, 31.9-45.0) years, but men were generally older than women; the men were 39.3 (33.7-46.4) years of age compared to the women's age of 32.4 (27.5-38.6) years ($p<0.001$). The median time between diagnosis and the start of cART for patients diagnosed in 1996 or later was 0.25 (IQR, 0.10-1.00) years for men and 0.23 (0.09-0.76) years for women ($p=0.007$).

The median CD4 cell count for men at the start of cART was 186 (IQR, 70-300) $\times 10^6$ cells/l and the median CD8 cell count for men was 850 (550-1260); the median CD4 count for women at the start was 210 (100-340) $\times 10^6$ cells/l, and the median CD8 count for women was 760 (500-1112) ($p<0.001$). After 24 weeks of cART, CD4 counts had increased to 310 (IQR, 180-460) $\times 10^6$ cells/l for men and 340 (210-504) for women. In previously therapy-naïve patients, CD4 cell counts rose from 190 (IQR, 73-300) $\times 10^6$ cells/l at start of cART to 320 (190-470) at 24 weeks for men and from 210 (103-340) to 347 (220-510) for women. The median CD4 count for men increased further to 360 (IQR, 230-520) $\times 10^6$ cells/l and 380 (253-550) for women at 48 weeks after start of cART. After 24 weeks, CD8 counts were 960 (IQR, 670-1300) $\times 10^6$ cells/l for men and 820 (600-1170) for women, whereas they were 980 (690-1330) $\times 10^6$ cells/l for men and 850 (601-1210) for women after 48 weeks; there were no differences in CD8 cell counts at these time points between pre-treated and naïve patients ($p>0.01$).

In the therapy-naïve population, median CD4 cell counts at the start of cART were 200 (IQR, 90-311) $\times 10^6$ cells/l in 1996, and they decreased to 180 (60-360) in 2000 ($p<0.001$). Between 2000 and 2005, CD4 cell counts were 180 (IQR, 70-288) $\times 10^6$ cells/l and did not change over time ($p=1.0$). Thereafter, CD4 counts increased to 230 (IQR, 155-290) $\times 10^6$ cells/l in 2007 ($p<0.001$). This increase, however, was only apparent in the heterosexually infected population.

At 24 weeks, 83.4% (5527 of 6631) men and 79.7% (1531 of 1920) women whose RNA levels were measured reached levels below 500 copies/ml. At 48 weeks after the start of cART, these proportions were 82.0% (5158 out of 6289) for men and 73.7% (1317 out of 1786) for women. For therapy-naïve patients, 89.6% of the men and 82.8% of the women had levels below 500 copies/ml at 24 weeks, whilst this was the case for 62.7% of men and 65.0% of women in the pre-treated population.

A summary of the most frequently used first-line cART combinations in the population from 1 June 2005 through 31 May 2006 and from 1 June 2006 through 31 May 2007 is shown in Table 4.2. In 2006-2007, tenofovir +emtricitabine+efavirenz was prescribed in 206 out of 598 (34.4%) cases, compared to 125 out of 794 (15.7%) in 2005-2006. Overall, the prescription of tenofovir increased from 433 cases (54.5%) in 2005-2006 to 398 cases (66.6%, $p<0.001$). Emtricitabine was part of 198 (24.9%) initial regimens in 2005-2006 and 300 (50.2%) in 2006-2007 ($p<0.001$), whereas the use of lamivudine decreased from 593 (74.7%) to 296 (49.5%) patients ($p<0.001$). Also, zidovudine was less frequently used: 282 (35.5%) patients in 2005-2006 received it, compared to 133 (22.2%) patients in 2006-2007 ($p<0.001$).

The most frequently used additions in 2006-2007 were efavirenz (335 patients, 56.0%), lopinavir (125, 20.9%), nevirapine (79, 13.2%) and atazanavir (42, 7.0%). Compared to 2005-2006, the proportion of patients using nevirapine (12.1%, $p=0.5$) and atazanavir (8.2%, $p=0.4$) did not differ. However, the proportion of patients starting efavirenz (49.6%, $p=0.02$) was lower in 2005-2006 than in 2006-2007, whereas a higher proportion started lopinavir (28.0%, $p=0.003$).

Discussion

Since last year, the HIV-infected population in the Netherlands as registered by the HIV Monitoring Foundation has increased by 1205 patients to a total of 13,264 patients[16]. The total number of person-years of follow-up increased by 17,218 and is now close to 100,000 person-years. Three-quarters of the population were still in follow-up on 1 June 2007. This proportion is probably an underestimation because some HIV treatment centres have a backlog in data collection of more than one year.

In recent years, 50% to 60% of the diagnosed patients were infected via homosexual contact, whereas approximately 35% were infected via heterosexual contact. The number of patients infected via injection drug use was very low, approximately 10 persons per year. The absolute number of diagnoses amongst homosexual men increased from 300 to 400 per year in the second half of the 1990s to more than 500 after 2004. In 2006, 513 diagnoses amongst MSM have been registered so far. Taking into account the backlog in registration, the real number of 2006 diagnoses is expected to be approximately 15% higher, thus approaching 600 diagnoses annually.

Since 2002, the number of patients originating from sub-Saharan Africa has declined. This is consistent with the decreasing number of people immigrating from Africa into the Netherlands[16]. In 2007, however, an increase in the proportion of sub-Saharan Africans in the heterosexual population was observed. Because this increase is not statistically significant, no conclusions can be drawn from it as yet.

The proportion of homosexual men diagnosed with a recent infection has increased to nearly 30% in the past two years. More than 50% of the MSM ever had a negative test. This most likely reflects the increasing frequency of testing as reported by sexually transmitted infection (STI) clinics[17]. In patients not diagnosed with a recent infection, the time between infection and diagnosis has decreased as the CD4 cell count at diagnosis has increased over calendar time. From these findings and the observation that the median age at diagnosis has increased, it can be concluded that that MSM are infected at an older age.

In the heterosexual population, the proportions of recent infections and of patients with a negative test ever before were much lower than in the MSM population, but they have also increased over time. The increase, however, has been much more pronounced in the female population, which might be attributable to the implementation of the national prenatal screening of pregnant women[18].

By June 2007, approximately 80% of the HIV-infected population were treated with cART. Almost 20% were not being treated with antiretroviral drugs, and a tiny fraction were receiving non-cART combinations. Almost half of all treated patients were now using a regimen containing tenofovir instead of zidovudine, which has a less favourable toxicity profile than tenofovir[19]. In addition, an increasing proportion of patients were using emtricitabine instead of lamivudine, probably because it is available in a fixed-dose combination with tenofovir. Tenofovir-containing regimens were prescribed to two-thirds of the patients starting cART between 1 June 2006 and 31 May 2007; half of the patients started with emtricitabine. In the total treated population, no changes were observed in the administration of nevirapine and the most frequently used protease inhibitors, but efavirenz-containing regimens gained popularity. Also in first-line cART, efavirenz-containing regimens were more often used, whilst regimens containing lopinavir became less common.

Since 2005, CD4 cell counts at the start of cART have appeared to be increasing in the heterosexual, but not in the homosexual, population. As in the heterosexual

population, CD4 cell counts at diagnosis are also increasing; this indicates that a larger proportion of patients can start cART in time, i.e., when CD4 cell counts are still above the threshold below which cART should be initiated. CD4 counts at diagnosis have also increased in the homosexual population, but because they were already in or above the threshold region in which cART should be started, this did not affect CD4 counts at the start of cART.

The prevalence of hepatitis B and C co-infection reportedly was approximately 10%. HBV was most frequently found in IDUs and MSM, whilst HCV was mostly found in IDUs. The HCV prevalence was also high in patients infected via other or unknown routes of transmission, especially in women. Some of these women were IDUs and commercial sex workers, so the mode of transmission could not be definitely determined. As pointed out in chapter 14, which studies the HBV and HCV co-infected populations in more detail, the prevalence of HCV was overestimated because of false-positive test results.

In conclusion, despite a decade of cART, the annual growth of the HIV-infected population has only increased since 1996. This increase has been most noticeable in the MSM population, but the annual number of diagnoses amongst heterosexuals has increased slightly over time. In the total population, the median CD4 cell counts were just below 500×10^6 cells/l, and cART was able to suppress the viral load below 500 copies/ml in the vast majority of patients. On the positive side, the growing proportion of recently HIV-infected patients means that the period when the infection can be transmitted by such individuals is shortened, and provided risk behaviour is reduced after HIV diagnosis, there should be fewer transmissions during that period.

	men (N=7867)		women (N=2228)		total (N=10,095)	
	N	%	N	%	N	%
transmission						
MSM	5619	71.4			5619	55.7
heterosexual	1358	17.3	1957	87.8	3315	32.8
IDU	257	3.3	96	4.3	353	3.5
blood (products)	106	1.3	54	2.4	160	1.6
vertical	21	0.3	18	0.8	39	0.4
other/unknown	506	6.4	103	4.6	609	6.0
age category (years)						
13-17	19	0.2	17	0.8	36	0.4
18-24	136	1.7	176	7.9	312	3.1
25-34	970	12.3	632	28.4	1602	15.9
35-44	2931	37.3	864	38.8	3795	37.6
45-54	2453	31.2	389	17.5	2842	28.2
55-64	1102	14.0	110	4.9	1212	12.0
≥65	256	3.3	40	1.8	296	2.9
region of origin						
the Netherlands	5246	66.7	654	29.4	5900	58.4
sub-Saharan Africa	666	8.5	948	42.5	1614	16.0
Western Europe	504	6.4	101	4.5	605	6.0
Latin America	542	6.9	199	8.9	741	7.3
Caribbean	248	3.2	116	5.2	364	3.6
years aware of HIV infection						
<1	518	6.6	141	6.3	659	6.5
1-2	1458	18.5	406	18.2	1864	18.5
3-4	1121	14.2	420	18.9	1541	15.3
5-10	2226	28.3	720	32.3	2946	29.2
>10	2524	32.1	536	24.1	3060	30.3
unknown	20	0.3	5	0.2	25	0.2

MSM: men having sex with men; IDU: injection drug use

Table 4.1: Characteristics of the HIV-infected population in follow-up as of 1 June 2007.

	1 June 2007 (N=8115)		1 June 2006 (N=7525)	
cART in the entire population	**N**	**%**	**N**	**%**
AZT+3TC+NVP	824	10.2	929	12.3
TDF+FTC+EFV	700	8.6	269	3.6
TDF+3TC+NVP	587	7.2	652	8.6
TDF+3TC+EFV	586	7.2	670	8.9
AZT+3TC+ABC	498	6.1	524	6.9
none	488	6.0	584	7.8
AZT+3TC+LOP/r	372	4.6	377	5.0
TDF+FTC+NVP	361	4.4	87	1.2
AZT+3TC+EFV	286	3.5	345	4.6
TDF+FTC+ATV/r	225	2.8	101	1.3

	2006-2007 (N=598)		2005-2006 (N=794)	
first-line cART	**N**	**%**	**N**	**%**
TDF+FTC+EFV	206	34.4	125	15.7
TDF+3TC+EFV	57	9.5	135	17.0
AZT+3TC+LOP/r	46	7.7	111	14.0
TDF+FTC+NVP	31	5.2	15	1.9
ABC+3TC+EFV	31	5.2	44	5.5
TDF+FTC+LOP/r	28	4.7	25	3.1
AZT+3TC+NFV	27	4.5	36	4.5
TDF+FTC+ATV/r	23	3.8	28	3.5
TDF+3TC+NVP	16	2.7	43	5.4
ABC+3TC+LOP/r	14	2.3	10	1.3

AZT: zidovudine; 3TC: lamivudine; NVP: nevirapine; TDF: tenofovir; FTC: emtricitabine; EFV: efavirenz; ABC: abacavir; LOP/r: lopinavir (ritonavir-boosted); ATV/r: atazanavir (ritonavir-boosted); NFV: nelfinavir.

Table 4.2: Overview of the most frequently used cART regimens in the entire treated populations as of 1 June 2007 and as of 1 June 2006 and in the populations starting cART between 1 June 2006 and 31 May 2007 and between 1 June 2005 and 31 May 2006.

	MSM	Heterosexual		Injection drug use		Blood (products)		Other/unknown		Total
Year of diagnosis	Men	Men	Women	Men	Women	Men	Women	Men	Women	
1996	364	82	82	34	13	3	4	42	5	629
1997	410	106	126	39	6	6	3	51	7	754
1998	314	97	113	19	3	6	6	31	7	596
1999	332	100	132	15	6	7	4	33	5	634
2000	342	146	204	11	3	4	2	33	7	752
2001	402	161	219	13	5	8	2	51	11	872
2002	446	155	257	12	1	11	5	63	5	955
2003	429	172	263	17	4	6	4	65	9	969
2004	529	174	251	9	2	4	3	83	11	1066
2005	565	180	233	11	3	3	5	67	8	1075
2006	513	122	154	5	3	2	3	53	3	858
2007	116	30	40	0	0	0	1	15	5	207
total	**4762**	**1525**	**2074**	**185**	**49**	**60**	**42**	**587**	**83**	**9367**

MSM: men having sex with men

Table 4.3: Annual number of diagnoses since 1996 stratified by gender and transmission risk group.

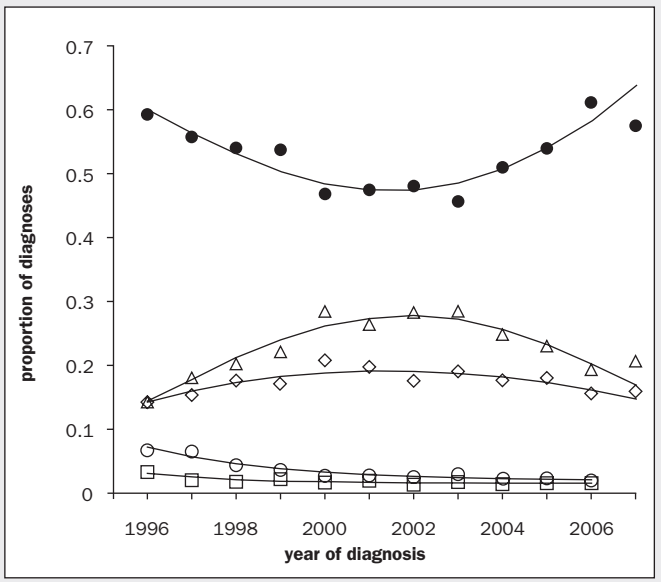


Figure 4.1: Annual proportions of diagnoses per transmission risk group. Dots represent homosexual men; triangles, heterosexual women; diamonds, heterosexual men; circles, injection drug users (men); squares, injection drug users (women); and lines, Poisson regression model quadratic in time.

Effect o

of cART

Changes in effectiveness of first-line cART over time

Luuk Gras

Introduction

Combination antiretroviral therapy (cART) has proven to be effective in reducing HIV production substantially[20] and for a long period of time[21], provided it is started in time[22] and administered in a way that adherence is near perfect[23, 24]. Thus, in the initiation of cART, not only is it important when to start therapy (see Chapter 9), but it is also important to determine what will comprise the first combination of antiretroviral drugs. Initial cART usually involves a triple combination with two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Current Dutch guidelines recommend 7 different combinations of 2 NRTIs in combination with either nelfinavir or ritonavir boosted lopinavir (both PIs), or efavirenz or nevirapine (both NNRTIs)[126].

The short-term response to first-line cART is strongly prognostic for further disease progression[25]. We compare short-term immunologic and virologic responses to the first-line cART regimen between drug classes and different calendar years of starting cART. In addition, we analyse the time to toxicity-related change in the initial cART and the time to first change in the initial cART for any reason (including toxicity).

Methods

Patients who started cART between 1 July 1996 and 31 December 2006 were selected. Of those, patients who were older than 16 years and were antiretroviral therapy-naive at the start of cART were included.

Short-term virologic marker response was defined as the proportion of patients reaching HIV RNA plasma levels less than 50 copies/ml at week 24 after the start of cART, as measured with a sufficiently sensitive assay. Immunologic marker response was defined as the absolute change in CD4 cell count at 24 weeks. The nearest measurement to 24 weeks that occurred between 12 and 36 weeks of initial cART was taken for both markers. In 6235 patients, CD4 cell measurements at the start of cART and 24 weeks thereafter were available, and HIV RNA plasma levels at the start and at 24 weeks of cART were available in 6557. Time to any change in the first-line regimen within 3 years after starting cART was analysed, as was time to a toxicity-related change within 1 year. Therapy interruptions were ignored if the initial cART regimen was restarted within 2 weeks.

Statistical analysis

Logistic regression was used to model the odds of having HIV RNA plasma levels of less than 50 copies/ml at week 24, and linear regression was used to model changes in the CD4 cell count at 24 weeks after the start of cART. Both were intention-to-treat analyses. The cumulative incidence of changes in the first-line cART regimen according to various reasons were calculated and graphically depicted. Cox proportional hazard models were used to analyse time to any change in the initial cART regimen and time to toxicity-related change. Time was censored if, at the date of the last contact, the patient was still on the initial cART regimen. In the analysis of toxicity-related therapy change, time was censored if the regimen was changed for any reason other than toxicity.

The following variables were associated with the above-mentioned outcomes: gender; age at the start of cART; clinical stage at the start of cART (CDC-C vs. CDC-A or -B); CD4 cell count at the start of cART (0-50, 50-200, 200-350, 350-500, and ≥500 cells/mm^3); HIV RNA at the start of cART (<4, 4-5, and ≥5 $\log_{10}$ copies/ml); hepatitis B co-infection (positive hepatitis B surface antigen [HBsAg] test); hepatitis C co-infection (either a positive hepatitis C virus [HCV] antibody or positive HCV RNA test result); region of origin (Netherlands, Caribbean/Latin America, sub-Saharan Africa, Southeast Asia, Western Europe/North America/Australia combined, and other); cART started during pregnancy; cART started during primary infection; and

the initial cART combination (NRTI backbone plus an unboosted PI; NRTI backbone plus a boosted PI; NRTI backbone plus an NNRTI; NRTI plus both a PI and an NNRTI; and combinations of at least 3 NRTIs.

Weight at the start of cART (<60, 60-70, 70-80, 80-90 and ≥90 kg) was included in the analysis of time to regimen change and time to toxicity-related change.

Variables included in multivariate analyses with a p value of 0.20 or higher were excluded from the final model. Plausible interaction terms were included only if their p-value was 0.05 or lower.

Results

Demographic and clinical characteristics of 7655 patients starting first-line cART between 1996 and 2006 are shown in Table 9.1 (See Chapter 9). The initial cART regimen consisted of an NRTI combination plus an NNRTI in 2907 patients (38.0%), an NRTI combination plus an unboosted PI in 2263 (29.6%), an NRTI combination plus a boosted PI in 2007 (26.2%), an NRTI combination plus both a PI and an NNRTI in 249 (3.2), and a combination consisting exclusively of NRTIs in 229 patients (3.0%), but the proportion varied according to calendar year of starting cART. Before 2000, the majority of patients who started cART did so with a combination including an unboosted PI. The proportion of patients starting with cART including an NNRTI in 2006 was 60.6%, 28.8% started with cART including a boosted PI, 5.8% with cART including an unboosted PI, 4.6% with a combination including both a PI and an NNRTI and 0.1% with a combination of at least 3 NRTIs. The group of patients starting cART with a regimen that included both a PI and an NNRTI consisted of 96 who began this therapy during primary infection (38.6%). The median weight at the start of cART was 70.9 kg (interquartile range [IQR] 62.5-79.9).

Virologic response at week 24

The immunologic and virologic short-term response to cART is shown in Table 5.1. In the 4044 patients with an HIV RNA concentration in plasma measured by an assay with a detection limit of 50 copies/ml or less, 74.3% had less than 50 copies/ml at 24 weeks after starting cART. Of those who commenced cART with a combination that included an NNRTI, HIV RNA levels less than 50 copies/ml were reached in 80.2% ; of those who started with a combination that included an unboosted PI, plasma HIV RNA levels less than 50 copies/ml were reached in 71.2%. In univariate analyses the odds ratio (OR) of plasma HIV RNA levels <50 copies/ml after week 24 of cART with a combination including a boosted PI compared to one including an NNRTI was 0.61 (95% confidence interval [CI] 0.52-0.72, p<0.0001) and the OR of cART including an unboosted PI compared to cART including an NNRTI was 0.29 (0.24-0.37, p<0.0001).

Table 5.2 shows the adjusted odds ratios for reaching an HIV RNA plasma concentration of <50 copies/ml at 24 weeks. Patients starting in or after 2005 had significantly higher odds of reaching plasma levels <50 HIV-RNA copies/ml compared to those starting in 2000 (OR 1.65; 95% CI 1.10-2.46, p<0.02). Patients starting cART that included an unboosted PI were less likely to have HIV RNA plasma levels of <50 copies/ml at week 24 compared with combinations including an NNRTI (OR 0.57; 95% CI, 0.40-0.82; p=0.002). There were no significant differences between patients starting cART that included an NNRTI compared with combinations including a boosted PI or a combination including NRTIs only. Patients originating from sub-Saharan Africa (p=0.006), Caribbean/Latin America (p=0.02), or other, non-Western region (p=0.01) had significantly lower odds of reaching an HIV RNA of <50 copies/ml than did patients of Dutch origin. Compared with patients with an HIV RNA plasma concentration between 4 and 5 $\log_{10}$ copies/ml at the start of cART, the OR of patients with a concentration of less than 4 $\log_{10}$ copies/ml was 0.63 (0.45-0.88; p=0.008). Lower odds of reaching an HIV RNA plasma concentration of less than 50 copies/ml at 24 weeks of initial cART were associated with other variables such as HIV infection

through injecting drug use, younger age at the start of cART, being pregnant at the start of cART, and having a CD4 count at the start of cART of 500 or more in comparison to a count between 200 and 350 cells/mm^3. There was no significant interaction between calendar year of starting cART and starting a cART regimen that included a boosted PI as compared to one that included an NNRTI (p=0.90) on the odds of reaching an HIV RNA concentration of less than 50 copies/ml.

Immunologic response at week 24

In the 6235 patients who had a CD4 cell count at the start and at 24 weeks of cART, the median change was 130 cells/mm^3 (IQR 60-213).

In univariate analyses (Table 5.3), mean changes in CD4 cell count were significantly higher in patients starting cART that included both a PI and an NNRTI, (mean change of 167 cells/mm^3, p=0.004) or included a boosted PI (154 cells/mm^3, p=0.0002), compared to an NNRTI (136 cells/mm^3). In adjusted analyses, the difference in CD4 count between patients starting cART that included a boosted PI instead of an NNRTI remained significant (mean difference of 16 cells/mm^3, SD 4.8, p=0.001). There was no evidence for an interaction of the calendar year of starting cART and the initial antiretroviral therapy combination on the change in CD4 count at week 24.

Furthermore, the mean change in CD4 cell count was 21 cells/mm^3 (standard deviation [SD] 6.0) higher in female patients than in male patients (p=0.0006); the change was 33 cells/mm^3 (p=0.0004) lower in patients who were infected through injecting drug use and 16 cells/mm^3 (p=0.006) lower in patients who were infected through heterosexual contact, compared to patients infected through homosexual contact. The mean change in CD4 count was 37 cells/mm^3 lower in sub-Saharan African patients than in patients originating from the Netherlands (p<0.0001). Finally, CD4 count increases were less in patients with lower HIV RNA plasma levels at the start of cART, in older patients, in patients with hepatitis B virus (HBV) or HCV co-infection, in patients who were pregnant at the start of cART, and in patients with CD4 counts that were either low (<50 cells /mm^3) or high (≥500 cells/mm^3).

Time to change of the initial cART regimen

Figure 5.1 shows the cumulative incidence of patients stopping or changing the initial cART regimen for any reason and for specific reasons. In total, 213 patients interrupted the initial cART regimen for up to 2 weeks (interruptions for longer than 2 weeks were regarded as cessation of the regimen). Within 1 year after starting cART, 52.8% of the patients had stopped or changed the initial regimen, and within 3 years, this number increased to 79.2%. The major reason for changing the regimen was related to toxicity of the drugs in use. Within 1 year after starting cART, 20.4% of the patients had stopped or changed the regimen because of toxicity and within 3 years, 26.6% had stopped or changed. Univariate differences in time to a change in the initial cART regimen between patients from different regions of origin were no longer significant in multivariate analyses (Table 5.4). Women had a higher hazard of changing the initial cART regimen; this was also true for those with a high CD4 count at the start of cART. The hazard ratio (HR) of any change in the first-line cART of patients with a CD4 count of 200-350 was 1.26 (95% CI 1.13-1.41, p<0.0001) compared to those with a count of 500 cells/mm^3 or more. Women starting cART during pregnancy had a higher hazard of changing cART (HR 1.86 [1.62-2.13, p<0.0001]), as did patients with a HCV co-infection (HR 1.14 [1.01-1.29, p=0.04]). Compared to patients starting cART that included an NNRTI, the HR of starting a cART regimen including both a PI and an NNRTI was 4.06 (3.51-4.71, p<0.0001), and the HR with cART that included an unboosted PI was 1.60 (1.46-1.75, p<0.0001). The HR of cART that included a boosted PI compared to that including an NNRTI was lower in later calendar years of the start of cART

(Figure 5.2). The HR of a change in the combination of drugs for any reason in 1999 for patients starting cART that included a boosted PI compared to those starting with the inclusion of an NNRTI was 2.56 (95% CI 2.04-3.20, p<0.0001), whereas for patients starting cART with a boosted PI in or after 2005, the HR was 1.26 (1.06-1.49, p=0.007).

Time to toxicity-related change in initial cART

In total, 1556 patients changed the initial cART combination within 1 year of starting the regimen because of toxicity. Most frequently recorded adverse events associated with the toxicity were: nausea in 277 patients (17.8%), anaemia in 188 (12.1%), rash in 159 (10.2%), diarrhoea in 149 (9.6%), and vomiting in 149 (9.6%).

Older age and lower weight at the start of cART were associated with a shorter time to a toxicity-related change in the regimen in multivariate analyses. When weight was included continuously in the model (excluding 170 patients with no recorded weight at the start of cART) the HR was 0.96 (95% CI 0.94-0.98, p=0.0002) for every 5 kg less. The HR of female gender (Table 5.5) was 1.41 (1.20-1.66, p<0.0001) compared to male gender. Infection through heterosexual contact was associated with a lower hazard (HR 0.85, p=0.03) of a toxicity-related regimen change than infection transmitted by men having sex with men (MSM).

The HR of a toxicity-related change of patients starting cART that included both a PI and an NNRTI compared with cART that included an NNRTI was 2.59 (2.04-3.30, p<0.0001). Compared to an initial cART regimen that included an NNRTI, the HR of regimens that included a boosted PI was 1.19 (1.05-1.35, p=0.007) and those with an unboosted PI 0.75 (0.63-0.89, p=0.001). As in the analysis of time to any change in the initial regimen, there was a significant interaction between calendar year of starting cART and the combination of antiretroviral therapy. An initial cART regimen between 1999 and 2001 that included a boosted PI was associated with a shorter time to a toxicity-related change than cART that included an NNRTI, whereas the difference was not significant in patients starting cART between 2002 and 2006 (Figure 5.3).

Discussion

Currently, an NNRTI or a boosted PI is included in the combination of antiretroviral drugs used in the majority of patients starting cART. We found no significant differences in short-term virologic outcome between cART including an NNRTI and a regimen including a boosted PI. There was an increase of 31 cells/mm^3 in CD4 count at week 24 in patients starting with a boosted PI compared to those starting with an NNRTI, but whether this is clinically meaningful depends on CD4 count response in the longer term. There was no significant difference in the risk of a toxicity-related change between patients starting cART that included an NNRTI and patients starting with a boosted PI in or after 2002. However, patients starting cART that included a boosted PI had a shorter time to change in the regimen for any reason. Our results agree with those of a recent systematic overview of combination therapy in HIV infection; that study concluded that virologic responses at week 24 and week 48 in patients starting cART that included an NNRTI or a boosted PI were superior to those that included an unboosted PI or only NRTIs. Changes in CD4 count were higher in patients starting with a boosted PI compared to those starting with an NNRTI, and NNRTI-based cART was superior to that which included an unboosted PI[129]. cART combinations including a boosted PI or an NNRTi are better able to suppress viral load than combinations that include an unboosted protease inhibitor[29, 130-133]. Apart from more potent therapy, better management of toxicities and adherence[134] also contributes to improved virologic outcome.

The improved short-term virologic outcome in later calendar years persisted after adjusting for the type of cART combination (cART including a boosted PI,

an unboosted PI, an NNRTI, a PI, and an NNRTI, or a combination of exclusively NRTIs). This finding indicates that there is residual confounding through variables not adjusted for in the analysis. The specific drugs used in the NRTI component in the combination may also affect efficacy. Virologic responses were better with combinations of tenofovir and lamivudine or emtricitabine[26]. The increasing proportion of patients starting cART with these NRTIs in later calendar years might explain the better virologic outcome in more recent calendar years.

Patients of non-Western origin and younger patients showed a diminished virologic response after 24 weeks, and patients of non-Western origin also had smaller gains in CD4 cell count. Poorer virologic response by non-indigenous patients in the Netherlands has been previously reported[28]. Other studies[21, 29, 30] also reported better virologic response in older patients from a Western background, in contrast to a recent study[27]. Differences in adherence between older and younger patients and between patients from different regions of origin may play a role. Likewise, a lower virologic response and a higher probability of a toxicity-related change or a change for any reason was also found more frequently in patients starting cART with a high CD4 cell count, and again, this might be related to adherence. Feeling healthy is a reason for not taking medication[31, 32, 135]. Therefore, a closer follow-up of non-Western patients and younger patients, as well as those with high CD4 counts, may improve the virologic response. Keeping HIV RNA levels at low levels is important, since levels higher than 1000 copies/ml are strongly associated with less restoration of CD4 cells in patients on uninterrupted cART[3, 136], with selection of resistant virus strains[44, 137], and with progression of disease[138, 139].

We found a higher risk of a toxicity-related therapy change in patients with lower weight, and after adjustment for weight, we also found a higher risk in women than in men. Therapeutic drug monitoring of patients and lowering of dosage of antiretrovirals (if considered virologically safe) could be of benefit to patients considered at high risk of drug toxicity[33].

Patients starting cART during a pregnancy had a lower probability of having an HIV RNA plasma concentration <50 copies/ml, but had a higher mean increase in CD4 count at week 24. Pregnant women starting cART whilst their CD4 counts are still high are more likely to stop taking antiretroviral drugs after the delivery. This would explain the higher probability of having viral load measurements >50 copies/ml at week 24, but there is also limited data to suggest that pregnant women are at risk of suboptimal drug concentrations, possibly due to induction of hepatic drug-metabolising enzymes, changes in gastrointestinal transit times, increases in body water and fat, and changes in the expression of drug transporters. HIV-infected pregnant women show a decline in the absolute CD4 count during the first trimester, followed by a gradual increase until normal levels 6 months postpartum[140]. The more pronounced increase in CD4 count in pregnant women found in our analysis might be explained by the diminished absolute CD4 count prior to starting cART during pregnancy. A diminished immunoreactivity is helpful in preventing rejection of the fetus[141].

In conclusion, virologic responses to an initial cART regimen have improved since the introduction of cART in 1996. Initial therapy that includes a boosted PI or an NNRTi has superior virologic efficacy to that including an unboosted PI or a combination including only NRTIs. In patients starting cART that included either a boosted PI or an NNRTI in or after 2002, there was no significant difference in the risk of a toxicity-related change.

cART including	Patients with plasma measured by sensitive HIV RNA assay*	Patients (%) with HIV RNA<50 cps/ml at w 24	Patients with CD4 cell measurements*	Median (IQR) CD4 count at the start of cART (cells/mm^3)	Median (IQR) change in CD4 count (cells/mm^3)
unboosted PI	439	239 (54.4)	1786	235 (90-385)	126 (60-220)
boosted PI	1260	897 (71.2)	1700	140 (50-257)	137 (70-220)
NNRTI	2003	1607 (80.2)	2364	192 (100-280)	120 (60 200)
Both PI and NNRTI	166	127 (76.5)	200	295 (120-542)	150 (68 265)
NRTIs only	176	134 (76.1)	185	230 (150-360)	100 (40 187)
Total	4044	3004 (74.3)	6235	190 (80-310)	130 (60-213)

Table 5.1: Immunologic and virologic marker responses to treatment at 24 weeks after the start of cART.

* Measurements at the start and after 24 weeks of cART.

IQR: interquartile range; cART: combination antiretroviral therapy; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor

		Univariate		Multivariate	
		OR (95% CI)	**p**	**OR (95% CI)**	**p**
Gender	Female vs. Male	0.74 (0.63-0.86)	0.0001		
Transmission risk group	Homosexual	1.00		1.00	
	Blood-blood	0.93 (0.50-1.76)	0.83	1.05 (0.42-2.60)	0.91
	Heterosexual	0.70 (0.61-0.82)	<0.0001	0.81 (0.60-1.09)	0.17
	IDU	0.67 (0.47-0.96)	0.03	0.24 (0.14-0.44)	<0.0001
	Other	0.83 (0.61-1.12)	0.21	1.04 (0.62-1.74)	0.87
Region of origin	Netherlands	1.00		1.00	
	Caribbean/ Latin America	0.94 (0.75-1.18)	0.61	0.67 (0.47-0.94)	0.02
	Other	1.10 (0.83-1.46)	0.49	0.61 (0.41-0.90)	0.01
	Sub-Saharan Africa	0.72 (0.61-0.86)	0.0002	0.63 (0.45-0.88)	0.006
	Western Europe/North America/Australia	1.13 (0.82-1.55)	0.46	0.88 (0.54-1.44)	0.62
Age at the start of cART (per 5 yr increase)		1.06 (1.03-1.10)	0.0004	1.05 (0.99 -1.12)	0.09
CD4 count at the start of cART (cells/mm^3)	<50	0.61 (0.48-0.76)	<0.0001	0.56 (0.39-0.82)	0.002
	50-200	0.82 (0.67-0.99)	0.04	1.18 (0.87-1.61)	0.30
	200-350	1.00		1.00	
	350-500	0.62 (0.47-0.81)	0.0006	0.56 (0.38-0.81)	0.002
	>=500	0.42 (0.31-0.56)	<0.0001	0.62 (0.41-0.94)	0.03
HIV RNA at the start of cART (log_{10} copies/ml)	<4	0.41 (0.32-0.53)	<0.0001	0.63 (0.45-0.88)	0.008
	4-5	1.00		1.00	
	≥5	0.51 (0.43-0.61)	<0.0001	0.79 (0.60-1.05)	0.10
Calendar year of starting cART	1999	0.85 (0.60-1.21)	0.38	0.92 (0.55-1.55)	0.76
	2000	1.00		1.00	
	2001	1.11 (0.82-1.51)	0.48	1.18 (0.75-1.84)	0.48
	2002	1.11 (0.83-1.47)	0.49	0.86 (0.57-1.30)	0.47
	2003	1.20 (0.90-1.60)	0.20	0.77 (0.51-1.15)	0.20
	2004	1.51 (1.14-2.00)	0.004	1.14 (0.75-1.74)	0.53
	≥2005	1.71 (1.32-2.23)	0.0001	1.65 (1.10-2.46)	0.02
CDC stage	C vs. A/B	0.93 (0.79-1.09)	0.35	1.50 (1.13-1.98)	0.004
Pregnant at the start of cART		0.40 (0.32-0.51)	<0.0001	0.57 (0.37 -0.86)	0.008
Initial cART combination	NNRTI	1.00		1.00	
	NRTI only	0.79 (0.55-1.13)	0.19	0.82 (0.50-1.35)	0.44
	PI and NNRTI	0.80 (0.55-1.17)	0.25	1.02 (0.57-1.83)	0.94
	boosted PI	0.61 (0.52-0.72)	<0.0001	0.91 (0.70-1.19)	0.51
	unboosted PI	0.29 (0.24-0.37)	<0.0001	0.57 (0.40-0.82)	0.002

Table 5.2: Results of univariate and multivariate logistic regression of the probability of reaching HIV RNA <50 cps/ml at week 24.

			Univariate		Multivariate	
		Mean change in CD4 count from baseline (cells/mm^3)	Mean difference (SE) with reference group	p	Mean difference (SE) with reference group	p
Gender	Male	144	0		0	
	Female	142	-2 (4.4)	0.68	21 (6.0)	0.0006
CD4 count at the start of cART (cells/mm^3)	<50	125	-29 (5.7)	<0.0001	-36 (5.8)	<0.0001
	50-200	150	-4 (4.7)	0.37	-8 (4.7)	0.10
	50-200	154	0		0	
	350-500	149	-5 (6.5)	0.41	-9 (6.5)	0.15
	≥500	106	-48 (7.3)	<0.0001	-58 (7.6)	<0.0001
HIV RNA at the start of cART (log_{10} copies/ml)	<4	105	-32 (6.3)	<0.0001	-34 (6.5)	<0.0001
	4-5	137	0		0	
	≥5	159	22 (4.2)	<0.0001	24 (4.3)	<0.0001
Transmission risk group	Homosexual	154	0		0	
	IDU	106	-48 (9.4)	<0.0001	-33 (11.6)	0.004
	Heterosexual	134	-20 (4.0)	<0.0001	-16 (5.7)	0.006
	Blood-blood	120	-34 (16.2)	0.04	-27 (16.3)	0.09
	Other	152	-2 (8.3)	0.84	10 (8.4)	0.22
Region of origin	Netherlands	152	0		0	
	Caribbean/Latin America	140	-12 (6.3)	0.06	-12 (6.5)	0.06
	Sub-Saharan Africa	122	-30 (4.9)	<0.0001	-37 (6.2)	<0.0001
	Western Europe/North America/Australia	134	-18 (7.8)	0.02	-14 (0.0)	0.07
	Other	146	-6 (7.4)	0.42	-8 (7.4)	0.27
Age at starting cART (per 5 yr increase)			-1 (0.9)	0.19	-3.5 (1.0)	0.0004
CDC stage	A/B	144	0			
	C	141	-3 (4.2)	0.45		
HBV	-	144	0			
	+	123	-21 (7.3)	0.003	-15 (7.2)	0.03
HCV	-	145	0		0	
	+	114	-31 (7.1)	<0.0001	-18 (8.7)	0.04
cART started during pregnancy	No	142	0		0	
	Yes	162	20 (8.3)	0.02	52 (10.1)	<0.0001
Initial cART combination	NNRTi	136	0		0	
	NRTi only	129	-7 (11.3)	0.51	12 (11.5)	0.30
	PI and NNRTi	167	31 (10.9)	0.004	22 (11.4)	0.054
	boosted PI	154	18 (4.7)	0.0002	16 (4.8)	0.001
	unboosted PI	142	6 (4.6)	0.20	6 (6.5)	0.32

Table 5.3: Results of univariate and multivariate linear regression of the change in CD4 count (cells/mm^3) between the start of cART and week 24.

*SE: standard error; cART: combination antiretroviral therapy; IDU: injecting drug use; HBV: hepatitis B virus; HCV: hepatitis C virus; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor. Model further adjusted for calendar year of starting cART.

		Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p
Gender	Male	1.00			1.00		
	Female	1.33	(1.25-1.42)	<.0001	1.23	(1.13-1.34)	<.0001
CD4 count at the start	<50	1.31	(1.21-1.43)	<.0001	1.16	(1.05-1.28)	0.0025
of cART (cells/mm^3)	50-200	1.08	(1.01-1.17)	0.04	1.03	(0.95-1.11)	0.46
	50-200	1.00			1.00		
	350-500	1.24	(1.12-1.36)	<.0001	1.13	(1.03-1.25)	0.01
	≥500	1.54	(1.38-1.72)	<.0001	1.26	(1.13-1.41)	<.0001
HIV RNA at the start of cART	<4	1.29	(1.17-1.41)	<.0001	1.10	(1.00-1.22)	0.04
(log_{10} copies/ml)	4-5	1.00			1.00		
	≥5	1.09	(1.02-1.16)	0.009	1.02	(0.95-1.09)	0.54
Transmission risk group	Homosexual	1.00			1.00		
	IDU	1.05	(0.85-1.31)	0.64	1.16	(1.01-1.32)	0.03
	Heterosexual	1.17	(1.10-1.24)	<.0001	0.95	(0.87-1.03)	0.19
	Blood-blood	1.17	(1.02-1.33)	0.02	0.88	(0.71-1.10)	0.28
	Other	0.93	(0.82-1.05)	0.23	0.86	(0.76-0.97)	0.02
Region of origin	Netherlands	1.00			1.00		
	Caribbean/Latin America	1.09	(1.00-1.20)	0.045	1.10	(1.00-1.21)	0.045
	Sub-Saharan Africa	1.16	(1.08-1.24)	<.0001	1.09	(1.00-1.19)	0.06
	Western Europe/North America/Australia	0.85	(0.76-0.95)	0.005	0.87	(0.78-0.98)	0.02
	Other	1.06	(0.95-1.18)	0.32	1.04	(0.93-1.16)	0.50
Age at the start of cART (per 5 yr increase)		0.98	(0.96-0.99)	0.0007			
CDC Stage	A and B	1.00			1.00		
	C	1.16	(1.09-1.23)	<.0001	1.15	(1.07-1.23)	<.0001
cART started during pregnancy		2.38	(2.14-2.64)	<.0001	1.86	(1.62-2.13)	<.0001
Initial cART combination	NNRTI	1.00			1.00		
	NRTI only	0.94	(0.78-1.12)	0.46	0.93	(0.78-1.12)	0.44
	PI and NNRTI	4.08	(3.55-4.69)	<.0001	4.06	(3.51-4.71)	<.0001
	boosted PI	1.74	(1.62-1.87)	<.0001	* See Figure 5.2		
	Single PI	1.54	(1.44-1.65)	<.0001	1.60	(1.46-1.75)	<.0001

Table 5.4: Results of univariate and multivariate proportional hazard regression of the time to the first change in the regimen.

