REPORT 2006

MONITORING OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN THE NETHERLANDS

STICHTING HIV MONITORING

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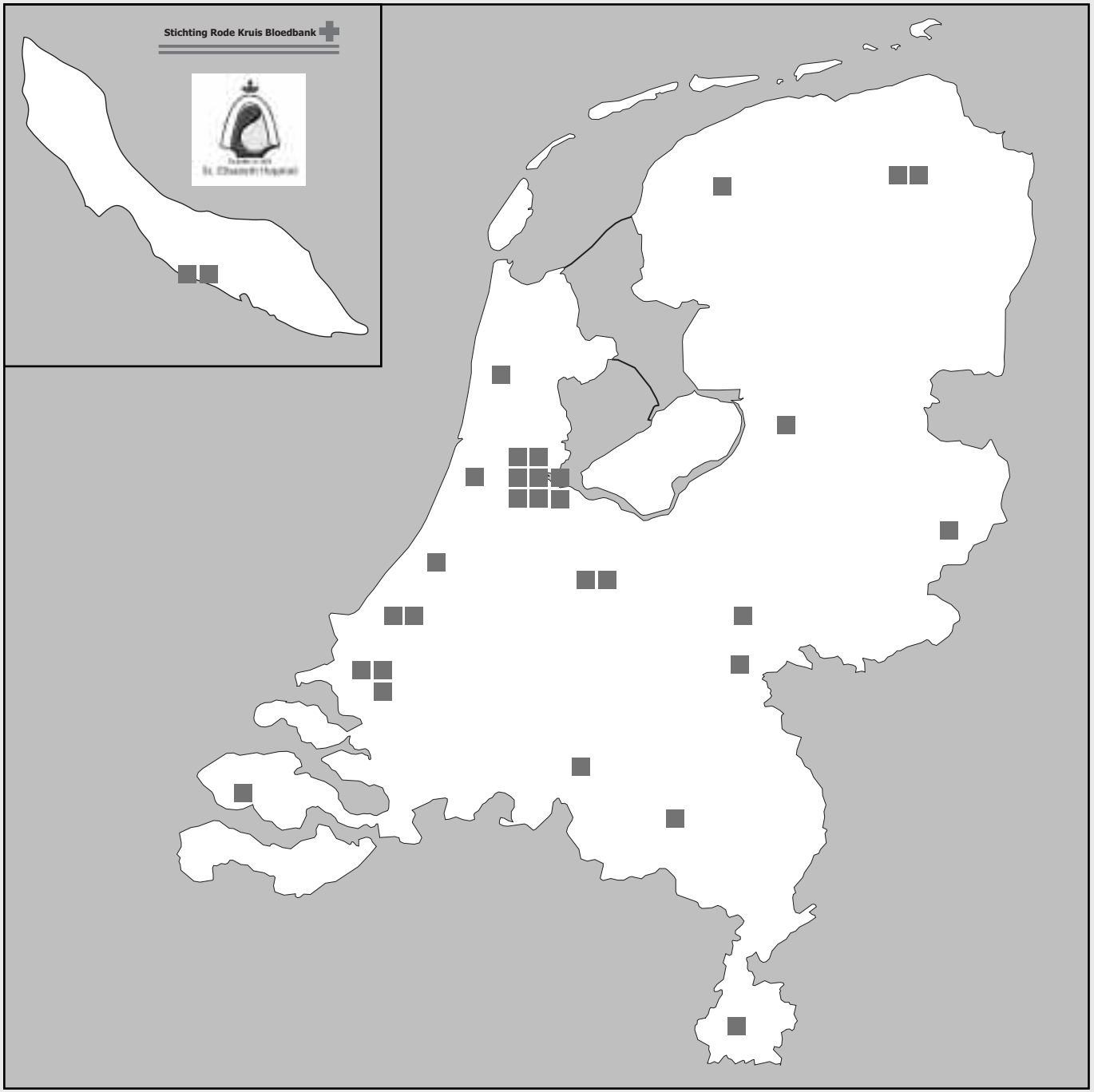
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Introd

uction

Frank de Wolf

Treatment of human immunodeficiency virus (HIV) infection with so-called highly active antiretroviral therapy (HAART) has reached its 10th anniversary. In the Netherlands, HAART has been widely used since its introduction in 1996, when antiretroviral drugs with 3 different mechanisms of inhibiting HIV became available. A combination of 3 drugs, with at least 2 of them from different inhibitory classes, would become the standard of treatment for HIV-infected patients.

Since official registration of the new antiretroviral drugs to be used in HAART would have taken considerable time, the Minister of Health in the Netherlands decided in 1996 to provisionally allow new antiretroviral drugs for routine treatment before the registration procedure was finalised. Antiretroviral drugs could be prescribed only by physicians who treated the acquired immunodeficiency syndrome (AIDS) and could be distributed only through the existing AIDS Treatment Hospitals. In addition, the effect of HAART was to be evaluated through a collaborative nationwide study coordinated by the Academic Medical Hospital of the University of Amsterdam.

After a preparatory phase, during which data on the effect of HAART had already been collected, this study, called AIDS Therapy Evaluation in the Netherlands (ATHENA), was started in 1998. Four years later, after the project had successfully ended, Parliament decided to reorganise HIV patient care such that the treatment of HIV and AIDS became the task of hospitals specifically designated as HIV Treatment Centres. Monitoring of HIV was to be part of that designation. In February 2002, the HIV Monitoring Foundation (HMF) was established as the executive organisation for the monitoring of HIV-infected patients in collaboration with the HIV Treatment Centres. The ATHENA dataset was handed over to the HMF, and it formed the basis for the new national HIV monitoring database. For continuity, the data collected in publications since the establishment of the HMF are referred to as the ATHENA observational cohort.

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 1 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.

A primary activity through which the HMF seeks to accomplish its mission is to make data available for HIV/AIDS-related research. To support the use of such data, an accurate and periodically updated description of the HIV-infected population from which HMF draws its data is of great importance. This fifth annual report provides that 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 the epidemic that result from 10 years' large-scale, lifetime treatment of HIV.

Ten inhibitors of the HIV enzyme reverse transcriptase that are subdivided into 8 nucleoside/nucleotide inhibitors and 2 non-nucleoside inhibitors, 9 protease inhibitors, and 1 inhibitor of fusion of HIV to the cell surface are currently registered in the Netherlands for the treatment of HIV. In addition, 5 drugs of the nucleoside/nucleotide class are used in 4 different combinations, reflecting successful attempts to simplify dosages. The goal of antiretroviral treatment is to decrease the morbidity and mortality rates that are generally associated with HIV-infection. A combination of 3 or more active drugs is needed to achieve this aim in most patients. Effective treatment

results in long lasting viral suppression, although current drugs do not eradicate HIV infection and lifelong treatment may be needed. Viral suppression improves a patient's immune response as turnover rates of CD4 and CD8 cell populations return to near normal levels. Two major issues complicate treatment of HIV: insufficient viral suppression that may result in HIV becoming resistant to antiretroviral drugs; and subsequent therapy failure and serious side effects such as hepatic, renal and mitochondrial toxicities, metabolic changes, and immune reconstitution disease.

In this report, we discuss HAART-related issues including:

- The efficacy of HAART over the last 10 years, the improvements and limitations of new HAART regimens, and issues of when to start treatment;
- Changes in the incidence of adverse events and toxicity of HAART over time;
- HAART in injecting drug users;
- Failure of HAART and the development of drug resistance;
- Changes in morbidity and mortality since the introduction of HAART in 1996.

The report also offers an update on the infected population in the Netherlands, presenting data on:

- Changes over time in the characteristics of the infected population;
- The disappearance of mother-to-child transmission of HIV and the increasing number of Dutch HIV-infected women becoming pregnant;
- Co-infection with hepatitis B or C virus.

For the first time, we will report on the quality of the data. Maximizing the data quality is, obviously, crucial for data analyses. Maintaining and optimising quality control procedures are issues discussed in this report amongst others.

Finally, we report on our efforts to monitor HIV in the Netherlands Antilles. In collaboration with the Red Cross Blood Bank of Curaçao and the St. Elisabeth Hospital in Willemstad, Curaçao, data collection from HIV-infected patients was started at the end of 2005. The interconnection between the Netherlands Antilles and the Netherlands will be discussed.

The HMF continues to participate in studies performed within the framework of the Anti-Retroviral Therapy Cohort Collaboration (ART-CC), which encompasses 15 cohorts from various European countries, the United States, and Canada. For ART-CC, the only data used are those obtained from patients starting HAART 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 HAART regimens.

Besides ART-CC, a new European collaboration between observational cohorts was started. COHERE (Collaboration of Observational HIV Epidemiological Research in Europe) 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 answers. The first research project is investigating the effect of age on HAART outcomes.

The long-standing collaboration with the Department of Infectious Disease Epidemiology of the Medical Faculty of Imperial College in London has recently resulted in a model analysing the impact of large-scale administration of HAART on the epidemic in the Netherlands. In addition, after last year's report on transient viraemia during HAART, the collection of data and development of a mathematical model assessing the impact of superinfection has 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 done by HMF's data monitors. Data preparation and analyses are done 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.

As of 1 June 2006, 12,059 patients infected with HIV were included in the HMF programme. The number of HIV-infected patients continues to increase, and, in contrast to our previous findings, the pace is not slowing. The question is still open as to whether this is due to an influx of persons who were already infected some time in the past or who have been infected recently. However, on the basis of CD4 cell counts, new cases are apparently being diagnosed in patients at an earlier stage of infection, which suggests an increasing number of recently infected individuals.

Samen

vatting

Frank de Wolf

Dataverzameling en datakwaliteit

De controle op de verzameling en de kwaliteit van de gegevens is cruciaal voor de waarde van observationele gegevens die door de Stichting HIV Monitoring (SHM) verzameld worden. Gebleken is echter dat vergelijking met de bron van 10% van de van patiënten verzamelde gegevens onvoldoende is om de kwaliteit van gegevens te waarborgen. Daarom worden sinds kort op maat toegesneden procedures voor de verificatie en kwaliteitsbeoordeling van onze gegevens gebruikt.

In de database ingevoerde gegevens over de demografie, de HIV-ziektegeschiedenis en transmissiewijze en – waar aan de orde – de doodsoorzaak van alle patiënten worden nu door vergelijking met de schriftelijke bron geverifieerd. Bovendien zijn er op basis van de kliniek van HIV 23 procedures ontwikkeld voor de controle van de consistentie van ingevoerde gegevens, waarmee onduidelijke gegevens kunnen worden geselecteerd. Bovendien wordt tenminste 1% van alle records in de database random geselecteerd voor vergelijking met de schriftelijke bron.

Naast deze procedures worden gegevens over cardiovasculaire afwijkingen van patiënten beoordeeld in het kader van de DAD (Data Collection on Adverse Events of Anti-HIV Drugs) studie. Methodes en resultaten van de vergelijking van ingevoerde gegevens met de schriftelijke bron zijn opgeslagen in een daarvoor speciaal ontworpen Microsoft Access database. Naar aanleiding van de vergelijking met de schriftelijke bron worden niet alleen de gegevens in de nationale HIV monitoring database (Oracle Clinical) gewijzigd, maar worden ook de wijzigingen in de vorm van audit trail data daarin opgeslagen.

Uit de eerste resultaten van deze nieuwe wijze van kwaliteitscontrole blijkt dat 6% van de gegevens over de transmissiewijze en de ziektegeschiedenis van HIV niet of niet geheel juist zijn. Dat percentage is in vergelijking met andere observationele studies naar HIV –voor zover dat wordt gemeld – laag. De invloed van de geconstateerde fouten op de uitkomsten van onderzoek met de ATHENA gegevens wordt nu verder geanalyseerd.

Karakteristieken van de geregistreerde populatie

Vergeleken met het wetenschappelijk verslag van 2005 werden 1205 nieuwe patiënten met een infectie met het humaan immunodeficiëntievirus (HIV) geregistreerd en zijn nu cumulatief 12.059 patiënten met een totale follow-up van 80.764 persoonsjaren onderdeel van het nationale observationele ATHENA cohort. Daaronder vallen 9254 mannen (77,5%) en 2699 vrouwen (22,6%) met een leeftijd van tenminste 13 jaar op 1 juni 2006; 106 (0,9%) patiënten waren op die datum jonger dan 13. Het alsmaar groeiend aantal nieuw vastgestelde HIV infecties is mogelijk het gevolg van een continue instroom uit de grote groep personen die zich niet bewust is van het feit dat men al een langere tijd geïnfecteerd is. Maar ook mensen met een recente infectie kunnen bijdragen aan de toename van het aantal geregistreerde gevallen, wat zou betekenen dat de verspreiding van HIV weer toeneemt.

De overgrote meerderheid van de patiënten is geïnfecteerd met HIV-type 1 en minder dan 1% met HIV-type 2. De man-vrouw verdeling is in vergelijking met 2005 nauwelijks veranderd en mannen vormen meer dan driekwart van de geregistreerde geïnfecteerde patiënten. In combinatie met de verdeling over de verschillende risicogroepen, waaruit blijkt dat 52,2% is geïnfecteerd via homoseksueel contact, leidt dat tot de conclusie dat mannen die seks hebben met mannen nog steeds de HIV-epidemie in Nederland bepalen. Daarnaast is er een kleinere, maar

wel geleidelijk aan groeiende groep mensen die is geïnfecteerd via heteroseksuele contacten. Meer dan de helft daarvan is vrouw.

De verdeling van de leeftijd op het moment van de HIV-diagnose is niet veranderd: mannen zijn in meerderheid tussen de 25 en 44 jaar en vrouwen tussen de 18 en 34 jaar. Vrouwen zijn mediaan 7 jaar jonger dan mannen wanneer de HIV diagnose wordt gesteld. Ook andere demografische karakteristieken zijn niet veranderd: de meerderheid van de mannen is van Nederlandse origine en geïnfecteerd met HIV-subtype B, terwijl de meerderheid van de vrouwen afkomstig is uit Zuidelijk Afrika en geïnfecteerd is met een non-B subtype. In totaal 749 HIV-positieve vrouwen werden zwanger.

Zesenvijftig jongens en 50 meisjes met een huidige mediane leeftijd van 10 jaar zijn in de registratie opgenomen. De meeste van hen waren bij diagnose 1 jaar of jonger en kregen de infectie via de moeder. Dit resultaat duidt er op dat preventiemaatregelen ter voorkoming van de overdracht van HIV van moeder naar kind (behandeling met antiretrovirale middelen van de zwangere en prenatale screening op HIV) effectief zijn. Echter, omdat migratie vanuit endemische HIV-gebieden in Afrika en Azië – hoewel in steeds minder mate – door zal gaan, moet rekening gehouden worden met een langzame toename in het aantal HIV-positieve kinderen.

Sinds 2002 wordt 80% van de geregistreerde HIV-geïnfecteerde patiënten die geregeld worden gezien in één van de 24 HIV Behandelcentra, behandeld met highly active antiretroviral therapy (HAART). Bijna 20% wordt niet behandeld met antiretrovirale middelen en een zeer kleine fractie wordt behandeld met een combinatie van middelen die niet overeenkomstig de definitie van HAART is. De patiënten die niet worden behandeld, voldoen in meerderheid nog niet aan de criteria, die volgens de huidige richtlijnen worden gehanteerd om met HAART te beginnen. De combinatie van middelen die als eerste keus wordt gebruikt bij de start van de behandeling van HIV is wel veranderd: de non-nucleoside reverse transcriptase remmers tenofovir en emtricitabine hebben de gedurende een lange tijd gebruikte standaardcombinatie van zidovudine en lamivudine vervangen.

Onderzocht werd hoe vaak bij patiënten met een HIV infectie ook een infectie met het hepatitis B (HBV) of hepatitis C virus (HCV) was gevonden. Niet alle geregistreerde HIV-positieve patiënten werden getest op HBV of HCV, maar onder de geteste patiënten bleek 10% een coïnfectie met HBV en 9% een coïnfectie met HCV te hebben. De meeste coïnfecties werden gevonden in de groep injecterende druggebruikers Minder dan 10% van de patiënten met een coïnfectie wordt behandeld voor HBV of behandeld met een HAART-combinatie die ook is aanbevolen voor de behandeling van HCV.

TIEN JAAR HAART

Veranderingen in de met HIV besmette groep

Mannen met homoseksuele contacten (MSM)

Van de 8996 mannen met een HIV-diagnose zijn er 6170 (68,6%) besmet via homoseksueel contact. Het aantal nieuwe diagnoses onder homoseksuele mannen bedroeg 361 in 1996, daalde tot 313 in 1998 en steeg vanaf dat moment tot 495 in 2005. De meeste mannen, 4549 (73,7%), zijn Nederlanders en 88,8% werd besmet in Nederland; 3,6% werd besmet in andere landen in West-Europa. Het mediane aantal CD4 cellen bij diagnose steeg van 255 x 10^6 cellen/l in 1996 tot 400 in 2005 ($p<0,0001$). De mediane leeftijd van de Nederlandse mannen bij diagnose steeg van 36,9 jaar in 1996 tot 40,7 jaar in

2005. De leeftijd van niet-Nederlandse homoseksuele mannen steeg eveneens, maar niet significant (p=0,02), van 33,5 tot 36,4 jaar.

Er werd een toename gevonden in het aantal patiënten in deze groep met een laatste negatieve HIV-testuitslag: van 109 (32,3%) in 2000 tot 251 (50,7%) in 2005. In diezelfde periode steeg het percentage mannen met een negatieve HIV-test 18 maanden of minder voor de eerste positieve HIV-test van 12,1% naar 25,3%. Het mediane aantal CD4 cellen was op dat moment 510 x 10^6 cellen/l (95% betrouwbaarheidsinterval, 370-700) en de mediane HIV-RNA plasmaspiegel 4,8 $\log_{10}$ kopieën/ml (4,1-5,2); deze waarden bleven in de loop van de tijd hetzelfde en werden niet beïnvloed door de leeftijd op het moment van diagnose. Het aantal CD4 cellen bij diagnose bij patiënten waarbij geen sprake was van een recente infectie steeg van 220 x 10^6 cellen/l in 1996 tot 360 in 2006.

Via heteroseksueel contact besmette patiënten

In totaal 3843 patiënten werden besmet via heteroseksueel contact, waaronder 1604 (13,9% van de totale geregistreerde populatie, 41,7% van de heteroseksuele groep) mannen en 2239 (19,4% van de totale geregistreerde populatie en 58,3% van de heteroseksuele groep) vrouwen. Per jaar werden tussen 2000 en 2005 gemiddeld 158 mannen en 231 vrouwen geregistreerd zonder dat het aantal nieuwe HIV-diagnoses significant over de tijd veranderde.

De meeste patiënten werden besmet in Nederland (42,6%) of Zuidelijk Afrika (41,1%). De meeste heteroseksuele mannen waren van Nederlandse afkomst (37,3%); andere belangrijke regio's waren Zuidelijk Afrika (34,8%), Zuid-Amerika (10,3%) en het Caribische gebied (5,2%). Bijna de helft van de heteroseksuele vrouwen kwam uit Zuidelijk Afrika (48,9%), 24,9% was Nederlands, 9,3% was van Zuid-Amerikaanse origine en 5-8% kwam uit het Caribische gebied. Het percentage patiënten afkomstig uit Zuidelijk Afrika steeg tussen 1996 en 2002 van 33,1% tot 57,6% en daalde vervolgens tot 40,3% in 2005 en 2006. Daartegenover stond een daling van het percentage Nederlandse patiënten van 40,5% in 1996 tot 19,3% in 2001, gevolgd door een stijging tot 31,8% in 2005 en 2006. Het aantal nieuwe Nederlandse HIV-patiënten steeg van 82 in 2002 tot 115 in 2005, terwijl het aantal afkomstig uit Zuidelijk Afrika daalde van 238 tot 148.

Ongeacht de regio van herkomst waren mannen ouder op het moment van de HIV-diagnose dan vrouwen en hadden mannen een lager aantal CD4 cellen en een hogere HIV-RNA concentratie in het bloed. Over het algemeen waren, in vergelijking met Nederlanders, mannen en vrouwen afkomstig uit Zuidelijk Afrika bij diagnose jonger en werden lagere aantallen CD4 cellen gemeten. Ook bij patiënten uit Zuid-Amerika, het Caribische gebied en Zuid/Zuidoost-Azië werd bij diagnose een lager aantal CD4 cellen gemeten dan bij Nederlanders.

Bij 12,6% van de tussen 1996 en 2003 gediagnosticeerde heteroseksuele patiënten was ook een voorafgaande negatieve HIV-test bekend; 4,4% werden geregistreerd als recente infectie. Vanaf 2004 neemt het percentage recente infecties onder vrouwen geleidelijk toe van 4,5% in 2004 tot 9,1% in 2005 en 16,1% in 2006. Een dergelijke toename werd niet gevonden onder heteroseksuele mannen. In totaal nam het percentage door heteroseksueel contact besmette patiënten met een bekende laatste negatieve HIV-test toe tot 30,7%.

Injecterende druggebruikers

Injecterend druggebruik bleek de meest waarschijnlijke besmettingsroute bij 594 (5,2%) patiënten, waaronder 436 (73,4%) mannen en 158 (26,6%) vrouwen. De meeste patiënten, 372 (62,6%), werden besmet voor 1996 en slechts 88 (14,8%) tussen 2000 en 2005. De meeste druggebruikers zijn Nederlanders (392 patiënten, 66,0%) of

afkomstig uit een van de andere West-Europese landen (100 patiënten, 16,8%). Van de 222 patiënten die in of na 1996 werden gediagnosticeerd, werd 34,2% behandeld in één van de HIV-behandelcentra in Amsterdam, 29,3% in één van de andere centra in de Randstad en 25,2% in het zuiden van Nederland, in het bijzonder Maastricht (18,9%).

Mortaliteit en AIDS

In totaal werd in de gehele groep van 11.709 patiënten met voldoende follow-up 3468 maal AIDS geregistreerd op het moment van of direct na de HIV-diagnose. Bij 2048 patiënten werd 6 weken of meer na de HIV-diagnose AIDS geregistreerd. De AIDS-incidentie daalde van 9,6 (95% CI, 8,5-10,8) diagnoses per 100 persoonsjaren in 1996 tot 2,0 (1,7-2,3) in 2005. Gedurende 66.595 persoonsjaren follow-up overleden 984 patiënten, hetgeen neerkomt op een gemiddelde mortaliteit van 1,48 (CI 1,39-1,57) overledenen per 100 persoonsjaren.

De mortaliteit veranderde niet over de tijd. Er werden in 36.428 persoonsjaren follow-up 395 overledenen geregistreerd onder die patiënten bij wie in of na 1996 de HIV-infectie werd vastgesteld. In 1996 werd bij 76% van de overleden patiënten een aan HIV gerelateerde doodsoorzaak geregistreerd en in 2005 bij 39%, terwijl gedurende dezelfde periode het percentage niet aan HIV gerelateerde doodsoorzaken steeg van 10% tot 50%. Met behulp van een prognostisch model kon worden aangetoond dat een 34-jarige patiënt, waarbij de HIV-diagnose tussen 1998 en 2005 werd vastgesteld en bij wie bij diagnose tenminste 200 x 10^6 CD4 cellen/l werden gemeten, een 5 maal hogere kans loopt om te overlijden dan een niet-geïnfecteerde 34 jarige van hetzelfde geslacht. Deze grotere kans om te overlijden wordt geleidelijk aan minder met het toenemen van de leeftijd; 50-jarige patiënten hebben uiteindelijk een kans om te overlijden die minder dan twee keer hoger is.

Overdracht van resistent HIV

Bij 25% van de 2927 tussen 2003 en 2005 gediagnosticeerde patiënten werd binnen 1 jaar na diagnose het HIV protease en reverse transcriptase (RT) gen getypeerd. Daaronder waren RT- en proteasesequenties van 207 patiënten met een na 2001 vastgestelde recente HIV-infectie (definitie: een HIV diagnose gedurende de acute fase van de infectie of binnen twee jaar na de laatste negatieve HIV-test) beschikbaar. Primaire met resistentie geassocieerde mutaties werden aangetoond bij 10 (4,8%) van deze patiënten. Bij slechts 3 patiënten werd een combinatie van mutaties gevonden die past bij een hoog resistentieniveau tegen tenminste 1 antiretroviraal middel. Met resistentie geassocieerde mutaties werden gevonden in 63 (7,4%) van 853 niet recent geïnfecteerde patiënten. Bij 34 (10,2%) van de 332 via homoseksueel contact geïnfecteerde mannen werd resistentie aangetoond en bij 11 (4,5%) van de 246 via heteroseksueel contact besmette patiënten (p=0,01).

Doeltreffendheid van HAART

In de afgelopen 10 jaar zijn de richtlijnen voor het moment waarop en met welke combinatie van antiretrovirale middelen met HIV besmette patiënten moeten worden behandeld veranderd, evenals de toepassing van die richtlijnen in de praktijk. Mortaliteit- en morbiditeitratio's en korte en lange termijn veranderingen van het aantal CD4 cellen en van de HIV-RNA concentratie in plasma na het starten van HAART werden bestudeerd in met name die patiënten in ons cohort die niet eerder waren behandeld met antiretrovirale middelen (therapienaïeve patiënten). Gekeken werd naar veranderingen per kalenderjaar waarin met HAART werd gestart, rekeninghoudend met de demografische en klinische karakteristieken van patiënten.

Patiënten die met HAART begonnen tussen 1997 en 1999 hadden een hoger aantal CD4 cellen (mediaan 230/mm^3) dan patiënten die tussen 2000 en 2001 en

tussen 2002 en 2005 begonnen (voor beide groepen met 180 CD4 cellen/mm^3). De kans om te overlijden was hoger wanneer met HAART werd begonnen, terwijl het aantal CD4 cellen tot beneden 50 cellen/mm^3 was gedaald (hazard ratio 1,75; 95% CI, 1,15-2,68; p=0,0095) dan wanneer werd begonnen bij 200 tot 350 CD4 cellen/mm^3. Patiënten met AIDS op het moment dat HAART werd gestart, hadden ook een hogere kans om te overlijden dan patiënten met geen of minder symptomen van HIV (2,56; CI, 1,69-3,87; p<0,0001). Bovendien was het risico om te overlijden groter voor die patiënten die met HAART begonnen in de jaren 2002 tot 2005 (1,58; CI, 1,17-2,14; p=0,003).

In vergelijking met patiënten die bij de start 200 tot 350 CD4 cellen/mm^3 hadden, bleek ook de kans op een nieuwe AIDS-diagnose nadat met HAART was begonnen, hoger voor patiënten die de behandeling begonnen met minder dan 50 CD4 cellen/mm^3 (HR 2,73, p<0,0001) of met een aantal tussen 50 en 200 (1,66, p=0,0007). De kans op AIDS na start HAART bleek tussen de jaren waarin met behandeling was gestart, niet te verschillen.

Virologisch succes, dat wil zeggen wanneer binnen 24 weken nadat met HAART was begonnen de HIV-RNA concentratie in plasma tot beneden 500 kopieën/ml was gedaald, werd in 1996 bij 70,9% van de patiënten bereikt. Dit percentage steeg tot 85,7% in de groep patiënten die tussen 1997 en 1999 begonnen en nam langzaam toe tot 87,7% voor de starters tussen 2000 en 2001 (p=0,14 vergeleken met 1997-1999) en tot 89,7% voor de starters tussen 2002 en 2005 (p<0,0001).

Patiënten met een initieel HAART-regiem waarin een enkele proteaseremmer (PI) was opgenomen, hadden een kleinere kans op virologisch succes vergeleken met patiënten die met een non-nucleoside remmer (NNRT) bevattend regiem begonnen (odds ratio 0,58; 95% CI 0,45-0,74; p<0,0001). De mate van virologisch succes bleek niet verschillend, wanneer behandeling werd gestart met 2 of meer PI's bevattende regiems.

Gedurende in totaal 10,812 persoonsjaren HAART-behandeling van therapienaïeve patiënten trad bij 338 van hen binnen 3 jaar na start een virale rebound op tot boven 500 HIV-RNA kopieën/ml. De incidentie van virologisch falen was 31,9 per 1000 persoonsjaren HAART. Het relatieve risico op virologisch falen was voor patiënten die met HAART begonnen tussen 2002 en 2005, lager dan voor hen die begonnen tussen 1997 en 1999 (RR 0,45; p<0,0001).

Deze resultaten wijzen erop, dat de introductie van nieuwe, doeltreffender en misschien minder toxische HAART-regiems leiden tot een betere onderdrukking van de vermenigvuldiging van HIV dan de eerder gebruikte regiems, maar niet tot verbetering van de mortaliteit- en morbiditeitratio's. Het is mogelijk dat de hogere doeltreffendheid van nieuwe HAART-combinaties wordt gecompenseerd, omdat in een later stadium van de HIV-infectie dan voorheen met behandeling wordt begonnen.

Bijwerkingen en toxiciteit

Zowel bijwerkingen als toxiciteit van HAART kunnen leiden tot verminderde therapietrouw en zelfs tot het stoppen of onderbreken van behandeling. Dat kan leiden tot suboptimale concentraties van antiretrovirale middelen en vervolgens de ontwikkeling van resistentie. Het optreden van therapieveranderingen door toxiciteit onder 6935 therapienaïeve patiënten uit het observationele ATHENA cohort en verschillen in tijd tot de eerste therapieverandering werden bestudeerd, waarbij de meest frequent gebruikte HAART regiems werden vergeleken.

Patiënten werden gedurende 3 jaar nadat met HAART was begonnen voor in totaal 16.491 persoonsjaren gevolgd, waarvan 14.858 persoonsjaren (90,1%) op

antiretrovirale therapie. De incidentie van HAART-regiemveranderingen door toxiciteit bleek 23,6 (95% CI, 22,8-24,4) per 100 persoonsjaren behandeling. De incidentie was het hoogst (67,7 per 100 persoonsjaren) gedurende de eerste 3 maanden HAART en daalde naar 29,5 per 100 persoonsjaren 3 tot 6 maanden en vervolgens tot 13,1 per 100 persoonsjaren 24 tot 36 maanden (p<0,0001) na start HAART. Patiënten die tussen 2002 en 2005 met HAART begonnen, hadden een 0,77 (0,73-0,83, p<0,0001) keer lagere kans om door toxiciteit van regiem te veranderen dan patiënten die tussen 1997 en 1999 begonnen. Verandering van HAART-regiem door toxiciteit deed zich vaker voor bij vrouwen (p<0,0001), bij via heteroseksueel contact geïnfecteerde patiënten (p=0,0002), bij patiënten met ≥500 CD4 cellen/mm^3 bij de start van HAART (p=0,01, vergeleken met 200 tot 350 CD4 cellen/mm^3), bij patiënten met een HIV-RNA spiegel bij start van 4 log_{10} kopieën/ml of meer (p=0,0003 in vergelijking met minder dan 4 log_{10}), bij patiënten met AIDS voor start van HAART (p=0,0001) en bij oudere patiënten (p=0,004 voor elk jaar). Patiënten met een initieel HAART-regiem bestaande uit TDF+3TC+NVP (tenofovir, lamivudine en nevirapine) of TDF+3TC+EFV (tenofovir, lamivudine en efavirenz) bleken minder vaak door toxiciteit van regiem te veranderen dan patiënten die met AZT+3TC+NVP (zidovudine, lamivudine en nevirapine) begonnen. De verschillen tussen de andere regiems waren niet significant.

Resistentie tijdens HAART

Het percentage virologisch falen onder patiënten die voor de start met HAART al waren behandeld met antiretrovirale middelen, daalde van 50% in 1997 tot 16% in 2006. In dezelfde periode nam het percentage falers onder de therapie naïeve patiënten geleidelijk toe van 6% in 1997 tot 11% in 2004, waarna het opnieuw daalde tot 8% in 2006. Van de totale groep falers werden 2115 RT- en proteasesequenties verkregen en bij 1680 (79,4%) daarvan werd tenminste 1 resistentiegeassocieerde mutatie gedetecteerd.

Het resistentiepatroon veranderde per kalenderjaar: resistentie tegen zidovudine en stavudine daalde tussen 1996 en 2006, terwijl resistentie tegen lamivudine steeg. Significante resistentie tegen nevirapine en efavirenz steeg eveneens en werd in respectievelijk 53% en 40% van de patiënten, waarbij dat in 2005 werd bepaald, aangetroffen. Resistentie tegen proteaseremmers was het meest frequent rond 1999 en daalde daarna.

Per juni 2006 bleken in totaal 10.053 patiënten nog steeds actief te worden gevolgd. Van 1108 (11,0%) patiënten was tenminste 1 sequentie met een met resistentie geassocieerde mutatie verkregen. Bij 1032 (93,1%) van deze patiënten bleek er sprake te zijn van een hoge mate van resistentie tegen tenminste 1 antiretroviraal middel. Het aantal patiënten waarbij een hoge mate van resistentie tegen middelen behorend tot dezelfde groep van antiretrovirale middelen werd aangetroffen, bedroeg 387 (38%). Resistentie tegen middelen uit 2 groepen werd bij 451 patiënten (44%) gevonden en resistentie tegen alle drie groepen van antiretrovirale middelen bij 194 (19%).

HAART bij HIV-positieve druggebruikers

Tussen 1996 en 2005 zijn 488 van de 607 (80,4%) door intraveneus druggebruik besmette patiënten met HAART begonnen. Het mediane aantal CD4 cellen bij de start van de behandeling daalde licht van 222 cellen/μL (interquartile range: 90-330) tussen 1996 en 1998 tot 184 (60-290) in latere jaren (p<0,001). Patiënten die tussen 1996 en 1998 met HAART begonnen, hadden een lagere virale load dan de patiënten die begonnen tussen 2002 en 2005 (p<0,001). Tussen 1996 en 1998 bereikte 60% van de patiënten na 6 maanden HAART een HIV-RNA spiegel beneden 500 kopieën/ml en dit percentage steeg tot 82% bij die patiënten die tussen 2002 en 2005 waren begonnen. De kans dat binnen

6 maanden na start HAART het aantal CD4 cellen met 50/μL was gestegen, was in de periode 1999-2001 niet hoger dan in de periode 1996-1988. Maar na 2002 was de kans op een dergelijke CD4 cel toename 1,27 maal hoger dan tussen 1996 en 1998. Onder homoseksuele mannen bleek de kans op een stijging met 50 CD4 cellen na start HAART 1,54 maal hoger, wanneer behandeling werd gestart tussen 2002 en 2005 vergeleken met 1996-1999 (overall, p<0,0001).

HIV-positieve druggebruikers die tussen 1999 en 2001 met HAART begonnen, hadden een 1,97 keer hogere kans op virologisch succes (HIV-RNA plasma spiegels lager dan 500 kopieën/ml) na 6 maanden dan degenen die startten tussen 1996 en 1998; deze kans was 1,52 keer hoger voor de groep die tussen 2002 en 2005 was gestart (overall, p=0,006). De kans op virologisch succes na 6 maanden HAART was 2,16 maal hoger voor homoseksuele mannen die tussen 1999 en 2001 met behandeling begonnen en 2,11 keer hoger wanneer werd gestart tussen 2002 en 2005 (overall, p<0,0001). Het lijkt er dus op dat de initiële verbetering van de virologische respons na start HAART sinds de introductie van deze behandeling in 1996 bij injecterende druggebruikers niet heeft doorgezet.

Het aantal CD4 cellen bij de start met HAART was bij druggebruikers lager dan bij homoseksuele mannen: 210 CD4 cellen/μL (IQR: 80-300 cellen/μL) versus 295 cellen/μL (IQR:90-320 cellen/μL; p<0,001). In de eerste 6 maanden HAART steeg het aantal CD4 cellen in beide groepen in dezelfde mate. Daarna steeg het aantal CD4 cellen sneller onder homoseksuele mannen (p<0,001).

Druggebruikers bleken een lagere HIV-RNA plasmaconcentratie te hebben dan homoseksuele mannen: 4,5 $\log_{10}$ kopieën/ml (IQR:4,0-5,2) tegen 4,8 $\log_{10}$ kopieën/ml (IQR:4,4-5,4; p<0,001). In zowel druggebruikers als homoseksuele mannen werd in de eerste 6 maanden HAART een sterke HIV-RNA daling gezien, hoewel sterker bij homoseksuele mannen (p<0,001). Na de eerste 6 maanden zette de daling zich voort, hoewel bij druggebruikers niet meer significant. Er bleef een significant verschil in de mate van daling tussen druggebruikers en homoseksuele mannen (p=0,01).

Tijd tot de eerste AIDS-diagnose bleek tussen druggebruikers en homoseksuele mannen niet te verschillen. Wel was er een significant verschil in tijd tot overlijden (p<0,0001, log-rank test). Tien jaar na de HIV diagnose bleek 17% van de druggebruikers die werden behandeld met HAART, te zijn overleden terwijl in dezelfde periode 9% van de met HAART behandelde homoseksuele mannen overleed.

Toenemend aantal zwangerschappen

De recente invoering in Nederland van routine-screening op HIV van zwangere vrouwen en van andere preventieve maatregelen heeft geleid tot reductie van de overdracht van HIV van moeder naar kind tot 2%. Aangenomen werd dat hierdoor het aantal zwangerschappen zou kunnen stijgen. Van de 3054 vrouwen die tussen 1996 en 2005 in het ATHENA cohort werden gevolgd, zijn er 749 zwanger geworden en waren er in totaal 980 zwangerschappen. Tien vrouwen bleken geïnfecteerd met HIV-2. Vrouwen werden voor het eerst zwanger op een mediane leeftijd van 28 jaar (IQR: 24-33); 458 (75%) vrouwen waren afkomstig uit Zuidelijk Afrika en 107 (14%) uit Nederland. Van de 184 afkomstig uit andere regio's bleken 48 vrouwen afkomstig uit Suriname en 35 uit de Nederlandse Antillen. De mediane leeftijd bij zwangerschap varieerde tussen de etnische groepen, waarbij Nederlandse vrouwen significant ouder waren dan niet-Nederlandse vrouwen.

Over de gehele periode tussen 1996 en 2005 bleek de incidentie 54 (95% CI: 50-58) zwangerschappen per 1000 persoonsjaren follow-up te zijn. De incidentie steeg van 31 per 1000 persoonsjaren in 1996 tot 71 in

2005 (p<0,001) en was het hoogst onder vrouwen afkomstig uit Zuidelijk Afrika met een toename van 83 tot 94 per 1000 persoonsjaren tussen 1996 en 2005. Onder Nederlandse vrouwen steeg de zwangerschapsincidentie van 7 in 2006 tot 48 per 1000 persoonsjaren in 2005 (p=0,02).

In 36% van de vrouwen werd de diagnose HIV gesteld tijdens de zwangerschap. Het percentage vrouwen dat niet wist dat ze met HIV besmet waren, veranderde in de jaren 1996-2005 niet. Er waren wel significante verschillen tussen vrouwen van verschillende herkomst. Nederlandse vrouwen werden vaker zwanger in de wetenschap met HIV te zijn besmet dan niet-Nederlandse vrouwen.

Dalende overdracht van moeder naar kind

De meeste HIV-positieve kinderen in Nederland werden besmet via transmissie van moeder naar kind en waren in Nederland geboren. Het aantal via moeder-kind transmissie besmette kinderen is inmiddels sterk afgenomen. De behandeling met antiretrovirale middelen van geïnfecteerde kinderen start nu op steeds jongere leeftijd vergeleken met de periode voor 2000, hetgeen wordt bevestigd door het hoger aantal CD4 cellen dat wordt gemeten op het moment van de start van HAART in de jaren na 2000. Kennelijk zijn kinderartsen minder behoudend geworden als het gaat om de antiretrovirale behandeling van zeer jonge kinderen.

Er werden tot nu toe in totaal 132 kinderen, 72 (54%) jongens en 61 (46%) meisjes, geregistreerd die met HIV werden besmet op een leeftijd onder 13 jaar; 106 zijn nu nog steeds jonger dan 13 jaar. De mediane leeftijd op het moment van de HIV-diagnose was 1,2 jaar; 83 (63%) kinderen werden in Nederland geboren, maar 76 (92%) van hen had tenminste één niet-Nederlandse ouder. De meeste kinderen hadden ten minste een vader of een moeder afkomstig uit Zuidelijk Afrika. Overdracht van moeder naar kind was de besmettingsroute bij 120 kinderen (91%) en 113 van hen werden geboren voor 2003. Vanaf 2003 daalde het percentage kinderen met een HIV-infectie.

Het mediane aantal CD4 cellen bij diagnose bedroeg 720 x 10^6 cellen/l en de mediane HIV-RNA concentratie was 5,0 $\log_{10}$ kopieën/ml. Mediaan 2,5 maanden na diagnose werd bij 112 kinderen HAART behandeling begonnen. Snel na start HAART nam het aantal CD4 cellen toe van 635 x 10^6 cellen/l tot 1150 x 10^6 cellen/l na 24 weken. Mediane HIV-RNA spiegels daalden van 5,4 naar 2,6 $\log_{10}$ kopieën/ml. Gedurende de eerste 6 maanden behandeling met HAART steeg het aantal CD4 cellen significant. Het aantal nam daarna nog steeds toe, hoewel niet significant, met uitzondering van die kinderen met een leeftijd van 2 jaar of ouder bij de start.

HIV-RNA plasmaconcentraties bleken significant lager bij kinderen die na 2000 met HAART begonnen (p<0,0001). Gedurende de eerste 6 maanden HAART daalden de HIV-RNA spiegels significant en die daling zette zich na deze initiële fase voort. Het jaar waarin met HAART werd begonnen, was niet van invloed op de mate van daling.

Screening van HIV-positieve patiënten op hepatitis B of C

HIV-geïnfecteerde patiënten die tevens met het hepatitis B (HBV) of C virus (HCV) zijn besmet, lopen een hoger risico op het ontwikkelen van leverziekten. Bijna 65% van de in het ATHENA cohort geregistreerde patiënten werden gescreend op de aanwezigheid van een coïnfectie met HBV of HCV en dat percentage nam over de tijd toe.

Van de 11.688 HIV-geïnfecteerde patiënten met voldoende follow-up werden 8007 (69%) getest voor hepatitis B surface antigen (HBsAg) binnen 1 jaar na de HIV-diagnose en 7424 (64%) voor HCV-antistoffen of

HCV-RNA. Van de voor HBsAg geteste patiënten bleken er 591 (7%) positief en van de voor HCV-antistoffen of HCV-RNA geteste patiënten waren er 735 (10%) positief.

Mannelijk geslacht, jongere leeftijd en een HIV-diagnose voor 1996 waren risicofactoren voor een coïnfectie met HBV. Ook patiënten uit Zuidelijk Afrika, het Caribische gebied en Zuidoost-Azië hadden een hoger risico voor een HBV-coïnfectie. Via heteroseksueel contact met HIV geïnfecteerde patiënten hadden een – niet significant – lager risico voor besmetting met HBV, terwijl druggebruikers een significant hoger risico hadden. Risicofactoren voor HCV waren regio van herkomst, transmissiegroep, het jaar van HIV-diagnose en het jaar waarin met HAART werd begonnen. Vergeleken met Nederlandse patiënten hadden patiënten uit andere Europese landen een significant hoger risico op coïnfectie met HCV, terwijl patiënten uit Zuidelijk Afrika, het Caribische gebied en Zuid-Amerika en de patiënten waarbij recent de HIV-diagnose werd gesteld, minder risico hadden voor een HCV-coïnfectie. Via heteroseksueel verkeer met HIV besmette patiënten en druggebruikers bleken een hoger risico op coïnfectie met HCV te hebben dan homoseksuele mannen.

In totaal 4723 patiënten werden getest voor anti-HBc en anti-HBs antistoffen en 363 (8%) waren anti-HBc-negatief en anti-HBs-positief, een antistofrespons die wordt gevonden na HBV-vaccinatie. Homoseksuele mannen en patiënten van andere Europese landen dan Nederland bleken een hogere kans te hebben om te zijn gevaccineerd.

Binnen 1 jaar na HIV-diagnose werd bij 2152 (30%) van de patiënten met een positieve uitslag van één van de HBV- of HCV-testen de diagnose AIDS gesteld. De tijd tot AIDS bleek niet geassocieerd te zijn met HBV- of HCV-coïnfectie. In de groep patiënten met een coïnfectie overleden gedurende de follow-up 541 (8%) personen. De kans op overlijden was het hoogst bij patiënten met een HCV-coïnfectie ($p<0,0001$). Coïnfectie met HBV of HCV bleek niet geassocieerd met ontwikkeling van AIDS. De kans op overlijden was 1,54 keer hoger bij patiënten met een coïnfectie met HBV en 2,30 keer hoger bij een coïnfectie met HCV.

Migranten en Curaçao

Aan het eind van 2005 werd samen met de Rode Kruis Bloedbank en het St. Elisabeth Hospitaal in Willemstad op Curaçao begonnen met de registratie en data-verzameling van in eerste instantie 194 op dat moment nog in leven zijnde met HIV geïnfecteerde patiënten, die in het St. Elisabeth Hospitaal werden gevolgd. 63,4% van de patiënten is man en bij 27,6% van hen bleek homoseksueel contact de meest waarschijnlijke besmettingsroute. Dit percentage was significant lager ($p<0,001$) vergeleken met de percentages die werden gevonden onder homoseksuele mannen van de Nederlandse Antillen (55,6%) en Suriname (46,5%) die in Nederland werden behandeld.

Op het moment van de HIV-diagnose waren er tussen Antilliaanse patiënten in Nederland en die in Curaçao geen verschillen voor wat betreft het aantal CD4 cellen en de concentratie HIV-RNA. Ook de stijging in het aantal CD4 cellen na start van HAART was vergelijkbaar tussen deze twee groepen, maar wel lager dan in de groep Surinaamse patiënten, ondanks vergelijkbare aantallen bij de start. Het percentage patiënten met een goede virologische respons (HIV-RNA tot beneden 500 kopieën/ml) was voor de drie populaties vergelijkbaar, maar het percentage waarbij de HIV-RNA concentratie ook na een langere follow-up onder 500 kopieën/ml bleef, daalde in de in Curaçao gevolgde groep, terwijl dat hetzelfde bleef in de andere twee in Nederland gevolgde groepen.

Het aantal voor HAART beschikbare antiretrovirale middelen in Curaçao is reden voor enige zorg.

De beperkingen in het aantal behandelopties leidt er waarschijnlijk toe, dat patiënten in Curaçao, in vergelijking met patiënten in Nederland, ook als dat wenselijk is niet zo snel van eerste HAART-regiem kunnen veranderen. Uiteindelijk zou de beperking van beschikbare antivirale middelen in combinatie met uitstel van verandering van een HAART-regiem kunnen leiden tot verminderde onderdrukking van virus-vermenigvuldiging en mogelijk tot resistentie.

Sum

mary

Frank de Wolf

Data collection and data quality

Control of the collection and quality of data is crucial to the value of observational data like those collected by the HIV Monitoring Foundation (HMF). Source data verification (SDV) of a random 10% of all the patients has been reported to be insufficient for improvement of data quality. Therefore, customized procedures have been implemented for verifying and assessing the quality of the data.

Data on demographics, history of HIV infection, HIV transmission, and cause of death of all patients were controlled by SDV. Twenty-three consistency checks based on clinical knowledge rules were used to select ambiguous data samples, and at least a 1% sample of all database records was selected randomly each year for SDV. In addition, data on patients' cardiovascular accidents were reviewed by SDV as part of the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study. The methods and outcomes of the SDV procedures were registered in a specifically designed Microsoft Access quality assessment (QA) database. Data changes as a result of SDV were stored as audit trail data in an Oracle Clinical database.