*HR: hazard ratio; CI: confidence interval; IDU: injecting drug use; HBV: hepatitis B virus; HCV: hepatitis C virus; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor

		Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p
Gender	Male	1.00			1.00		
	Female	1.13	(1.01-1.27)	0.03	1.41	(1.20-1.66)	<.0001
CD4 count at the start	<50	1.17	(1.00-1.37)	0.047			
of cART (cells/mm^3)	50-200	1.01	(0.89-1.15)	0.87			
	50-200	1.00					
	350-500	1.09	(0.91-1.31)	0.33			
	≥500	1.31	(1.08-1.60)	0.006			
HIV RNA at the start of cART	<4	0.91	(0.76-1.09)	0.31			
(log_{10} copies/ml)	4-5	1.00					
	≥5	1.04	(0.93-1.16)	0.54			
Transmission risk group	Homosexual	1.00			1.00		
	IDU	0.84	(0.55-1.29)	0.43	0.71	(0.46-1.10)	0.12
	Heterosexual	0.96	(0.86-1.07)	0.44	0.85	(0.74-0.98)	0.03
	Blood-blood	0.93	(0.73-1.19)	0.57	0.84	(0.65-1.09)	0.18
	Other	0.84	(0.67-1.05)	0.12	0.80	(0.64-1.01)	0.06
Region of origin	Netherlands	1.00					
	Caribbean/Latin America	1.01	(0.86-1.19)	0.90			
	Sub-Saharan Africa	0.85	(0.74-0.97)	0.01			
	Western Europe/North America/Australia	0.89	(0.73-1.09)	0.26			
	Other	0.97	(0.80-1.18)	0.78			
Age at the start of cART (per 5 yr increase)		1.03	(1.00-1.05)	0.03	1.04	(1.01-1.06)	0.007
CDC stage at the start of cART	A,B	1.00			1.00		
	C	1.19	(1.07-1.33)	0.001	1.14	(1.02-1.27)	0.02
cART started during pregnancy		0.63	(0.46-0.85)	0.002	0.75	(0.54-1.04)	0.08
Initial cART combination	NNRTI	1.00			1.00		
	3 NRTI only	0.77	(0.55-1.09)	0.14	0.78	(0.55-1.11)	0.17
	PI and NNRTI	2.87	(2.30-3.59)	<.0001	2.59	(2.04-3.30)	<.0001
	boosted PI	1.28	(1.13-1.45)	<.0001		* see Figure 5.3	
	unboosted PI	0.94	(0.83-1.07)	0.37	0.75	(0.63-0.89)	0.001
Weight at the start of cART (kg)	<60	1.29	(1.12-1.49)	0.0006	1.26	(1.08-1.48)	0.003
	60-70	1.07	(0.94-1.23)	0.30	1.06	(0.93-1.22)	0.36
	70-80	1.00			1.00		
	80-90	0.90	(0.77-1.06)	0.20	0.90	(0.77-1.06)	0.22
	≥90	0.85	(0.69-1.04)	0.12	0.85	(0.69-1.04)	0.12

Table 5.5: Results of univariate and multivariate proportional hazard regression of toxicity related change in the initial cART.

*HR hazard ratio; CI: confidence interval; cART: combination antiretroviral therapy; IDU: injecting drug use; HBV: hepatitis B virus; HCV: hepatitis C virus; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor.

		Change for any reason			Toicity related change		
		HR	95% CI	p	HR	95% CI	p
Gender	Male	1.00			1.00		
	Female	1.23	(1.13-1.34)	<.0001	1.41	(1.20-1.66)	<.0001
CD4 count at the start	<50	1.16	(1.05-1.28)	0.0025			
of cART (cells/mm^3)	50-200	1.03	(0.95-1.11)	0.46			
	50-200	1.00					
	350-500	1.13	(1.03-1.25)	0.01			
	≥500	1.26	(1.13-1.41)	<.0001			
HIV-RNA at the start of	<4	1.10	(1.00-1.22)	0.04			
cART (log_{10} copies/ml)	4-5	1.00					
	≥5	1.02	(0.95-1.09)	0.54			
Transmission risk group	Homosexual	1.00			1.00		
	IDU	1.16	(1.01-1.32)	0.03	0.71	(0.46-1.10)	0.12
	Heterosexual	0.95	(0.87-1.03)	0.19	0.85	(0.74-0.98)	0.03
	Blood-blood	0.88	(0.71-1.10)	0.28	0.84	(0.65-1.09)	0.18
	Other	0.86	(0.76-0.97)	0.02	0.80	(0.64-1.01)	0.06
Region of origin	Netherlands	1.00					
	Caribbean/Latin America	1.10	(1.00-1.21)	0.045			
	Sub-Saharan Africa	1.09	(1.00-1.19)	0.06			
	Western Europe/North America/Australia	0.87	(0.78-0.98)	0.02			
	Other	1.04	(0.93-1.16)	0.50			
Age at the start of cART (per 5 yr increase)		1.00			1.04	(1.01-1.06)	0.007
CDC stage	A and B	1.00			1.00		
	C	1.15	(1.07-1.23)	<.0001	1.14	(1.02-1.27)	0.02
cART started during pregnancy		1.86	(1.62-2.13)	<.0001	0.75	(0.54-1.04)	0.08
Initial cART combination	NNRTI	1.00			1.00		
	NRTI only	0.93	(0.78-1.12)	0.44	0.78	(0.55-1.11)	0.17
	PI and NNRTI	4.06	(3.51-4.71)	<.0001	2.59	(2.04-3.30)	<.0001
	boosted PI		* See Figure 5.2			* see Figure 5.3	
	Single PI	1.60	(1.46-1.75)	<.0001	0.75	(0.63-0.89)	0.001
Weight at the start of cART (kg)	<60				1.26	(1.08-1.48)	0.003
	60-70				1.06	(0.93-1.22)	0.36
	70-80				1.00		
	80-90				0.90	(0.77-1.06)	0.22
	≥90				0.85	(0.69-1.04)	0.12

Table 5.6: Results of multivariate proportional hazard regression of the time to the first change in the regimen (left) and time to toxicity-related change (right).

HR: hazard ratio; CI: confidence interval; cART: combination antiretroviral therapy; IDU: injecting drug use; HBV: hepatitis B virus; HCV: hepatitis C virus; PI: protease inhibitor;

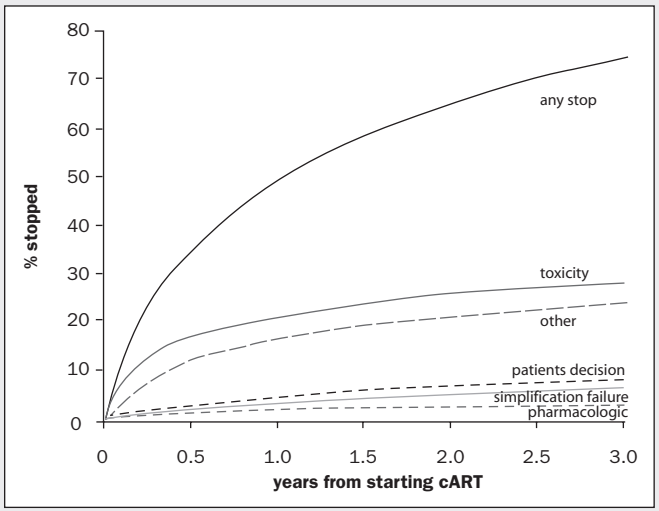


Figure 5.1: Cumulative incidence of change in the initial cART regimen.

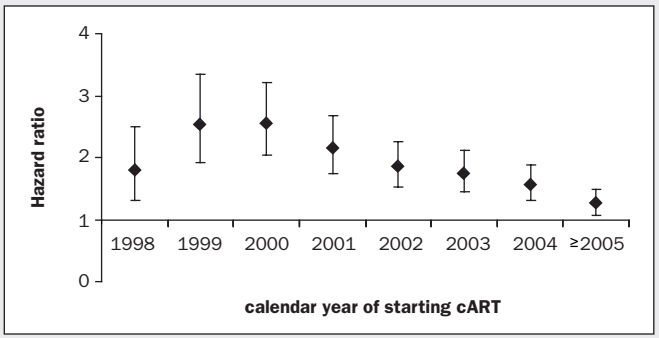


Figure 5.2: Interaction between calendar year of starting cART with the effect of RTV-boosted cART relative to NNRTI-based cART on the hazard ratio of any change in the initial regimen.

cART: combination retroviral therapy; RTV: ritonavir; NNRT: non-nucleoside reverse transcriptase inhibitor

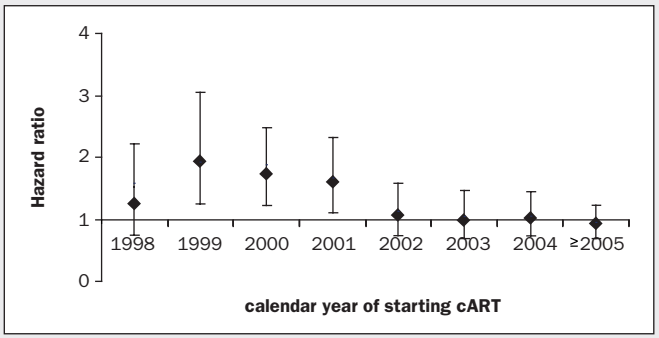


Figure 5.3: Interaction between calendar year of starting cART with the effect of RTV-boosted cART relative to NNRTI-based cART on the hazard of a toxicity-related change in the initial regimen.

cART: combination retroviral therapy; RTV: ritonavir; NNRT: non-nucleoside reverse transcriptase inhibitor

cART regim

nen change

Short-term virologic response and toxicity-related changes on a new cART regimen after first-line cART

Luuk Gras

Introduction

In a substantial proportion of patients, the initial regimen for combination antiretroviral therapy (cART) is changed for reasons ranging from toxicity or virologic failure to nonadherence or simplification[34, 35]. Patients who change their initial regimen because of virologic failure have been shown to be at risk of subsequent virologic failure with a second-line regimen and likewise, patients who switch the initial regimen because of toxicity are at increased risk for toxicity in the new regimen[36, 37]. However, with the increasing availability of new drugs and drug classes for use in second-line therapy, the chances for a long and durable suppression of plasma viral load without serious toxicity on second-line cART may have increased in more recent years.

In this chapter we evaluate short-term virologic efficacy of a new cART combination in patients who changed the first-line cART regimen because of toxicity or virologic failure. We also evaluate the time to change for any reason and time to a toxicity-related change of the new regimen.

Methods

Patients included in the analyses in this chapter are a subset of the patients who started first-line cART as described in Chapter 5. In summary, they were antiretroviral therapy-naïve and at least 16 years of age at the start of cART. In addition, only patients were included who had made a change in the combination of drugs in first-line cART and had started a new combination of cART before 31 December 2006. Dose changes were ignored.

Short-term virologic marker response was defined as the proportion of patients with HIV RNA plasma levels determined by a sufficiently sensitive assay to be less than 50 copies/ml at week 24 after the start of second-line cART. The measurement nearest to 24 weeks that was taken between 12 and 36 weeks after the start of the new cART regimen was used. Time to any change in the new regimen within 3 years after the start was analysed, as was time to a toxicity-related change within 1 year. Therapy interruptions were ignored if the regimen was restarted within 2 weeks. These endpoints were compared according to calendar year of the start of the new cART and the reason for changing the first-line cART. In multivariate analyses, only those patients were included who switched first-line cART because of toxicity or virologic failure.

Statistical analysis

Logistic regression was used to model the odds of having HIV RNA plasma levels of less than 50 copies/ml at week 24 after the start of the new cART. An intention-to-treat approach was taken. The cumulative incidence of changes in the new cART regimen according to various reasons for changing were calculated and graphically depicted with competing risk models[142, 143]. Cox proportional hazard models were used to analyse time to any change in the new regimen and time to toxicity-related change. Time was censored if at the date of the last contact the patient was still on the new cART. In the analysis of toxicity-related therapy change, time was censored if the regimen was changed for any reason other than toxicity.

The following variables were associated with the above-mentioned outcomes: gender; age at the start of the new cART; clinical stage at the start of the new cART (CDC-C vs. CDC-A or B); CD4 cell count at the start of the new cART (0-50, 50-200, 200-350, 350-500, and ≥500 cells/mm^3); hepatitis B co-infection (positive hepatitis B surface antigen [HBsAg] test); hepatitis C co-infection (either a positive hepatitis C virus [HCV] antibody or positive HCV RNA test result); region of origin (Netherlands, Caribbean/Latin America, sub-Saharan Africa, Southeast Asia, Western Europe/North America/Australia combined, and other); calendar year of starting the new cART; number of months spent on first-line

cART (<3, 3-12 and >12 months); and time between stopping the first cART and starting the new regimen (0, 1-14 days, 2 weeks-3 months, and >3 months).
Body weight at the start of the new cART regimen (<60, 60-70, 70-80, 80-90 and ≥90 kg) was included in the analysis of time to regimen change and time to toxicity-related change. The HIV RNA plasma level at the start of the new regimen was not included in multivariate models, since this was thought to be an intrinsic part of a switch because of virologic failure.
Variables included in multivariate analyses with a p-value of 0.20 or higher were excluded from the final model. Plausible interaction terms were only included if their p-value was 0.05 or lower.

Results

Of the 7655 patients who started first-line cART, 5942 stopped for at least 2 weeks or changed the regimen. In total, 4947 patients switched to a new cART regimen before 31 December 2006. The most frequently recorded reason for the change in first-line cART was toxicity in 1982 patients (40.1%), followed by simplicity of a new regimen in 516 (10.4%), virologic failure in 446 patients (9.0%), and patient decision in 412 (8.3%).

The majority of patients were male (76.7%), infected through homosexual contact (52.1%), and from the Netherlands (55.2%). cART that included a non-nucleoside reverse transcriptase inhibitor (NNRTI) was the most frequently used combination in the new cART (45.0%), followed by cART that included a boosted protease inhibitor (PI) (25.5%) and cART that included an unboosted PI (15.1%). In the majority of patients (53.9%) a change in the combination of NRTI drugs was made and in 24.4% this was the only change in the cART regimen. In total 23.3% changed from cART including an NNRTI to cART including a PI, 9.9% changed from an unboosted PI to a boosted PI, 7.8% from an NNRTI to a PI, 9.2% changed to a new cART including only NRTI and 14.6% made a change within the same type of cART. Most patients (78.2%) switched from first-line to the new cART without interruption. Table 6.1 shows clinical and demographic characteristics at the start of the new cART, according to reason of change from the first-line cART.

Virologic response 24 weeks after starting the new regimen

The plasma HIV RNA was measured with an assay having a detection limit of 50 copies/ml or less in 3286 patients. Of these patients, 2781 (84.6%) had <50 copies/ml or less after 24 weeks on the new cART. The proportion of patients with <50 HIV RNA copies/ml at week 24 was highest in those who switched from first-line cART because of the simplicity of a new regimen (94.6%); it was 85.0% in those who switched because of toxicity, and it was lowest in patients who failed on the first-line regimen (70.4%).

In 1586 patients who switched to a new combination of cART because of either toxicity or failure, an association was found in univariate analyses between a higher probability of reaching an HIV RNA plasma concentration of <50 copies/ml at 24 weeks on the new regimen and a higher CD4 count at the start of the new regimen (Odds ratio [OR] per 100 cells/mm^3 increase 1.08; 95% confidence interval [CI] 1.02-1.15, p=0.006), HIV infection through homosexual contact as compared to heterosexual contact (OR 1.35; 1.02-1.79; p=0.03), co-infection with HCV (OR 1.94; 1.02-3.67; p=0.04), older age at the start of the new regimen (OR per 5 years older 1.15, 1.08-1.23, p=0.0001), and a longer time spent on the initial cART before the switch (OR of 3-12 months compared to ≥12 months 0.71; 0.51-0.98, p=0.04). However, the same association was not found in multivariate logistic regression models. Of the 653 patients with a plasma HIV RNA level ≤50 copies/ml at the start of the new regimen, 602 (92.2%) still had levels ≤50 copies/ml at week 24. This compares to 702 patients (75.2%) with plasma HIV RNA levels >50

copies/ml at week 24 out of the 933 patients with levels >50 copies/ml at the start of the new cART. The OR of patients with >50 copies/ml at the start of the new cART reaching an HIV RNA concentration <50 copies/ml compared with patients who had levels of ≤50 at the start was 0.25 (0.18-0.36, p<0.0001). However, this variable was not included in multivariate models since it was thought to be part of the definition of virologic failure, which had led to changing of the first-line cART.

The odds ratios obtained in multivariate models are shown in Table 6.2. Patients originating from regions other than the Netherlands were at an increased risk of not having a plasma HIV RNA of <50 copies/ml at 24 weeks after the start of the new cART; the OR of patients originating from Caribbean/Latin American regions was 0.39 (95% CI 0.24-0.62, p<0.0001), for patients from sub-Saharan Africa 0.41 (0.26-0.63, p<0.0001), and for patients from Western Europe/North America/Australia combined 0.41 (0.21-0.81, p=0.01), as compared to Dutch patients. There was an interaction effect between calendar year of starting the new cART and the reason for stopping the first-line cART. Patients who switched because of therapy failure had a lower probability of reaching a plasma level of <50 HIV RNA copies/ml after 24 weeks of the new cART than did patients who switched because of toxicity. However, patients who switched because of failure prior to 2003 had an even lower probability of reaching that level than did patients switching for the same reason in or after 2003; the ORs compared to switching because of toxicity in or after 2003 were 0.28 (0.17-0.47, p<0.0001) and 0.61 (0.37-1.00, p=0.049). The OR of switching because of failure before 2003 compared to a switch owing to failure in or after 2003 was 0.47 (0.25-0.85, p=0.01). There was no significant difference in probability of reaching an HIV RNA plasma concentration <50 copies/ml in patients switching because of toxicity before 2003 and in those switching because of toxicity in or after 2003. The ORs of patients with a therapy interruption were significantly lower compared to those of patients with no interruption.

Time to change of the new cART regimen

Figure 6.1 shows the cumulative incidence of patients stopping or changing the new cART regimen for any reason and according to specific reasons. Within 1 year after starting the new cART regimen, 41.4% (95% CI 40.0-42.8) of the patients had stopped or changed the new regimen, and within 3 years this number increased to 67.5% (66.0-68.9). In patients who had switched the first-line regimen because of the simplicity of a new regimen, the percentage who changed the new regimen within 1 year was much lower, 23.8% (20.2-27.9), and 46.0% (41.0-51.3) for a change within 3 years. The major reason for changing the new regimen was related to toxicity. Within 1 year after starting the new cART, 20.4% of the patients had stopped or changed the regimen because of toxicity, and 26.6% changed within 3 years.

In the 2428 patients who had changed the first-line cART because of toxicity or virologic failure, the hazard ratio (HR) of a change in the new regimen for patients starting this new cART in 1997 compared to that for patients starting the new cART in 2004 was 1.59 (95% CI 1.28-1.96; p<0.0001). The hazard of regimen change for patients starting a new cART regimen after 1997 were not significantly different between different calendar years of starting. The hazard ratio of time to change in the new cART for any reason for patients who switched the initial regimen because of failure compared to that for patients who switched because of toxicity was 1.07 (0.94-1.21; p=0.31). A shorter time to change of the new cART regimen for any reason was associated in univariate analyses with infection through heterosexual contact as compared to homosexual contact (HR 1.17, 95% CI 1.05-1.30; p=0.005), sub-Saharan African as compared to Dutch origin (HR 1.21; 1.06-1.38; p=0.006), and younger age (HR per 5 years decrease 1.04 ;1.01-1.06; p=0.002), but in multivariate analyses these variables were no longer significantly associated with time to change.

Variables significantly associated with time to regimen change in multivariate analyses are shown in Table 6.3. Patients with a shorter time on the first-line cART, patients with CD4 counts <200 cells/mm^3 at the start of the new cART, and women had a higher risk for a change in the new regimen. In addition, there was an interaction effect of calendar year of the start of the new cART and the reason for change of initial cART. Time to change of the new cART was not significantly different between patients who had switched because of toxicity and patients who switched in or after 2003 because of virologic failure. However, before 2003 switching because of failure was associated with an increased risk of changing the new cART; before 2003 the HR for switching because of failure compared with switching for the same reason in or after 2003 was 1.44 (1.14-1.82; p=0.003).

Time to toxicity-related change in the new cART

Patients who switched their initial cART to a new simplified regimen had a lower probability of a toxicity-related change within 1 year from the start of the new regimen (11.0%) than did patients who switched because of toxicity (28.3%) or virologic failure of first-line cART (29.9%).

In the 2428 patients who switched to a new regimen because of virologic failure or toxicity of the first-line cART, 540 patients changed the new regimen because of toxicity within 1 year after starting. In univariate analyses in these 2428 patients, the hazard of a toxicity-related therapy change from the new cART was lower in patients switching because of virologic failure with the first-line regimen than in those switching because of toxicity (HR 0.62 [95% CI 0.48-0.80, p=0.0002]). A body weight of less than 60 kg at the start of the new cART (HR 1.53, 1.10-2.13, p=0.01, compared to 70-80 kg) and a therapy interruption between first-line and the new cART regimen (HR 1.25, 1.12-1.40, p<0.0001 compared to no interruption) were associated with a shorter time to a toxicity-related change of the new regimen univariately, but these associations were not significant in multivariate analyses. The results of the multivariate analyses are shown in Table 6.3. The hazard ratio of a toxicity-related change in the new regimen for patients who changed their first-line cART because of virologic failure compared to those who changed because of toxicity was 0.79 (0.61-1.03, p=0.08). An increased risk of a toxicity-related therapy change within 1 year after starting the new cART was associated with female gender, a longer time spent on first-line cART, and an earlier calendar year of starting the new cART. The hazard ratio of a toxicity-related regimen change comparing the start of the new cART in or before 2000 with the start after 2000 was 0.64 (0.54-0.77, p<0.0001). Because early modification of first-line cART is mainly related to toxicity, we also ran a model excluding the time spent on first-line cART. The HR of patients who switched the first-line regimen because of virologic failure compared to those who switched because of toxicity changed to 0.65 (0.50-0.84, p=0.001). There was no evidence for an interaction effect between the reason for switching first-line cART and calendar year of starting the new cART regimen on the time to a toxicity-related change of therapy.

Discussion

Patients who switched the first-line cART because of virologic failure in or after 2003 compared to those who switched before 2003 had a higher probability of reaching a plasma HIV RNA of <50 copies/ml at week 24 of a new combination of cART, and they had a lower probability of changing the new regimen for any reason. The risk of a toxicity-related regimen change decreased with later calendar years of starting the new cART, most notably after 2000. These results indicate an improvement in HIV treatment after changing the initial cART over the years. This could be due to the introduction in recent calendar years of more virologically effective, less toxic drugs with a lower pill burden[38]. Genotypic

resistance-guided HIV-treatment decisions for patients with a plasma viral load >1000 copies/ml could have contributed to the better short-term virologic efficacy[39], whilst therapeutic drug monitoring[40] could have contributed to the decrease in toxicity-related regimen changes.

We looked at the short-term response to cART after changing the initial cART as a marker for further disease progression. Short-term response to first-line cART has been shown to be prognostic for disease progression[25], but it is unknown if the same holds true for cART regimens after the first-line cART is changed.

We found that a shorter time on the initial cART regimen was associated with a shorter time on the new cART. Another study found early modification of first-line cART to be associated with a poorer clinical outcome[144]. A change within the first few months after starting cART initially has been related mainly to toxicity. Female patients had a higher risk of changing the first-line cART, and remained at higher risk for a toxicity-related change on the new regimen. Individualizing patients' regimens and dosage to optimize plasma drug concentrations is therefore important, especially in female patients, to avoid early modification of the regimen because of toxicity. Multiple switches of cART do not seem to be associated with short-term decreased restoration of CD4 counts[145] but might affect adherence, virologic outcome, and further disease progression.

Therapy interruptions were associated with a lower probability of reaching plasma HIV RNA concentrations below 50 copies/ml at week 24. Structured[146, 147] and unstructured therapy interruption[148] have been associated with progression of disease and should therefore be avoided.

Patients originating from regions other than the Netherlands were at increased risk of not reaching a plasma HIV RNA concentration of <50 copies/ml on first-line cART (Chapter 5) and of not reaching a concentration of <50 copies/ml on the new cART combination; these risks were independent of the reasons for the switch from first-line cART. It is possible that adherence plays a major role, and measures to improve adherence in these patient groups should be taken.

Comparing long-term marker responses on first-line cART or on subsequent cART regimens is more complicated than comparing short-term marker responses because of the frequent changing of regimens. Patients who change therapy are more likely to have a poorer marker response[149]. Changing of the regimens depends not only on the lack of response and on the toxicity of drugs, but also on the availability of options for change.

In summary, short-term virologic response on a new cART combination after changing the initial cART regimen because of failure has improved in later calendar years, but non-Dutch patients have a poorer short-term virologic response compared to that of Dutch patients. Patients who have started a new cART in later calendar years are at decreased risk for toxicity-related regimen changes after a switch from first-line cART.

		Reason for change of first-line cART					
		Virological failure		Toxicity		Other	
		N	%	N	%	N	%
Total		446	9.0	1982	40.1	2519	50.9
Male gender		359	80.5	1519	76.6	1914	76.0
Transmission risk group	Homosexual	229	51.3	1076	1076	1272	50.5
	IDU	11	2.5	82	82	120	4.8
	Heterosexual	177	39.7	693	693	945	37.5
	Blood-blood	6	1.3	24	24	45	1.8
	Other	23	5.2	107	107	137	5.4
Region of origin	Netherlands	236	52.9	1129	1129	1367	54.3
	Caribbean/Latin America	58	13.0	225	225	236	9.4
	Other	24	5.4	151	151	184	7.3
	Sub-Saharan Africa	109	24.4	332	332	533	21.2
	Western Europe/North America/Australia	19	4.3	145	145	199	7.9
HIV RNA <500 copies/ml at start new cART		115	25.8	1194	60.2	1729	68.6
CDC-C event prior to start new cART		175	39.2	643	32.4	743	29.5
New cART	unboosted PI	54	12.1	394	394	300	11.9
	boosted PI	225	50.4	452	452	591	23.5
	NNRTI	127	28.5	954	954	1145	45.5
	PI + NNRTI	29	6.5	58	58	144	5.7
	NRTI	11	2.5	124	124	339	13.5
No interruption between first-line and new regimen		373	83.6	1465	73.9	2031	80.6
Calendar year of starting new cART	<=1997	30	6.7	157	157	52	2.1
	1998-2000	118	26.5	611	611	697	27.7
	2001-2003	145	32.5	593	593	879	34.9
	2004-2006	153	34.3	621	621	891	35.4
		Med	**IQR**	**Med**	**Med**	**IQR**	**IQR**
Age at starting new cART		38.6	33.3-44.4	39.2	33.4-46.8	38.7	32.8-46.0
CD4 cell count at start new cART (cells/mm^3)		261	139-427	302	180-490	350	210-550
Months on initial cART		11	5-23	4	1-14	11	4-26

Table 6.1: Clinical and demographic characteristics at the start of the new cART in 4947 patients according to reason of switch of the first line cART.

cART: combination antiretroviral therapy; IDU: injecting drug use; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; Med: median; IQR: interquartile range

		Multivariate		
		OR	**95% CI**	**p**
Region of origin	Netherlands	1.00		
	Caribbean/ Latin America	0.39	(0.24-0.62)	<0.0001
	Other	0.59	(0.30-1.13)	0.11
	Sub-Saharan Africa	0.41	(0.26-0.63)	<0.0001
	Western Europe/North America/ Australia	0.41	(0.21-0.81)	0.01
Age at the start of the new cART (5 yr increase)		1.10	(1.00-1.21)	0.04
Time between first-line and new cART	No interruption	1.00		
	1-14 days	0.41	(0.25-0.68)	0.0005
	2 weeks -3 months	0.39	(0.23-0.69)	0.001
	≥3 months	0.47	(0.26-0.84)	0.01
Calendar year of starting	≥2003 toxicity	1.00		
the new cART and	<2003 toxicity	1.28	(0.85-1.93)	0.23
reason for switching first-line	≥2003 failure	0.61	(0.37-1.00)	0.049
	<2003 failure	0.28	(0.17-0.47)	<0.0001

Table 6.2: Results of multivariate logistic regression model of the probability of reaching an HIV RNA plasma concentration of <50 copies/ml at 24 weeks after starting the new cART.
OR: odds ratio; CI: confidence interval; cART: combination antiretroviral therapy

		Change for any reason			Toxicity related change		
		HR	95% CI	p	HR	95% CI	p
Gender	Male	1.00			1.00		
	Female	1.25	(1.11-1.40)	0.0002	1.39	(1.15-1.68)	0.0007
CD4 count at the start	<50	1.30	(1.06-1.61)	0.01			
of the new cART (cells/mm^3)	50-200	1.15	(1.00-1.33)	0.049			
	50-200	1.00					
	350-500	1.06	(0.90-1.24)	0.49			
	≥500	1.11	(0.95-1.30)	0.17			
Calendar year of	≤1997				1.90	(1.29-2.78)	0.001
starting the new cART	1998				2.07	(1.43-2.98)	0.0001
	1999				1.49	(1.00-2.22)	0.051
	2000				1.93	(1.34-2.78)	0.0005
	2001				1.22	(0.82-1.82)	0.33
	2002				1.18	(0.78-1.78)	0.44
	2003				1.35	(0.90-2.01)	0.14
	2004				1.00		
	≥2005				1.20	(0.84-1.72)	0.32
Reason for switching first-line cART	Toxicity				1.00		
	Failure				0.79	(0.61-1.02)	0.08
Calendar year of starting the	≥2003 toxicity	1.00					
new cART and reason	<2003 toxicity	0.99	(0.88-1.11)	0.81			
for switching first-line	≥2003 failure	1.03	(0.83-1.27)	0.80			
	<2003 failure	1.49	(1.25-1.78)	<0.0001			
HBV	Negative				1.00		
	Positive				0.56	(0.36-0.87)	0.01
Months spent on first line cART	<3	2.13	(1.86-2.44)	<0.0001	2.04	(1.63-2.56)	<0.0001
	3-12	1.44	(1.25-1.65)	<0.0001	1.35	(1.06-1.72)	0.01
	>12	1.00			1.00		

Table 6.3: Results of multivariate proportional hazard regression of the time to the first change in the cART regimen (left) and time to toxicity-related change (right).

*HR hazard ratio; CI: confidence interval; cART: combination antiretroviral therapy; HBV: hepatitis B virus.

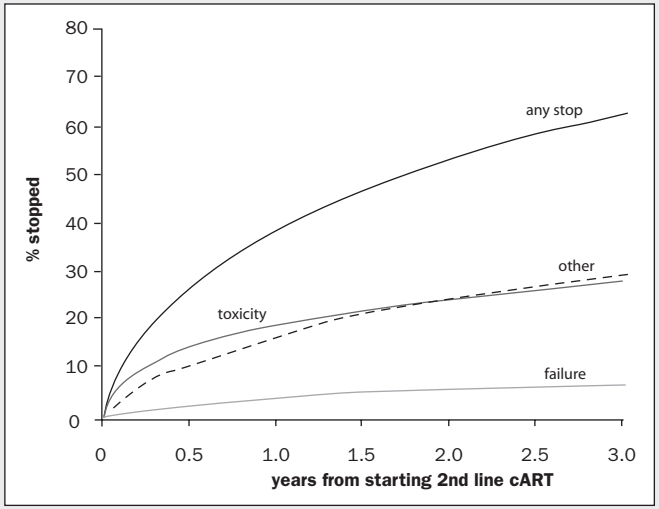


Figure 6.1: Cumulative incidence of change in the new combination antiretroviral therapy (cART) regimen

Resist

tance

Trends in resistance over time

Ard van Sighem

Introduction

Although treatment with combination antiretroviral therapy (cART) generally suppresses plasma HIV RNA levels below the quantification limit of currently used assays, the virus is still replicating, albeit at a lower level[41, 42]. Thus, a strong, but incomplete, suppression of HIV replication may be achieved with prolonged treatment with cART. However, if adherence to treatment is nonoptimal, it may lead to a selection of HIV-1 viruses that escape cART-induced suppression because of resistance[43, 44]. The presence of resistant strains of virus limits future therapy options and may lead to a worsened prognosis[45]. The prevalence of resistant virus in patients who fail on therapy may be as high as 80%[46-48].

Resistant strains of virus may also be transmitted to uninfected patients. In recent years, the prevalence of drug-resistant viruses in newly infected patients in Europe and North America has varied between 5% and 25%. After 1998, transmission of resistant virus strains was observed in 6% of newly infected participants of the Dutch Amsterdam Cohort Studies[49].

In this chapter, we present an update on the transmission of resistant virus strains in the Netherlands. In addition, the prevalence of resistance in the cART-treated population is described.

Methods

Resistance measurements were based on isolation of HIV-1 RNA in plasma of patients and amplification of the protease gene and part of the reverse transcriptase (RT) gene of the virus. HIV-1 RT and protease were genotyped with the use of the amplified genes in a sequencing procedure. Sequences were compared to subtype B wild-type virus and scanned for specific mutations at codons known to be associated with resistance to the three major classes of anti-HIV drugs: nucleoside RT inhibitors (NRTI), non-nucleoside RT inhibitors (nNRTI), and protease inhibitors (PI).

Mutations conferring resistance to NRTI included M41L, A62V, K65R, D67N, K70R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, T215D/N/S/C/E (denoted T215X), K219Q/E, and an insertion after position 69. Mutations conferring nNRTI resistance included L100I, K103N, V106A/M, V108I, Y181C/I, Y188C/L/H, G190S/A, P225H, M230L, and P236L. The major PI resistance-associated mutations were D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, V82A/F/T/S, I84V, N88S, and L190M[204]. A genotypic resistance interpretation algorithm developed by Stanford University was used to assign a drug penalty score for each mutation associated with drug resistance[205]. The total score for a drug was determined by summing all individual mutation scores and was then translated into an inferred drug susceptibility, according to a 5-level scheme: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance.

Transmission of drug-resistant virus strains was studied in two separate patient groups: those with a recent infection or those with a new HIV diagnosis. Patients with a recent infection were diagnosed either during the acute infection or had tested positive for HIV-1 less than 2 years after their last negative test. All other patients with a known positive test for HIV-1 were assigned to the group with new diagnoses. For both groups, an available sequence within one year after diagnosis and before the initiation of antiretroviral treatment was required.

Data on viral load measurements were used to define the start and end point of failures that occurred after initiation of antiretroviral treatment. For the present study, failure was defined as at least one viral load measurement above 500 copies/ml. A period of failure was considered to start at the midpoint of the interval

between the last measurement below 500 copies/ml and the first one above that level. Analogously, the period of failure was considered to end at the midpoint of the interval between the last measurement above 500 copies/ml and the first one below that level. It should be noted that this definition of failure did not take into account the use of therapy. The annual proportion of failing patients, which was corrected for therapy use, was calculated as the ratio of the number of patients failing to the number of patients being followed during the year.

The annual prevalence of high-level resistance was calculated as the prevalence of resistance amongst the patients who experienced virological failure and who were tested for resistance. The maximum resistance score for individual drugs from previous resistance tests was carried forward. Only genotypic sequences were used that had been obtained during treatment or, at most, 2 weeks after cessation of therapy, thus allowing for uncertainties in the date at which therapy was stopped. Patients were considered resistant to a class of antiretroviral drugs if they had high-level resistance to at least one drug from the class. Lamivudine and emtricitabine were considered as a separate class.

A logistic model was used to analyse the probability of having a genotypic resistance test during a period of failure, adjusting for region of origin, transmission route, age, viral load, CD4 count, hospital, year of failure, year of start of cART, and pre-treatment with non-cART regimens. To adjust for testing bias, estimates of resistance prevalences were weighted by the inverse of the probability of having a resistance test.

For proportions, exact confidence intervals were calculated; they were compared by a chi square test or, if sample sizes were small, by Fisher's exact test. For continuous variables, medians were reported with the interquartile range (IQR).

Results

Transmission of drug-resistant virus

Table 7.1 shows the characteristics of both the 459 recently infected patients and the 1153 who were newly diagnosed and had a resistance test within 1 year after diagnosis. The majority of the recently infected patients were men of Dutch origin who were infected by homosexual contact, which totalled 290 patients (63.2%) whereas, in the group of newly diagnosed patients, a larger proportion of patients were women originating from sub-Saharan Africa who were infected via heterosexual contact. Between 2003 and 2006, 1080 sequences were obtained in the combined group of newly diagnosed and recently infected patients. During the same period, there were 3968 HIV diagnoses, as shown in Table 4.3. Hence, a sequence was obtained for 27.2% of the diagnosed patients.

Amongst the 459 recently infected patients, resistance-associated mutations were found in 25 patients (5.4%), of whom 5 were infected during or before 1996. The number of patients with recent infections with a sequence between 1994 and 2001 was limited, and as a result, the percentage with resistance fluctuated between 0% and 20% (Figure 7.1). After 2001, resistance was found in 16 of the 327 recently infected patients (4.9%, 95% CI 2.8–7.8).

Of the 327 patients with a recent infection after 2001, 321 were susceptible to all protease inhibitors, 309 to all NRT inhibitors, and 321 to all nNRT inhibitors. Two patients (0.6%) had intermediate or high-level resistance to at least one protease inhibitor, 8 patients (2.4%) to at least one NRTI, and 4 patients (1.2%) to at least one nNRTI. Overall, 11 patients (3.4%) had intermediate or high-level resistance to at least one drug. One patient, who was infected at the end of 2004 or early 2005, had high-level resistance to all drug classes.

Resistance-associated mutations were found in 92 (8.0%) of 1153 newly diagnosed patients. The majority of the resistant sequences, 81 (88%), were obtained from the

935 patients diagnosed during or after 2002. The annual percentage of transmissions of resistant virus strains varied between 0% and 10% (Figure 7.1). After 2001, the proportion of patients with at least one mutation was 8.7% (95% CI 6.9–10.7), slightly higher than in patients with a recent infection (p=0.03). Amongst the 484 patients infected via homosexual contact, 58 (12.0%) had at least 1 mutation, compared to 18 (5.2%) of the 346 patients infected via heterosexual contact (p<0.001). Resistance was also more common amongst patients infected with a B subtype virus (10.6%), compared to those with a non-B subtype (4.0%) (p=0.001).

In the group of 935 patients who were diagnosed after 2001, intermediate or high-level resistance to protease inhibitors was found in 7 (0.7%) patients, to NRT inhibitors in 27 (2.9%) patients, and to non-nucleoside RT inhibitors in 20 (2.1%) patients. These proportions did not differ from those observed in patients with a recent infection (p>0.3). In total, 44 (4.7%) patients had intermediate or high-level resistance to at least one antiretroviral drug. Two patients had high-level resistance to drugs from all three classes.

Resistance during treatment

The annual proportion of pre-treated patients who failed on cART declined from 60% in 1997 to 19% in 2006 (14% in 2007). During the same period, the proportion of previously therapy-naïve patients who experienced failure remained between 10% and 14%. In the group of pre-treated patients, the fraction of failing patients from whom a sequence was obtained increased from 9% in 1997 to 28% in 2003, but the fraction declined thereafter to 9% in 2006. In the therapy-naïve group, the fraction of patients with a sequence was 27% in 2003, and it decreased to 11% in 2006. Overall, 95% of the sequences obtained from pre-treated patients and 77% of those from therapy-naïve patients contained one or more resistance-associated mutations.

In the total population, 2655 sequences were obtained after the start of cART, of which 1345 (50.7%) were obtained from pre-treated patients and 1310 (49.3%) from previously therapy-naïve patients. Of these sequences, 2027 (76.3%) contained at least one resistance-associated mutation, whereas the rest, 628 (23.7%), contained none. Resistance was found in 1189 (88.4%) of pre-treated patients and in 838 (64.0%) of the therapy-naïve patients (p<0.001).

The nature of drug resistance observed per calendar year changed over time (Figure 7.2). The proportion of patients with high-level resistance to zidovudine decreased from 53% (95% CI 41-64) in 1996 to 15% (9-23) in 2006, whilst the proportion of those with resistance to stavudine decreased from 46% (35-58) in 1996 to 12% (7-19) in 2006 (p<0.001). Meanwhile, the proportion of patients with resistance to lamivudine (and emtricitabine) did not change significantly over time (p=0.8), that is, 56% (45-67) in 1996 and 66% (57-74) in 2006. Also, resistance to didanosine did not change over time (p=0.2), whereas resistance to abacavir declined (p<0.001). High-level resistance to tenofovir was rare, 2.5% (0.3-9) in 1996 and 0.8 (0.0-5) in 2006 (p=0.06). However, when intermediate and high levels of resistance to tenofovir were combined, the level of resistance was 54% (42-65) in 1996 and declined to 21% (14-29) in 2006 (p<0.001).

Resistance to nNRTIs increased after the introduction of nevirapine and efavirenz as part of the cART regimen in about 1998. High-level resistance to nevirapine increased from 44% (34-54) in 1999 to 60% (51-69) in 2006. High-level resistance to efavirenz was less common; it increased from 33% (24-43) in 1999 to 44% (35-54) in 2006.

Resistance to protease inhibitors also increased after the widespread introduction of PIs in about 1996. High-level resistance to the older generation of PIs, including nelfinavir, saquinavir, and indinavir, peaked about 1999 and became less common thereafter. Less than 10% of

the sequences were fully resistant to lopinavir, tipranavir, and darunavir. In 2005, intermediate or high levels of resistance to lopinavir were found in 26% of the sequences, to tipranavir in 21%, and to darunavir in 17%.

Of the 10,136 periods of failure that were used in the logistic model, 2006 (19.8%) included a resistance test. Weighting was applied to the overall prevalence of resistance between 2000 and 2005. The unweighted estimate of resistance to lamivudine was 68.9%, whereas the weighted estimate was 70.3%. For the other nucleoside RT inhibitors, class resistance was found in 39.7% of the patients without weighting and in 42.1% with weighting. Resistance to non-nucleoside RT inhibitors increased from 48.9% to 50.0%, whilst resistance to protease inhibitors increased from 36.7% to 40.0%.

As of June 2007, a total of 10,095 HIV-1-infected adult patients were still being actively followed. In 1220 (12.1%) of those patients, at least one sequence had been obtained with resistance-associated mutations, and of those 1220, 1064 (87.2%) had high-level resistance to at least one antiretroviral drug. The number of patients with high-level resistance to drugs from one class was 436 (35.7%). Resistance to drugs from two classes was found in 462 patients (37.9%), whereas 168 (13.8%) were found to be resistant to drugs from all three classes. High-level resistance to at least one NRTI was found in 937 (76.8%) of the patients, to at least one nNRTI in 603 (49.4%), and to at least one PI in 330 (27.0%). Table 7.2 shows the inferred resistance level for each individual antiretroviral drug in the group of 1220 patients.

Discussion

The rate of transmission of drug-resistant HIV-1 in the Netherlands remains low. In the current analysis, only 4.8% of the recently infected patients had a resistant strain, but amongst newly diagnosed patients, a higher percentage of resistance was found. These percentages are comparable with those observed in other Western countries, although increasing percentages of resistance have been reported elsewhere[50-54]. When mutations were translated into a predicted susceptibility score, approximately 4% of the patients in both groups were infected with a strain that carried intermediate or high-level resistance to at least one antiretroviral drug. Hence, although a major resistance-associated mutation is present, it is not necessarily a sign of full resistance.

The higher proportion of newly diagnosed patients with resistance-associated mutations than that seen in recently infected patients was found to be due to a higher percentage of patients with an M41L mutation, either as an only mutation in RT or in combination with a T215X mutation. The M41L mutation has been shown to be stable in patients infected with a resistance-carrying virus strain[55]. Most likely, the patients harbouring an M41L mutation were infected in the 1990s, when resistance to zidovudine and stavudine was most abundant.

The stable and low level of transmission of resistant virus strains is somewhat surprising given the increase in the number of cART-treated patients since 1996. One explanation is that the proportion of patients failing therapy has decreased over time, and, as a consequence, the reservoir of possibly infectious patients – those having RNA levels above 500 copies/ml – is relatively small. On the other hand, it also confirms that most HIV infections are transmitted from HIV-infected individuals who are untreated or are not yet even aware of their infection (see chapter 13)[56, 57].

As observed previously, the prevalence of resistance to specific antiretroviral drugs has changed over time in correlation with changes in antiretroviral drug use[58]. Thus, resistance to nNRTIs has increased, whilst resistance to the older generation of protease inhibitors

has declined. Surprisingly, high-level resistance to tenofovir, which is by now widely used in the Netherlands, has remained at a low level. This can be explained partly by the intermediate level of resistance that is assigned to the tenofovir-related K65R mutation by the Stanford algorithm. But, even intermediate resistance to tenofovir gradually declined since 1996. The higher prevalence in the 1990s was most likely the result of cross-resistance with didanosine and abacavir.

It should be noted that the definition of failure was different from the one used in last year's report[163]. In the present report, one measurement above 500 copies/ml was considered adequate, whereas previously, two consecutive measurements were required. As a result, the percentage of failing patients increased by a factor of 1.2 to 1.3. The reason for changing the definition is that during failures associated with a single viral load measurement, it was not uncommon to perform a resistance test.

It was found that almost 11% of the patients who were still being followed by the HIV Monitoring Foundation harboured virus strains with high-level resistance to at least one antiretroviral drug. This percentage is probably an underestimation since other cohorts with more frequent sampling for resistance have found prevalences of approximately 25%[44, 206]. The estimation of prevalence of resistance amongst failing patients, however, seemed to be very accurate since similar results were produced by taking into account testing bias.

	new diagnoses, N=1153		recent infections, N=459	
	N	**%**	**N**	**%**
male gender	885	76.8	422	91.9
region of origin				
the Netherlands	639	55.4	352	76.7
sub-Saharan Africa	206	17.9	16	3.5
transmission category				
MSM	616	53.4	360	78.4
heterosexual contact	390	33.8	61	13.3
injection drug use	18	1.6	11	2.4
other/unknown	129	11.2	27	5.9
non-B subtype	325	28.2	77	16.8
≥ 1 RAMs				
any drug	92	8.0	25	5.4
PIs	15	1.3	5	1.1
NRTIs	66	5.7	20	4.4
nNRTIs	25	2.2	3	0.7
intermediate/high-level resistance				
any drug	49	4.2	18	3.9
PIs	8	0.7	3	0.7
NRTIs	31	2.7	13	2.8
nNRTIs	20	1.7	5	1.1
	median	**IQR**	**median**	**IQR**
CD4 (10^6 cells/l)	290	120–494	496	350-680
RNA ($\log_{10}$ copies/ml)	4.8	4.2–5.3	4.9	4.2–5.4
age (years)	37.3	30.3–44.4	35.3	30.0–42.4

MSM: men having sex with men; RAM: resistance-associated mutation; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; nNRTI: non-nucleoside reverse transcriptase inhibitor

Table 7.1: Characteristics of both newly diagnosed and recently infected patients at HIV diagnosis.

		susceptible		potential low-level		low-level		intermediate		high-level	
		N	%	N	%	N	%	N	%	N	%
protease inhibitors[a]	fAPV	810	66.4	29	2.4	109	8.9	157	12.9	105	8.6
	IDV	785	64.3	37	3.0	80	6.6	123	10.1	185	15.2
	NFV	746	61.2	3	0.2	24	2.0	107	8.8	330	27.1
	SQV	795	65.2	38	3.1	48	3.9	136	11.2	193	15.8
	LPV	809	66.3	42	3.4	99	8.1	187	15.3	73	6.0
	ATV	759	62.2	29	2.4	113	9.3	184	15.1	125	10.2
	TPV	828	67.9	62	5.1	111	9.1	159	13.0	50	4.1
	DRV	819	67.1	75	6.1	134	11.0	173	14.2	9	0.7
nucleoside RT inhibitors[b]	3TC	269	22.0	34	2.8	40	3.3	36	3.0	840	68.9
	FTC	269	22.0	34	2.8	40	3.3	36	3.0	840	68.9
	ABC	141	11.6	342	28.0	147	12.0	364	29.8	225	18.4
	AZT	481	39.4	25	2.0	108	8.9	247	20.2	358	29.3
	d4T	420	34.4	64	5.2	162	13.3	274	22.5	299	24.5
	ddI	418	34.3	97	8.0	123	10.1	363	29.8	218	17.9
	TDF	518	42.5	112	9.2	206	16.9	356	29.2	27	2.2
non-nucleoside RT inhibitors[b]	EFV	572	46.9	28	2.3	89	7.3	93	7.6	437	35.8
	NVP	549	45.9	43	3.5	12	1.0	5	0.4	610	50.0

fAPV: fos-amprenavir; IDV: indinavir; NFV: nelfinavir; SQV: saquinavir; LPV: lopinavir; ATV: atazanavir; TPV: tipranavir; DRV: darunavir; RT: reverse transcriptase; 3TC: lamivudine; FTC: emtricitabine; ABC: abacavir; AZT: zidovudine; d4T: stavudine; ddI: didanosine; TDF: tenofovir; EFV: efavirenz; NVP: nevirapine;

[a]protease not available for 10 patients

[b]RT not available for 1 patient

Table 7.2: Number of patients in follow-up in June 2007 with evidence of resistance to specific antiretroviral drugs, according to the Stanford mutation scoring algorithm.

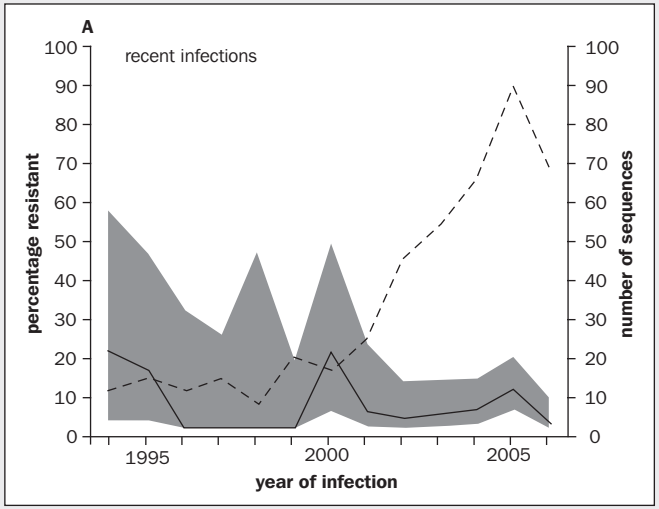
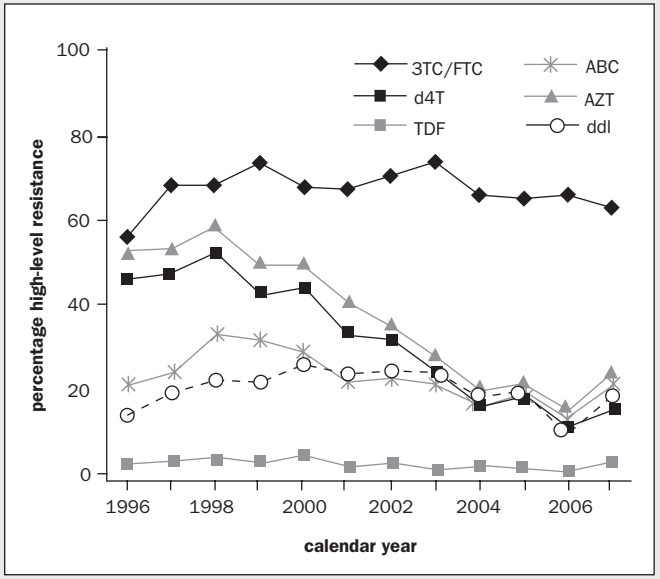
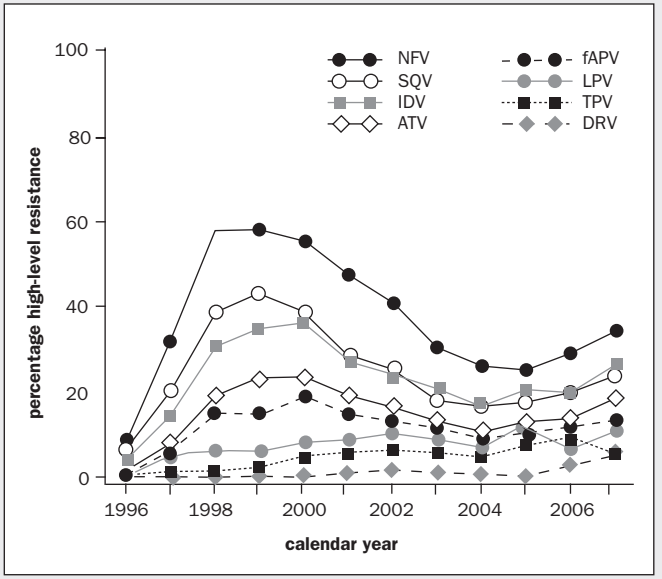


Figure 7.1: Percentage of transmissions of resistant virus as a function of calendar time amongst recently infected (a) and newly diagnosed (b) patients. The black line represents the percentage whilst the grey areas are the 95% confidence intervals. The dashed line is the number of sequences that was obtained in each year (right axis).





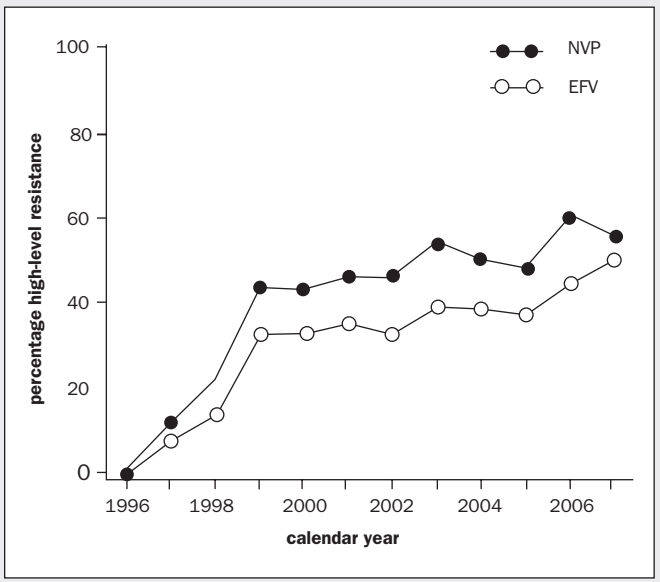


Figure 7.2: Percentage of patients with high-level resistance, according to the Stanford mutation score algorithm.

NVP: nevirapine; EFV: efavirenz; 3TC/FTC: lamivudine/emtricitabine; d4T: stavudine; ddI: didanosine; AZT: zidovudine; ABC: abacavir; TDF: tenofovir; NFV: nelfinavir; IDV: indinavir; fAPV: fos-amprenavir; TPV: tipranavir; SQV: saquinavir; ATV: atazanavir; LPV: lopinavir; DRV: darunavir.

Pregna

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cART and treatment response in pregnant women

Colette Smit

Introduction

Mother-to-child-transmission (MTCT) is the most important route of HIV transmission amongst HIV-infected children in the Netherlands.

Without intervention, the risk of MTCT in HIV-infected pregnant women is 15% to 20%[150]. HIV-infected women with detectable HIV RNA levels have a high risk of vertical HIV transmission[151]. Also, low CD4 cell counts are a risk factor for MTCT[152]. From 1998 onwards, HIV-infected pregnant women in the Netherlands have been treated with combination antiretroviral therapy (cART) to reduce the maternal viral load. Treatment of HIV-infected women with cART during pregnancy and of newborns in their first weeks of life, in combination with elective caesarian delivery in cases of a detectable maternal viral load, has lowered the risk of MTCT to 2%[60].

In the Netherlands, the number of pregnancies amongst HIV-infected women is highest in those originating from sub-Saharan Africa, but the incidence is increasing amongst HIV-infected women of Dutch origin. Compared to the non-Dutch women, women of Dutch origin are more often aware of their HIV infection when they become pregnant[16]. Nowadays, a large proportion of women who are HIV-infected are diagnosed during their pregnancy as a result of the national HIV pregnancy screening[61], and they start cART for the first time during their pregnancy to prevent MTCT.

CD4 cell count, an important prognostic marker in HIV infection, is affected by pregnancy. Hormones produced during the pregnancy down-regulate the immune response to prevent rejection of the foetus[62]. A decline in CD4 cell counts during pregnancy may be associated with the pregnancy itself and not with the HIV disease progression or with a less effective response to treatment, whereas initiation of cART during pregnancy may increase CD4 cell counts.

In this chapter, we compare the virologic and immunologic response between two groups of women: those who initiated cART before their pregnancy and those who initiated cART during their pregnancy.

Methods

Study population

The study population consisted of all HIV-infected pregnant women who were registered in the HIV monitoring database and then monitored longitudinally. All pregnancies between 1 January 1998 and 1 June 2007 were analysed. We then included only those pregnancies occurring for the first time after the HIV diagnosis.

Data for all registered HIV-positive pregnant women were collected according to the standard HIV monitoring protocol. Since 2006, additional pregnancy-related data have been retrospectively collected. These data include duration of the pregnancy, birth or induced or spontaneous abortion, mode of delivery, and complications. However, the additional pregnancy-related data collection was not yet complete for all pregnant women at the time of our analysis. For the present study, we included the data from only the pregnant women for whom the collection of additional data was complete.

Statistical analyses

Analyses were conducted for HIV-infected pregnant women. We stratified by geographic origin, categorised as Dutch or non-Dutch, and by the time of cART initiation, categorised as before or during pregnancy. Women who started cART before pregnancy were considered to be early initiators of cART, while those who started cART during pregnancy were considered to be late initiators.

The chi square test was used to look for differences between women of different geographic origins in known HIV status before pregnancy, HIV transmission route, time of cART initiation, and presence of

undetectable HIV RNA levels during delivery. Differences in the median age, CD4 cell counts, and HIV RNA levels of pregnant women with different geographic origins were tested with the Wilcoxon-Mann-Whitney test.

The immunologic and virologic trajectories during pregnancy were analysed via a random effect model. Its design allowed for a random intercept for CD4 cell counts and HIV RNA plasma levels per individual. We described time in weeks after the beginning of the pregnancy. When an HIV diagnosis was made during pregnancy, time was still described as weeks from the start of pregnancy, but CD4 cell counts and HIV RNA plasma levels were missing for the first weeks of the pregnancy.
Changes in CD4 cell counts and HIV RNA plasma levels were modelled piecewise. Since changes in CD4 cell counts and HIV RNA plasma levels might have occurred during the pregnancy, the slopes were allowed to change at weeks 20 and 28 of the pregnancy. If HIV RNA levels were below the quantification limit, we took half the quantification limit as the HIV RNA level. HIV RNA $\log_{10}$ values were used instead of absolute values.

Results

Demographic characteristics

Data was collected for a total of 710 pregnancies that occurred amongst 570 women between 1 January 1998 and 1 June 2007.
We selected the first pregnancy for which data was collected (n=570). The majority (85%) of the pregnant women were of non-Dutch origin. Dutch women (77%) were more often aware of their HIV-positive status before their pregnancy than women of non-Dutch origin (48%). Dutch women were significantly older when they became pregnant compared to non-Dutch women. Overall, 85% of the women delivered a baby, whereas 15% of the women underwent an abortion (induced or spontaneous), and these percentages did not differ significantly between Dutch and non-Dutch women.

Treatment

Overall, 509 women used cART; 33% started cART before they became pregnant, and most (57%) started cART during their pregnancy. Of the women who were already using cART before their pregnancy, 59 changed their regimen during the pregnancy. The proportion of women who started cART during pregnancy did not significantly differ between those of Dutch origin and those of non-Dutch origin.
Table 8.2 shows the most commonly used treatment regimens amongst pregnant women between 1998 and 2007. Zidovudine (AZT) / lamivudine (3TC) + nelfinavir was the most frequently prescribed combination for all years, except for 2006. In more recent years, AZT/3TC + nevirapine also was often prescribed (31% in 2002 and 33% in 2003).

CD4 cell counts during pregnancy

The median CD4 cell counts at the beginning of the pregnancy, at week 20, and during delivery are shown in Table 8.1. Dutch women had significantly higher CD4 cell counts at all three time points compared to women of non-Dutch origin.
The piecewise modelled immunologic trajectory during pregnancy amongst HIV-infected women who initiated cART before pregnancy and amongst those who initiated cART during pregnancy is shown in Figure 8.1. In the first 20 weeks of the pregnancy, CD4 cell counts decreased significantly in both groups. Between week 20 and 28, CD4 cell counts started to increase ($p<0.001$), and this increase was more dramatic amongst women who initiated cART during pregnancy. After week 28, CD4 cell counts tended to remain stable, and the slopes between the women who initiated cART before pregnancy and those who initiated treatment during pregnancy did not differ significantly.

Viral load during pregnancy

Table 8.1 shows the median HIV RNA plasma levels at the beginning of pregnancy, at week 20, and at delivery.

HIV RNA plasma levels did not differ significantly at any time during the pregnancy. The piecewise modelled HIV RNA plasma levels stratified by the time of cART initiation (before versus during the pregnancy) are presented in Figure 8.2. Women who initiated cART before their pregnancy had significantly lower HIV RNA levels than those who commenced cART for the first time during the pregnancy. In the first 20 weeks of pregnancy, HIV RNA levels decreased amongst women who initiated cART during their pregnancy ($p<0.001$), but such levels did not change significantly amongst those who were already using cART. Between weeks 20 and 28, a strongly significant decline was seen in both groups. This decline was steeper amongst women who initiated cART during the pregnancy, relative to women who initiated cART before the pregnancy ($p<0.001$). After week 28, the HIV RNA levels started to increase slightly amongst both groups, but this increase was sharper amongst women who initiated cART during the pregnancy ($p<0.001$).

At time of delivery, 63% of the women had an undetectable viral load; this percentage was lower amongst women of non-Dutch origin (49%). Amongst those women who initiated cART before their pregnancy, 70% had undetectable HIV RNA levels at the time of delivery, whereas amongst those who initiated cART during their pregnancy, 64% had undetectable HIV RNA levels at delivery; this difference was not significant.

Discussion

Suppressing HIV RNA levels to prevent MTCT is an important intervention amongst HIV-infected pregnant women. Most of the women in our study delivered with undetectable HIV RNA plasma levels. Women who initiated cART during their pregnancy had higher HIV RNA plasma levels in the first two trimesters of the pregnancy than did those women who initiated cART before they became pregnant, but the HIV RNA plasma levels of both groups reached the same level at the time of delivery.

Dutch and non-Dutch women had similar HIV RNA levels at the beginning of and during pregnancy. However, Dutch women had higher CD4 cell counts during pregnancy compared to women of non-Dutch origin. The majority of non-Dutch women originated from sub-Saharan Africa, and differences in CD4 cell counts probably reflect ethnic differences in CD4 cell counts between women of Dutch and non-Dutch origin.

The decline in CD4 cell count in the first two trimesters of pregnancy amongst women who were already on treatment and amongst those who initiated cART during pregnancy may be explained by hormonal changes. The immune system is altered during the reproductive process, because the reproductive hormones have an immunosuppressive function[62]. This immune suppression does not accelerate the HIV progression, and the increases in CD4 cell counts in the last trimester of the pregnancy have been shown to be pregnancy-related, as well[63]. However, in our study the increase in CD4 cell counts between weeks 20 and 28 amongst women who initiated cART during pregnancy is likely be to a response to treatment, because most women initiated cART between weeks 20 and 28.

The results of this study show a substantial decrease in HIV RNA levels amongst women who initiated cART before their pregnancy, as well as amongst those who started treatment during their pregnancy. The decline in HIV RNA levels was most marked between weeks 20 and 28. According to the current treatment guidelines, initiation of cART is recommended between weeks 20 and 28[64]. A sharp decline in HIV RNA levels was also seen amongst women who were already on cART. This probably reflects a change in regimen to a more effective combination or to a more preferable

combination in pregnancy, or the decline may be due to an earlier temporary interruption of cART by a portion of the women at the beginning of pregnancy, when the embryo is most vulnerable to teratogenic effects of treatment. Use of cART during pregnancy is associated with prematurity, gestational diabetes, and preeclampsia[153]. Combinations including nelfinavir or nevirapine are well tolerated during pregnancy[65]. In the Netherlands, a combination including nelfinavir is the most frequently used regimen amongst pregnant women. Despite the sharp decline in HIV RNA plasma levels amongst pregnant women receiving cART, 30% to 36% still had a detectable viral load during delivery. A recent study showed that a nevirapine-containing regimen was associated with a shorter time to undetectable HIV RNA plasma levels, and the results of that study suggest that a nevirapine-containing regimen is more favourable than a nelfinavir-containing regimen for use in treatment-naïve women with low CD4 cell counts ($<250 \times 10^6$ cells/l)[154]. The risk of MTCT is very low amongst women who are effectively treated with cART,[66] but an elective caesarian section is recommended in the event that the maternal viral load is >50 copies/ml. In our study, 60% of the women with a detectable viral load underwent an elective caesarian section (data not shown).

In conclusion, although women who initiated cART during their pregnancy had higher HIV RNA levels and lower CD4 cell counts compared to those who already were using cART before they became pregnant, the CD4 cell counts and HIV RNA plasma levels at the time of delivery did not differ between the two groups.

		Total	Dutch	Non-Dutch	p-value
Number (%)		570	83 (15)	487 (85)	<0.001
Known HIV infection before pregnancy(%)		298 (52)	64 (77)	234(48)	<0.001
Age at start pregnancy	(median, IQR)	29 (24-33)	30 (26-35)	28 (24-33)	0.006
Transmission route:	Heterosexual (%)	534(94)	71 (86)	463 (95)	0.003
	IDU (%)	5 (1)	3 (4)	2 (0.4)	
	Other/unknown (%)	30 (5)	9 (2)	21 (4)	
Start cART	Before pregnancy (%)	186 (33)	38 (46)	148 (30)	0.09
	During pregnancy (%)	323 (57)	38 (46)	285 (58)	
	no cART during pregnancy (%)	61 (11)	7 (8)	54 (11)	
Pregnancy outcome:	Partus**	483 (85)	69 (83)	414 (85)	0.85
	Abortion (%)	85 (15)	14 (17)	71 (15)	
	Unknown (%)	2 (0.4)	0	2 (0.4)	
CD4 cell count at start pregnancy *	(x 10^6 cells/l) (median, IQR)	470 (310-660)	558 (470-905)	410 (296-620)	0.001
CD4 cell count week 20*	(x 10^6 cells/l) (median, IQR)	390 (256-550)	550 (450-730)	367 (240-510)	<0.0001
CD4 cell counts at delivery*	(x 10^6 cells/l) (median, IQR)	450 (310-640)	650 (520-852)	430 (281-590)	<0.0001
HIV RNA level at start pregnancy *	(log_{10} copies/ml) (median, IQR)	2.3 (1.4-3.8)	3.0 (1.4-3.9)	2.2 (1.4-3.8)	0.09
HIV RNA level at week 20*	(log_{10} copies/ml) (median, IQR)	2.5 (1.4-3.7)	2.5 (1.4-3.7)	2.5 (1.4-3.8)	0.97
HIV RNA level at delivery*	(log_{10} copies/ml) (median, IQR)	1.4 (1.4-2.4)	1.4 (1.4-2.3)	1.4 (1.4-2.4)	0.19
Undetectable HIV RNA levels at time of delivery (%) ***		292 (63)	54 (65)	238 (49)	0.22

* irrespective to treatment

**includes live births and fetal deaths

*** HIV RNA measurement at time of delivery available for 465 pregnancies

IQR: interquartile range; IDU: injecting drug use; cART: combination antiretroviral therapy

Table 8.1: Demographic and clinical characteristics of HIV-infected pregnant women in the Netherlands.

Total number of pregnant women included in this analysis	N=570	
Most common regimen:		**n/known regimens (%)**
1998	AZT/3TC + NFV	9/20 (45)
1999	AZT/3TC + NFV	13/27 (48)
	AZT/3TC + NVP	3/27 (11)
2000	AZT/3TC + NFV	30/57 (53)
	AZT/3TC + NVP	10/57 (18)
2001	AZT/3TC	4/68 (6)
	AZT/3TC + NFV	31/68 (46)
	AZT/3TC + NVP	12/68 (18)
2002	AZT/3TC + NFV	28/77 (36)
	AZT/3TC + NVP	24/77 (31)
2003	AZT/3TC + NFV	46/106 (43)
	AZT/3TC + NVP	35/106 (33)
	AZT/3TC + LOP/r	6/106 (6)
2004	AZT/3TC + NFV	35/71 (49)
	AZT/3TC + LOP/r	15/71 (21)
2005	AZT/3TC + NFV	16/43 (37)
	AZT/3TC + NVP	5/43 (12)
2006	AZT/3TC + NVP	2/8 (25)
	AZT/3TC + SAQ+RTV	2/8 (25)

AZT: zidovudine; 3TC: lamivudine; NVP: nevirapine; Lop/r: lopinavir/ritonavir; NFV: nelfinavir; IDV: indinavi; SAQ: saquinavir; RTV: ritonavir

Table 8.2: Most commonly used treatment regimens amongst pregnant women, between 1998 and 2007.

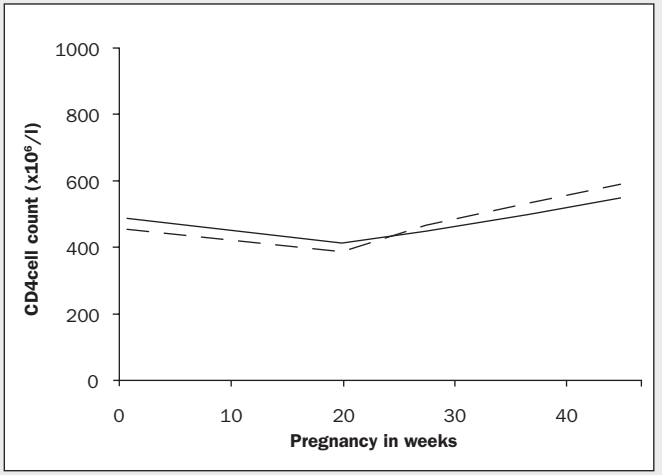


Figure 8.1: CD4 cell counts during pregnancy amongst women who initiated cART before they became pregnant (solid line) and amongst women who initiated cART during their pregnancy (dashed line).

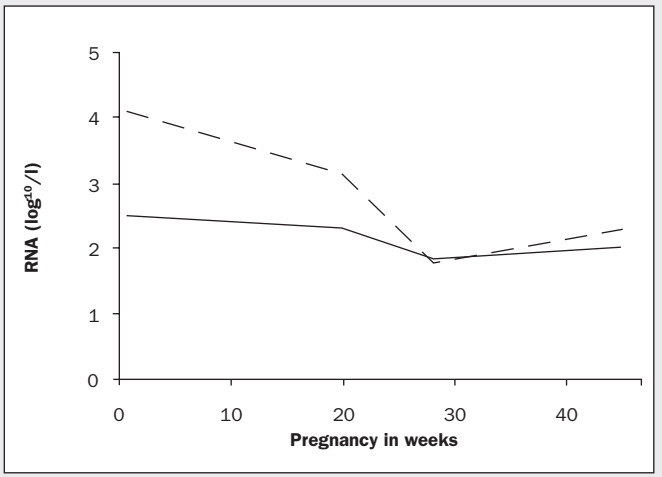


Figure 8.2: HIV RNA levels during pregnancy amongst women who initiated cART before they became pregnant (solid line) and amongst women who initiated cART during their pregnancy (dashed line).

Causes

of death

Changing causes of death with increasing time on cART

Luuk Gras

Introduction

Combination antiretroviral therapy (cART) reduces mortality and morbidity rates in HIV-infected patients[16, 67, 93, 155]. A significant proportion of deaths in HIV-1-infected patients are now caused by non-HIV-related events[67, 68]. Therefore, monitoring causes of death may help to target interventions if certain causes of death become predominant[69, 156].

The decision when to start cART is based on a trade-off between possible complications of long-term antiretroviral drug use[157-160] and the benefits of the timely reversal of the deterioration of the immune system. Dutch guidelines[126] recommend starting cART whilst CD4 cell counts are still at least 200 cells/mm^3. This threshold stems from the results of studies showing that delaying the start of cART until CD4 cell numbers decline below 200 cells/mm^3 is associated with faster disease progression and death[92, 161, 162]. Nevertheless, nearly 50% of patients starting cART do so when CD4 cell counts are below 200 cells/mm^3 [163].

Here we evaluate differences in the proportion of patients who start cART with a CD4 count below 200 cells/mm^3 as well as mortality and morbidity rates after the start of cART, according to calendar year and demographic and clinical characteristics at the start of cART. In addition, we compare causes of death after the start of cART in HIV-1-infected patients who were previously antiretroviral therapy-naïve to the causes of death in the general Dutch population.

Methods

Study population and endpoints

Patients with HIV-1 who commenced cART between 1 July 1996 and 31 December 2006 were selected from the AIDS Therapy Evaluation in the Netherlands (ATHENA) observational cohort[164]. They were 16 years of age or older and antiretroviral therapy-naïve at the start of cART, which was defined as a combination of 3 or more antiretroviral drugs from 2 or more drug classes or a combination of 3 or more nucleoside reverse transcriptase inhibitors (NRTI) including tenofovir or abacavir. Death and new AIDS-defining events occurring after the initiation of cART were the two primary endpoints. In univariate analyses, we evaluated the probability of death and of AIDS occurring within 10 years after cART initiation. On the basis of clinical data at the time of death, causes of death were classified as HIV-related, non-HIV-related, or therapy-related. We also classified causes of death according to the Coding of Death in HIV (CODE) scheme[165], except for Hodgkin's lymphoma, which was classified as a non-AIDS-defining malignancy. In order to compare later with earlier calendar years of cART initiation, we restricted the multivariate analyses to endpoints occurring within 3 years of starting cART.

Statistical analysis

The chi^2 and Kruskall–Wallis tests were used to assess differences between baseline strata. Univariate and multivariate Cox proportional hazards models were used to assess the effect of baseline characteristics on time to death and time to the first new CDC-C event within 3 years after the start of cART. The cumulative incidence function of competing causes of death were modelled and plotted[142, 143].

The CD4 cell count at the start of cART was missing for 9.9% of the patients included in the multivariate analyses, and the HIV RNA plasma level was missing for 13.2% of the patients. In order to use complete data procedures and obtain statistically valid estimates of parameters, we imputed new values for these missing observations with multiple imputation. Imputation is the practice of substituting missing data with plausible values. Instead of substituting a single value for each missing value, multiple imputation[166, 167] replaces each missing value with a set of plausible values that represent the uncertainty about the correct value to impute. For the analyses in this chapter, we imputed

missing data 5 times, thus creating 5 different data sets. Each data set was then analyzed by standard methods, and the results were combined to produce estimates and confidence intervals that incorporated missing-data uncertainty.

A Markov chain Monte Carlo (MCMC) method[168] that assumes multivariate normality was used to impute values for missing CD4 counts (in log cells/mm^3) and missing HIV RNA plasma levels (in $\log_{10}$ copies/ml) at the start of cART. The method took into account the dependency of CD4 cell count and HIV RNA plasma concentration at the start of cART on the following variables: gender, calendar year of starting cART, CDC-C or CDC-B diagnosis prior to the start of cART, age at the start of cART, cART started during a pregnancy or primary infection, transmission risk group, AIDS diagnosis or death within one year after starting cART, and region of origin. The CD4 cell count was back transformed after imputation into cells/mm^3.

The following variables were associated with time to death and new AIDS-defining events after the start of cART: gender; age at the start of cART; clinical stage at the start of cART (CDC-C, CDC-B, and CDC-A); category of CD4 cell count at the start of cART (0-50, 50-200, 200-350, 350-500, and ≥500 cells/mm^3); category of HIV RNA at the start of cART (<4, 4-5, and ≥5 $\log_{10}$ copies/ml); hepatitis B co-infection (positive hepatitis B surface antigen [HBsAg] test); hepatitis C (HCV) co-infection (either a positive HCV antibody or positive HCV RNA test result); region of origin (Netherlands; Caribbean/Latin America; sub-Saharan Africa; Western Europe, North America, and Australia combined; and other). Age, CD4 count, and HIV RNA plasma concentration at the start of cART were also modelled continuously with cubic splines with knots at the 5th, 25th, 50th, 75^{th,} and 95th percentile[169, 170]. In the multivariate analysis of time to death, patients with specific CDC-C events prior to the start of cART or within the first 3 years after the start were compared to patients without a CDC-C event by time-dependent variables. Variables included in multivariate analyses with a p value of 0.20 or higher were excluded from the final model.

Results

CD4 cell count at the start of cART

Between 1 July 1996 and 31 December 2006 7655 HIV-infected patients started cART. Table 9.1 shows that the majority were male (75.2%) and originated from the Netherlands (52.8%). Of the 874 patients of Caribbean/Latin American origin, 297 were from Caribbean countries and 577 from Latin America. The majority of the 562 patients in the Western Europe/North America/Australia group were from Western Europe (444); 101 North American and 17 Australian patients comprised the remainder. A CDC-C event before the start of cART occurred in 28.7% of patients; the most frequent CDC-C events were *Pneumocystis carinii* pneumonia in 691 patients, tuberculosis in 390, Kaposi's sarcoma in 307, toxoplasmosis in 174, candidiasis infection in 134, non-Hodgkin's lymphoma in 111, and wasting syndrome in 109 patients.

The percentage of patients starting cART during a pregnancy increased from 0.2% in 1996-1997 to 8.4% in 2004-2006 ($p<0.0001$). The percentage of patients starting cART during primary infection also increased from 2.2% in 1996-1997 to 6.3% in 2004-2006 ($p<0.0001$).

The median age at the start of cART was 37 years, and median HIV RNA concentration in plasma was 5.0 $\log_{10}$ copies/ml. The median CD4 count fluctuated from 250 in 1996-1997 to 190 in 1998-2000, 180 in 2001-2003, and 190 cells/mm^3 in 2004-2006 ($p<0.0001$). Table 9.2 shows that, of the patients for whom a CD4 cell count at the start of cART was available, in 1997 37.5% started cART below the threshold of 200 CD4 cells/mm^3, compared to, on average, 52.9% in the period 2000-2006 ($p<0.0001$).

After multiple imputation of missing pre-cART CD4 counts and HIV RNA measurements, the univariate odds ratio (OR) of starting cART below the 200 cells/mm^3 threshold was 0.52 (95% confidence interval [CI] 0.41-0.66, p<0.0001) for a patient starting in 1997 compared to a patient starting in 2000. The OR for patients starting in 2006 compared to that in 2000 was 0.78 (0.62-0.98, p=0.04). Odds ratios in multivariate analyses, adjusting for demographic variables (region of origin, age at the start of cART, proportion of pregnant women, and transmission risk group), were similar to those obtained in univariate analyses (Table 9.3). Patients originating from regions other than the Netherlands/Western Europe/North America, patients of older age, and patients from the unknown/other transmission risk group were at an increased risk of starting cART with a CD4 count <200 cells/mm^3. Women starting cART during a pregnancy were at a decreased risk of starting below 200 cells/mm^3 compared to non-pregnant patients (OR 0.21 [0.16-0.28], p<0.0001). No significant interaction was found between the risk of starting cART with <200 CD4 cells/mm^3 and the calendar year of starting cART and transmission risk group, gender, age, or region of origin.