The overall percentage of inaccuracies in data on HIV transmission and history of HIV infection was 6%, which was low compared to the percentages reported in other collections of observational data related to HIV. The influence of such inaccuracies on the outcome of data analyses is currently under investigation.

Characteristics of the registered population

In comparison to the 2005 scientific report, 1205 newly diagnosed patients were registered in the ATHENA observational cohort on HIV, resulting in a cumulative number of 12,059 patients with a follow-up time of 80,764 person-years. The cohort included 9254 men (77.5%) and 2699 women (22.6%) who were 13 years of age or older as of 1 June 2006; 106 (0.9%) patients were younger than 13 years. The continuing increase of newly diagnosed patients might reflect an ongoing influx of persons who were unaware of their infection for a longer period of time. On the other hand, more recently infected individuals might contribute to the rise in the number of registered cases, which would indicate an increasing spread of HIV.

The majority of patients at this time are infected with HIV type 1, whereas less than 1% have HIV type 2. The distribution of men and women has not changed substantially in comparison to 2005, with males comprising more than three-quarters of the HIV-infected population. Given the distribution of transmission risk groups, with 52.2% infected through homosexual contact, we conclude that the HIV epidemic still mainly involves men having sex with men (MSM). There is a smaller, albeit slowly growing, proportion of patients infected through heterosexual contact. More than half of the heterosexually infected patients are women.

The age distribution at HIV diagnosis does not seem to have changed over time. The majority of men were diagnosed with HIV when they were between 25 and 44 years of age and women were between 18 and 34 years of age. Women were about 7 years younger when diagnosed with HIV compared to men. Also, other demographics of the infected population did not change; the majority of men originated from the Netherlands and were infected with a subtype B virus, whereas the majority of women originated from sub-Saharan Africa and were infected with a non-B subtype of HIV. In total, 749 women became pregnant.

Fifty-six boys and 50 girls with a median current age of 10 years were registered. Most of them were diagnosed with HIV at 1 year of age after mother-to-child

transmission (MTCT). This indicates that the measures for prevention of MTCT (antiretroviral treatment of the pregnant women and prenatal HIV testing of pregnant women) are effective. However, migration from an area where HIV is endemic may still add to the slow rise in the number of children with a positive test result.

From 2002 onward, approximately 80% of the registered HIV-infected patients, including both men and women, who are seen regularly in one of the 24 HIV Treatment Centres have been treated with highly active anti-retroviral therapy (HAART). Almost 20% are not being treated with antiretroviral drugs, and a tiny fraction are being treated with a combination of antiretroviral drugs that does not fit the definition of HAART. The subpopulation of untreated patients reflects mainly the group of those recently diagnosed with HIV who are not eligible for HAART, according to the current treatment guidelines. The combination of drugs used in first-line HAART has changed since the introduction of the nucleoside reverse transcriptase inhibitors (NRTIs) tenofovir and emtricitabine to replace the long standing standard of zidovudine and lamivudine.

Amongst patients tested, co-infection with hepatitis B (HBV) was found in 10% and hepatitis C virus (HCV) in 9%. The highest figures were seen amongst injecting drug users. Less than 10% of co-infected patients are currently registered as being treated for HCV or treated with a HAART combination recommended for the treatment of HBV.

TEN YEARS HAART

Changes in the HIV-infected population

MSM

For 6170 (68.6%) of the 8996 men with an HIV-1 diagnosis, the reported mode of transmission was homosexual contact. The annual number of diagnoses amongst MSM was 361 in 1996; it decreased to 313 in 1998 and then steadily increased to 495 in 2005. The majority of MSM, 4549 (73.7%), were of Dutch origin; 88.8% were infected in the Netherlands, and 3.6% in other countries in Western Europe. Median CD4 cell counts at diagnosis increased from 255 x 10^6 cells/l in 1996 to 400 in 2005 ($p<0.0001$). The median age at diagnosis increased over time from 36.9 years in 1996 to 40.7 years in 2005 for patients of Dutch origin, whilst for other MSM, age also increased, albeit not significantly ($p=0.02$), from 33.5 to 36.4 years.

The number of patients who had ever had a negative HIV test increased from 109 (32.3%) in 2000 to 251 (50.7%) in 2005. During the same period, the proportion of MSM with an HIV-1 negative test 18 months, at most, before diagnosis (interpreted as a recent infection) increased from 12.1% to 25.3%. For patients with a recent infection, median CD4 counts at diagnosis were 510 x 10^6 cells/l (95% CI, 370-700), and HIV RNA plasma levels were 4.8 $\log_{10}$ copies/ml (4.1-5.2); these measurements did not change over time or with age at diagnosis. CD4 counts at diagnosis in patients without a recent infection increased from 220 x 10^6 cells/l in 1996 to 360 in 2006.

Heterosexually infected patients

Of the 3843 patients infected via heterosexual contact, 1604 (13.9% of the total population, 41.7% of the heterosexual group) were men, and 2239 (19.4% of the total population and 58.3% of heterosexuals) were women. Between 2000 and 2005, the mean annual number of diagnoses was 158 for men and 231 for women, without a significant change over time. Most patients were either infected in the Netherlands (42.6%) or in sub-Saharan Africa (41.1%).

The majority of the heterosexual men originated from the Netherlands (37.3%); patients originated from other

regions including sub-Saharan Africa (34.8%), Latin America (10.3%), and the Caribbean (5.2%). Almost half of the heterosexual women originated from sub-Saharan Africa (48.9%), and 24.9% were of Dutch origin, whereas only 5.8% originated from the Caribbean and 9.3% from Latin America. Between 1996 and 2002, the proportion of patients originating from sub-Saharan Africa increased from 33.1% to 57.6% and thereafter decreased to 40.3% in 2005 and 2006. In contrast, the proportion of Dutch patients decreased from 40.5% in 1996 to 19.3% in 2001 and increased again to 31.8% in 2005 and 2006. The number of diagnoses amongst patients of Dutch origin increased from 82 in 2002 to 115 in 2005, whilst those amongst patients from sub-Saharan Africa decreased from 238 to 148 during the same period.

Regardless of the region of origin, men were older at diagnosis than women and had lower CD4 counts and higher viral loads. Men and women from sub-Saharan Africa were generally younger and had lower CD4 counts than their Dutch counterparts. Patients from Latin America, the Caribbean, and South/Southeast Asia likewise had lower CD4 counts than Dutch patients.

Between 1996 and 2003, 12.6% of the patients had ever had a negative HIV test, whereas 4.4% were diagnosed with a recent infection. From 2004 onward, the proportion of recent infections amongst women steadily increased from 4.5% in 2004 to 9.1% in 2005 to 16.1% in 2006, whilst there was no such increase amongst men. Likewise, the proportion of patients with a negative test at any time before diagnosis increased to 30.7%.

Injection drug users

For 594 (5.2%) patients, including 436 (73.4%) men and 158 (26.6%) women, the reported mode of transmission was injection drug use. The majority of the patients, 372 (62.6%), were infected before 1996; only 88 (14.8%) were infected between 2000 and 2005. Most injection drug users originated from the Netherlands (392 patients, 66.0%) and other Western European countries (100 patients, 16.8%). Of the 222 patients diagnosed in or after 1996, 34.2% were treated in a hospital in Amsterdam, 29.3% in another hospital in the Randstad, and 25.2% in the southern part of the Netherlands, in particular in Maastricht (18.9%).

Mortality and AIDS

In the total population of 11,709 patients, 3468 diagnoses of AIDS were registered at or after an HIV diagnosis. New AIDS diagnoses were made in 2048 patients 6 weeks or longer after an HIV diagnosis. From 1996 onward, the incidence of AIDS declined from 9.6 (95% CI, 8.5-10.8) diagnoses per 100 person-years in 1996 to 2.0 (1.7-2.3) in 2005. In the same group, 984 cases of death were recorded during 66,595 person-years of follow-up, corresponding to an average mortality of 1.48 (95% CI, 1.39-1.57) deaths per 100 person-years that did not change with calendar time.

Amongst those patients who were diagnosed in or after 1996, 395 deaths were recorded during 36,428 person-years. HIV-related causes accounted for 76% of deaths in 1996 and for 39% of deaths in 2005, whereas the proportion of non-HIV-related deaths increased from 10% to 50% during this period. A prognostic model showed that 34-year-old patients diagnosed between 1998 and 2005 with CD4 counts of 200 x 10^6 cells/l or higher had, at most, a probability of dying within 1 year that was 5 times higher than that of uninfected individuals of the same age and gender. This excess mortality decreased with age and was less than 2 times higher for 50-year-old patients.

Transmission of drug-resistant HIV

In 25% of the 2927 patients diagnosed with HIV between 2003 and 2005, a protease and reverse transcriptase (RT) genotypic sequence was obtained within 1 year after diagnosis. These RT and protease

sequences were available after 2001 for 207 patients who had a recent infection (defined as the receipt of an HIV diagnosis either during acute infection or within 2 years after a negative HIV test), and major resistance-associated mutations were found in 10 (4.8%) patients. However, the pattern of mutations implied high-level resistance to at least 1 antiretroviral drug in only 3 patients. In the group of 853 patients who had a sequence but could not be classified as recently infected, resistance-associated mutations were found in 63 (7.4%) of them. Amongst the 332 patients infected via homosexual contact, mutations were found in 34 (10.2%) patients, compared to 11 (4.5%) of the 246 heterosexually infected patients (p=0.01).

Improvement of HAART efficacy

Guidelines and practices for when and how to treat HIV-infected patients with HAART have changed over the past 10 years. Mortality and morbidity rates and short- and long-term responses of CD4 cell counts and HIV RNA concentration in plasma were studied after the start of HAART in the therapy-naïve participants included in the ATHENA cohort, according to calendar year at the start of HAART and the patients' demographic and clinical characteristics.

A higher median CD4 cell count of 230 cells/mm^3 was found amongst patients starting HAART in 1997 through 1999, compared to 180 cells/mm^3 found amongst those starting HAART in both 2000 through 2001 and 2002 through 2005. Patients initiating HAART with a CD4 cell count of less than 50 cells/mm^3 had a hazard ratio for death of 1.75 (95% CI, 1.15-2.68; p=0.0095) compared to patients with 200 to 350 cells/mm^3. Patients with a CDC-C event at the start of HAART had a hazard ratio of 2.56 (1.69-3.87; p<0.0001) compared with a CDC-A or CDC-B event. The hazard ratio for death was higher for those starting HAART in calendar years 2002 through 2005: 1.58 (1.17-2.14, p=0.003).

The hazard for a new AIDS-defining event after the start of HAART was also increased when the CD4 cell count at the start of HAART was lower than 50 cells/mm^3 (2.73, p<0.0001) or between 50 and 200 (1.66, p=0.0007) compared with 200 to 350 cells/mm^3. There were no differences according to calendar year of the start of HAART.

In 1996, 70.9% of the patients achieved an HIV RNA concentration in plasma of <500 copies/ml 24 weeks after starting HAART. This proportion increased to 85.7% for those starting in 1997 through 1999 and slowly increased further to 87.7% for patients who started in 2000 through 2001 (p=0.14 compared to 1997-1999) and to 89.7% for those starting from 2002 through 2005 (p<0.0001).

Patients starting a HAART regimen that included a single protease inhibitor (PI) were less likely to reach an HIV RNA of <500 copies/ml compared with those starting a regimen that included a non-nucleoside reverse transcriptase (NNRT) (odds ratio, 0.58; 95% CI, 0.45-0.74; p<0.0001). There were no significant differences between patients starting HAART that included an NNRT and patients starting HAART that included 2 or more PIs. During 10,812 person-years on HAART, 338 patients experienced viral rebound to 500 or more HIV RNA copies/ml within 3 years of the first virologic success, corresponding to an incidence rate of 31.9 per 1000 person-years on HAART. The adjusted relative risk for patients starting HAART from 2002 through 2005 compared with that of those starting HAART from 1997 through 1999 was 0.45 (p<0.0001).

The introduction of HAART regimens with more effective and less toxic combinations of antiretroviral drugs has induced a more effective suppression of HIV RNA plasma levels than previous HAART combinations, but it has not translated into improved survival or morbidity rates. Starting HAART in a later

phase of the infection may contribute to this contradictory effect.

Side effects and toxicity

Adverse events and toxic responses to HAART can lead to poorer patient adherence or even discontinuation of treatment, causing suboptimal drug levels and possibly therapy failure and drug resistance. The incidence of toxicity-driven therapy changes was studied longitudinally amongst 6935 antiretroviral therapy-naïve participants in the ATHENA observational cohort, and differences in the time to the first toxicity-driven regimen change were compared between frequently used HAART combinations.

During the first 3 years after starting HAART, patients were followed for a total of 16,491 person-years, of which 14,858 person-years (90.1%) involved therapy with antiretroviral drugs. The overall incidence of toxicity-driven regimen changes was 23.6 (95% CI, 22.8-24.4) per 100 person-years of antiretroviral therapy. The incidence was highest (67.7 per 100 person-years) during the first 3 months after the start of HAART and declined to 29.5 per 100 person-years between 3 and 6 months and further to 13.1 per 100 person-years between 24 and 36 months ($p<0.0001$).

Multivariate analyses showed that patients starting HAART in 2002 through 2005 had a risk that was 0.77 (0.73-0.83, $p<0.0001$) times that in patients starting between 1997 and 1999. The incidence of toxicity-driven regimen changes was higher in female patients ($p<0.0001$), patients infected through heterosexual contact compared to homosexual contact ($p=0.0002$), patients with pre-HAART CD4 cell counts ≥500 cells/mm^3 compared to those with counts of 200 to 350 cells/mm^3 ($p=0.01$), patients with a pre-HAART HIV RNA level of 4 log_{10} copies/ml or more compared to those with a level less than 4 ($p=0.0003$), patients with a prior CDC-C event ($p=0.0001$), and patients who were of older age ($p=0.004$ for each year).

Patients starting HAART with TDF+3TC+NVP (tenofovir, lamivudine, and nevirapine) or TDF+3TC+EFV (tenofovir, lamivudine, and efavirenz) were found to be the least likely to change regimen because of toxicity when compared to those starting with AZT+3TC+NVP (zidovudine, lamivudine, and nevirapine), whereas other regimens did not differ significantly from each other.

Resistance during HAART treatment

The proportion of pre-treated patients on HAART who virologically failed declined from 50% in 1997 to 16% in 2006. During the same period, the fraction of failures amongst therapy-naïve patients on HAART increased slightly from 6% in 1997 to 11% in 2004 and decreased to 8% in 2006. In the population of patients with failure, 2115 sequences were obtained. Of these sequences, 1680 (79.4%) contained at least 1 resistance-associated mutation, and 435 (20.6%) contained none.

The nature of the drug resistance observed per calendar year changed over time. Resistance to zidovudine and stavudine decreased between 1996 and 2006, whilst resistance to lamivudine increased. High-level resistance to nevirapine and efavirenz increased and was found in 53% and 40%, respectively, of patients with a sequence in 2005. Resistance to protease inhibitors was highest around 1999 and declined thereafter.

As of June 2006, a total of 10,053 patients were still in active follow-up. At least 1 sequence with a resistance-associated mutation was obtained In 1108 (11.0%) patients. Of these patients, 1032 (93.1%) had high-level resistance to at least 1 antiretroviral drug. The number of patients with high-level resistance to drugs from 1 drug class was 387 (38%). Resistance to drugs from 2 drug classes was found in 451 patients (44%), whilst 194 (19%) were found to be resistant to drugs from all 3 classes.

Injecting drug users and the effect of HAART

Of 607 patients infected via injecting drug use (IDU), 488 started HAART between 1996 and 2005. The median CD4 cell count at the start of HAART decreased slightly from 222 cells/μL (interquartile range: 90-330) in 1996 through 1998 to 184 (60-290) in the more recent years (p<0.001). IDUs who initiated therapy in 1996 through 1998 had a lower viral load relative to those who started in 2002-2005 (p<0.001). In 1996 through 1998, HIV RNA levels in 60% of the IDUs declined to 500 or less copies/ml after 6 months of HAART, and this proportion increased to 82% in 2002 through 2005.

The chance of improving CD4 cell counts by at least 50 CD4 cells/μL after the start of HAART in 1999 through 2001 did not significantly change compared to the chance for such improvement in 1996 through 1998. However, after 2002, it was 1.27 times higher than that in 1996 through 1999. Amongst homosexual men, the chance of reaching a similar rise in CD4 cell counts was in 2002 through 2005 1.54 times higher than that in 1996 through 1999 (overall, p<0.0001).

Compared to those commencing HAART between 1996 and 1998, IDUs who started between 1999 and 2001 had a 1.97 higher chance of achieving an HIV RNA plasma level of 500 or less copies/ml in the first 6 months, and this chance was 1.52 for 2002 through 2005 (overall, p=0.006). The chance of a successful virologic response after 6 months of HAART amongst homosexual men was 2.16 times higher for patients starting between 1999 and 2001 and 2.11 times higher for those starting in 2002 through 2005 (overall, p<0.0001). This suggested that the initial improvement of the virologic response after the introduction of HAART in 1996 was not sustained amongst IDUs.

IDUs had lower CD4 cell counts when starting HAART compared to homosexual men: 210 cells/μL (80-300 cells/μL) versus 295 cells/μL (90-320 cells/μL; p<0.001), respectively. During the first 6 months after HAART initiation, slopes of increasing CD4 cell counts were similar for both groups. Thereafter, CD4 cell counts continued to increase, but the slope amongst homosexual men increased more rapidly (p<0.001).

IDUs had a lower viral load (4.5 $\log_{10}$ copies/ml; 4.0-5.2]) relative to homosexual men (4.8 $\log_{10}$ copies/ml; 4.4-5.4) (p<0.001). In the first 6 months after HAART initiation, a strong decline in viral load was observed amongst both groups, the stronger amongst homosexual men (p<0.001). After the initial 6 months, the decline in viral load continued, although amongst IDUs the decline was not significant and the difference in slopes between IDUs and homosexual men remained significant (p=0.01).

The time to the first AIDS event did not differ between IDUs and homosexual men, but a significant difference in time to death was observed (p<0.0001). Ten years after receiving an HIV diagnosis, 17% of the HAART-treated IDUs had died, whereas 9% of the homosexual men had died during the same period of follow-up.

Increasing number of pregnancies

Because routine HIV-antibody screening amongst pregnant women has been recently introduced in the Netherlands and HIV prevention methods have reduced the risk of mother-to-child transmission to 2%, it is likely that the number of pregnancies amongst HIV-infected women will increase. Out of 3054 women who were being followed in the ATHENA observational cohort between 1996 and 2005, 749 became pregnant, and a total of 980 pregnancies occurred. Ten women were infected with HIV-2. Median age at first pregnancy was 28 years (IQR, 24-33); 458 (75%) came from sub-Saharan Africa, and 107 (14%) were Dutch. Of the 184 women originating from other regions, 48 came from Surinam and 35 from the Netherlands Antilles. The

median age at the time of pregnancy varied between ethnic groups; women originating from the Netherlands were significantly older than non-Dutch women.

Overall, the incidence was 54 (95% CI, 50-58) pregnancies per 1000 person-years. The incidence increased significantly from 31 pregnancies per 1000 person-years in 1996 to 71 in 2005 ($p<0.001$) and was higher amongst women from sub-Saharan Africa, increasing from 83 per 1000 person-years in 1996 to 94 in 2005. Amongst Dutch women, the incidence increased from 7 pregnancies per 1000 person-years in the mid-1990s to 48 in 2005 ($p=0.02$).

HIV was diagnosed during pregnancy in 36% of the women. The fraction of women unaware of their HIV status at the point of becoming pregnant did not significantly change over time. However, significant differences were found between women of different geographic origins. Dutch women became pregnant knowing their HIV status (86%) more often than non-Dutch women (56-60%) ($p<0.001$). The proportion of pregnant women who initiated HAART before or during their pregnancy increased from 12% in 1996 to 82% in 2005 ($p<0.001$).

Decreasing mother-to-child transmission

In the Netherlands, most children with HIV were vertically infected, and most of these children were also born in the Netherlands. The number of children infected by mother-to-child transmission has been decreasing over time, probably as a result of the HIV screening amongst pregnant women. Currently, young children with HIV are being treated earlier in their infection than they were before the year 2000; this is shown by a higher baseline CD4 cell count in the children who initiated HAART after 2000, suggesting that treating physicians became less reluctant to treat young HIV-infected children.

A total of 132 children, 72 (54%) boys and 61 (46%) girls, were registered as having been infected when they were younger than 13 years of age; 106 of them are currently 13 years or younger. The median age at HIV diagnosis was 1.2 years; 83 (63%) were born in the Netherlands, but 76 (92%) of them had at least one parent originating from outside the Netherlands. The majority had at least one parent from sub-Saharan Africa. MTCT was the route of infection for 120 children (91%), and 113 of them were born before 2003. The proportion of vertically infected children with a diagnosis of HIV has decreased since 2003.

At HIV diagnosis, the median CD4 count was 720×10^6 cells/L, and the median HIV RNA levels were 5.0 $\log_{10}$ copies/ml. HAART was initiated in 112 children, with a median of 2.5 months after the diagnosis of HIV. The median CD4 cell count improved from 635×10^6 cells/L soon after HAART initiation and increased to 1150×10^6 cells/L after 24 weeks of treatment. The median HIV RNA levels decreased from 5.4 $\log_{10}$ copies/ml to 2.6 $\log_{10}$ copies/ml. During the first 6 months of HAART, CD4 cell counts increased significantly ($p<0.001$). Thereafter, counts increased further, but not significantly, except for children who were 2 years or older at the time of starting HAART.

HIV RNA levels were significantly lower amongst those children who initiated HAART after the year 2000 ($p<0.0001$). In the first 6 months of therapy, HIV RNA levels declined significantly in those patients ($p<0.001$); after the initial response, the HIV RNA levels continued to decrease ($p=0.006$). The rate of decrease in HIV RNA levels did not differ between calendar time periods.

Screening of HIV-infected patients for hepatitis B and C

HIV-infected persons with a hepatitis B or C co-infection are at increased risk for the development of liver-related

diseases. Approximately 65% of HIV-infected patients registered in the ATHENA observational cohort were screened for the presence of a co-infection, and this proportion has increased over time.

Of the 11,688 HIV-infected patients in the HIV monitoring cohort, 8007 (69%) had a hepatitis B surface antigen (HBsAg) test result within 1 year after HIV diagnosis, and 7424 (64%) were tested for hepatitis C virus (HCV) antibodies or RNA. Amongst patients tested for HBsAg, 591 (7%) had a positive test result. Amongst patients tested for HCV-antibodies or RNA, 735 (10%) had a positive result.

Risk factors for HBV co-infection were male sex, younger age, and receiving a diagnosis of HIV before 1996. Patients from sub-Saharan Africa, the Caribbean, and Southeast Asia had a higher risk of HBV co-infection. Heterosexually HIV-infected patients had a nonsignificant lower risk of being co-infected with HBV, whereas injecting drug users had a significantly higher risk of HBV co-infection compared to that in homosexual men. Factors associated with HCV co-infection were region of origin, transmission group, calendar year of HIV diagnosis, and year of the start of HAART treatment. Compared to patients of Dutch origin, patients from other European countries had a significantly higher risk of HCV co-infection, whereas patients from sub-Saharan Africa and the Caribbean and Latin America and those who were recently diagnosed with HIV were less likely to be co-infected with HCV. Heterosexually HIV-infected patients and injecting drug users had a significant higher risk of HCV co-infection compared with homosexual men.

HBV vaccination was defined as the patient having a negative result on hepatitis B core antibody (anti-HBc) testing and a positive result on hepatitis B surface antibody (anti-HBs) testing. A total of 4723 patients were tested for anti-HBc and anti-HBs antibodies, and 363 patients (8%) had anti-HBc-negative and anti-HBs-positive test results, indicative of a positive response to HBV vaccination. Homosexual men and patients from other European countries (excluding the Netherlands) were more likely to be vaccinated against HBV.

A total of 2152 (30%) of the patients with a positive result for one of the HBV or HCV tests within 1 year after their HIV diagnosis progressed to AIDS. The time to an AIDS event was not associated with HBV or HCV co-infection ($p=0.36$). In addition, 541 (8%) died during follow-up. The probability of dying was not the same for all patients; the probability of dying was highest amongst those with an HCV co-infection ($p<0.0001$, log-rank test). HBV and/or HCV co-infection was not associated with progression to AIDS. However, the adjusted hazards of death were 1.54 times higher amongst those with an HBV co-infection and 2.30 times higher amongst patients who were co-infected with HCV.

Migrant populations and Curaçao

At the end of 2005, HMF started registration and data collection for 194 HIV-infected patients living in Curaçao who are now being followed and monitored in the St. Elisabeth Hospital in Willemstad. Of these patients, 63.4% are men, and homosexual contact was reported as the most likely mode of transmission for 27.6% of them. This was significantly ($p<0.001$) less than the corresponding proportions of MSM of Antillean (55.6%) or Surinamese origin (46.5%) treated in the Netherlands.

At diagnosis, there were no differences in CD4 cell counts and RNA levels between Antilleans in the Netherlands and patients in Curaçao. The increase in CD4 counts after the start of HAART was also similar between the 2 populations, but lower than in patients of Surinamese origin, despite similar CD4 counts at the start of HAART. The proportion of patients reaching RNA levels below 500 copies/ml was similar for the

3 populations, but the proportion with levels remaining below 500 copies/ml decreased with longer follow-up in the population in Curaçao, whereas it remained constant in the other 2 populations.

The number of antiretroviral drugs available for treatment of patients in Curaçao is a reason for concern. This lack of treatment options is probably why patients in Curaçao did not switch their first HAART regimen as quickly as patients in the Netherlands did when a switch was needed. Eventually, limited availability of different antiretroviral drugs combined with a delayed switch to another HAART regimen leads to inferior suppression of HIV RNA levels and possibly development of drug resistance.

Data c

quality

Assessment and improvement of
the quality of the HIV monitoring data

Sima Zaheri

Introduction

The validity of conclusions drawn from collected clinical data depends on the quality of data in regard to completeness, reliability, and validity[1]. Control of data quality and collection is a crucial element for all clinical research[2-5], and it is especially crucial for observational data like those collected by the HIV Monitoring Foundation (HMF). Assessment of the quality, reliability, and validity of the data should be verified. The inclusion of a high number of patients results in a large amount of data and makes comparison of all collected data with source documents impossible. A strategy for improving data quality on so many patients has been studied by the random selection of 10% of a total number of patients for "source data verification" (SDV); this percentage was reported as insufficient for improvement of data quality[6,7]. Therefore, customized procedures for continuous monitoring of the accuracy of data and, subsequently, for resolution of the discrepancies may be a good alternative[6].

Data collection

Patient data (Appendix 1) are collected for the HMF in 24 hospitals acknowledged by the Dutch Minister of Health as HIV treatment centres. 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 physician, enter the data online into the national HIV Monitoring database after each patient's visit. The national database is developed in Oracle Clinical® (OC), a system that is specifically designed for the data management of clinical trials and that complies with ICH-GCP (International Conference on Harmonisation-Good Clinical Practices) and FDA (Food and Drug Administration) guidelines.

Data quality

As of January 2006, new customized procedures were implemented for verifying and assessing the quality of the data. These procedures are based on certain assumptions.

- First, cohort studies are vulnerable to selection bias[8]. Therefore the quality of data items that are used for selection of appropriate groups for comparison studies should be guaranteed. The patient's medical file should be consulted to validate these data and to retrieve the correct values. In case of the ATHENA cohort, it concerns specially data on demographics, history of HIV infection, HIV transmission, and cause of death.
- Second, the association between two or more data items can be determined by use of clinical knowledge. Consistency checks can highlight areas in the database where the data may be invalid. Simple consistency checks are built into the database as online real time discrepancy checks. More complex consistency checks should be performed offline to select ambiguous data samples for SDV.
- In addition to consistency checks, at least a 1% sample of all database records should be selected randomly for SDV[6].
- Third, the methods by which the validity and the outcome of the data were tested should be registered appropriately. Evaluation of outcomes can provide further insight into the quality of colleted data and the pitfalls of collection and monitoring procedures.

Customized procedures for the verification and assessment of data quality

Routine sample selections for SDV

Data on all deceased patients and on those who were reviewed in relation to cardiovascular accidents as part of the DAD (Data Collection on Adverse Events of Anti-HIV Drugs) study were selected for SDV on a regular basis. Because of a disproportionate number of registered double HIV infections (HIV-1 and HIV-2), data on patients registered as infected with HIV-2 were also selected for routine SDV. In addition, 1% of data were randomly selected for SDV.

Sample selection for SDV based on consistency checks

The association between different data items was discussed and determined on the basis of clinical knowledge and guidelines. Twenty-three consistency checks were determined. Data samples were selected from the HMF dataset with the use of data queries. For each data sample, it was decided which data items should be verified. Table 4.1 provides an example of some rules of clinical knowledge, the respective queries, and the data items to be verified.

Sample selection based on the 23 consistency checks resulted in 1554 cases to be verified. To evaluate the new procedures for SDV based on consistency checks, it was decided to start with the SDV of a small sample derived from an important consistency check. The chosen query identified all cases treated with a combination of 3 or more tuberculostatic agents, but without a simultaneously recorded CDC AIDS-defining event.

Registration of interpretive SDV results: Quality assessment (QA) database

Each data query resulted in a data table that contained the patient identification number and hospital code. These data tables were imported into the separately designed quality assessment (QA) database where they received a unique code and an assigned date of creation. Data entry screens were built into the QA database for entry of the name of data monitor, the date, the period, and interpretation of outcome of SDV (Figure 4.1, right).

Registration of data changes as a result of SDV: audit trail data in OL

The OC database contains a robust audit trail mechanism. Every value ever entered into the database is stored in the database. OC attaches a “response entry time stamp” and an identifier (ID) to every value entering the database, with the ID specific to the data entry field. When the value of a data entry field changes, the old value is tagged with an additional time stamp, “end time stamp”, and the new one receives a new “response entry time stamp” (Figure 4.1, left). This allows straightforward generation of a chronologic report for a single patient and a single data entry field and subsequently, the complete history of all the changes to that field. For that purpose, the start and stop date/time of the data corrections should be registered. Therefore, a SDV data entry screen was built into the OC database that enables the data collectors to enter the date and time of corrections made to the data as a result of SDV.

Since a large amount of data concerning HIV transmission and history of HIV infection (830 cases) were verified as part of routine SDV, it was decided to select the respective data changes in OC for data quality analysis. To evaluate the results of SDV, audit trail data stored in OC from the date of SDV until 7 days later were selected for comparison. Data with a “response entry time stamp” before and “end time stamp” on or after the SDV date represented the situation before SDV. Data with a “response entry time stamp” before the SDV date and an “end time stamp” on or after the SDV date plus 7 days represented the situation 7 days after SDV. For each data entry field, the value before and 7 days after the SDV were compared. A value before SDV was considered ”correct” if it had an identical value after SDV. An empty field before SDV was assumed to represent a ”missing” value; if it was filled after SDV, in reverse order, it was assumed to be ”incorrect”. Every value entered into the database as a result of a SDV that differed from the value before the SDV was also considered to be ”incorrect”.

Results of the quality assessments of 3 selected data items

a) History of HIV infection and HIV transmission

Table 4.2 represents the total number of correct, incorrect, and missing values for various data entry fields. The total number of entries was fewer than 830 for 2 entry fields: ACUTE_PRIM_HIV_INF and NONB_TYPE. That can be explained by the fact that in 2005

the NONB_TYPE entry field was replaced by ACUTE_PRIM_HIV_INF. That also explains the extremely high number of missing values (60%) for the entry field ACUTE_PRIM_HIV_INF; this entry field did not exist at the time of entry by the data collector, but it did exist at the time of the SDV by the data monitor. Therefore, the results of SDV for these two fields will not be taken into account. The number of missing values ranged from 1% to 10% for the 15 data entry fields. The total number of errors did not vary widely for the different items and did not appear to be significant (Figure 4.2). However, for the 3 fields with the highest number of errors, that is, data entry field HIV2_NEG_ED [has the patient ever negatively tested for HIV-2?] with 20% error, data entry field HIV1_FST_POS_DT [date of the first positive HIV-1 test]) with 19% error, and data entry field TRANS_MODE_SEX [in case of sexual transmission, specify either a steady transmission route or multiple sexual contact] with 16% error, the errors can be clarified by the difficulty and interpretive nature of the respective questions. Information on HIV-2 negative testing should be retrieved from the Western blot or immunoblot with a negative HIV2 band (or antigp36/ antigp105). Often only the positive or negative result of HIV-1 infection is mentioned in the conclusion of the test. The data collector should interpret the patterns of the antibody bands and retrieve the negative result of HIV-2 testing. Date of the first positive HIV-1 test is subject to inaccuracies, since more than one positive HIV-1 test result is often reported in the medical files. The data collector has to find the oldest Western blot test that reports a positive HIV-1 result. Information on whether the patient was infected through sexual contact with a steady partner or through multiple sexual contacts should be retrieved from the data on the sexual behaviour of the patient in the medical file, which is also subject to ambiguous interpretation.

b) CDC AIDS-defining events

The clinical knowledge rule states that only patients who had CDC events including various forms of Mycobacterium infection (tuberculosis, Mycobacterium avium [complex or infection] [MAC/MAI], Mycobacterium kansasii [disseminated or extrapulmonary], or Mycobacterium [atypical or disseminated or extrapulmonary]) should have been registered as being treated with a combination of 3 or more tuberculostatic agents (isoniazide, rifampicine, ethambutol, pyrazinamide, rifabutine, morphozinamide, protionamide, claritromycine, azitromycine). On the basis of this rule a query was made to identify all cases treated with a combination of 3 or more tuberculostatic agents, but without a simultaneously recorded CDC event. Any case identified by this query was assumed to have a missing CDC event. The data sample derived from this query was almost completely verified by the data monitors (63 out of 67 cases). The outcome of SDV was entered into the QA database.

Evaluation of SDV showed that in 49 (out of 67) cases, data were correctly extracted from the medical files. The different reasons for recording tuberculostatic agents without the specified CDC events are summarized in Table 4.3. In 25 (out of 49) cases tuberculostatic agents were immediately prescribed because of the suspicion of Mycobacterium infection. However, tests in these cases returned negative results. Seven (out of 49) cases were infected with a Mycobacterium species that was not listed as a CDC event, according to the guidelines. In 12 (out of 49) cases just 1 tuberculostatic drug (claritromycine) was prescribed for 3 episodes. These cases were wrongly selected due to a formulation error in the query.

Fifty-five (67 minus 12) cases were correctly selected by the query. In 14 (out of 55) cases, the CDC event was missing; in 1 case the CDC event was found out to be redundant. In summary, in 37 (71%) cases data were collected correctly, and in 15 cases (29%) they were collected incorrectly.

Conclusions

Implementation of customized data verification procedures and the registration of the SDV outcomes in the OC and QA databases have generated useful information on the quality and accuracy of data in the HMF database.

The QA database contains detailed information about all QA procedures and the interpretive outcome of SDV, whereas the audit trail data in OC contains all the actual changes to data subjected to SDV. Assessment of missing and incorrect records with OC audit trail data is based on 100% mutual agreement during SDV between the data collector and the data monitor, and it can provide information about the quality of different data entry fields. However, this assessment can be an overestimation since it is based on exact matches. The QA database, on the other hand, is more descriptive and sensitive to subjective interpretation of data monitors, and it yields more insight into the pitfalls of data collection procedures.

For an ideal quality assessment, information from both databases should be combined. Audit trail information is suitable for the assessment of the quality of raw data, such as laboratory results. In turn, information from the QA database is preferred for the assessment of the quality of interpretive data.

When the probability of overestimation is considered, the overall percentage of 6% inaccuracies in data on HIV transmission and history of HIV infection is a good result compared with other collections of observational data related to HIV[3, 9, 10]. However, these inaccuracies still could have a major impact on conclusions drawn from these data. Therefore, their influence on the outcome of data analyses should be investigated.

The results of the SDV of data on CDC events did not sustain the assumption that all cases selected by the query would have a missing CDC event. However, the SDV resulted in the finding of 14 new CDC events, which is an improvement in data quality, and it provided more insight into this particular clinical knowledge rule in practice.

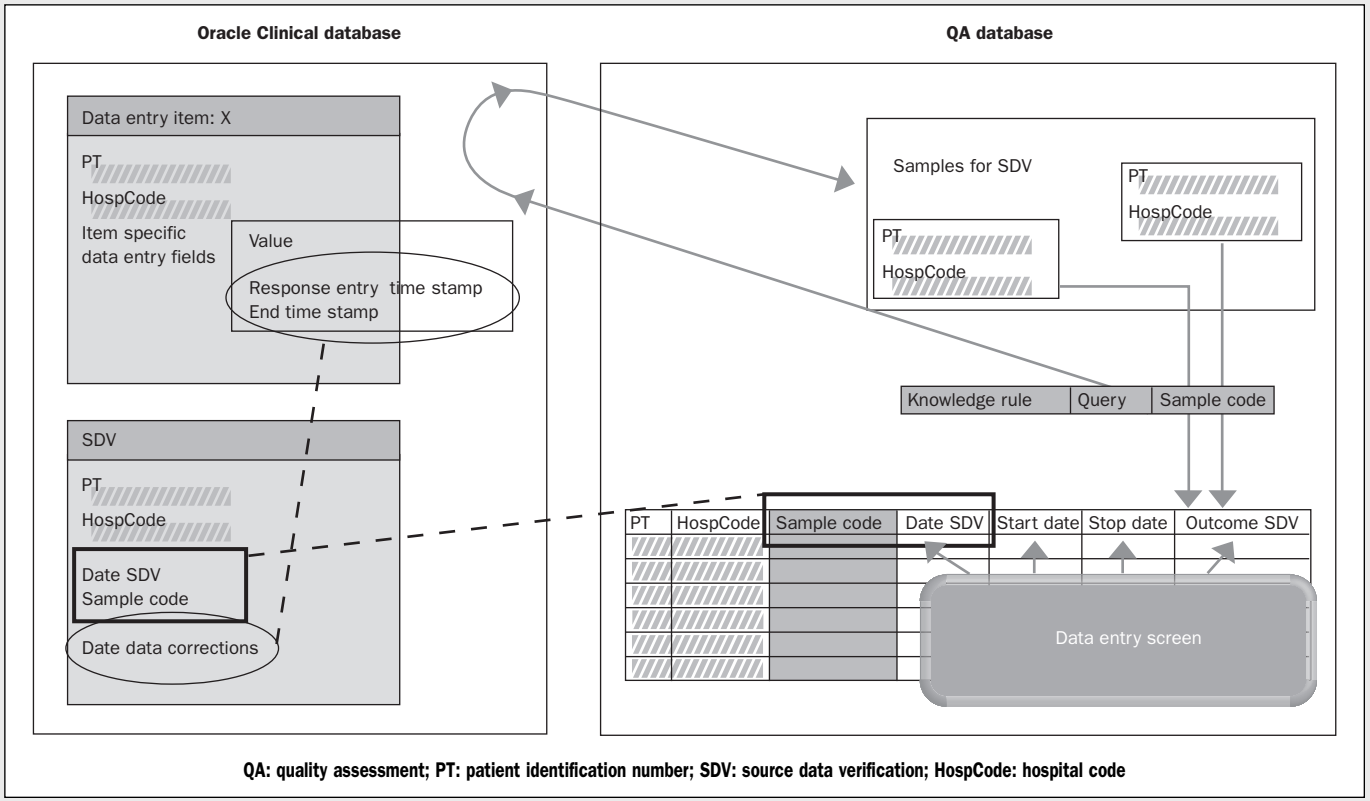


Figure 4.1: Illustration of data in the QA database and the link with patient data in OC. The image on the left illustrates the National HIV Monitoring OC database containing patient data. Every value entered in the database receives a "response entry time stamp" and if deleted or changed, an "end time stamp" is assigned. The date/time of SDV and subsequent data corrections are entered in the SDV data entry screen and can be used to select the relevant information on the outcome of SDV.

The image on the right illustrates the QA database containing quality assessment data. The samples to be verified are selected from patients' data in the National HIV Monitoring OC database on the basis of knowledge rules and the respective queries. The results are imported in the QA database as data tables. Each query and respective data table is coded. Additional SDV information and interpretive outcomes are entered by data monitors into the database.

Data regarding SDV in both databases can be linked based on PT, HospCode, SDV date, and sample code.

Sample Code	Knowledge rule	Sample selection date	Query	Data to be verified
AeCm001_DM	Anti-diabetic agents should not be prescribed to a patient who is not diabetic	16-feb-06	Identify all cases with recorded anti-diabetic agents and not recorded as being diabetic	Co-medication and adverse events
AeLa001_lact	Patients with lactate acidosis have at least 2 consecutive episodes of elevated lactate (<5,2 mmol/l)	12-feb-06	Identify all cases with 2 consecutive episodes of elevated lactate (<5,2 mmol/l) and not recorded as having had lactate acidosis	Lab results for lactate and adverse events
CdCm001_TBC	A combination of 3 anti-tuberculosis agents should not be prescribed to a patient suffering from tuberculosis (extra) pulmonary, Mycobacterium avium (complex or infection) (MAC/MAI), Mycobacterium kansasii (disseminated or extrapulmonary) or (Mycobacterium atypical or disseminated or extrapulmonary)	22-feb-06	Identify all cases recorded 3 tuberculostatic agents (isoniazide, rifampicine, ethambutol, pyrazinamide, rifabutine, morphozinamide, protionamide, claritromycine, azitromycine) but without a simultaneously recorded CDC event	Co-medication and CDC events. If tuberculostatic agents were correctly collected, search for test results

Table 4.1: Three examples of sample selections for source data verification (SDV) based on the query derived from the knowledge rule.

	ACUTE_PRIM_HIV_INF		CNTRY_INF		HIV1_FPDT_ACC		HIV1_FST_POS_DT		HIV1_LNDT_ACC		HIV1_LST_NEG_DT		HIV1_NEG_ED		HIV2_FPDT_ACC		HIV2_FST_POS_DT	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Correct	162	38	806	97	711	86	669	81	762	92	743	90	707	85	787	95	783	94
Incorrect	11	3	8	1	38	5	96	12	39	5	58	7	92	11	33	4	40	5
Missing	258	60	16	2	81	10	65	8	29	3	29	3	31	4	10	1	7	1
Total error	269	62	24	3	119	14	161	19	68	8	87	10	123	15	43	5	47	6
Total entry	**431**	**100**	**830**	**100**	**830**	**100**	**830**	**100**	**830**	**100**	**830**	**100**	**830**	**100**	**830**	**100**	**830**	**100**

Legend:

ACUTE_PRIM_HIV_INF	Was the patient diagnosed with a primary HIV infection?	HIV1_LNDT_ACC	Date accuracy of the last negative HIV-1 test
CNTRY_INF	Country where the patient became infected, if not in the Netherlands	HIV1_LST_NEG_DT	Date of the last negative HIV-1 test
HIV1_FPDT_ACC	Date accuracy of the first positive HIV-1 test	HIV1_NEG_ED	Has the patient ever tested negative for HIV-1?
HIV1_FST_POS_DT	Date of the first positive HIV-1 test	HIV2_FPDT_ACC	Date accuracy of the first positive HIV-2 test
		HIV2_FST_POS_DT	Date of the first positive HIV-2 test

Table 4.2: Number of correct, incorrect, and missing values for various data entry fields

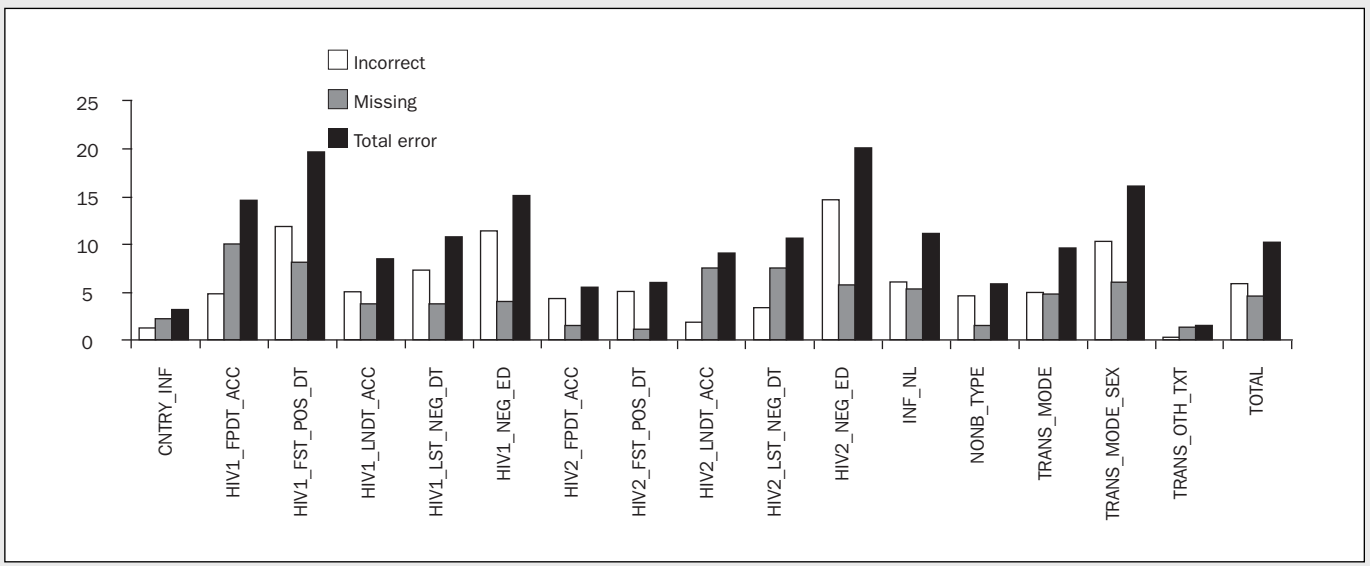


Figure 4.2: Percentage of incorrect and missing values in data entry fields for history of HIV infection and HIV transmission (see Table 4.2 for meanings of abbreviations).

HIV2_LNDT_ACC		HIV2_LST_NEG_DT		HIV2_NEG_ED		INF_NL		NONB_TYPE		TRANS_MODE		TRANS_MODE_SEX		TRANS_OTH_TXT		TOTAL	
N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
757	91	744	90	666	80	740	89	678	94	753	91	699	84	820	99	11825	90
13	2	26	3	119	14	48	6	31	4	39	5	83	10	1	0	733	6
60	7	60	7	45	5	42	5	9	1	38	5	48	6	9	1	570	4
73	9	86	10	164	20	90	11	40	6	77	9	131	16	10	1	1303	10
830	**100**	**830**	**100**	**830**	**100**	**830**	**100**	**718**	**100**	**830**	**100**	**830**	**100**	**830**	**100**	**13128**	**100**

HIV2_LNDT_ACC	Date accuracy of the last negative HIV-2 test
HIV2_LST_NEG_DT	Date of the last negative HIV-2 test
HIV2_NEG_ED	Has the patient ever tested negative for HIV-2?
INF_NL	Whether patient became infected in the Netherlands
NONB_TYPE	Chance of infection with non-B HIV-1 subtype
TRANS_MODE	Most likely transmission route
TRANS_MODE_SEX	In case of sexual transmission, specify the most likely transmission source
TRANS_OTH_TXT	Specify transmission route, when it is not one of the listed routes

Reason	Number of cases
Suspicion of infection with a Mycobacterium, cases turned out to be negative after they were tested.	25
Wrongly selected by the query	12
Infected with a Mycobacterium kind, which is not classified as CDC event according to the guidelines.	7
Tuberculostatic agents were prescribed for treatment of other events.	2
Not clear yet, should be discussed with the physician	1
Test results were wrongly assigned to another patient	1
Tuberculostatic agents were prophylactically prescribed	1
Patient was infected with Mycobacterium before infection with HIV-1. Therefore, it was not defined as a CDC event.	1
Total	**49**

Table 4.3: Reasons for recording tuberculostatic agents and not respective CDC events.