Cause of death

During 36,392 person-years of follow-up after initiation of cART, 463 of 7655 patients died. Figure 9.1 shows the cumulative incidence curves of all-cause mortality, according to specific causes of death. The cause of death was related to HIV in 212 patients (45.8%), not related to HIV in 190 (41.0%), related to therapy in 5 (1.1%), and unknown in 56 patients (12.1%). The Kaplan-Meier estimate of all-cause mortality 10 years after starting cART was 10.6%. The estimate for HIV-related death was 3.7%, for non-HIV-related death 5.5%, for death of unknown cause 1.3%, and for therapy-related death 0.1%. The major cause of death was HIV-related during the first 7 years after starting cART. After 7 years, and up to 10 years, of cART, the major cause of death was non-HIV-related.

Table 9.5 shows the cause of death for 242 patients (52.3%) who died before 1 January 2004 and 221 (47.7%) thereafter. The most frequently recorded cause of death (176 patients) was AIDS-defining. AIDS-defining infection (77 patients) and AIDS-defining malignancy (72 patients) occurred just as frequently, whilst 27 patients were recorded as having died because of AIDS without further classification. Non-AIDS-defining malignancy was the cause of death in 63 patients, non-AIDS-defining infection in 27 patients, and cardiovascular complications in 28 patients. There was not enough information to determine the cause of death in 56 patients (12.1%). No significant difference was found between the proportion of specific causes of death before 1 January 2004 and the proportion after that date, except for death due to cardiovascular complications and death caused by suicide, which were more frequent in or after 2004 (both p=0.02). Table 9.6 shows that 134 deaths related to cancer (AIDS-defining and non-AIDS-defining) occurred during 36,326 person-years of follow-up. The overall incidence of cancer-related death after the start of cART was 3.69/1000 person-years (PY) of follow-up (95% CI, 3.09-4.37). The standardized incidence of age and gender in the general Dutch population was 0.73/1000 PY. The figures for non-AIDS-defining cancers were 1.71/1000 PY (95% CI, 1.31-2.19) in the HIV-infected population and 0.70/1000 PY in the general Dutch population. The incidence of non-AIDS-defining cancers amongst female HIV-infected patients was comparable to that of the general female population (0.37 vs. 0.39/1000 PY), whilst in male patients the incidence was much higher than in the general male population (2.09 vs. 0.81/1000 PY).

Figure 9.1b shows the cumulative incidence of the 6 most frequent causes of death after starting cART. The cumulative incidence of death ascribed to AIDS-defining cancers after starting cART was very similar to that of infections. These two causes of death, AIDS-defining cancers and infections, were the major causes of death during the first 7 years after the start of cART. After 7 years of cART, the cumulative incidence of

death because of non-AIDS-defining malignancies was higher than that of AIDS-defining cancers or AIDS-defining infections.

Figure 9.2 shows the median last CD4 count prior to each specific cause of death. The median CD4 count prior to a death because of an AIDS-defining infection was lower than that with an AIDS-defining malignancy, being 50 cells/mm^3 (Interquartile range [IQR], 20-140) and 120 (40-200), respectively (p=0.01). The same trend was seen in non-AIDS-defining infections (median last CD4 count, 116 cells/mm^3 [IQR, 40-210]) and non-AIDS defining malignancies (median, 174 cells/mm^3 (91-368). Median CD4 counts prior to death because of non-AIDS-defining infections were higher than in non-AIDS-defining infections. Median last CD4 counts were highest in the 7 patients who died because of substance abuse (490 cells/mm^3), and they were also high in those who died because of cardiovascular complications (358 cells/mm^3 [IQR, 200-570]) or committed suicide (310 cells/mm^3 [215-600]).

All-cause mortality

Of patients starting cART, 269 died within the first 3 years thereafter. Male gender, a lower baseline CD4 cell count, an HIV RNA level of 100,000 copies/ml or higher at the start of cART, a CDC-B or CDC-C event prior to the start of cART, HIV infection through injecting drug use, older age, hepatitis B virus (HBV) co-infection, and Dutch origin (as compared to sub-Saharan origin) were significantly associated with a shorter time to death in univariate analyses (data not shown). In addition, patients starting cART in 2001 through 2006 had an increased hazard of death compared with patients starting in 1998 through 2000 (HR 1.74 [0.97-3.10, p=0.06]).

In multivariate analyses of time to death within 3 years after cART initiation, gender, Dutch origin, HBV and hepatitis C virus (HCV) co-infection were no longer significantly associated with an increased risk of death (Table 9.4). Hazard ratios (HR) for death were lowest for those starting cART in calendar years 1998 through 2000. Compared to patients starting cART in this period, those starting in 1996-1997 had a HR of 1.64 (95% CI 1.11-2.43, p=0.01) and those starting in 2001-2006 1.61 (1.18-2.19, p=0.002). The time to death for patients starting cART in 2001-2006 was not significantly different from 1996-1997 (p=0.91). Injecting drug use as the HIV transmission route was associated with a shorter time to death (p<0.0001) than the route of men having sex with men (MSM). The effect of baseline CD4 count on the hazard ratio of death relative to a count of 200 cells/mm^3 is shown in Figure 9.3a. For CD4 counts <100 cells/mm^3 the HR decreases rapidly with higher cell counts. For CD4 count above 100 cells/mm^3 the hazard ratio decreases more slowly, but there is a monotone trend for a lower hazard ratio of death with an increasing CD4 count at the start of cART. The effect of age on HR of death is shown in Figure 9.3c. Neither a linear (p=0.13) nor a nonlinear (p=0.55) effect of $\log_{10}$ transformed baseline HIV RNA was noted on the hazard of death within 3 years of starting cART. Patients with a CDC-C event at the start of cART had an HR of 4.16 (95% CI 2.95-5.86; p<0.0001) and those with a CDC-B event had an HR of 2.13 (1.43-3.19, p=0.0002), compared with those who had no CDC-C or -B event at the start of cART.

In a separate analysis (adjusted for the same confounders), patients with specific CDC-C events before and after the start of cART were compared to patients without CDC-C events. Hazard ratios for death within 3 years of starting cART differed considerably according to the type of CDC-C event, as shown in Figure 9.3d. Patients with progressive multifocal leucoencephalopathy or non-Hodgkin's lymphoma (including primary brain lymphoma) were at highest risk of death (HR 16.72 [10.74-26.02, p<0.0001] and 13.29 [9.77-18.07, p<0.0001], respectively) compared to those with no CDC-C event. Patients diagnosed with AIDS dementia had an HR of 5.08 (3.34-7.71,

p<0.0001) and with *Mycobacterium avium/kansasii* 4.01 (2.40-6.70, p<0.0001). The hazard of death for patients with isosporiasis, tuberculosis (pulmonary or extrapulmonary), wasting syndrome, recurrent pneumonia, mycobacterium infection (atypical), or cryptosporidiosis or cryptococcosis (extrapulmonary) infection was not significantly different from those without a CDC-C event. Patients with P. *carinii* pneumonia had a lower hazard of death (HR 0.83 [0.57-1.21], p=0.34) compared to those with no CDC-C event

New CDC-C events

During 34,861 person-years of follow-up, at least one new AIDS-defining event developed in 765 patients, and in 545 patients, at least one new event developed within 3 years of starting cART. The Kaplan-Meier estimate of the development of a new AIDS-defining event within 3 years was 8.6% (95% CI 8.0-9.2) and 18.9 (17.7-20.1) after 10 years.

The six most frequent events occurring within 3 years were: Kaposi's sarcoma in 70 patients; oesophageal candidiasis in 60; tuberculosis in 56; non-Hodgkin's lymphoma in 52; recurrent pneumonia (more than 1 episode in a 1-year period) in 47; and toxoplasmosis of the brain in 33.

Baseline characteristics that were univariately associated with a shorter time to a new AIDS-defining event within 3 years of starting cART were: a low baseline CD4 cell count; baseline HIV RNA higher than 100,000 copies/ml, occurrence of a CDC-C event before cART initiation; co-infection with HBV or HCV; older age; injecting drug use as the HIV transmission route; and having a sub-Saharan African, Western European/North American/Australian, or Caribbean/Latin American country of origin rather than a Dutch origin (results not shown).

After adjusting for baseline variables, we found that the hazard for a new CDC-C event between different calendar years for the start of cART were not significantly different between each other (see Table 9.4). Patients of sub-Saharan African, Western European/North American/Australian, or Caribbean/Latin American origin still had a higher hazard for a new CDC-C event than patients from the Netherlands. A prior CDC-C or -B event was also independently associated with a shorter time to a new AIDS-defining event. There was a weak linear effect of older age on the hazard of a new CDC-C event (HR per 5-year increase 1.04 [1.00-1.09, p=0.06]). The age at the start of cART was also modelled with cubic splines, but we found no evidence of a nonlinear effect (p=0.20). Figure 9.4 shows there was a strong nonlinear effect of baseline CD4 count on the hazard ratio of a new CDC-C event relative to a baseline CD4 count of 200 cells/mm^3 (p=0.0006). For baseline CD4 counts <300 cells/mm^3, the hazard ratio declined with higher CD4 counts, whereas the hazard ratio did not decrease further for baseline CD4 count higher than 300 cells/mm^3.

Discussion

Our study confirms that the start of cART when CD4 cell counts are below 200 cells/mm^3 and when the history includes an AIDS-defining illness is associated with a higher probability of subsequent progression to AIDS and death[22, 92, 99]. We also found that the probability of death continued to decrease with higher baseline CD4 counts, including with very high CD4 counts, whereas the risk of the development of a new AIDS event was similar across baseline counts above 300 CD4 cells/mm^3.

Despite the importance of starting cART when CD4 counts are still above 200 cells/mm^3, more than 50% of patients, overall, started cART with counts below 200 cells/mm^3. This suggests that mortality and morbidity rates would improve if more patients had access to cART earlier in the course of the infection. Patients originating from regions other than the Netherlands were at an increased risk of starting cART too late (i.e., with counts below 200 CD4 cells/mm^3). The increase in proportion of patients starting cART above this

threshold in 2006 compared with the period 2001-2005 is therefore encouraging. It cannot be explained by changes in socio-demographic characteristics of patients starting cART in 2006 compared with those starting in 2001-2005, since we adjusted multivariate hazard ratios for region of origin, gender, and transmission risk group. The higher proportion of patients starting cART with CD4 counts above 200 cells/mm^3 might indicate changes in testing or follow-up policies.

One explanation for the lower probability of death for patients starting cART in 1998 to 2000 than that in other starting years is an incomplete registration of HIV-related deaths in the Netherlands before monitoring of HIV started in 2002. The hazard of death for patients starting cART between 1997 and 2001 compared to that for patients starting cART between 2002 and 2006 was decreased only during the first year of treatment (results not shown). This indicates that a number of patients who died shortly after starting cART might have been missed.

Non-HIV-related and non-AIDS-defining causes of death (in particular, death following a non-AIDS-defining malignancy) became the major causes of death in patients who had been on cART for a longer period of time. As treatment has turned HIV infection into a chronic disease, causes of death in HIV-infected patients have come to resemble more closely those seen in the general population; this is reflected in the increasing incidence of death due to non-AIDS defining malignancies and cardiovascular complications with longer time on cART, as well as the higher proportion of deaths due to cardiovascular complications seen after 1 January 2004, in our cohort of treated patients, as found in other cohorts[69]. In addition, time on certain antiretroviral drugs or drug classes might also increase the risk of cardiovascular complications, although this remains controversial[158, 159, 171-173]. Certain drugs are known to cause depression in a large proportion of patients[174], but whether the higher uptake of efavirenz can explain the increase in suicides is doubtful[175, 176].
The cancer-related mortality rate in the cART-treated population was nearly 5 times as high as in the age- and gender-standardized general Dutch population. The incidence of death because of non-AIDS-defining cancer was almost as common as that of AIDS-defining cancer, but it was not higher, as was reported elsewhere[70]. Death due to non-AIDS-defining cancer in the population of males with HIV infection was more than twice as high compared to the age-standardized general male Dutch population, whilst that in the female patients was comparable to that in the general female Dutch population. This, and the low CD4 prior to death, indicates that immunodeficiency may be associated with the risk of fatal non-AIDS-defining cancers, as suggested by some[70-72] studies, but not found by others[73-75].
The high number of patients in whom the cause of death was unknown hampers drawing firmer conclusions. Insight into the causes of death is crucial to better target interventions, and continued monitoring of causes of death, preferably as judged by a panel including physicians, should therefore continue.

Modelling continuous variables, such as age, CD4 count, and HIV RNA plasma concentration, with cubic splines had the advantage of avoidance of arbitrarily chosen cut-off points, at which the risk of the endpoint would suddenly increase, which is biologically implausible. Our finding of an ongoing improvement in the risk of death with increasing CD4 cell counts at the start of cART, even when counts are above 500 cells/mm^3, suggests that starting cART earlier than current guidelines recommend might be beneficial. The risk of AIDS after starting cART appeared to be the same across CD4 cell counts, once the counts were above 300 cells/mm^3. A recent study showed a decreasing rate of AIDS and death with a higher current CD4 cell count when the count was 350 cells/mm^3 or greater[177].

We did not find an independent association of HCV co-infection with a shorter time to death. Because of the strong correlation of HCV co-infection with HIV infection through injecting drug use, it is difficult to disentangle these two effects. Other studies have found an increased mortality rate in patients co-infected with HCV[95, 178, 179], although conflicting results have been reported[180-182]. In contrast to results reported by the EuroSIDA study[183], we have not found a significantly increased risk of death from all causes in patients co-infected with HBV in univariate or multivariate analyses.

There was considerable variety in the hazard of death according to the type of AIDS-defining event. In patients experiencing progressive multifocal encephalopathy and non-Hodgkin's lymphoma, the hazard was more than 10 times that of patients without an AIDS-defining event. On the other end of the spectrum, the most frequently diagnosed AIDS-defining event, *P. carinii* pneumonia, did not increase the risk of death, and neither did herpes simplex infection. Because chemoprophylaxis has changed the prognosis of *P. carinii* pneumonia, this event should not be treated in the same way as other AIDS-defining events in models of prognosis.

In summary, patients starting cART with CD4 cell counts below 200 cells/mm^3 have a higher probability of disease progression or death compared to those with counts of 200 cells/mm^3 and above. The aim to increase the proportion of patients starting cART above this threshold requires targeting patients originating from regions other than the Netherlands. With an increased duration of time on cART, there is a shift from HIV-related to non-HIV-related causes of death. The occurrence of non-AIDS-defining infections and cancers might be immunodeficiency-related. The incidence of non-AIDS-defining cancers in male patients is much higher than that in the general male population. Prevention and treatment of non-HIV-related serious diseases will need to be part of HIV care in the Netherlands.

		N	%
Total		7655	
Gender	Male	5755	75.2
Transmission risk group	MSM	3764	49.2
	IDU	364	4.8
	Heterosexual contact	2931	38.3
	Blood-blood contact	118	1.5
	Other	478	6.2
Region of origin	Netherlands	4041	52.8
	W-Europe/N-America/Australia	562	7.3
	Caribbean/Latin America	874	11.4
	Sub-Saharan Africa	1617	21.1
	Other	561	7.3
Clinical stage	CDC-A	4240	55.4
	CDC-B	1218	15.9
	CDC-C	2197	28.7
HBV	negative	6475	84.6
	positive	527	6.9
	unknown	653	8.5
HCV	negative	5885	76.9
	positive	605	7.9
	unknown	1165	15.2
Started cART during pregnancy		440	5.7
Started cART during primary infection		359	4.7
		Med	**IQR**
Age at starting cART		37.0	31.0-44.0
CD4 cell count at starting cART (cells/mm^3)		190	80-310
HIV RNA at starting cART (log_{10} cps/ml		5.00	4.48-5.38

Table 9.1: Baseline characteristics of 7655 therapy-naïve patients starting cART between 1 July 1996 and 31 December 2006.

MSM: men having sex with men; IDU: injecting drug use; HBV: hepatitis B virus; HCV: hepatitis C virus; med: median; IQR: interquartile range

	NA*	<200		≥200	
	N	N	%	N	%
Year of starting cART					
1996	58	138	46.3	160	53.7
1997	80	272	37.5	454	62.5
1998	80	283	51.7	264	48.3
1999	89	270	48.5	287	51.5
2000	89	288	52.1	265	47.9
2001	64	364	55.0	298	45.0
2002	61	367	53.3	322	46.7
2003	61	377	52.9	336	47.1
2004	57	425	55.1	347	44.9
2005	48	401	53.5	349	46.5
2006	70	301	47.7	330	52.3
Total	757	3486	50.5	3412	49.5

Table 9.2: Patients starting combination antiretroviral therapy (cART) with a CD4 count <200 and ≥200 cells/mm^3.

*NA: No pre-cART CD4 count available.

		Univariate			Multivariate		
		OR	95% CI	p	OR	95% CI	p
Gender	Male	1.00			1.00		
	Female	0.76	(0.68-0.85)	<0.0001	0.74	(0.63-0.86)	0.0001
Age at starting cART (per 5 year increase)		1.10	(1.07-1.12)	<0.0001	1.10	(1.07-1.13)	<0.0001
Calendar year of starting cART	1996	0.77	(0.59-1.01)	0.06	0.77	(0.59-1.02)	0.0683
	1997	0.52	(0.41-0.66)	<0.0001	0.53	(0.42-0.66)	<0.0001
	1998	0.95	(0.75-1.22)	0.71	0.97	(0.77-1.22)	0.78
	1999	0.87	(0.69-1.09)	0.22	0.82	(0.65-1.05)	0.11
	2000	1.00			1.00		
	2001	1.07	(0.85-1.34)	0.59	1.01	(0.80-1.27)	0.96
	2002	1.05	(0.83-1.32)	0.68	1.04	(0.83-1.31)	0.74
	2003	0.98	(0.78-1.22)	0.84	0.97	(0.77-1.21)	0.76
	2004	1.15	(0.93-1.44)	0.20	1.09	(0.88-1.36)	0.43
	2005	1.02	(0.81-1.28)	0.87	0.99	(0.79-1.24)	0.95
	2006	0.78	(0.62-0.98)	0.04	0.73	(0.58-0.93)	0.01
Pregnant during the start of cART	No	1.00			1.00		
	Yes	0.23	(0.18-0.30)	<0.0001	0.21	(0.16-0.28)	<0.0001
Transmission risk group	Homosexual	1.00			1.00		
	Heterosexual	1.22	(1.09-1.37)	0.0005	1.45	(1.24-1.70)	<0.0001
	IDU	1.01	(0.80-1.26)	0.96	1.12	(0.89-1.42)	0.34
	Blood to blood contact	1.17	(0.77-1.78)	0.45	1.21	(0.78-1.85)	0.40
	Other	2.37	(1.90-2.95)	<0.0001	2.10	(1.67-2.64)	<0.0001
Region of origin	Netherlands	1.00			1.00		
	WE/NA/A	1.11	(0.89-1.38)	0.35	1.18	(0.94-1.49)	0.15
	Latin America	1.34	(1.14-1.57)	0.0003	1.47	(1.23-1.74)	<0.0001
	Sub-Saharan Africa	1.30	(1.14-1.47)	0.0001	1.58	(1.34-1.87)	<0.0001
	Other	1.62	(1.34-1.96)	<0.0001	1.71	(1.40-2.09)	<0.0001

Table 9.3: Univariate and multivariate odds ratio's of starting cART with a pre-cART CD4 count <200 cells/mm^3 in 7296 patients (patients starting cART during primary infection are excluded).

OR: odds ratio; CI: confidence interval; cART: combination antiretroviral therapy; IDU: injecting drug use; WE/NA/A: Western Europe/North America/Australia

		Death			AIDS		
		HR	95% CI	p	HR	95% CI	p
Gender	Male	1.00					
	Female	0.73	(0.51-1.05)	0.09			
Region of origin	Netherlands				1.00		
	Caribbean/Latin America				1.47	(1.08-1.99	0.01
	W-Europe/N-America/Australia				1.48	(1.08-2.02	0.02
	Sub-Saharan Africa				1.39	(1.10-1.76	0.006
	Other				1.35	(1.03-1.76	0.03
Calendar year of starting cART	1996-1997	1.92	(1.09-3.40)	0.02	1.00	(0.71-1.41)	0.98
	1998	1.36	(0.72-2.58)	0.34	0.80	(0.54-1.19)	0.27
	1999	1.16	(0.59-2.26)	0.67	0.79	(0.53-1.18)	0.25
	2000	1.00			1.00		
	2001	1.54	(0.83-2.87)	0.17	1.11	(0.78-1.59)	0.57
	2002	2.14	(1.19-3.86)	0.01	0.84	(0.57-1.23)	0.36
	2003	2.42	(1.35-4.34)	0.003	1.06	(0.74-1.52)	0.76
	2004	2.38	(1.33-4.25)	0.003	1.09	(0.76-1.56)	0.63
	2005-2006	1.96	(1.09-3.54)	0.02	0.90	(0.63-1.28)	0.55
Transmission risk group	Homosexual	1.00					
	IDU	4.12	(2.82-6.02)	<0.0001			
	Heterosexual	1.10	(0.81-1.51)	0.53			
	Blood-blood	1.16	(0.47-2.86)	0.75			
	Other	1.34	(0.90-2.00)	0.16			
Age at starting cART (per 5 year increase)					1.04	(1.00-1.09)	0.055
Clinical stage	CDC-A	1.00			1.00		
	CDC-B	2.12	(1.42-3.17)	0.0003	1.45	(1.06-1.97)	0.02
	CDC-C	4.11	(2.92-5.79)	<0.0001	4.07	(3.20-5.17)	<0.0001

Table 9.4: Multivariate hazard ratios (HR) and 95% confidence intervals (CI) of time to death and time to a new AIDS event within 3 years after starting cART, Cox proportional hazards models. Figures 9.2a-c show the multivariate effect of continuously modelled age, CD4 count and HIV RNA at the start of cART.

cART: combination antiretroviral therapy; IDU: injecting drug use.

		<2004		≥2004		Total	
		N	%	N	%	N	%
Total		242	100.0	221	100.0	463	100.0
Death due to AIDS defining causes		94	38.8	82	37.1	176	38.0
	Infection	42	17.4	35	15.8	77	16.6
	Malignancy	37	15.3	35	15.8	72	15.6
	AIDS, not specified	15	6.2	12	5.4	27	5.8
Non AIDS defining malignancy		29	12.0	34	15.4	63	13.6
Non AIDS defining infection		18	7.4	9	4.1	27	5.8
Liver failure/cirrhosis and HBV/HCV co-infection		8	3.3	7	3.2	15	3.2
Diabetes Mellitus			2	0.9	2	0.4	
Lactic acidosis		3	1.2	1	0.5	4	0.9
Cardiovascular complications		13	5.4	26	11.8	39	8.4
	MI	7	2.9	14	6.3	21	4.5
	Stroke	2	0.8	3	1.4	5	1.1
	Other ischemic heart disease			1	0.5	1	0.2
	Heart or vascular (other causes)	4	1.7	8	3.6	12	2.6
Lung related		4	1.6	5	2.3	9	1.9
Liver failure (without HBV/HCV)		4	1.7	1	0.5	5	1.1
Renal failure		5	2.1			5	1.1
Non-natural death		23	9.5	23	10.4	46	10.9
	Accident or other violent death	8	3.3	1	0.5	9	1.9
	Suicide	7	2.9	18	8.1	25	5.4
	Euthanasia	8	3.3	4	1.8	12	2.6
Substance abuse		4	1.7	3	1.4	7	1.5
Other cause*		5	2.1	4	1.8	9	1.9
Unknown		32	13.2	24	10.9	56	12.1

Table 9.5: Cause of death according to date of death before or after 1 January 2004.

* Other causes include haematological, respiratory, gastro-intestinal tract, gynaecological, and central nervous system disorders.

HBV: hepatitis B virus; HCV: hepatitis C virus; MI: myocardial infarction

	N	Incidence per 1000 PY (95% CI)	Incidence per 1000 PY in Dutch population
Death due to cancer	134	3.69 (3.09-4.37)	0.73
♂	122	4.33 (3.60-5.17)	0.84
♀	12	1.47 (0.76-2.67)	0.40
AIDS-defining cancer	72	1.98 (1.55-2.50)	**
♂	63	2.24 (1.72-2.86)	**
♀	9	1.10 (0.50-2.10)	**
Non-AIDS-defining cancer	62	1.71 (1.31-2.19)	0.70*
♂	59	2.09 (1.59-2.70)	0.81*
♀	3	0.37 (0.08-1.08)	0.39*

Table 9.6: Incidence of death due to cancer after starting cART.

*Reported figures for the general Dutch population were derived as the incidence of all cancer-related death minus the incidence of non-Hodgkin's lymphoma-related death.

** Figures for the Dutch population not available.

PY: person years of follow-up; CI: confidence interval; cART: combination antiretroviral therapy

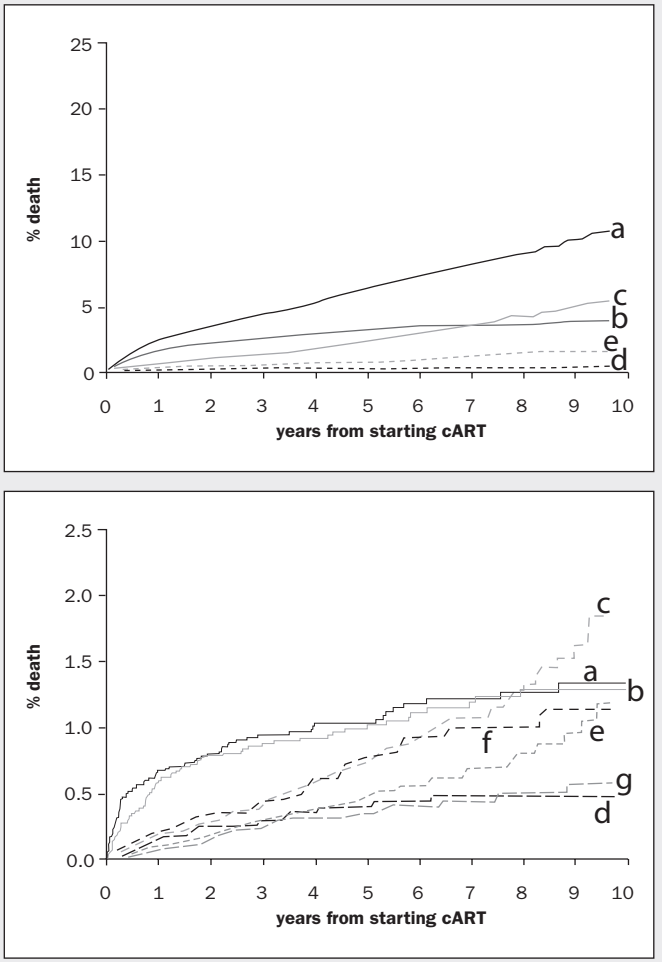


Figure 9.1 a and b: Cumulative incidence curves of death after starting combination antiretroviral therapy (cART) in 7655 ART-naïve patients according to whether the cause of death was HIV-related, non-HIV-related or therapy-related (top) and according to the Causes of Death in HIV (CODE) scheme (bottom).

Top a: death from all causes; b: HIV-related death; c: non-HIV-related death; d: therapy-related death; e: death due to unknown cause.

Bottom a: death due to AIDS-defining infections, b: death due to AIDS-defining cancers, c: death due to non-AIDS-defining cancers, d: death due to non AIDS-defining infections, e: death due to cardiovascular complications, f: death due to suicide, euthanasia or violence, g: death due to AIDS (unspecified).

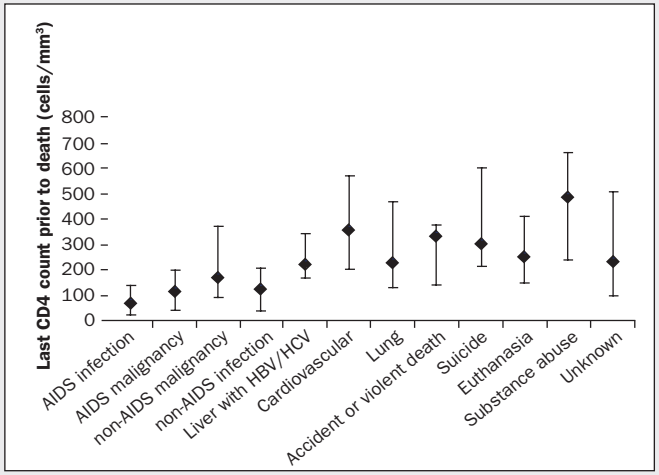


Figure 9.2: Last CD4 count prior to death according to specific causes of death. The median value is denoted by the diamond and lines show the interquartile range.
HBV: hepatitis B virus; HCV: hepatitis C virus.

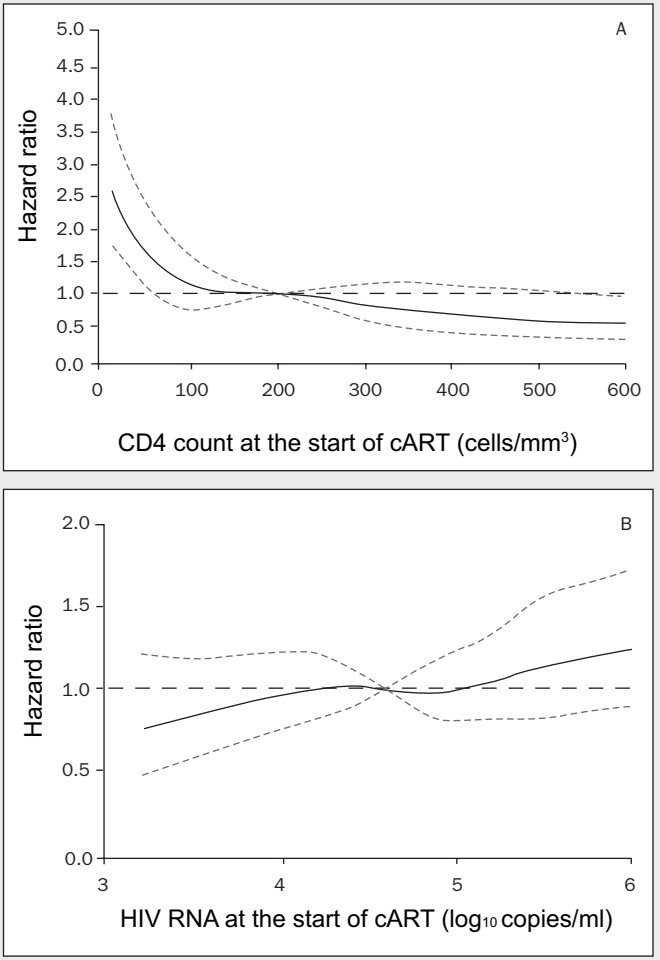
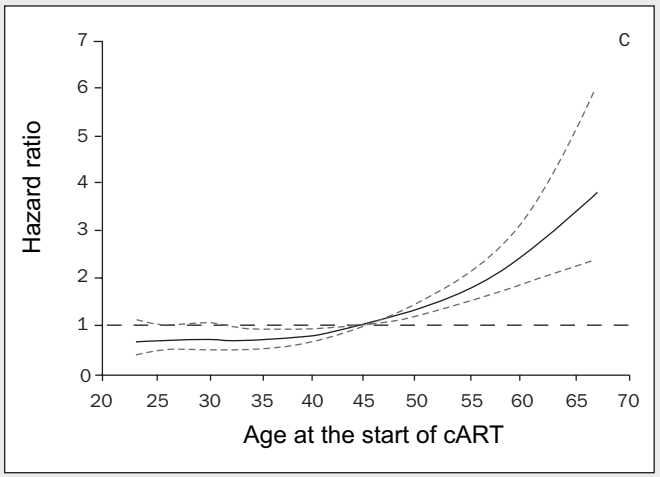
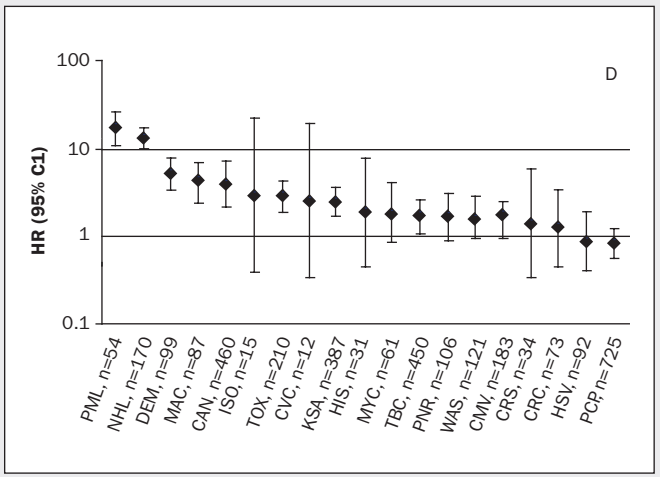


Figure 9.3 a-d: Hazard ratio (95% CI) of death of all causes within 3 years of starting cART according to (top panels, left to right) CD4 count at the start of cART, HIV RNA plasma concentration at the start of cART, and age at the start of cART and (bottom panel) CDC-C events prior to the start of cART. Model is further adjusted for calendar year of the start of cART, gender, and transmission risk group (Table 9.4). Hazard ratios of the specific CDC-C diseases are relative to no AIDS-defining event.
HR: hazard ratio; CI: confidence interval; cART: combination antiretroviral therapy; PML:





progressive multifocal leucoencephalopathy, NHL: non-Hodgkin's lymphoma (including primary brain lymphoma); DEM: AIDS dementia complex; MAC: Mycobacterium avium/kansasii; CAN: candidiasis; ISO: isosporiasis; TOX: toxoplasmosis of the brain; CVC: cervical cancer; KSA: Kaposi's sarcoma; HIS: histoplasmosis; MYC: atypical mycobacterium; TBC: tuberculosis; PNR: pneumonia recurrent; WAS: wasting syndrome; CMV: cytomegalovirus disease; CRS: cryptosporidiosis; CRC: cryptococcosis extrapulmonary; HSV: herpes simplex virus; PCP: Pneumocystis carinii pneumonia

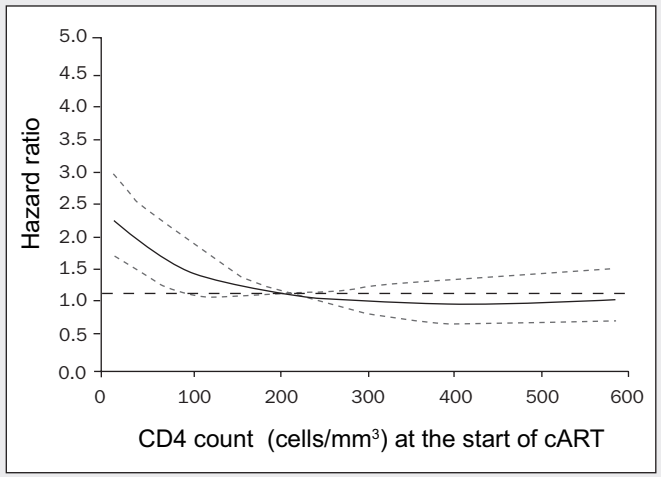


Figure 9.4: Hazard ratio (95% CI) of new AIDS event within 3 year of starting cART according to CD4 count at the start of cART, relative to 200 cells/mm^3.
CI: confidence interval; cART: combination antiretroviral therapy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Immune response of HIV-1-infected children to cART

Colette Smit

The term "children" in this chapter refers to all individuals younger than 18 years of age, unless otherwise noted in the text.

Introduction

Mother-to-child-transmission (MTCT) is the major route of HIV infection amongst children worldwide[184], including in the Netherlands[16]. As with adults[76], the life expectancy of HIV-infected children has improved dramatically since combination antiretroviral therapy (cART) became generally available[77]. The virologic and immunologic responses to cART have been studied extensively in adults, but only a few studies have been conducted in HIV-1-infected children. Children have a better capacity than adults for reconstitution of CD4 cells[78], which has been linked to a higher thymus function in children. With age, the absolute CD4 cell counts decreases, and the immune response varies with age[79, 80]. Together, these two factors complicate evaluation of the immune response amongst HIV-1-infected children on cART.

In this chapter we report on the immune response and virologic response of the HIV-1-infected children who have been followed between 1 January 1997 and 1 June 2007 in the AIDS Therapy Evaluation in the Netherlands (ATHENA) observational cohort. In addition, the demographic characteristics of the HIV-infected children currently in follow-up are described.

Study population and methods

All HIV-1-infected children in the Netherlands are followed and treated in one of the four specifically designated paediatric HIV treatment centres. For our study, we divided the population of HIV-1-infected children into two groups: those who were in follow-up at any time between 1 January 1997 and 1 June 2007, and those who are currently being followed and treated in one of the centres.

Children currently in follow up

For this analysis, we selected all HIV-1-infected patients who were younger than 18 years of age, alive, and in follow-up as of 1 June 2007. Patients were considered in follow-up if data had been collected for them in the preceding year. In this analysis, patients 0 through 12 years of age as of 1 June 2007 are referred to as "children" and those 13 years of age up to 18 years as "adolescents".

Total population of HIV-1- infected children and adolescents ever in follow up

Our study of the immune response after the start of cART included all patients infected with HIV-1 by MTCT or blood contact who were younger than 18 years of age at the time of diagnosis and who were diagnosed between 1 January 1997 and 1 June 2007. In cases where the mode of transmission was missing, we assumed that MTCT was the most likely route. Patients who were infected through homosexual or heterosexual contact (n=102) were excluded from our study. In this analysis, patients diagnosed with HIV from the ages of 0 through 12 years are referred to as "children" and those from the age of 13 years up to the age of 18 years as "adolescents".

Statistical analysis

In addition to the routine demographic data for the children (age 0-12 years) and adolescents (age 13-17 years), information on the region of origin of the parents was reported. Countries of origin were divided into six categories: the Netherlands, North America/Europe excluding the Netherlands, Latin America/the Caribbean, sub-Saharan Africa, South/Southeast Asia, or other. The route of transmission was defined as MTCT, blood contact, or an unknown route of transmission.

Children and adolescents currently in follow up

We described the demographic and clinical characteristics of HIV-1-infected children and adolescents who were in follow-up as of 1 June 2007. We also included their

current cART regimen and the median CD4 cell count and HIV RNA level based on the most recent measurement between 1 June 2006 and 1 June 2007.

Total population of HIV-1- infected children

Changes in absolute CD4 cell counts and in percentage and in HIV RNA plasma levels after cART initiation were assessed with a random effect model, which allowed for a random intercept. The slope was allowed to change at 12 weeks after cART initiation. Since CD4 cell counts are age-related, we subdivided the children into two groups: young children, who were 2 years of age or less at the time of cART initiation, and older children, who were 3 years up to18 years of age at cART initiation[80].

Results

Children and adolescents currently in follow-up

As of 1 June 2007, 87 HIV-1-infected children (age 0 through 12 years) and 32 adolescents (age 13 through 17 years) were alive and in follow-up in Netherlands.

The majority of the children and adolescents currently in follow-up were infected through MTCT (Table 10.1). The median age at HIV diagnosis was 1.1 years (interquartile range [IQR], 0.5-4.1) for children and 4.4 years (1.5-9.0) for adolescents. Most children and adolescents were born in the Netherlands, whereas 86% of the children and 62% of the adolescents had at least one parent who originated from sub-Saharan Africa.

The current median CD4 cell count for young children (≤ 2 years of age) was 1065×10^6 cells/l (IQR, 840-1470), and it was lower amongst the older children (> 2 up to 13 years) and adolescents (≥ 13 up to 18 years) (Table 10.1).

Currently, the most commonly used treatment regimens for HIV-1-infected children and adolescents are a combination of zidovudine, lamivudine, and efavirenz (AZT+3TC+EFV); abacavir, lamivudine, and efavirenz (ABC+3TC+EFV); or abacavir, lamivudine, and lopinavir (ritonavir-boosted) (ABC+3TC+LOP/r) (Table 10.2).

Demographic characteristics of the total population of HIV-1-infected children

The demographic and clinical characteristics of HIV-1-infected children and adolescents in the ATHENA cohort are presented in Table 10.3.

Between 1 January 1997 and 1 June 2007, 123 children (age 0-12 years) and 17 adolescents (age 13-17 years) were diagnosed with HIV-1. The main route of transmission was MTCT, with 3 children and 6 adolescents infected through blood contact. The majority of the children originated from the Netherlands, and most of the adolescents originated from sub-Saharan Africa. Although 58% of the children were born in the Netherlands, there were only 7 children whose parents both originated from the Netherlands, and 67% of the children had at least one parent who originated in sub-Saharan Africa.

Most children and adolescents were diagnosed with HIV in 2000 or later. The median age of HIV diagnosis amongst children was 2.4 years (IQR, 0.7-5.5) and 16.9 years amongst adolescents (16.5-17.4).

Out of the total population of children and adolescents, 5 have been lost to follow up. All five of those patients originated from sub-Saharan Africa, and 3 of them were older than 18 years at the date of last contact.

None of the children died between 1 January 1997 and 1 June 2007. However, 2 of the adolescents died; both were born in sub-Saharan Africa and had an unknown route of HIV transmission. These adolescents were diagnosed with HIV when one was 16 and the other was 17 years of age; both were treated with cART and died within 1.5 years after receiving the diagnosis. All other children who reached the age of 18 years were still alive as of 1 June 2007; from the age of 18 on, HIV-infected patients are followed in the adult population.

Clinical characteristics of the total population of HIV-1- infected children and adolescents

cART was administered to 85% children (age 0-12 years) and 71% of the adolescents (age ≥ 13-17 years) (Table 10.3). The median time between HIV diagnosis

and the start of cART was 0.9 months (IQR, 0.4-2.4) for young children (≤ 2 years of age) at the time of HIV diagnosis. The time between HIV diagnosis and cART initiation was longer for older children (age > 2-12 years) at diagnosis (2.1 months [IQR,1.0-3.9]) and for adolescents at diagnosis (2.1 months [1.1-5.9]).

cART was initiated in 85% of the HIV-1-infected children and in 71% of the adolescents. The most common regimens used for the first time are shown in Table 10.4, stratified by patient age at cART initiation. The combination of stavudine, lamivudine, and nelfinavir (D4T+3TC+NFV) was the most common first regimen, and it was administered to 23% of the young children at the time of cART initiation.

The most frequent regimens for older children at the time of cART intiation, were the combinations of zidovudine, lamivudine, and indinavir (AZT+3TC+IDV) in 21% and zidovudine, lamivudine, and lopinavir (ritonavir-boosted) (AZT+3TC+LOP/r) in 19%. The most frequently reported reasons for therapy change were toxicity (17%) and simplification (18%).

The median CD4 cell counts at the start of cART were 1058×10^6 cells/l (IQR, 442-1690) for young children at the time of cART initiation, and the counts increased to 1710×10^6 cells/l (IQR, 1090-2425) at 24 weeks after the start of cART. Older children at cART initiation had lower baseline CD4 cell counts (350×10^6 cells/l [IQR, 100-600]). CD4 cell counts amongst the older children increased to 650×10^6 cells/l (IQR, 390-920) at 24 weeks after cART initiation.

Adolescents had lower CD4 cell counts than both the young and older groups of HIV-infected children. At baseline, the median CD4 cell count was 206×10^6 cells/l (IQR, 11-206), and it then increased to 372×10^6 cells/l (201-550) after 24 weeks of cART.

Amongst the young children at the time of cART initiation, HIV RNA levels decreased from 5.8 $\log_{10}$/ml (IQR, 5.3-6.0) at baseline to 2.6 $\log_{10}$/ml (2.1-2.6) at 24 weeks after the start of cART. Amongst the older children, HIV RNA levels were somewhat lower, and they decreased from 4.9 $\log_{10}$/ml (IQR, 4.3-5.6) at baseline to 1.7 $\log_{10}$/ml (1.7-2.6) at 24 weeks of cART. Amongst the adolescents, HIV RNA levels decreased from 5.0 $\log_{10}$/ml (IQR, 4.7-5.3) at baseline to 1.7 $\log_{10}$/ml (1.7-2.6) at week 24.

Immune response amongst HIV-1- infected children

The changes in absolute CD4 cell counts after cART initiation amongst HIV-1-infected children, stratified by age of cART initiation, is shown in Figure 10.1a. In this analysis, the population of children was divided into two groups, according to the age at the time of cART initiation: young children (≤ 2 years) and older children (> 2 years up to 18). The young children had significantly higher CD4 cell counts compared to the older children.

In the first 12 weeks of cART, the CD4 cell counts did not change significantly amongst the young children at the time of cART initiation. However, a significant increase in CD4 cell counts in the first 12 weeks on cART was observed amongst the older children at the time of cART initiation. After 12 weeks of cART, no significant changes in CD4 cell counts were seen in either group, and the slopes of CD4 cell counts did not significantly differ between the groups of young children and older children.

The changes in CD4 cell percentages amongst the HIV-1-infected young and older children since they commenced cART were modelled piecewise and are presented in Figure 10.1b. Older children had significantly higher CD4 cell percentages than young children at time of cART initiation. In the first 12 weeks on cART, the CD4 cell percentages increased in both groups, but the increase was significantly more rapid amongst the older children at the time of cART initiation. From 12 weeks of cART on, the CD4 percentages still increased significantly faster amongst the older children. During the first year on cART, the CD4 cell percentages remained higher amongst the older children at the time of cART initiation compared to the young children.

Virologic response amongst HIV-1-infected children

The changes in HIV RNA plasma levels amongst HIV-1 infected children who began cART are shown in Figure 10.2. In this analysis, the population of children was divided into two groups, according to age at the time of cART initiation: young children (≤ 2 years) and older children (> 2 years up to 18). The older children had significantly higher HIV RNA plasma levels at the time of cART initiation than did the young children. During the first 12 weeks on cART, a strong significant decline in HIV RNA plasma levels was seen in both groups. This decline was stronger amongst the older children at the time of cART initiation. More than 12 weeks after the initiation of cART, the decrease in HIV RNA plasma levels remained significant, whereas the virologic response significantly differed between the age groups, again stronger amongst the older children.

Discussion

This chapter describes the demographic and clinical characteristics of HIV-1-infected children in the Netherlands. Most HIV-infected children in the Netherlands were infected by MTCT. Although most of these were born in the Netherlands, only a very few had both parents who originated from the Netherlands[185]. The majority were receiving cART. Although the young children (≤ 2 years of age) at the start of cART had higher absolute CD4 cell counts, the older children (> 2 up to 18 years of age) initiating cART had higher CD4 percentages and a faster increase in CD4 percentages.

Age-related variation in the absolute numbers of CD4 cells have been described previously in HIV-uninfected children[80]. Absolute CD4 cell counts decline with increasing age, which explains the significantly higher CD4 cell counts amongst HIV-1-infected young children. The CD4 cell percentages are probably a better marker for comparing the immunologic response after cART between groups of children of different ages. Older children at the time of cART initiation had significantly higher CD4 cell percentages, and the proportion of CD4 cells increased more rapidly amongst the older children. Suppression of the HIV RNA levels is needed for the recovery of thymic function and, thus, for the return of CD4 cells[81]. Older children starting cART are more likely to achieve an undetectable viral load than young children. This poorer virologic response amongst HIV-1-infected young children receiving cART has been described previously[79]. In our study, older children had lower HIV RNA levels at the start of cART and also at 24 weeks after the start. A higher CD4 percentage at baseline and during the first year on cART is likely to be a result of the higher virologic suppression seen in the group of older children.

The results of this study indicate that the immunologic and virologic response amongst HIV-1-infected children on cART is age-dependent. Although young children have higher CD4 cell counts, the immune response is stronger in older children, as reflected by the higher CD4 percentages.

Demographic Characteristics	Children N (%)	Adolescents N (%)
Total	87	34
Gender		
- boy	47 (54)	19 (55)
- girl	40 (46)	15 (44)
Route of transmission:		
- MTCT*	84 (97)	31 (91)
- Blood contact	0	3 (9)
- Unknown	3 (3)	0
Region of origin:		
- the Netherlands	55 (63)	18 (52)
- Europe	1 (1)	2 (6)
- Latin America/Caribbean	3 (3)	2 (6)
- Sub Saharan Africa	26 (30)	10 (29)
- South/Southeast Asia	-	-
- Other	2 (2)	2 (6)
Region of parents:		
- both the Netherlands	4 (5)	2 (6)
- one or both Sub-Saharan Africa	59 (68)	20 (59)
- one or both other region	24 (28)	12 (35)
Year at HIV diagnosis		
- <1998	16 (18)	20 (59)
- 1998-2000	14 (16)	4 (12)
- 2000-2003	33 (38)	4 (12)
- >2003	24 (28)	6 (18)
Age at diagnosis		
≤ 2 years of age	50 (57)	11
> 2 years of age	37 (43)	23
Clinical Characteristics at 1 June 2007		
cART use	80 (91)	32 (94)
Current CD4 cell counts(x 10^6 cells/l) (median, IQR)**		
≤ 2 years of age	1065 (840-1470)	
> 2 years of age	650 (530-960)	705 (530-870)
Current Undetectable viral load		
≤ 2 years of age	44 (88)	
> 2 years of age	27 (73)	25 (74)
Current Baseline HIV RNA (log_{10}/ml) (median, IQR)**		
≤ 2 years of age	1.7 (1.6-1.7)	
> 2 years of age	1.7 (1.6-2.5)	1.7(1.6-2.0)

**IQR, interquartile range; *MTCT, mother to child transmission.

Table 10.1: Demographic and clinical characteristics of HIV-1-infected children (age 0-12 years) and adolescents (age 13-17 years) in follow-up as of 1 June 2007.

Most common regimen	Most recent regimen amongst children and adolescents in follow-up as of 1 June 2007	
	Children	Adolescents
AZT+3TC+ABC	6/80	5/32
AZT+3TC+NVP	2/80	
AZT+3TC+LOP/r	6/80	1/32
AZT+3TC+NFV	1/80	
AZT+3TC+EFV	12/80	3/32
ABC+3TC+EFV	17/80	4/32
ABC+3TC+lop/R	14/80	4/32
ABC+3TC+ ATV+RTV		3/32
D4T+3TC+NFV	2/80	
D4T+3TC+LOP/r	3/80	
Ddl+3TC+ABC+EFV		1/32

AZT: zidovudine; 3TC: lamivudine; IDV: indinavir; ABC: abacavir; LOP/r: lopinavir (ritonavir-boosted); NFV: nelfinavir; EFV: efavirenz; D4T: stavudine; ddl: didanosine; ATV; atazanavir; RTV; ritonavir

Table 10.2: Most recent regimen amongst children (age 0-12 years) and adolescents (age 13-17 years) in follow-up as of 1 June 2007.

Demographic characteristics at diagnosis	Children N (%)	Adolescents N (%)
Total	123 (%)	17 (%)
Gender		
- boy	68 (55)	13 (76)
- girl	55 (45)	4 (24)
Route of transmission:		
- MTCT	112 (91)	1 (6)
- Blood contact	3 (2)	6 (35)
- Unknown	8 (7)	10 (59)
Region of origin:		
- the Netherlands	72 (58)	-
- Europe	2 (2)	1 (6)
- Latin America/Caribbean	4 (3)	1 (6)
- Sub-Saharan Africa	40 (33)	15 (88)
- South/Southeast Asia	2 (2)	-
- Other	3 (2)	-
Region of parents:		
- both the Netherlands	7 (6)	-
- one or both sub-Saharan Africa	83 (67)	-
- one or both other region	33 (18)	17 (100)
Year at HIV diagnosis		
- <1998	12 (10)	1 (6)
- 1998-2000	21 (17)	4 (24)
- 2000-2003	47 (38)	10 (59)
- >2003	43 (35)	2 (12)
Age at diagnosis		
≤ 2 years of age	56 (46)	
> 2 years of age	67 (54)	
Lost to follow up	1 (1)	4 (24)
Deaths	0	2 (12)
Clinical characteristics at diagnosis		
CD4 cell counts at diagnosis (x 10^6 cells/l) (median, IQR)		
≤ 2 years of age	1160 (350-1950)	
> 2 years of age	510 (260-785)	410 (180-590)
HIV RNA at diagnosis (log_{10}/ml) (median, IQR)		
≤ 2 years of age	5.4 (4.4-5.9)	
> 2 years of age	5.0 (4.5-5.5)	4.6 (3.9-5.0)

Clinical characteristics at cART initiation	Children N (%)	Adolescents N (%)
cART use	105 (85)	12 (71)
Baseline CD4 cell counts (x 10^6 cells/l) (median, IQR)		
≤ 2 years of age	1058 (442-1690)	
> 2 years of age	350 (100-600)	206 (11-266)
Baseline HIV RNA (log_{10}/ml) (median, IQR)		
≤ 2 years of age	5.8 (5.3-6.0)	
> 2 years of age	4.9 (4.3-5.6)	5 (4.7-5.3)
Clinical characteristics at 24 weeks after cART initiation		
CD4 cell counts at T1 (x 10^6 cells/l) (median, IQR)		
≤ 2 years of age	1710 (1090-2425)	
> 2 years of age	650 (309-920)	372 (201-550)
HIV RNA at T1 (log_{10}/ml) (median, IQR)		
≤ 2 years of age	2.6 (2.1-2.9)	
> 2 years of age	1.7 (1.7-2.6)	1.7 (1.7-1.9)
Undetectable HIV RNA levels at T1		
≤ 2 years of age	46 (82)	
> 2 years of age	64 (96)	16 (94)

Baseline: start of cART; t1, 24 weeks after start cART; IQR, interquartile range; MTCT, mother to child transmission.

Table 10.3: Demographic and clinical characteristics of HIV-1-infected children (age 0-12 years) and adolescents (age 13-17 years) ever in follow-up between 1 January 1997 and 1 June 2007 in the ATHENA observational cohort.

Most common regimen	Children		Adolescents
	≤ 2 years of age	> 2 years of age	≥ 13 years of age
AZT	2/53		
AZT+3TC+IDV	10/53	11/53	
AZT+3TC+ SAQ+RTV			1/12
AZT+3TC+ABC			
AZT+3TC+NVP	3/53		3/12
AZT+3TC+LOP/r	7/53	10/53	3/12
AZT+3TC+NFV	3/53	5/53	1/12
AZT+3TC+EFV	1/53	4/53	
ABC+3TC+EFV			
ABC+3TC+lop/R			
ABC+3TC+ ATV+RTV			
D4T+3TC+NFV	12/53	8/53	
D4T+3TC+IDV			1/12
D4T+3TC+SAQ+RTV			2/12
D4T+3TC+LOP/r		4/53	
Ddl+3TC+ABC+EFV	4/53	6	
3TC+TDF+EFV			1/12

AZT: zidovudine; 3TC: lamivudine; IDV: Indinavir; ABC: abacavir; LOP/r: lopinavir (ritonavir-boosted); NFV: nelfinavir; EFV: efavirenz; D4T: stavudine; ddl: didanosine; ATV: atazanavir; RTV: ritonavir; SAQ: saquinavir

Table 10.4: First regimen amongst children in follow-up between 1 January 1997 and June 2007 in the ATHENA observational cohort.

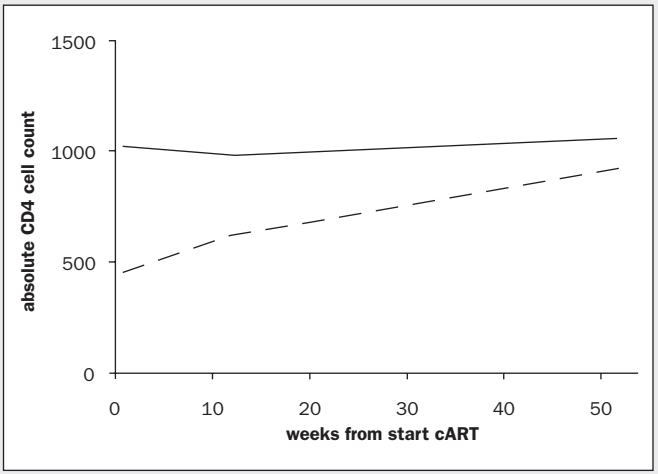

Figure 10.1a: Absolute CD4 cell counts amongst HIV-1-infected children, since start of cART. (Solid line: young children (≤ 2 years of age) at time of cART initiation. Dashed line: older children (> 2 years-17 years of age) at the time of cART initiation.)

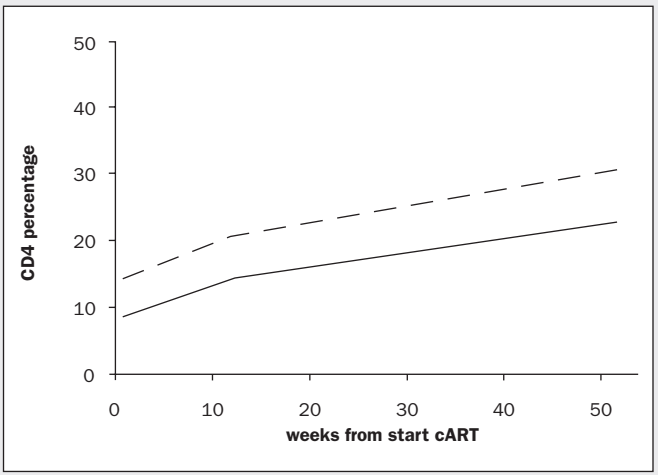

Figure 10.1b: CD4 cell percentages amongst HIV-1 infected children, since start of cART. (Solid line: young children (≤ 2 years of age) at time of cART initiation. Dashed line: older children (> 2 years-17 years of age) at the time of cART initiation.)

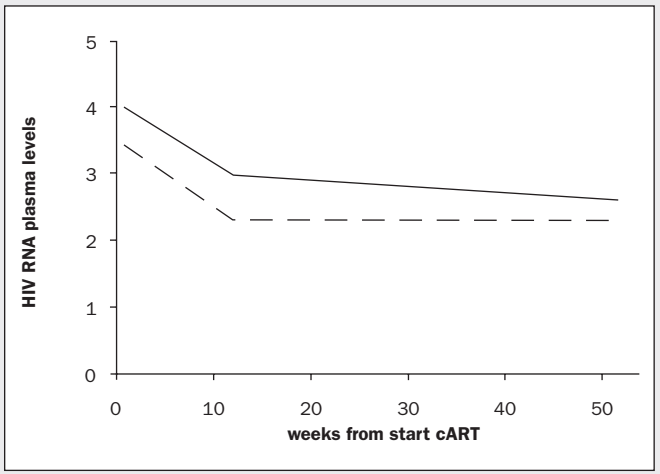

Figure 10.2: HIV RNA plasma levels amongst HIV-1 infected children, since start of cART. (Solid line: young children (≤ 2 years of age) at time of cART initiation. Dashed line: older children (> 2 years -17 years of age) at time of cART initiation.)

Hepat

titis C

CD4 cell response to treatment of hepatitis C co-infection

Colette Smit

Introduction

Co-infection with hepatitis C virus (HCV) is common amongst HIV-infected individuals, with a prevalence of HCV in HIV-infected individuals ranging from 6% to as high as 82% when a history of injecting drug use is reported[82, 83]. Since the introduction of combination antiretroviral therapy (cART), the HIV-related morbidity and mortality rates have dramatically declined. However, several studies have shown an increase in deaths related to liver disease since cART became widely available[84, 85]. The progression of liver disease associated with HCV is known to be accelerated in HIV-infected individuals, and since HIV-infected patients live longer today than in the past, a larger number of patients remain at risk for the development of liver-related disease.

Therefore, treatment of HCV in HIV/HCV-co-infected patients is becoming more important. From 1998 onwards, the standard treatment for HCV has been a combination of interferon (IFN) and ribavirin (RBV)[86, 87], but more recently, pegylated interferon (PEG-IFN) has been used[88]. A combination of PEG-IFN and RBV has been shown to be more effective than IFN+RBV for the treatment of chronic HCV infection in HIV-co-infected individuals, mainly in patients infected with HCV genotypes 1 and 4[89], but decreases in CD4 cell count have been observed during HCV treatment[89]. Although, short-term complications such as opportunistic infections have not been reported[89], it is unknown whether these declines in CD4 cell count have a negative impact on the long-term effect of HIV treatment[90].

In this chapter, we examine the CD4 cell counts and HIV RNA trajectories during HCV treatment among HIV/HCV-co-infected patients. Furthermore, differences in all-cause mortality were compared amongst HCV-co-infected patients who were treated, those who were untreated, and HIV mono-infected individuals.

Study population and Methods

All patients participating in the AIDS Therapy Evaluation in the Netherlands (ATHENA) observational cohort who were screened for HCV co-infection and were at least 18 years of age at the time of HIV diagnosis were included in this analysis.

HCV co-infection was defined by a positive HCV-antibody test (EIA, Axsym) and preferably confirmed with a positive HCV RNA test (measured by a qualitative polymerase chain reaction); 1240 patients had a positive test result for HCV antibody, and 791 of these patients were retested for HCV RNA. Twenty-nine percent of the patients who tested positive for HCV antibody (227 out of 791) had a negative result on an HCV RNA test, and therefore, they were classified as HCV-negative. For 449 positive test results for HCV antibody, a confirmatory result on HCV RNA testing was lacking. Since a high proportion of the HCV infections will become chronic, we chose to classify these samples as HCV-positive.

Hepatitis C treatment

Patients who were using interferon alfa-2b or peg-interferon alfa-2b together between 1 January 1996 and 1 June 2007 were selected for the HCV-treatment group. None of the patients had received previous treatment with interferon. Eighty-three patients received (PEG)-IFN treatment, 58 patients underwent treatment with (PEG)-IFN plus RBV, and 25 patients underwent (PEG)-IFN treatment without RBV.

Changes in CD4 cell count and HIV RNA load during HCV treatment are described for this specific group.

Statistical analysis

In the HCV treatment group, the immunologic and virologic trajectories during HCV-treatment were analysed via a random effect model. Its design allowed for a random intercept for CD4 cell counts and HIV RNA levels per individual. We described time in weeks before and after the start of (PEG)-IFN. Changes in CD4 cell counts and HIV RNA levels were modelled piecewise. Since changes in CD4 cell counts could occur shortly after the start of (PEG)-IFN treatment, the slopes were allowed to change at the start of (PEG)-IFN

treatment, and at week 12, week 24, and week 48 after the start of (PEG)-IFN. If HIV RNA levels were below the quantification limit, the midpoint between this limit and 0 was selected as the HIV RNA level. HIV RNA $\log_{10}$ values were used instead of absolute values.

To evaluate the long-term effect of HCV treatment on the progression to death, three different patient groups were defined: 1) those having HIV without HCV (HIV+/HCV-) who received cART, 2) those with both HIV and HCV (HIV+/HCV+) who received cART and temporary (PEG)-IFN during follow-up, and 3) HIV+/HCV+ patients who received cART only. With the Kaplan-Meier method, we estimated the time between initiation of cART to all-cause mortality for each patient group. The risk of AIDS and death was estimated for each patient group by a Cox proportional hazards model. The follow-up time was from the date of the initiation of cART to that of last contact, most recent follow-up visit, first AIDS-defining event, death, or 1 June 2007. Variables considered as potential covariates in the multivariate models were: age at HIV diagnosis per 10-year increase, transmission route (homosexual, heterosexual, injecting drug use, and "other"), region of origin (the Netherlands, the rest of Europe, sub-Saharan Africa, Latin America/Caribbean, and "other"), baseline CD4 cell counts, and HIV RNA levels.

Results

Of the 13,099 HIV-infected patients in the HIV monitoring cohort, 10,777 (82%) were screened for the presence of HCV antibodies. Demographic and baseline characteristics of the study population are presented in Table 11.1.

Amongst patients tested for HCV, the prevalence was 9%. HCV RNA was present in 564 of the 1013 patients with a positive test result for HCV antibody; for the other 449 patients with a positive HCV antibody, the presence of HCV RNA was not determined, or the test results were not reported during the data collection.

A majority (82%) of the patients infected with HIV by injecting drug use were co-infected with HCV. The HIV/HCV-co-infected patients were somewhat younger than the HCV-negative population, more often female, and less often originating from sub-Saharan Africa, Latin America, or the Caribbean.

(PEG)-IFN

Eight percent (83 out of 1013) of the HIV/HCV-co-infected patients were treated with IFN or PEG-IFN; of those patients, 69 had already been treated with cART before they received (PEG)-IFN, 9 started cART after finishing (PEG)-IFN, and the remaining 5 were not treated for their HIV infection.

For 15 (PEG)-IFN treated patients, a HCV RNA test result was missing. Among the 68 patients with multiple HCV RNA test results, 35 (51%) patients achieved an undetectable HCV RNA level after (PEG)-IFN treatment.

The median duration of HCV treatment was 22 weeks (interquartile range [IQR], 11-38). However, the (PEG)-IFN treated patients who were able to achieve undetectable HCV RNA levels received treatment for a longer period of time (median, 37 weeks [IQR, 25-119]).

CD4 cell counts during (PEG)-IFN treatment

The median CD4 cell count at the start of (PEG)-IFN and after 24 weeks of treatment are shown in Table 11.1. The median CD4 cell count at the time of (PEG)-IFN initiation was 400×10^6 cells/l (IQR, 270-610), but decreased to 240×10^6 cells/l (IQR,140-460) after 24 weeks of treatment with (PEG)-IFN.

The piecewise modelled trajectories of CD4 cell counts during (PEG)-IFN treatment are presented in Figure 11.1. During the first 12 weeks of treatment, CD4 cell counts declined significantly ($P<0.0001$). Between weeks 12 and 24, CD4 cell counts continued to decrease significantly, but less dramatically than in the first 12 weeks. After week 24 (when most of the patients discontinued their

(PEG)-IFN treatment), a non-significant increase in CD4 cell count was found. The CD4 percentages were available for 54 patients at week 0 and for 48 patients between weeks 20 and 28. The CD4 percentage was 25% at week 0 and 27% between weeks 20 and 28.

HIV RNA levels during (PEG)-IFN treatment

Table 11.1 shows the HIV RNA levels at the start of (PEG)-IFN and 24 weeks thereafter. The median HIV RNA levels increased from 1.4 $\log_{10}$ copies/ml (IQR,1.4-2.9) at (PEG)-IFN initiation to 1.7 $\log_{10}$ copies/ml (IQR,1.4-3.9) after 24 weeks. The modelled virologic trajectory showed a small non-significant increase in HIV RNA levels in the first 12 weeks; this tended to remain stable between weeks 12 and 24 and started to decrease after week 24 (Figure 11.1b).

Impact of (PEG)-IFN on AIDS and death

A total of 3293 (31%) of the HIV-infected patients, 28% of the HIV+/HCV- patients, 31% of the HIV/HCV-co-infected patients with (PEG)-IFN, and 38% of the non-treated HIV/HCV-co-infected patients progressed to have AIDS (Table 11.1).

Overall, 8602 (80%) of the patients initiated cART; HCV-co-infected patients were more often treated with cART than those who were not co-infected. The time from cART initiation to development of AIDS was not associated with hepatitis co-infection (p=0.05, log-rank test).

The adjusted risk of progression to AIDS was 0.84 (95% confidence interval [CI], 0.11-6.40) in HIV/HCV-co-infected patients receiving (PEG)-IFN compared to HIV/HCV-co-infected patients who did not receive treatment. Among patients with HIV only, the risk of progression to AIDS was also non-significantly lower (Table 11.2).

Death resulted during follow-up in 835 (8%) of the patients. As shown in Figure 11.2, HCV-co-infected patients died significantly more rapidly than the non-co-infected patients (p log rank test <0.0001). Time to death did not significantly differ between HCV co-infected patients receiving (PEG)-IFN and those not receiving treatment.

Five years after cART initiation, all-cause mortality was highest amongst those patients with a HIV/HCV-co-infection who did not receive (PEG)-IFN (10% [CI,8-12]); the mortality rate among the HIV/HCV co-infected patients receiving (PEG)-IFN was lower at 5% (3-14), and 5 years after the start of cART, 4% (3-4) of the non-co-infected patients had died.

Patients with an HIV/HCV-co-infection who received (PEG)-IFN were observed to have a somewhat lower risk of death than HIV/HCV-co-infected patients who did not receive (PEG)-IFN, whereas those with HIV who were not co-infected with HCV had a significantly decreased risk of death (Table 11.2).

Discussion

This study shows that only a small proportion of the HIV/HCV-co-infected patients are treated for HCV. Amongst those patients who were treated for HCV, a major decrease in CD4 cell counts was observed with (PEG)-IFN treatment. However, the CD4 percentages remained stable, and the risk of progression to AIDS did not increase. The risk of death in the patient group treated with (PEG)-IFN was higher than that in the non-co-infected patients, but this increase was not significant and not as high as the risk of death in HIV/HCV-co-infected patients who did not receive treatment.

The low implementation of HCV treatment in the HIV/HCV-co-infected population in the Netherlands is a concern. In our study, only 8% of the co-infected patients received HCV treatment, which is comparable to the Swiss HIV cohort study[91] in which 23% of the HIV/HCV-co-infected patients were eligible for HCV treatment, but only 8% actually received HCV treatment.

Another concern is the finding that 12% of the HIV-infected patients were not screened for HCV antibodies. HCV-infected patients in need of HCV treatment are amongst this group. To further reduce the impact of HCV-co-infection on morbidity and mortality, HIV-infected patients need to be screened for HCV. The proportion of HIV-infected patients being screened for HCV antibodies is increasing; it has risen from 64%, as reported in the scientific report of 2006[16], to 82% in 2007.

The increased risk of death in the HIV/HCV patient group compared to the HIV-mono-infected patients has been described in earlier studies[84, 85]. We found a lower risk of death in the HIV/HCV patient group that received treatment with (PEG)-IFN compared to the HIV/HCV-co-infected group that was not treated, which is probably a result of the selection of patients. HCV treatment is complicated and not recommended in the presence of decompensated cirrhosis, neuropsychiatric disorders, or alcohol abuse[90, 186]. In patients with low CD4 cell counts and high HIV RNA levels, the suppression of HIV RNA and an increase in CD4 cell count through cART needs to be considered before the initiation of HCV treatment[187]. Consequently, HIV/HCV-co-infected patients with advanced HIV infection are less likely to receive HCV treatment.

The decline in CD4 cell counts during (PEG)-IFN treatment has been described previously[89, 188]. As in our study, the CD4 cell percentage did not decrease in those trials, and during the decrease in CD4 cell count, the risk of progression to AIDS did not increase. This indicates that a declining CD4 cell count does not result in poorer immune function. However, as in our study, the majority of the patients included in these trials had high CD4 cell counts. Since CD4 cell counts decline to about half of the baseline values during (PEG)-IFN treatment, such drops may still have an effect on the risk of AIDS in those patients with CD4 cell counts below 200. The response to treatment with (PEG)-IFN in patients with low CD4 cell counts is controversial; some studies have shown a poor response to HCV treatment amongst patients with low CD4 cell counts, whereas others have not[189, 190].

Some limitations to our study should be mentioned. First, we were not able to confirm all positive test results for HCV antibody with an HCV RNA test. The samples that were positive for HCV antibody but were not confirmed were classified as HCV-positive, which might have resulted in an overestimation of the HCV prevalence, or there might have been an underestimation of the increased risk of death in the HIV/HCV-co-infected group. Second, no conclusions can be drawn from this analysis regarding response to HCV treatment without the availability of data on HCV genotype and HCV RNA test results at the end of treatment for all patients. However, the results from this study are not derived from a clinical trial and are representative of the general population of HIV/HCV-co-infected patients.

In conclusion, although CD4 cell counts sharply declined during (PEG)-IFN treatment, no effect on AIDS-related morbidity or mortality was observed. Unfortunately, the low implementation of HCV treatment in the HIV/HCV-co-infected population will not reduce the morbidity and mortality related to liver disease. Therefore, efforts should be made to make HCV treatment more accessible to the general population of HIV/HCV-co-infected patients.

Acknowledgements

We thank J. Arends for his clinical input.

		Total	HIV+/HCV-	HIV+/HCV+ (PEG)-IFN	HIV+/HCV+
Demographic characteristics					
Number (%)		10777	9764 (91)	83 (1)	930 (9)
HCV RNA test result	Positive	-	-	68	496
	Missing	-	-	15	434
Age (median, IQR)		35 (29-42)	35 (29-42)	31 (25-37)	33 (28-40)
Gender	Male	8423 (78)	7659 (78)	63 (76)	701 (75)
	Female	2354 (22)	2105 (22)	20 (24)	229 (25)
Transmission category:	Homosexual	5760 (53)	5537 (57)	22 (27)	201 (3)
	Heterosexual	3548 (33)	3397 (35)	16 (19)	135 (4)
	IDU	560 (5)	102 (1)	22 (27)	436 (78)
	Other/unknown	909 (8)	728 (7)	23 (28)	158 (17)
Region of origin:	Netherlands	6018 (56)	5398 (55)	56 (67)	564 (61)
	Europe	929 (9)	731 (7)	18 (22)	180 (19)
	Sub-Saharan Africa	1851 (17)	1791 (18)	2 (2)	58 (6)
	Latin America/Caribbean	1232 (11)	1176 (12)	1 (1)	55 (6)
	Other	747 (7)	668 (7)	6 (7)	73 (8)
Number of AIDS events (%)		3293 (31)	2905 (28)	31 (37)	357 (38)
Number of deaths (%)		835 (8)	633 (6)	12 (14)	190 (20)
Baseline characteristics					
cART initiation		8602 (80)	7742 (79)	78 (94)	782 (84)
CD4 cell count at cART initiation (x 10^6 cells/l) (median, IQR)		190 (80-310)	190 (80-310)	241 (90-403)	180 (90-300)
HIV RNA levels at cART initiation (log_{10} copies/ml) (median, IQR)		4.9 (4.3-5.3)	4.9 (4.3-5.3)	4.6 (3.7-5.3)	4.8 (4.1-5.3)
CD4 cell count at (PEG)-IFN initiation (x 10^6 cells/l) (median, IQR)				400 (270-610)	
HIV RNA levels at (PEG)-IFN initiation (log_{10} copies/ml) (median, IQR)				1.4 (1.4-2.9)	
CD4 cell count percentage (median, IQR)				25 (16-34) **	
24 weeks after start (PEG)-IFN treatment					
CD4 cell counts (x 10^6 cells/l) (median, IQR)		-	-	240 (140-460)	-
CD4 cell count percentage (median, IQR)				27 (18-37)#	
HIV RNA levels (log_{10} copies/ml) (median, IQR)		-	-	1.8 (1.4-3.9)	-
HCV RNA clearance during follow up				35 (42)	14 (2)

** 29 CD4 percentages were missing
# 35 CD4 percentages were missing

HCV: hepatitis C virus; (PEG-IFN: pegylated interferon; IQR: interquartile range; cART: combination antiretroviral therapy

Table 11.1: Demographic and baseline characteristics among HIV-infected patients without HCV-co-infection, HIV/HCV-co-infected patients who were treated with (PEG)-IFN, and HIV/HCV-co-infected patients who were not treated.

	AIDS		Death	
	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)**
HIV/HCV-co-infected,				
no (PEG)-IFN	1	1	1	1
HIV/HCV-co-infected, receiving (PEG)-IFN earlier	0.68 (0.09-5.11)	0.84 (0.11-6.40)	0.60 (0.14-2.49)	0.89 (0.21-3.76)
HIV non-co-infected patients	1.00 (0.59-1.70)	0.84 (0.49-1.43)	0.46 (0.31-0.66)	0.59 (0.36-0.97)

* adjusted for age at HIV diagnosis, sex, risk group, ethnicity, baseline CD4 cell count and HIV RNA levels.
**adjusted for age at HIV diagnosis, sex, risk group and baseline CD4 cell count .

HCV: hepatitis C virus; HR: hazard ratio; CI: confidence interval; (Peg)-IFN: pegylated interferon

Table 11.2: Risk of an AIDS-defining event and death amongst HIV/HCV-co-infected patients after receiving HCV treatment compared to HIV/HCV-co-infected patients not treated for their HCV infection.

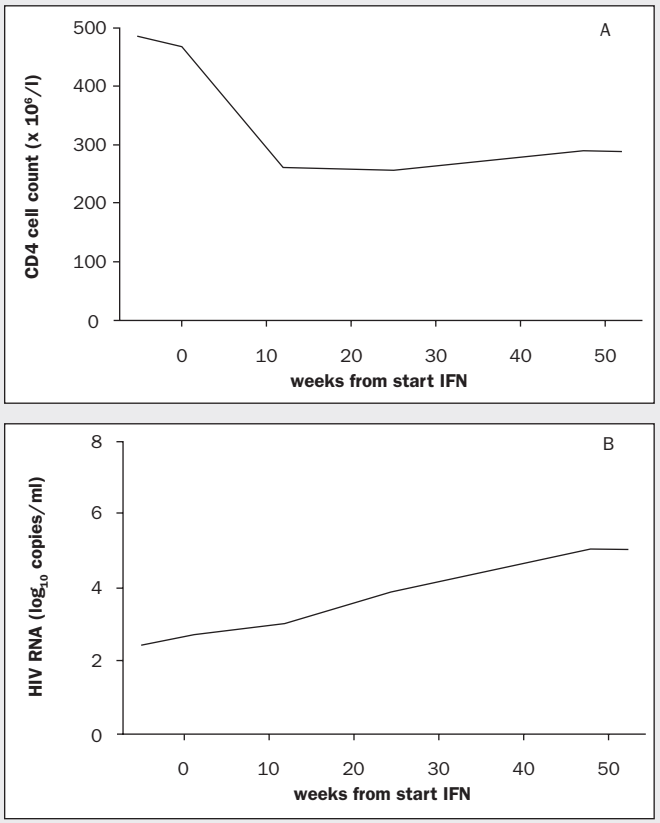

Figure 11.1a/b: Piecewise modelled trajectories of CD4 cell counts (A) and HIV RNA level (B) during (PEG)-IFN treatment amongst HIV/HCV-co-infected patients. Time is in weeks from (PEG)-IFN initiation, slopes were allowed at week 0, 12, 24 and 48.
(PEG)-IFN: pegylated interferon; HCV: hepatitis C virus

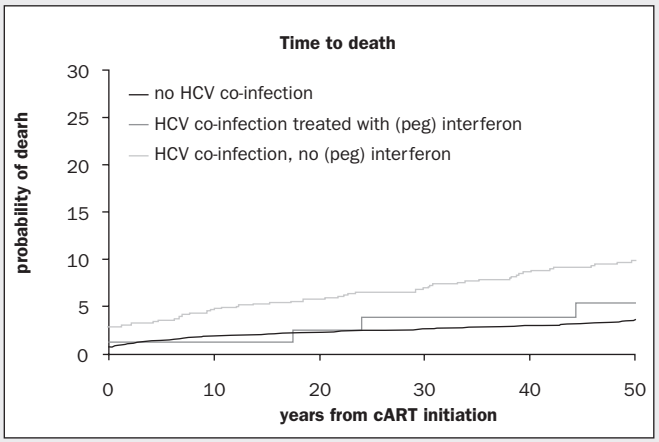

Figure 11.2: Probability of death during the first 5 years of cART use, among HIV-infected patients, HIV/HCV-co/infected patients treated with (PEG)-IFN during these 5 years and HIV/HCV-co-infected patients who were never treated with (PEG)-IFN.
cART: combination antiretroviral therapy; HCV: hepatitis C virus; (PEG)-IFN: pegylated interferon

Death a

nd AIDS

Ard van Sighem

Introduction

Since the introduction of combination antiretroviral therapy (cART) a decade ago, the HIV-related mortality and incidence rates of AIDS in Europe and North America have declined substantially in treated patients compared to those in untreated patients[67, 92-95]. As a result, the prognosis of HIV-infected patients has improved, and for successfully treated patients, it has been shown that mortality rates approach those of uninfected patients[96-99, 191]. Hence, HIV is gradually acquiring the characteristics of a chronic, rather than a lethal, disease.

This chapter presents an updated analysis of annual mortality rates and incidence of AIDS in the total HIV-infected population and in the cART-treated population in the Netherlands since 1996. A prognostic model is presented for predicting survival probabilities of HIV-infected patients after diagnosis with HIV. This model complements existing models, which hitherto assessed survival only in cART-treated patients or in patients who tested positive for HIV without a concurrent AIDS diagnosis[16,96].

Population and methods

The total study population consisted of 12,915 HIV-1-infected patients with a known date of HIV diagnosis. From this population, a subpopulation of 10,227 (79.2%) patients was selected that comprised all patients who started cART between 1995 and 1 June 2007, the data-freeze date for this report. All deaths and cases of AIDS (CDC-C events) occurring in the total population in 1996 or later were assessed[15]. On the basis of the clinical data at the time of death, causes of death were scored as HIV-related, non-HIV-related, or unknown.

Annual mortality and AIDS incidence rates were calculated as the number of deaths or AIDS cases per year divided by the total number of person-years of follow-up during that year. The Poisson distribution was used to calculate 95% confidence intervals (CI) for rates. The significance of changes in rates over time was assessed with generalized linear models.