Appendix 4.1: data

Upon patient entry into the HMF database, the following information is collected:

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	For sexual transmission,
	Was the patient diagnosed with a primary HIV infection? (yes, no, most likely)	the most likely transmission
HIV transmission	The most likely transmission route:	route is entered: either a
	homosexual	steady sexual partner or
	heterosexual	multiple sexual contacts
	IDU	
	blood and blood products	
	during pregnancy/partum	
	via breastfeeding	
	other and unknown	
	Country where the patient became infected	

Appendix 4.1 (1)**:** data

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, cogenital defects, perinatal exposure to ARV therapy and co-medication, antenatal complications

Appendix 4.1 (2)**:** data

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?	Duration of ruptured membranes
	Date of delivery/abortion	Mode of delivery
	Sex of the baby	Caesarian section?
	Duration of pregnancy	Fetal scalp electrode
	Child number	Episiotomy or rupture
	Prophylactic antibiotics?	Birth weight of the baby
	Intra-uterine infection	Apgar scores after 1 minute/5 minutes
	Duration of dilation	Duration of stay in the incubator
	Duration of expulsion	Perinatal mortality
		Breast-feeding?
Complications during pregnancy	Complications during and/or after birth?	Intra-uterine retardation of growth
	Blood loss during the first half of pregnancy?	(sonography<p5%)?
	Blood loss during second half of pregnancy?	PPROM (preterm premature rupture of outer mem-
	Intercurrent infection?	branes) at how many weeks?
	Version (attempt) with breech presentation?	Abdominal trauma at how many weeks?

Appendix 4.1 (3)**:** data

After patient enrollment, clinical data are collected every time the patient is seen by his or her treating physician. These data contain the following information:

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 using 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	Sexual dysfunction (loss of libido, erection failure)
	Myopathy	Alcohol or drug abuse
	Lactate acidosis	Non-CDC malignancies
	Hepatic cirrhosis	Diabetes mellitus
	Osteopenia / Osteoporosis	Myocardial infarction
	Hepatic steatosis	Hypertension
	Hepatic encephalopathy	Arrhythmia
	Pancreatitis	Stroke
	Nephrolithiasis	Coronary artery by-pass grafting
	Renal failure	Coronary angioplasty / stenting
	Lipodystrophy, fat loss in extremities	Carotid endarterectomy
	Lipodystrophy, central fat accumulation	Pregnancy
	Rash	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	Modification of the regimen
	Immunological failure	Plasma “ART” drug levels related
	Patient’s decision	Structured treatment interruption
	Toxicity	Newly available medication
	New CDC-B and or CDC-C events	Other
	Interaction with co-medication	Unknown
Co-medication Start and stop date and the medication status at current visit (ongoing: yes or no)	CDC events, prophylaxis	Anabolic steroids and appetite stimulants
	CDC events, treatment	Hepatitis B treatment
	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*
	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 <75 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

Appendix 4.1 (4)**:** data

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 *Start and stop date, status at current visit* *Care and education*	Psychologist, pedagogue, psychiatrist, speech therapist, physiotherapist, rehabilitation worker, social worker 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

Appendix 4.1 (5)**:** data

Base

lines

Characteristics of the patients included in the ATHENA national observational cohort

Frank de Wolf

Introduction

The work presented in the 2006 annual scientific report is based on the analyses of data obtained from a total of 12,059 patients infected with HIV. After 5 successive years of rising totals, the total number of patients in 2006 again has increased by 1205 patients.

In this chapter, we will present results of the demographic changes of the population registered through the HIV Monitoring Foundation (HMF) system. In addition, the characteristics at baseline are described in order to provide an overview of the population of infected patients at the start of highly active antiretroviral therapy (HAART).

Patient numbers, median follow-up, and geographic distribution

Data obtained from 12,059 patients with 80,764 person years of follow-up were available as of 1 June 2006. The study included 9254 men (77.5%) and 2699 women (22.6%) who were 13 years of age or older as of 1 June 2006; 106 (0.9%) patients were younger than 13 years (Table 5.1).

The median (interquartile range [IQR]) age of the adult population was 43 (36.6-50.1) year. The age distribution at the time of HIV diagnosis is summarised in Table 5.2. Of the men, 69.8% were infected when they were 25 to 44 years of age; of the women, 65.0% were infected when they were 18 to 34 years of age. Women were diagnosed with HIV at a median age of 30 years (IQR, 24.9-36.1) and therefore were significantly ($p<0.0001$) younger than men, whose median age at diagnosis was 36.1 years (30.4-43.1). The median follow-up of the study population was 5.6 years (IQR, 2.4-10.0); the median follow-up for men was 6 years (2.5-10.3) and 4.7 (2.1-8.8) for women. Since 1998, the median time between health-care visits increased from a median of 69 days (IQR, 36-98) to 98 days (66-133) in 2005 to 105 days (75-139) in 2006. Similar decreases in frequencies for plasma viral load and CD4 cell measurements were found. The West of the Netherlands – Amsterdam, Rotterdam, Utrecht, and The Hague – still harbour the majority (75.1 percent) of the known HIV-infected population in the Netherlands (Figure 5.1).

HIV diagnosis

Infection with HIV is usually diagnosed in serum by an HIV-1/HIV-2 antibody assay in combination with a HIV-1 p24 antigen assay[11], followed by Western blot confirmation of an antibody response specific for HIV-1, HIV-2, or both. Table 5.3 summarises the HIV serotyping results at diagnosis. Amongst 97.7% of the HIV-infected population, seroreactivity to HIV-1 was detected and confirmed. Antibodies to HIV-2 were found in 0.6% of the population, and seroreactivity to both HIV-1 and HIV-2 was found in 0.7%. In 1% of the registered population, serologic results were inconclusive or unknown.

In addition to the serotyping at diagnosis, genotypic data were obtained from 2860 (23.9%) of the patients on the basis of the sequencing of the HIV-1 pol gene. The vast majority of the population (77.4%) were infected with HIV-1 subtype B. However, a significant difference was found between men and women: an HIV-1 subtype B was found in only 40.9% of the women, in contrast to 87.5% of the men. Since the genotyping results were obtained as additional products of genotypic determination of resistance, the results might be biased. However, the differences between men and women seem to be in accordance with the data regarding HIV transmission risk and country of origin or country of HIV infection.

Baseline trends over time

The absolute number of HIV diagnoses registered per year amongst adults is depicted in Figure 5.2. The date of diagnosis was missing for 188 patients. A steady increase of new diagnoses has been seen over the years, with a peak of 641 new diagnoses in 1996 and 762 in 1997,

when HAART became available in the Netherlands as the standard treatment for HIV. Since 1989, the number of new diagnoses has increased even more, to 1041 in 2004 and 964 in 2005. The registration of new diagnoses over 2006 is still incomplete. The relative portion of women in the total number of new diagnoses increased slowly from 17.5% in 1990 to 29% in 2003. Thereafter, both the absolute and relative number of women amongst the newly diagnosed adults decreased (Figure 5.3).

The distribution of transmission risk groups amongst the adult HIV-infected population is summarised in Table 5.4. Male homosexual transmission is still the largest transmission risk group; in total, that group accounts for 6234, or 52.2%, of the registered HIV-infected patients. In total, 4000 (33.5%) adults were infected through heterosexual contact, with women comprising the largest group of 2336. Of all women, 86.6% were infected through heterosexual contact. Injecting drug use has become a relatively small risk group; 4.8% of the men and 7% of the women are registered as being infected via this route.

CD4 cell numbers at the time of HIV diagnosis amongst the adult population had a median of 300 cells/mm^3 (IQR, 110–500). There were no differences in the counts of men compared to those of women (Figure 5.4). Numbers declined to 190 cells/mm^3 (IQR, 80-310) when HAART was initiated and increased to 310 (180-470) at 24 weeks of treatment and to 350 (211-516) at 28 weeks. The median of the most recently measured CD4 cell counts in the HAART-treated population was 461 cells/mm^3 (IQR, 320-650).

Virus production at diagnosis was 4.8 log HIV RNA copies/ml and did not change much compared to the HIV RNA plasma concentration at the start of HAART. The response to HAART in the adult population was dramatic (Figure 5.5), in that at 24 weeks the plasma concentration of HIV RNA declined by more than 2 log, to median 2 (IQR, 1.7-2.7) log copies/ml. At 24 weeks after the start of HAART, the median HIV RNA plasma concentration did not change. Pre-HAART HIV RNA levels in women were significantly lower compared to those in men, although both groups reached similar post-treatment levels at 24 and 48 weeks.

HIV-infected children

As of the first of May 2006, 106 children below 13 years of age were registered as HIV-infected; of those, 56 were boys, and 50 were girls (Table 5.5). Most children were diagnosed with HIV between 2000 and 2005, with a peak of new diagnoses registered from 2001 through 2003, which was followed by a rapid decline (Figure 5.6). The median age at diagnosis was 1.1 years (IQR, 0.4-3.7). Mother-to-child transmission was recorded for 100 of these children, whilst the transmission route was unknown for the remaining 6 children. The median weight at diagnosis was 11.2 kg (IQR, 7.2-15.1), which increased to 11.8 kg (7.5-15.1) at the start of HAART. AIDS was diagnosed in 38.7% of these children.

The median current age is 10.2 years. The median CD4 cell count at diagnosis was 760 cells/mm2 (IQR, 350-1760) and declined to 635 (190-1155) at the start of antiretroviral treatment, which induced a subsequent increase to 1150 cells/mm^3 (711-1860) after 24 weeks of treatment and to 1585 cells/mm^3 (903-2300) after 48 weeks. The median for the most recent CD4 cell counts was 950 cells/mm^3 (IQR, 775-1445).

Changes in HIV-1 RNA plasma concentration were seen after the start of antiretroviral therapy. RNA levels were 5.4 log copies/ml (IQR, 4.7-5.8) at diagnosis, and 5.4 (4.7-5.9) at the start of antiretroviral treatment. At 24 and 48 weeks of treatment, median levels were 2.6 (IQR, 1.7-2.8) and 2.4 (1.7-2.6) log HIV-1 RNA copies/ml.

Pregnant women

739 women infected with HIV-1 and 10 infected with HIV-2 became pregnant; a total of 980 pregnancies were registered between 1996 and 2005. The overwhelming majority of the women (94%) were infected through heterosexual contact. The median age at first pregnancy was 28 years (IQR, 24-33). A majority of 565 (75%) women originated from sub-Saharan Africa, whilst 107 (14%) were Dutch; 48 women were from Surinam, and 35 were from the Netherlands Antilles. The median age at the time of pregnancy varied, but Dutch women were older than those who were not Dutch.

Antiretroviral treatment

HAART was administered to 8292 patients in 2006. Non-HAART, or antiretroviral therapy (ART), drug combinations were given to 73 patients, and 2136 patients did not receive any ART. The relative distribution of patients receiving HAART, ART, or no ART over time is depicted in Figure 5.7, which shows the increase of patients receiving HAART since its introduction in 1996 and the decrease of patients being treated with non-HAART antiretroviral drug combinations.

The proportion of patients not being treated with antiretroviral drugs declined from 43% in 1996 to approximately 20% in 2000, and it has remained stable since then.

No significant differences were found between men and women receiving HAART in 2006, in contrast to the first years of the HAART era, when the percentage of women being treated was somewhat lower than the percentage of men.

A summary of the most frequently used first-line HAART combinations amongst the antiretroviral drug-naïve patient population in 2005 and 2006 and in 2004 and 2005 is presented in Table 5.6. Clearly, the use of zidovudine (AZT) in first-line HAART is declining, and emtricitabine (FTC) is becoming part of HAART combinations more often. Between July 2005 and the end of June 2006, 550 patients started HAART, and FTC was prescribed as part of the HAART combination in a total of 135 (24.5%) cases; for the years 2004 and 2005, 94 (11.7%) of the total of 801 patients starting HAART received FTC as part of the regimen. The prescription of tenofovir (TDF) as part of HAART increased from 43.9% in patients who started HAART to 54.5%. The prescription of lamivudine (3TC) decreased from 87.6% of the patients starting HAART in 2004 and 2005 to 75.1% of those starting HAART in 2005 and 2006. There was an increased decline in AZT prescription from 50.9% in 2004 and 2005 to 34.4% in 2005 and 2006.

3TC+TDF was used as the nucleoside reverse transcriptase inhibitor (NRTI) backbone in the HAART combination of 160 patients starting HAART between the first of July 2005 and 30th June 2006 and was used somewhat more frequently than AZT+3TC (142 patients). The combination TDF+FTC was used in the initial HAART regimens of 133 patients. The most frequently used addition to the backbone was efavirenz (272 patients), followed by ritonavir-boosted lopinavir (219).

Co-infections

Given the similar routes of transmission, hepatitis C virus (HCV) infection is often found amongst HIV-infected injecting drug users, and hepatitis B virus (HBV) infection is frequently found amongst HIV-infected homosexual men.

The HCV status was known for 9474 patients (91%), of whom 1005 (10%) were HCV-positive. The HCV prevalence was, as expected, highest amongst injecting drug users: 486 (89%) were co-infected with HCV ($p<0.0001$), with men and women co-infected in equal proportion. In the population infected with HIV

through heterosexual contact, the HCV prevalence was 5% in both men and women. The prevalence was higher amongst those infected heterosexually than amongst men infected homosexually, of whom 3% of the total of 5358 were HCV-positive. HCV was more prevalent among those infected by blood-blood contact, which was 29% (men 43% and women 8%), and amongst men and women for whom the infection route was unknown, which totalled 12% for men and 49% for women. Of the patients co-infected with HCV, 854 (85%) were receiving HAART. A total of 90 (9%) of the 1005 HCV-co-infected patients were registered as being treated for HCV.

To determine the prevalence of chronic HBV infection amongst HIV-infected patients, a total of 10,500 were tested for hepatitis B surface antigen (HBsAg); 781 (7%) tested positive. HBV was most prevalent amongst injecting drug users, of whom 50 (10%) were co-infected. Male drug users were most frequently found to be positive for HBsAg (12%; p=0.002). The HBV prevalence was 7% for patients homosexually infected with HIV. Amongst heterosexually HIV-infected patients, the overall HBV prevalence was 7%, significantly higher amongst men (9%) than amongst women (5%; p<0.0001). Co-infection with HBV was found in 3% of the patients who acquired HIV through blood-blood contact and in 10% of those without a known route of transmission of HIV.

Of the patients co-infected with HIV, 662 (85%) were receiving HAART. In 57 of those cases, HAART contained a combination of lamivudine and tenofovir, the recommended treatment for HBV in HIV/HBV co-infected patients[12–18].

Conclusions

The ATHENA observational cohort population grew between July 2005 and July 2006, with the addition of 1205 newly registered HIV-infected patients, to a total of 12,059, with a median follow-up time of more than 80,000 person-years. It remains to be seen at the end of 2006 if the increase will be sustained; however, so far, it is in accordance with the steady increase of approximately 800 to 1000 patients per year since 2002. The increase might reflect the ”tip of the iceberg” effect: large numbers of infected people were not aware of their HIV infection for a long period of time, but they knew they were at risk. Since the introduction of HAART in 1996, individual behaviour associated with HIV testing may have changed, and subsequently, a continuous influx of newly diagnosed people has been seen. On the other hand, more recently infected individuals may add to the increase in the registered cases, which would indicate an ongoing spread of HIV.

The vast majority of patients are infected with HIV type 1, whereas less than 1% are infected with HIV type 2. The distribution of men and women has not changed substantially in comparison with 2005, with males comprising more than three-quarters of the HIV-infected population. Given the distribution of transmission risk groups, with 52.2% infected through homosexual contact, we conclude that the HIV epidemic is still mainly one amongst men having sex with men. There is a smaller, but slowly growing, proportion of patients infected through heterosexual contact. More than half of the heterosexually infected patients are women. Moreover, 87% of the women registered are reported to have been infected through heterosexual contact.

The age distribution at HIV diagnosis has not appeared to change over time. The majority of men are diagnosed with HIV between 25 and 44 years of age, and women between the ages of 18 and 34 years. The age at which women are diagnosed with HIV remains about 7 years younger than men. Also, other demographics of the infected population have not changed: the majority of men originate from the Netherlands and are infected with a subtype B virus, whereas the majority of women

originate from sub-Saharan Africa and are infected with a non-B subtype of HIV. In total, 749 women have become pregnant.

Fifty-six boys and 50 girls with a median current age of 10 years are registered. Most of them were diagnosed with HIV at 1 year of age after mother-to-child transmission (MTCT). This indicates that the measures taken to prevent MTCT (pre-natal HIV testing and antiretroviral treatment of pregnant women) are effective. However, migration from HIV endemic areas may still add to a slow rise in the number of positive children.

From 2002 on, approximately 80% of the registered HIV-infected patients seen regularly in 1 of the 24 HIV Treatment Centres are being treated with HAART, women and men alike. Almost 20% are not being treated with antiretroviral drugs, and a tiny fraction are receiving a combination of antiretroviral drugs that does not fit the definition of HAART. The subpopulation of untreated patients reflects mainly the group of patients recently diagnosed with HIV who are not eligible for HAART, according to the current treatment guidelines. The combination of drugs used in first-line HAART has changed since the introduction of the NRTIs tenofovir and emtricitabine to replace the longtime standard of zidovudine and lamivudine.

High prevalences were found for co-infection with HBV or HCV, and the highest was amongst injecting drug users. Chronic HBV or HCV infection does not impact progression of HIV disease to AIDS or viral and immunologic responses to HAART[19, 20]. However, the risk of death related to liver disease is higher amongst those co-infected with HIV. Despite that, less than 10% of patients are currently registered as receiving treatment for HCV or receiving a HAART combination recommended for the treatment of HBV.

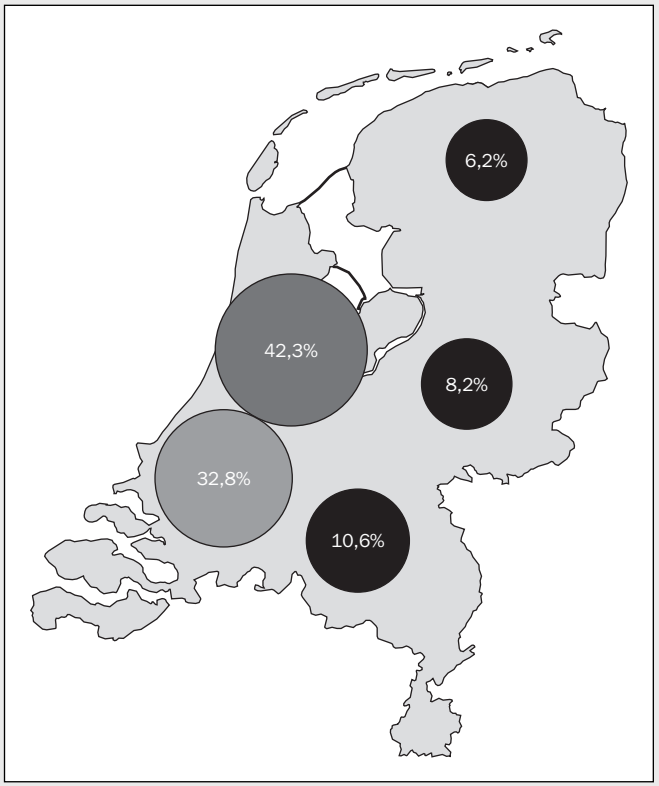


Figure 5.1: Distribution of the population of HIV-infected individuals registered in one of the HIV Treatment Centres throughout the Netherlands.

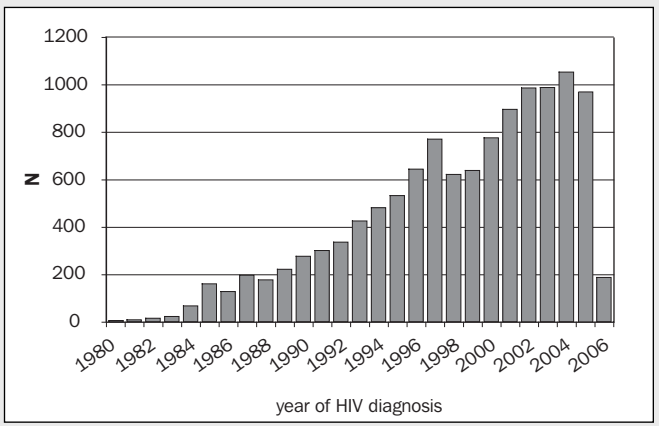


Figure 5.2: Number of HIV diagnoses per calendar year.

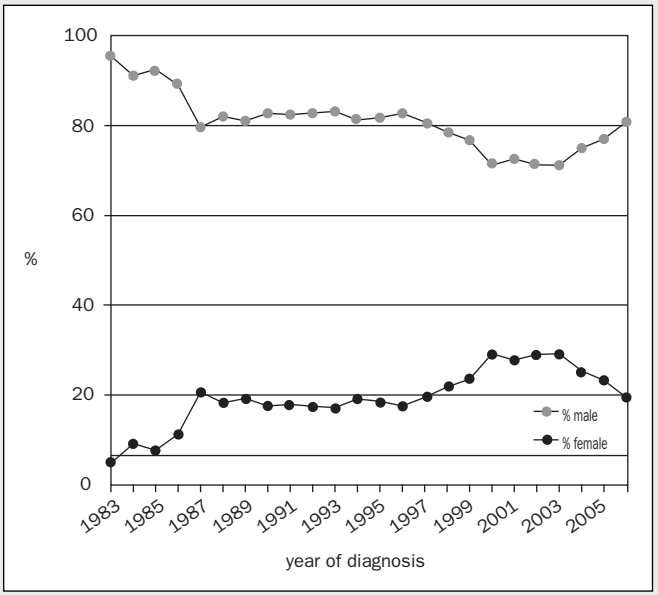


Figure 5.3: The proportion of adult men and women per year with an HIV diagnosis.

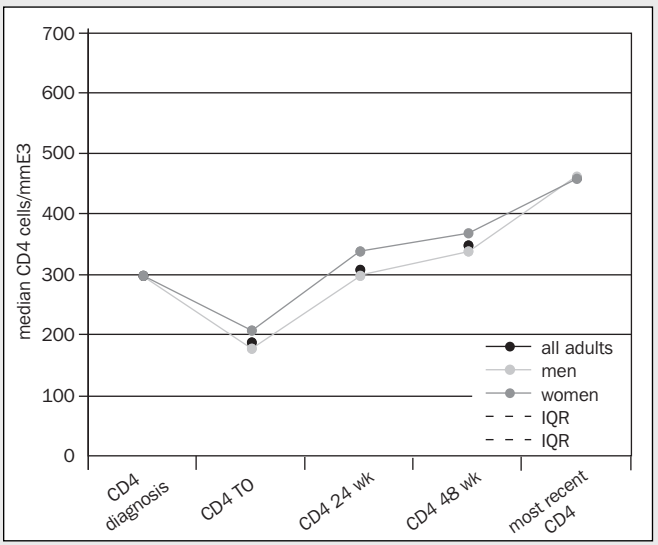


Figure 5.4: Median CD4 cell counts at HIV diagnosis, at start of HAART (T0), and at 24 and 48 weeks after start of HAART, together with the most recent CD4 cell count amongst the whole HAART-treated population (black line) and the counts for men (light grey) and women (dark grey). Dotted lines indicate the interquartile range (IQR).

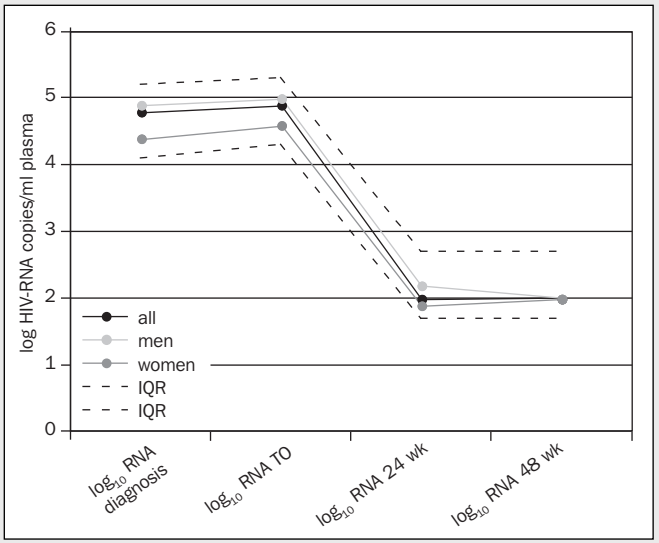


Figure 5.5: Median HIV RNA plasma concentration (log copies/ml) at diagnosis, at start of HAART (T0), and at 24 and 28 weeks after start of HAART amongst the whole HAART-treated population (black line), men (light grey), and women (dark grey). Dotted lines indicate the interquartile range (IQR).

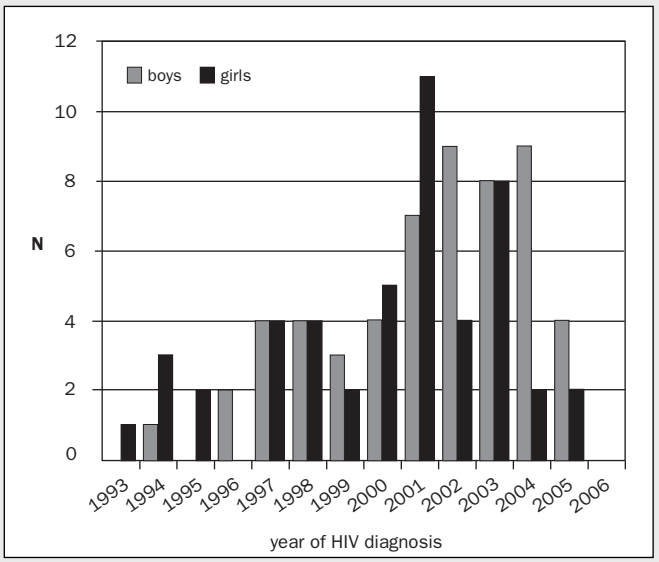


Figure 5.6: Number of diagnoses of HIV per year for 106 children (girls, black bars; boys, grey bars) who were 13 years of age or younger in 2006.

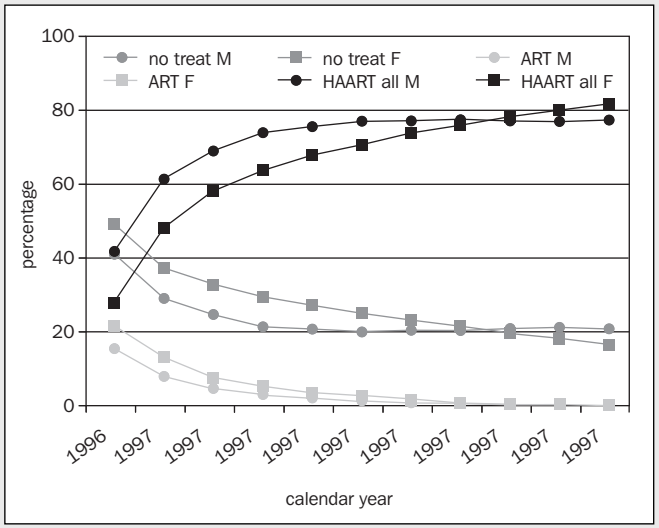


Figure 5.7: Percentage of women (squares) and men (dots) receiving HAART (black line), other antiretroviral treatment (light grey), and no treatment (dark grey) over time since the introduction of HAART in 1996.

	Adult		Child		Total	
	n	%	n	%	n	%
Male	9254	77.5	56	52.9	9310	77.3
Female	2699	22.6	50	47.2	2749	22.8
Total	**11953**	**100.1**	**106**	**100.1**	**12059**	**100.1**

Table 5.1: Number of patients included in the registration and monitoring of HIV in the Netherlands.

	Male		Female		Total	
Age at diagnosis of HIV	**N**	**%**	**N**	**%**	**N**	**%**
0	73	0.8	40	1.5	113	0.9
<13	88	0.9	69	2.5	157	1.3
13-17	40	0.4	97	3.5	137	1.1
18-24	725	7.8	562	20.4	1287	10.7
25-34	3310	35.6	1226	44.6	4536	37.6
35-44	3188	34.2	515	18.7	3703	30.7
45-54	1365	14.7	165	6	1530	12.7
55-64	437	4.7	63	2.3	500	4.1
>=65	84	0.9	12	0.4	96	0.8
Total	**9310**	**100**	**2749**	**99.9**	**12059**	**99.9**

Table 5.2: Age distribution at HIV diagnosis of patients registered since 1996 at one of the HIV Treatment Centres.

	Male		Female		Total	
HIV antibody response	**N**	**%**	**N**	**%**	**N**	**%**
Unknown	91	1	29	1.1	120	1
HIV-1	9074	98.1	2601	96.4	11675	97.7
HIV-2	38	0.4	38	1.4	76	0.6
HIV-1/2	51	0.6	31	1.1	82	0.7
HIV-1 subtype						
Unknown	6979	75.4	2114	78.3	9093	76.1
A	39	0.4	47	1.7	86	0.7
B	1991	21.5	239	8.9	2230	18.7
C	62	0.7	89	3.3	151	1.3
CRF01AE	46	0.5	20	0.7	66	0.6
CRF02AG	83	0.9	99	3.7	182	1.5
D	11	0.1	27	1	38	0.3
F	4	0	6	0.2	10	0.1
G	19	0.2	29	1.1	48	0.4
Other	20	0.2	29	1.1	49	0.4

Table 5.3: Distribution of the HIV-1, HIV-2, and the HIV-1/-2 antibody response amongst adults registered and monitored for HIV and the distribution of HIV-1 subtypes based on available pol sequence data of HIV-1 infected adults.

Adults	Male		Female		Total	
Transmission risk	**N**	**%**	**N**	**%**	**N**	**%**
homosexual	6234	67.4			6234	52.2
heterosexual	1664	18.0	2336	86.6	4000	33.5
injecting drug user	445	4.8	162	6.0	607	5.1
blood (products)	136	1.5	64	2.4	200	1.7
vertical	13	0.1	13	0.5	26	0.2
unknown	762	8.2	124	4.6	886	7.4

Table 5.4: Transmission risk groups (number and percentage of total) amongst the infected adult patients included in the registration and monitoring of HIV.

Children	Male		Female		Total	
Transmission risk	**N**	**%**	**N**	**%**	**N**	**%**
vertical	53	94.6	47	94	100	94.3
unknown	3	5.4	3	6	6	5.7

Table 5.5: Transmission risk groups (number and percentage of total) amongst infected children (between 0 and 13 years of age in 2006) included in the registration and monitoring of HIV.

	Year of first HAART regimen					
	2004-2005		2005-2006		Total	
First HAART regimen	**N**	**%**	**N**	**%**	**N**	**%**
Total	801	100.0	550	100.0	1351	100.0
3TC+TDF+EFV	162	20.2	97	17.6	259	19.2
AZT+3TC+LOP/r	138	17.2	68	12.4	206	15.2
TDF+FTC+EFV	63	7.9	90	16.4	153	11.3
AZT+3TC+EFV	72	9.0	20	3.6	92	6.8
AZT+3TC+NVP	62	7.7	14	2.5	76	5.6
AZT+3TC+NFV	52	6.5	24	4.4	76	5.6
3TC+TDF+NVP	47	5.9	29	5.3	76	5.6
AZT+3TC+ABC+LOP/r	35	4.4	16	2.9	51	3.8
ABC+3TC+EFV	12	1.5	33	6.0	45	3.3
AZT+3TC+ABC+EFV	13	1.6	27	4.9	40	3.0
3TC+TDF+LOP/r	23	2.9	14	2.5	37	2.7
AZT+3TC+LOP/r+EFV	22	2.7	10	1.8	32	2.4
TDF+FTC+LOp/r	9	1.1	20	3.6	29	2.1
TDF+FTC+ATV/r	12	1.5	16	2.9	28	2.1
3TC+TDF+ATV/r	14	1.7	12	2.2	26	1.9
ABC+3TC+LOP/r	8	1.0	9	1.6	17	1.3
TDF+FTC+NVP	7	0.9	7	1.3	14	1.0
Other	50	6.2	44	8.0	94	7.0

Table 5.6: Overview of first-line HAART combinations most frequently used in previously antiretroviral therapy-naive patients starting treatment between 1 July 2004 and 30 June 2005 and between 1 July 2005 and 30 June 2006.
FTC=emtricitabine, TDF=tenofovir, AZT=zidovudine, 3TC=lamivudine, ddI=didanosine, ABC=abacavir, NVP=nevirapine, EFV=efavirenz, LOP/r=lopinavir/ritonavir boosted, NFV=nelfinavir, ATV/r=atazanavir/ritonavir boosted.

Trends o

TEN YEARS **HAART**

over time

The HIV epidemic in the first decade of HAART

Ard van Sighem

Introduction

Ten years ago, highly active antiretroviral therapy (HAART) became widely available for treatment of HIV-infected patients in the Netherlands. As a result, plasma viral load levels decreased, and the deterioration of the immune system slowed down both in individual patients and in the total HIV-infected population. Disease progression decelerated or even halted, and the mortality rates and incidence of AIDS plummeted[21-24].

A reduction in viral load also reduces the infectiousness of patients with HIV[25]. Therefore, the widespread use of HAART might be expected to have reduced the HIV epidemic in the Netherlands. Paradoxically, since 1996, the number of diagnoses has never been as high as in the last few years, especially amongst men having sex with men (MSM)[26].

In this chapter, the changes in the demographic and clinical characteristics of the HIV-infected population at the time of diagnosis during the first decade of HAART are described. The recent trends in the populations infected via homosexual or heterosexual contact are compared with data on other sexually transmitted infections (STIs).

Study population and methods

The study population consisted of 11,709 patients infected with HIV-1 with a known year of HIV diagnosis. Of those, 11,559 (98.7%) were diagnosed at 13 years of age or older. Patients were classified according to their transmission risk category, including those who acquired their infection via homosexual contact (MSM), via heterosexual contact, or via injection drug use (IDU). Countries of origin or infection 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, and Australia and the Pacific islands. $CD4^+$ and $CD8^+$ T cell counts and plasma HIV RNA levels at diagnosis were determined to be the measurements taken within the first 12 weeks after the diagnosis was made that were closest to the time of diagnosis and prior to the start of therapy. The distributions of age at diagnosis for MSM and heterosexual men and women were compared with similar data on genital chlamydial infection, gonorrhoea, (infectious) syphilis, and HIV from attendees at STI clinics[27].

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[28]. 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 using 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%[29]. 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’s characteristics at diagnosis. 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 using Wilcoxon-Mann-Whitney and chi square nonparametric tests. The significance of proportional changes over time was assessed with logistic regression modelling. For

continuous variables, changes over time were studied using generalised linear models; medians were reported with the interquartile range (IQR). For percentages, exact binomial 95% confidence intervals (CI) were calculated.

Results

Men having sex with men

For 6170 (68.6%) of the 8996 men with an HIV-1 diagnosis, the reported mode of transmission was homosexual contact (Table 6.1). The majority of these patients, 4113 (66.7%), were diagnosed in 1996 or later. The annual number of diagnoses amongst MSM was 361 in 1996; the number decreased to 313 in 1998 and then steadily increased to 495 in 2005 (Table 6.2; Figure 6.1). The proportion of MSM in the annual tally decreased from 58.1% in 1996 to a nadir of 44.5% in 2003; it increased thereafter to 60.3% in 2006 (Figure 6.2). Most MSM were of Dutch origin, 4549 (73.7%), whereas 471 (7.6%) originated from other Western European countries, 383 (6.2%) from Latin America, 171 (2.8%) from the Caribbean, and 174 (2.8%) from South/Southeast Asia. These proportions did not change over time (p=0.5).

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 cell counts were 340 (140–530) x 10^6 cells/l. Patients originating from the Netherlands had higher RNA levels than other patients, specifically, 4.9 (IQR, 4.3-5.3) $\log_{10}$ copies/ml for the patients of Dutch origin and 4.8 (4.1–5.2) for the others (p<0.0001), but CD4 counts did not differ (p=0.02). Median CD4 cell counts increased from 255 (IQR, 93–425) x 10^6 cells/l in 1996 to 400 (230–590) in 2005 and 430 (230–680) in 2006 (p<0.0001).

The median age at diagnosis was 37.6 (IQR, 31.9–44.6) years; it was higher for patients of Dutch origin, for whom it was 38.9 (33.2–46.1) years, compared to patients from other regions, for whom it was 33.8 (28.9–39.7) years (p<0.0001). The median age increased over time from 36.9 (IQR, 31.7–45.5) years in 1996 to 40.7 (34.5–46.5) years in 2005 (p=0.0001) for patients of Dutch origin; the median age of the other patients also increased from 33.5 (29.8–39.4) to 36.4 (29.8–43.0) years, albeit not significantly (p=0.02). Of the MSM diagnosed in 1996, 259 (71.8%) were asymptomatic, 30 (8.3%) presented with a CDC-B event, and 72 (19.9%) with a CDC-C event. In comparison, of the MSM diagnosed in 2004, 434 (85.3%, p<0.0001) were asymptomatic, 29 (5.7%, p=0.002) presented with a CDC-B event, and 46 (9.0%, p<0.0001) presented with a CDC-C event.

In total, 660 (16.1%) patients diagnosed in or after 1996 had a negative test for HIV-1 18 months, at most, before diagnosis (classified as a "recent infection"). Between 1996 and 2000, the proportion of recent infections was 10.3% and did not change over time (p=0.2). Thereafter, it increased (p<0.0001) from 41 out of 337 (12.1%) in 2000 to 125 out of 495 (25.3%) in 2005, and in 2006 the proportion increased still further to 30 out of 111 (27.0%). A recent infection was found in 380 out of 2120 (17.9%) patients who were 38 years of age or younger at the time of diagnosis. In older patients, a recent infection was less common (p=0.0007), specifically, 280 out of 1993 (14.0%). For patients with a recent infection, median CD4 counts were 510 (IQR, 370–700) x 10^6 cells/l, and HIV RNA plasma levels at diagnosis were 4.8 (4.1–5.2) $\log_{10}$ copies/ml, and they did not change over time or with age at diagnosis. The number of patients who ever had a negative HIV test increased from 109 (32.3%) in 2000 to 251 (50.7%) in 2005.

CD4 cell counts at diagnosis in the 3453 patients without a negative HIV test in the 18 months prior to the diagnosis increased from 220 (IQR, 80–400) x 10^6 cells/l in 1996 to 360 (200–646) in 2006 (p<0.0001). For

patients older than 38 years at diagnosis, CD4 counts were 260 (IQR, 80–462) x 10^6 cells/l, compared to 320 (140–500) for patients younger than 38 years (p<0.0001). In addition, RNA levels at diagnosis decreased from 5.0 (IQR, 4.3–5.5) $\log_{10}$ copies/ml in 1996 through 1997 to 4.8 (4.1–5.2) in 2005 through 2006 (p=0.004). RNA levels were higher in patients older than 38 years at diagnosis, 5.0 (IQR, 4.4–5.3) $\log_{10}$ copies/ml, than they were in younger patients, 4.8 (4.2–5.3) (p<0.0001). The changes in CD4 counts and RNA levels over calendar time did not depend on the patient's age (p>0.1).

The age distribution of MSM with an HIV diagnosis in or after 2004 was similar to that of MSM with syphilis amongst STI clinic attendees (Figure 6.3). The corresponding distributions of HIV (in STI clinics), gonorrhoea, and chlamydia agreed less well with data from the HIV Monitoring Foundation (HMF) on HIV and were skewed to younger ages.

For 4397 (71.3%) MSM, the most likely country of infection was known. A majority of 3905 (88.8%) were infected in the Netherlands, whilst 159 (3.6%) patients were infected in other countries in Western Europe. The country of infection was known for 82 of 139 (59.0%) patients originating from the Netherlands Antilles or Aruba and for 98 of 159 (61.6%) patients from Surinam. Of the 82 from the Antilles, 15 (18.3%) were infected there and 61 (74.4%) were infected in the Netherlands, whilst of the 98 patients from Surinam, 12 (12.2%) were infected in Surinam and 84 (85.7%) in the Netherlands.

For 1626 (26.4%) men in the MSM population, the HIV-1 subtype could be determined. Of these, 1578 (97.1%) were infected with subtype B, and the proportion of patients infected with subtype B did not change between 1996 and 2006 (p=0.1). Other subtypes found amongst MSM were AE (18 patients), C (11), AG (8), A (5), G (4) and other non-B subtypes (2).

Heterosexual men and women

Of the 3843 patients infected via heterosexual contact, 1604 (13.9% of the total population and 41.7% of the heterosexual group) were men and 2239 (19.4% of the total population and 58.3% of heterosexuals) were women. The proportion of heterosexual men in the annual number of diagnosed patients increased from 13.0% in 1996 to 17.8% between 2000 and 2003 and decreased thereafter to 12.5% in 2006. For heterosexual women, a similar pattern was observed: 13.2% in 1996, 26.6% between 2000 and 2003, and a decrease to 16.9% in 2006 (Figure 6.2). Between 2000 and 2005, the mean annual number of diagnoses was 158 for men and 231 for women, without a significant change over time (p=0.2).

The most frequently reported regions of origin for heterosexual men were the Netherlands (598 patients, 37.3%) and sub-Saharan Africa (558 patients, 34.8%). Other regions were Latin America (165 patients, 10.3%), Europe excluding the Netherlands (116 patients, 7.2%), and the Caribbean (83 patients, 5.2%). Almost half of the heterosexual women originated from sub-Saharan Africa (1095 patients, 48.9%), whilst 558 patients (24.9%) were of Dutch origin. The proportion of female patients originating from the Caribbean (130, 5.8%) and Latin America (207, 9.3%) was similar to that of male patients, whilst 124 women (5.5%) originated from South/Southeast Asia and 89 (4.0%) from Europe excluding the Netherlands.

Between 1996 and 2002, the proportion of patients originating from sub-Saharan Africa increased from 33.1% to 57.6% (p<0.001). Thereafter, this proportion declined to 40.3% in 2005 through 2006 (p<0.001). This pattern was counterbalanced by a decrease in the proportion of Dutch patients from 40.5% in 1996 to a nadir of 19.3% in 2001 (p<0.001), with a subsequent increase to 31.8% in 2005 through 2006 (p<0.001). The number of diagnoses amongst patients of Dutch origin

increased from 82 in 2002 to 115 in 2005, whilst that amongst patients from sub-Saharan Africa decreased from 238 to 148 during the same period.

The median age, CD4 cell count, and HIV RNA level at diagnosis for heterosexual men and women from the most frequently reported regions of origin are shown in Table 6.3. In general, regardless of the region of origin, men were older at the time of diagnosis than women were, and men had lower CD4 counts and higher viral loads. A comparison of characteristics of men and women from different regions of origin showed no differences between Dutch patients and patients from other European countries. On the other hand, men and women from sub-Saharan Africa were generally younger and had lower CD4 counts than their Dutch counterparts. Patients from Latin America ($p<0.001$), the Caribbean ($p<0.001$), and South/Southeast Asia ($p=0.003$) likewise had lower CD4 counts than Dutch patients. There were no differences in viral load between patients from different regions. CD8 cell counts at diagnosis were not different between men (788 [IQR, 480–1200] x 10^6 cells/l) and women (800 [520–1110]) ($p=0.9$), and the counts also did not differ between patients from different regions of origin. In general, no significant changes occurred in age, CD4 counts, or RNA levels between 1996 and 2006.

Between 1996 and 2003, 104 out of 2383 (4.4%) patients who were diagnosed with HIV had a last negative HIV test within 18 months prior to the diagnosis, whilst 301 (12.6%) patients ever had a negative test. These proportions were similar for men and women ($p=0.8$). Of the 617 patients originating from the Netherlands, 117 (19.0%) ever had a negative test and 46 (7.5%) had a negative test in the 18 months prior to diagnosis, whilst for the 1766 patients born outside the Netherlands, 184 (10.4%) ever had a negative test and 58 (3.3%) had a negative test in the 18 months before diagnosis ($p<0.001$). From 2004 onward, however, the proportion of recent infections amongst women increased from 4.5% in 2004 to 9.1% in 2005 to 16.1% in 2006 ($p=0.008$), whilst there was no such increase amongst men ($p=0.9$). Likewise, the proportion of patients with a negative test at any time before diagnosis increased to 30.7% (73 out of 238 patients, $p<0.001$).

The age distribution at HIV diagnosis for heterosexual men and women of Dutch origin who received the diagnosis in or after 2000 corresponded with the distribution of syphilis in both populations (Figure 6.3). In contrast, chlamydia, gonorrhoea, and HIV amongst STI clinic attendees were mainly observed in the populations less than 30 years of age.

For 2803 (72.9%) patients, the most likely country of infection was registered. Of those 2803 patients, 1194 (42.6%) were infected in the Netherlands, and 1151 (41.1%) were infected in sub-Saharan Africa. The majority of the patients who were infected in the Netherlands (722, 60.5%) also originated from the Netherlands, whilst 139 (11.6%) originated from sub-Saharan Africa, 121 (10.1%) from Surinam and 55 (4.6%) from the Netherlands Antilles and Aruba. Of the patients who were infected in sub-Saharan Africa, 1060 (92%) were also born in sub-Saharan Africa, whilst 77 (6.7%) of them originated from the Netherlands. Of the patients from the Netherlands Antilles and Aruba, 62 (50.8%) of 122 were infected in the home country, as were 56 (30.8%) of 182 from Surinam.

Of the 837 patients with a known HIV-1 subtype, 368 (44.0%) originated from sub-Saharan Africa and 469 (56.0%) from other regions. The most prevalent subtype amongst patients from other regions was B (342 patients, 72.9%). Other reported subtypes were AE (36 patients, 7.7%), AG and C (23 each, 4.9%), A (19, 4.1%), G (12, 2.6%), D (6, 1.3%), F (1, 0.2%) and other non-B subtypes (7, 1.5%). Seventeen patients (47%) harbouring a subtype AE virus were infected in Thailand, whilst

4 patients were reported to have been infected in the Netherlands. The country of infection was unknown for 13 (36%) patients with subtype AE. Patients with subtype AG were mainly infected in the Netherlands (11 patients) or western Africa (4), whilst the country of infection was unknown for 5 patients.

The distribution of subtypes was different for the patients from sub-Saharan Africa. Only 11 patients (3.0%) were infected with a subtype B virus. The most frequent subtype was AG (123 patients, 33.4%), found mainly in patients originating from Ghana (35 patients, 28.5%), Sierra Leone (21, 17.1%) and other countries in western Africa above the equator (58, 47.2%). Subtype C was found in 96 patients (26.1%), of whom 33 (34%) originated from Ethiopia, 16 (17%) from Burundi, and 16 (17%) from Zambia and other countries in the eastern and southern part of Africa. Other subtypes were A (47 patients, 12.8%), D (25, 6.8%), G (23, 6.3%), F (9, 2.5%), AE (3, 0.8%), and other non-B subtypes (31, 8.4%). The majority of these other subtypes were found in 76 patients originating from western and middle Africa below the equator (Congo, Congo, Angola, etc.) (55.1%) and in 39 patients from western Africa above the equator (28.3%). For 40 (28.8%) out of 139 patients from sub-Saharan Africa who were infected in the Netherlands, the HIV-1 subtype was known. Only 4 (10%) patients were infected with subtype B, whilst 15 (38%) were infected with AG, 7 (18%) with subtype C, and 6 (15%) with subtype A.

Injection drug users

For 594 (5.2%) patients, including 436 (73.4%) men and 158 (26.6%) women, the reported mode of transmission was injection drug use (IDU). The majority of the patients, 372 (62.6%), were infected before 1996; only 88 (14.8%) were infected between 2000 and 2005, and in 2006 no patient has as yet been reported to have been infected via injection drug use. The majority of the IDU population originated from the Netherlands (392 patients, 66.0%) and other Western European countries (100 patients, 16.8%). Other regions of origin were Latin America (22 patients, 3.7%), Eastern Europe (15 patients, 2.5%), North Africa and the Middle East (13 patients, 2.2%) and South/Southeast Asia (12 patients, 2.2%). The majority of the patients from Latin America, 19 (86%), were of Surinamese origin, whilst 10 patients from North Africa and the Middle East originated from The Maghreb.

Of the 222 patients diagnosed in or after 1996, 76 (34.2%) were treated in a hospital in Amsterdam, 65 (29.3%) in another hospital in the Randstad, and 56 (25.2%) in the southern part of the Netherlands, in particular Maastricht (42 patients, 18.9%). The median age at diagnosis was 37.6 (IQR, 32.3–42.7) years. Median CD4 counts, CD8 counts and viral load were 268 (IQR, 84–502) x 10^6 cells/l, 810 (510–1250) x 10^6 cells/l and 4.7 (4.2–5.2) $\log_{10}$ copies/ml, respectively. There were no differences in these characteristics between men and women and between IDUs originating from inside and outside the Netherlands. However, IDUs from outside the Netherlands were younger than those of Dutch origin: 33.7 (IQR, 28.6–40.5) versus 38.6 (34.9–42.9) years (p=0.002).

The majority of the 112 injection drug users with a known HIV-1 subtype were infected with subtype B (106 patients, 95%). Three patients were infected with subtype A, 2 with subtype AE and 1 with subtype G.

Discussion

Since the widespread introduction of HAART in 1996, the face of the HIV epidemic in the Netherlands has changed. Whereas in 1996 the majority of the HIV diagnoses were amongst MSM and only a quarter were amongst heterosexuals, by the turn of the millennium those who acquired HIV via heterosexual or homosexual contact accounted for an equal share of the annual number of diagnoses. However, by 2006, the majority of the epidemic's new diagnoses are again amongst MSM.

Although the epidemic has now reverted to the situation in 1996, there are at least two major differences. First, the number of patients who acquired their infection via injection drug use has fallen to a level of 10 to 15 cases annually, which is most likely due to a decline in injection drug use[30]. Second, although the proportion of diagnoses in heterosexually infected patients has decreased, the absolute number of diagnoses has remained stable at a level of approximately 300 cases per year, and an increase has been observed in heterosexual men and women of Dutch origin. Besides, the number of individuals infected via MSM increased from 300 cases per year in 1998 to almost 500 in 2005.

Several factors might have lead to this growing number of diagnoses. First, the intervening potential of HAART commences only after the HIV infection has been diagnosed, and it is steered by treatment guidelines. Thus, some of the new infections will be caused by HIV-infected individuals who are unaware of their infection[31]. Furthermore, there are indications of an increase in unsafe sex practices that has possibly counterbalanced the beneficial effect of HAART on the epidemic[32-34]. Currently, HMF is developing a mathematical model that aims to evaluate the impact of both these factors on the HIV epidemic.

In the population of MSM, the annual number of diagnoses has been growing since 1998. The increase in the proportion of MSM with a recent infection or with a less deteriorated immune system at diagnosis indicates that at least part of the increase in the number of diagnoses can be explained by more frequent testing for HIV. From these findings and the observation that the median age at diagnosis is increasing, it can be concluded that MSM are infected at an older age[35].

From 2004 onward, the proportion of heterosexually infected women with a recent negative HIV test has increased, which might be attributable to the implementation of the national prenatal screening of pregnant women[36]. In the total population infected via heterosexual contact, CD4 counts and HIV RNA levels at diagnosis have not changed over calendar time, and, up until 2004, the proportion of patients with a HIV-negative test in the recent past also had not changed. These findings suggest that HIV incidence amongst heterosexuals has remained constant over time. This is compatible with the annual prevalence of HIV, gonorrhoea, and syphilis amongst STI clinic attendees, which remained fairly stable after 2000, despite an increasing number of consultations[27]. The increase in the number of consultations was also apparent in our data in which an increasing proportion of the newly diagnosed patients had a prior HIV-negative test.

For patients infected via sexual contact, the age distribution at diagnosis agreed very well with that observed for syphilis amongst STI clinic attendees. This suggests that syphilis and HIV are circulating in the same sexual networks. Approximately 20% of the cases of syphilis amongst homosexual men were found in patients who were already HIV-positive[27, 37]. To what extent the observed changes in incidence of syphilis reflect changes in HIV incidence is a still subject of debate[38, 39].

In the heterosexual population, genital chlamydial infection and gonorrhoea were mainly found in younger patients. Also, the majority of HIV diagnoses amongst female STI clinic attendees were found in this group. This probably reflects the differences in demographic characteristics between the HIV-infected population and the population visiting STI clinics. In general, heterosexual STI clinic attendees were younger and more likely to be of Dutch origin than the patients in HMF. The almost flat distribution of syphilis over age categories suggests that syphilis occurs in separate sexual networks from chlamydia and gonorrhoea.

As already indicated in our previous report, the number of patients originating from sub-Saharan Africa declined after 2002[26]. This was consistent with the decreasing number of people immigrating from Africa into the Netherlands since 2002. The number of immigrants from sub-Saharan Africa reportedly declined from 14,980 in 2002 to 6207 in 2005 (Statistics Netherlands, available via http://statline.cbs.nl). The majority of the patients from sub-Saharan Africa were also infected there, and the distribution of subtypes across patients from sub-Saharan Africa corresponded with the endemic distribution observed in this region. The small proportion of Africans who were infected in the Netherlands with a subtype B virus strain indicates that the Africans living in the Netherlands form a closed group, with HIV transmission occurring mostly among themselves.

In conclusion, despite 10 years of HAART, the annual growth of the HIV epidemic in the Netherlands has only increased since 1996, especially amongst older homosexual men. The steady annual growth of the epidemic in the heterosexual population results from a balance between a reduction in immigration from sub-Saharan Africa and an increase in the number of diagnoses amongst heterosexuals born in the Netherlands. HAART alone is unable to halt further expansion of the HIV epidemic in the Netherlands. Instead, changes in sexual behaviour are necessary to achieve this goal. Because the populations most vulnerable for HIV and other STIs show a wide variability regarding age, origin, and sexual preference and practices, tailor-made prevention and intervention strategies are required.

Transmission risk group	Men		Women		Total	
	N	%	N	%	N	%
Homosexual contact	6170	68.6			6170	53.4
Heterosexual contact	1604	17.8	2239	87.4	3843	33.2
Injection drug use	436	4.9	158	6.2	594	5.1
Blood (products)	118	1.3	57	2.2	175	1.5
Other/unknown	668	7.4	109	4.3	777	6.7
Total	**8996**		**2563**		**11559**	

Table 6.1: Number of HIV-1 diagnoses in the total population stratified by gender and transmission risk group.

Year of diagnosis	MSM	Heterosexual		Injection drug use		Blood (products)		Other/unknown		Total
	Men	Men	Women	Men	Women	Men	Women	Men	Women	
1996	361	81	82	34	13	3	4	38	5	621
1997	404	104	125	40	6	6	4	50	5	744
1998	313	96	113	19	2	6	5	32	6	592
1999	325	99	129	14	6	6	4	34	4	621
2000	337	146	201	11	2	4	2	30	7	740
2001	394	156	218	13	5	8	2	53	9	858
2002	442	156	257	13	1	11	5	61	5	951
2003	422	164	256	18	5	6	4	67	7	949
2004	509	169	243	9	1	4	3	80	10	1028
2005	495	159	209	8	2	2	4	68	3	950
2006	111	23	31	0	0	1	2	14	2	184
Total	**4113**	**1353**	**1864**	**179**	**43**	**57**	**39**	**527**	**63**	**8238**

MSM: men having sex with men

Table 6.2: Annual number of diagnoses since 1996 stratified by gender and transmission risk group.

	Men			Women		
	Age (year)	CD4 (10^6 cells/l)	RNA (log_{10} copies/ml)	Age (year)	CD4 (10^6 cells/l)	RNA (log_{10} copies/ml)
the Netherlands	40.5	290	5.0	34.6	450	4.3
	33.8-49.9	70-500	4.3-5.4	28.0-45.4	170-650	3.6-5.0
Europe	36.7	244	5.0*	32.1	390	4.6*
	32.8-48.6	80-400	4.3-5.4	28.2-37.5	250-550	3.5-5.0
sub-Saharan Africa	33.9	160	4.9	28.4	270	4.3
	28.1-38.5	70-313	4.3-5.2	23.6-33.9	130-430	3.5-5.0
Latin America	38.1	156	4.9	30.9	280	4.4
	33.4-46.7	33-325	4.2-5.1	26.3-38.2	100-440	3.8-5.0
the Caribbean	37.7	100	4.7*	31.1	300	4.4*
	32.3-43.2	30-255	4.3-5.1	23.6-39.0	100-500	3.9-5.0
South/Southeast Asia	41.7	150*	4.7*	31.3	135*	4.8*
	37.1-48.9	50-380	4.1-5.1	28.2-36.1	29-315	4.1-5.1
Total	**36.7**	**190**	**4.9**	**30.5**	**290**	**4.4**
	31.4-44.2	**60-383**	**4.3-5.3**	**25.2-36.6**	**128-490**	**3.6-5.0**

*p>0.01, men vs. women; all other men-women comparisons, p<0.01.

Table 6.3: Age, CD4 count, and RNA plasma level at diagnosis for heterosexual men and women from the most prevalent regions of origin. Medians are reported with interquartile ranges (IQR).

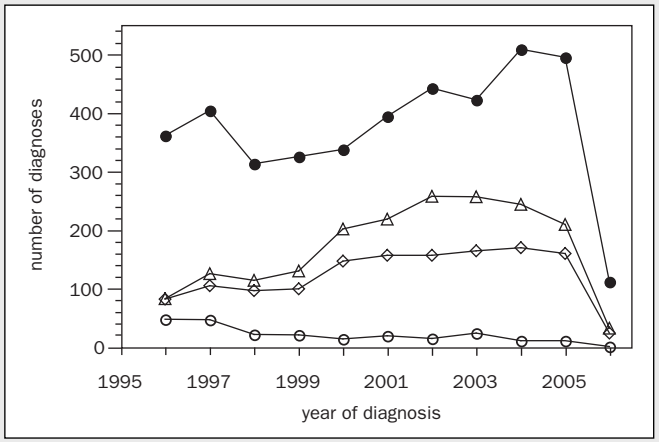


Figure 6.1: Annual number of diagnoses per transmission risk group. Dots represent homosexual men; triangles, heterosexual women; diamonds, heterosexual men; and circles, injection drug users.

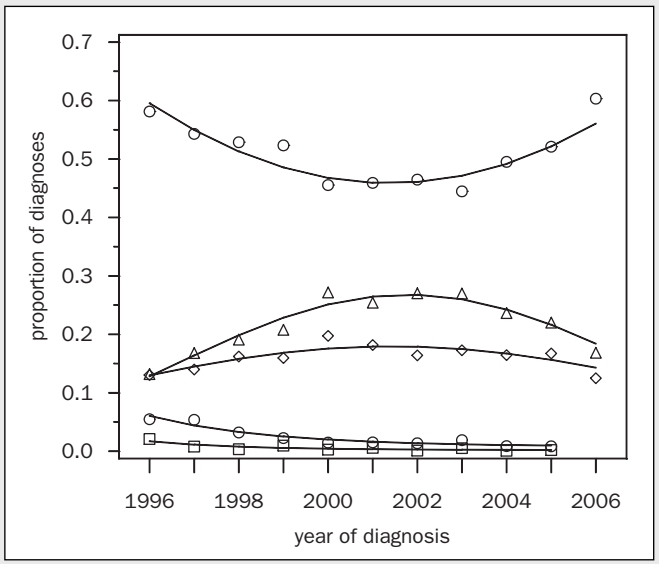


Figure 6.2: Annual proportions of diagnoses per transmission risk group. Dots represent homosexual men; triangles, heterosexual women; diamonds, heterosexual men; circles, injection drug users (men); squares, injection drug users (women); and lines, logistic model fit.

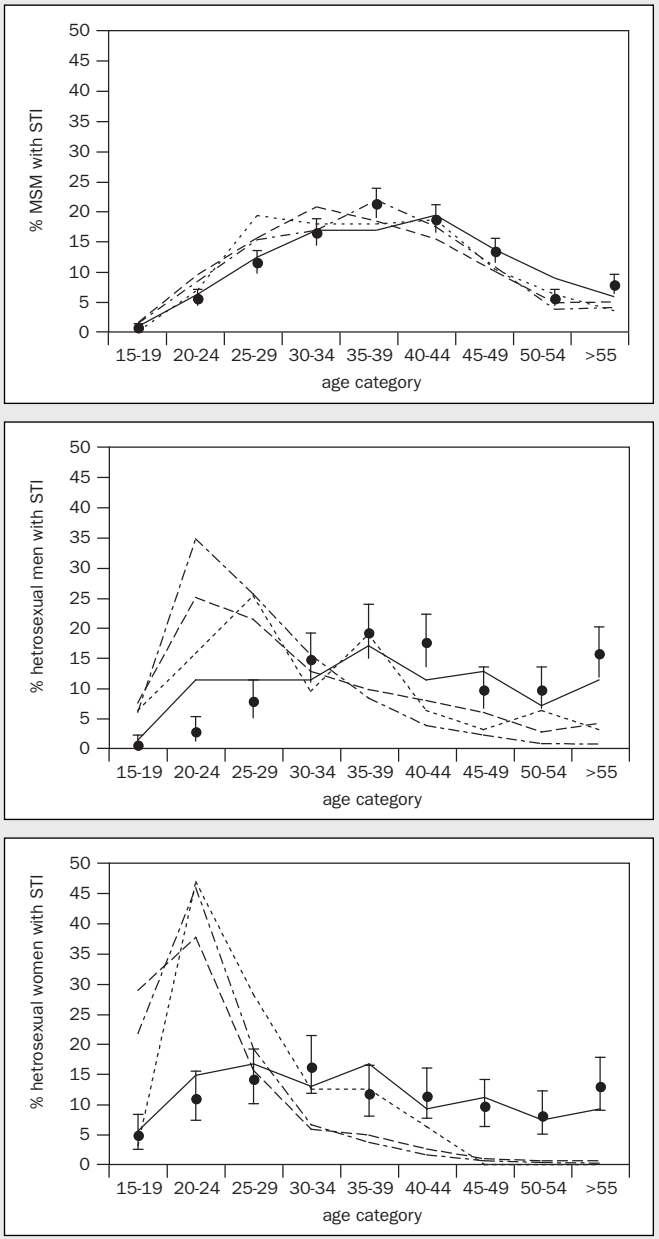


Figure 6.3: Age distribution for cases of sexually transmitted infections (STI) by transmission risk category. HIV data from the HIV Monitoring Foundation is represented by the black dots with 95% confidence intervals, whilst the lines represent data from STI clinic attendees: syphilis (solid line), chlamydia (dashed-dotted line), gonorrhoea (dashed line) and HIV (dotted line).

Effect of

TEN YEARS **HAART**

f HAART

Improved virologic efficacy of HAART in later calendar years

Luuk Gras

Introduction

Highly active antiretroviral therapy (HAART) reduces the short-term mortality and morbidity rates in HIV-infected patients[21, 24, 40]. The decision when to start HAART is based on a trade-off between possible complications of long-term antiretroviral drug use[41-44] and the benefits of the timely reversal of the deterioration of the immune system. New Dutch guidelines, published in 2005[45], differ from the previous ones[46] in that the initiation of HAART in asymptomatic patients is recommended whilst CD4 cell counts are still at least 200 cells/mm^3. This new threshold stems from the results of studies showing that delaying the start of HAART until CD4 cell numbers decline below 200 cells/mm^3 is associated with faster disease progression and death[23, 47, 48]. The revised advice for beginning therapy earlier follows what has been common practice for a number of years. Other studies, however, show that the prognosis is improved when patients start HAART whilst CD4 cell counts are still above 350 cells/mm^3[49-51], although the absolute risk benefit is small[23].

Here we evaluate differences in mortality and morbidity and in the short-term and long-term responses of CD4 cell count and HIV RNA concentration in plasma after starting HAART, according to calendar year, demographic and clinical characteristics at the start of HAART.

Methods

Study population and endpoints

In total, 8884 patients with HIV-1 who commenced HAART between 1 July 1996 and 31 December 2005 were selected from the ATHENA observational cohort[52]. Patients were 16 years of age or older at the start of HAART, 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 HAART were the two primary endpoints. In univariate analyses, we evaluated the probability of death and probability of AIDS developing within 10 years after HAART initiation in antiretroviral therapy (ART)-naïve patients compared with those in ART-experienced patients. We restricted multivariate analyses to 6835 ART-naïve patients since such analyses of ART-experienced patients have been described before[53]. Furthermore, in multivariate analyses, we focused on the endpoints occurring within 3 years after the start of HAART, because the calendar year was included as a confounder and because the follow-up period was shorter in those initiating HAART in later calendar years. Short-term virologic and immunologic marker response was measured by the proportion of patients reaching HIV RNA levels less than 500 copies/ml and by the change in CD4 cell count at 24 weeks, which was defined as the nearest measurement to 24 weeks that occurred between 12 and 36 weeks after starting HAART. In 5684 patients, CD4 cell measurements at the start of HAART and 24 weeks after the start of HAART were available, and 5608 had both HIV RNA measurements available.

Long-term virologic responses were studied in 6092 patients who had reached initial virologic success (defined as 2 consecutive measurements <500 copies/ml) within 9 months after the start of HAART. Two consecutive measurements of 500 copies/ml or higher whilst HAART was being given were considered as a rebound of virus production. The cut-off of 500 copies/ml, instead of 50, enabled inclusion of patients who had started HAART in earlier calendar years. Only the first viral rebound within 3 years of initial virologic success in each patient was considered.

Finally, long-term CD4 cell responses to HAART were studied in a subset of 554 patients who had been receiving uninterrupted HAART for at least 7 years. CD4 cell measurements were longitudinally modelled

with the aim of providing an estimate of the immune system's maximum capacity for long-term CD4 cell restoration. Furthermore, CD4 cell counts measured closest to weeks 24, 48, and 72 after the start of HAART (within a time frame of 12 weeks) and, subsequently, at 24-week intervals up to 360 weeks were selected, and median increases in CD4 cell counts at these time-points were graphically summarized.

Statistical analysis

Kaplan-Meier estimates of the probability of patients reaching an endpoint were used to present the results of univariate analyses. The chi square and Kruskal–Wallis test were used to assess differences between baseline strata. Univariate and multivariate Cox proportional hazards models were used to model 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 HAART. Logistic regression was used to model the odds of reaching HIV RNA levels less than 500 copies/ml, and linear regression was used to model changes in the CD4 cell count 6 months after the start of HAART. The statistical model for the longitudinal analyses of CD4 cell changes up to 7 years after the start of HAART was a mixed effects model with a random intercept and 4 random slopes for each patient. A first order autoregressive covariance structure was used to correlate intra-individual serial measurements. We divided the 7-year period into four intervals: 0 to 6 months after the start of HAART; 6 months to 3 years; 3 to 5 years; and 5 to 7 years. Slopes were allowed to differ between intervals, which were chosen by visual inspection of the graphs of median CD4 cell responses. CD4 cell counts were square-root transformed to comply with model assumptions. The slopes of CD4 cell count changes during each interval were estimated for 5 pre-HAART CD4 cell count strata: less than 50; 50 to 200; 200 to 350; 350 to 500; and 500 or more cells/mm^3. The other variables were allowed to have the same effect between the start of HAART and 7 years thereafter (i.e., the entire period of time) or to have a different effect in each of the 4 time intervals described. Poisson regression was used to model the incidence of rebound of HIV RNA within 3 years after first virologic success per person-years on HAART. Person-years on HAART were calculated from the date of first virologic success until the date of first viral rebound, date of death, date when lost-to-follow-up, or the date three years after the first virologic success. The following variables were associated with the above mentioned outcomes: gender; age at the start of HAART; clinical stage at the start of HAART (CDC-C vs. CDC-A or B); CD4 cell count at starting HAART (0-50, 50-200, 200-350, 350-500, and ≥500 cells/mm^3); HIV RNA at the start of HAART (<4, 4-5, and ≥5 $\log_{10}$ copies/ml); hepatitis B co-infection (positive HBsAg test); hepatitis C co-infection (either a positive HCV antibody or positive HCV-RNA test result); and region of origin (Netherlands; Caribbean/Latin America; sub-Saharan Africa; Southeast Asia; Western Europe, North America, and Australia combined; and "other"). The initial HAART combination (single PI-based regimen, ≥2 PI's, single non-nucleoside reverse transcriptase inhibitor [NNRTi], PI+NNRTi, and ≥3 NRTi) was included in the analysis of short-term immunologic and virologic outcome. Variables included in multivariate analyses with a p-value of 0.20 or higher were excluded from the final model.

Results

CD4 cell numbers at the start of HAART are shown in Figure 7.1 per calendar year of starting HAART for all therapy-naïve patients and, more importantly, for the subgroup of 2188 asymptomatic therapy-naïve patients with an HIV RNA plasma concentration less than 100,000 cps/ml. According to the guidelines, the decision to start HAART in asymptomatic therapy-naïve patients with a HIV RNA plasma level less than 100,000 copies/ml is based on the number of CD4 cells. There was a lower median CD4 cell count of 285 cells/mm^3 in 1996, compared with 340 in 1997 and 330 cells/mm^3 in

1998. Patients starting HAART from 1997 through 1999 had higher CD4 cell counts compared with those starting in 2000 through 2006 (p <0.0001).

To reflect the effect of different treatment guidelines and practices on responses to therapy, 4 time periods during which HAART was initiated are introduced in the remainder of this chapter: 1) 1996, the first introduction of HAART; 2) 1997-1999, the early HAART period; 3) 2000-2001, the intermediate HAART period; and 4) 2002-2005, the late HAART period.

Of the 8884 patients infected with HIV-1 who started HAART between 1 July 1996 and 31 December 2005, 2029 (23%) were already treated with antiretroviral drugs. The probability of progression to death and progression to AIDS in both therapy-naïve and therapy-experienced patients is shown in Figure 7.2 a and b. During 29,888 person-years of follow-up (PYFU) 393 therapy-naïve patients died (incidence rate 13.15 per 1000 PYFU; 95% CI, 11.88-14.52), and amongst pre-treated patients 382 patients died within a total of 14171 PYFU (incidence rate, 26.96/1000 PYFU; 24.32-29.80). In all patients, the cumulative probability of death within 10 years from the start of HAART was 15.5% (95% CI, 14.2-16.9); the probability significantly differed (log-rank p<0.0001) between therapy-experienced (22.4%; 20.4-24.7) and therapy-naïve patients (11.2%; 9.4-13.4). The risk of an AIDS-defining event occurring within 10 years after the start of HAART was 16.4% (15.3-17.6) and, like mortality, was significantly higher (p<0.0001) in therapy-experienced patients (24.6%; 21.2-28.5) compared with naïve patients (15.4%; 13.7-17.1).

We subsequently restricted our study to 6835 patients who were therapy-naïve when commencing HAART. Baseline characteristics are summarized in Table 7.1. A higher proportion of women, heterosexually infected patients, and patients originating from countries other than the Netherlands started HAART in later calendar years as compared with earlier calendar years (all, p<0.0001). The proportion of hepatitis C virus (HCV)-positive patients was also not equally divided over the 4 time periods (p=0.01). The distribution of hepatitis B virus (HBV) co-infection, age when starting HAART, and HIV RNA levels when starting HAART were not significantly different between calendar years. In the 758 patients of Caribbean/Latin America origin, 252 were from Caribbean countries and 506 from Latin America. The majority of the 585 patients in the Western Europe/North America/Australia group were from Western Europe (481); 88 North American and 16 Australian patients comprised the remainder.

Death

During 16,491 person-years of follow-up, 254 patients died within 3 years of starting HAART. Male gender, a lower baseline CD4 cell count, an HIV RNA level of 100,000 copies/ml or higher at the start of HAART, a CDC-B or CDC-C event prior to the start of HAART, HIV infection through injecting drug use, older age, HBV co-infection, and Dutch origin (as compared to sub-Saharan origin) were significantly associated with a shorter time to death in univariate analyses (Table 7.2). In addition, patients starting HAART in 2002 through 2005 had an increased hazard of death compared with patients starting in 1997 through 2001.

In multivariate analyses of time to death within 3 years after HAART initiation, gender and Dutch origin were no longer significantly associated with an increased risk of death (Table 7.2). Hazard ratios (HR) for death were highest for those starting HAART in calendar years 2002 through 2005. Older age, injecting drug use as the HIV transmission route, and HCV co-infection were all associated with a shorter time to death. Patients initiating HAART with a CD4 cell count of less than 50 cells/mm^3 had a hazard ratio of 2.26 (95% CI 1.47-3.45; p=0.0002) compared to patients with 200 to 350 cells/mm^3. Patients with a CDC-C event at the start of HAART had an HR of

2.33 (1.77-3.07; p<0.0001) compared with a CDC-A or CDC-B event. When the CD4 cell count at the start of HAART was included as a continuous variable, for every 100 cells more, the HR of death within 3 years was 0.78 (0.69-0.88; p<0.0001).

New CDC-C events

During 15,732 person-years of follow-up, at least one new AIDS-defining event developed in 491 patients within 3 years after the start of HAART. The 6 most frequent events were: Kaposi's sarcoma in 67 patients; tuberculosis in 54; oesophageal candidiasis in 52; recurrent pneumonia (more than 1 episode in a 1-year period) in 40; Burkitt's or immunoblastic lymphoma in 40; and toxoplasmosis of the brain in 36. For patients beginning HAART in 2000 or 2001, the unadjusted hazard ratio of a new AIDS-defining event after HAART was started was 1.27 (95% CI, 1.00-1.62; p=0.047) compared with that in 1997 through 1999.

Other baseline characteristics that were univariately associated with a shorter time to a new AIDS-defining event after starting HAART were: a low baseline CD4 cell count; occurrence of a CDC-C event before HAART initiation; co-infection with HBV; and a sub-Saharan African, Western European/North American/Australian, or Caribbean/Latin American country of origin rather than a Dutch origin (Table 7.3). After adjusting for baseline variables, we found that the hazards for a new CDC-C event between different calendar years of the start of HAART were no longer significantly different. 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 event and low CD4 cell count at the initiation of HAART were also independently associated with a shorter time to a new AIDS-defining event.

Short-tem virologic and immunologic response

The immunologic and virologic short-term response to HAART is shown in Table 7.4. In 1996, 70.9% of the patients achieved an HIV RNA level of <500 copies/ml 24 weeks after starting HAART (Table 7.4). This increased to 85.7% for those starting in 1997 through 1999 and slowly increased further for patients who started from 2000 through 2001 (p=0.14 compared to 1997-1999) and from 2002 through 2005 (p<0.0001 compared to 1997-1999). Table 7.5 shows the adjusted odds ratios (OR) for reaching an HIV-RNA of <500 copies/ml after 24 weeks. Apart from a lower OR for patients starting HAART in 1996, there were no differences in the odds of reaching an HIV RNA of <500 copies/ml at week 24 among patients starting HAART in different calendar years. Patients starting HAART that included a single PI were less likely to reach an HIV RNA of <500 copies/ml compared with those including an NNRT (OR, 0.58; 95% CI, 0.45-0.74; p<0.0001). There were no significant differences between patients starting HAART that included an NNRT compared with HAART that included 2 or more PI's. Patients originating from sub-Saharan Africa (p=0.0005) and Caribbean/Latin America (p=0.0003) had a lower OR of reaching an HIV RNA of <500 copies/ml compared with 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 HAART, the OR of patients having less than 4 $\log_{10}$ copies/ml was 0.59 (95% CI, 0.46-0.77; p=0.0001), and the OR of those having 5 $\log_{10}$ copies/ml or more was 0.73 (95% CI, 0.60-0.89; p=0.002). Other variables associated with lower odds of reaching an HIV RNA of less than 500 copies were infection through injecting drug use compared with infection through homosexual contact, younger age, and having a pre-HAART CD4 cell count of 350 or more cells/mm^3.

Median change in CD4 cell count at 24 weeks after the start of HAART in the 5608 patients with a CD4 cell measurement at the start of HAART and at 24 weeks after the start was 130 cells/mm^3 (IQR, 60-210) and was

not significantly different according to the calendar year of starting HAART. However, the median CD4 cell count at 6 months was 364 cells (204-540) for patients starting HAART from 1997 through 1999 and was higher when compared to other years.

In multivariate analyses (Table 7.5), mean changes in CD4 cell count did not significantly differ between calendar years of starting HAART from 1997 onwards. The overall estimated mean change for a homosexually infected reference patient originating from the Netherlands, starting HAART between 1997 and 1999 with a CD4 cell count between 200 and 350 cells/mm^3 and an HIV-RNA between 4 and 5 $\log_{10}$ copies/ml, aged 35 years, without HBV/HCV co-infection, and without a prior CDC-C event was 139 CD4 cells/mm^3 (SD, 18.8). The values in Table 7.5 are changes relative to the mean CD4 cell change of this reference patient. The mean CD4 cell count increase was 30 cells/mm^3 (SD, 6.2) less in female patients compared with that in male patients ($p<0.0001$), 34 cells/mm^3 (SD, 6.7) less in patients from sub-Saharan Africa compared with Dutch patients ($p<0.0001$), and 46 cells/mm^3 (SD, 13.2) less in patients who were infected through injecting drug use compared to patients infected through homosexual contact ($p=0.0004$). Furthermore, CD4 cell increases were less in patients with lower HIV RNA levels when starting HAART, in older patients, in injecting drug users, and in patients with HBV or HCV co-infection. Compared with patients on HAART regimens containing a single NNRT, patients treated with HAART containing 2 or more PI's had a higher mean CD4 cell increase of 17 cells/mm^3 (SD, 5.2, $p=0.0006$), and those treated with HAART containing a PI plus an NNRT had a higher mean increase of 40 cells/mm^3 (SD, 11.8, $p=0.0007$).

Long-term virologic and immunologic response

Out of a total of 6835 patients, we selected 6092 patients who had reached HIV RNA levels of less than 500 copies/ml within 9 months after starting HAART. During 10,812 PYFU, 338 patients experienced viral rebound to 500 or more copies/ml during HAART use within 3 years of the first virologic success, corresponding to an incidence rate of 31.9 per 1000 PYFU. Higher rates were found in female patients, patients originating from Latin America/Caribbean or sub-Saharan African countries compared to the Netherlands, patients starting HAART in earlier calendar years, patients with lower CD4 cell counts and higher HIV RNA concentration at the start of HAART, and younger patients (Table 7.6).

Patients starting HAART in later calendar years remained at a lower risk of viral rebound whilst on HAART in adjusted analyses (Table 7.7); the adjusted relative risk (RR) of starting HAART from 2002 to 2005 compared with that of those starting HAART from 1997 to 1999 was 0.45 (95% CI, 0.35-0.58; $p<0.0001$). Only patients originating from sub-Saharan Africa had a significantly ($p<0.0001$) increased risk of viral rebound compared to patients of Dutch origin (RR, 1.90; 95% CI, 1.49-2.43). The relative risk of patients with a pre-HAART CD4 cell count of less than 50 cells/mm^3 was 1.42 (1.06-1.98) compared with 200 to 350 cells/mm^3 ($p=0.02$). A younger age at the start of HAART and a pre-HAART HIV RNA of less than 4 $\log_{10}$ copies/ml were also associated with a lower risk of viral rebound.

Finally, we studied long-term changes in CD4 cell count from the start of HAART to 7 years thereafter in a subset of 554 patients who had remained on uninterrupted HAART for 7 years. These patients had started HAART between 1 July 1996 and 30 June 1998. Median CD4 cell numbers and changes from baseline are shown in Figure 7.3a. The median CD4 cell count increased from 221 cells/mm^3 (IQR, 80-340) at the start to 607 cells/mm^3 (440-800) after 7 years of HAART. The median CD4 cell count at 7 years was 410 for those with a pre-HAART CD4 cell count less than 50 cells/mm^3, 548 for those with a count of 50 to 200, 660 for a count

of 200 to 350, 780 for a count of 350 to 500, and 870 for those with pre-HAART CD4 cell count of 500 or more cells/mm^3 (Figure 7.3a). Overall, increases were highest in the first months on HAART (median, 136 cells/mm^3 during the first 24 weeks) and levelled off over time (40 cells/mm^3 in weeks 96-144 and 0 cells/mm^3 in weeks 312-360). Median increases in CD4 cell counts after 7 years of HAART were very similar for the 4 pre-HAART CD4 cell count strata below 500 cells/mm^3 (367-410 cells/mm^3), whilst increases were smaller (287 cells/mm^3) for patients in the ≥500 cells/mm^3 stratum, as Figure 7.3b shows (Wilcoxon test p=0.007).

In a mixed effect model, female sex (p=0.002), region of origin (Dutch/European/North American/Australian origin vs. other, p=0.05), an HIV RNA plasma level more than 4.5 $\log_{10}$ copies/ml at the start of HAART compared with less than 4.5 $\log_{10}$ copies/ml (p=0.01) and more than 1300 CD8 cells/mm^3 compared with less than 1300 (p=0.0007) were associated with higher increases in CD4 cell count between the start of HAART and 6 months thereafter, but not after this period. Only older age (≥50 yrs compared with <50, p<0.0001) and periods of viraemia (HIV RNA ≥1000 copies/ml, p<0.0001) were associated with smaller increases in CD4 cell count between 6 months and 7 years after the start of HAART.

Discussion

Our study confirms the results of others, that is, the risk factors of starting HAART with a CD4 cell number <200 cells/mm^3 and a prior CDC-C event are independently associated with a higher probability of progression to AIDS and death. With the exception of the lower pre-HAART CD4 cell count in patients beginning HAART in 1996, who probably delayed starting antiretroviral therapy until effective therapy was available, CD4 cell counts of patients starting HAART in earlier calendar years were higher than those of patients starting later. Overall, more than 50% of patients started HAART with a CD4 cell number <200 cells/mm^3. This indicates that mortality and morbidity rates could improve when more patients are able to start HAART earlier.

We also looked at the effect of HAART on short- and long-term outcomes over the years by comparing outcomes according to the calendar year of starting HAART. A higher percentage of patients reached HIV RNA levels below 500 copies/ml after 24 weeks of HAART from 2002 through 2005 compared to 1997 through 1999, and long-term virologic response was better in patients starting HAART between 2002 and 2005. However, this improved short-term outcome is in contrast to an increased hazard of death within 3 years of starting HAART for patients who began HAART from 2002 through 2005, even after adjusting for confounders. CD4 cell counts at the start of HAART were lower in later calendar years, but the higher mortality rate in patients starting HAART in later calendar years persisted after controlling for pre-HAART CD4 cell count. One of the possible explanations for the effect of the calendar year on mortality is an incomplete registration of HIV-related deaths in the Netherlands before the start of HIV monitoring in 2002. We found that the hazard of death for patients starting HAART from 1997 through 2001 compared with that for patients starting HAART from 2002 through 2005 was only decreased during the first year after starting HAART. This indicates that a number of patients who died shortly after starting HAART might not have been included. Other explanations include residual confounding and a truly increased hazard of death in patients starting HAART in 2002 through 2005. However, if the latter is the case, one would also expect an increased hazard for new AIDS-defining events for patients starting HAART in 2002 through 2005. In our study, we did not find significant differences in hazards of new AIDS-defining events between calendar years.

The improved short- and long-term virologic outcome in later calendar years can be explained by the increased use of drug combinations containing two protease inhibitors and non-nucleoside reverse transcriptase inhibitors. These HAART combinations are better able to suppress viral load compared with combinations that include a single protease inhibitor[54-58]. The lower incidence of viral rebound during HAART use in later calendar years can also be explained by more effective antiretroviral therapy combinations[59, 60]. Apart from more potent therapy, better management of toxicities and adherence[61] also contributes to improved virologic outcome.

A higher proportion of patients from sub-Saharan Africa experienced a new AIDS-defining event after starting HAART. Moreover, these patients showed a diminished virologic response after 24 weeks and had smaller gains in CD4 cell count. Viral RNA rebound to above 500 copies/ml after virologic success was more frequent amongst the sub-Saharan African patients. Poorer virologic response by non-indigenous patients in the Netherlands has been previously reported[62]. This may be the result of poorer adherence. Therefore, a closer follow-up of sub-Saharan African patients may improve the virologic response. A lower virologic response was also found more frequently in patients starting HAART with a high pre-HAART CD4 cell count, and again, this might be related to adherence. Feeling healthy is a reason for not taking medication[52, 63, 64]. Keeping HIV RNA levels <500 copies/ml is important, since higher levels are strongly associated with less restoration of CD4 cells in patients on uninterrupted HAART(65) and with progression of disease[66, 67].

A good virologic response is more frequent amongst older patients than younger patients, both in the short- and long-term. Again, differences in adherence may play a role. However, older patients experience smaller gains in CD4 cell count 24 weeks after starting HAART, and patients on uninterrupted HAART who are aged 50 years or more at the start of HAART also have smaller gains between 24 weeks and 7 years compared with those who are aged less than 50 years. A larger CD4 cell gain in treated patients has previously been associated with younger age[68, 69], and a smaller gain has been attributed to lower thymic function with older age[70, 71]. Because patients with higher CD4 cell counts (also at levels above ≥200 cells/mm^3) have a lower risk of the development of new AIDS events[72], it may be appropriate to start antiretroviral therapy earlier in older patients than in younger patients.

HCV co-infection is associated with a significantly shorter time to death. The risk of a new CDC-C event after starting HAART was also increased in HCV co-infected patients, but this failed to reach statistical significance. Increases in CD4 cell counts during the first few months after the start of HAART are smaller in HCV co-infected patients. Other studies have found an increased mortality in patients co-infected with HCV[73-75], although conflicting results have been reported[76, 77].

In contrast to results reported by the EuroSIDA study[20], we have not found a significantly increased risk of mortality from all causes in patients co-infected with HBV in univariate or multivariate analyses. Although the mean change in CD4 cell count at 6 months after the start of HAART is 19 cells/mm^3 lower in patients co-infected with HBV, there is no effect of either HCV or HBV co-infection on long-term CD4 cell counts. However, since the analysis of long-term CD4 cell changes was restricted to 554 patients who had been on uninterrupted HAART for 7 years, the lack of an effect may also be due to small sample size.

In conclusion, patients starting HAART with CD4 cell counts less than 200 cells/mm^3 have a higher probability of progression of disease or death compared to patients

with ≥200 cells/mm^3 or more. Since the widespread introduction of HAART in 1996, new HAART combinations have been introduced that induce a more effective suppression of HIV RNA plasma levels than early HAART combinations, but this has not translated into improved survival or morbidity rates.

		Year of starting HAART								Total	
		1996		1997-1999		2000-2001		2002-2005			
		N	%	N	%	N	%	N	%	N	%
Total		**354**		**2067**		**1362**		**3052**		**6835**	
Gender	Male	305	86.2	1694	82.0	993	72.9	2133	69.9	5125	75.0
Transmission risk group	Homosexual	235	66.4	1176	56.9	617	45.3	1306	42.8	3334	48.8
	IDU	15	4.2	119	5.8	57	4.2	80	2.6	271	4.0
	Heterosexual	65	18.4	612	29.6	576	42.3	1392	45.6	2645	38.7
	Other	39	11.0	160	7.7	112	8.2	274	9.0	585	8.6
Region of origin	Netherlands	254	71.8	1284	62.1	646	47.4	1445	47.3	3629	53.1
	Western Europe/North America/Australia	36	10.2	217	10.5	118	8.7	214	7.0	585	8.6
	Caribbean/Latin America	17	4.8	208	10.1	164	12.0	369	12.1	758	11.1
	Other	8	2.3	47	2.3	32	2.3	84	2.8	171	2.5
	Sub-Saharan Africa	30	8.5	253	12.2	349	25.6	831	27.2	1463	21.4
	Southeast Asia	9	2.5	58	2.8	53	3.9	109	3.6	229	3.4
Clinical stage	CDC-A, B	242	68.4	1502	72.7	983	72.1	2193	71.9	4920	71.9
	CDC-C	112	31.6	565	27.3	379	27.8	859	28.1	1915	28.0
HBV	-	281	79.4	1730	83.7	1092	80.2	2521	82.6	5624	82.3
	+	20	5.6	147	7.1	90	6.6	212	6.9	469	6.9
	Unknown	53	15.0	190	9.2	180	13.2	319	10.5	742	10.9
HCV	-	143	66.5	1326	76.9	892	77.7	2028	76.5	4389	76.5
	+	22	10.2	146	8.5	103	9.0	173	6.5	444	7.7
	Unknown	50	23.3	253	14.7	153	13.3	451	17.0	907	15.
Starting combination	Single PI	344	97.2	1293	62.6	261	19.2	229	7.5	2127	31.1
	≥2 PI*	7	2.0	475	23.0	387	28.4	973	31.8	1824	26.7
	NNRT	2	0.6	269	13.0	566	41.2	1594	52.2	2431	35.6
	PI + NNRT	1	0.3	29	1.4	56	4.1	125	4.1	211	3.1
	≥3 NRT			1	0.1	92	6.8	131	4.3	224	3.3
		Med	**IQR**	**Med**	**IQR**	**Med**	**IQR**	**Med**	**IQR**	**Med**	**IQR**
Age at starting HAART		36.5	32.1-43.0	37.1	32.1-44.3	37.3	31.1-44.1	37.6	31.2-44.5	37.3	31.5-44.4
CD4 cell count at starting HAART (cells/mm^3)		220	95-330	230	80-380	180	70-314	180	80-280	198	80-320
HIV-RNA at starting HAART (log_{10} cps/ml)		4.9	4.4-5.4	5.0	4.4-5.4	5.0	4.5-5.4	5.0	4.5-5.3	5.0	4.5-5.4

Table 7.1: Baseline characteristics of 6835 therapy-naïve patients starting HAART between 1 July 1996 and 31 December 2005. IDU: injecting drug use; HBV: hepatitis B virus; HCV: hepatitis C virus; PI: protease inhibitor; NNRT: non-nucleoside reverse transcriptase; NRT: nucleoside RT; med: median; IQR: interquartile range; *Lopinavir boosted with ritonavir is included in the ≥ 2 PI group.

		Univariate			Multivariate		
		HR	95% CI	p-value	HR	95% CI	p-value
Gender	Male	1.00			1.00		
	Female	0.63	0.46-0.88	0.007	0.71	0.49-1.04	0.08
Region of origin	Netherlands	1.00					
	Caribbean/Latin America	0.70	0.45-1.09	0.11			
	Western Europe/North America/ Australia	1.09	0.73-1.65	0.67			
	Sub-Saharan Africa	0.56	0.38-0.81	0.002			
	Other	1.58	0.86-2.91	0.14			
	Southeast Asia	0.42	0.15-1.13	0.08			
Calendar year of starting HAART	1996	1.57	0.95-2.61	0.08	1.22	0.72-2.05	0.46
	1997-1999	1.00			1.00		
	2000-2001	0.91	0.62-1.33	0.62	0.90	0.61-1.32	0.58
	2002-2005	1.63	1.21-2.19	0.0012	1.58	1.17-2.14	0.003
CD4 cell count at starting HAART (cells/mm^3)	<50	3.91	2.65-5.78	<0.0001	2.26	1.47-3.45	0.0002
	50-200	1.92	1.29-2.85	0.001	1.45	0.97-2.17	0.07
	200-350	1.00			1.00		
	350-500	0.74	0.39-1.43	0.37	0.90	0.47-1.73	0.74
	≥500	0.52	0.22-1.24	0.14	0.75	0.32-1.80	0.53
	missing	2.69	1.70-4.25	<0.0001	1.42	0.85-2.39	0.18
Transmission risk group	Homosexual	1.00			1.00		
	IDU	2.79	1.62-4.78	0.0002	2.25	1.27-4.00	0.005
	Heterosexual	1.11	0.79-1.55	0.55	1.25	0.90-1.74	0.18
	Other	2.03	1.28-3.24	0.003	1.64	1.12-2.40	0.01
HIV-RNA at starting HAART (log_{10} cps/ml)	<4	0.70	0.37-1.30	0.26	0.81	0.43-1.52	0.50
	4-5	1.00			1.00		
	≥5	1.87	1.35-2.59	0.0002	1.27	0.91-1.77	0.16
	missing	2.98	2.06-4.31	<0.0001	2.01	1.32-3.07	0.001
Age at starting HAART (per year increase)		1.05	1.04-1.06	<0.0001	1.04	1.03-1.05	<0.0001
Clinical stage	CDC-A / B	1.00			1.00		
	CDC-C	3.66	2.85-4.68	<0.0001	2.33	1.77-3.07	<0.0001
HCV	-	1.00			1.00		
	+	2.46	1.73-3.50	<0.0001	2.00	1.26-3.17	0.003
	unknown	1.94	1.45-2.59	<0.0001	1.72	1.28-2.31	0.0003
HBV	-	1.00					
	+	1.15	0.71-1.86	0.58			
	unknown	2.02	1.48-2.77	<0.0001			

Table 7.2: Univariate and multivariate hazard ratios (HR) and 95% confidence intervals (CI) of time to death within 3 years after starting HAART. IDU: injecting drug use; HCV: hepatitis C virus; HBV: hepatitis B virus

		Univariate			Multivariate		
		HR	95% CI	p-value	HR	95% CI	p-value
Gender	Male	1.00					
	Female	0.93	0.76-1.15	0.51			
Region of origin	Netherlands	1.00			1.00		
	Caribbean/Latin America	1.60	1.23-2.08	0.0005	1.56	1.19-2.05	0.001
	Western Europe/North America/Australia	1.42	1.05-1.93	0.02	1.40	1.03-1.90	0.03
	Sub-Saharan Africa	1.31	1.05-1.65	0.02	1.38	1.08-1.77	0.01
	Other	1.29	0.74-2.25	0.37	1.20	0.68-2.11	0.53
	Southeast Asia	1.07	0.64-1.81	0.79	0.92	0.54-1.57	0.77
Calendar year of starting HAART	1996	1.31	0.90-1.91	0.16	1.30	0.89-1.90	0.17
	1997-1999	1.00			1.00		
	2000-2001	1.27	1.00-1.62	0.048	1.19	0.93-1.52	0.16
	2002-2005	1.12	0.90-1.39	0.31	1.08	0.86-1.35	0.51
CD4 cell count at starting HAART (cells/mm^3)	<50	4.35	3.27-5.78	<0.0001	2.73	2.01-3.72	<0.0001
	50-200	2.06	1.55-2.75	<0.0001	1.66	1.24-2.22	0.0007
	200-350	1.00			1.00		
	350-500	0.60	0.36-1.01	0.055	0.65	0.39-1.10	0.11
	≥500	1.09	0.68-1.75	0.73	1.22	0.76-1.97	0.40
	missing	2.69	1.91-3.77	<0.0001	2.08	1.47-2.95	<0.0001
Transmission risk group	Homosexual	1.00					
	IDU	1.48	0.99-2.23	0.058			
	Heterosexual	1.21	0.99-1.46	0.058			
	Other	1.47	1.09-2.00	0.01			
HIV-RNA at starting HAART (log_{10} cps/ml	<4	0.85	0.58-1.25	0.42			
	4-5	1.00					
	≥5	1.58	1.27-1.97	<0.0001			
	missing	2.04	1.56-2.68	<0.0001			
Age at starting HAART (per year increase)		1.01	1.00-1.02	0.0236	1.01	1.00-1.02	0.09
Clinical stage	CDC-A / B	1.00			1.00		
	CDC-C	2.99	2.50-3.57	<0.0001	1.54	1.38-1.72	<0.0001
HCV	-	1.00			1.00		
	+	1.20	0.87-1.64	0.26	1.31	0.95-1.80	0.0939
	unknown	1.25	1.00-1.56	0.051	1.13	0.87-1.47	0.3565
HBV	-	1.00			1.00		
	+	1.39	1.02-1.90	0.04	1.30	0.95-1.78	0.1027
	unknown	1.39	1.07-1.80	0.01	1.25	0.93-1.70	0.1426

Table 7.3: Univariate and multivariate hazard ratios (HR) of time to a new AIDS-defining event within 3 years of starting HAART. CI: confidence interval; IDU: injecting drug use; HCV: hepatitis C virus; HBV; hepatitis B virus

	Patients with HIV-RNA measurements*	Patients (%) with HIV-RNA<500 cps/ml at week 24	Patients with CD4 cell measurements*	Median (IQR) CD4 cell count at week 24 (cells/mm³)	Median (IQR) change in CD4 cell count (cells/mm³)
1996	203	144 (70.9)	276	330 (209-466)	117 (50 210)
1997-1999	1704	1461 (85.7)	1695	364 (204-540)	130 (59 220)
2000-2001	1175	1030 (87.7)	1126	310 (190-480)	120 (60 220)
2002-2005	2602	2335 (89.7)	2511	320 (200-460)	130 (60 210)
Total	**5684**	**4970 (87.4)**	**5608**	**330 (200-487)**	**130 (60-210)**

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

Table 7.4: Immunological and virological marker responses to treatment at 24 weeks after the start of HAART.