Of the patients with a known date of diagnosis, a second subgroup was selected that consisted of 6171 patients who were diagnosed at 16 years of age or older between 1998 and 2006. Those patients had to be either untreated until the end of follow-up or treated with cART without antiretroviral treatment prior to the start of cART. Furthermore, a measurement of CD4 counts and viral load within 12 weeks after diagnosis but prior to treatment was required. Centers for Disease Control (CDC) stage at diagnosis was defined as the most serious CDC event recorded within 6 weeks after diagnosis[15].

In this group, progression to death was analysed by a multivariate hazards model. The hazard of death was calculated as the sum of an expected hazard and a function containing patient-specific covariates. The expected hazard depended on the patient's age and gender and was estimated from the annual mortality rate in the general population in the Netherlands between 2000 and 2005 [Actuarial Association, Woerden, 2007, soon available via http://www.ag-ai.nl]. Patient-specific covariates were retained in the model if their exclusion yielded a significantly less accurate model ($p<0.01$, likelihood ratio test). The hazard ratio (HR) was calculated for each covariate together with a Wald 95% CI. Initially, all AIDS-defining events at diagnosis were included in the model where individual patients could have had multiple events. Patients with multiple AIDS events were then classified according to the event with the highest hazard ratio.

The model showed that after adjusting for other covariates, patients with CD4 counts below 200×10^6 cells/l who were diagnosed in or before 2000 had a lower hazard of death than patients diagnosed after 2000. To remove this bias, the model was refitted with use of stabilised inverse

probability of treatment weights (IPTW)[192]. Weights were obtained by fitting a logistic regression model that included possible confounders: gender, transmission route, age, region of origin, hospital, individual AIDS-defining events, CDC-B status, and whether the patients died within a year after diagnosis.

Results

Mortality and incidence of AIDS

In the total group of 12,915 patients with 78,635 person-years of follow-up since 1996, 1127 cases of death were recorded (Table 12.1). This number corresponded with an average mortality of 1.43 (95% CI 1.35–1.52) deaths per 100 person-years. The mortality slightly decreased over time (p=0.008), from 1.95 (1.55–2.41) in 1997 to 1.23 (0.87–1.68) in 2007 (Figure 12.1). When patients who had an AIDS diagnosis within 6 weeks after an HIV diagnosis (N=2004) were excluded, the overall mortality was reduced to 1.22 (1.14–1.31) per 100 person-years and did not change over time (p=0.3). The mortality rate was also lower, 1.07 (0.98–1.17), and likewise did not change over time (p=0.8), when only patients diagnosed in or after 1996 were considered (N=9534, 45,163 person-years of follow-up, 483 cases of death).

For the total group, 3791 AIDS diagnoses were registered at or after HIV diagnosis. There were 2225 new AIDS diagnoses recorded 6 weeks or longer after an HIV diagnosis, of which 1771 (79.6%) were recorded in or after 1996. The total follow-up until AIDS diagnosis was 66,533 years, yielding an average AIDS incidence of 2.66 (95% CI 2.54–2.79). From 1996 onwards, there has been a decline (p<0.001) in AIDS diagnoses per 100 person-years from 9.2 (8.2–10.3) in 1996 to 1.6 (1.4–2.4) in 2006 (Figure 12.1). Incidences were higher before 2000 when only patients diagnosed in or after 1996 were considered, such as 13.7 (9.8–18.7) in 1996, but after 2000 the incidence of AIDS did not differ from that in the total group.

The population of patients starting cART consisted of 2325 patients with prior antiretroviral treatment (18,555 person-years of follow-up since 1996, 504 deaths) and 7902 previously therapy-naïve patients (38,622 person-years of follow-up, 469 deaths). The mortality rate declined from 4.5 (3.0–6.5) per 100 person-years in 1996 to 1.21 (0.82–1.71) in 2007. On average, the mortality after 2000 was 1.49 (1.38–1.62) and tended to decline over time (p=0.05; p=0.1 if 2007 was excluded). In the therapy-naïve population, mortality was lower than in the pre-treated population, that is, 1.17 (1.05–1.29) compared to 2.41 (2.13–2.71) per 100 person-years after 2000. Between 1996 and 2007, the overall mortality in the naïve population was 1.21 (1.11–1.33) per 100 person-years and did not change over time (p=0.06). When patients with an AIDS diagnosis in the year prior to the start of cART were excluded, the mortality rate was 1.32 (1.22–1.44) per 100 person-years and also did not change over time (p=0.09).

In the total group who ever started cART, 1196 AIDS diagnoses were registered during 52,392 person-years of follow-up after the start of cART. The incidence of new AIDS diagnoses decreased dramatically from 14.7 (11.9–18.1) in 1996 to 2.05 (1.64–2.54) in 2000. Thereafter, the AIDS incidence was on average 1.76 (1.62–1.90) per 100 person-years with a decrease (p<0.001) slower than before 2000 to 1.34 (1.08–1.63) in 2006. In the therapy-naïve population (35,938 person-years of follow-up), the incidence of AIDS after 2000 was similar to that in the pre-treated population (16,454 person-years of follow-up), being 1.71 (1.57–1.88) per 100 person-years in the therapy-naïve population and 1.65 (1.41–1.93) in the pre-treated population.

Figure 12.2 shows that the proportion of patients who died of HIV-related causes between 1996 and 2007 declined from 77% to 36% (p<0.001). This decrease was counterbalanced by an increase in the proportion of non-HIV-related causes, 9% in 1996 and 41% in

2007 ($p<0.001$). The proportion of patients for whom the cause of death was not registered or could not be classified was 13% and did not change over time ($p=0.3$). In patients on cART, non-HIV-related causes accounted for 48% and HIV-related causes for 40% of the combined 2006 and 2007 cases of death. Of the 456 HIV-related causes of death, 251 (55%) occurred in patients who had an AIDS diagnosis in the year before the start of cART. When these patients were excluded, the proportion of non-HIV-related causes was 48%, and HIV-related causes comprised 35%.

Prognostic model

The study population for the prognostic model consisted of 6171 patients (47.8% of the HIV-1-infected population), with a total follow-up of 21,917 person-years. Characteristics of the patients are shown in Table 12.2. During follow-up 231 deaths were recorded, corresponding to an average mortality rate of 1.05 (95% CI, 0.92-1.20) per 100 person-years. Of the patients presenting with AIDS at HIV diagnosis, 20 (19%) of those who died did so before the start of cART. The proportion of patients dying before the start of cART was 11% (8 out of 73) for patients diagnosed in or before 2000 and 25% (39 out of 158) for patients diagnosed thereafter ($p=0.02$).

Hazard ratios (HR) of covariates associated with progression to death are shown in Table 12.3. Also shown are the hazard ratios for a similar model that was fitted to 4978 patients (115 cases of death) from the total population who did not have an AIDS event at diagnosis and who were not infected via injection drug use. The most important covariates associated with progression to death were lower CD4 cell counts, infection via intravenous drug use (IDU), and, for those with a concurrent AIDS event at diagnosis, the type of AIDS event. Even after the age at diagnosis was taken into account in the hazard of death as expected from the mortality rate in the general population, there still was a residual effect of age on death in patients who were diagnosed at the age of 50 years or older (HR 2.32 [95% CI, 1.60-3.35]). This effect of age persisted when patients with AIDS events and patients infected via IDU were excluded.

The model showed that patients who were diagnosed after 2000 had a higher risk of death, specifically, 2.3 (1.0-5.0) for patients with CD4 cell counts above 200×10^6 cells/l and 2.4 (1.5-3.9) for patients with counts below 200×10^6 cells/l, compared to patients diagnosed in or before 2000 with counts below 200×10^6 cells/l. Likewise, patients with CD4 cell counts above 200×10^6 cells/l and diagnosed in or before 2000 had a higher risk of death, which was 2.8 (1.2-6.4). Because these hazard ratios were not significantly different from each other, a dichotomous variable was included in the model indicating whether patients were diagnosed in or before 2000 with CD4 counts below 200×10^6 cells/l (HR 2.41 [1.47-3.94]). An HIV diagnosis after 2000 was significantly associated with a worse prognosis in the total population but not in the non-IDU patients without a concurrent AIDS-defining event at diagnosis, although the hazard ratio was similar in the two models.

In the IPTW model, an HIV diagnosis in or before 2000 with less than 200×10^6 cells/l at diagnosis was not significantly associated with progression to death. In the model for the total population, hazard ratios generally increased, whilst for the model of the population of non-IDU patients without AIDS, the hazard ratios remained almost the same or decreased. Confidence intervals tended to broaden.

Discussion

Since 1996, the overall mortality rate in the HIV-infected population in the Netherlands has slightly declined to a level just above 1 death per 100 person-years of follow-up, which was lower than reported in a recent Danish

study[98]. In contrast, mortality rates in the cART-treated population have declined over time to a level similar to those in the total infected population. However, this decline was observed only in the pre-treated population; since the pre-treated population accounts for only 18% of the total HIV-infected population, this explains why the effect of cART in the total population was minimal. Presently, the mortality rate amongst pre-treated patients is still 2 times higher than amongst therapy-naïve patients, although the incidence of AIDS events is the same in both populations.

In our last report, the mortality rate of 0.84 (95% CI 0.54–1.24) reported for 2006 was substantially lower than that observed for 2005[16]. In the current analysis, the rate for 2006 increased to 0.97 (95% 0.79-1.19), still lower than the currently reported value for 2005, 1.40 (1.18-1.66), but less sharp. The mortality rate currently reported for 2007 was higher than for 2006. However, as already pointed out in our last report, because the data collection for 2007 (and, for some treatment centres, also for 2006) has not yet been completed, no firm conclusions can be drawn from these observations.

Although mortality rates only slightly declined over time, there was a substantial shift in the causes of death. In 1996, most causes of death were HIV-related, but since 2000 almost half of them have been attributable to causes not directly related to the HIV infection. For 15% to 20% of the patients, the cause of death could not be classified owing to lack of complete information. In order to have a more uniform and internationally accepted classification of cause of death, the HMF adopted the CoDe (Coding of Death in HIV) classification scheme[165]. The first results of this CoDe classification are shown elsewhere in this report.

The prognostic model showed that some AIDS-defining events had a stronger association with progression to death than others. A concurrent diagnosis with progressive multifocal leukoencephalopathy (PML), malignant lymphoma, or AIDS dementia complex was, in order of decreasing hazard ratio, associated with a very poor survival probability[193]. Also patients with toxoplasmosis had a poor prognosis, but other AIDS events were not significantly associated with prognosis, except via an overall time-dependent AIDS-associated hazard. Some AIDS-defining events are at least as serious as toxoplasmosis, e.g. cryptosporidiosis, but the frequency of those events in the study population was very low[193]. Other AIDS-defining events like Pneumocystis carinii pneumonia (PCP) and candidiasis can be effectively treated and are not lethal per se.

According to the model, patients diagnosed with CD4 cell counts below 200×10^6 cells/l had a better prognosis when diagnosed in or before 2000 than thereafter. Most likely, this result is due to a bias in the inclusion of patients. Before 2001, the ATHENA study registered only patients on cART. Since 2001, the HIV Monitoring Foundation (HFM) registered essentially all patients with HIV who were alive at the time of registration. Thus, HIV-infected patients who did not use cART and who died before 2001 were not included in the database, although some of those patients were included retrospectively after HMF commenced data collection. Still, relatively more patients diagnosed after 2000 than ones diagnosed before then died before the start of cART. Use of the IPTW method, which gives more weight to patients diagnosed before 2000 with low CD4 cell counts, largely removed the bias introduced by the transition from ATHENA to HMF.

In the population of patients diagnosed after 2000, calendar year had no effect on progression to death when adjusted for all the other covariates. This indicates that even if the prognosis of patients diagnosed after 2000 has been less favourable than it was for those diagnosed before 2000, at least, it is not becoming worse over time.

This model for progression to death complements, but does not replace, the previous model that took into account the initial response to therapy to predict progression to death after the start of cART[96]. In the event that a patient starts cART, the probability of survival after the initial response will be predicted more accurately with our earlier model.

	AIDS			death	
	total	≥ 6 weeks after diagnosis	after start of cART	total	after start of cART
≤1995	727	454	1	1	-
1996	358	285	90	43	29
1997	303	180	130	84	68
1998	246	132	115	82	73
1999	233	134	115	90	88
2000	243	112	86	83	80
2001	254	146	97	77	76
2002	294	155	122	120	84
2003	282	135	103	138	117
2004	273	157	110	142	125
2005	314	172	114	134	120
2006	221	135	94	95	82
2007	43	28	20	39	31
	3791	**2225**	**1197**	**1128**	**973**

cART: combination antiretroviral therapy

Table 12.1: Annual number of cases of death and AIDS.

CDC status	aymptomatic		CDC-B		CDC-C		total	
	4535	73.5%	518	8.4%	1118	18.2%	6171	100%
	N	%	N	%	N	%	N	%
gender, male	3374	74.3	419	80.8	886	79.2	4679	75.8
transmission category								
MSM	2422	53.4	282	54.4	466	41.6	3170	51.3
heterosexual contact	1796	39.6	174	33.5	474	42.3	2444	39.6
injection drug use	62	1.3	13	2.5	13	1.1	88	1.4
other/unknown	255	5.6	49	9.4	165	14.7	469	7.6
region of origin								
the Netherlands	2464	54.3	318	61.3	543	48.5	3325	53.8
sub-Saharan Africa	991	21.8	80	15.4	263	23.5	1334	21.6
other	1080	23.8	120	23.2	312	27.9	1512	24.5
started cART	2892	63.7	468	90.3	1063	95.0	4423	71.6
progression to death	92	2.0	31	5.9	108	9.6	231	3.7
before cART	22	24	5	16	20	19	47	20
	median	**IQR**	**median**	**IQR**	**median**	**IQR**	**median**	**IQR**
age	35.8	29.4–42.7	38.5	32.9–46.4	38.8	32.9–47.1	36.6	30.3–43.6
CD4 (10^6 cells/l)	390	230–580	130	50–310	44	20–110	304	119–510
$\log_{10}$ RNA (copies/ml)*	4.6	4.0–5.0	5.0	4.7–5.5	5.1	4.9–5.6	4.8	4.2–5.2
follow-up (years)	3.1	1.5–5.2	3.7	1.5–5.9	3.5	1.4–6.0	3.2	1.5–5.4
total follow-up (person-years)	15676		2005		4236		21917	

*available for 4362 asymptomatic patients, 497 patients with a CDC-B event, and 1029 patients with a CDC-C event.

CDC: Centers for Disease Control and Prevention; MSM: men having sex with men; cART: combination antiretroviral therapy; IQR: interquartile range

Table 12.2: Patient characteristics.

	total population			population excluding IDU and AIDS at diagnosis		
	HR	**95% CI**	**p**	**HR**	**95% CI**	**p**
age at diagnosis >50 years	2.29	1.59-3.32	$<10^{-3}$	2.55	1.31-4.95	0.006
	2.36	1.63-3.41	$<10^{-3}$	2.44	1.20-4.96	0.01
IDU	4.27	2.03-9.00	$<10^{-3}$	-		
	4.24	1.97-9.09	$<10^{-3}$	-		
log CD4 at diagnosis (10^6 cells/l) per unit increase	0.67	0.58-0.77	$<10^{-3}$	0.54	0.44-0.67	$<10^{-3}$
	0.70	0.60-0.81	$<10^{-3}$	0.56	0.45-0.69	$<10^{-3}$
CDC-B at diagnosis	2.55	1.46-4.44	$<10^{-3}$	2.15	1.17-3.97	0.01
	2.66	1.53-4.62	$<10^{-3}$	2.05	1.11-3.82	0.02
AIDS at diagnosis						
PML	46	18-113	$<10^{-3}$	-		
	52	21-128	$<10^{-3}$	-		
lymphoma	25	14-46	$<10^{-3}$	-		
	28	15-52	$<10^{-3}$	-		
AIDS dementia	11	5.1-22	$<10^{-3}$	-		
	13	6.3-26	$<10^{-3}$	-		
toxoplasmosis	4.2	2.0-8.8	$<10^{-3}$	-		
	4.7	2.3-9.7	$<10^{-3}$	-		
other	1.76	1.02-3.04	0.04	-		
	1.91	1.12-3.28	0.02	-		
diagnosis after 2000 or CD4 at diagnosis >200 × 10^6 cells/l	2.41	1.47-3.94	$<10^{-3}$	2.94	1.16-7.47	0.02
	1.53	0.92-2.55	0.1	1.98	0.73-5.37	0.2
baseline hazard*	**est.**	**95% CI**	**p**	**est.**	**95% CI**	**p**
intercept	7.04	6.41-7.67	$<10^{-3}$	7.69	6.57-8.81	$<10^{-3}$
	6.64	6.02-7.25	$<10^{-3}$	7.26	6.11-8.40	$<10^{-3}$
log time (years)						
no AIDS	0.30	0.09-0.51	0.006	0.30	0.09-0.52	0.005
	0.29	0.08-0.51	0.008	0.29	0.06-0.52	0.02
AIDS	0.75	0.57-0.93	$<10^{-3}$	-		
	0.75	0.57-0.92	$<10^{-3}$	-		

IPTW: inverse probability of treatment weighting; IDU: injection drug use; CI: confidence interval; CDC: Centers for Disease Control and Prevention; PML: progressive multifocal leukoencephalopathy; est.: parameter estimate; *parameters should be multiplied by -1.

Table 12.3: Covariates and hazard ratios (HR) associated with progression to death. For each covariate, the upper row shows the hazard ratios for the main model, whereas the lower row shows the hazard ratios for the IPTW model.

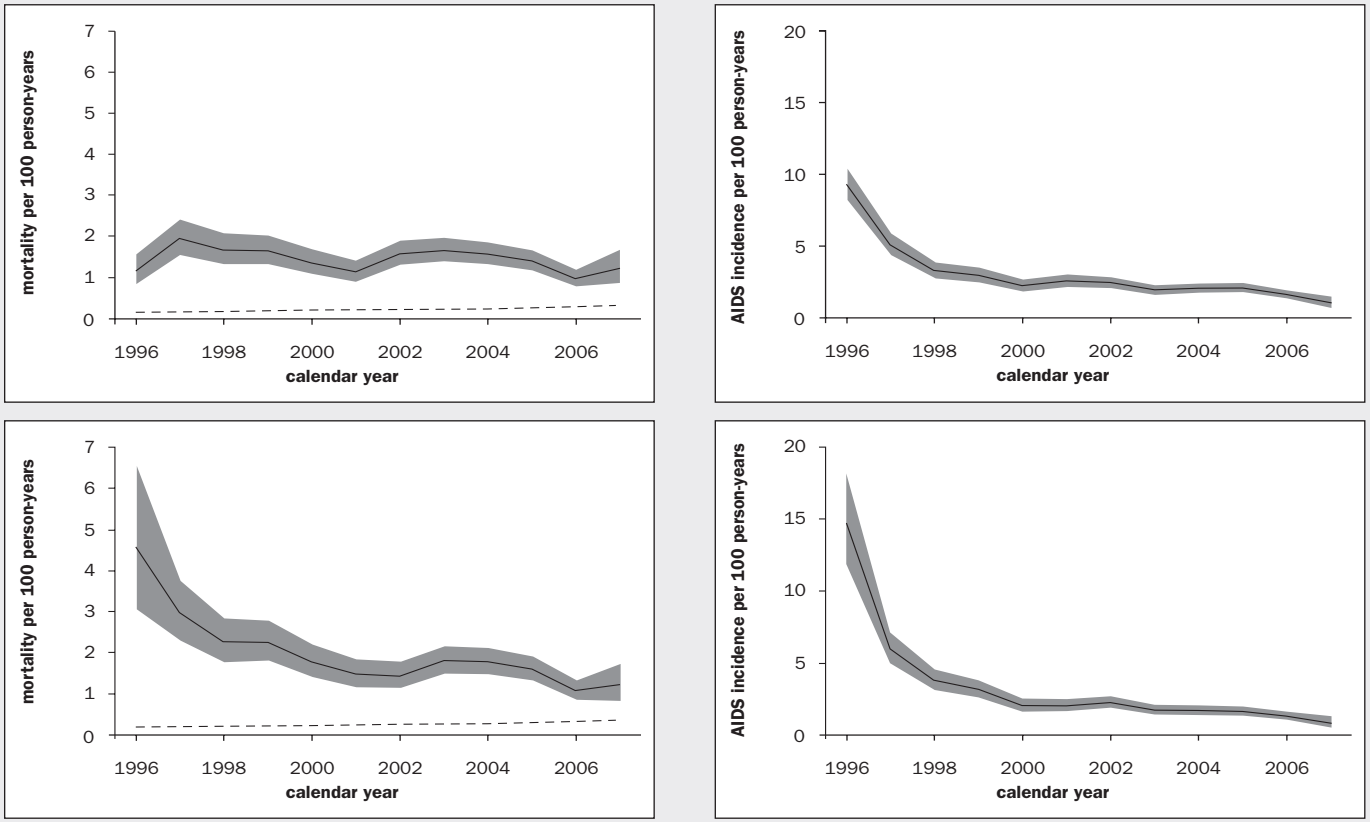

Figure 12.1: Mortality and incidence of AIDS as a function of calendar year after diagnosis (upper plots) and after start of cART (lower plots). The black lines represent the incidence, whilst the grey areas are the 95% confidence intervals. The dotted line is the mortality rate expected for age- and gender-matched individuals from the general Dutch population.

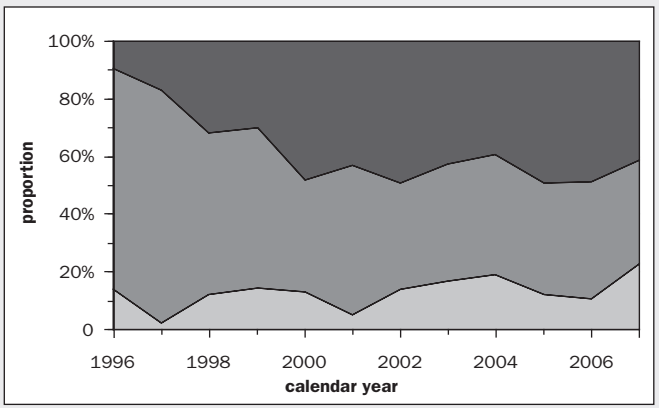

Figure 12.2: Proportion of deaths by calendar year from causes not related to HIV (top), causes related to HIV (middle), and unknown causes (bottom).

Resurgent

t epidemic

The HIV-1 epidemic amongst MSM in the Netherlands

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Introduction

In the beginning of the 1980's, the first AIDS cases in the Netherlands were found amongst men having sex with men (MSM)[100]. From 1996 onwards, combination antiretroviral therapy (cART) has become widely available. Because cART dramatically reduces plasma and seminal viral load and since infectivity is correlated with viral load, the widespread use of cART might thus be expected to have reduced the incidence of HIV infection[101-107]. Paradoxically, the annual number of diagnoses amongst MSM is increasing not only in the Netherlands but also in other Western countries[16, 108]. Also, increases in risk behaviour and in diagnoses of syphilis and gonorrhoea have been reported[17, 109, 110].

Mathematical models have shown that an increase in risk behaviour can counterbalance the beneficial effect of cART[111-118]. In the present study, we aim to evaluate the separate impact of risk behaviour, HIV testing behaviour, and cART on the HIV epidemic in MSM in the Netherlands by means of a mathematical model fitted to data from the ATHENA cohort and from the Amsterdam Cohort Studies.

Methods

A mathematical model describing HIV transmission and cART use among MSM in the Netherlands was constructed. The model describes natural disease progression, diagnosis, and subsequent use of cART. The rate of new HIV-1 infections was modelled as a function of the number of currently infected individuals and that of individuals entering the country with infections acquired abroad. Relative changes in infectiousness were related to the relative rate of high-risk sexual contacts, to the stage of the infection, to whether patients were diagnosed (on the assumption that diagnosed individuals might take fewer risks), and to treatment.

Disease progression in the absence of cART was described by a unidirectional flow through five compartments, with a mean stay in each of 1.89 years. This model best describes disease progression in 130 MSM seroconverters from the Amsterdam Cohort Studies before cART. Patients at the start of the disease progression were assigned for 0.24 year to an extra initial compartment that represented primary infection. The last stage of infection was equated with AIDS. Primary infection and the last stage of infection were considered relatively more infectious than the other stages. Imported infections were all assumed to be at the stage of primary infection when the patients entered the Netherlands. For patients with an unknown country of infection, it was assumed that they were split according to the ratio observed respective to the country of birth in patients for whom the country of infection was known.

In the cART era, patients started cART after being diagnosed and were either treated successfully or experienced therapy failure. During successful treatment, cART was assumed to block both HIV transmission and disease progression. Patients experiencing treatment failure were assumed to have periods of successful treatment before failure. After failure, patients moved through the unidirectional stage of natural disease progression until treatment was again successful. It was assumed that there were three cART treatment opportunities before patients failed completely and progressed to death.

The net transmission rate was a time-varying function, which measured the relative rate at which HIV-positive infectious individuals infected new individuals. It was standardised and set as equal to 1 for untreated, undiagnosed individuals in the asymptomatic stage of infection during the first phase of the epidemic (1980-1983); thus, all other values were measured relative to that one. The transmission rate was used as a measure of change in risk behaviour.

The reproduction number, $R(t)$, is defined as the average number of people an infected person at time t would infect over his entire infectious lifespan, if conditions remained the same as at time t. It incorporates all

factors including risk behaviour, effect of diagnosis, and the effects of treatment with cART in preventing infection. If the within-country $R(t)$ is greater than 1, then the epidemic will grow exponentially, driven by local transmission, and conversely, if this number is less than 1, the epidemic will contract to a number proportional to the number of imported cases.

The model was fitted to the observed time-series of annual new diagnoses and of annual new AIDS cases[16, 194, 195]. These data were constrained by the diagnosis rate and the net transmission rate, which made it feasible to simultaneously estimate these unknown parameters. The analysis was stratified into 4 distinct historical intervals: 1980-1983, when the first AIDS cases were diagnosed; 1984-1995, when serologic testing became available, HIV awareness was increasing, and the first mono- and dual-antiretroviral therapies were introduced; 1996-1999, which was the early cART era; and 2000-2004, which is the current cART era.

The dependence of the model predictions on underlying assumptions was assessed with an extensive sensitivity analysis. Variations that were considered included: use of transmission probability per sex act instead of relative infectivity; different assumptions regarding cases with an unknown source of infection; lower infectiousness during primary infection; an earlier versus a later start of treatment; different percentage of patients failing treatment; more treatment opportunities; no reduction or cessation of risk behaviour after awareness of infection; slower disease progression; death rate in successfully treated individuals; only cART or a diagnosis at specific stages of progression; different assumptions regarding disease stage of imported infections; later implementations of cART; five time periods; and added diagnostic data for people with an unknown transmission route. The assumptions with the largest impact were found not to fit the data. None of the other assumptions altered the model predictions after they were refit to the data.

Results

Figures 13.1 and 13.2 show the model curves that resulted in the best fit with the observed annual number of diagnoses and AIDS diagnoses. The number of new infections amongst MSM per year in the Netherlands peaked in 1983, with 802 new infections, and that number was approximately 250 in the 15 years thereafter. Subsequently, the number of new infections increased from 224 in 1999 to 554 in 2004.

Between 1980 and 1983, the estimate for the reproduction number $R(t)$ was 2.39 (95% CI, 2.17-2.76), indicating an expanding epidemic. Between 1984 and 1995, the net transmission rate declined by a factor of 2.33 (2.03-2.83) relative to the period before, thereby indicating large reductions in risk behaviour. As a result, the reproduction number $R(t)$ was reduced to 0.89 (0.85-0.93), which is below one, and thus, just below the epidemic threshold.

After 1995, when cART was introduced, the reproduction number declined further to 0.76 (95% CI, 0.70-0.86). The reduction could have been larger if the transmission rate had not increased by 18% (3-34). During the period 2000 to 2004, the net transmission rate was estimated to have increased even more, returning to a level only 29% (22-72) below the value in the initial period of 1980 to 1983. A reduction in the estimated mean time from infection to diagnosis, which was 3.71 (3.49-3.97) years between 1984 and 1995 and 2.90 (2.84-3.03) years in the period after 2000, resulted in a much lower reproduction number than that in the initial period. Still, for the last period, $R(t)$ was estimated to be 1.04 (0.98-1.09), near or above the critical epidemic threshold, thus indicating that HIV once again has been spreading epidemically amongst MSM in the Netherlands.

The model predictions were subjectively verified for consistency with data in the ATHENA database on the number of currently living MSM (Figure 13.3). The quality of the fit was considered acceptable, given that the

model was not fitted to these data. From the model, it was estimated that 24% of all living HIV-positive MSM were unaware of their HIV-positive status at the start of 2005. These individuals accounted for 90% of the new infections. According to the model, by 2015 the number of known HIV-infected MSM will be 10,997.

On the basis of the best model fit, a number of hypothetical scenarios from 1995 onwards were explored. Without cART to limit infectiousness in treated patients, the epidemic under current conditions would have been much larger, with an estimated 7609 infections arising between 1995 and 2004, instead of the estimated 3665 in the main model. If, on the other hand, cART had been introduced but without any increases in the net transmission rate, the number of new infections during this period would have been only 1647. If cART had been introduced and if there had been the same increase in the net transmission rate, but with no increase in the rate of diagnosis, the cumulative number of new infections would have been 4132. Finally, if no changes had occurred since 1995, that is, no cART and no increase in risk and testing behaviour, this number would have been 2984. Thus, on the basis of these model estimates, it can be concluded that cART has played an important role in limiting transmission, but that any gains made have been more than offset by an increase in the net transmission rate. Had these increases not occurred in the cART era, the reproduction number $R(t)$ would have declined to 0.6, and the epidemic would have been in a convincing decline.

In addition, a number of hypothetical scenarios for the coming decade were explored. If nothing would change, the epidemic would spread uncontrolled, and the cumulative number of infections between 2005 and 2015 would reach 7815. If the frequency of testing was increased, such that the mean time from infection to diagnosis (and subsequent treatment) was reduced to one year, the cumulative number would be reduced to 3879. If the quality of treatment being offered was improved, such that the fraction of patients failing each line of therapy was halved, then the cumulative number of infections would reach 7262. If the net transmission rate was reduced to pre-cART levels, the cumulative number of infections could be reduced to 1630. Finally, if all three interventions could be successfully implemented, the number could be further reduced to only 952 new infections. From this analysis, it can be concluded that reducing the net transmission rate has the greatest impact on the epidemic.

Discussion

The joint effect of cART and risk behaviour on HIV incidence has been studied previously with mathematical models and empirical data[111-116]. Although those studies were based on different assumptions, all of them concluded that the benefits of cART in reducing transmission of HIV could be offset by an increase in risk behaviour. Our study shows new evidence that this has actually occurred in the MSM population in the Netherlands.

A key feature of this study is that the existence of a national database recording diagnoses of HIV infection and AIDS and deaths allows a reliable estimation of the rate of diagnosis. Thus, the model shows that there has been a recent increase in the diagnosis rate that reflects more frequent testing. The increase in testing was also apparent from the ATHENA data, since the number of MSM who were diagnosed within two years after being infected increased from approximately 10% in the second half of the 1990s to almost 30% in most recent years. Nevertheless, testing rates in the Netherlands are still low compared to other developed countries[196, 197].

One of the predictions of the model – assuming that all factors remained constant – was that the number of MSM with AIDS at diagnosis would increase over time. This result is expected since the annual number of infections increases, but the rate of diagnosis and, hence, the stage of infection at diagnosis does not change. The predicted number of AIDS diagnoses reached a nadir in 2003, with a subsequent increase thereafter.

Another prediction of the model – again assuming that all factors remained constant – was that the known HIV-infected population in 2015 would consist of almost 11,000 patients. In the next chapter, a mathematical model is presented that is able to predict the age distribution of MSM and heterosexually infected patients over time, but only for those who are aware of their HIV infection. This model predicts that there will be 10,637 infected MSM in 2015, which is just 360 less than in the model presented in this chapter.

Our model was also able to capture the HIV-infected population who were not yet aware of their infection. Thus, the total HIV-infected MSM population in 2005 was estimated at 6336. This is considerably lower than our previous estimate of 8500 homosexual men, which included men aged only between 15 and 49 years, which was obtained from a program developed by the Joint United Nations Programme on HIV and AIDS (UNAIDS) and the World Health Organization (WHO)[1]. Our estimated percentage of HIV-infected individuals unaware of their infection agreed with findings of a large sexually transmitted infection (STI) clinic in Amsterdam[196].

According to the model, cART slowed the HIV epidemic, although the number of prevented HIV infections could have been greater if the net transmission rate had not increased after 1995. The model suggests that the only way to substantially reverse the epidemic spread and reduce the $R(t)$ well below 1 is to reduce the net transmission rate from current levels. Hence, prevention focussing on reducing risk behaviour remains as crucial as it previously was in reducing the epidemic. However, a timely diagnosis also adds to the retraction of the epidemic, and more frequent testing might indirectly induce changes in risk behaviour. Therefore, in the Netherlands, testing should (again) focus on those groups who display high risk behaviour.

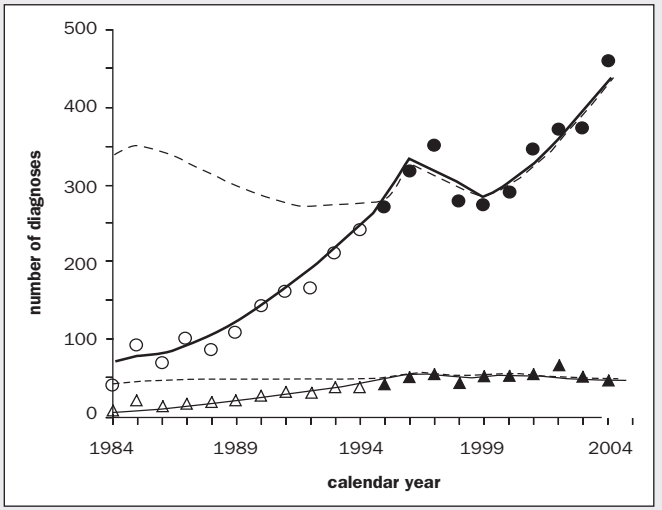

Figure 13.1: Annual number of diagnoses amongst MSM in the Netherlands. Thick lines and black dots represent cases acquired in the Netherlands, whereas thin lines and black triangles are cases acquired abroad. Empty triangles and empty circles represent years when data is available only for patients surviving until 1996, and dashed lines represent the estimated actual number of diagnoses. NB: Data on diagnoses were derived from data older than presented in the rest of this report.

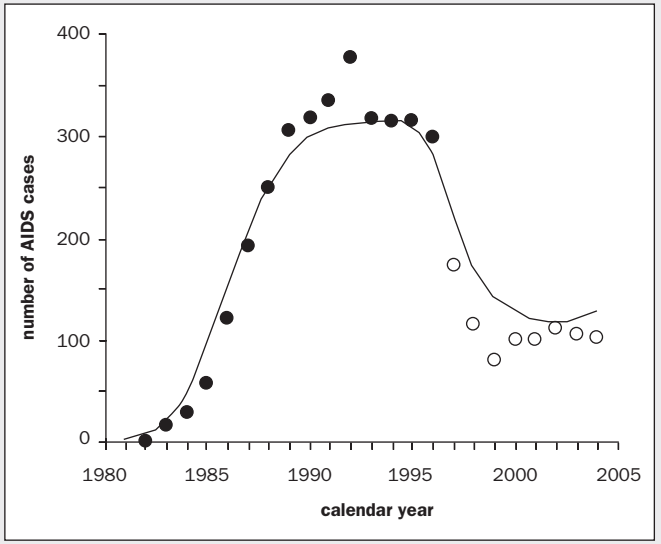

Figure 13.2: Number of new diagnoses of AIDS over time. Black dots represent data from the Dutch Health Inspectorate that were used in the fit. The empty circles are data from HMF and were used for model verification (not fitted).

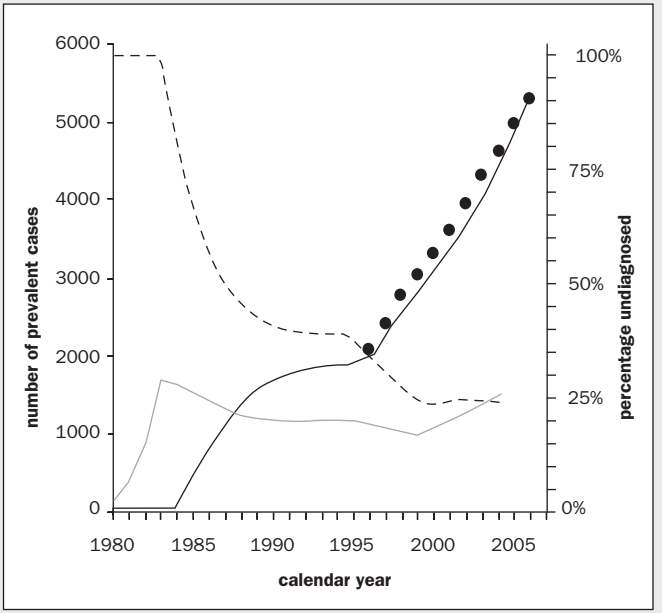

Figure 13.3: Number of prevalent cases as of 1 January of each calendar year. The dots represent the number of patients in ATHENA in follow-up. The thick black line is the number of prevalent cases predicted by the model. The thin black line (left axis) and dashed line (right axis) represent the number and percentage of patients who are unaware of their infection.


Age

The HIV-infected population in the coming ten years

Ard van Sighem

Introduction

As a result of the decreasing mortality and morbidity rates among HIV-infected patients due to the widespread treatment with combination antiretroviral therapy (cART), the HIV-infected population in the Western world is ageing[16, 119, 120]. In this chapter, using a mathematical model, we estimate the size and the ageing of the known HIV-infected population in the Netherlands in the coming years.

Methods

All patients who had an HIV-1 diagnosis before 1 January 2000 and were still alive and in follow-up at that date were selected from the ATHENA national observational cohort. These patients constituted the HIV-1-infected population in follow-up at 1 January 2000. Patients 12 years of age or younger and infected via non-sexual or unknown transmission routes were excluded. Analogously, the HIV-infected population on 1 January 2005 was defined.

A mathematical model consisting of a set of ordinary differential equations (ODEs) was used to describe changes in the HIV-infected population over calendar time since 2000. The model captured changes in the population, stratified by age, that resulted from new diagnoses or from death or loss to follow-up. Separate equations were used for men having sex with men (MSM), for men and women infected via heterosexual contact, and for men and women infected via other or unknown transmission routes. Also, separate equations were used for individuals originating from the Netherlands, sub-Saharan Africa, and other regions.

The growth rate of the patient population as a result of new diagnoses was estimated by fitting a linear model to the annual number of diagnoses recorded between 2000 and 2005 in the ATHENA cohort. Changes over calendar time in the proportion of newly diagnosed patients originating from each of the three regions were taken into account with a Poisson regression model. The age distributions of patients diagnosed between 2000 and 2005 were modelled with gamma distributions, discarding patients infected via other routes who were diagnosed at 12 years of age or younger.

The rate at which individuals disappeared from the HIV-infected populations – known as the rate of "death" – was estimated from the distribution of time from diagnosis (for patients diagnosed between 2000 and 2005) or from 1 January 2000 (for patients diagnosed before 2000 and still alive in 2000) until the date of death or, if patients were still alive, the latest date at which patients were known to be still in follow-up. Patients who were still in follow-up at 1 January 2006 were censored at that date. An exponential survival model was used to estimate the rates of death.

To predict the size and age distribution of the population in follow-up in 2015, it was assumed that from 2006 onwards, trends observed in the data between 2000 and 2005 would continue. In addition, four hypothetical scenarios were explored: (A) no new HIV-infected patients would originate from sub-Saharan Africa after 2006, (B) after 2006 the number of diagnoses amongst MSM would remain at the 2006 level, (C) a 10% or 20% increase would be expected in the number of diagnoses amongst patients of non-Dutch origin after 2006, (D) the year of diagnosis would be included in the model that was fitted to the age distribution of MSM.

Differential equations were solved numerically in Berkeley Madonna version 8.3.9 with the Runge-Kutta 4 algorithm. All other analyses were performed with SAS software (version 9.1.3; SAS Institute, Cary, North Carolina, USA).

Results

The total HIV-infected population in follow-up at 1 January 2000 consisted of 5666 individuals, of whom 3306 (58.3%) were MSM, 1407 (24.8%) were heterosexuals, and 953

(16.8%) were infected via other transmission routes (Table 14.1). In total, 672 (11.9%) patients were younger than 30 years, 1002 (17.7%) were 50 or older, and 4660 (82.2%) were between 15 and 50 years of age.

According to the linear model that was fitted to the data, the annual number of diagnoses amongst homosexual men increased from 348 in 2000 to 558 in 2005. During the same period, the number of diagnoses amongst heterosexual men increased from 148 to 182 and increased in heterosexual women from 221 to 255. No significant changes over time were observed in the number of diagnoses amongst patients infected via other or unknown transmission routes. The annual number of diagnoses was 79 amongst men and 15 amongst women.

Between 2000 and 2005, the proportion of newly diagnosed sub-Saharan Africans in the heterosexual population decreased from 52% to 42%, whereas the proportion of Dutch patients increased from 21% to 31%. In the MSM population, the proportion of patients from each region did not change over time, being below 2% for patients from sub-Saharan Africa, and approximately 74% for MSM originating from the Netherlands. For those infected via other transmission routes, the proportion of patients from sub-Saharan Africa decreased from 33% to 20%, whereas the proportion of patients from other regions increased from 25% to 35%.

As of 1 January 2005, 9081 patients were in follow-up, whereas the ODE model predicted 9152, a difference of less than 1%. According to the data, 4933 homosexual men were in follow-up, whereas 4982 were predicted (1.0% difference). For the other four groups, the difference between model predictions and data never exceeded 2%: heterosexual men, data 1216, model 1236 (1.6%); heterosexual women, data 1771, model 1764 (0.4%); other men, data 888, model 898 (1.1%); other women, data 273, model 271 (0.7%). The number of non-MSM patients originating from the Netherlands, from sub-Saharan Africa, and from other regions was, according to the model, 1583 (17.3%), 1413 (15.4%), and 1174 (12.8%), respectively, whereas the data showed 1551 (17.1%) from the Netherlands, 1439 (15.8%) from sub-Saharan Africa, and 1158 (12.8%) from other regions. The average age of the HIV-infected population increased from 40.7 years in 2000 to 42.8 (model 42.7) years in 2005. The population that was between 15 and 50 years of age comprised 6944 patients (model 6992).

According to the model, on the assumption that trends observed between 2000 and 2005 would continue thereafter, the HIV-infected population in 2015 would consist of 18,275 patients, 2.0 times more than in 2005. In total, 6888 (37.7%) patients would be 50 years of age or older, 1568 (8.6%) would be 30 years of age or younger, while 11,298 (61.8%) patients would be expected to be between 15 and 50 years of age (Table 14.1, Figure 14.1). The proportion of patients infected via other or unknown transmission routes was estimated to decline from 12.8% in 2005 to 7.6% in 2015. This decrease was counterbalanced by a predicted increase in the proportion of MSM and, to a lesser extent, in the proportion of heterosexuals.

Between 2000 and 2005, the mean age of the total population increased from 40.7 years to 42.7 years and was predicted to increase thereafter to 46.1 years in 2015 (Figure 14.2). For MSM, the mean age was 44.5 years in 2005, and it was estimated to increase to 47.3 years by 2015. For heterosexuals, the mean age was 39.4 in 2005, and it was predicted to be 43.3 in 2015. In the population infected via other or unknown routes of infection, the mean age increased from 43.6 in 2005 and was estimated to increase to 48.8 years in 2015. For the latter group, as well as for MSM, the annual increase in age was predicted to continue to slow down from 2005 onward. In the heterosexual population, however, the annual increase was predicted to first accelerate and then to level off after 2010.

According to scenario A, the HIV-infected population in 2015 would consist of 17,120 individuals, which is 7% less than in the main model. The proportion of patients less than 30 years of age would decrease to 6.7%, and 39.8% would be 50 years or older. The MSM population would not be affected to a great extent, since its size is 10601 patients, which is only 36 patients fewer than in the main model. The heterosexual population would decrease from 6232 to 5176 patients (-17%), whereas the other/unknown population would drop from 1406 to 1343 patients (-4%).

If the annual number of diagnoses amongst homosexual men remained at the 2006 level after 2006 (scenario B), the number of MSM in 2015 would amount to 9369, 12% less than in the main model. In total, 6637 (39.0%) individuals would be 50 years or older, which is 4% less than in the main model.

A 10% increase in the annual number of diagnoses amongst individuals of non-Dutch origin, would yield a population of 18,647 patients in 2015 (+2% compared to the main model). If the increase was 20%, the 2015 population would consist of 19,018 (+4%) patients. In that case, the heterosexual population would total 6625 (+6%) patients, whereas the population infected via other routes of transmission would consist of 1406 (+4%) patients, and the MSM population would consist of 10,932 (+3%) patients.

In scenario D, the mean age of the MSM population at diagnosis would increase by 0.9% each year, corresponding to 0.3 to 0.4 years per year. In this scenario, the MSM population in 2015 would consist of 10,617 patients, slightly fewer than in the main model. In total, 5007 (47.2%) MSM would be 50 years of age or older, whereas the total population more than 50 years old would increase to 7531 individuals, an increase of 9% compared to the main model (Figure 14.2).

Discussion

According to our model, the HIV-infected population in follow-up in 2015 is expected to be 3.3 times larger than the population in 2000, or 2.0 times larger than the population in 2005. The number of patients more than 50 years of age is predicted to increase by a factor of 6.3, whereas the number of patients less than 30 years of age is expected to increase by a factor of 1.5.

An HIV-infected population twice the size of the population currently being followed might be expected to put a substantial strain on HIV health care in the Netherlands. Previously, we estimated that one year of treatment for an HIV-infected individual costs 12,500 euro[6]. Hence, when the per capita costs and the population size are multiplied, the cost of HIV treatment will increase from 115 million euro annually in 2005 to 230 million euro in 2015.

In addition to escalating costs, the treatment of the disease will be complicated by the increasing age of the HIV-infected population. In older patients, the restoration of CD4 cells is generally less favourable than in younger patients[2-4]. Moreover, the appearance of age-related diseases and other non-HIV-related illnesses could complicate the treatment of HIV. In addition, few studies have examined the tolerability and safety of antiretroviral drugs in older HIV-infected patients[5]. In older patients renal and hepatic functions decrease, which could lead to a reduced tolerability compared to that in younger patients. Another complication could be drug-drug interactions between antiretroviral drugs and medication used for treatment of age-related morbidities.

One feature of the model is that it estimates only the number of patients in follow-up in any of the HIV treatment centres in the Netherlands who are, by definition, patients who know they are HIV-infected. Recently, we estimated that the HIV-infected population

aged between 15 and 50 years of age in the Netherlands – including those unaware of their infection – amounted to 18,500 individuals[1]. In our analysis, we found that 6944 patients in the data and 6992 in the model were in the same age category. This implies that more than 60% of the HIV-infected patients are not yet in follow-up, and thus, most likely, not yet aware of their HIV infection. However, the uncertainty in the estimate was quite large: it varied between 10,000 and 28,000 individuals. In addition, because of the number of patients refusing registration in HMF and the backlog in registration, the number of those in follow-up is likely to be larger than the reported 6944, albeit only slightly.

Despite the simple structure and parameterisation of the model, we were able to reproduce the 2005 population with satisfactory accuracy. For instance, one assumption in the model was that the rate of death was a constant corresponding to an exponential distribution of survival times. For some subpopulations, however, survival times were not exponentially distributed. Nevertheless, the results of an exponential fit were used as parameters in the ODE model.

HIV-infected patients 12 years of age or younger either in 2000 or at the time of HIV diagnosis if the diagnosis was made between 2000 and 2005 were excluded from the analyses. This procedure removed 63 patients from the population in follow-up in 2000 and 110 from the population in follow-up in 2005. Most of these patients were children infected by mother-to-child transmission. Inclusion of the children would pull the age distribution in the other/unknown transmission group towards the younger ages. A gamma distribution would not adequately describe the data in this case since the age at diagnosis in patients less than 12 years clusters at zero. Presently, the annual number of newly infected children is close to zero (see chapter 4). Therefore, the number of those children is not expected to contribute substantially to the HIV-infected population between 2005 and 2015.

We explored a few hypothetical scenarios using the model. These scenarios were based on the assumption that all other factors remained constant. More than 1000 new cases would be avoided if either infections amongst sub-Saharan Africans would be halted or if the number of diagnoses amongst homosexual men would remain at the level of those in 2006. The first of these two scenarios, however, would be hard to realise since most patients of sub-Saharan African origin are infected in that region[16]. Reducing the number of diagnoses would then only be possible if immigration from sub-Saharan Africa declined. The second scenario might be possible if risk behaviour amongst MSM decreases. An increase in the annual number of diagnoses amongst individuals of non-Dutch origin for all transmission groups would mainly affect the heterosexual population.

The last scenario that was explored was not exactly a hypothetical scenario, but rather a more complex fit to the data. This fit took into account the increasing age at diagnosis amongst MSM as a result of the increasing age of the source population, which was on average more than 40 years. The largest gain in reducing the number of new diagnoses amongst MSM might therefore be obtained by a reduction in risk behaviour amongst middle-aged MSM.

	total		≤ 30 years		≥ 50 years	
population in 2000	**N**	**%**	**N**	**%**	**N**	**%**
MSM	3306	58.3	286	8.7	677	20.5
men, heterosexual	606	10.7	54	8.9	136	22.4
women, heterosexual	801	14.1	223	27.8	63	7.9
men, other	705	12.4	70	9.9	111	15.7
women, other	248	4.4	39	15.7	15	6.0
total	**5666**		**672**	**11.9**	**1002**	**17.7**
population in 2005						
MSM	4933	54.3	282	28.7	1372	64.7
men, heterosexual	1216	13.4	130	13.2	303	14.3
women, heterosexual	1771	19.5	455	46.3	172	8.1
men, other	888	9.8	76	7.7	232	10.9
women, other	274	3.0	40	4.1	42	2.0
total	**9081**		**1093**	**12.0**	**2121**	**23.4**
population in 2015						
MSM	10637	57.5	606	5.7	4364	41.0
men, heterosexual	2547	13.9	203	8.0	1007	39.5
women, heterosexual	3685	20.0	669	18.2	814	22.1
men, other	1109	6.5	63	5.7	568	51.2
women, other	297	2.1	27	9.2	134	45.1
total	**18275**		**1568**	**8.6**	**6888**	**37.7**

MSM: men having sex with men

Table 14.1: Known HIV-infected population in 2000 and 2005 and the expected population in 2015. The total population, the population of patients 30 years of age or younger, and patients 50 years of age or older, categorised by transmission group are shown. Please note that numbers in 2015 are rounded and might not add up to the total number given or to 100%.

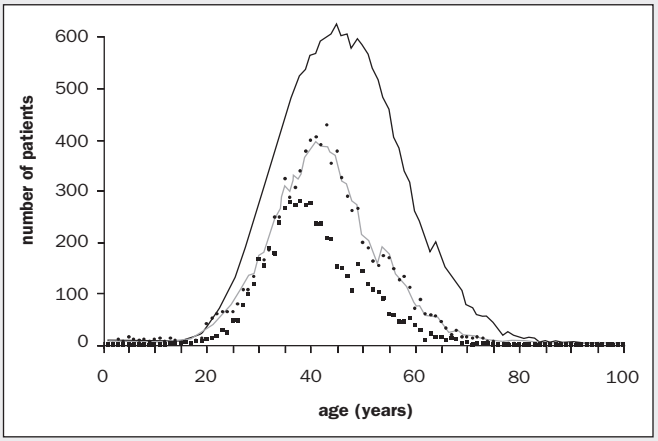

Figure 14.1: Data and model predictions for the total HIV-infected population in follow-up; population 2000 (data), squares; population 2005 (data), dots; population 2005 (model), grey line; population 2015 (model), black line.

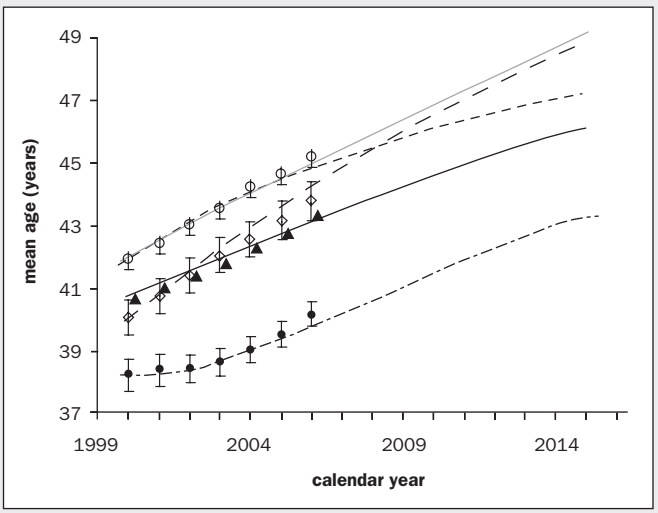

Figure 14.2: Mean age as a function of calendar time according to the ODE model compared with data for the total population (solid line, triangles), for the MSM population (short dashes, circles), for the heterosexual population (short and long dashes, dots), and for the population infected via other or unknown routes of transmission (long dashes, diamonds). Error bars indicate the 95% confidence interval on the mean. The grey line indicates the mean age of the MSM population according to scenario D. To avoid overlap of data points, data of the total population were shifted 0.2 years along the horizontal axis.

Quality of

HIV care

Quality of HIV care and the impact of late presentation at the clinic

Colette Smit

Introduction

HIV and AIDS care and antiretroviral treatment is provided by 23 health care institutes throughout the Netherlands. These institutes, including all 8 academic hospitals, are acknowledged by the Dutch Ministry of Health, Welfare and Sport as HIV treatment centres. These centres, as part of their mission are obliged to provide the HIV Monitoring Foundation (HMF) with data on the diagnostics, follow-up, and treatment of all HIV-infected patients in care, including those in outpatient care. HMF reports to the Ministry of Health not only on the HIV epidemic and the results of anti HIV treatment, but also on the quality of HIV and AIDS care provided.

In the study of quality of care, much attention is given to internal processes, sometimes including a comparison to a national average. However, a comparison of different centres is not straightforward, because the indicators of good patient management and successful initiation of combination antiretroviral therapy (cART) can be influenced by the profile of patients and by the attributes of the centre itself.

When survival is taken as a crucial indicator for quality of care, late presentation, as well as differences in patient profile, may play an important role. Patients who present at the hospital late in the course of their disease may place a large demand on clinical resources, and some will have a poor treatment outcome[121, 122]. Earlier studies in the United Kingdom have shown that black African patients, in particular, tended to present for care at a late stage of infection, as indicated by low CD4 cell counts[122-124]. Initial presentation for care by individuals with low CD4 cell counts might also depend on demographic characteristics of a specific patient population.

In this chapter, we compare the survival rates after the start of cART amongst the different HIV treatment centres, taking into account the differences in the patient population, as well as the impact of late presentation for care.

Methods

Study population and HIV treatment centres

All patients who initiated antiretroviral treatment in one of the Dutch HIV treatment centres (HTC) and who were diagnosed with HIV between 1 January 1997 and 1 June 2007, when cART was generally available, were included in this study of the quality of HIV care. All adult HTCs were included, except for the St. Elisabeth Hospital in Willemstad (Netherlands Antilles). HTCs were reported not by name, but by randomly assigned codes.

Data on demographics, death, CD4 cell count, use of cART, and visit frequency were obtained from the HMF database.

Late presenters were defined as patients whose CD4 cell count at the time of the first visit to an HIV treatment centre was $<200 \times 10^6$ cells/l.

Statistical methods

The median CD4 cell count at first presentation to an HTC and at initiation of cART were calculated for the total population and separately for each HTC.

The risk of death within 5 years after cART initiation was estimated with a Cox proportional hazards model. Time was from the date of cART initiation to that of last contact, death, or 1 June 2007.

First, a multivariate model was constructed with data for the total population. We examined the effect of the following variables: gender, age (per 10-year increase), exposure category (men having sex with men [MSM], heterosexual, injecting drug use [IDU], or other/unknown [including blood contact and vertical HIV transmission]), region of origin (Netherlands, Western Europe and North America excluding the Netherlands, Caribbean/ Latin America, sub-Saharan Africa, or other), CD4 cell count at first presentation, CD4 cell count at cART initiation, HIV RNA plasma levels at cART initiation, symptoms at first presentation, median number of visits per year, calendar year of

HIV diagnosis, and hepatitis C (HCV) co-infection. Second, the final multivariate model was used to compare the risk of death for each HTC with that for the total population.
The risk of death was estimated for only those HTCs with at least 10 deaths between 1997 and 2007. Data for patients treated in an HTC with fewer than 10 deaths were still taken into account in the total population as the reference group.

Kaplan-Meier estimates of the probability of death were plotted, stratified by the CD4 cell count at first presentation at the clinic.
In a multivariate logistic regression model, we selected predictors for late presentation. Factors considered in this analysis were gender, age, exposure category, region of origin, symptoms at first presentation, and calendar year of diagnosis.

Results

General characteristics

Between 1 January 1997 and 1 June 2007, 8616 patients received a diagnosis of HIV infection and presented for care at one of the HIV treatment centres in the Netherlands for the first time (Table 15.1). The majority of the patients were male, and half of the patients originated from the Netherlands. However, there were differences in the demographic characteristics of the patient population between hospitals. The percentage of patients originating from the Caribbean and Latin America ranged from 1% to 30%, and the percentage of patients originating from sub-Saharan Africa varied from 1% to 40%.

The median CD4 cell count at first presentation for care was 308×10^6 cells/l (interquartile range [IQR], 120-510). Patients originating from the Netherlands and other Western countries had significantly higher CD4 cell counts than those originating from the Caribbean/Latin America, sub-Saharan Africa, and the other regions. Figure 15.1 shows the median CD4 cell count at presentation and at cART initiation in the total population and the median CD4 cell count for each treatment centre. The median CD4 cell count at the first presentation significantly differed amongst HTCs. In 6 centres, the median CD4 cell count at first presentation exceeded the national median, whereas in 11 HTCs, the patient population arrived with lower CD4 cell counts than those of the total population.

The median CD4 cell count at cART initiation was 180×10^6 cells/l (IQR, 70-290). CD4 cell count at the first presentation and at cART initiation were highly correlated. For HTCs where the majority of patients presented early, the median CD4 cell counts at cART initiation generally exceeded the national average (Figure 15.1).

Late presentation

Of all patients presenting for care at one of the HTCs in the Netherlands, 35% had a CD4 cell count below 200×10^6 cells/l at diagnosis, which met the definition of late presentation.
In the univariate analysis, late presentation was associated with older age; transmission risk in other/unknown category; origin from sub-Saharan Africa, the Caribbean, or Latin America; and symptoms at first visit. In contrast, an HIV diagnosis between 2003 and 2007 was associated with a lower risk of late presentation. In the multivariate analysis, all these variables, including male gender, remain independently associated with late presentation (Table 15.2).

Figure 15.2 shows the probability of death since the start of cART, stratified by CD4 cell count at presentation. Patients who presented with CD4 cell counts below 200 died significantly more rapidly than those who presented with at least 200×10^6 cells/l ($P<0.0001$, log rank test).

Comparison of HIV treatment centres with the total population

In total, 403 of patients diagnosed with HIV from 1 January 1997 onwards died. Among them, 288 died within 5 years after cART initiation. Table 15.3 shows the results of the univariate and multivariate analyses. The univariate analysis included the total population, and it showed that male gender, older age, IDU or other/unknown HIV risk, low CD4 cell counts at cART initiation, symptoms at first presentation, a recent HIV diagnosis, and HCV co-infection were associated with a shorter time to death. In contrast, originating from sub-Saharan Africa and being diagnosed before 2000 were associated with a longer time to death.

In the multivariate analysis, male gender, older age, HIV infection through heterosexual contact, IDU or other HIV risk, and calendar year of HIV diagnosis were independently associated with the risk of death within 5 years after cART initiation in the total population.

This multivariate model was used to compare the risk of death for each HTC population with that of the total population. Figure 15.3 presents the adjusted risk of death for each HTC relative to the risk of death in the total population of HIV-infected patients in the Netherlands. For most HTCs, the risk of patient death in the first 3 years on cART did not significantly differ from the national average. The risk of patient death was highest for HTCs C2, C6, and C17. These differences were significant for HTCs C2 and C17; for C6 the risk of death did not remain significant after adjusting for gender, age, HIV transmission category, and clinical differences in the patient population (according to the multivariate model as described above). Of all the HTCs, HTC C2 had the lowest median CD4 cell count at presentation, and HTC C6 had a lower median CD4 cell count than that in the total population. However, after adjustment for CD4 cell count at presentation and demographic differences, the risk of death slightly shifted toward the risk of death in the total population, but the risk of death remained significantly higher for HTCs C2 and C17. The risk of death that was found to be lower in 7 HTCs was not significantly different from the average risk of death in the total population.

Discussion

Major differences in survival for patients on cART were observed in the Netherlands. Although differences in survival became smaller after adjusting for differences in gender, age, HIV transmission category, and CD4 cell counts at HIV diagnosis, patients in 2 HTCs still had a significantly higher risk of death than that in the total population.

In our study, 35% of the HIV-infected patients presented for care with low CD4 cell counts. Entering care early in the course of the disease determines whether cART can be initiated according to the treatment guidelines, when it is most efficacious[198]. Current treatment guidelines recommend initiating cART when the CD4 cell count is between 200 and 350 x 10^6 cells/l[126]. Although 65% of the patients presented for care early enough for cART to be successful, the median CD4 cell counts at cART initiation in the total population were below the number recommended. Nine percent of the patients who presented for care with at least 200 × 10^6 CD4 cells/l initiated cART when CD4 cell counts were below 200 × 10^6 cells/l. Therefore, we conclude that the late initiation of cART found in our study cannot be explained fully by patients' late presentation for care.

We show that late presentation was more common among patients who were male, infected though heterosexual contact, and of non-Dutch origin. These findings are in line with studies in the United Kingdom (UK)[122-124]. However, the proportion of late presenters is higher in the Netherlands (35%) than that in the UK (23%)[199]. Overall, HIV-infected patients in the Netherlands tend to first present at the HTC with CD4 cell counts similar to those of men and women in West Africa[125], which is surprising in view of the greater opportunities for testing and treatment available in the Netherlands. This pattern of late presentation is a cause of concern, since these patients do

not have the opportunity to start cART in time. Although the proportion of late presenters has become smaller in more recent years, 26% of the patients who were recently diagnosed with HIV still had CD4 cell counts below 200×10^6 cells/l at diagnosis.

Patients who present late might have a poorer prognosis and benefit less from cART[92, 122]. Presenting late not only has clinical consequences, but also it is estimated that the cost of direct care in the year after HIV diagnosis is at least 200% higher for late presenters than it is for early presenters[121]. Early diagnosis of HIV could reduce the medical costs in the first year after HIV diagnosis. Moreover, early diagnosis also should help prevent further HIV transmission by those who are unaware of their infection[106]. Unawareness of an HIV infection is high among individuals presenting with a sexually transmitted infection (STI) at the STI clinics[200] and among heterosexual migrants[201]. These individuals are probably less active in requesting HIV testing, are less likely reached by routine testing programmes, or are more likely to refuse HIV testing[202].

This study has some limitations. First, the populations served by the different HIV treatment centres are not always representative of the total population of HIV-infected individuals, and even after adjusting for differences in demographic characteristics, residual confounding might still exist. Second, we compared the risk of death amongst 17 different treatment centres, and we might have found some significant differences amongst HIV treatment centres as a result of multiple testing. To reduce the chance of such a type 1 error, we also calculated 99% confidence intervals; even with these wider confidence intervals, the risk of death in HIV treatment centres C2 and C17 remained significantly higher than in the total population.

In summary, we could not fully explain the differences in the clinical success of cART amongst HTCs by the differences in the stage of HIV infection at patient presentation for care. Patients who present late tend to be of non-Dutch origin and infected with HIV through heterosexual contact. Efforts should be made to increase early testing and to improve awareness of HIV in these individuals.

HTC	Total N(%)	Deaths N(%)	Age Median (IQR)	Male N(%)	Late presenters N(%)	Visits per year Median (IQR)
Centres with at least 10 deaths						
C1	919 (11)	37(4)	39(33-47)	826(90)	283(31)	3(2-3.5)
C2	142(2)	15(11)	39(32-46)	102(72)	67(48)	4(3-5.3)
C3	1261(15)	43(3)	37(31-43)	876(69)	377(35)	3(3-4)
C4	344(4)	17(5)	36(29-45)	255(74)	123(36)	4(3-5)
C5	284(3)	13(5)	38(32-46)	206(73)	114(41)	3(2-4)
C6	300(3)	28(9)	38(31-46)	219(73)	101(35)	4(2.5-4)
C7	260(3)	21(8)	38(31-48)	202(78)	98(38)	4(3-5.5)
C8	641(7)	20(3)	37(31-46)	482(75)	204(34)	3.5(3-5)
C9	187(2)	11(6)	39(32-45)	147(79)	78(42)	4(3-4.5)
C10	939(11)	44(5)	38(31-44)	656(70)	377(41)	2.5(2-3)
C11	378(4)	11(3)	38(31-44)	265(70)	131(35)	3(2.5-3.3)
C12	174(2)	11(6)	37(32-43)	122(70)	68(40)	3(2-4)
C13	214(2)	12(6)	37(29-44)	167(78)	77(36)	4(3-5)
C14	357(4)	21(6)	39(33-46)	312(87)	96(27)	3(2-3)
C15	345(4)	20(6)	37(30-45)	254(74)	102(33)	2.5(2-3.5)
C16	339(4)	17(5)	37(32-46)	242(71)	124(37)	3(2-4)
C17	268(3)	21(8)	37(31-45)	207(77)	98(37)	4(3-4)
HTC with <10 deaths						
C18	204(2)	3(1)	39(33-43)	195(96)	36(18)	3(2-3)
C19	116(1)	8(7)	36(31-46)	87(75)	50(44)	3(2-3)
C20	171(2)	5(3)	39(35-44)	162(95)	46(27)	3(2-4)
C21	120(1)	7(6)	37(29-45)	85(71)	44(39)	3(2-4)
C22	57(1)	6(11)	39(31-46)	37(65)	23(41)	4(3-5)
C23	220(3)	5(2)	36(29-41)	143(65)	54(25)	3(2-4)
C24	170(2)	2(1)	37(28-44)	115(68)	60(36)	3(2.5-4)
C25	206(2)	5(2)	37(30-45)	151(73)	71(36)	3(2-4)
Total number of patients	**8616**	**403(5)**	**38(31-45)**	**6515(76)**	**2902(35)**	**3(2-4)**

Table 15.1: Number of patients stratified by HIV treatment centre, diagnosed with HIV after 1 January 1997 and monitored by the HIV Monitoring Foundation.

		OR (95%CI)	Overall p value
Gender:	Male	1	<0.0001
	Female	0.68 (0.59-0.79)	
Age (per 10-year increase)		1.32 (1.26-1.39)	<0.0001
Exposure category:	MSM	1	<0.0001
	Heterosexual	1.68 (1.45-1.94)	
	IDU	1.52 (1.07-2.15)	
	Other	2.40 (1.99-2.90)	
Region of origin	Netherlands	1	<0.0001
	Western	1.07 (0.85-1.31)	
	Caribbean/ Latin America	1.56 (1.32-1.84)	
	Sub-Saharan Africa	2.17 (1.85-2.54)	
	Other	1.74 (1.43-2.13)	
Symptoms at first presentation	No	3.78 (3.41-4.19)	
	Yes		
Calendar year of HIV diagnosis	<2000	1.02 (0.87-1.18)	<0.0001
	2000-2002	1	
	2003-2007	0.65 (0.55-0.74)	

CI: confidence interval; MSM: men having sex with men; IDU: injecting drug use

Table 15.2: Demographic characteristics associated with late presentation, multivariate analysis

		Univariate		Multivariate	
		HR (95% CI)	Overall P-value	HR (95% CI)	Overall P-value
Gender:	Male	1		1	0.01
	Female	0.58 (0.38-0.86)	0.006	0.57 (0.37-1.72)	
Age (per 10-year increase)		1.57 (1.39-1.77)	<0.0001	1.52 (1.35-1.73)	<0.0001
Exposure category:	MSM	1	<0.0001	1	<0.0001
	Heterosexual	1.23 (0.89-1.71)		1.67 (1.16-2.41)	
	IDU	5.09 (2.70-9.63)		8.22 (4.33-15.62)	
	Other	2.83 (1.87-4.27)		2.44 (1.60-3.72)	
Region of origin	Netherlands	1	0.05		
	Western	0.50 (0.23-1.06)			
	Caribbean/ Latin America	1.00 (0.65-1.52)			
	Sub-Saharan Africa	0.60 (0.40-0.90)			
	Other	0.96 (0.55-1.67)			
Cd4 cell count at first presentation	< 200	1.82 (1.36-2.43)	<0.0001	1.25 (0.91-1.71)	0.17
	≥ 200	1			
Cd4 cell count at cART initiation*	<50	3.41 (2.11-5.50)	<0.0001		
(x 10^6 cells/l)	50-200	1.40 (0.84-2.32)			
	200-350	1			
	350-500	0.77 (0.33-1.80)			
	≥ 500	0.44 (0.13-1.45)			
	missing	3.97 (2.45-6.43)			
HIV RNA plasma levels	<4	1	0.39		
(log_{10} copies/ml)	4-5	1.22 (0.63-2.36)			
	≥ 5	1.46 (0.78-2.75			
Symptoms at first presentation	No	1	0.001	1.41 (1.05-1.89)	0.02
	Yes	1.92 (1.44-2.56)			
Median number of visits per year	< 5	1	0.77		
	≥ 5	1.06 (0.73-1.54)			
Calendar Year of HIV diagnosis	<2000	0.41 (0.25-0.68)	<0.0005	0.37 (0.22-0.61)	<0.0001
	2000-2002	1		1	
	2003-2007	1.66 (1.16-2.38)		1.60 (1.11-2.28)	
HCV co-infection	No	1	0.01		
	Yes	1.91 (1.15-3.19)			

*Since CD4 cell count at first presentation and Cd4 cell count at cART initiation are highly correlated, we included only Cd4 cell count at first presentation in the multivariate analyses.

cART: combination antiretroviral therapy; HR: hazard ratio; CI: confidence interval; MSM: men having sex with men; IDU: injecting drug use; cART: combination antiretroviral therapy; HCV: hepatitis C virus

Table 15.3: Risk of death within 5 years after cART initiation in the total population of HIV-infected patients, diagnosed after 1 January 1997.

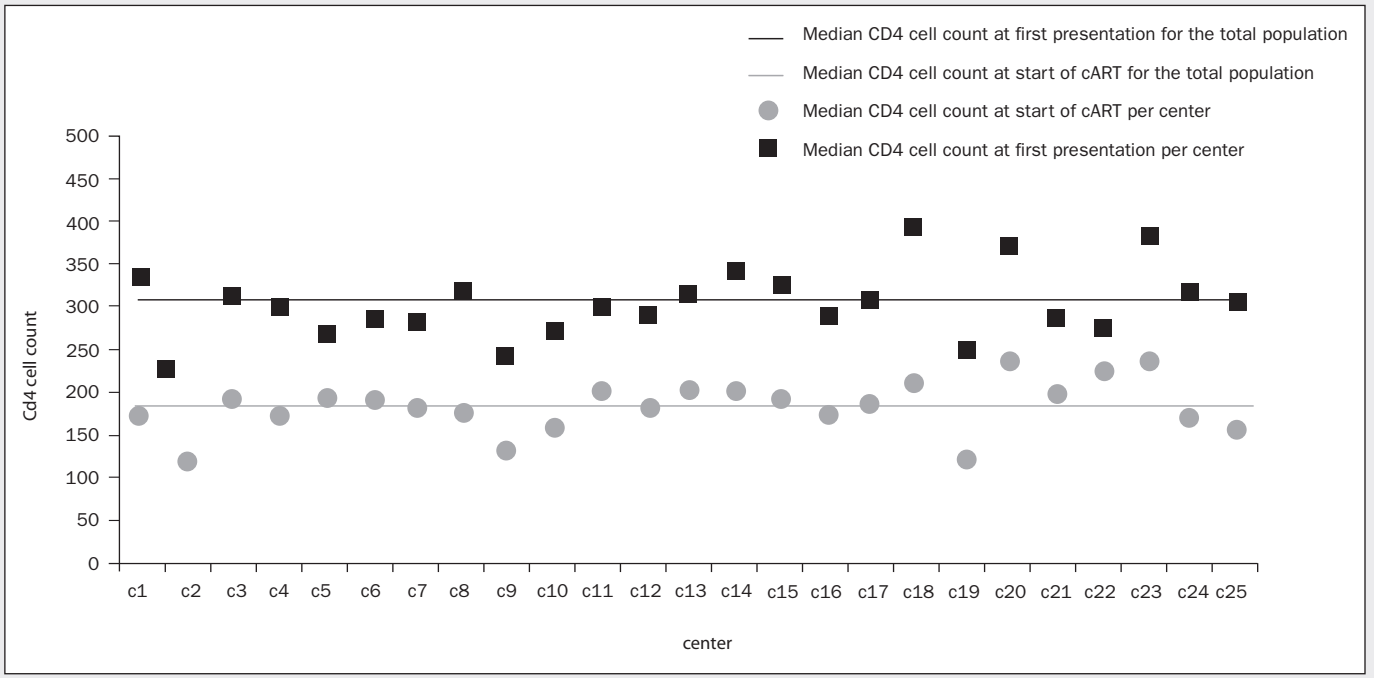

Figure 15.1: Association between CD4 cell counts at first presentation at the centers and time of cART initiation.

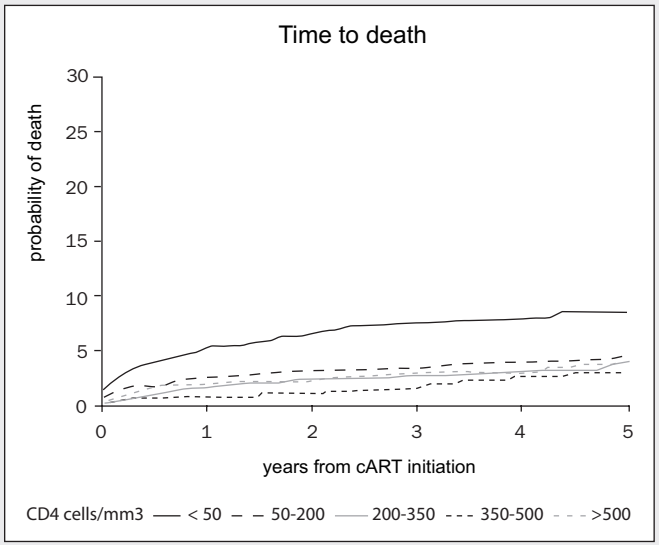

Figure 15.2: Probability of death in the first 5 years after the start of combination antiretroviral therapy (cART), stratified by CD4 cell counts at first presentation.

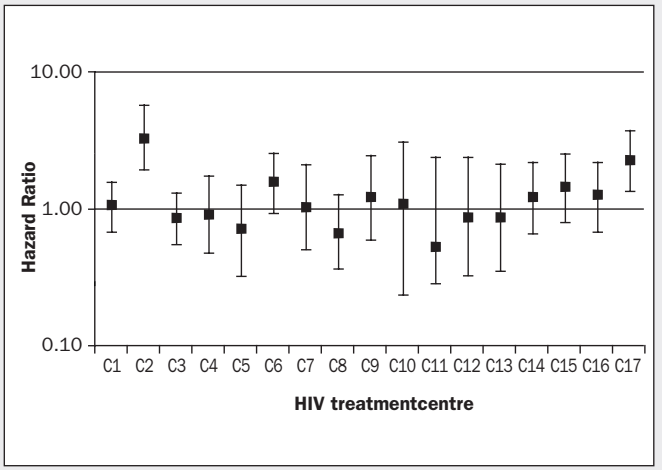

Figure 15.3: The risk adjusted for gender, age, exposure category, CD4 cells and symptoms at first presentation and calendar year of HIV diagnosis of death within 5 years after cART initiation for each specific center compared to the total population; cART: combination antiretroviral therapy

Special Reports 16-17

Amsterdam C

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The Amsterdam Cohort Studies on HIV infection

Hanneke Schuitemaker
for the ACS group

Introduction

The Amsterdam Cohort Study (ACS) on Human Immunodeficiency Virus (HIV) infection and AIDS amongst homosexual men was initiated in 1984, followed shortly by the Amsterdam Cohort Study amongst drug users in 1985. The ACS, a collaboration of the Amsterdam Health Service (AHS), the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation, and the University Medical Center Utrecht (UMCU), is part of the Netherlands HIV Monitoring Foundation and financially supported by the Netherlands National Institute for Public Health and the Environment.

Thus far, 2299 homosexual men (HM) and 1663 (injecting) drug users (DU) have been included in the ACS. Every 3 to 6 months participants complete a standardized questionnaire designed to obtain information regarding medical history, sexual and/or drug use behaviour, underlying cognitions, health care use, depression, psychological disorders, and demographics. In addition, they undergo a medical examination (HIV-positive participants and, in the past, HIV-negative drug users as well) and blood is drawn for biologic and immunologic tests and storage.

Of the 2299 HM, 571 were HIV-positive at study entry, and 192 seroconverted during follow-up. For the 1663 DU, 323 were HIV-positive at study entry, and 95 seroconverted during follow-up By December 31 2006, 323 HM and 385 DU had died; other participants were requested to leave the study or left at their own request. On average, 90% to 92% of participants who visited the ACS during a given calendar year returned for a follow-up visit the next year. In total, HM visited the Amsterdam Health Service 45,444 times and DU 23,948 times.

Website: http://www.amsterdamcohortstudies.org/

The cohorts in 2006

Homosexual men

In 2006, 536 HM were followed at the Health Service of Amsterdam. Sixty of them were newly recruited in 2006. From 2005, recruitment was open for HM of all ages with at least one sexual partner in the preceding 6 months. Of the HM followed in 2006, 497 men were HIV-negative, and 39 men were HIV-positive. The HIV-positive men, of whom 29 were HIV seroconverters, were followed according to the HIV onderzoek onder positieven (HOP) protocol, which was initiated in October 2003 for HM who seroconverted or were HIV-positive at study entry in the cohort of young HM after 1999. From June 2006, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants were also invited to participate in the ACS.

In 2005, 218 HIV-infected HM who were recruited as part of the ACS before 1999 were seen at the Jan van Goyen Clinic or at one of the 22 other HIV treatment centres in the Netherlands. Sixty-two of them were HIV seroconverters. Plasma and cells from HIV-positive HM in active follow-up at the Jan van Goyen Clinic were stored for those who (1) seroconverted during follow-up, (2) had been defined as slow/non progressor or matched fast progressor in 1996, and (3) were HIV-positive for more than 10 years and had a CD4 count greater than 400 cells/mm^3 after 10 years of follow-up after a positive HIV result without effective therapy (n=94).

Drug users

In 2006, 472 drug users were followed at the Health Service of Amsterdam; of those, 67 were young drug users aged 30 years or less and recruited after 2000. In 2006, 19 new drug users were included because of the possibility that they received hepatitis C treatment within the cohort setting (the so-called Dutch-C study). The cohort remained open to drug

users less than 30 years of age who had used cocaine, heroin, or amphetamines at least 3 times a week in the 2 months preceding enrolment. Sixty-six of the 472 drug users were HIV-infected; of those, 22 seroconverted during follow-up in the ACS.
In 2005, within the DU cohort, a feasibility study was started to evaluate the possibility of hepatitis C virus (HCV) testing and treatment combined with methadone programs. As part of this project (the Dutch-C study), by the end of 2006, 19 HCV mono-infected DU of the cohort had initiated HCV therapy.

HIV incidence

Thirteen homosexual men and no drug users seroconverted for HIV in 2006. Three of them last received a negative HIV test result in 2001, 2004, and 2005, respectively, which implies that the actual moment of HIV infection could have been before 2006. However, we have included these three in the 2006 count. HIV incidence is around 1.8 per 100 person-years amongst HM and less than 1 per 100 person-years amongst DU. Figures 16.1 and 16.2 show the yearly HIV incidence rates for homosexual men and drug users since the start of the ACS through 2006.

Transmission of therapy resistant HIV strains

A total of 100 primary HIV-1 infections (32 AMC hospital and 68 ACS) were identified from 1994-2002. Transmission of drug-resistant mutations decreased over calendar time, with 20% of infection-bearing drug-resistant mutations transmitted before 1998 versus only 6% after 1998 (Bezemer et al, AIDS 2004). In 2005, 2 out of 9 seroconverters within the ACS became infected with a drug-resistant strain. Of 13 HIV seroconverters with a first HIV-positive test result within the ACS in 2006 (all HM), a sequence could be obtained for 12. Of these, one was found to be infected with a drug-resistant strain.