		HIV-RNA <500 copies/ml			Change in CD4 cell count		
		OR	95% CI	p-value	cells/mm³	SD*	p-value
Gender	Male				0.00		
	Female				30.1	6.2	<0.0001
Region of origin	Netherlands	1.00			0.00		
	Caribbean/Latin America	0.60	0.46-0.79	0.0003	-12.9	7.1	0.07
	Western Europe/North America/Australia	1.00	0.72-1.40	0.99	-11.5	7.6	0.13
	Sub-Saharan Africa	0.63	0.49-0.82	0.0005	-33.9	6.7	<0.0001
	Other	0.59	0.37-0.94	0.03	1.8	13.3	0.89
	Southeast Asia	0.83	0.52-1.32	0.44	-19.6	11.2	0.08
Calendar year of starting HAART	1996	0.43	0.31-0.62	<0.0001	-23.3	10.1	0.02
	1997-1999	1.00			0.0	.	.
	2000-2001	1.11	0.86-1.42	0.42	-2.3	6.4	0.72
	2002-2005	1.22	0.97-1.54	0.09	-5.7	5.9	0.33
CD4 cell count at starting HAART (cells/mm³)	<50	1.00	0.76-1.32	0.98	-37.9	6.3	<0.0001
	50-200	1.05	0.83-1.31	0.69	-11.6	5.1	0.02
	200-350	1.00			0.0	.	.
	350-500	0.74	0.56-0.97	0.03	-8.7	6.9	0.20
	≥500	0.69	0.51-0.93	0.02	-60.7	7.9	<0.0001
	missing	0.58	0.41-0.82	0.002			
	Homosexual	1.00			0.00		
	IDU	0.34	0.21-0.56	<0.0001	-46.2	13.2	0.0004
Transmission risk group	Heterosexual	0.80	0.64-0.99	0.04	-16.1	6.1	0.009
	Other	0.97	0.69-1.36	0.84	1.3	8.0	0.88

Table 7.5: Probability of reaching HIV-RNA plasma level < 500 cps/ml and change in CD4 cell count at 24 weeks of HAART. *SD: standard deviation; OR: odds ratio; CI: confidence interval; IDU: injecting drug use; HBV: hepatitis B virus; HCV: hepatitis C virus; PI: protease inhibitor; NNRT: non-nucleoside reverse transcriptase; NRT: nucleoside RT

		HIV-RNA <500 copies/ml			Change in CD4 cell count		
		OR	95% CI	p-value	cells/mm³	SD*	p-value
HIV-RNA at starting	<4	0.59	0.46-0.77	0.0001	-25.2	6.9	0.0003
HAART (log_{10} cps/ml	4-5	1.00			0.00		
	≥5	0.73	0.60-0.89	0.002	23.7	4.6	<0.0001
	missing				5.4	8.6	0.53
Age at starting HAART (per 5 year increase)		1.11	1.05-1.16	0.0001	-4.8	1.1	<0.0001
HCV	-	1.00			0.00		
	+	1.47	0.97-2.21	0.07	-19.9	9.3	0.03
HBV	-				0.00		
	+				-17.1	7.8	0.03
Starting combination	Single PI	0.58	0.45-0.74	<0.0001	9.0	6.3	0.15
	≥ 2 PI	0.88	0.70-1.11	0.28	17.7	5.2	0.0006
	NNRT	1.00			0.0		
	PI + NNRT	1.33	0.75-2.37	0.33	40.3	11.8	0.0007
	≥ 3 NRT	0.68	0.43-1.07	0.0975	7.8	11.6	0.50

Table 7.5: (continued)

		No of PYFU on HAART	No of viral rebounds >500 cps/ml	Incidence rate/1000 PYFU
Total		**12169.03**	**388**	**31.9 (28.8-35.2)**
Gender	Male	9595.08	292	30.4 (27.0-34.1)
	Female	2573.96	96	37.3 (30.2-45.5)
Region of origin	Netherlands	7119.06	193	27.1 (23.4-31.2)
	Caribbean/Latin America	1176.98	41	34.8 (25.0-47.3)
	Western	984.76	24	24.4 (15.6-36.3)
	Sub-Saharan Africa	2182.28	111	50.9 (41.8-61.3)
	Other	274.25	10	36.5 (17.5-67.1)
	South-East Asia	431.71	9	20.8 (9.5-39.6)
Calendar year of starting HAART	1996	496.24	24	48.4 (31.0-72.0)
	1997-1999	4537.17	174	38.3 (32.9-44.5)
	2000-2001	3040.86	110	36.2 (29.7-43.6)
	2002-2005	4094.76	80	19.5 (15.5-24.3)

Table 7.6: Incidence of viral rebound on HAART (2 consecutive HIV-RNA measurements >500 cps/ml) in 5304 patients with previous virological success (2 consecutive HIV-RNA measurements <500 cps/ml) within 9 months of starting HAART. PYFU: person-years of follow-up; HCV: hepatitis C virus; HBV: hepatitis B virus

		No of PYFU on HAART	No of viral rebounds >500 cps/ml	Incidence rate/1000 PYFU
Transmission risk group	<50	2031.01	80	39.4 (31.2-49.0)
	50-200	3858.17	127	32.9 (27.4-39.2)
	200-350	3260.78	86	26.4 (21.1-32.6)
	350-500	1418.78	45	31.7 (23.1-42.4)
	≥500	887.39	28	31.6 (21.0-45.6)
Age at starting HAART	Homosexual	6563.04	192	29.3 (25.3-33.7)
	IDU	398.44	10	25.1 (12.0-46.2)
	Heterosexual	4263.96	151	35.4 (30.0-41.5)
	Other	943.58	35	37.1 (25.8-51.6)
	<25	625.28	38	60.8 (43.0-83.4)
	25-30	1435.98	54	37.6 (28.2-49.1)
	30-35	2434.02	95	39.0 (31.6-47.7)
	35-40	2737.54	73	26.7 (20.9-33.5)
	40-45	1954.05	53	27.1 (20.3-35.5)
	45-50	1252.13	41	32.7 (23.5-44.4)
	50-55	867.31	18	20.8 (12.3-32.8)
	>55	862.72	16	18.5 (10.6-30.1)
HIV-RNA at starting	<4	1124.82	26	23.1 (15.1-33.9)
HAART (log_{10} cps/ml)	4-5	4318.05	136	31.5 (26.4-37.3)
	≥5	5667.64	185	32.6 (28.1-37.7)
	missing	1058.52	41	38.7 (27.8-52.5)
	>55	862.72	16	18.5 (10.6-30.1)
Clinical stage at	CDC-A, B	8750.2	264	30.2 (26.6-34.0)
starting HAART	CDC-C	3418.83	124	36.3 (30.2-43.2)
HCV	-	9367.75	298	31.8 (28.3-35.6)
	+	866.88	21	24.2 (15.0-37.0)
	Not available	1934.41	69	35.7 (27.8-45.1)
HBV	-	10106.57	317	31.4 (28.0-35.0)
	+	851.79	32	37.6 (25.7-53.0)
	Not available	1210.67	39	32.2 (22.9-44.0)

Table 7.6: (continued)

		RR*	95% CI**	p-value
Region of origin	Netherlands			
	Caribbean/Latin America	1.27	0.92-1.75	0.1538
	Western Europe/North America/Australia	0.87	0.58-1.29	0.4814
	Sub-Saharan Africa	1.90	1.49-2.43	<0.0001
	Other	1.31	0.72-2.38	0.3843
	South-East Asia	0.73	0.39-1.37	0.3239
Calendar year of starting HAART	1996	1.30	0.86-1.97	0.2133
	1997-1999	1.00		
	2000-2001	0.84	0.67-1.06	0.1362
	2002-2005	0.45	0.35-0.58	<0.0001
CD4 cell count at starting HAART (cells/mm^3)	<50	1.42	1.06-1.90	0.0196
	50-200	1.24	0.96-1.61	0.1007
	200-350	1.00		
	350-500	1.19	0.84-1.67	0.3234
	≥500	1.21	0.81-1.81	0.3530
	Missing	0.93	0.57-1.51	0.7579
Age at starting HAART (per 5 yr increase)		0.90	0.86-0.95	0.0003
HIV RNA at starting HAART (log_{10} copies/ml)	<4	0.67	0.45-0.99	0.0451
	4-5	1.00		
	≥5	1.08	0.87-1.34	0.4632
	missing	1.30	0.90-1.89	0.1609

Table 7.7: Adjusted relative risk of viral rebound on HAART. *RR: relative risk; CI: confidence interval

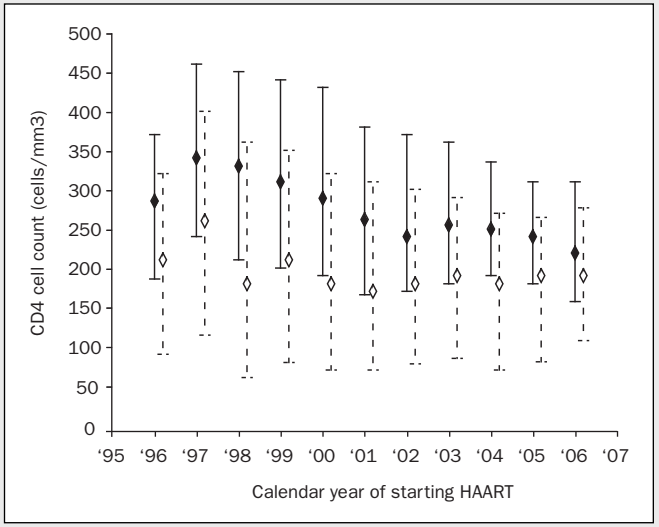
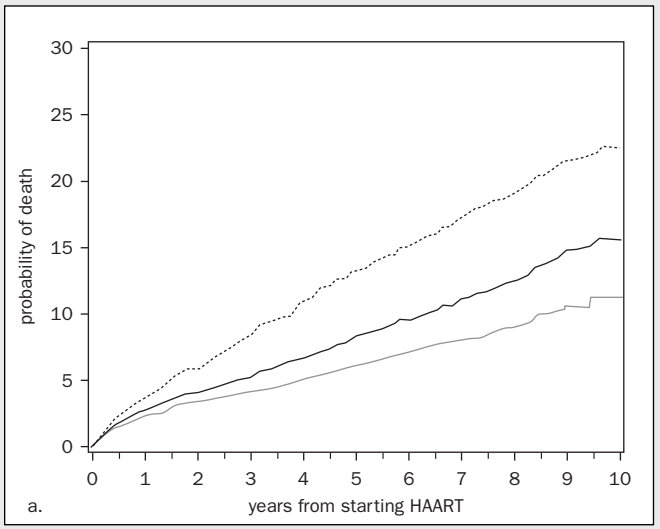


Figure 7.1: Median (IQR) CD4 cell counts at the start of HAART in 2188 asymptomatic, therapy-naïve patients with HIV RNA <100,000 copies/ml (solid lines) and in all 6334 therapy-naïve patients (dashed lines).



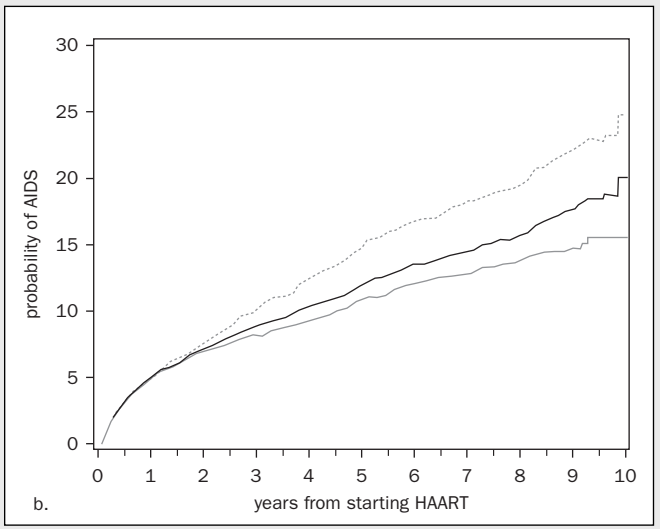
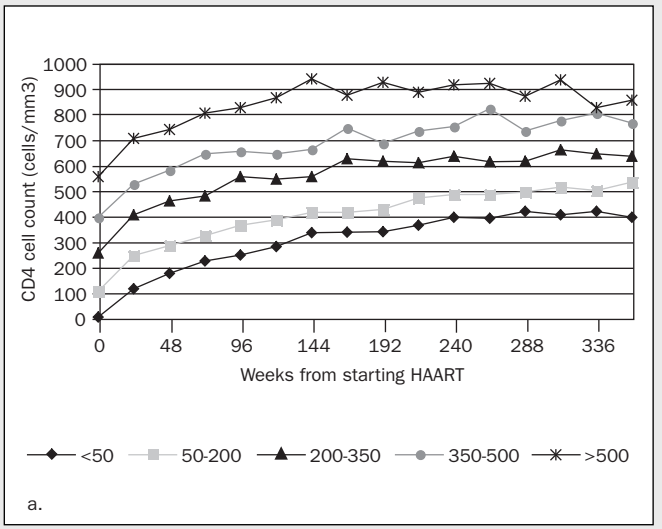


Figure 7.2a and b: Kaplan-Meier destinaties (95% CI) of the probability of death (a) and onset of AIDS (b) for 8884 patients starting HAART between 1 July 1996 and 31 December 2005 (black line) subdivided into pre-treated patients (dashed grey line) and therapie-naïve patients (solid grey line).



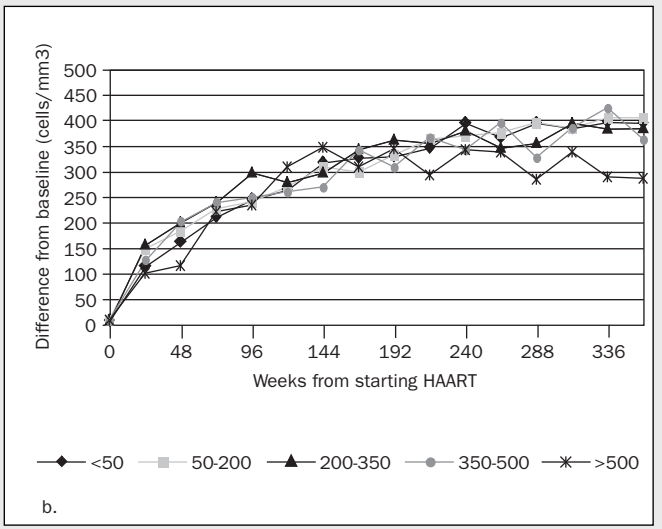


Figure 7.3a and b: Median CD4 cell count (a) and median difference between current CD4 cell count and pre-HAART CD4 count (b), according to 5 pre-HAART CD4 cell strata in 554 patients starting HAART between 1 July 1996 and 30 June 1998 and remaining on uninterrupted HAART for 7 years.

TOXI

TEN YEARS **HAART**

icity

Improved toxicity profile of recent HAART regimens

Luuk Gras

Introduction

Progression to AIDS and death among HIV-infected patients has substantially slowed since the introduction of highly active antiretroviral therapy (HAART)[21, 24, 78]. However, so far, continuous and lifelong HAART is needed because the combination of drugs from different classes that are currently in use do not eradicate HIV from the body[79]. Patients may suffer from adverse events and clinical manifestations owing to the toxic effect of antiviral drugs on cells and cell metabolism[80, 81]. In addition, these adverse events and toxic responses can reduce quality of life[81, 82], especially in patients who are treated at an early, asymptomatic stage of infection. Furthermore, adverse events and toxicity may result in poorer adherence by patients or even discontinuation of treatment, causing suboptimal drug levels and possibly treatment failure[83, 84] and resistance[44].

We investigated the incidence of toxicity-driven therapy changes longitudinally in the ATHENA cohort and compared differences in the time to the first toxicity-driven regimen change between frequently used HAART combinations.

Methods

A selection of 6835 patients from the ATHENA observation cohort were included. The characteristics of this study population are described in Chapter 7. Five time periods after starting HAART were identified (0-3, 3-6, 6-12, 12-24, and 24-36 months). For each period, the number of toxicity-driven changes in the HAART regimen and the person-years on antiretroviral drugs (PYART) were calculated. Thus, more than 1 toxicity-driven regimen per patient per period was allowed. Follow-up of the patient was censored at the date of death or at the last outpatient clinical visit, CD4 cell count, or HIV RNA measurement, whichever came first. The incidence of toxicity-driven regimen changes was calculated as the total number of these changes divided by the total PYART in a period or in a particular patient group. The adverse events associated with the discontinued drugs were tabulated.

We then studied differences between various drug combinations for starting HAART and time to the first toxicity-driven therapy switch. We selected patients starting HAART between 1 January 2000 and 31 December 2005 who started with LOP/r, NVP, or EFV, combined with either AZT+3TC or TDF/3TC, the 2 recently most frequently used nucleoside reverse transcriptase inhibitor (NRTi) backbones. Time to interruption because to toxicity of any of the drugs in the initial HAART combination was the endpoint for analysis. Time was censored if any of the drugs was stopped for any reason other than toxicity, at the date of death, or at the end of follow-up, whichever came first. Since the stopping of any drug at the request of the patient might also be related to toxicity, we performed sensitivity analyses with either a toxicity-driven drug stop or a stop on the patient's request as the endpoint.

Recently, statistical methodology has been developed with the aim of replicating the findings of a randomized clinical trial (RCT) with observational data[85, 86]. We applied one of these methods, marginal structural models (MSM), by fitting inverse probability of treatment weighting (IPTW) estimates, and we compared these with estimates obtained through standard analyses.

Statistical analyses

A Poisson regression model was used for the analysis of the number of toxicity-driven therapy changes during the first 3 years after starting HAART. A first-order autoregressive correlation structure was used to account for serial toxicity-driven regimen changes per patient.

Cox proportional hazards (PH) regression and Kaplan-Meier estimates were used to model the time to first toxicity-driven change in the initial HAART regimen.

IPTW weights were obtained by modelling the probability of starting with EFV in a logistic regression model that included possible confounders (CD4 cell count and HIV RNA at the start of HAART, gender, age at starting HAART, transmission risk group, region of origin, calendar year of starting HAART, hepatitis B virus [HBV] or hepatitis C virus [HCV] co-infection, and clinical stage at the start of HAART). Patients were assigned weights inversely proportional to their probability of starting on the observed non-nucleoside reverse transcriptase inhibitor (NNRT) (either NVP or EFV). This adjusts for non-random treatment allocation. For example, female patients were less likely to start HAART on a regimen that included EFV. Women who started with EFV were thus assigned higher weights. The causal effect of starting with AZT+3TC and EFV compared to NVP was finally estimated by weighted Cox proportional hazards regression of time to toxicity-driven regimen change.

Variables included in multivariate models with a significance level of ≥0.20 were excluded from the final model.

Results

Incidence of toxicity-driven regimen change during the first 3 years after starting HAART

Baseline characteristics of the 6835 patients are shown in Table 7.1 of Chapter 7. In short, a higher proportion of women, heterosexually infected patients, and patients originating from countries other than the Netherlands started HAART in later calendar years compared with earlier calendar years (all, p<0.0001). Between 1997 and 1999, median CD4 cell numbers at the start of HAART were higher than between 2000 and 2001 and between 2002 and 2005 (both, p<0.0001). The use of a single protease inhibitor (PI) in the HAART combination declined from 97.2% in the patients starting in 1996 to 7.5% in the patients starting between 2002 and 2005. The majority (52.2%) of the patients starting between 2002 and 2005 did so with an NNRT-based combination.

During the first 3 years after starting HAART, patients were followed for a total of 16,491 person-years; of those, 14,858 person-years (90.1%) included therapy with antiretroviral drugs. The overall incidence of toxicity-driven regimen changes was 23.6 (95% CI, 22.8-24.4) per 100 PYART. Patients could change the regimen more than once in a period. During follow-up, 4478 of the patients (65.5%) did not change the regimen because of toxicity. The maximum number of changes because of toxicity in a single patient was 14. The incidence was highest (67.7 per 100 PYART) during the first 3 months after starting HAART; it declined to 29.5 per 100 PYART between 3 and 6 months and further declined to 13.1 per 100 PYART between 24 and 36 months after the start of HAART (p<0.0001; Table 8.1). The incidence of toxicity-driven changes was slightly lower in patients starting in 2002 through 2005 (22.5 per 100 PYART) compared to that in patients starting in 1997 through 1999 (24.6; p=0.11). Furthermore, the incidence of changes because of toxicity was 27.8 per 100 PYART among female patients compared to 22.5 in male patients (p<0.0001) and was higher in those starting with a CD4 cell count ≥500 cells/mm^3 compared to those starting with 200-350 cells/mm^3 (29.3 per 100 PYART vs. 23.0; p=0.006). The incidence of toxicity-driven regimen changes increased with older age at the start of HAART (p=0.004 for every year older). Finally, the incidence was lower in patients originating from sub-Saharan Africa compared to patients from Europe/North-America/Australia (p=0.02) and higher in patients who had a CDC-C event at the start of HAART (p=0.01).

Table 8.2 shows the estimated relative risks obtained through multivariate Poisson regression models. The adjusted risk of a toxicity-driven regimen change between 3 and 6 months after starting HAART was 0.43 (95% CI,

0.38-0.48; p<0.0001) times lower than the risk of a change between 0 and 3 months, and it decreased further with increasing time on HAART. The risk of female patients was 1.55 (95% CI, 1.40-1.72; p<0.0001) times higher than that of male patients. Patients starting HAART in 2002 through 2005 had a 0.77 (0.73-0.83, p<0.0001) times lower risk compared to those starting between 1997 and 1999. Finally, the risk of a toxicity-driven therapy change was 0.80 (95% CI, 0.72-0.88; p=0.0002) times lower in patients infected through heterosexual transmission compared to that in those infected through homosexual transmission; in addition, it was 1.24 (1.08-1.41; p=0.01) times higher in patients with pre-HAART CD4 cell count ≥500 cells/mm^3 compared to those with 200-350 cells/mm^3; 0.81 (0.71-0.92; p=0.007) times lower in patients with a pre-HAART HIV RNA <4 $\log_{10}$ copies/ml compared to that in patients with 4-5 $\log_{10}$ copies/ml; 1.16 (1.07-1.25; p=0.0003) times higher in patients with a prior CDC-C event; and 1.04 (1.03-1.06; p=0.0001) times higher for every 5 years of older age at the start of HAART. There was no significant association of HBV or HCV co-infection with the risk of toxicity-driven therapy change. We also did not find evidence of interaction between the calendar year of starting HAART and pre-HAART CD4 cell count, HIV RNA, or CDC staging of the disease on the incidence of toxicity-driven regimen change.

Time to first toxicity-driven regimen change

In total, clinical and demographic characteristics of 2345 patients starting HAART between 1 January 2000 and 31 December 2005 with a regimen that included either LOP/r, NVP, or EFV in combination with either AZT/3TC or TDF/3TC are listed in Table 8.3. Since this was not a randomized study, baseline characteristics were not equally distributed between patients starting HAART that included LOP/r, EFV, or NVP. A lower proportion of women started on regimens including LOP/r. Patients starting LOP/r had more advanced disease, higher pre-HAART HIV RNA levels, lower pre-HAART CD4 cell counts, and more often had a CDC-C diagnosis at the start of HAART.

In total, 1308 patients (55.8%) stopped one of the antiretroviral drugs within the first 3 years after starting HAART; 671 (28.6%) did so because of toxicity or at their own request, and 544 (23.2%) because of toxicity only. Figure 8.1 shows the Kaplan-Meier estimates of the probability of change in the regimen and is further subdivided into toxicity-driven change and the combined endpoint of toxicity-driven change or change at the request of the patient. Six months after starting HAART, 30.7% (95% CI, 28.8-32.6) of the patients had stopped at least 1 of the drugs included in the starting combination; at 12 months, the number increased to 43.1% (41.0-457.2), and at 5 years it had risen to 72.6% (69.7-75.3). A toxicity-driven change within six months was recorded in 17.4% (15.9-19.1) of the patients, within 12 months in 22.0% (20.2-23.9), and at five years in 35.4% (32.0-39.0). If changes in the regimen at the patient's request were also included, these percentages were slightly higher: 19.9% (18.3-21.7) within 6 months, 26.0 (24.1-28.0) within 12 months, and 43.5% (39.9-47.2) within 5 years.

Since there was evidence of interaction of the NRTi backbone combination and the PI/NNRT addition with time to toxicity-driven regimen change, we included regimens in the model instead of modelling the NRT and PI/NNRT component separately (Table 8.4). The hazard of a toxicity-driven therapy change of patients starting with TDF/3TC/NVP was significantly lower compared with all other regimens, HR 0.34 (95% CI, 0.19-0.60; p=0.0002), compared to AZT/3TC/NVP. Patients starting on TDF/3TC/EFV were also at a significantly lower risk of a toxicity-driven therapy change compared to AZT/3TC/NVP (p=0.008), AZT/3TC/EFV (p=0.0002), AZT/3TC/LOP/r (p=0.004), but not to TDF/3TC/LOP/r (p=0.33). The regimens including

LOP/r or AZT/3TC were not significantly different from each other.

Other patient characteristics associated with a shorter time to toxicity-driven therapy change were female gender (p=0.004), older age (p=0.04), and having had a prior CDC-B event (p=0.04) or a CDC-C event (p= 0.004). After adjusting for these factors, we also found a significant effect of calendar year of starting HAART on toxicity-driven regimen change. Patients starting in 2003 and 2004 had a shorter time to regimen change owing to toxicity compared to those starting in 2001, HR 1.35 (95% CI, 1.01-1.81; p=0.04) and 1.47 (1.09-1.98; p=0.01), respectively. When type of regimen was not included in the model, the effect of calendar year of starting HAART was not significant.

Table 8.5 shows the most frequently recorded reason for stopping at least 1 of the drugs in the initial HAART regimen. The adverse events are listed according to the discontinued drug(s), which were AZT, 3TC, TDF, LOP/r, NVP, or EFV. Since adverse events were not linked to specific drugs, adverse events listed in a specific column might not be related directly to the drug, but instead to another drug discontinued at the same time. Drugs discontinued by 66 patients (12%) out of the total of 544 patients who changed the initial HAART regimen because of adverse events could not be linked with specific adverse events. Neurologic/psychiatric events were the most frequently reported adverse events in patients who stopped EFV because of toxicity (41%). Dizziness was the most frequently reported type of neurologic event, and it was reported in 14.2% of the patients who stopped EFV because of toxicity. Gastrointestinal adverse events were the most frequently reported adverse events in those who discontinued LOP/r for toxicity-related reasons, with diarrhoea developing in 32.2% of the patients. Haematologic adverse events were reported in 42% of the patients who stopped AZT, with anemia occurring in 30.6%. Dermatologic adverse events were reported in 47.9% of the patients who discontinued NVP because of toxicity and in 33.3% of those who discontinued TDF for the same reason. Rash was the most frequently reported type of dermatologic event; it developed in 41.1% of those stopping NVP and in 20.8% who stopped TDF. In the patients who discontinued 3TC, dermatologic (28.4%) and gastrointestinal (30.5%) events were most frequently reported.

We then used a marginal structural model as a sensitivity analysis to investigate causal estimates for the time to first toxicity-driven therapy change. In total, 1094 patients were included; 460 of those started with AZT+3TC+EFV and 634 with AZT+3TC+NVP. Table 8.6 shows the results from 3 different models. The unadjusted estimates from the standard Cox regression model showed that patients starting with EFV had a significantly shorter time to toxicity-driven regimen change compared to those starting with NVP, HR 1.28 (95% CI, 1.02-1.60). However, in adjusted models and with marginal structural models, the difference in hazards between patients starting HAART that included EFV and NVP were no longer significant.

Discussion

Toxicity is the most frequently registered reason for interrupting or stopping treatment with certain antiretroviral drugs in a HAART regimen. The incidence of toxicity-driven changes was highest in the first 3 months after the start of HAART and was significantly less amongst patients starting HAART between 2002 and 2005 compared to those starting before 2002. Furthermore, women and patients of older age were more likely to discontinue antiretroviral drugs because of toxicity than were men and younger patients.

Our finding that patients with a higher pre-HAART CD4 cell count changed the regimen because of toxicity within a shorter time period is in agreement with earlier reports on the loss of quality of life caused by

treatment of HIV at an early stage of the infection [87, 88]. However, other studies did not find that higher pre-HAART CD4 cell counts had an effect on the discontinuation of antiretroviral drugs because of toxicity[88, 89].

In accordance with results from other studies[87, 89, 90], we found that female gender is associated with a higher risk of toxicity-driven therapy changes. This has been attributed to a lower body mass index[91] and a higher drug concentration in plasma in women[92] and suggests that dosages should be adjusted according to a patient's body weight to reduce the probability of emerging toxicity. However, virologic suppression should always be maintained. A level of HIV RNA at the start of HAART <4 $\log_{10}$ copies/ml was associated with fewer toxicity-related changes in the regimen. Other studies reported a similar effect of most recent HIV RNA[88, 93].

We did not find that HBV or HCV co-infection had an effect on the incidence of toxicity-related therapy changes. HBV or HCV co-infection increases the risk of hepatoxicity[90, 94], and it has been shown to increase the risk of any adverse event[90]. Liver-related death has been shown to be the most frequent cause of non-AIDS-related deaths among patients treated for HIV. Apart from being associated with immunodeficiency, liver-related death was associated with older age, infection through injecting drug use (relative risk [RR], 2.0; 95% CI, 1.2-3.4), HCV co-infection (6.7; 4.0-11.2) and active HBV infection (3.7; 2.4-5.9)[95]. We did not see an increased risk of toxicity in patients co-infected with HCV, in contrast to the findings in other studies[87]; this might be because of differences between cohorts receiving anti-HCV treatment prior to or concurrently with HAART to reduce the chance of liver-related toxicities[96] or because of lack of power.

The incidence of toxicity-driven therapy changes was found to be significantly lower in patients starting HAART in 2002 through 2005. One might not expect to see such a strong effect on the basis of the incidence rates according to calendar year of starting HAART shown in Table 8.1. However, the adjusted analyses risk rates of patients starting HAART between 2002 and 2005 are so much stronger because patients starting in 2005 contributed data only during the first few months after starting HAART, i.e., when the incidence of toxicity-driven therapy changes was highest. Hence, the reported incidence figures for patients starting HAART between 2002 and 2005 reported in Table 8.1 are somewhat upwardly biased. An improved toxicity profile of more recent antiretroviral drugs has been reported previously[87]. Reducing toxicity is of importance because discontinuation of HAART can lead to poorer virologic outcome[83]. However, a change of regimens owing to toxicity does not necessarily lead to poorer virologic response, and poor virologic outcome might be mainly adherence-related[97, 98].

The lower risk of mitochondrial toxicity in patients treated with TDF or 3TC compared to AZT[99] explains the longer time to toxicity-driven therapy changes in patients starting with TDF/3TC/NVP or TDF/3TC/EFV compared to those starting a HAART regimen that included LOP/r or an AZT/3TC NRT backbone. Besides a lower hazard of toxicity-driven therapy change in patients starting on TDF/3TC/NVP or TDF/3TC/EFV, we found an independent effect of a shorter time to toxicity-driven therapy change in patients starting in later calendar years. This might be because of the increasing availability of NRTs has given patients suffering from toxicity more treatment options in more recent calendar years. Patients with mild forms of toxicity might find it easier to change their initial HAART regimen with the availability of more alternative treatment options in more recent calendar years.

The IPTW estimates of the marginal structural model were similar to those of a standard Cox proportional

hazards regression model adjusted for demographic and clinical characteristics. The advantage of the IPTW estimates is that they are causal estimates instead of associative estimates[86]. The validity of the method depends on all prognostic factors that predict treatment allocation being initially recorded in the ATHENA and then correctly modelled[86]. Unrecorded psychosocial or other factors could influence treatment allocation and estimated hazards.

In conclusion, changes in antiretroviral drugs used in HAART combinations over the years have resulted in a substantial decrease in toxicity-driven regimen changes since 2002. In particular, patients starting with TDF/3TC combined with either EFV or NVP could continue the regimen without serious side effects for a longer period of time than patients starting with a AZT/3TC nucleoside reverse transcriptase inhibitor backbone.

		No of PYART	Number of toxicity driven therapy changes	Incidence rate/100 PYART (95% CI)	Relative risk	p-value
Total		**14858**	**3509**	**23.6 (22.8-24.4)**		
Months after	0-3	1620	1097	67.7 (63.8-71.8)	1.00	
starting HAART	3-6	1526	450	29.5 (26.8-32.4)	0.44	<0.0001
	6-12	2801	557	19.9 (18.3-21.6)	0.29	<0.0001
	12-24	4861	873	18.0 (16.8-19.2)	0.27	<0.0001
Gender	24-36	4050	532	13.1 (12.0-14.3)	0.19	<0.0001
	Male	11614	2608	22.5 (21.6-23.3)	1.00	
Region of origin	Female	3244	901	27.8 (26.0-29.6)	1.24	<0.0001
	Caribbean/Latin America	1520	373	24.5 (22.1-27.2)	1.01	0.89
	Europe/North America/ Australia	9628	2336	24.3 (23.3-25.3)	1.00	
	Sub-Saharan Africa	2856	606	21.2 (19.6-23.0)	0.87	0.02
	Other	353	79	22.4 (17.7-27.9)	0.92	0.55
	Southeast Asia	501	115	22.9 (18.9-27.5)	0.95	0.59
Calendar year of	1996	948	237	25.0 (21.9-28.4)	1.02	0.76
starting HAART	1997-1999	5517	1356	24.6 (23.3-25.9)	1.00	
	2000-2001	3471	808	23.3 (21.7-24.9)	0.95	0.35
	2002-2005	4922	1108	22.5 (21.2-23.9)	0.92	0.11
	<50	2417	612	25.3 (23.4-27.4)	1.10	0.14
CD4 cell count	50-200	4566	1040	22.8 (21.4-24.2)	0.99	0.81
at starting	200-350	3779	870	23.0 (21.5-24.6)	1.00	
HAART (cells/mm^3)	350-500	1635	422	25.8 (23.4-28.4)	1.12	0.12
	≥500	1028	301	29.3 (26.1-32.8)	1.27	0.006
	Missing	1433	264	18.4 (16.3-20.8)	0.80	0.01
Transmission risk group	Homosexual	7778	1852	23.8 (22.7-24.9)	1.00	
	IDU	541	146	27.0 (22.8-31.8)	1.13	0.23
	Heterosexual	5318	1238	23.3 (22.0-24.6)	0.98	0.64
	Other	1221	273	22.3 (19.8-25.2)	0.94	0.41
HIV RNA at starting	<10000	1346	294	21.9 (19.4-24.5)	0.88	0.11
HAART (copies/ml)	10000-100000	4836	1204	24.9 (23.5-26.3)	1.00	
	≥100000	6703	1619	24.2 (23.0-25.4)	0.97	0.50
	Missing	1973	392	19.9 (17.9-21.9)	0.80	0.002

		No of PYART	Number of toxicity driven therapy changes	Incidence rate/100 PYART (95% CI)	Relative risk	p-value
Age at starting HAART	<25	848	182	21.5 (18.5-24.8)	0.94	0.59
	25-30	1830	418	22.8 (20.7-25.1)	1.00	0.92
	30-35	3043	693	22.8 (21.1-24.5)	1.00	
	35-40	3290	740	22.5 (20.9-24.2)	0.99	0.84
	40-45	2319	551	23.8 (21.8-25.8)	1.04	0.54
	45-50	1492	401	26.9 (24.3-29.6)	1.18	0.03
	50-55	1017	258	25.4 (22.4-28.7)	1.11	0.23
	>55	1020	266	26.1 (23.0-29.4)	1.15	0.14
Clinical stage at	CDC-A, B	10484	2393	22.8 (21.9-23.8)	1.00	
starting HAART	CDC-C	4374	1116	25.5 (24.0-27.1)	1.12	0.01
HCV	-	11192	2694	24.1 (23.2-25.0)	1.00	
	+	1123	280	24.9 (22.1-28.0)	1.04	0.62
	Not available	2543	535	21.0 (19.3-22.9)	0.87	0.04
HBV	-	12237	2932	24.0 (23.1-24.8)	1.00	
	+	1042	239	22.9 (20.1-26.0)	0.96	0.59
	Not available	1579	338	21.4 (19.2-23.8)	0.89	0.17

PYART: person-years on antiretroviral therapy; 95% CI: 95% confidence interval; HCV: hepatitis C virus; HBV: hepatitis B virus

Figure 8.1: Incidence of toxicity-driven therapy changes per 100 person-years in patients on antiretroviral therapy.

		Relative risk (95% CI)	p-value
Months after			
starting HAART	0-3	1.00	
	3-6	0.43 (0.39-0.48)	<0.0001
	6-12	0.29 (0.26-0.32)	<0.0001
	12-24	0.26 (0.24-0.28)	<0.0001
	24-36	0.18 (0.17-0.20)	<0.0001
Gender	Male	1.00	
	Female	1.55 (1.40-1.72)	<0.0001
Transmission risk group	Homosexual	1.00	
	Injecting drug user	0.98 (0.82-1.16)	0.82
	Heterosexual	0.80 (0.72-0.88)	0.0002
	Other	0.87 (0.76-0.99)	0.03
Calendar year			
of starting HAART	1996	1.07 (0.93-1.23)	0.40
	1997-1999	1.00	
	2000-2001	0.94 (0.86-1.03)	0.36
	2002-2005	0.77 (0.71-0.83)	<0.0001
CD4 cell count at starting			
HAART (cells/mm^3)	<50	1.05 (0.94-1.18)	0.36
	50-200	0.98 (0.89-1.07)	0.52
	200-350	1.00	
	350-500	1.12 (1.00-1.26)	0.11
	≥500	1.24 (1.08-1.41)	0.01
	missing	0.83 (0.71-0.98)	0.07
HIV RNA at starting			
HAART (copies/ml)	<10000	0.81 (0.71-0.92)	0.007
	10000-100000	1.00	
	≥100000	0.98 (0.91-1.06)	0.51
	missing	0.85 (0.74-0.97)	0.047
Each 5-year increase			
in age at starting HAART		1.04 (1.03-1.06)	0.0001
Clinical stage at			
starting HAART	CDC-A,B	1.00	
	CDC-C	1.16 (1.07-1.25)	0.0003

95% CI: 95% confidence interval

Table 8.2: Variable independently associated with the number of toxicity-driven therapy changes during the first 3 years after starting HAART.

		HR (95% CI)	p-value
Sex	Male	1.00	
	Female	1.33 (1.09-1.61)	0.004
Age at starting HAART			
(per 5-year increase)	1.04 (1.00-1.09)	0.04	
Clinical stage at			
starting HAART	CDC-A	1.00	
	CDC-B	1.29 (1.01-1.64)	0.04
	CDC-C	1.34 (1.10-1.63)	0.004
NRT combination	AZT+3TC+LOP/r	1.00 (0.77-1.28)	0.99
	3TC+TDF+LOP/r	0.86 (0.48-1.53)	0.61
	AZT+3TC+EFV	1.16 (0.92-1.48)	0.21
	3TC+TDF+EFV	0.65 (0.47-0.89)	0.008
	AZT+3TC+NVP	1.00	
	3TC+TDF+NVP	0.34 (0.19-0.60)	0.0002
Calendar year			
of starting HAART	2000	1.17 (0.84-1.63)	0.35
	2001	1.00	
	2002	1.06 (0.78-1.43)	0.72
	2003	1.35 (1.01-1.81)	0.04
	2004	1.47 (1.09-1.98)	0.01
	2005	1.08 (0.75-1.56)	0.67

HR: Hazard ratio; CI: confidence interval

Table 8.4: Hazard ratios and 95% confidence intervals obtained through Cox regression of time to first toxicity-driven regimen change.

		LOP/r		EFV		NVP		Total	p-value	CD4 cell count (cells/mm³)	
		N	%	N	%	N	%	N		Median (IQR)	
	Total	701	100.0	861	100.0	783	100.0	2345			
Sex	Male	550	78.5	652	75.7	502	64.1	1704	<0.0001	180	80-270
	Female	151	21.5	209	24.3	281	35.9	641		180	77-270
Transmission risk group	Homosexual	337	48.1	380	44.1	318	40.6	1035	<0.0001	200	100-294
	IDU	16	2.3	20	2.3	23	2.9	59		172	90-240
	Heterosexual	283	40.4	371	43.1	386	49.3	1040		163	60-250
	Other	65	9.3	90	10.5	56	7.2	211		120	40-230
Region of origin	Netherlands	384	54.8	393	45.6	339	43.3	1116	<0.0001	200	90-290
	Europe/North-America/Australia	49	7.0	65	7.5	54	6.9	168		170	80-260
	Caribbean+Latin America	58	8.3	109	12.7	114	14.6	281		184	60-280
	Other	11	1.6	28	3.3	21	2.7	60		180	60-250
	Sub-Saharan Africa	171	24.4	228	26.5	237	30.3	636		160	70-248
	Southeast Asia	28	4.0	38	4.4	18	2.3	84		140	40-240
Clinical stage at starting HAART	CDC-A	343	48.9	465	54.0	547	69.9	1355	0.0001	220	150-296
	CDC-B	99	14.1	130	15.1	109	13.9	338		180	80-270
	CDC-C	259	36.9	266	30.9	127	16.2	652		60	20-150
NRT combination	AZT+3TC	639	91.2	460	53.4	634	81.0	1733	<0.0001	180	80-280
	TDF+3TC	62	8.8	401	46.6	149	19.0	612		170	60-250

	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	p-value
Age at starting HAART	39 (32-46)	38 (32-44)	36 (30-44)	38 (31-44)	<0.0001
HIV RNA at starting HAART (copies/ml)	5.1 (4.9-5.6)	5.0 (4.6-5.2)	5.0 (4.6-5.2)	5.0 (4.6-5.3)	<0.0001
CD4 cell count at starting HAART (cells/mm³)	130 (40-220)	170 (70-260)	225 (130-314)	180 (80-270)	<0.0001

Table 8.3: Baseline characteristics of 2345 therapy-naïve patients starting HAART between 1 January 2000 and 31 December 2005 with regimens including NVP, LOP/r, or EFV combined with either AZT+3TC or TDF+3TC.

		AZT	3TC	TDF	LOP/r	NVP	EFV
No. patients started		1733	2345	612	701	783	861
No. patients stopped during follow-up because of toxicity		295	166	36	129	86	152
No. patients with linked adverse event		265	141	24	115	73	134
		%	%	%	%	%	%
	diabetes mellitus	0.4	0.7		0.9		
	cholesterol elevated	1.1	1.4		7.8		0.0
	triglycerides elevated	0.4	0.7		5.2		1.5
	lipodistrophy - fat loss	3.0	0.7		0.9		
	lipodistrophy - fat accumulation				1.7		
CARDIOVASCULAR		0.4	0.7			1.4	
DERMATOLOGIC		14.0	28.4	33.3	6.1	47.9	21.6
	rash	9.8	22.0	20.8	3.5	41.1	17.2
	itchiness	1.1	2.8	8.3	0.9	4.1	1.5
	eczema	0.4	0.7	4.2		1.4	0.7
GASTROINTESTINAL		24.5	30.5	4.2	59.1	23.3	7.5
	nausea	14.7	15.6		20.9	15.1	3.0
	vomiting	7.5	11.3		10.4	8.2	3.0
	diarrhoea	4.5	7.8	4.2	32.2	1.4	0.7
HAEMATOLOGIC		42.6	12.1		9.6	1.4	2.2
	pancytopenia	2.3	1.4		1.7		
	anaemia	30.6	6.4		4.3		0.7
	leucopenia	10.9	1.4		2.6		0.7
MUSCULOSKELETAL		1.5	1.4		1.7	4.1	
	myopathy/muscle wasting	0.4	0.7		0.9	1.4	
	arthralgia	0.4	0.7			1.4	
RENAL TOXICITY		0.4	2.1	25.0		1.4	2.2
	nephrolithiasis		4.2				
	renal insufficiency	0.4	1.4	12.5		1.4	1.5
	creatinine elevated		8.3				
	proteinuria elevated		0.7	4.2			0.7
SYSTEMIC		6.8	8.5	8.3	7.8	6.8	7.5
	general malaise	1.5	2.8	4.2	2.6	0.0	1.5
	fatigue	4.2	2.1		4.3	1.4	3.0
	fever	1.9	4.3	4.2	0.9	5.5	3.0

	AZT	3TC	TDF	LOP/r	NVP	EFV
NEUROLOGIC/PSYCHIATRIC	5.3	7.8	8.3	1.7	6.8	41.0
headache	2.6	3.5		1.7	2.7	3.0
dizziness	1.1	1.4		0.9	2.7	14.2
paraesthesia		0.7	4.2			0.7
peripheral neuropathy	1.1	2.1		2.6	1.4	0.7
nightmares		0.7	4.2			6.0
depression	0.8	2.1		1.7		5.2
LIVER-RELATED TOXICITY	3.4	7.1	4.2	1.7	19.2	3.0
pancreatitis	0.4	1.4	4.2			1.5
icterus	1.1	2.1			5.5	
ALAT elevated	1.5	2.8		0.9	6.8	0.7
ASAT elevated	0.8	1.4			6.8	0.7
gamma-GT elevated	0.8	1.4		3.5	5.5	
alkaline phosphatase raised	0.4	0.7			4.1	
VISUAL		0.7	4.2			1.5
OTHER	8.7	15.6	16.7	7.8	13.7	16.4

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; gamma-GT: gamma glutamyl transpeptidase

Table 8.5: Adverse events causing stop of at least one drug in the initial HAART regimen. Only the most frequent adverse events are reported.

	HR (95% CI)	p-value
Unadjusted	1.28 (1.02-1.60)	0.03
Adjusted	1.17 (0.92-1.50)	0.20
IPTW	1.13 (0.90-1.43)	0.29

HR: hazard ratio; 95% CI: 95% confidence interval; IPTW: inverse probability treatment weighting

Table 8.6: Hazard ratios and 95% confidence intervals of time to first toxicity-driven regimen change. Univariate and multivariate estimates and estimates obtained by marginal structural models with use of IPTW. Multivariate models adjusted for gender, age, prior CDC-C or B event, calendar year of starting HAART, and CD4 cell count at the start of HAART.

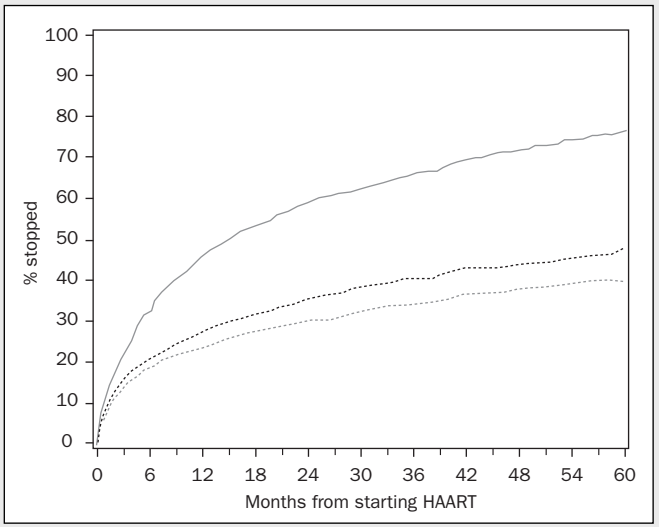


Figure 8.1: Kaplan-Meier estimates of the percentage of patients who stopped one or more of the initial antiretroviral drugs (black solid line), the percentage of patients with a toxicity-driven stop of one or more of the initial drugs (grey dashed line), and the percentage of patients who stopped because of toxicity or patients' choice of one or more of the initial drugs (black dashed line) on uninterrupted HAART for 7 years.

Resist

TEN YEARS **HAART**

tance

Resistance after 10 years HAART

Ard van Sighem

Introduction

Although treatment with HAART generally suppresses plasma HIV RNA levels below the quantification limit of currently used assays, HIV is still replicating, albeit at a lower level[100, 101]. This strong but incomplete suppression of HIV replication achieved with prolonged treatment with HAART, in combination with a nonoptimal adherence, may lead to selection of HIV-1 viruses that escape HAART-induced suppression because of resistance[102, 103]. The presence of resistant strains of virus limits future therapy options and may lead to a worsened prognosis. The prevalence of resistant virus in patients who fail on therapy may be as high as 80%[104-106].

Resistant strains of virus may also be transmitted to uninfected patients. In recent years, the prevalence of drug-resistant viruses in newly infected patients varied between 5% and 25% in Europe and North America[107, 108]. After 1998, transmission of resistant virus strains was observed in 6% of newly infected participants of the Dutch Amsterdam Cohort Studies[109].

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 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 3 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, E44D, A62V, K65R, D67N, T69D, K70R, L74V, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, T215D/N/S/C/E (denoted T215X), K291Q/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 L90M[110]. The NRTI-resistance-related mutations E44D and V118I occur also as natural polymorphisms, and when each occurs in isolation, their significance is unknown. Therefore, we counted them as mutations only when they occurred in combination with other NRTI-resistance-related mutations[111]. A genotypic resistance interpretation algorithm developed by Stanford University was used to assign a drug penalty score for each drug-resistance-associated mutation[112]. 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 either a recent infection or those with a new HIV diagnosis. Patients with a recent infection were either diagnosed 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 two consecutive viral load measurements 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 was calculated as the ratio of the number of patients failing and the number of patients being followed during each year and was corrected for therapy use.

Results

Transmission of drug-resistant virus

Table 9.1 shows the characteristics of both the 298 recently infected patients and the 853 who were newly diagnosed. The majority of the recently infected patients were men of Dutch origin who were infected by homosexual contact, 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 2005, 732 sequences were obtained in the combined group of newly diagnosed and recently infected patients. During the same period, there were 2927 HIV diagnoses according to Table 6.2 in chapter 6. Hence, a sequence was obtained for 25.0% of the diagnosed patients.

Amongst the 298 recently infected patients, resistance-associated mutations were found in 18 (6.0%) patients, of whom 4 were infected in or before 1996. The number of recent infections between 1994 and 2001 was limited, and as a result, the percentage of patients with resistance fluctuated between 0% and 25% (Figure 9.1). After 2001, resistance was found in 4.8% (95% CI 2.3–8.7) of the 207 recently infected patients.

Of the 207 patients with a recent infection after 2001, 204 patients were susceptible to all protease inhibitors, whereas 2 patients had low-level resistance and 1 patient had high-level resistance to at least one protease inhibitor. One patient had low-level resistance to nNRTIs, and two patients had high-level resistance. Resistance to NRTIs was more frequent: 6 patients had low-level resistance, 4 patients intermediate resistance, and 2 high-level resistance. High-level resistance to at least 1 drug class was observed in 3 patients. One patient, who was infected in 2004, had high-level resistance to all drug classes. Another patient harboured an M184V mutation, conferring high-level resistance to lamivudine and emtricitabine[113]. The third patient had a K103N mutation which is associated with high-level resistance to all available nNRTIs[114, 115].

In the group of 853 new diagnoses, resistance-associated mutations were found in 63 (7.4%) patients. The majority of the resistant sequences, 51 (81%), were obtained in or after 2002. The annual percentage of transmissions of resistant virus strains varied between 0% and 10% (Figure 9.1). After 2001, the proportion of patients with at least one mutation was 7.7% (95% CI 5.8–10.1). Amongst the 332 patients infected via homosexual contact, 34 (10.2%) patients had at least one mutation, compared to 11 (4.5%) of the 246 heterosexual patients (p=0.01). Resistance tended to be more common amongst patients infected with a subtype B virus (9.4%) compared to those with a non-B subtype (4.0%) (p=0.02).

The group of patients with a new diagnosis in or after 2002 consisted of 659 patients. Of those, 632 (95.9%) were fully susceptible to protease inhibitors, 20 (3.0%) had low-level resistance, 3 had intermediate resistance, and 3 had high-level resistance, whilst for 1 patient the protease sequence was not available. High-level resistance to nNRTIs was observed in 10 (1.6%) patients, whilst 2 patients had intermediate levels of resistance, 10 had low-level resistance, and 637 (96.7%) were susceptible to all nNRTIs. Low-level resistance to NRTIs was observed in 22 patients, intermediate

resistance in 11 patients, and high-level resistance in 7 patients. One patient had high-level resistance to all 3 drug classes. Three other patients had high-level resistance to NRTIs and nNRTIs, but not to protease inhibitors, whereas one patient was fully resistant to PIs and NRTIs, but not to nNRTIs. Nine other patients had high-level resistance to only 1 class of antiretroviral drugs.

Resistance during treatment

The proportion of pre-treated patients who failed on HAART declined from 50% in 1997 to 16% in 2006 (Figure 9.2). During the same period, the fraction of failures amongst therapy-naïve patients on HAART increased slightly from 6% in 1997 to 11% in 2004 and was 8% in 2006. In the group of pre-treated patients, the fraction of failing patients from whom a sequence was obtained increased from 12% in 1996 to 28% in 2003, but the fraction declined thereafter to 17% in 2005. In the therapy-naïve group, the fraction of patients with a sequence was 25% in 2003 and 11% in 2005. Overall, 97% of the sequences from pre-treated patients and 79% of those from naïve patients contained 1 or more resistance-associated mutations.

In the population of patients with virological failure after the start of HAART, 2115 sequences were obtained. Of these sequences, 1680 (79.4%) contained at least 1 resistance-associated mutation, and 435 (20.6%) contained none. The majority of the resistant sequences, 1107 (65.9%), were obtained in pre-treated patients, whereas the remaining 573 (34.1%) sequences were obtained from previously therapy-naïve patients. Multiple sequences per patient were allowed, but at most, 1 per year was permitted. Of the 435 sequences without any mutation, 233 (53.6%) were obtained from patients not on therapy, whereas 142 (8.5%) of the sequences with at least one mutation were from patients without therapy. Prevalence of resistance over time was considered in the 1680 sequences with at least one resistance-associated mutation.

The nature of the drug resistance observed per calendar year changed over time (Figure 9.3). The proportion of patients with high-level resistance to zidovudine decreased from 56% in 1996 to 25% in 2005, whilst the proportion of those with high-level resistance to stavudine decreased from 51% in 1996 to 23% in 2005 ($p<0.001$). Meanwhile, the proportions of sequences with high-level resistance to lamivudine increased from 53% in 1996 to 65% in 2005 ($p<0.001$). Resistance to abacavir and didanosine did not change over time. High-level resistance to tenofovir was rare and decreased between 1996 and 2005 from 3% to 1% ($p=0.008$). Intermediate resistance to tenofovir was much more frequent; it was 56% in 1996 and decreased to 29% in 2005 ($p<0.001$).

Resistance to nNRTIs increased after the introduction of nevirapine and efavirenz as part of the HAART regimen in approximately 1998. From 1999, high-level resistance to nevirapine increased from 45% to 53% in 2005 ($p<0.001$). High-level resistance to efavirenz was less common; it increased from 31% in 1999 to 40% in 2005 ($p<0.001$).

Resistance to protease inhibitors also increased after the widespread introduction of PIs in approximately 1996. High-level resistance to the older generation of PIs, including nelfinavir, saquinavir and indinavir, peaked around 1999 and became less common thereafter. Less than 10% of the sequences were fully resistant to lopinavir/(ritonavir boosted), tipranavir and darunavir (TMC114). In 2005, intermediate levels of resistance to lopinavir/(ritonavir boosted) were found in 16% of the sequences, to tipranavir in 19%, and to darunavir in 23%.

High-level resistance in the group of previously therapy-naïve patients (573 sequences) was less common. The prevalence of resistance to each individual PI and NRTI was less than 20%, except for resistance to lamivudine (3TC), which was found in 75% of the sequences. On the other hand, resistance to nNRTIs had the same prevalence as in the total group of patients.

As of June 2006, a total of 10,053 patients were still being actively followed. In 1108 (11.0%) of patients, at least one sequence had been obtained with resistance-associated mutations. Of these patients, 1032 (93.1%) had high-level resistance to at least 1 antiretroviral drug. The number of patients with high-level resistance to drugs from 1 drug class was 387 (38%). Resistance to drugs from 2 drug classes was found in 451 (44%), whereas 194 (19%) were found to be resistant to drugs from all 3 classes. High-level resistance to at least 1 NRTI was found in 938 (91%) of the patients, to at least 1 nNRTI in 584 (57%), or to at least 1 PI in 354 (34%). Table 9.2 shows the inferred resistance level for each individual antiretroviral drug in the group of 1108 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 were infected with a resistant strain, but amongst newly diagnosed patients, a higher percentage was observed. These percentages are comparable with those observed in other Western countries[107, 108, 116, 117]. However, when mutations were translated into a predicted susceptibility score, approximately 4% of the patients in both groups were infected with a virus strain with intermediate or high-level resistance to at least 1 antiretroviral drug. This finding indicates that the presence of a major resistance-associated mutation is not necessarily a sign of full resistance.

The stable and low level of transmission of resistant virus strains is somewhat surprising given the increase in the number of HAART-treated patients since 1996. A possible explanation is that the proportion of failing patients has decreased over time and that, as a consequence, the reservoir of possibly infectious patients – patients having RNA levels above 500 copies/ml – is relatively small. It is also possible that most HIV infections are transmitted from HIV-infected individuals who are not yet treated or are even unaware of their infection[31, 118].

Since 2002, the standard of care in some hospitals in the Netherlands has been to obtain a protease and RT sequence in all patients newly diagnosed with HIV infection. This is illustrated in Figure 9.1, in which the dashed lines show an increasing number of sequences obtained in each year since 2002. The estimates of the percentage of resistant transmissions have been accurate only since 2002. Presently, on average 25% of the diagnosed patients have a baseline sequence.

National and international guidelines now recommend obtaining a sequence at diagnosis only in those populations that have an increased risk of being infected with a resistant virus strain[45, 119, 120]. As our data indicate, these populations include patients infected via homosexual contact and those infected with a subtype B strain, with a large overlap between the two populations. The drawback to these recommendations is that they reduce the chances of observing a future increase in resistant transmissions that may occur in populations now at low risk. For instance, the roll-out of widespread treatment in Africa will undoubtedly increase the prevalence of drug-resistance in that area. This drug resistance could subsequently lead to an increase in baseline resistance in migrant populations in the Netherlands infected with a non-B subtype virus.

As observed previously, the prevalence of resistance to specific antiretroviral drugs changed over time in correlation with changes in antiretroviral drug use[26, 121]. Thus, resistance to nNRTIs increased whilst resistance to the older generation of protease inhibitors declined. Surprisingly, high-level resistance to tenofovir, which is by now widely used in the Netherlands, was rare. This can be explained by the intermediate level of resistance assigned to the tenofovir-related K65R mutation by the Stanford interpretation algorithm. The increased levels of intermediate resistance to tenofovir in the 1990s was the result of cross resistance, as is resistance to tipranavir and darunavir, two drugs that are not yet registered in the Netherlands.

It was found that 11.0% of the patients who were still being followed by the HIV Monitoring Foundation (HMF) harboured virus strains with high-level resistance to at least 1 antiretroviral drug. A study in the United Kingdom showed that the risk of 1 or more of the major mutations listed by the International AIDS Society-USA (IAS-USA) was 27% after 6 years of HAART[122]. In the HAART Observational Medical Evaluation and Research (HOMER) cohort, resistance was found in 25% of the patients with a viral load above 1000 copies/ml during the first 30 months after they started HAART[103]. Hence, given these results from other countries and the fact that a sequence was obtained from, at most, 25% of the failing patients followed by HMF, the prevalence of resistance that was found is likely to be an underestimation.

	new diagnoses, N=853		**recent infections, N=298**	
	N	**%**	**N**	**%**
male gender	649	76.1	271	90.9
region of origin				
the Netherlands	499	58.5	229	76.8
sub-Saharan Africa	153	17.9	13	4.4
transmission category				
MSM	453	53.1	231	77.5
heterosexual contact	285	33.4	45	15.1
injection drug use	13	1.5	3	1.0
other/unknown	102	12.0	19	6.4
non-B subtype	249	29.2	56	18.8
≥ 1 RAMS				
any drug	63	7.4	18	6.0
PIs	12	1.4	2	0.7
NRTIs	43	5.0	16	5.4
nNRTIs	16	1.9	2	0.7
intermediate/high-level resistance				
any drug	36	4.2	13	4.4
PIs	8	0.9	1	0.3
NRTIs	23	2.7	10	3.4
nNRTIs	12	1.4	4	1.3
	median	IQR	median	IQR
CD4 (10^6 cells/l)	290	120–500	500	360-682
RNA ($\log_{10}$ copies/ml)	4.9	4.3–5.3	4.9	4.2–5.4
age (years)	37.0	30.6–43.9	35.7	29.8–42.4

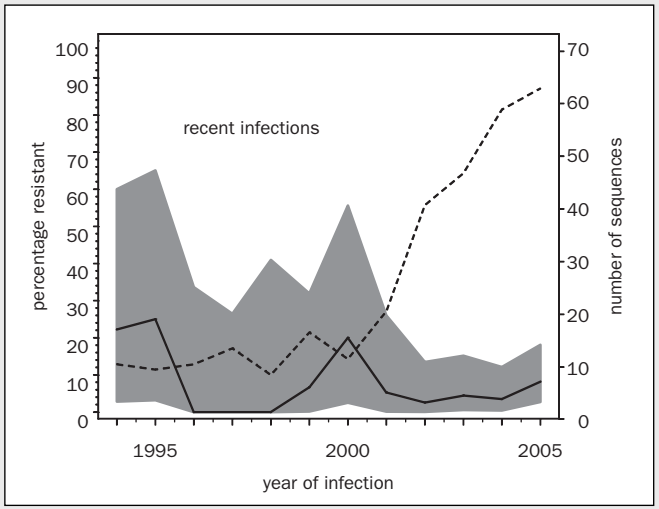
MSM: men having sex with men; RAMS: resistance-associated mutation; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; nNRTI: non-nucleoside reverse transcriptase inhibitor

Table 9.1: Characteristics at HIV diagnosis of both newly diagnosed and recently infected patients.

	susceptible		potential low-level resistance		low-level resistance		intermediate resistance		high-level resistance	
	N	%	N	%	N	%	N	%	N	%
protease inhibitors										
fAPV	690	62.3	24	2.2	107	9.7	179	16.2	106	9.6
IDV	662	59.8	34	3.1	82	7.4	128	11.6	200	18.1
NFV	622	56.1	4	0.4	17	1.5	111	10.0	352	31.8
SQV	665	60.0	32	2.9	59	5.3	142	12.8	208	18.8
LPV/r	690	62.3	37	3.3	101	9.1	200	18.1	78	7.0
ATV	639	57.7	25	2.3	110	9.9	204	18.4	128	11.6
TPV	711	64.2	58	5.2	112	10.1	172	15.5	53	4.8
TMC114	700	63.2	66	6.0	145	13.1	188	17.0	7	0.6
nucleoside RT inhibitors										
3TC	173	15.6	36	3.3	39	3.5	30	2.7	829	74.8
FTC	173	15.6	36	3.3	39	3.5	30	2.7	829	74.8
ABC	88	7.9	283	25.5	132	11.9	368	33.2	236	21.3
AZT	389	35.1	24	2.2	79	7.1	235	21.2	380	34.3
d4T	336	30.3	54	4.9	132	11.9	266	24.0	319	28.8
ddI	334	30.1	67	6.1	11	10.0	365	32.9	230	20.8
TDF	414	37.4	94	8.5	193	17.4	376	33.9	30	2.7
non-nucleoside RT inhibitors										
EFV	492	44.4	26	2.3	79	7.1	77	6.9	433	39.1
NVP	470	42.4	40	3.6	11	1.0	4	0.4	582	52.5

fAPV: fos-amprenavir; IDV: indinavir; NFV: nelfinavir; SQV: saquinavir; LPV/r: lopinavir/(ritonavir boosted); ATV: atazanavir; TPV: tipranavir; TMC114: darunavir; 3TC: lamivudine; FTC: emtricitabine; ABC: abacavir; AZT: zidovudine; d4T: stavudine; ddI: didanosine; TDF: tenofovir; EFV: efavirenz; NVP: nevirapine.

Table 9.2: Number of patients being followed in June 2006 with evidence of resistance to specific antiretroviral drugs, according to the Stanford mutation scoring algorithm.



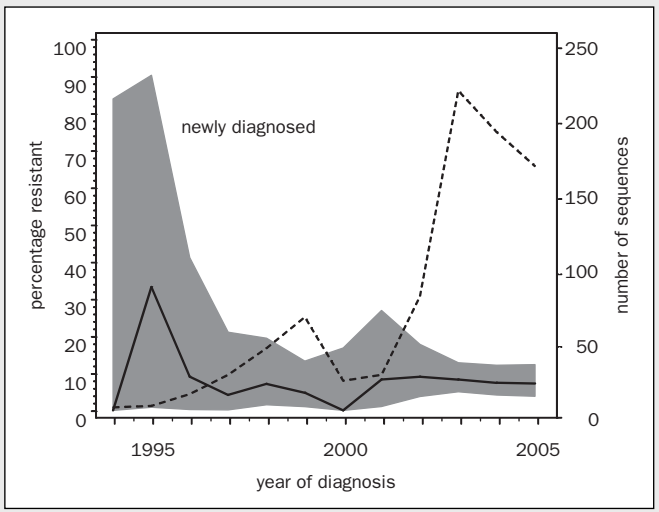


Figure 9.1: Percentage of transmissions of resistant virus as a function of time amongst recently infected and newly diagnosed patients. The black line represents the percentage whilst the grey areas are the 95% confidence intervals. The dashed line is the number of sequences that was obtained in each year (right axis).

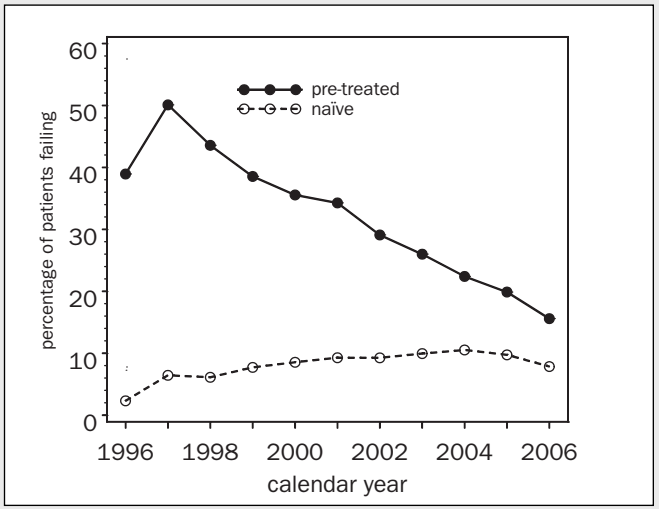
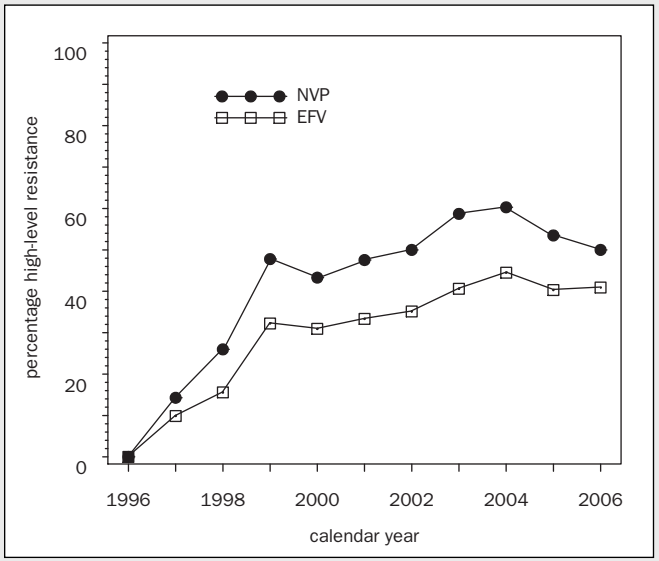
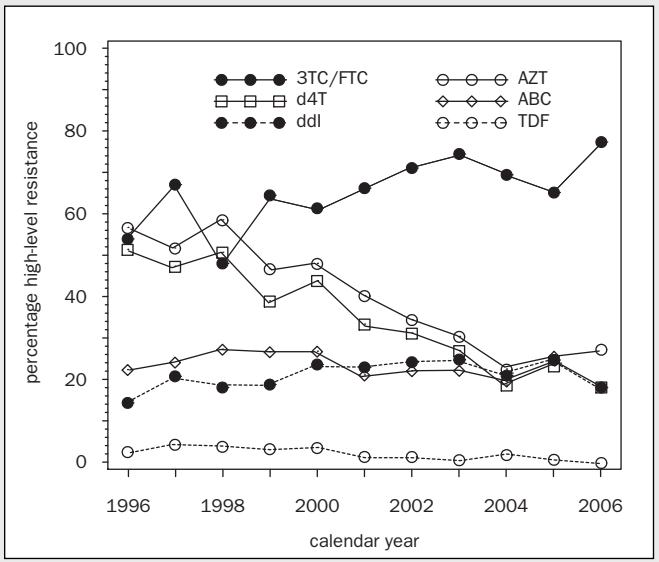


Figure 9.2: Percentage of pre-treated and therapy-naïve patients having virological failure per year.





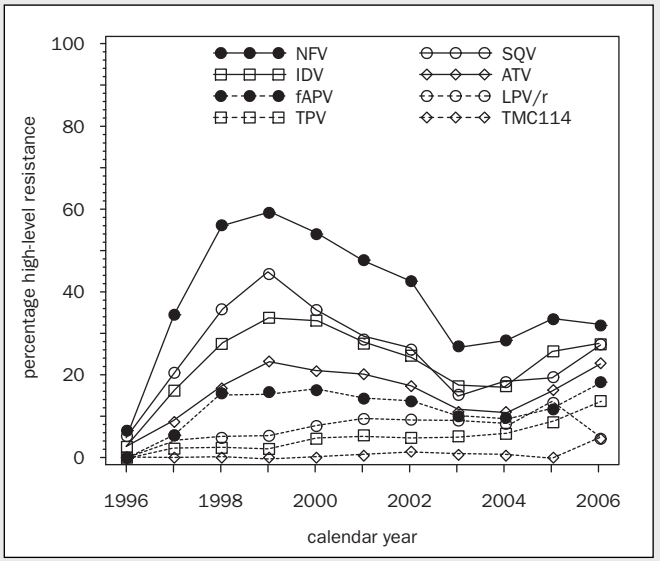


Figure 9.3: Percentage of patients with high-level resistance according to the Stanford mutation score algorithm; NVP: nevirapine; EFV: efavirenz; 3TC/FTC: lamivudine/emtricitabine; d4T: stavudine; ddI: didanosine; AZT: zidovudine; ABC: abacavir; TDF: tenofovir; NFV: nelfinavir; IDV: indinavir; fAPV: fos-amprenavir; TPV: tipranavir; SQV: saquinavir; ATV: atazanavir; LPV/r: lopinavir/(ritonavir boosted); TMC114: darunavir.

Death a

TEN YEARS **HAART**

nd AIDS

Ard van Sighem

Introduction

Since the introduction of highly active antiretroviral therapy (HAART) a decade ago, HIV-related mortality rates and incidence of AIDS in Europe and North America have declined substantially in patients receiving the therapy, compared to those of untreated patients [23, 24, 40, 75, 123]. 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 [66, 124, 125]. Hence, HIV is gradually acquiring the characteristics of a chronic, rather than a lethal, disease. The possibility of adequate treatment and a changing attitude towards HIV has encouraged insurance companies in the Netherlands, the first in the world, to offer life insurance policies to HIV-infected patients.

This chapter presents an updated analysis of annual mortality rates and incidence of AIDS in the HAART-treated population in the Netherlands since 1996. The observed patterns are compared with annual mortality and incidence of AIDS in the total HIV-infected population. A new prognostic model is shown for predicting survival probabilities of HIV-infected patients after diagnosis with HIV. This model complements existing models, which hitherto assessed only survival in HAART-treated patients[124].

Population and methods

The total study population consisted of 11,709 patients infected with HIV-1 with a known date of diagnosis. From this population, a subpopulation of 9331 (79.7%) patients was selected that comprised all patients who started HAART between 1995 and 1 June 2006, 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[126]. On the basis of 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 after diagnosis or after initiation of HAART during that year. The Poisson distribution was used to calculate 95% confidence intervals (CI) for rates. The significance of changes in rates over time were assessed with generalized linear models.

Of the 11,709 patients with a known date of diagnosis, a second subgroup was selected consisting of patients 16 years of age or older who were diagnosed between 1998 and 2005. Those patients had to be either untreated until the end of the follow-up or treated with HAART without having received antiretroviral therapy prior to the start of HAART. Furthermore, measurements of CD4 counts and viral load within 12 weeks after diagnosis but prior to treatment were required. CDC stage at diagnosis was defined as the most serious CDC event recorded within 6 weeks after diagnosis[126].

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 [Actuarial Association, Woerden, 2002, 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% confidence interval (CI). The standardised mortality ratio (SMR) was defined as the 1-year mortality of HIV-infected patients relative to the general population. Hence, a patient with SMR r had an r times higher probability of dying within 1 year than did an uninfected individual of the same age and gender.

A mixed effects model was used to analyse longitudinal data on CD4 counts in the first 4 years after diagnosis, according to different baseline strata for CD4 count (<50, 50–200, 200–350, 350–500, and ≥500 x 10^6 cells/l)[26]. In the model, the square root of time was used, since this appeared to be linearly related with changes in CD4 counts. A first-order autoregressive covariance structure was used to correlate intra-individual serial measurements.

Results

Mortality and incidence of AIDS

In the total group of 11,709 patients with 66,595 person-years of follow-up since 1996, 984 deaths were recorded (Table 10.1). This number corresponded with an average mortality rate of 1.48 (95% CI, 1.39–1.57) deaths per 100 person-years. The mortality did not change significantly over calendar time (p=0.09), being 1.16 (0.84–1.57) in 1996 and 0.84 (0.54–1.24) in 2006 (Figure 10.1). When patients who had an AIDS diagnosis within 6 weeks after an HIV diagnosis (N=1850) were excluded, the overall mortality was reduced to 1.24 (1.15–1.33) per 100 person-years. The mortality rate was also lower, 1.08 (0.98–1.20), and it likewise did not change over time (p=0.6) when only patients diagnosed in or after 1996 were considered (N=8390, 36,428 person-years of follow-up, 395 cases of death).

For the total group, 3468 AIDS diagnoses were registered at or after HIV diagnosis. There were 2048 new AIDS diagnoses recorded 6 weeks and onward after registration of an HIV diagnosis; of those new AIDS diagnoses, 1598 (78.0%) were recorded in or after 1996. The total follow-up up until the AIDS diagnosis was 56,050 years, yielding an average AIDS incidence of 2.85 (95% CI, 2.71–2.99). From 1996 onward, there was a decline (p<0.0001) from 9.6 (8.5–10.8) AIDS diagnoses per 100 person-years in 1996 to 2.0 (1.7–2.3) in 2005 (Figure 10.1). Since 2003, the incidence of AIDS has not changed (p=0.9). Incidences were higher before 2000, 13.7 (9.8–18.7) in 1996, when only patients diagnosed in or after 1996 were considered, but after 2000, the incidence of AIDS did not differ from that in the total group.

The population of patients starting HAART consisted of 2287 patients who had had prior antiretroviral treatment (16,588 person-years of follow-up since 1996; 464 deaths) and 7044 previously therapy-naïve patients (31,441 person-years of follow-up; 390 deaths). The mortality declined from 4.4 (95% CI, 2.9–6.4) per 100 person-years in 1996 to a level of 1.54 (1.26–1.86) in 2005. In 2006, the mortality was 0.87 (0.54–1.32), which was borderline significantly different from 2005 (p=0.02). On average, the mortality after 2000 was 1.55 (1.41–1.69) and did not change over time (p=0.5). In the therapy-naïve population, mortality after 2000 was lower than in the pre-treated population, being 1.19 (1.06–1.34) compared to 2.48 (2.17–2.82) per 100 person-years. Between 1996 and 2006, the overall mortality in the naïve population was 1.24 (1.12–1.37) per 100 person-years and did not change over time (p=0.2). When patients with an AIDS diagnosis in the year prior to the start of HAART were excluded, the mortality was 1.33 (1.22–1.46) per 100 person-years and also did not change (p=0.07).

In the total group who ever started HAART, 1066 AIDS diagnoses were registered during 44,051 person-years of follow-up after the start of HAART. The incidence of new AIDS diagnoses decreased sharply from 14.8 (95% CI, 11.9–18.2) in 1996 to a level of 2.06 (1.64–2.55) in 2000. Thereafter, the AIDS incidence was on average 1.81 (1.66–1.98) per 100 person-years and decreased (p=0.004), albeit at a slower pace than before 2000, to 1.58 (1.28–1.92) in 2005. In the therapy-naïve population (29,334 person-years of follow-up), the incidence of AIDS after 2000 was similar to that in the pre-treated population (14,717 person-years of follow-up), being 1.81 (1.63–2.00) and 1.83 (1.54–2.16) per 100 person-years, respectively.

Figure 10.2 shows that the proportion of patients who died of HIV-related causes between 1996 and 2005 declined from 76% to 39% (p<0.001). This decrease was counterbalanced by an increase in the proportion of non-HIV-related causes from 10% in 1996 to 50% in 2005 (p<0.001). The proportion of patients for whom the cause of death was not registered or could not be classified was 15% and did not change over time (p=0.3). In patients on HAART who died in 2005, non-HIV-related causes accounted for 51% of cases and HIV-related causes for 36%. The majority, 226 (58%), of the 391 HIV-related deaths occurred in patients who had received an AIDS diagnosis in the year before the start of HAART. When these patients were excluded, the proportion of non-HIV-related causes of death was 58% and that for HIV-related causes of death was 27%.

Prognostic model

The study population for the prognostic model consisted of 5130 (43.8%) patients with a total follow-up of 16,635 person-years. Characteristics of the patients are shown in Table 10.2. During follow-up 171 deaths were recorded, corresponding to an average mortality rate of 1.03 (95% CI, 0.88–1.19) per 100 person-years. Of the 3769 asymptomatic patients, 15 died before the start of HAART, whilst 8.4 deaths would have been predicted. For those diagnosed with a CDC-B or CDC-C event, 4 out of 435 (0.3 predicted) and 12 out of 926 (0.2 predicted) died before the start of HAART.

In total, 1422 patients had more than 4 years of follow-up; 508 of those (35.7%) were diagnosed after 2000. Patients diagnosed in or before 2000 with CD4 counts at diagnosis in the ranges of <50 x 10^6 cells/l, 50–200, 200–350, 350–500 and ≥500 had CD4 counts 192 weeks after diagnosis of 320 x 10^6 cells/l (interquartile range 200–400), 381 (270–510), 517 (390-700), 540 (400–720) and 605 (451–810), respectively. For patients diagnosed after 2000, the median CD4 counts at 192 weeks for the same CD4 cell count intervals at diagnosis were: 380 x 10^6 cells/l (250–485; p=0.2), 410 (328–530; p=0.2), 470 (360–600; p=0.05), 470 (350–570; p=0.002), and 510 (390–694; p=0.001), respectively. Hence, for patients who had CD4 counts at diagnosis exceeding 350 x 10^6 cells/l, CD4 counts at 192 weeks were lower for those who were diagnosed after 2000 compared to those diagnosed in or before 2000. This was also apparent from the longitudinal model where the change in CD4 counts was 8.2 (95% CI, 5.0–11.4) x 10^6 cells/(l year$^{1/2}$) and 7.0 (3.4–10.7) x 10^6 cells/(l year$^{1/2}$) less for the two highest CD4 intervals in patients diagnosed after 2000 compared to the intervals in those diagnosed in or before 2000.

Patients with CDC stage C were excluded from the model fit since 57 (69%) of the 83 patients who died did so within one year. Even after taking into account mortality rates in the general population, patients older than 50 years at diagnosis had a risk of death 3.04 (95% CI, 1.90–4.87) times higher than patients younger than 50 years of age. Also, patients infected via injection drug use were excluded from the fit. Of the 4142 patients eligible for inclusion in the prognostic model, 81 (2.0%) died during 13,219 person-years of follow-up. Of those who died, 19 (23%) had less than 50 x 10^6 CD4 cells/l at diagnosis. The only covariates significantly associated with survival were the log-transformed CD4 count at diagnosis (hazard ratio 0.66; 95% CI, 0.51–0.85, per unit increase) and CDC stage B at diagnosis (3.50; 95% CI, 1.67–7.32; CDC stage B vs. stage A). The increased risk of death associated with older age that is usually observed, was, according to the model, fully compensated for by the expected increased hazard in the non-HIV-infected population.

For 20-year-old asymptomatic male patients, the mortality was expected to be 3.5 (95% CI, 2.4–5.4) times higher than in the general population when CD4 counts at diagnosis were 600 x 10^6 cells/l, and the mortality was predicted to be 8.1 (5.0–13.6) times higher when CD4

counts were 50 x 10^6 cells/l (Figure 10.3, upper panel). Until patients reached the age of 30 years, SMRs did not change significantly, but thereafter they declined; at the age of 50 years patients with CD4 counts of 600 x 10^6 cells/l had an expected mortality rate 1.4 times higher than that in the general population, and for patients with counts of 50 x 10^6 cells/l the rate was 2.2 times higher. Figure 10.3 (lower panel) shows the predicted survival probabilities up to the age denoted on the horizontal axis for HIV-infected individuals still alive at the age of 34 years compared with uninfected individuals.

When only patients with CD4 counts of 50 x 10^6 cells/l or higher were considered, log-transformed CD4 count was no longer significantly associated with progression to death (p=0.4). To study whether patients diagnosed in or before 2000 had a different prognosis from those diagnosed thereafter, we included the year of diagnosis as a dichotomous variable. For patients with CD4 counts at diagnosis exceeding 350 x 10^6 cells/l, we did not find an association of the year of diagnosis with outcome (p=0.5; 28 cases of death).

Discussion

Since 1996, the overall mortality rate in the HIV-infected population in the Netherlands has remained stable at a level between 1 and 2 deaths per 100 person-years of follow-up. In contrast, mortality rates in the HAART-treated population have declined over time. This decline, however, was observed only in the pre-treated population and, because pre-treated patients account for only 20% of the HIV-infected population, HAART's effect on the mortality in the total population was limited. The pre-treated population was generally in poorer condition at the start of HAART, and as a result those patients experienced a higher mortality rate than therapy-naïve patients. 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.

Although mortality rates did not change over time, there was a shift in the cause of death from being mostly HIV-related in 1996 to half now resulting from conditions not directly attributable to the HIV infection[75]. We found HIV-related causes amongst HAART-treated patients mainly in those who already had AIDS at the start of HAART. 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 classification of causes of death, the HIV Monitoring Foundation (HMF) adopted the CoDe (Coding of Death in HIV) classification scheme. Unfortunately, the data collected via CoDe were not yet available for analysis.

Surprisingly, the mortality rate in 2006 has been substantially lower than that observed in 2005. However, because the data collection for 2006 has not yet been completed, it is dangerous to draw conclusions based on this observation. Nevertheless, a decrease is not expected since the method of data collection has not changed since last year. Moreover, the reduction in the number of deaths in the first months of 2006 compared to the same period in 2005 was seen in all HIV treatment centres.

Patients who were diagnosed before 2000 and survived at least 4 years had a more favourable response in CD4 counts than did the patients diagnosed after 2000. This difference was observed only for patients with CD4 counts of 350 x 10^6 cells/l or higher at diagnosis and coincided with changes in guidelines on therapy initiation. Since 1996, these guidelines for the start of HAART have evolved from a "hit it early and hard" approach, where HAART was started when CD4 counts were below 500 x 10^6 cells/l, to the present recommendations in which HAART is started when

CD4 counts are between 200 and 350 x 10^6 cells/l[46, 127]. There were no indications that an earlier start was associated with a better prognosis.

The only predictors for survival rates after diagnosis were CD4 counts and a concurring CDC-B event at the time of diagnosis, with lower mortality observed in patients who had higher CD4 counts. However, the association of CD4 counts at diagnosis with progression to death was not very strong; removal of patients with CD4 counts below 50 x 10^6 cells/l yielded a model where CD4 counts were no longer associated with survival. This probably indicates that HAART is started according to the guidelines for patients with higher CD4 counts. If CD4 counts are above the recommended level for therapy initiation, HAART will be postponed, whilst HAART is started as soon as patients with CD4 counts at critical levels are diagnosed. Thus, the net effect will be that CD4 counts at diagnosis are not very strongly correlated with outcome, unless they are below critical levels. A second possibility, however, is that the number of deaths in the model is too limited to detect a significant effect of CD4 counts. The limited discriminatory ability of CD4 counts was also apparent from the small differences in standardised mortality ratios and overall predicted survival for patients with CD4 counts between 200 and 600 x 10^6 cells/l.

Patients with a concurring AIDS event at diagnosis had a considerably higher risk of death, especially in the population more than 50 years of age. This is probably due to a limited restoration of the immune system for elder patients after the start of HAART[68]. The incidence of AIDS after diagnosis or after initiation of HAART was about 2 cases per 100 person-years. Interestingly, after 2000, there was no longer any difference in AIDS incidence between previously therapy-naïve and pre-treated patients. This indicates that the pre-treated patients who survived AIDS-free until 2000 now have the same risk of progression to AIDS as previously therapy-naïve patients[24].

The model for progression to death complements, but does not replace, the previous model for progression to death after the start of HAART that took into account the initial response to HAART[124]. In the event that a patient starts HAART, 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 HAART	Total	After start of HAART
Until 1995	721	450	1	-	-
1996	354	290	90	42	28
1997	296	179	129	84	68
1998	248	129	116	81	73
1999	229	138	115	91	89
2000	237	111	85	80	77
2001	248	143	98	76	76
2002	291	154	119	118	82
2003	267	127	97	135	116
2004	261	150	101	131	117
2005	276	149	100	121	107
2006	40	28	16	25	21
	3468	**2048**	**1067**	**984**	**854**

Table 10.1: Characteristics at HIV diagnosis of both newly diagnosed and recently infected patients.

CDC status	Asymptomatic		CDC-B		CDC-C		Total	
	3769	75.3%	435	7.9%	926	16.8%	5130	100%
	N	%	N	%	N	%	N	%
Gender, male	2769	73.5	348	80.0	741	80.0	3858	75.2
Transmission category								
MSM	1946	51.6	240	55.2	395	42.7	2581	50.3
Heterosexual contact	1543	40.9	150	34.5	393	42.4	2086	40.7
Injection drug use	53	1.4	9	2.1	10	1.1	72	1.4
Other/unknown	227	6.0	36	8.3	128	13.8	391	7.6
Region of origin								
The Netherlands	2008	53.3	268	61.6	456	49.2	2732	53.3
Sub-Saharan Africa	875	23.2	72	16.6	217	23.4	1164	22.7
Other	886	23.5	95	21.8	253	27.3	1234	24.1
Started HAART	2361	62.6	395	90.8	884	95.5	3640	71.0
Progression to death	61	1.6	26	6.0	84	9.1	171	3.3
before HAART	15	25	4	15	12	14	31	18
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age	35.7	29.4–42.4	38.4	32.6–46.4	38.4	32.7–46.3	36.4	32.5–46.4
CD4 (10^6 cells/l)	380	220–570	130	41–310	50	20–110	300	113–500
$\log_{10}$ 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)	2.8	1.3–4.6	3.4	1.3–5.4	3.2	1.3–5.4	2.9	1.3–4.9
Total follow-up (person-years)	11878		1535		3221		16635	

MSM: men having sex with men; IQR: interquartile range

Table 10.2: Patient characteristics.

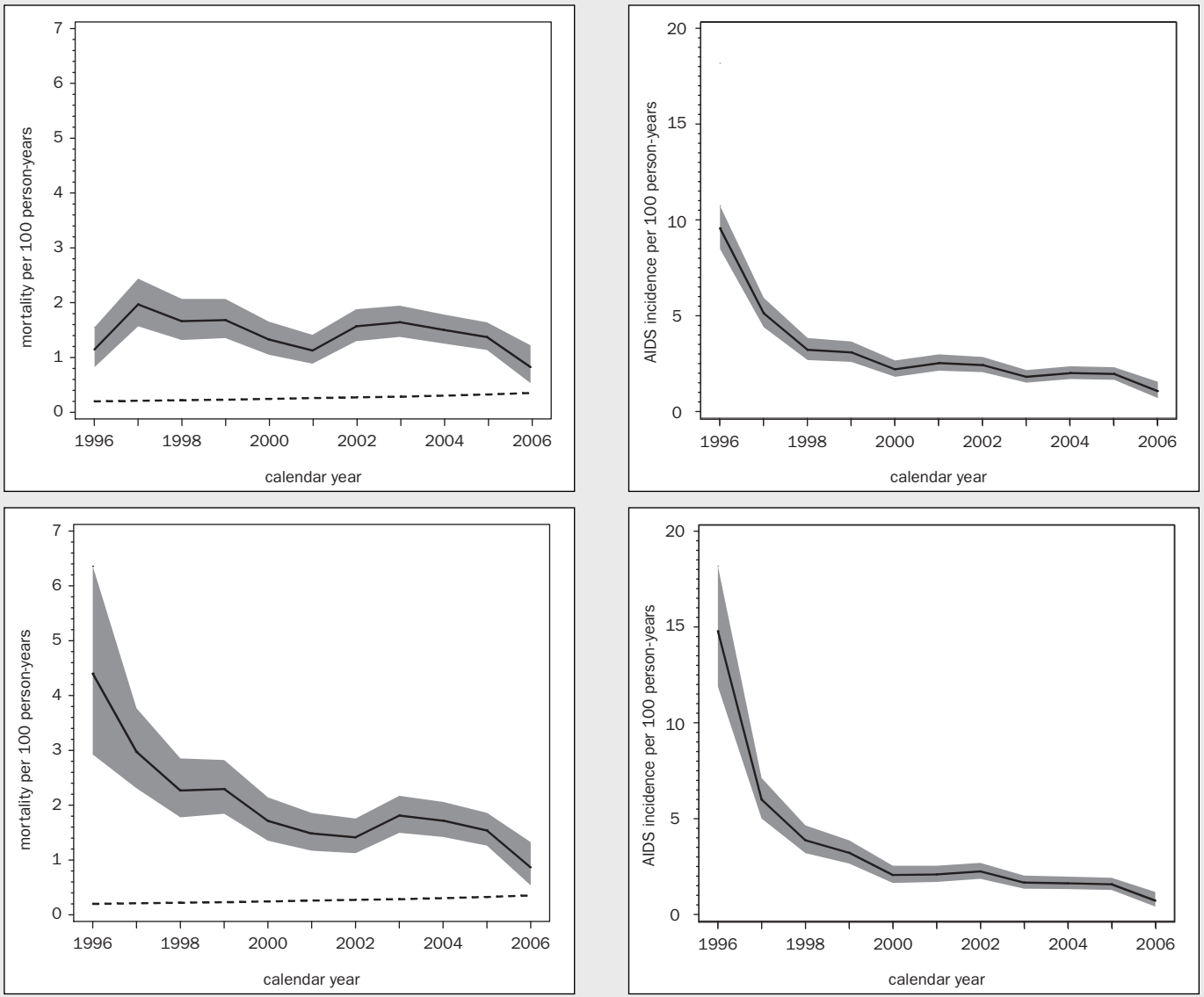


Figure10.1: Mortality and incidence of AIDS as a function of calendar year after diagnosis (upper panels) and after start of HAART (lower panels). The black lines represent the incidence, whilst the grey areas are the 95% confidence intervals. The dotted line is the mortality expected in age- and gender-matched individuals from the general Dutch population.