Risk behaviour

In the cohort of HIV-negative HM, trends in the incidence of HIV and sexually transmitted infections (STI) were concurrent amongst young men until 1995. However, since 1995, there has been a significant increase in the incidence of syphilis and gonorrhoea (see Figure 16.3), but no change in HIV incidence (van der Bij et al, Sex Transm Infect 2005; 81:31-7). In 2006, the 6-monthly questionnaire of the HM was expanded to include questions regarding knowledge and use of post-exposure prophylaxis.

In the cohort of HIV-negative DU, reports of both injecting and borrowing needles significantly declined over the period 1985-2004 (Lindenburg et al, AIDS 2006). Reports of sexual risk behaviour and STI at follow-up visits decreased before 1996, but not after 1996 (see Figure 16.4).

HCV, HBV and HSV-1 co-infections

In 2006, the retrospective testing for HCV was completed amongst 1276 DU and 1846 DU with at least 2 cohort visits. Amongst ever-injecting DU, the prevalence of HCV antibodies was 85% at study entry, and 31% were co-infected with HIV. All but one of the HCV seroconversions occurred in ever-injecting drug users. The HCV and HIV incidence amongst DU since the start of ACS are shown in Figure 16.5. The yearly HCV incidence dropped from 28 per 100 person-years in the 1980s to 2 per 100 person years in recent years. The HCV incidence in ever-injecting DU was on average 4.4 times greater than the HIV incidence, a pattern seen over the entire study period. The HCV prevalence was 1% amongst HM at study entry. All HCV seroconversions occurred in HIV-positive HM. The HCV incidence by HIV serostatus since the start of the ACS is shown in Figure 16.6.
Hepatitis B virus (HBV) prevalence (i.e., positive test for hepatitis B surface antigen [HbsAg] at study entry) is 50% amongst DU and 60% amongst HM

with at least 2 study visits. Herpes simplex virus type 2 (HSV-2) prevalence is 47% amongst young 431 DU (18-30 years) recruited in 1985-1989, but it declined to 14% amongst the 171 young DU recruited in 2000-2004. Data on HBV, herpes simplex virus type 1 (HSV-1) and HSV-2 prevalence and incidence for the total group of HM and IDU is expected to be completed in 2007.

Highly active antiretroviral therapy (HAART) uptake

For the 218 HIV-positive homosexual men visiting the Jan van Goyen Clinic or one of the other HIV treatment centres in the Netherlands in 2005, 177 (81%) received any form of antiretroviral therapy. The viral load was < 400 cells/ml (bDNA) for 157/177 (89%).

Of the 66 HIV-positive drug users who visited the Health Service of Amsterdam in 2006, 38 (58%) received any combination of antiretroviral therapy. Of these, 31 (82%) had an undetectable viral load (Nuclisens < 400 copies/ml) at their latest visit.

Steering committee: The politburo

In 2006 the Politburo met several times. Twenty-one proposals for use of data and/or samples (serum/ PBMCs) were submitted to the politburo: 13 from Sanquin, 7 from UMCU, and 1 from the AHS, All have been approved, some of them after revision.

Publications in 2006 that include ACS data

1. Pillay D, Bhaskaran K, Jurriaans S, Prins M, Masquelier B, Dabis F, Gifford R, Nielsen C, Pedersen C, Balotta C, Rezza G, Ortiz M, de Mendoza C, Kucherer C, Poggensee G, Gill J, Porter K; CASCADE Virology Collaboration. The impact of transmitted drug resistance on the natural history of HIV infection and response to first-line therapy
   AIDS 2006;20:21-8
2. Thiébaut R, Jacqmin-Gadda H, Walker S, Sabin C, Prins M, Del Amo J, Porter K, Dabis F, Chêne and the CASCADE Collaboration. Determinants of response to first HAART regimen in antiretroviral-naïve patients with an estimated time since HIV seroconversion
   HIV Medicine 2006;7:1-9
3. Smit C, Lindenburg K, Geskus RB, Brinkman K, Coutinho RA, Prins M. Highly active anti retroviral therapy (HAART) among HIV infected drug users: a prospective cohort study of sexual risk and injecting behaviour
   Addiction 2006;101:433-40
4. Krol A, Lensen R, Veenstra J, Prins M, Schuitemaker H, Coutinho RA. Impact of CCR5 Δ32/ + Deletion on Herpes Zoster Among HIV-1-Infected Homosexual Men
   Eur J Epidemiol. 2006;21:469-73
5. Smit C, Geskus R, Walker S, Sabin C, Coutinho R, Porter K, Prins M. CASCADE Collaboration
   Effective therapy has altered the spectrum of cause-specific mortality following HIV seroconversion
   AIDS 2006;20:741-9
6. Witteveen E, van Ameijden EJC, Schippers G. Motives for and Against Injecting Drug Use Among Young Adults in Amsterdam: Qualitative Findings and considerations for disease prevention
   Substance use and Misuse 2006;7:1001-16
7. Bezemer D, de Ronde A, Prins M, Porter K, Gifford R, Pillay D, Masquelier B, Fleury H, Dabis F, Back N, Jurriaans S, and van der Hoek L on behalf of the CASCADE collaboration. Evolution of transmitted HIV-1 with drug-resistance mutations in the absence of therapy: effects on CD4+ T-cell count and HIV-1 RNA load
   Antiviral Therapy 2006;11:173-8
8. Shao W, Lazaryan A, Dorak MT, Penman-Aguilar A, Wilson CM, Margolick JB, Goedert JJ, Prins M, Tang J, Kaslow RA. Cohort- and time-specific associations of CTLA4 genotypes with HIV-1 disease progression. AIDS 2006;20:1583-90

9. Davidovich U, de Wit J, Stroebe W. Relationship characteristics and risk of HIV infection: Rusbult's investment model and sexual risk behavior of gay men in steady relationships
Journal of Applied Social Psychology 2006;36:22-40
10. Lindenburg CE, Krol A, Smit C, Buster MC, Coutinho RA, Prins M
Decline in HIV incidence and injecting, but not in sexual risk behaviour, seen in drug users in Amsterdam: a 19-year prospective cohort study
AIDS 2006;20:1771-5
11. Touloumi G, Pantazis N, Antoniou A, Stirnadel HA, Walker SA, Porter K, on behalf of the CASCADE Collaboration. Highly active antiretroviral therapy interruption: predictors and virological and immunologic consequences
JAIDS 2006;42:554-61
12. Groot F, van Capel TM, Kapsenberg ML, Berkhout B, de Jong EC
Opposing roles of blood myeloid and plasmacytoid dendritic cells in HIV-1 infection of T cells: transmission facilitation versus replication inhibition
Blood 2006;108:1957-1964
13. Cornelissen M, Jurriaans S, Prins JM, Bakker M, van der Kuyl AC
Absence of seroreversion in 80 HAART-treated HIV-1 seropositive patients with at least five-years undetectable plasma HIV-1 viral load
AIDS Research and Therapy 2006;3:3
14. Berkhout B, Back NKT, de Ronde A, Jurriaans S, Bakker M, Parkin NT, van der Hoek L
Identification of alternative amino acid substitutions in drug resistant variants of the HIV-1 reverse transcriptase
AIDS 2006;20:1515-1520
15. Naarding MA, Dirac AM, Ludwig IS, Speijer D, Lindquist S, Vestman EL, Stax MJ, Geijtenbeek TBH, Pollakis G, Hernell O, Paxton WA
Bile salt-stimulated lipase from human milk binds DC-SIGN and inhibits human immunodeficiency virus type 1 transfer to CD4+ T cells
Antimicrobial Agents and Chemotherapy
2006;50:3367-3374

Theses in 2006 that include ACS data

February 24, 2006, Utrecht. U Davidovich. Promotor: W. Stroebe. Co-promotor: Dr. J. de Wit.
Liaisons dangereuses -HIV risk behavior and prevention in steady gay relationships.

September 5, 2006. M.J. Geels. Promotor: Prof dr J. Goudsmit, co-promotor: Dr. W.A. Paxton. Sequence analysis as a tool to determine viral evolution and escape from host immune responses in HIV-1-infected individuals.

October 4, 2006, Amsterdam. G. Tjon. Promotor: Prof. R.A. Coutinho Co-promotor: Dr. S. Bruisten
Molecular epidemiology of hepatitis A in the Netherlands

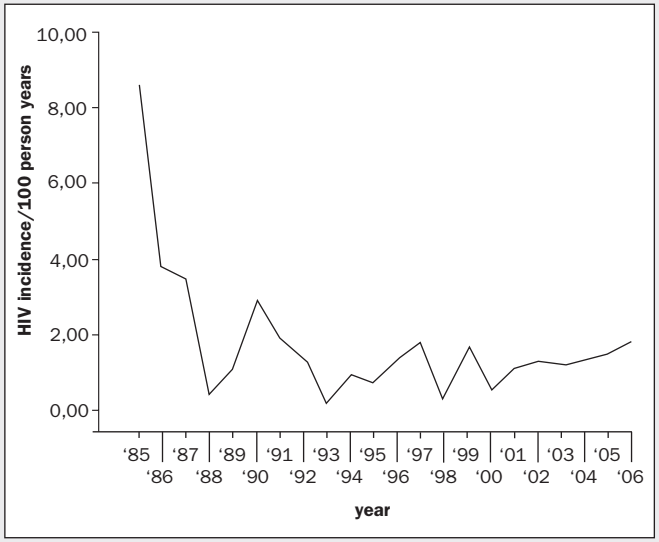

Figure 16.1: HIV incidence per calendar year in the Amsterdam Cohort Study amongst homosexual men (HM)

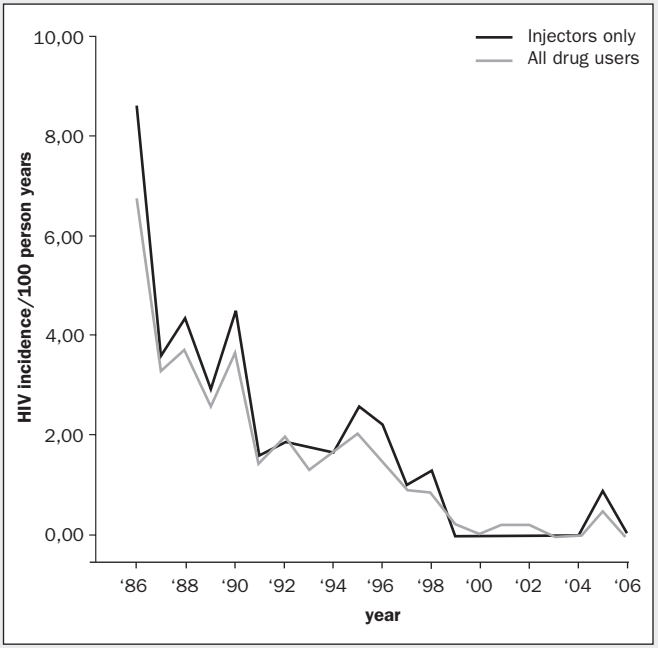

Figure 16.2: HIV incidence per calendar year in the Amsterdam Cohort Study amongst drug users

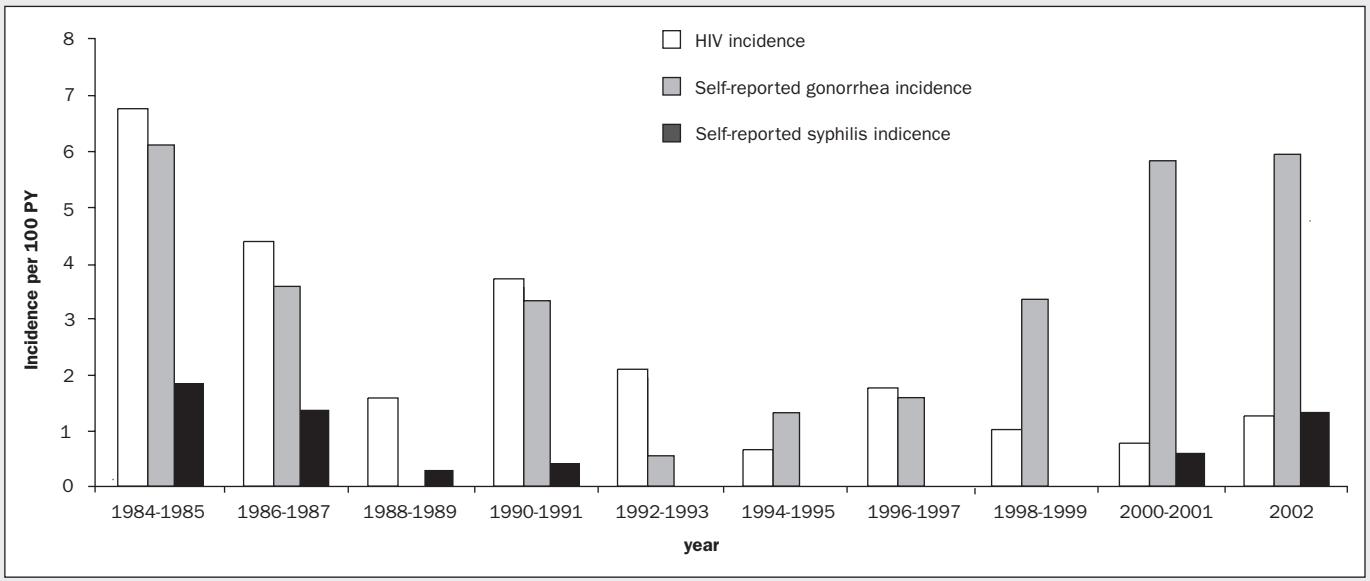

Figure 16.3: Incidence of gonorrhea, syphilis, and HIV per 100 person-years (PY) amongst 863 HIV-negative young (≤ 30 years at entry to 35 years) gay men, in Amsterdam 1984-2002.

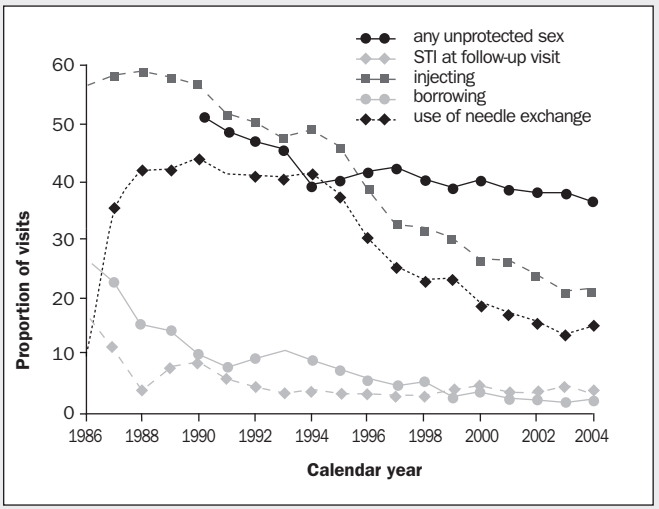

Figure 16.4: Proportion of visits per calendar year at which injecting and sexual risk behaviour was reported amongst 1315 drug users (DU) who were HIV-negative on ACS entry, 1986-2004.

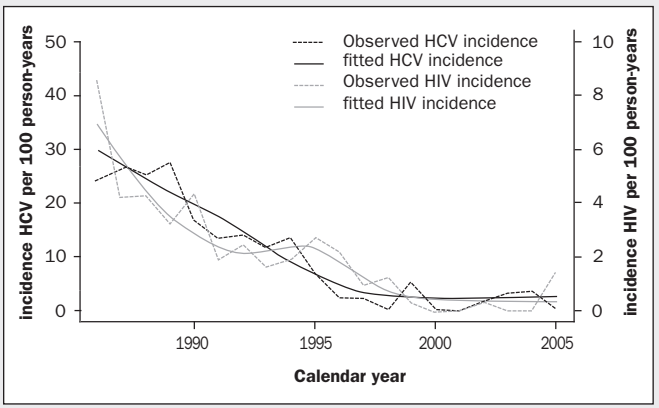

Figure 16.5: Observed and fitted hepatitis C virus (HCV) (left y-axis) and HIV (right y-axis) incidence curves amongst drug users (DU).

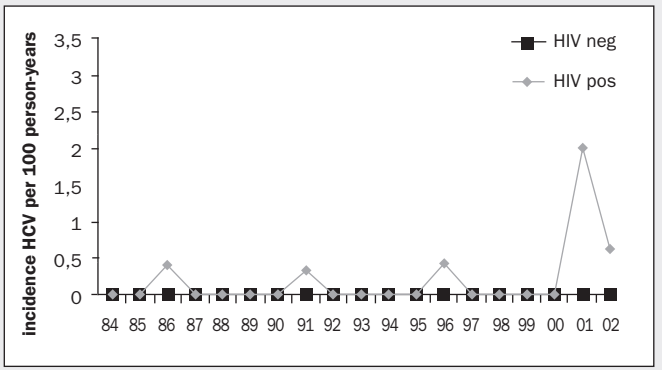

Figure 16.6: Observed hepatitis C virus (HCV) incidence amongst HIV-negative and HIV-positive homosexual men (HM).

Cura

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Curaçao and migrant populations

Ard van Sighem, Ashley Duits

Introduction

At the end of 2005, the HIV Monitoring Foundation (HMF) started registration and data collection for HIV-infected patients living in Curaçao. Initially, a group of about 200 patients who were still in follow-up at that time were included. At the beginning of 2007, a second group consisting of approximately 60 deceased patients was added. Meanwhile, in the past two years, about 30 newly diagnosed patients have been included in the HMF registration.

In our report of last year, patient characteristics and treatment outcomes in infected individuals in Curaçao were compared to those in the Surinamese and Antillean migrant populations in the Netherlands[16]. In the present report, an update of this analysis is presented. In addition, the total population in Curaçao is described.

Methods

The total study population in Willemstad consisted of 292 patients. A subpopulation of 206 HIV-1-infected patients (71%) was defined by selecting those patients who were in follow-up in or after 2006. This group was compared with a group of 825 patients registered in the Netherlands that consisted of those originating from the Netherlands Antilles or Aruba (326 patients) or Suriname (499 patients). $CD4^+$ and $CD8^+$ T cell counts and plasma HIV RNA levels at HIV diagnosis were defined by the measurement closest to the time of diagnosis, given that the measurement was within the first 12 weeks after the establishment of the diagnosis and prior to the start of therapy. The same variables were measured at the start of cART closest to and, at most, 12 weeks before the start of cART; after the start of cART, the values were obtained during each 24-week interval closest in time to the middle of the interval.

For the total population in Curaçao and for the three populations in follow-up in 2006 or thereafter, characteristics at HIV diagnosis and at the start of cART were compared. The frequency of measurements or clinical visits was calculated as the ratio of the number of visits or measurements to the total number of person-years in follow-up. Resistance was assessed as described in chapter 7. Patients were classified as resistant to an individual drug if the genotypic resistance interpretation algorithm score was “intermediate” or “high-level”.

Proportions were compared by a chi square test or, if sample sizes were small, by Fisher’s exact test. Differences in age, T cell counts, and RNA levels were tested with Wilcoxon-Mann-Whitney and chi square nonparametric tests. For continuous variables, medians were reported with interquartile ranges (IQR). Cox proportional hazard models were used to perform time-to-event analyses. Hazard ratios from these models were quoted with Wald 95% confidence intervals (CI). The Poisson distribution was used to calculate 95% CI for rates and for frequencies of measurements.

Changes over time in the proportion of patients with HIV RNA levels below 500 copies/ml were studied via general linear regression modelling. Correlations between longitudinal measurements for each patient were taken into account by means of a first-order autoregressive covariance structure. Generalising estimating equations were used to account for correlation between observations, and confidence intervals were estimated by the empirical estimator of the covariance matrix of parameter estimates.

Results

Total population

The total HIV-infected population recorded in Curaçao amounted to 292 patients, with a total follow-up since HIV diagnosis of 2077 person-years. Of these patients, a majority of 284 (97%) were infected with HIV-1. One patient was infected with HIV-2, and in the five other patients, seroreactivity to both HIV-1 and HIV-2 was

found. In total, 59 patients (20%) were diagnosed in or before 1995; of those, 24 (40%) were in the group of deceased patients, and 35 (15%) were in the group who were still alive. According to Table 17.1, the majority of the patients were male (68%), infected via heterosexual contact (67%), and originated from the Netherlands Antilles or Aruba (79%).

For 110 (38%) patients, the most likely country of infection was known. Most patients, 96 (87%), were reported to have been infected in the Antilles, whereas 10 (9%) patients brought their infection from Hispaniola. The HIV-1 subtype was known for 102 (35%) patients; all of them harboured a subtype B strain.

The median age at diagnosis was 37.9 (IQR, 31.9-45.9) years and did not differ between patients who were still alive and those who had died (p=0.9). Only 22 (8%) patients presented with an AIDS-defining event. However, at the start of cART, 41 (14%) patients had experienced an AIDS event in the previous year. In the population that was still alive, CD4 counts increased from 297 (93-505) $\times 10^6$ cells/l at diagnosis to 357 (235-510) at present.

Between 2001 and 2006, the frequency of RNA measurements was 2.21 (95% CI, 2.12-2.31) per year in the group of patients who was still alive, whereas it was only 0.94 (0.76-1.16) in the group of deceased patients. The frequencies of CD4 measurements were slightly higher, 2.38 (2.27-2.47), in the patients who were still alive than they were in those who died, 1.27 (1.05-1.52). The overall visit frequencies were 2.83 (2.72-2.93) and 2.08 (1.80-2.39), respectively.

The most frequently used initial cART regimens in Curaçao were lopinavir+zidovudine+lamivudine (77 patients, 38%), nelfinavir+stavudine+lamivudine (72 patients, 35%) and indinavir+zidovudine+lamivudine (23 patients, 11%). The prescription of antiretroviral drugs changed over calendar time (Figure 17.1). From 1996 onwards, the number of patients using indinavir increased to 71% of the treated population and steadily decreased thereafter to almost zero in 2006. This decrease was counterbalanced by an increase in the percentage of patients using nelfinavir. From 2000 onwards, lopinavir was increasingly used. Zidovudine and lamivudine were frequently used in the backbone, either as separate drugs or as combivir. The proportion of patients taking stavudine paralleled the use of nelfinavir. Around the turn of the century, 60% to 70% of the treated patients used stavudine, but its use became less popular thereafter. At the end of 2006, 44 (35%) patients were registered as using stavudine.

In 31 patients (11%) an HIV genome sequence was obtained within one year after HIV diagnosis and before the start of cART in the period between 2003 and 2006. In none of these sequences were resistance-associated mutations found (0% [95% CI, 0-11]).

Comparison with migrant populations

In total, 1031 patients were in follow-up in or after 2006, including 206 (20.0%) patients in Curaçao and 499 (48.4%) from Suriname and 326 (31.6%) from the Netherlands Antilles and Aruba who were in follow-up in the Netherlands. The total follow-up in each of the three populations was 1579, 2262, and 3211 person-years, respectively. The overall proportion of men was 69.1% (712 patients) and did not differ between the three subpopulations (p=0.2). The proportion of patients infected via homosexual contact was higher in the Surinamese (33.7%) and Antillean population living in the Netherlands (40.5%) than in the population in Curaçao (19.9%, p<0.001).

Patients in Curaçao were older at diagnosis, 38.0 (31.8-46.6) years, than both the Surinamese, who were 34.3 (28.7-41.6) years at diagnosis, and the Antillean patients in the Netherlands, who were 33.2 (27.0-39.7) years of age at diagnosis (p<0.001). Median CD4 counts at

diagnosis were 275 (90-490) × 10^6 cells/l and varied slightly across the three groups (p=0.04), that is, 276 (90-499) × 10^6 cells/l for patients in Curaçao, 320 (110-500) × 10^6 cells/l for patients from the Antilles in the Netherlands, and 250 (70-466) × 10^6 cells/l for patients from Suriname in the Netherlands. In patients who started cART, CD4 counts at diagnosis were lower, 200 (54-380) × 10^6 cells/l (p<0.001). There was no difference at diagnosis in CD8 cell counts, which were 854 (500-1227) × 10^6 cells/l (p=0.5), or in RNA levels, which were 4.6 (3.9-5.1) $\log_{10}$ copies/ml (p=0.1). In total, 128 (12.4%) patients were diagnosed with an AIDS-defining event at the time of HIV diagnosis, whereas 68 (6.6%) were diagnosed with a CDC-B event as the most serious event. Overall, these proportions did not differ between the three populations (p=0.03), but patients from Curaçao had an AIDS diagnosis less often (6.8%, p=0.008) than did patients from Suriname (15.2%) or the Antilles (11.7%) who were living in the Netherlands.

In total, 793 (76.9%) patients started cART, including 694 (87.5%) therapy-naïve patients and 99 (12.5%) who were pre-treated with non-cART regimens. According to a Kaplan–Meier estimate, the median time from diagnosis to the start of cART was 1.50 (1.19-1.98) years for the total population; however, if patients starting cART whilst being pre-treated with non-cART regimens were excluded, the median time was 1.17 (0.96-1.62) years. There was no difference in the time to initiation of cART between the three groups when adjusting for CD4 count at diagnosis, age, and transmission group: hazard ratios were 0.93 (95% CI, 0.69-1.25) for patients from Curaçao and 1.07 (0.86-1.33) for patients from the Antilles who were living in the Netherlands, compared to patients of Surinamese origin. At the start of cART, CD4 counts were 180 (64-300) × 10^6 cells/l for patients from the Antilles and 180 (50-280) × 10^6 cells/l for patients from Suriname living in the Netherlands, but they were significantly lower, 119 (39-222) × 10^6 cells/l, for patients from Curaçao (p=0.003, when Curaçao was compared with Antilles/Suriname). In total, 109 (10.6%) patients had experienced a CDC-B event in the year prior to the start of cART, and 189 (18.3%) had experienced a CDC-C event (p=0.02, comparing the three groups).

Between 2001 and 2006, the frequency of RNA load measurements per person-year of follow-up was 2.20 (2.11-2.30) for patients in Curaçao, 2.71 (2.62-2.80) for patients from the Antilles in the Netherlands, and 2.94 (2.86-3.01) for Surinamese patients in the Netherlands. CD4 counts were measured more frequently than RNA levels in patients from Curaçao (2.39 [2.29-2.50]) per person-year) and at similar rates for patients in the Netherlands, which were 2.66 (2.58-2.75) for the Antilleans and 2.93 (2.86-3.00) for the Surinamese. The average number of clinical visits was 2.84 (2.73-2.96) in Curaçao, 3.14 (3.04-3.23) for the Antilleans in the Netherlands, and 3.08 (3.00-3.16) for the Surinamese patients.

After 24 weeks of cART, of 640 patients in whom viral loads were measured, 514 (80.3%) had a viral load level below 500 copies/ml. This proportion did not differ between the three populations (p=0.8). The median CD4 count was 281 (170-440) × 10^6 cells/l and likewise did not differ between the three populations (p=0.04). In the previously therapy-naïve population, 82.0% had an RNA level below 500 copies/ml (p=0.005, compared to pre-treated population), whereas the median CD4 cell count at 24 weeks was 290 (170-440) × 10^6 cells/l (p=0.2).

For naïve patients, the median time to the first switch in therapy was 1.20 (1.05-1.41) years. However, patients in Willemstad switched their initial cART regimen after a median time of 2.89 (2.11-3.35) years, which was considerably later than patients of Antillean or Surinamese origin in the Netherlands who switched after only 0.95 (0.79-1.11) years (p<0.001). Of the 200 patients who interrupted their first regimen and started

a new regimen after a period without treatment, 64 (32%) used their initial regimen again. In Curaçao, 21 (55%) of 38 restarted their initial regimen, whereas only 43 (27%) of 162 Surinamese or Antilleans in the Netherlands ($p<0.001$) did so.

Five years after the start of cART, 285 (41%) patients were still in follow-up, including 56 (39%) in Curaçao, 89 (42%) from the Antilles living in the Netherlands, and 140 (41%) from Suriname living in the Netherlands. At that time, 42% of the patients in Curaçao, 65% of the Antilleans living in the Netherlands, and 77% of the Surinamese patients had a viral load below 500 copies/ml ($p<0.001$). Median CD4 cell counts were 384 (224-608) $\times 10^6$ cells/l for patients in Curaçao, 480 (280-590) $\times 10^6$ cells/l for Antilleans in the Netherlands, and 520 (340-740) $\times 10^6$ cells/l for Surinamese patients in the Netherlands ($p=0.03$). Figure 17.2 shows the median CD4 cell counts and the proportion of previously therapy-naïve patients with HIV RNA levels below 500 copies/ml after the start of cART. According to the logistic model, the proportion of patients with RNA below 500 copies/ml did not change over time for those of Surinamese or Antillean origin in the Netherlands, but it significantly declined over time after the start of cART for patients in Curaçao (slope -0.0031 [-0.0050;-0.0012] $\log_{10}$ copies/ml/week, $p=0.002$).

Between 2003 and 2006, 28% of the patients in Curaçao who started cART whilst they were antiretroviral therapy-naïve subsequently experienced virological failure. For Surinamese and Antillean patients in the Netherlands, this proportion was 10% and 11%, respectively.

Resistance to individual protease inhibitors was found in 6% to 15% of the 208 patients – including both previously therapy-naïve and pre-treated patients – with at least one sequence after the start of cART. Resistance to nelfinavir was found in 25% of the patients, and this proportion was lower amongst patients from Suriname (13%) than amongst Antillean patients in the Netherlands and in Curaçao (34%, $p<0.001$). In 25% of the patients, resistance to efavirenz was found, and 30% of the patients were resistant to nevirapine. These proportions were lower in patients from Curaçao; specifically, 8% were resistant to efavirenz, and 10% were resistant to nevirapine ($p<0.001$). Resistance to lamivudine and emtricitabine was found in 45% of the patients, whereas resistance to other nucleoside RT inhibitors varied from 7% to 19% of the patients.

Discussion

Our analysis shows that the HIV-infected population in Curaçao as registered by the HIV Monitoring Foundation is similar in demographics to two Caribbean migrant populations in the Netherlands. Patients in Curaçao are, however, significantly older at diagnosis than Surinamese and Antilleans in the Netherlands, and a smaller proportion report homosexual contact as the most likely route of infection. At the time of diagnosis, there was no difference in clinical characteristics between the three populations.

Although there was no significant difference in CD4 cell counts at diagnosis and in the time to the start of cART, patients from Curaçao had lower CD4 counts at the start of cART. This paradoxical result is probably due to the scarcity of data, since patients in Curaçao who started cART tended to already have lower CD4 counts at diagnosis. Nevertheless, the short-term therapy outcome in the Netherlands Antilles was comparable to that in the Surinamese and Antillean migrant populations in the Netherlands. The long-term therapy outcome was, however, substantially worse in Curaçao, where only about 50% of the patients were able to suppress HIV RNA below 500 copies/ml, compared to 70% to 80% of the patients in the Netherlands. A negative effect on CD4 counts was less pronounced, most likely as a result of the slower dynamics of CD4 cells.

The patients' decreasing ability to suppress viral load is probably a consequence of the limited number of therapy options in Curaçao. Just three regimens account for more than 80% of all regimens administered to patients in Curaçao. Ritonavir, which is used to achieve optimal blood levels of protease inhibitors, is not available in Curaçao, except in a fixed-dose combination with lopinavir. Hence, the number of boosted protease-containing regimens is limited. Non-nucleoside RT inhibitors are also not available, and neither are fixed-dose combinations like Kivexa, Truvada and Trizivir. Of the drugs that are available in Curaçao, nelfinavir is hardly used in the Netherlands for the treatment of adult non-pregnant patients since it can cause diarrhoea, and only one mutation in the protease gene is sufficient to render the virus resistant to nelfinavir. Stavudine is rarely used in the Netherlands today, since it has been associated with an increased risk of peripheral neuropathy and lipoatrophy[203]. Also, zidovudine is less frequently used in the Netherlands and is often replaced by tenofovir.

Although the proportion of patients in Curaçao who failed cART was higher than amongst the Surinamese and Antillean patients in the Netherlands, the prevalence of resistance was similar and followed the availability of antiretroviral drugs. Despite the large proportion of failures, transmission of resistant virus strains was not found. This might indicate that newly diagnosed patients were infected before the introduction of cART in Curaçao. It could also mean that most transmissions were from patients who were not yet treated or who were not yet aware of their HIV infection.

Our analysis is limited by the way in which the registered Curaçao population was established. Because of the batch-wise inclusion of patients – one batch of patients in follow-up at the time of registration and a second batch of patients who already had died – the registered population probably is not representative of the total HIV-infected population on the island. This limits the possibilities for survival analyses, since patients who are lost to follow-up are generally not part of the registered population. The inclusion method also biases the population that was used in comparison with migrant populations in the Netherlands towards a population that is in relatively good condition. Patients in Curaçao, for instance, less often had an AIDS-defining event at diagnosis or at the start of cART compared to Antillean and Surinamese patients in the Netherlands. However, registration in Curaçao is ongoing, and the selection bias in the population might be resolved in the foreseeable future.

In conclusion, the absence in Curaçao of most antiretroviral drugs presently available in the Netherlands for the treatment of HIV-infected patients is a major concern. It leads to inferior suppression of HIV RNA levels, development of drug resistance, and a faster disease progression than is seen in patients in the Netherlands. As a consequence, patients seeking care might greatly strain the scarce resources on the island, and the associated costs might outweigh those necessary for adequate cART when all treatment options are available. Moreover, the number of infectious individuals will increase, forming a growing reservoir for further transmission of HIV to the uninfected population.

		Alive, N=232		Dead, N=60		Total, N=292	
		N / median	% / IQR	N / median	% / IQR	N / median	% / IQR
gender, male		150	65	48	80	198	68
transmission	MSM	43	19	8	13	51	18
	heterosexual	155	67	41	68	196	67
	other/unknown	34		11		45	
country of birth	Antilles	177	76	54	90	231	79
	Haiti	35	15	3	5	38	13
	Dominican Republic	10	4	2	3	12	4
treated with cART		167	72	37	62	204	70
diagnosis	CD4 (10^6 cells/l)	297	93-505	110	61-311	268	81-475
	RNA (log_{10} copies/ml)	4.5	4.0-5.2	4.8	3.5-6.0	4.5	3.9-5.4
	age (years)	37.9	31.8-46.0	37.9	32.1-45.0	37.9	31.9-45.9
	AIDS	12	5	10	17	22	8
	time to cART	1.5	0.4-4.3	1.7	0.2-4.2	1.6	0.4-4.3
	follow-up (years)	5.8	2.6-10.3	3.2	1.4-7.5	5.4	2.2-9.6
start of cART	CD4 (10^6 cells/l)	125	43-227	54	11-173	109	35-220
	RNA (log_{10} copies/ml)	5.0	4.6-5.5	5.1	3.8-5.6	5.1	4.5-5.5
	age (years)	41.1	35.1-49.0	40.3	36.8-47.7	40.9	35.2-48.9
	AIDS	21	9	20	33	41	14
	follow-up (years)	4.2	1.5-6.7	1.4	0.5-4.2	3.4	1.3-6.3
present	CD4 (10^6 cells/l)	357	235-510	50	7-120	342	202-485
	RNA <500 copies/ml	91	39	10	17	101	35
	age (years)	44.5	39.4-52.4	46.1	42.4-55.2	45.3	39.8-53.2

IQR: interquartile range; MSM: men having sex with men; cART: combination antiretroviral therapy

Table 17.1: Characteristics of the HIV-infected population in Curaçao.

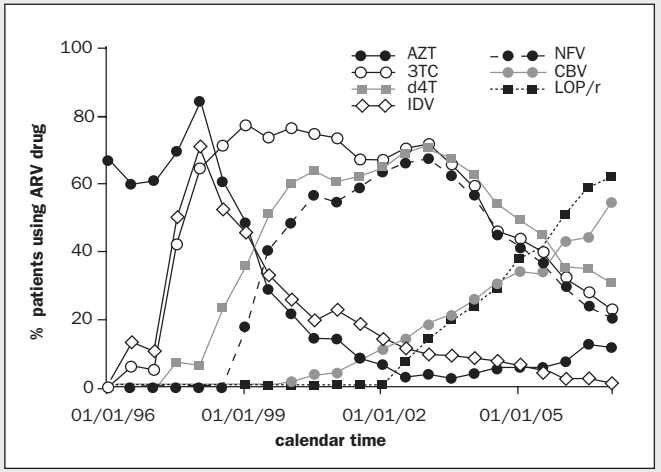
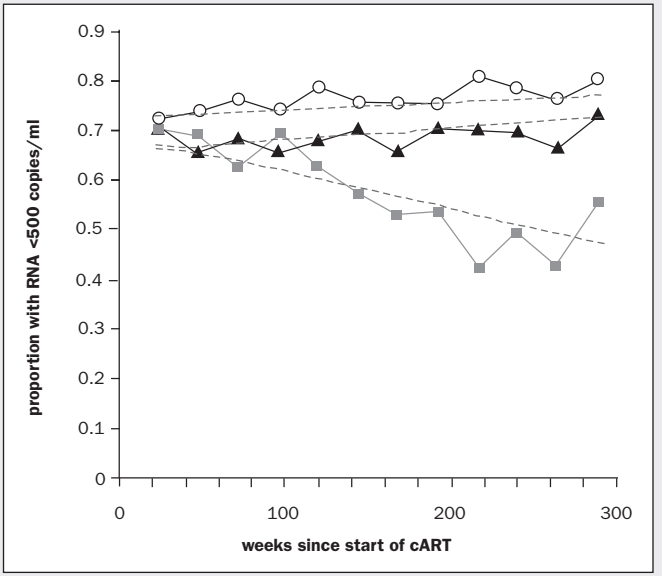


Figure 17.1: Percentage of treated patients using specific antiretroviral drugs over calendar time. AZT: zidovudine; 3TC: lamivudine; d4T: stavudine; IDV: indinavir; NFV: nelfinavir; CBV: zidovudine+lamivudine; LOP/r: lopinavir (ritonavir boosted).



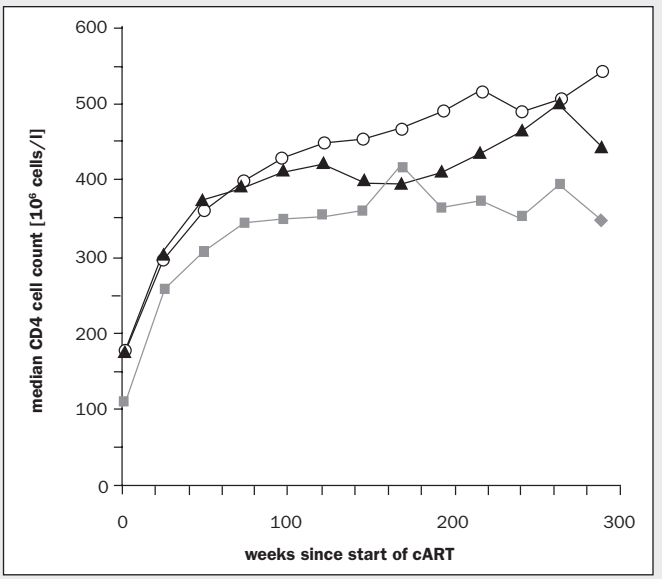


Figure 17.2: HIV RNA levels below 500 copies/ml and CD4 cell counts after the start of cART for previously therapy-naïve patients treated in Willemstad, Curaçao (squares) and for those from the Antilles (triangles) and Suriname (circles) living in the Netherlands. The dotted line represents the result of a generalised estimating equations model.

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Publications 2007

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A.I. van Sighem
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Poster presentations

Improved toxicity profile of recent HAART regimens
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Increased progression to liver disease and death in HIV-HCV compared to HBV co-infected patients.
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A CD4 threshold below 350 cells/mm^3 for initiation of HAART is associated with a higher risk of AIDS
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Modelling the age distribution of the HIV-infected population in the Netherlands
AI van Sighem, DO Bezemer, F de Wolf. 11th Workshop on HIV Observational Databases, 22 March 2007.

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Incidence of nevirapine-associated hypersensitivity reactions is different in patients with prior treatment experience compared to treatment-naïve patients The ATHENA cohort study
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Colophon

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Mission
The HIV Monitoring Foundation is appointed by the Dutch Minister of Health, Welfare and Sports (Ministerie van Volksgezondheid, Welzijn en Sport) as the national executive organization for the registration and monitoring of HIV-infected patients in follow-up in one of the Dutch Treatment Centres. Our mission is to further the knowledge and understanding of the epidemiology and the course of the treated and untreated HIV infection.

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