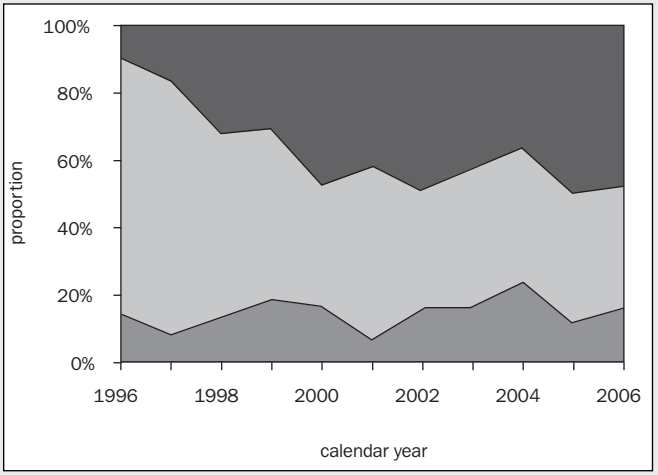
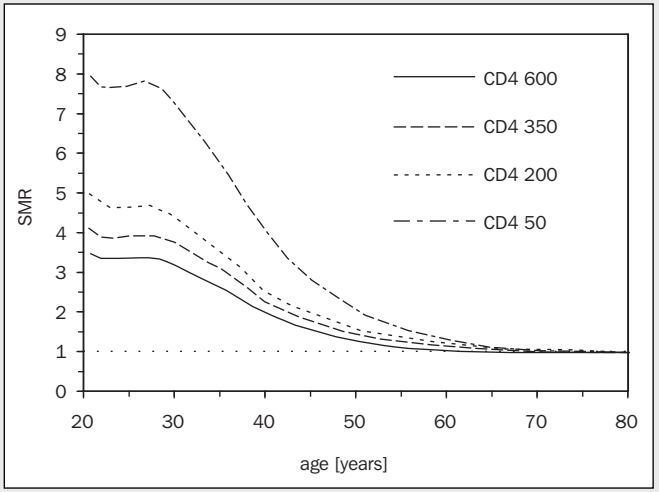


Figure10.2: Proportion of deaths from (top to bottom) non-HIV-related causes, HIV-related causes, and unknown causes.



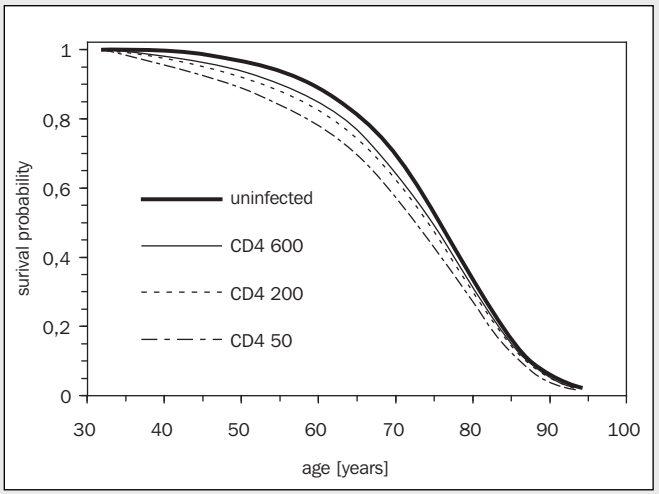


Figure10.3: Standardised mortality ratios (SMR) (upper panel) and expected survival probabilities up to the age on the horizontal axis (lower panel) for male patients without a concurrent CDC-B event at diagnosis for different CD4 counts: 600 (solid line), 350 (dashed line), 200 (dotted line) and 50 x 10^6 cells/l (dashed-dotted line). Predicted survival is calculated for a 34-year-old man. The thick solid line represents the survival probability for an uninfected individual.

Drug

TEN YEARS **HAART**

users

Injecting drug users and the effect of HAART

Colette Smit

Introduction

HAART has been shown to be effective in different populations[22, 128, 129]. However, data on injecting drug users (IDU) are limited.

Increased mortality rates have been found amongst IDU, and the benefits of HAART appear to be less strong in IDU[23, 75, 123, 130, 131]. Although the proportion of HAART initiation amongst drug users is increasing[132] relative to other HIV risk groups, IDU still appear to be less likely to commence HAART[133], and if HAART is initiated, the start occurs later in the HIV infection[134]. This delayed access to therapy may cause a poorer immunologic and virologic response. In an earlier study amongst drug users on HAART, short-term responses to HAART were similar to those amongst homosexual men, although HAART initiation amongst drug users was delayed[135]. Other studies showed less obvious virologic and immunologic responses in the short- and long-term[136, 137].

In the present study, we studied whether short-term responses to therapy changed over time and whether response to therapy differs between IDU and homosexual men.

Study population and methods

HIV-infected adult patients who commenced HAART after 1996 and in whom injecting drug use was the most likely route of transmission were selected for this analysis. Treatment-naïve, as well as pre-treated, patients were included. HAART was defined as including at least 3 antiretroviral drugs from at least 2 drug classes or a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen containing abacavir or tenofovir.

Short-term response by calendar time

Initial virologic success was measured as the proportion of drug users who achieved an HIV RNA level of ≤500 copies/ml 6 months after commencing HAART, and initial immunologic response was measured as an increase in CD4 cell count of at least 50 cells/μL 6 months after HAART initiation.

The odds ratios for achieving an undetectable viral load and achieving an increase in CD4 cell count of 50 cells/μL or more were modelled within a logistic regression model, using the generalised estimation equation (GEE) with an autoregressive covariance matrix to adjust for correlations between measurements within the same patient. Calendar years of HAART initiation were stratified as 1996-1998, 1999-2001, and 2002-2005 and were included in the model, with 1996-1998 as the reference period.

Comparison of short-term response between IDU and homosexual men

The immunologic and virologic responses amongst drug users were compared with homosexual men in one model. The response of CD4 cell count and viral load after HAART initiation was piecewise modelled in a random effect model, which allowed for a random intercept. The slope was allowed to change at 6 months after HAART initiation.

If HIV RNA levels were below the quantification limit, the midpoint between this limit and 0 was used as the HIV RNA level. HIV RNA $\log_{10}$ values were used instead of absolute values.

Patients without any CD4 or viral load measurement at the start of HAART were excluded from the analysis.

Results

A total of 607 patients were infected via injecting drug use; of those, 488 started HAART between 1996 and 2005. Table 11.1 shows the patients' characteristics at baseline by calendar time period and CD4 cell counts and HIV RNA levels after 6 months of HAART.

The median CD4 cell count at the start of HAART decreased from 222 cells/μL (IQR: 90-330) in 1996-1998 to 184 cells/μL (IQR: 60-290) in the more recent years ($p<0.001$). IDU who initiated therapy in 1996-1998 had a lower viral load relative to those who started in 2002-2005 ($p<0.001$).

In 1996-1998 60% of the IDU achieved an HIV RNA level of 500 or less copies/ml at 6 months after HAART initiation, whereas in 2002-2005 this proportion increased to 82%.

Short-term response by calendar time

Immunologic effectiveness

Table 11.2 shows the adjusted odds ratios (OR) for reaching an increase in CD4 cell count of at least 50 cells/μL at 6 months after the start of HAART by the calendar time period of HAART initiation for all patients, with separate categories for IDU and homosexual men. Overall, the risk of reaching a successful increase in CD4 cell counts significantly changed compared to 1996-1999 (overall, p<0.0001). In IDU, the overall risk of reaching a successful increase in CD4 cell count did not significantly change over time; however after 2002, the OR of reaching a successful increase in CD4 cell count was 1.27 (95% CI: 1.08-1.49) times higher than that between 1996-1999.
Amongst homosexual men, the OR of reaching an increase in CD4 cells of at least 50 cells/μL or more increased between 1996 and 2005 (overall, p<0.0001).

Virologic success

Compared to the IDU who started therapy between 1996-1998, the odds ratio for IDU reaching HIV RNA levels of 500 or less copies/ml was 1.97 (95% CI: 1.73-2.24) for 1999-2001, and it was 1.52 (1.27-1.83) in 2002-2005 (overall, p=0.006) (Table 11.3). This suggested that the initial virologic response became better after HAART became available, but did not improve over time. However, the initial virologic response amongst homosexual men was stronger (overall, p<0.0001).

CD4 cell counts and HIV RNA levels

The immunologic and virologic responses of IDU with a CD4 cell count or HIV RNA measurement at the time of HAART initiation (n=396) were compared with those of homosexual men (n=3794).

CD4 cell counts

IDU had lower CD4 cell counts when starting HAART (median 210 cells/μL; IQR: 80-300 cells/μL) compared with homosexual men (295 cells/μL; 90-320 cells/μL) (p<0.001). The modelled immunologic response is shown in Figure 11.1. During the first 6 months after HAART initiation, CD4 cell counts increased in both groups, with similar slopes for both IDU and homosexual men. More than 6 months after the start of HAART, CD4 cell counts continued to increase amongst both groups, but the slopes differed significantly between IDU and homosexual men (p<0.001); CD4 cell counts increased faster amongst homosexual men.

HIV RNA levels

At time of HAART initiation, IDU had a lower viral load (HIV RNA level 4.5 $\log_{10}$ copies/ml; IQR: 4.0-5.2) relative to homosexual men (4.8 $\log_{10}$ copies/ml; IQR:4.4-5.4; p<0.001). In the first 6 months after HAART initiation, a strong decline in viral load was observed amongst both IDU and homosexual men (Figure 11.2). This decline was stronger amongst homosexual men (p<0.001). More than 6 months after HAART initiation, the decrease in viral load did not remain significant amongst IDU. Still, a significant difference (p=0.01) in the slopes between IDU and homosexual men was seen with HIV RNA levels showing a slower decrease amongst IDU.

AIDS and Death

During follow-up, 251 (41%) of the IDU progressed to AIDS, and 146 (24%) died. The time to the first AIDS event did not differ between IDU and homosexual men. However, a significant difference in time to death was observed between IDU and homosexual men (p<0.0001, Log-Rank test). Ten years after receiving an HIV diagnosis, 17% of the HAART-treated IDU had died, whereas 9% of the homosexual men died during the same period of follow-up.

Discussion

In the present study, the short-term response after HAART initiation amongst IDU and homosexual men were compared, and trends in immunologic and virologic responses were studied over time. Strong virologic and immunologic responses were seen shortly after HAART initiation amongst IDU, and the proportion of successfully treated IDU increased over time. Although the virologic response was effective, it was not as strong as that seen amongst homosexual men; the immunologic response, in contrast, was similar to that found in homosexual men.

In this study, lower baseline CD4 cell counts in IDU compared with those in homosexual men show that the initiation of HAART is delayed in IDU, although this delay did not cause a different immunologic response between IDU and homosexual men in the first 6 months of treatment. Several factors may cause the delay. Injecting drug users may arrive at the hospital with a more advanced HIV infection. Also, since IDU have lower CD4 cell counts relative to those of homosexual men at the time of HIV diagnosis, it is possible that IDU have been infected with HIV longer by the time of diagnosis, resulting in a more advanced HIV infection when they come to a hospital for HIV treatment. Delayed HAART initiation may, in addition, reflect provider caution in prescribing HAART to IDU. Reported barriers for prescribing HAART are patients' current drug use, ability to keep appointments, housing, and adherence[138]. IDU who are less adherent are less likely to attain undetectable HIV RNA levels, but since 82% of the IDU achieved an undetectable load after 6 months, poor adherence is questionable.

Although HIV RNA levels decrease strongly after HAART initiation, this response is not as strong as the virologic response amongst homosexual men. Earlier studies demonstrate similar responses between IDU and homosexual men[133, 135], also after a delayed start of HAART. This contradictory result could be explained by the higher proportion of pre-treated IDU (19%) relative to that of pre-treated homosexual men (6%). It has been shown that HIV-infected persons who have had prior treatment are less likely to achieve an undetectable viral load[139]. However, a sensitivity analysis that excluded those with prior treatment showed the same results.

Because of the lower baseline CD4 cell count level and poorer virologic response, it is likely that the response to long-term therapy will be less effective. However, the time to the first AIDS event did not differ between IDU and homosexual men. On the other hand, IDU had a higher probability of dying compared to that of homosexual men, which may be a result of poorer virologic response, as well as the increased risk of non-natural death amongst IDU in the HAART-era because of overdose or suicide[75].

Although the selection of HIV-infected injecting drug users in this study might be limited to those with access to care, the results of this study show that such users who have adequate access can be treated effectively. The treatment response is improving over time, and the short-term CD4 and HIV RNA responses in later years for IDU are moving closer to those for homosexual men. However, earlier HAART initiation is important to improve the long-term response in injecting drug users.

Year of starting HAART	No. patients	Baseline Age, median (IQR)	Male(%)	CD4 cell count, median (IQR) cells/µL	Log_{10} viral load, median (IQR)	Treatment response at 6 months after HAART initiation CD4 cell count, median (IQR) cells/µL	Log_{10} viral load, median (IQR)	No. Of patients with viral load<500 (%)
1996-1998	243	47 (42-51)	168 (69)	222 (90-330)	4.6 (3.9-5.2)	332 (160-450)	2.6 (2.3-3.3)	117 (60)
1999-2001	141	45 (41-50)	104 (74)	217 (90-287)	4.7 (4.1-5.2)	300 (150-410)	1.8 (1.7-2.9)	91 (73)
2002-2005	96	43 (39-48)	73 (77)	184 (60-290)	4.9 (4.1-5.0)	262 (110-350)	1.7 (1.7-1.9)	63 (82)
Unknown	8	-	-	-	-			
Total	3	45 (41-50)	445 (88)					

IQR: interquartile range

Table 11.1: Characteristics of injecting drug users at baseline and after 6 months of therapy, by calendar time period of the start of HAART

Year of starting HAART	All*	IDU*	Homosexual men*
1996-1998 (reference)	1	1	1
1999-2001	1.29 (1.24-1.35)	0.92 (0.83-1.02)	1.41 (1.35-1.48)
2002-2005	1.55 (1.47-1.63)	1.27 (1.08-1.48)	1.54 (1.44-1.62)

CI: confidence interval; IDU: injecting drug user

* Multivariate analyses, adjusted for baseline viral load, baseline CD4 cell count, age, sex and repeated measurements within one patient

Table 11.2: Odd ratios (95% CI) for achieving an increase in CD4 cell count of at least 50 cells/µL.

Year of starting HAART	All*	IDU*	Homosexual men*
1996-1998 (reference)	1	1	1
1999-2001	2.11 (2.02-2.20)	1.97 (1.73-2.24)	2.16 (2.06-2.26)
2002-2005	2.08 (1.97-2.18)	1.52 (1.27-1.83)	2.11 (2.01-2.23)

CI: confidence interval; IDU: injecting drug user

* Multivariate analyses, adjusted for baseline viral load, baseline CD4 cell count, age, sex and repeated measurements within one patient

Table 11.3: Odd ratios (95% CI) for achieving HIV-1 RNA viral load ≤500 ml/copies.

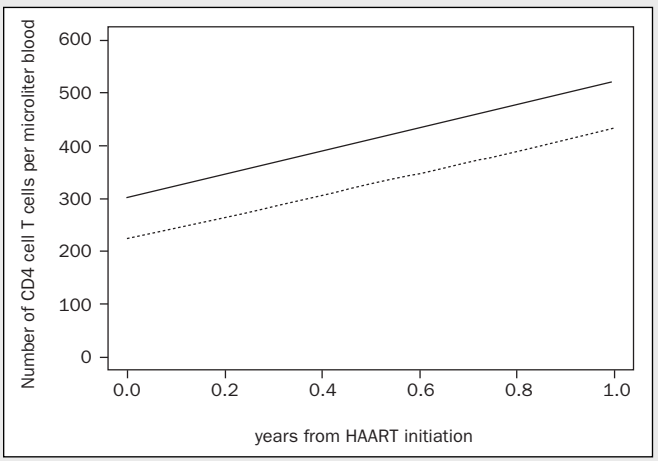


Figure11.1: Immunologic response, piecewise modelled course of CD4 cell counts after HAART initiation among homosexual men (black line) and injecting drug users (dashed line).

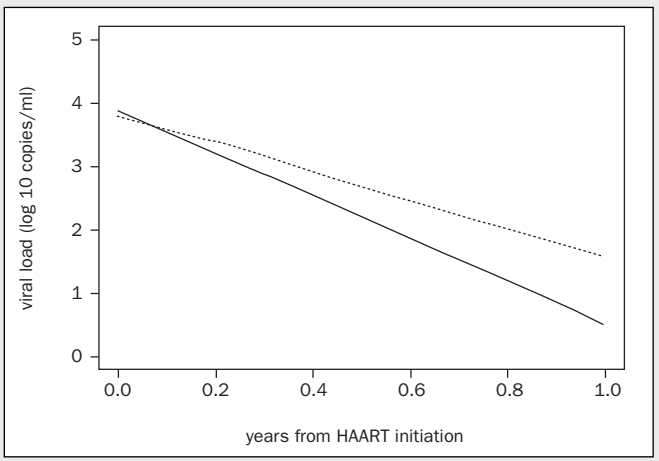


Figure11.2: Virologic response, piecewise modelled course of CD4 cell counts after HAART initiation among homosexual men (black line) and injecting drug users (dashed line).

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TEN YEARS **HAART**

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Pregnancies amongst HIV-infected women

Colette Smit

Introduction

Mother-to-child transmission (MTCT) of HIV is the most important route of transmission amongst children[140]. However, as a result of improved prevention in Western countries, MTCT has been reduced dramatically in the last 10 years. Administration of HAART to the mothers during pregnancy and at delivery and to the newborn children in their first weeks of life, in combination with caesarean delivery, has decreased HIV transmission rates from between 15 and 40%[141] to 2%[142].

Knowledge of the HIV status of pregnant women is necessary to reduce the risk of MTCT. In January 2004, voluntary HIV-antibody testing of pregnant women according to the opting out method was introduced in the Netherlands[143]. With this method, pregnant women are informed that an HIV-antibody test will be included in the prenatal screening, unless the women decline to have it performed. In a pilot study amongst pregnant women in Amsterdam, the effectiveness of this method of HIV screening was evaluated[36]. The study showed an increase in the HIV prevalence amongst pregnant women compared to 10 years earlier, and most HIV infections were found amongst women originating from sub-Saharan Africa[36].

It is likely that the number of pregnancies amongst HIV-infected women will increase with the improved prevention of MTCT and newly routine screening of pregnant women. The purpose of this chapter is to describe the pregnancies amongst HIV-infected women in the Netherlands and to evaluate changes in demographic characteristics and treatment regimens over time.

Methods

Study population

The study population consisted of all HIV-infected women aged at least 18 years who were registered and followed longitudinally in the ATHENA observational cohort. All pregnancies occurring amongst these women between 1996 and 2005 were included in the analyses, and the youngest pregnant woman was 18 years old.

The registered pregnancy dates by definition did not represent the first day of the last menstrual period as the starting point, and no distinction was made according to birth or abortion (either spontaneous or induced). Therefore, pregnancy is defined as having a pregnancy registered in the ATHENA database.

Data for all registered pregnant women was collected following the regular ATHENA protocol (see Chapter 4), and data were available for the date of HIV diagnosis, age, route of transmission, region of origin, and current and history of therapy use. However, collection of additional pregnancy-related data (such as outcome of the pregnancy: birth or induced/spontaneous abortion and the mode of delivery) was not completed at the time of analysis. For this reason, we will not focus on pregnancy outcome, and the mode of delivery is described for only half of the pregnancies.

Statistical methods

Analyses were conducted for all women and stratified by geographic origin that was categorised as Dutch, sub-Saharan African, or “other”. The chi square test was used to look for differences in known HIV status before pregnancy between women of different geographic origin, and the Cochran-Armitage test for trend was used to evaluate changes over time in the mode of delivery. Differences in the median age of pregnant women of different geographic origins were tested with the Wilcoxon Mann-Whitney test.

The number of pregnancies per calendar year, with a 95% confidence interval (CI), were calculated per 1000 person-years. All women were considered to be “at risk” for pregnancy, and that number was taken into account when calculating the person-time. Person-time was measured from the time of the HIV diagnosis until the last visit, death, point when the patient was lost to

follow up, or as of 1 January 2006. A Poisson regression model was used to test the effect of calendar year on the occurrence of pregnancy.

Results

Out of 3054 women who were being followed in the ATHENA observational cohort between 1996 and 2005, 749 became pregnant. A total of 980 pregnancies occurred amongst these 749 women during that time. Ten women were infected with HIV-2. Median age at first pregnancy was 28 years (IQR: 24-33). For 94% of the women, heterosexual contact was the route of HIV transmission. The country of origin for 458 (75%) was sub-Saharan Africa, and 107 (14%) were Dutch. Of the 184 women originating from other regions, 48 came from Surinam and 35 from the Netherlands Antilles. The median age at time of their pregnancy varied between ethnic groups; women originating from the Netherlands were significantly older than non-Dutch women (Table 12.1).

Incidence of pregnancy amongst HIV-infected women and geographic origin of the mothers

Overall, the incidence was 54 (95% CI: 50-58) pregnancies per 1000 person-years. The overall incidences according to geographic origin are presented in Figure 12.1. The overall incidence of pregnancy significantly increased from 31 per 1000 person-years (py) in 1996 to 71 per 1000 py in 2005 ($p<0.001$). The incidence was higher amongst women originating from sub-Saharan Africa, increasing from 83 per 1000 py in 1996 to 94 per 1000 py in 2005. Amongst Dutch women, the number of pregnancies significantly increased from 7 per 1000 py in the mid-1990s to 48 per 1000 py in 2005 ($p=0.02$).

HIV diagnosis during pregnancy

HIV was diagnosed during pregnancy in 36% of the women. The fraction of women unaware of their HIV status at the point of becoming pregnant did not significantly change over time. However, significant differences were found between women of different geographic origin. Dutch women became pregnant knowing their HIV status (86%) more often than non-Dutch women (56-60%) ($P<0.001$).

Treatment

Overall, 402 (54%) of the women were receiving HAART before becoming pregnant, and 205 women initiated HAART during their pregnancy (Table 12.2).

The proportion of pregnant women who initiated HAART before or during their pregnancy increased from 12% in 1996 to 82% in 2005 ($P<0.001$).

In 1996, an AZT (zidovudine) /3TC (lamivudine) regimen was most commonly used amongst pregnant women. However, between 1997 and 2005, a regimen of AZT/3TC + NFV (nelfinavir) became the most prescribed combination. Other common regimens are shown in Table 12.2.

Mode of delivery

Of the 980 pregnancies, data on the mode of delivery was available for 494 pregnancies.

279 babies were delivered vaginally, and 209 were delivered by caesarean delivery; in 6 pregnancies the mode of delivery was unknown. The proportion of caesarean deliveries did not change over time ($p=0.37$), and no differences were found between women of Dutch origin and non-Dutch women.

Discussion

Amongst HIV-infected women registered and monitored in the ATHENA observational cohort, the number of pregnancies has increased over time.

Although the number of pregnancies was highest amongst women originating from sub-Saharan Africa, the incidence did not increase over time in this group, whereas it did increase amongst Dutch HIV-infected women. Compared to non-Dutch women, women of Dutch origin were older at the time of pregnancy, and they knew their HIV-positive status more often.

Differences in the incidence of pregnancies between women of different geographical origin have been found previously, and incidence rates of pregnancy have been reported to be higher amongst women originating from Africa[144]. The decision to become pregnant after receiving a diagnosis of HIV infection has been found to be culturally and socially related[145]. In our study, the proportion of women who were unaware of their HIV infection when they became pregnant was higher amongst non-Dutch women. This can be explained largely by the characteristics of the HIV epidemic in the Netherlands, where a substantial proportion of the heterosexually infected individuals are women from sub-Saharan African countries in whom HIV is diagnosed for the first time as part of the prenatal screening programme in the Netherlands.
In Dutch women who were on average older, awareness of their HIV infection, in combination with a better knowledge of improved MTCT prevention[142], may have resulted in more carefully planned pregnancies with a reduced proportion of induced abortion[145]. Before the availability of HAART, the proportion of induced abortion amongst HIV-infected women was higher[146].
With the success of HAART in achieving undetectable viral load, the benefit of caesarean delivery has been questioned[147, 148]. Nevertheless, an earlier study amongst pregnant women showed that half of the women had detectable viral loads at time of delivery[149]. Therefore, in the future it will be important to analyse the HIV RNA levels at time of delivery in association with caesarean delivery.

The increase in pregnancies amongst Dutch women who are aware of their HIV-positive status, suggests that these women are prepared to plan their pregnancy with the knowledge that the risk of MTCT has been dramatically reduced in the HAART era.

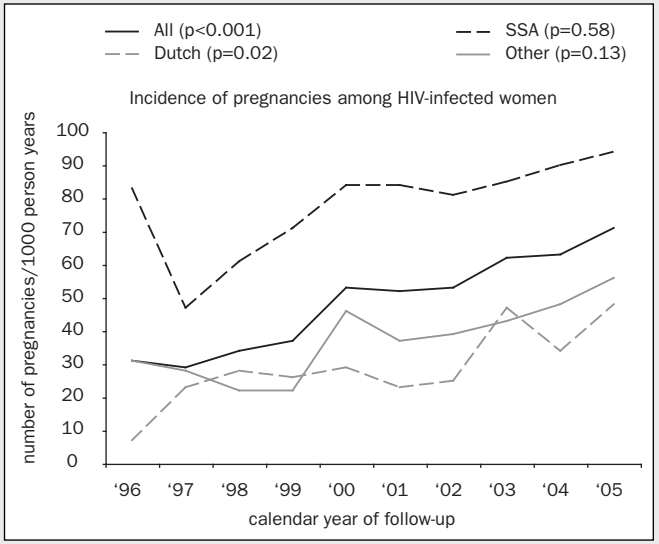

Figure 12.1: Number of pregnancies per 1000 person-years amongst HIV-infected women, overall and according to region of origin.

	All		Dutch		Sub-Saharan African		Other	
	total	HIV diagnosis during pregnancy	total	HIV diagnosis during pregnancy	Total	HIV diagnosis during pregnancy	total	HIV diagnosis during pregnancy
1996	25	8 (32)	2	0 (0)	15	6 (40)	8	2 (25)
1997	30	8 (27)	8	0 (0)	13	5 (38)	9	3 (33)
1998	45	14 (31)	11	1 (9)	22	8 (36)	12	5 (42)
1999	57	24 (42)	12	3 (25)	33	17 (52)	12	4 (33)
2000	97	51 (52)	14	1 (7)	61	43 (71)	22	7 (32)
2001	111	43 (39)	13	2 (15)	73	27 (37)	25	14 (56)
2002	122	41 (34)	14	3 (21)	80	29 (36)	28	9 (32)
2003	166	69 (42)	27	3 (11)	105	50 (48)	34	16 (47)
2004	162	55 (34)	21	2 (10)	106	36 (34)	35	17 (49)
2005	165	41 (25)	29	6 (21)	98	24 (24)	38	11 (29)
Total	980	354 (36)	151	21(14)	606	245 (40)	223	88 (39)
Age at pregnancy (median, IQR*)	28 (24-33)		31 (28-35)		28 (23-33)		28 (25-33)	

* IQR: interquartile range

Table 12.1: Total number of pregnancies per calendar year and per ethnic group and the number of pregnancies amongst women who were diagnosed with HIV during their pregnancy.

Total number of pregnant women	N=749	
No therapy before or during pregnancy	142	
Start therapy:		
- before pregnancy	402	
- during therapy	205	
Most common regimen:		n/known regimens (%)
1996	AZT	7/21 (33)
	AZT/3TC	8/21 (38)
1997	AZT/3TC	3/25 (12)
	AZT/3TC + NFV	4/25 (16)
	AZT/3TC + IDV	3/25 (12)
1998	AZT/3TC + NFV	9/31 (29)
	AZT/3TC + IDV	4/31 (13)
	AZT/3TC + NVP	4/31 (13)
1999	AZT/3TC + NFV	17/41 (41)
	AZT/3TC + NVP	6/41 (15)
2000	AZT/3TC + NFV	45/77 (58)
	AZT/3TC + NVP	9/77 (12)
2001	AZT/3TC	10/90 (11)
	AZT/3TC + NFV	29/90 (32)
	AZT/3TC + NVP	20/90 (22)
2002	AZT/3TC + NFV	29/84 (34)
	AZT/3TC + NVP	28/84 (33)
	AZT/3TC + NFV	51/124 (41)
2003	AZT/3TC + NVP	32/124 (26)
	AZT/3TC + LOP/r	7/124 (6)
2004	AZT/3TC + NFV	53/101 (52)
	AZT/3TC + LOP/r	21/101 (21)
2005	AZT/3TC + NFV	29/81 (36)
	AZT/3TC + NVP	8/81 (10)

AZT: Zidovudine; 3TC: Lamivudine; NVP: Nevirapine; Lop/r: Lopinavir/Ritonavir; NFV: Nelfinavir; IDV: Indinavir.

Figure 12.2: Treatment characteristics amongst pregnant women.

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TEN YEARS **HAART**

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Decrease in mother-to-child transmission

Colette Smit

Introduction

In the Netherlands, most children are infected by mother-to-child-transmission (MTCT), and one or both of the parents of the majority of HIV-infected children originate from AIDS-endemic countries[150]. Although several studies have shown an improved response to therapy and an improved prognosis for HIV-1 infected children who are treated with HAART[151-153], several factors complicate the treatment of these children. Generally, children are infected with HIV when their immune system is still immature, which causes a different HIV progression compared with that in adults[154]. Also, the immune response in children varies with age[155, 156]. This leads to uncertainty about when to start therapy. However, the 10 years of experience in treating HIV-infected children may have improved the short-term immunologic and virologic responses after HAART initiation. Since 2004, HIV-infected children in the Netherlands have been registered and monitored like infected adults by the HIV Monitoring Foundation (HMF).

This chapter will report on the changes in the immunologic and virologic responses to antiretroviral treatment amongst these children over time.

Study population and methods

The study population consisted of children defined as patients who were younger than 18 years of age on 1 January 2006 and infected with HIV-1 by MTCT via breast feeding or blood or, in cases where the mode of transmission was missing, by the receipt of an HIV diagnosis below the age of 13 years. Such children are registered and monitored as part of the ATHENA observational cohort. Clinical, epidemiologic, virologic, and immunologic data are collected from 4 specifically acknowledged paediatric HIV treatment centres. These centres participate in the monitoring of HIV through the HMF in Amsterdam.

In addition to the routine demographic data, information on the region of origin of the parents was collected for this study. Region of origin was categorised as the Netherlands, sub-Saharan Africa, or "other".

The proportion of children infected by MTCT was calculated in relation to the total number of annual HIV diagnoses.

To assess improvement in the immunologic and virologic response to therapy over time, we evaluated the effect of calendar time among children who initiated HAART. CD4 cell counts and HIV RNA levels were measured at baseline and after HAART initiation. The response of CD4 cell count and viral load after HAART initiation was piecewise modelled in a random effect model, which allowed for a random intercept. The slope was allowed to change at 6 months after HAART initiation. Calendar year of HAART initiation was subdivided into before the year 2000 and after 2000. All analyses were adjusted for sex, age at CD4 cell count or viral load measurement, and region of origin. If HIV RNA levels were below the quantification limit, the midpoint between this limit and 0 was used as the HIV RNA level. HIV RNA $\log_{10}$ copies/ml were used instead of absolute values. Children without any CD4 cell count or viral load measurement at the start of HAART were excluded from the analysis.

When we modelled the immunologic response, we divided the group into those who were 2 years or younger at time of HAART initiation and those older than 2 years at HAART initiation, because CD4 cell counts are age-related[157] and the immune response varies with age[155, 156].

Results

The study population consisted of 132 children of whom 72 (54%) were boys and 61 (46%) were girls. Characteristics of the children are presented in Table 13.1. The median age at HIV diagnosis was 1.2 years (interquartile range; 0.4-4.5).

Most children (83 out of 132; 63%) were born in the Netherlands, but 76 (92%) of them had at least one parent who originated outside the Netherlands (data

not shown). The majority had at least one parent from sub-Saharan Africa.
MTCT was the route of infection for 120 children (91%), and 113 of those who were infected that way were born before 2003. The proportion of vertically infected children with a diagnosis of HIV has decreased since 2003 (Figure 13.1). One boy was infected by blood contact in sub-Saharan Africa. Two girls diagnosed between the ages of 14 and 17 years were infected by sexual contact and were not included in the present analysis.

Short-term response by calendar time

At HIV diagnosis, the median CD4 count was 720 x 10^6 cells/L (IQR: 335-1545) and the median HIV RNA level was 5.0 $\log_{10}$ copies/ml (IQR: 4.4-5.6). Of the 132 children, 112 initiated HAART, and the median time between HIV diagnosis and HAART initiation was 0.2 years (IQR: 0.1-0.9). The median CD4 cell count at time of HAART initiation was 635 x 10^6 cells/L (IQR: 190-1155), but increased to 1150 x 10^6 cells/L (IQR: 711-1860) after 24 weeks of HAART treatment. The median HIV RNA levels decreased from 5.4 $\log_{10}$ copies/ml (IQR: 4.7-5.9) at HAART initiation to 2.6 $\log_{10}$ copies/ml (IQR: 1.7-2.8) 24 weeks after HAART initiation.

Figure 13.2a shows the immunologic response among children below 2 years of age at the time of HAART initiation (T0); the response is stratified by the calendar year of the start of HAART. At the time of HAART initiation amongst those children who began therapy after the year 2000, the CD4 cell counts were significantly higher than amongst those who commenced HAART before 2000 ($p=0.03$). In the first 6 months after HAART initiation, CD4 cell counts increased significantly ($p<0.001$). However, this increase did not significantly differ between calendar time periods. After 6 months, the CD4 cell counts were still increased, but this increase was not significant and did also not significantly differ between calendar time periods for HAART initiation.

Compared to children who started HAART at the age of two years or less, the older children had significantly lower CD4 cell counts at time of HAART initiation ($p<0.001$) (data not shown). The immunologic response amongst the children who were 2 years or older at time of HAART initiation is presented in Figure 13.2b. Among the older children, the CD4 cell counts increased after HAART initiation, and this increase was significant in the first 6 months after HAART initiation ($p<0.001$), as well as more than 6 months after initiation ($p<0.02$). However, the CD4 cell increase did not differ between calendar time period of HAART initiation.

In Figure 13.3, the virologic response after HAART initiation is shown for all children. HIV RNA levels were significantly lower amongst those who initiated HAART after the year 2000 ($p<0.0001$). In the first 6 months of therapy, HIV RNA levels declined significantly ($p<0.001$); after the initial response, the HIV RNA levels continued to decrease ($p=0.006$). The rate of decrease in HIV RNA levels did not differ between calendar time periods.

Discussion

Most HIV-positive children registered in the Netherlands are infected by MTCT. Whilst most of them were born in the Netherlands, only a few have both parents who originated in the Netherlands, and a majority have at least one parent from sub-Saharan Africa.
MTCT of HIV has been in decline since 2003. In January 2004, the voluntary HIV antibody testing of pregnant women was introduced in the Netherlands[143], and the decline in vertical transmission of HIV amongst those born after January 2004 is likely to be a result of this new HIV screening programme amongst pregnant women.

As of 1 January of 2006, data from the ATHENA observational cohort on 133 children were available. A total of 163 children were reported as being treated in one of the 4 paediatric HIV treatment centres. To date, data on 133 children can be used.

Higher CD4 cell counts at baseline for those children who initiated HAART after the year 2000 shows that currently young children are treated earlier in their HIV infection than those treated before 2000. In contrast, no changes in time of HAART initiation among children older than 2 years of age were observed. Knowledge of the effect, efficacy, toxicity, and safety of antiretroviral therapy in children has improved, and treating physicians now may be less hesitant to treat young children. Despite the existence of treatment guidelines for HIV-infected children[45], treatment policies vary amongst paediatric centres over Europe[158], and recently, it has been shown that children in the United Kingdom and Ireland are not receiving the optimal dose of antiretroviral therapy on the basis of their weight[159]. These findings implicate uncertainty in the prescription of HAART amongst HIV-1 infected children.

Since less follow-up is available to measure the outcomes of HAART initiation early in HIV infection, such as life expectancy, development of AIDS, death, side effects, and toxicity of HAART, monitoring of HIV-infected children remains important to evaluate the current treatment guidelines, as well as to optimise treatment.

	All (%)	Boys (%)	Girls (%)
Number	132	71 (54)	61(46)
Region of origin			
- The Netherlands	83 (63)	47 (65)	36 (61)
- Sub-Saharan Africa	37 (28)	19 (26)	18 (30)
- Other	12 (9)	6 (8)	12 (10)
Region of parents			
- both the Netherlands	8 (6)	6 (8)	2 (3)
- one or both Sub-Saharan Africa	87 (66)	49 (69)	38 (62)
- one or both other region	37 (28)	16 (22)	21 (34)
Route of transmission			
- MTCT	120 (91)	64 (90)	56 (92)
- Blood	1 (1)	1 (1)	0
- Unknown	11 (8)	6 (8)	5 (8)
Year of HIV diagnosis			
≤ 1995	18 (14)	7 (10)	11 (19)
1996-2000	27 (22)	16 (24)	11 (19)
2000-2003	45 (35)	22 (31)	23 (39)
2003-2006	39 (30)	25 (64)	14 (36)
Age at diagnosis			
≤ 2 years	69 (52)	33 (46)	36 (59)
> 2 years	63 (48)	38 (54)	25 (41)
HAART initiation			
At ≤ 2 years of age	45 (40)	26 (43)	19 (37)
At > 2 years of age	67(60)	35 (57)	32 (63)
Baseline CD4 cell counts (x10^6 cells/l) (median, IQR)			
≤ 2 years of age at baseline	850 (194-1480)	695 (170-1460)	882 (620-1890)
> 2 years of age at baseline	480 (130-970)	585 (285-1000)	420 (110-760)
CD4 cell counts (x10^6 cells/l) (median, IQR) at T1			
≤ 2 years of age at baseline	1760 (1150-2450)	1585 (920-2375)	2000 (1550-2690)
> 2 years of age at baseline	720 (535-1140)	720 (450-1150)	720 (580-1090)
Baseline HIV RNA (log_{10} copies/ml) (median, IQR)			
≤ 2 years of age at baseline	5.8 (5.5-6.1)	5.9 (5.6-6.2)	5.7 (5.4-5.9)
> 2 years of age at baseline	4.9 (4.3-5.5)	5.1 (4.7-5.7)	4.7 (4.2-5.4)
HIV RNA (log_{10} copies/ml) (median, IQR) at T1			
≤ 2 years of age at baseline	2.7 (2.3-2.9)	2.7 (2.5-2.9)	2.7 (1.8-2.9)
> 2 years of age at baseline	2.4 (1.7-2.6)	2.1 (1.7-2.6)	2.4 (1.7-2.6)

Baseline: start of HAART; T1: 24 weeks after start of HAART; IQR: interquartile range; MTCT: mother-to-child transmission

Table 13.1: Characteristics of HIV-1 infected children.

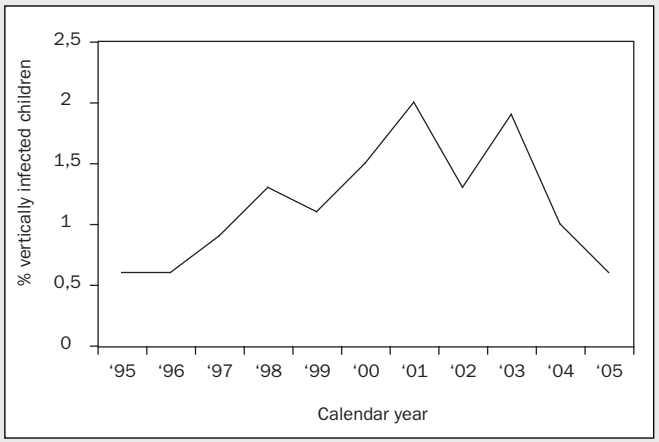

Figure 13.1: Percentage of children diagnosed with HIV amongst the annual number of HIV diagnoses. Only diagnosed children who are vertically infected with HIV are included.

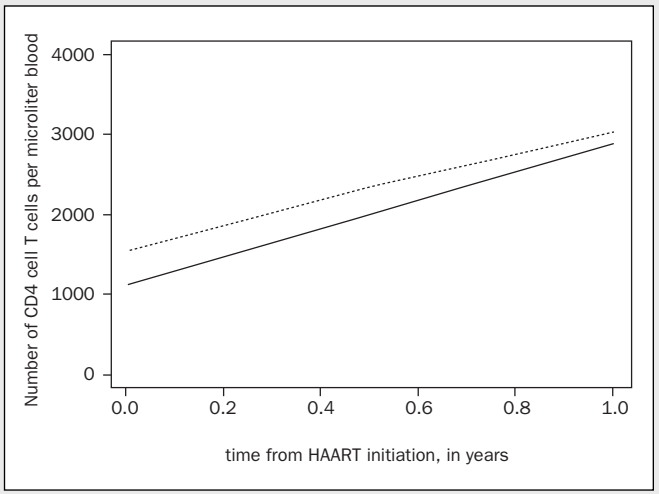

Figure 13.2a: Median CD4 cell count after HAART initiation in children less than two years of age at the start of HAART. Black line represents the children who initiated HAART before 2000, dashed line the children who initiated HAART after the year 2000.

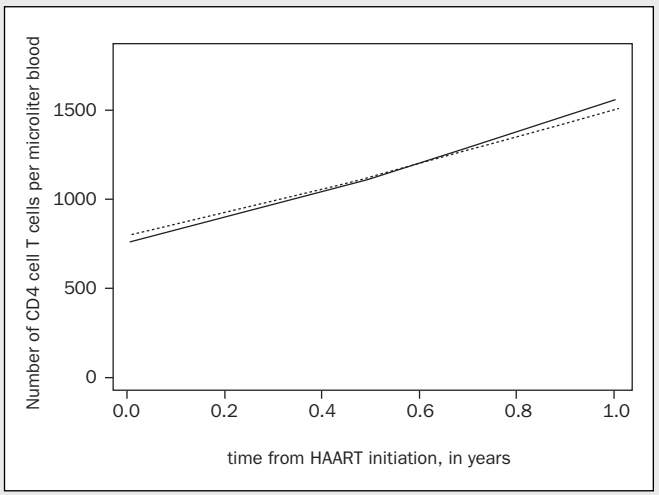

Figure 13.2b: Median CD4 cell count after HAART initiation in children older than two years of age at the start of HAART. Black line represents the children who initiated HAART before 2000, dashed line the children who initiated HAART after the year 2000.

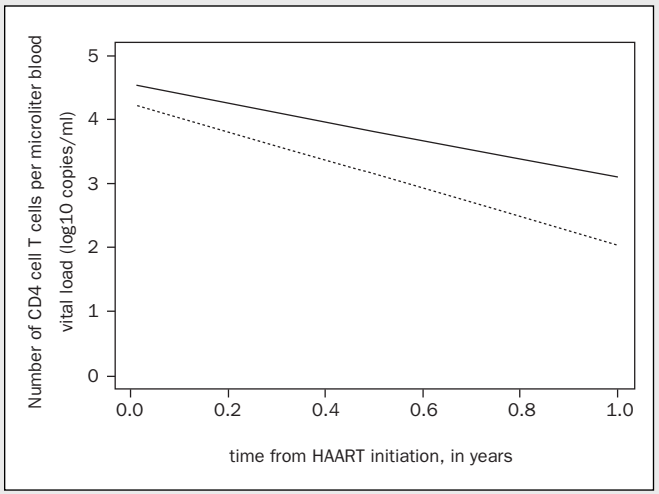

Figure 13.3: Median viral load after HAART initiation in children. Black line represents the children who initiated HAART before 2000, dashed line the children who initiated HAART after the year 2000.

Tubero

TEN YEARS **HAART**

culosis

Increased incidence of tuberculosis

Luuk Gras

Introduction

In developing countries, tuberculosis (TBC) is the most frequent and severe complication amongst HIV-infected patients. It is also the most frequent and severe CDC-class C AIDS-defining event[160], as well as the leading cause of death in these patients. Highly active antiretroviral therapy (HAART) reduces the incidence of TBC through immune restoration. However, in a number of patients with subclinical symptoms, TBC becomes apparent shortly after the initiation of HAART because of the immune reconstitution syndrome[161, 162]. Patients treated with HAART for a longer period of time do remain at risk for TBC[163]. Immigration of persons from countries with a high TBC prevalence has resulted in an increasing incidence of TBC in Western Europe, and the proportion of AIDS patients with TBC has risen[164]. In an international collaboration of cohorts from Europe and North America, including the Dutch ATHENA cohort, the TBC incidence was related to CD4 cell counts at the start of HAART and to the short-term virological and immunological response after the initiation of HAART. The calendar year of HAART initiation and the HIV-transmission risk group were also associated with TBC incidence. This association might be the result of residual confounding of ethnicity and/or country of birth since these risk factors were not available in this international study[165].

Information on country of birth is available in the ATHENA cohort. We estimated the incidence of TBC in the Netherlands after the initiation of HAART according to the region of origin, as well as other potential risk factors.

Methods

The selection of patients included those infected with HIV-1 who were antiretroviral therapy-naïve and older than 16 years when HAART was first started, specifically, between 1 July 1996 and 31 December 2005. Patients with TBC prior to starting HAART were excluded. HAART was defined as a combination of at least 3 drugs from more than 2 drug classes or a combination of at least 3 nucleoside reverse transcriptase inhibitors including tenofovir or abacavir.

The incidence of first diagnosis of TBC (either pulmonary or extrapulmonary) during the first three years after the start of HAART was analysed. Incidence rates were calculated according to gender, transmission risk group (homosexual, heterosexual, injection drug use [IDU], blood-to-blood, and "other"), calendar year at the start of HAART, age (<37 and ≥37 years), CD4 cell count (<50, 50-200, 200-350, 350-500, >500 cells/mm^3, and "missing") and HIV RNA at the start of HAART (<4, 4-5, ≥5 $\log_{10}$ copies/ml, and "missing"), region of origin (Europe/North America/Australia, Caribbean/Latin America, Sub-Saharan Africa and Southeast Asia/North Africa), and the time after HAART initiation (0-3, 3-6, 6-12, 12-24 and 24-36 months). Person-years of follow-up (PYFU) for each patient was calculated from the start of HAART until the date of the diagnosis of TBC, date of death, date when lost-to-follow-up, or the date 3 years after HAART initiation, whichever came first. Poisson regression was used to identify independent risk factors for the incidence of TBC.

Results

Demographic and clinical characteristics at the start of HAART of the 6421 included patients were similar to those included in Chapter 7 (Table 14.1). Overall, 76.4% of the patients were male, 50.9% were infected through homosexual contact, 64.3% originated from Europe, North America, or Australia, and 17.9% from sub-Saharan countries. An AIDS-defining event prior to the start of HAART other than TBC was found in 22.4%. The median CD4 cell count at the start of HAART was 200 cells/mm^3 (IQR, 8-320).

During the first 3 years after the start of HAART (15422 person-years of follow-up), 72 patients were diagnosed

with TBC. The overall incidence was 4.67 per 1000 PYFU (95% CI, 3.65-5.88). Extrapulmonary TBC was diagnosed in 27 patients (37.5%), pulmonary TBC in 42 (58.3%), and both pulmonary TBC and extrapulmonary TBC in 3 patients. The incidence was highest in the 3 months after the start of HAART and declined with longer follow-up time (Table 14.1). Patients starting HAART in earlier calendar years were less frequently diagnosed with TBC compared with those starting in later years. The incidence of TBC peaked in patients starting HAART in 2004 and 2005.

According to the region of origin, the incidence was highest in patients from sub-Saharan Africa (13.6 per 1000 PYFU; 95% CI, 9.5-18.9), followed by Southeast Asia/North Africa (9.6; 3.8-19.7), and Caribbean/Latin America (5.2; 2.5-9.6); it was lowest in patients from Europe/North America/Australia (2.0; 1.2-3.0). Furthermore, the lower the CD4 cell count at HAART initiation, the higher the incidence of TBC. TBC rates were very high in patients infected through blood-to-blood contact (17.7 per 1000 PYFU), but confidence intervals were wide (4.8-45.2) because of the small number of cases (4, all from regions other than Europe/North America/Australia).

In multivariate Poisson regression (Table 14.2), the calendar year of starting HAART was not a risk factor. Patients from regions outside Europe/North America/Australia had higher rates of TBC. Heterosexual and blood-to-blood transmission were also associated with higher rates of TBC, but since this finding is likely to be correlated with their region of origin, it was not included in the final model. Only CD4 cell counts below 50 cells/mm^3 at the start of HAART seemed to be associated with higher TBC rates. The risk ratio of TBC of patients starting with CD4 cell counts <50 cells/mm^3 as compared with those with ≥50 cells/mm^3 was 2.05 (1.20-3.50; p=0.009).

Discussion

The incidence of TBC in the Netherlands in patients receiving HAART has been increasing since the introduction of HAART in 1996. The high incidence of TBC among patients starting HAART in 2004 and 2005 is due to the short-term follow-up of these patients and the finding that the incidence of TBC is highest in the first few months after starting HAART. These factors, together with the association of a pre-HAART CD4 cell count of <50 cells/mm^3 with a higher risk of TBC, indicate a role for restoration of the host immune system occurring shortly after the start of HAART[161, 166]. Another possible explanation for the increased incidence is that the diagnosis of TBC is delayed in patients with symptoms of that disease at the time of starting HAART. Multivariate analyses show that the trend in increasing incidence of TBC over time is caused mainly by immigration of HIV-infected patients to the Netherlands from countries where TBC is endemic, most notably from sub-Saharan Africa.

The overall incidence of TBC in patients who started HAART was 4.67 per 1000 person-years of follow-up, almost identical to the 4.69 per 1000 PYFU in The Antiretroviral Therapy Cohort Collaboration (ART-CC) study(165). In contrast to that study, we were able to estimate incidence according to the patients' region of origin. Patients from sub-Saharan Africa were found to be at the highest risk of TBC after starting HAART, followed by patients from Southeast Asia/North Africa. Prevalence rates in Africa (5.18 per 1000 persons) and Southeast Asia (3.04 per 1000 persons) were reported by the World Health Organization (WHO) to be the highest in the world[166].

Treatment of HIV-infected patients co-infected with TBC is complicated by interactions of antiretroviral drugs with tuberculostatic drugs and by overlapping toxicity. Furthermore, tuberculostatic drugs (rifamycines)

tend to lower the plasma levels of antiretroviral drugs whilst antiretroviral drugs influence the pharmacokinetics of rifabutin. The recommended HAART combination for a patient with a CD4 cell count of <100 cells/mm^3 with TBC co-infection, includes efavirenz[45]. Combinations of drugs including nevirapine or lopinavir/ritonavir can lead to hepatotoxicity[167].

Although the risk of TBC declined with longer follow-up, it remained at considerably high levels. TBC is one of the AIDS-defining events that may occur when CD4 cell levels are relatively high[168].

In conclusion, the increasing development of TBC in later calendar years is due to immigration of patients from countries with a much higher prevalence of TBC than that found in the Netherlands. Therefore, when HAART is started in patients originating from countries with a high prevalence of TBC, latent TBC should be considered, especially if the CD4 cell counts are low.

		Events	PYFU	Incidence rate /1000 PYFU (95% CI)
	Total	72	15422	4.67 (3.65-5.88)
Time after start HAART	0-3	30	1582	18.96 (12.79-27.06)
(months)	3-6	11	1532	7.18 (3.58-12.85)
	6-12	9	2880	3.12 (1.43-5.93)
	12-24	14	5104	2.74 (1.50-4.60)
	24-36	8	4323	1.85 (0.80-3.65)
Gender	Male	49	11949	4.10 (3.03-5.42)
	Female	23	3472	6.62 (4.20-9.94)
Region of origin	Caribbean/Latin America	10	1909	5.24 (2.51-9.63)
	Europe/North America/Australia	20	10204	1.96 (1.20-3.03)
	Sub-Saharan Africa	35	2576	13.59 (9.46-18.90)
	Southeast Asia/North Africa	7	733	9.55 (3.84-19.68)
Year of start of HAART	1996	2	903	2.21 (0.27-8.00)
	1997	4	2248	1.78 (0.48-4.56)
	1998	6	1757	3.41 (1.25-7.43)
	1999	7	1772	3.95 (1.59-8.14)
	2000	12	1734	6.92 (3.58-12.09)
	2001	6	1934	3.10 (1.14-6.75)
	2002	10	1852	5.40 (2.59-9.93)
	2003	12	1626	7.38 (3.81-12.89)
	2004	9	1116	8.06 (3.69-15.30)
	2005	4	477	8.38 (2.28-21.46)
CD4 cell count (cells/mm^3)	<50	20	2556	7.82 (4.78-12.08)
at start of HAART	50-200	20	4422	4.52 (2.76-6.99)
	200-350	15	3739	4.01 (2.25-6.62)
	350-500	3	1973	1.52 (0.31-4.44)
	≥ 500	4	1243	3.22 (0.88-8.24)
	Missing	10	1489	6.72 (3.22-12.35)
Transmission risk group	Homosexual	17	8144	2.09 (1.22-3.34)
	Injection drug use	1	633	1.58 (0.04-8.80)
	Heterosexual	46	5434	8.47 (6.20-11.29)
	Blood-to-blood contact	4	226	17.66 (4.81-45.22)
	Other	4	984	4.06 (1.11-10.41)
HIV RNA (log_{10} cps/ml)	<4	10	1663	6.01 (2.88-11.06)
at start of HAART	4-5	18	5764	3.12 (1.85-4.94)
	≥ 5	29	5945	4.88 (3.27-7.01)
	Missing	15	2050	7.32 (4.10-12.07)
Age at start of HAART	<37	41	7403	5.54 (3.97-7.51)
	≥ 37	31	8018	3.87 (2.63-5.49)
CDC-C event prior to HAART	Yes	14	3334	4.20 (2.30-7.05)
	No	58	12088	4.80 (3.64-6.20)

PYFU: Person-years of follow-up CI: confidence interval

Table 14.1: Incidence of new TBC diagnoses during the first three years after the start of HAART, according to demographic and clinical characteristics.

		Relative risk (95% CI)	p-value
Time after start of HAART (months)	0-3	1.00	
	3-6	0.38 (0.19-0.76)	0.006
	6-12	0.17 (0.08-0.35)	<0.0001
	12-24	0.15 (0.08-0.28)	<0.0001
	24-36	0.10 (0.05-0.23)	<0.0001
CD4 count (cells/mm³) at start of HAART	<50	1.94 (0.99-3.81)	0.053
	50-200	1.08 (0.55-2.10)	0.83
	200-350	1.00	
	350-500	0.46 (0.13-1.60)	0.22
	≥ 500	0.96 (0.32-2.90)	0.95
	missing	1.54 (0.69-3.44)	0.29
Region of origin	West	1.00	
	Southeast Asia/North Africa	4.46 (1.88-10.58)	0.0007
	Caribbean/Latin America	2.36 (1.10-5.07)	0.03
	Sub-Saharan Africa	6.42 (3.70-11.14)	<0.0001

CI: confidence interval

Table 14.2: Risk factors independently associated with TBC incidence during the first three years after the start of HAART by multivariate Poisson regression.

HBV an

nd HCV

Screening of HIV-infected patients for hepatitis B and C co-infection

Colette Smit

Introduction

As a result of shared routes of transmission, hepatitis B (HBV) and hepatitis C (HCV) are highly prevalent amongst HIV-infected persons. HCV is a common infection amongst patients infected with HIV through injecting drug use or through blood or blood products. HBV is a common infection amongst both injecting drug users and homosexual men. Irrespective of co-infection with HIV, chronic HBV or HCV infection is associated with liver cirrhosis and failure and cancer[169, 170].

However, HIV infection alters the natural history of HBV. Higher rates of chronic HBV infection are found amongst persons co-infected with HIV, and progression of HBV-associated liver diseases is accelerated by the presence of HIV[171]. Conversely, the impact of HBV on the natural history of HIV is still unclear[20, 172].
Viral clearance of HBV is rare, and the main goal of anti-HBV treatment consists of virologic suppression. Several factors complicate anti-HBV treatment in HIV co-infected patients, and consequently, HIV co-infected patients do not achieve the same benefits of HBV treatment as patients infected only with HBV. Although HBV treatment is complicated by HIV co-infection, newer treatment options for chronic HBV infection increase the potential for successful management[16].

Also, progression of HCV disease is accelerated by HIV co-infection, with a more rapid development of fibrosis and cirrhosis[173]. The potential benefits of anti-HCV therapy, such as improved liver function, delayed progression of fibrosis, and possible viral eradication, are observed in HIV co-infected persons, as well as individuals infected with only HCV.

Despite the high prevalence of HBV and HCV and the opportunity to prevent liver-related diseases caused by HBV and HCV, there is no clear consensus on the treatment of these HIV co-infections[174]. However, screening of all HIV-infected patients is recommended for hepatitis B surface antigen (HBs-Ag) or antibody to hepatitis B surface antigen (anti-HBs), and when testing is negative for HBs-Ag or anti-HBs antibodies, it is recommended that HBV vaccination be offered[174]. In addition, screening of HIV-infected patients for HCV co-infection is recommended[174, 175].

Here we report results of screening for HBV and HCV infection, the HBV vaccination level, and the prevalence of HBV and/or HCV co-infection amongst HIV-infected patients in the Netherlands. Also the effect of HBV or HCV co-infection on the risk of progression of HIV disease is described.

Study population and methods

All patients were participants in the ATHENA cohort, HIV-positive, and at least 18 years old at time of the HIV diagnosis. Patients who had not been tested for HBV or HCV or patients with a HBV or HCV serology more than 1 year after their HIV diagnosis were excluded from this study.

Definition of HBV and HCV co-infection

HBV infection was defined by a positive HBV surface antigen (HBsAg) test result (EIA, Axsym) and HBV vaccination by a negative result on hepatitis B core antigen antibody (anti-HBc) testing (EIA, Axsym) and a positive result on anti-HBs testing (EIA, Axsym). An anti-HBc positive test result (EIA, Axsym) was used as a marker of exposure to HBV in the past. HCV infection was defined by a positive HCV-antibody test (EIA, Axsym) or a positive HCV RNA test.

Statistical analysis

Risk factors for HBV and HCV co-infection, as well as predictive factors for undergoing testing for HBV or HCV and being vaccinated against HBV infection, were determined using logistic regression models.
Variables considered as potential covariates in the multivariate models were gender, age at HIV diagnosis

per 10-year increase, region of origin (the Netherlands, the rest of Europe, sub-Saharan Africa, the Caribbean, Latin America and Southeast Asia), risk group (homosexual men, heterosexuals, injecting drug users, and "other"), calendar year of HIV diagnosis, calendar year of HAART initiation, and time from the HIV diagnosis to HBV or HCV serology. The multivariate models were built using the backward elimination procedure.

The effect of HBV and/or HCV co-infection on the time to a first AIDS-defining event (CDC-C event) or death was assessed using Cox proportional hazards models. Follow-up time was from the date of HIV diagnosis to that of last contact or most recent follow-up, an AIDS-defining event or death, or 1 January 2006. Models were adjusted for age at HIV diagnosis, gender, ethnicity, risk group, and HAART treatment.
Kaplan-Meier estimates of the probability of AIDS and death were plotted for the time to the first AIDS-defining event and death and stratified by co-infection. The patients were divided into 4 groups: HIV infection only, HIV infection with HBV and HCV co-infection, HIV infection with HBV co-infection, and HIV infection with HCV co-infection.
All analyses were performed using SAS software for Windows version 9.1 (SAS Institute Inc, USA).

Results

HBV and HCV screening amongst HIV-infected patients

Of the 11,688 HIV-infected patients in the HIV monitoring cohort, 8007 (69%) had received an HBs-Ag test result within 1 year after HIV diagnosis, and 7424 (64%) were tested for HCV antibodies or RNA. Predictive factors for undergoing testing for HBV and/or HCV co-infection are shown in Table 15.1.

In the multivariate analyses, region of origin, year of HIV diagnosis, and year of HAART initiation were predictive factors for the presence of HBV serology. HIV-infected patients of non-Dutch origin were more likely to be tested for HBV co-infection. Those who were diagnosed with HIV after 2001 were more often tested for HBV, whilst HIV-infected patients who initiated HAART were screened less often for HBV co-infection.

Predictive factors for HCV serology in multivariate analyses were age, region of origin, transmission risk group, time of HIV diagnosis, and year of HAART initiation. Older age and being of non-Dutch origin were predictive for having a positive test result for HCV. Compared to homosexual men, heterosexually infected patients and injecting drug users had a significantly higher predictive risk of being tested for HCV. Finally, patients who were recently diagnosed with HIV had a significantly higher predictive risk of being tested for HCV.

Risk factors for HBV and HCV co-infection

Amongst patients tested for HBs-Ag, 591 (7%) had a positive test result. Amongst patients tested for HCV-antibodies or RNA, 735 (10%) had a positive result. Risk factors for HBV and HCV co-infection are shown in Table 15.2. Risk factors for HBV co-infection were male sex, younger age, and being diagnosed with HIV before 1996. Patients from sub-Saharan Africa, the Caribbean, and Southeast Asia had a higher risk of HBV co-infection. Patients infected with HIV heterosexually had a non-significant lower risk of being co-infected with HBV, whereas injecting drug users had a significantly higher risk of HBV co-infection, compared to that of homosexual men.

Factors associated with HCV co-infection in the multivariate analyses were region of origin, transmission group, calendar year of HIV diagnosis, and year of HAART treatment. Compared to patients of Dutch

origin, patients from other European countries had a significantly higher risk of HCV co-infection, whereas patients from sub-Saharan Africa and the Caribbean and Latin America and those who were recently diagnosed with HIV were less likely to be co-infected with HCV.

Patients infected with HIV heterosexually and injecting drug users had a significantly higher risk of HCV co-infection compared with that of homosexual men.

Hepatitis B vaccination level in the population of HIV-infected patients

HBV vaccination was defined as having a negative result on anti-HBc testing and a positive result on anti-HBs testing. A total of 4723 patients were tested for both antibodies, and 363 patients (8%) had anti-HBc-negative and anti-HBs-positive test results.

The results of the multivariate analyses are presented in Table 15.2. Homosexual men and patients from other European countries (excluding the Netherlands) were more likely to be vaccinated against HBV.

Impact of HBV and/or HCV co-infection on AIDS and death

A total of 2152 (30%) of the patients, with a positive result for one of the HBV or HCV tests within 1 year after their HIV diagnosis progressed to AIDS. The time to an AIDS event was not associated with HBV or HCV co-infection (p=0.36, log-rank test).

Furthermore, 541 (8%) died during follow-up. The probability of dying was not the same for all patients; the probability of dying was highest amongst those with a HCV co-infection (P<0.0001, log-rank test).

The hazards ratios from the Cox proportional hazards model for progression to AIDS and death are presented in Table 15.3. HBV and/or HCV co-infection was not associated with progression to AIDS. However, the adjusted hazards of death were 1.54 times higher amongst those with an HBV co-infection and 2.30 times higher amongst patients who were co-infected with HCV.

The impact of HBV or HCV co-infection on the treatment response amongst patients who initiated HAART are described in Chapter 7.

Discussion

Amongst HIV-infected patients in this study, 67% were screened for HBs-ag antibodies and 64% for HCV antibodies within 1 year after receipt of the HIV diagnosis. No specific factors for predicting screening for co-infection could be identified, except that older HIV-infected patients and those infected by hetero-sexual contact or injecting drug use were screened more often for HCV co-infection.

The initiation of HAART was not associated with screening, but compared with the early years when HAART was available, those patients recently diagnosed with HIV are screened more often for HBV and HCV co-infection. In this study, the prevalence of HBV and HCV was 7% and 10% respectively, which is considerably higher than in the general Dutch population, where the HCV and HBV prevalence is 1 and 2%, respectively (www.who.int). Comparison with other HIV-infected populations is difficult, since the prevalence of HBV and HCV varies between HIV risk groups. However, the prevalence found in our study population is comparable to that of participants in a large cohort amongst Australian HIV-infected patients[176]. Risk factors for HBV or HCV co-infection were an origin from a European country other than the Netherlands or sub-Saharan Africa and infection with HIV through injecting drug use.

Although in our study HBV or HCV co-infection was associated with increased risk of dying, the impact

of HBV or HCV co-infection on mortality remains controversial[73, 76, 177, 178]. This association has been described in more detail in Chapter 7.

In the present study, homosexual men and HIV-infected patients from European countries other than the Netherlands more often had an anti-HBc negative and an anti-HBs positive test result, which is a marker for HBV vaccination. Overall, only 8% of the HIV-infected patients had serologic markers for HBV immunisation. The policy of HBV vaccination in the Netherlands targets specific groups: commercial sex workers, drug users, homosexual men, and heterosexuals with multiple sexual partners[179]. HIV-infected patients are not targeted as a group for HBV vaccination. Since transmission routes of HBV and HIV are overlapping, a large portion of the HIV-infected patients can be identified with one of the HBV vaccination target groups. The level of HBV vaccination amongst the target groups is low; 48 to 72% of the persons who should be vaccinated against HBV, according to the vaccination policy, are still susceptible for HBV[179]. Although measuring the anti-HBc and anti-HBs serostatus may underestimate the immunisation level in our study population, our results still confirm a low HBV vaccine level. The effect of HBV vaccination is limited in HIV-infected patients, and immunisation early in the HIV infection is important, because at that time HIV-infected patients are still able to respond adequately to the vaccine[180].

There are some limitations for our study that should be mentioned. The HBs-ag and HCV status is not collected through a standardised serologic screening and therefore is not available for all patients; this may result in a selection of patients with clinical signs of HBV or HCV co-infection.
The HBV co-infection status is based on a single HBs-Ag test result. In a chronic HBV infection, a patient can test Hbs-Ag positive at any time, whilst in an acute HBV infection the patient may have HBs-Ag antibodies for only approximately 4 months. We defined a chronic infection as one single Hbs-Ag positive test result, this result could also reflect an acute HBV infection. Since HIV-infected patients are likely to develop a chronic HBV infection[171], we assumed a positive HBs-Ag test result to be a chronic infection.

In conclusion, although the proportion of HIV-infected patients screened for HBV and HCV co-infection has increased over time, the HBV and HCV status of a substantial number of HIV-infected patients is still unknown. The HBV vaccination level in the population of HIV–infected patients is low. Structural screening of HIV-infected patients for the presence of HBV and HCV co-infection is needed, and HBV or HCV co-infected patients should be monitored to prevent hepatitis-related diseases amongst HIV-infected patients.

	Total (%)	HBV serology (Y/N)			HCV serology (Y/N)		
	N=11688	**N=8007 (%)**	**Univariate OR (95% CI)**	**Multvariate OR(95% CI)**	**N=7424 (%)**	**Univariate OR (95% CI)**	**Multvariate OR(95% CI)**
Gender (male)	9123 (78)	6226 (78)	1.00(0.99-1.01)	-	5795 (78)	1.00 (0.91-1.10)	-
Age at HIV diagnosis in years (median, IQR)	35 (29-42)	35 (29-42)	0.98(0.94-1.01)	-	35 (29-42)	1.04(1.01-1.08)	1.07(1.02-1.12)
Region of origin:							
Netherlands	6557 (56)	4434 (55)	1	1	4033 (54)	1	1
Europe	981 (8)	669 (8)	1.03 (0.89-1.19)	1.07(0.91-1.26)	644 (9)	1.20(1.04-1.38)	1.19 (1.01-1.39)
Sub-Saharan Africa	1906 (16)	1351 (17)	1.17 (1.04-1.30)	1.13(0.99-1.29)	1230 (17)	1.14(1.02-1.27)	1.00 (0.87-1.16)
Caribbean	605 (5)	421 (5)	1.10 (0.91-1.31)	1.44(1.15-1.80)	381 (5)	1.06(0.89-1.27)	1.13(0.92-1.39)
Latin America	842 (7)	592 (7)	1.13 (0.97-1.33)	1.13(0.94-1.35)	599 (8)	1.54(1.32-1.81)	1.49(1.25-1.79)
Southeast Asia	373 (3)	271 (3)	1.27 (1.01-1.61)	1.23(0.95-1.61)	254 (3)	1.34(1.07-1.67)	1.22(0.95-1.50)
Other	424 (4)	269 (3)	0.83 (0.68-1.02)	0.86(0.68-1.08)	283 (4)	1.26(1.02-1.55)	1.25(0.98-1.59)
Transmission group				-			
Homosexual	6224 (53)	4242 (53)	1		3885 (52)	1	1
Heterosexual	3917 (34)	2740 (34)	1.09(1.00-1.19)		2554 (34)	1.13(1.04-1.23)	1.07(1.02-1.-12)
Injecting drug use	590 (5)	378 (5)	0.83(0.70-0.99)		401 (5)	1.28(1.07-1.67)	1.88(1.52-2.32)
Other	957 (8)	647 (7)	0.98(0.84-1.13)		584 (8)	0.94(0.80-1.08)	0.96(0.82-1.13)
Calendar year of HIV diagnosis							
<1996	3302 (28)	2101 (26)	1	1	1705 (23)	1	1
1996-1998	2025 (17)	1314 (16)	1.06(0.94-1.19)	1.09(0.96-1.23)	1285 (17)	1.63(1.45-1.82)	2.46(2.16-2.81)
1999-2001	2235 (19)	1245 (16)	0.72(0.64-0.80)	0.79(0.68-0.92)	1527 (21)	2.02(1.81-2.26)	3.39(2.86-4.02)
>2001	4126 (35)	3347 (42)	2.40(2.21-2.73)	2.86(2.39-3.43)	2907 (39)	2.23(2.03-2.46)	4.51(3.77-5.39)
Year of HAART initiation							
No HAART treatment	2461 (21)	1855 (23)	1	1	1651 (22)	1	1
1996-1998	3619 (31)	2343 (29)	0.60(0.54-0.67)	0.68(0.57-0.80)	1978 (27)	0.59(0.53-0.66)	0.88(0.75-1.04)
1999-2001	2226 (19)	1187 (15)	0.37(0.33-0.42)	0.47(0.40-0.55)	1463 (20)	0.94(0.83-1.06)	0.91(0.75-1.07)
>2001	3382 (29)	2622 (33)	1.13(1.00-1.27)	0.84(0.73-0.99)	2332 (31)	1.09 (0.98-1.22)	0.85(0.75-0.97)
Time to serology since HIV diagnosis in years (median, IQR)	-	0.08 (0.01-0.8)	1.00(0.99-1.01)	1.01(1.01-1.02)	0.1 (0.02-1.12)	1.04 (1.03-1.05)	1.13(1.11-1.15)

HBV: hepatitis B virus; HCV: hepatitis C virus; CI: confidence interval; IQR: interquartile range

Table 15.1: Predictive factors for undergoing testing for HBV and/or HCV infection in HIV-infected patients in the Netherlands.

	HBV co-infection	HCV co-infection	HBV vaccination
	Multivariate OR(95% CI)	**Multivariate OR(95% CI)**	**Multivariate OR(95% CI)**
Gender (male)	2.33(1.76-3.10)	-	1.50 (0.96-2.34)
Age at HIV diagnosis in years (median, IQR)	0.91 (0.83-1.00))	-	-
Region of origin:			
Netherlands	1	1	1
Europe	1.21 (0.89-1.66)	2.38 (1.75-3.23)	1.48 (1.04-2.12)
Sub Saharan Africa	2.08 (2.12-3.79)	0.64 (0.46-0.90)	0.72 (0.47-1.10)
Caribbean	1.68 (1.14-2.48)	0.33 (0.17-0.65)	0.45 (0.19-1.03)
Latin America	0.94 (0.63-1.40)	0.84 (0.56-1.27)	0.60 (0.37-0.97)
South (east) Asia	1.90 (1.22-2.94)	0.86 (0.46-1.59)	1.08 (0.61-1.92)
Other	1.59 (1.05-2.44)	1.29 (0.80-2.10)	1.23 (0.68-2.24)
Transmission group			
Homosexual	1	1	1
Heterosexual	0.85 (0.65-1.11)	2.93 (2.22-3.86)	0.67 (0.46-0.97)
Injecting drug use	1.49 (1.04-2.13)	330.36 (216.91-503.15)	0.45 (0.20-1.04)
Other	1.04 (0.76-1.43)	8.65 (6.44-11.61)	0.92 (0.60-1.42)
Calendar year of HIV diagnosis			
<1996	1	1	-
1996-1998	0.65 (0.37-0.65)	0.45 (0.33-0.62)	
1999-2001	0.62 (0.47-0.82)	0.36 (0.25-0.52)	
>2001	0.58 (0.47-0.73)	0.30 (0.21-0.43)	
Year of HAART initiation			
No HAART treatment	-	1	1
1996-1998		0.74(0.51-1.09)	0.42 (0.31-0.58)
1999-2001		1.10 (0.75-1.61)	0.55 (0.39-0.76)
>2001		1.09 (0.80-1.50)	0.63 (0.49-0.84)
Time to serology since HIV diagnosis in years (median, IQR)	0.97 (0.96-0.99)	-	-

HBV: hepatitis B virus; HCV: hepatitis C virus; OR: odds ratio; CI: confidence interval; IQR: interquartile range

Table 15.2: Risk factors for HBV, HCV co-infection and HBV vaccination amongst HIV-infected patients in the Netherlands, results from the multivariate analyses.

Co-infection	AIDS		Death	
	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*
HIV-infected	1	1	1	1
HIV-, HBV- and HCV-infected	1.10 (0.89-1.30)	1.00 (0.83-1.21)	0.89 (0.63-1.25)	0.98 (0.69-1.37)
HIV- and HBV-infected	1.17 (1.02-1.35)	1.09 (0.91-1.32)	1.76 (1.45-2.14)	1.54 (1.17-2.05)
HIV- and HCV-infected	1.62 (1.08-2.43)	1.35 (0.87-2.08)	2.64 (1.62-4.30)	2.30 (1.32-4.00)

* adjusted for age at HIV diagnosis, sex, ethnicity, risk group, and HAART treatment

HCV: hepatitis C virus; HBV: hepatitis B virus; HR: hazard ratio; CI: confidence interval

Table 15.3: Determinants of time to a first AIDS-defining event and death amongst patients with and without HCV and/or HBV co-infection.

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Migrant populations and Curaçao

Ard van Sighem

Introduction

Two of the largest migrant populations in the Netherlands from HIV-endemic regions are Antillean and Surinamese. For the sexually active population aged between 15 and 49 years, the HIV prevalence in 2005 reportedly was 1.9% in Surinam (95% confidence interval [CI], 1.1-3.1) and between 1.4% and 2.3% in the Netherlands Antilles (excluding Aruba)[181]. This is higher than the estimated prevalence of 0.2% in the general population in the Netherlands, and it is also higher than that amongst Antilleans and Surinamese living in Amsterdam in whom the prevalence was 0.7% in 1997[182].

At the end of 2005, the HIV Monitoring Foundation (HMF) started registration and data collection for the HIV-infected patients living in Curaçao who are being followed and monitored in the St. Elisabeth Hospital in Willemstad. In this chapter, the first results of this monitoring are presented, and patient characteristics and treatment outcomes are compared with those of HIV-infected individuals originating from the Antilles or Surinam and living in the Netherlands.

Study population and methods

The total study population consisted of 194 patients infected with HIV-1 who were registered at the St. Elisabeth Hospital in Curaçao. This group of patients was compared with a group of 849 patients registered in the Netherlands that consisted of those originating from the Netherlands Antilles or Aruba (343 patients) or Surinam (506 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 HAART closest to, and at most 12 weeks before, the start of HAART; after the start of HAART, the values were obtained during each 24-week interval closest in time to the middle of the interval.

For the 3 populations, characteristics at HIV diagnosis and at the start of HAART were compared. The effect of HAART on CD4 cell counts and HIV RNA levels was studied in patients with at least 170 weeks of follow-up. Kaplan-Meier curves were used to assess the time to loss of follow-up. Patients were censored if they died or if they were still being followed after 1 June 2005. Present age and HAART regimen were determined on 1 June 2006, which marked the closure of the database.

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 using Wilcoxon-Mann-Whitney, and chi square nonparametric tests. For continuous variables, medians are reported with interquartile ranges (IQR). Hazard ratios from Cox proportional hazards models are quoted with Wald 95% CI.

Results

The majority of the 1043 patients in our study, 826 (79.2%), were diagnosed with HIV infection in or after 1996 (Figure 16.1). The average annual number of diagnoses did not change over calendar time ($p=0.8$) and was 15.4 in Curaçao, 25.4 amongst Antilleans in the Netherlands, and 40.5 in the Surinamese population in the Netherlands. Of the 194 patients in Curaçao, 123 (63.4%) were men, and for 34 (27.6%) of them homosexual contact was reported as the most likely mode of transmission (Table 16.1). This was significantly ($p<0.001$) less than the corresponding reported proportions of men having sex with men (MSM) of Antillean or Surinamese origin in the Netherlands; 55.6% of Antillean men in the Netherlands (138 out of 248) and 46.5% of Surinamese men (159 out of 342) were MSM ($p=0.03$, comparing Antillean and Surinamese men). The proportion of men (72.3%) tended to be higher amongst Antilleans in the Netherlands than in Curaçao ($p=0.03$). The

majority of the patients in Curaçao, 153 (78.9%), were born in the Netherlands Antilles, whereas 35 (18.0%) originated from Hispaniola (Haiti and Dominican Republic).

For 59.0% of the patients, the most likely country of infection was known. This proportion did not differ between patients in the Netherlands originating from Surinam (61.1%) and those originating from the Antilles (65.9%) (p=0.1), but it was lower for patients in Curaçao (41.2%) (p<0.001). The majority of the 80 patients in Curaçao with a reported country of infection, 68 (85%), were infected in the Netherlands Antilles. Of the 123 Antilleans living in the Netherlands, 54.4% were infected in the Netherlands, as were 73.1% of the 226 Surinamese living in the Netherlands, whereas 86 (38.1%) of the Antilleans and 76 (24.6%) of the Surinamese were infected in their country of origin.

Median CD4 counts at diagnosis were 341 (IQR, 98-505) x 10^6 cells/l for patients in Curaçao, which was similar to those for patients in the Netherlands originating from the Antilles (p=0.7), whereas patients from Surinam tended to have lower CD4 counts (p=0.04). There was no difference in CD8 cell counts (p=0.4) or HIV RNA levels (p=0.7) at diagnosis between the 3 populations. A CDC-C event at diagnosis was registered for 11 patients (5.7%) in Curaçao. This proportion was higher (p<0.001) amongst Antillean (16.6%) and Surinamese patients (13.1%) in the Netherlands.

The median age at diagnosis was 34.3 (IQR, 28.6-41.6) years for the whole population, 35.1 (29.6-42.2) years for men and 31.7 (26.2-39.6) years for women (p<0.001). This difference, however, was driven by the Surinamese population, since the men were only borderline significantly older (p=0.02) than women in Curaçao or in the Antillean population in the Netherlands. Both men and women in Curaçao, however, were older at diagnosis than Antilleans living in the Netherlands (p<0.001). The median time of follow-up after diagnosis was 5.0 (IQR, 2.1-8.8) years, and the total follow-up time after diagnosis was 6209 person-years, including 1177 person-years for the patients in Curaçao, 2144 person-years for the Antilleans in the Netherlands, and 2888 for the Surinamese population.

From 2001 onward, the frequency of RNA load measurements per person-year of follow-up was 2.25 (IQR, 2.14-2.36) for patients in Curaçao, 2.82 (2.73-2.92) for patients from the Antilles in the Netherlands, and 3.05 (2.97-3.13) for Surinamese patients. CD4 counts were measured more frequently than RNA levels in patients from Curaçao (2.43 [IQR, 2.32-2.55] per person-year) and at similar rates for patients in the Netherlands, which were 2.82 (2.72-2.91) for Antilleans and 3.06 (2.98-3.14) for Surinamese. The average number of clinical visits was similar amongst the 3 populations: 3.03 (IQR, 2.91-3.16) for patients in Willemstad, 3.21 (3.11-3.31) for Antilleans, and 3.16 (3.08-3.24) for Surinamese patients.

In total, 778 (74.6%) patients started HAART, including 120 (15.4%) patients who had previously received antiretroviral treatment and 658 (84.6%) patients who were therapy-naïve. There were no differences in these proportions between the 3 populations (p=0.2). The median time from diagnosis to the start of HAART was 0.4 years (IQR, 0.1-2.2) and did not differ between the 3 populations when CD4 counts at diagnosis were taken into account. Patients in Willemstad switched their initial HAART regimen after a median time of 3.1 years (IQR, 2.2-4.1) (Figure 16.2), which was considerably later than patients from the Antilles and Suriname in the Netherlands who switched initial regimens after only 0.9 years (0.8-1.2). The most frequently used initial HAART regimens in Curaçao were nelfinavir/lamivudine/stavudine (63 patients, 44.4%) and lopinavir/zidovudine/lamivudine (46 patients, 32.4%) (Table 16.2). Amongst the combined Antillean and Surinamese population in

the Netherlands, the most frequently used regimens were nevirapine (92 patients, 14.5%) and nelfinavir (66, 10.4%) in combination with zidovudine and lamivudine, whereas the 2 most frequently used initial regimens in Curaçao accounted for only 9.6% of the initial regimens in the Netherlands. Overall, the 7 most common initial regimens in the total population accounted for 88.0% of the initial regimens used in Curaçao, but only for 50.6% of the regimens used in the Netherlands.

At the closure of the database as of June 2006, LPV/r+AZT+3TC (lopinavir/ritonavir boosted, zidovudine, and lamivudine) and NFV+d4T+3TC (nelfinavir, stavudine, and lamivudine) were still the most commonly used regimens in Curaçao. On the other hand, in the Netherlands NVP+AZT+3TC (nevirapine, zidovudine, and lamivudine) remained the most frequently used regimen, followed by efavirenz, lamivudine, and tenofovir and no therapy at all. Of the 138 patients in Curaçao, 55 (39.9%) used a HAART regimen containing d4T (stavudine), whilst only 15 (2.8%) patients in the Netherlands were using that regimen.

Median CD4 counts at the start of HAART for patients treated in Willemstad were 135 (IQR, 39-244) x 10^6 cells/l. CD4 counts were higher for both Antilleans (160 [30-300] x 10^6 cells/l) and Surinamese (170 [50-287] x 10^6 cells/l), although not significantly (p=0.1). The median CD4 count at the start of HAART in the therapy-naïve population was 160 (50-283) x 10^6 cells/l and likewise did not differ between the 3 populations (p=0.3). In total, 320 (58.4%) therapy-naïve patients for whom CD4 counts were measured at the start of HAART had CD4 counts lower than 200 x 10^6 cells/l. Figure 16.3 shows the median CD4 cell counts and the proportion of patients with HIV RNA levels below 500 copies/ml for previously naïve HAART-treated patients who were followed for at least 170 weeks after the start of HAART. Patients of Surinamese origin seemed to have the best response to therapy. Changes in CD4 counts were similar for patients in Curaçao and for Antilleans in the Netherlands, but the proportion of patients with suppressed RNA decreased after 48 weeks of HAART in the population in Curaçao. After the start of HAART, AIDS developed in 30 (12.0%) patients from the Antilles and 53 (13.8%) from Suriname, compared with 6 (4.2%) patients in Curaçao.

Five years after HIV diagnosis, 83.9% (95% CI, 80.5-86.8) of the population diagnosed in or after 1996 were still being followed or had died. This proportion was similar for the 3 populations. However, a univariate Cox proportional hazards model showed that the drop-out rate was 5.0 times higher (2.0-12.5) for the Haitians than for the Antilleans in Curaçao. Of the population who started HAART, 86.7% (83.5-89.3) were still being followed after 5 years. Also in this case, there were no differences between the 3 populations, and the drop-out rate was 5.2 times higher (2.0-14.0) for Haitians compared to Antilleans.

Discussion

This first analysis of demographic characteristics and the course of the HIV infection of patients in Curaçao shows that there are many similarities between these patients and patients in the Netherlands of Antillean or Surinamese origin, as well as some major differences, especially in treatment response. At diagnosis, there were no differences in CD4 cell counts and plasma HIV RNA levels between Antilleans in the Netherlands and patients in Curaçao. The increase in CD4 counts after the start of HAART was also similar between these 2 populations, but lower than in patients of Surinamese origin despite similar CD4 counts at the start of HAART. The proportion of patients reaching RNA levels below 500 copies/ml was similar for the 3 populations, but the proportion with levels remaining below 500 copies/ml decreased with longer follow-up in the population in Curaçao, whereas it remained constant in the other 2 populations.

Patients' decreasing ability to suppress HIV RNA levels might reflect differences in compliance between those in Curaçao and those in the Netherlands. Unfortunately, no data were available on plasma drug levels for patients in Curaçao. Also, the extent to which development of drug resistance had a role could not be studied since genotypic sequences of patients in Curaçao were not yet available. Nevertheless, the data indicate that the first line regimen in patients in Curaçao lost its ability to sustain suppression of RNA and that a more effective regimen should be considered.

In this matter, however, the number of antiretroviral drugs available for treatment of patients in Curaçao is a reason for concern. Ritonavir, a protease inhibitor necessary to achieve optimal blood levels of other protease inhibitors, is not available except in combination with lopinavir. Hence, the number of available protease inhibitor-containing regimens is limited. Nelfinavir, a widely used protease inhibitor in Curaçao, is hardly used in the Netherlands for 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. Also, d4T (stavudine) is hardly used in the Netherlands today since it has been associated with an increased risk of peripheral neuropathy and lipoatrophy[183]. Abacavir, tenofovir, emtricitabine, and atazanavir, which reduce the pill burden and greatly simplify HAART regimens because they are available in fixed-dose combinations like Kivexa®, Truvada® and Trizivir®, are not available in Curaçao. This lack of treatment options is probably why patients in Curaçao did not switch their first HAART regimen as quickly as patients in the Netherlands did.

Although HIV RNA plasma levels and CD4 cell T cell counts were measured less frequently in Curaçao, the follow-up frequency was similar to that for patients in the Netherlands. Also, the proportion of patients who started HAART did not differ between the 3 populations, and neither did the proportion of patients who were lost to follow-up. The frequency of follow-up seemed to be better in patients in Curaçao who also originated from the Antilles compared to Antillean patients in the Netherlands.

Unfortunately, the current data do not allow for an analysis of mortality rates in the HIV-infected population in Curaçao since only patients who were alive at the end of 2005 have been included in the database thus far. This selection also explains the lower proportion of patients in Curaçao compared to those in the Netherlands who had an AIDS-defining event at HIV diagnosis or in whom AIDS developed after the start of HAART, conditions which are both correlated with an increased risk of death. Apart from that, it is difficult to determine whether patients who did not keep the appointment for their next scheduled visit were lost to follow-up or died. It is often undesirable to contact relatives to inquire about a patient's status; although this procedure is not uncommon in the Netherlands, the Antillean culture has not yet socially accepted HIV. It is likely that similar reasons underlie the low proportion of patients reported to have been infected via homosexual contact.

About one third of the Antilleans and Surinamese living in the Netherlands acquired their HIV infection in their country of origin. It has been reported that, during homeland visits, many migrants, especially men, have heterosexual contacts with casual partners, and they have unprotected sex with about half of these contacts[184-186]. Once the migrants are infected during such contacts, they may constitute a bridge population for transmission of HIV to the population in the Netherlands[182, 184]. The conditions for further spread of HIV are favourable since partner change rates amongst migrants are higher than in the general heterosexual population in the Netherlands and concurrent partner-

ships are reported more frequently in addition to a long-term relationship. As a result, migrant populations in the Netherlands account for a disproportionately higher percentage of sexually transmitted diseases compared with the general heterosexual population[27]. Future research should focus on characterising the large group of Dutch students after their internship in Curaçao, because this population could be important when considering the impact of bridge populations.

In conclusion, the quality of clinical care offered to HIV-infected patients in Willemstad is comparable with that offered in the Netherlands. However, in Curaçao the absence of some antiretroviral drugs presently available in the Netherlands for the treatment of HIV-infected patients is of concern because it eventually leads to inferior suppression of HIV RNA levels and possibly the development of drug resistance. Thus, the number of infectious individuals will increase, forming a growing reservoir for the bridge population to draw from. Therefore, for the benefit of both individual patients and the population as a whole, the availability of all HIV treatment options in Curaçao is of the utmost importance.

	Curaçao (N=194)		**Antilles** (N=343)		**Surinam** (N=506)	
	N	**%**	**N**	**%**	**N**	**%**
gender, male	123	63.4	248	72.3	342	67.6
transmission risk group						
homosexual contact	34	17.5	138	40.2	159	31.4
heterosexual contact	132	68.0	168	49.0	292	57.7
injection drug use	0		9	2.6	16	3.2
blood (products)	3	1.5	3	0.9	5	1.0
mother-to-child	0		1	0.3	1	0.2
other/unknown	25	12.9	24	7.0	33	6.5
country of birth						
Netherlands Antilles	153	78.9	277	80.8	-	
Aruba	0		66	19.2	-	
Suriname	1	0.5	-		506	100
Haiti	27	13.9	-		-	
Dominican Republic	8	4.1	-		-	
other	5	2.6	-		-	
CDC stage at diagnosis						
asymptomatic	172	88.7	280	81.6	386	76.3
CDC-B	11	5.7	18	5.2	36	7.1
CDC-C	11	5.7	45	13.1	84	16.6
treatment status						
untreated	52	26.8	92	26.8	121	23.9
HAART, pre-treated	15	7.7	48	14.0	57	11.3
HAART, naïve	127	65.5	203	59.2	328	64.8
diagnosis	median	IQR	median	IQR	median	IQR
CD4 (10^6 cells/l)	314	98-505	270	90-499	240	60-432
CD8 (10^6 cells/l)	986	592-1258	810	500-1185	810	478-1220
RNA $\log_{10}$ copies/ml)	4.6	4.2-5.2	4.6	3.9-5.0	4.7	4.1-5.1
age (years)	37.6	31.0-45.9	32.9	27.2-39.5	34.2	28.5-41.5
follow-up (years)	5.3	2.5-9.4	5.0	2.2-9.4	4.9	2.0-8.5
start of HAART						
CD4 (10^6 cells/l)	135	39-244	160	60-300	170	50-287
CD8 (10^6 cells/l)	736	474-1212	810	500-1170	760	460-1200
RNA ($\log_{10}$ copies/ml)	5.1	4.6-5.5	4.9	4.4-5.3	4.9	4.4-5.2
age (years)	40.5	34.1-49.3	37.1	31.4-42.2	36.4	30.7-43.4
present age (years)	43.6	38.4-51.9	41.0	34.7-47.1	41.5	34.7-48.5

* IQR: interquartile Range

Table 16.1: Characteristics of the patients in Curaçao and of the patients in the Netherlands originating from the Antilles and Surinam.

regimen at start of HAART	**Curaçao** (N=142)		**Antilles** (N=251)		**Surinam** (N=385)		**total** (N=778)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
NVP+AZT+3TC	1	0.7	41	16.3	51	13.2	93	12.0
NFV+3TC+d4T	63	44.4	15	6.0	8	2.1	86	11.1
LPV/r+AZT+3TC	46	32.4	16	6.4	22	5.7	84	10.8
NFV+AZT+3TC	1	0.7	29	11.6	37	9.6	67	8.6
EFV+3TC+TDF	0		13	5.2	31	8.1	44	5.7
IDV+AZT+3TC	14	7.7	12	4.8	12	3.1	38	4.8
EFV+AZT+3TC	0		8	3.2	27	7.0	35	4.5
other regimens	17	12.0	117	46.6	197	51.1	331	42.5
regimen at 1 June 2006	**Curaçao** (N=138)		**Antilles** (N=211)		**Surinam** (N=327)		**total** (N=676)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
LPV/r+AZT+3TC	53	38.4	9	4.3	20	6.1	82	12.1
NVP+AZT+3TC	1	0.7	26	12.3	41	12.5	68	10.1
none	7	5.1	18	8.5	30	9.2	55	8.1
EFV+3TC+TDF	0		17	8.1	38	11.6	55	8.1
NFV+3TC+d4T	41	29.7	1	0.5	1	0.3	43	6.4
NVP+3TC+TDF	0		15	7.1	20	6.1	35	5.2
EFV+TDF+FTC	0		7	3.3	13	4.0	20	3.0
other regimens	36	26.1	118	55.9	164	50.2	318	47.0

NVP: nevirapine; AZT: zidovudine; 3TC: lamivudine; NFV: nelfinavir; d4T: stavudine; LPV/r: lopinavir/(ritonavir boosted); EFV: efavirenz; TDF: tenofovir; FTC: emtricitabine.

Table 16.2: Most frequently used HAART regimens at the start of HAART and as of 1 June 2006 amongst patients in Curaçao and patients in the Netherlands of Antillean or Surinamese origin.

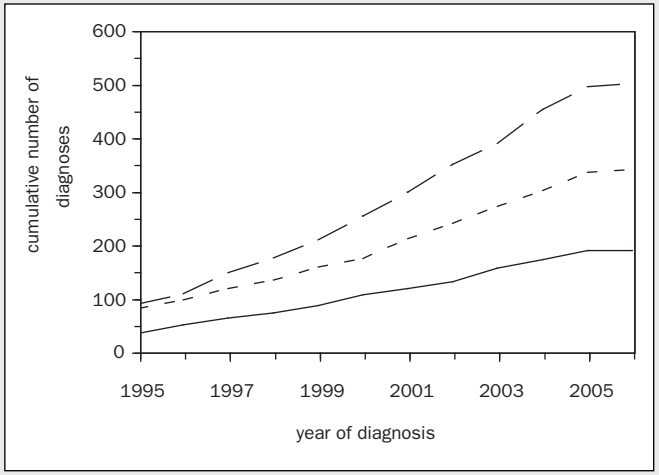


Figure 16.1: Cumulative number of HIV diagnoses amongst patients in Curaçao (solid line) and amongst Antilleans (short dashes) and Surinamese (long dashes) in the Netherlands.

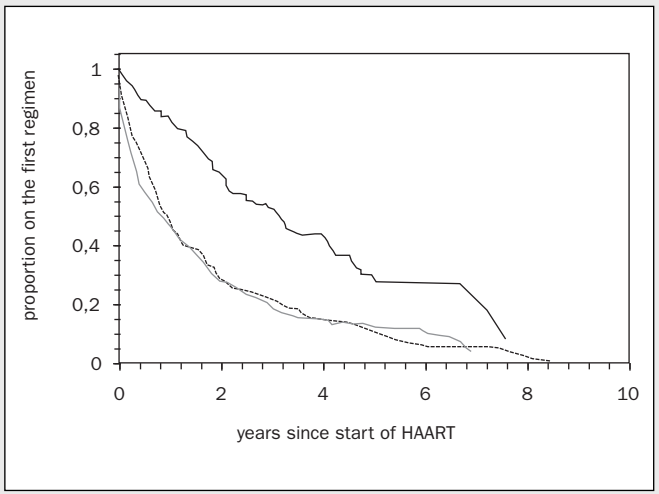
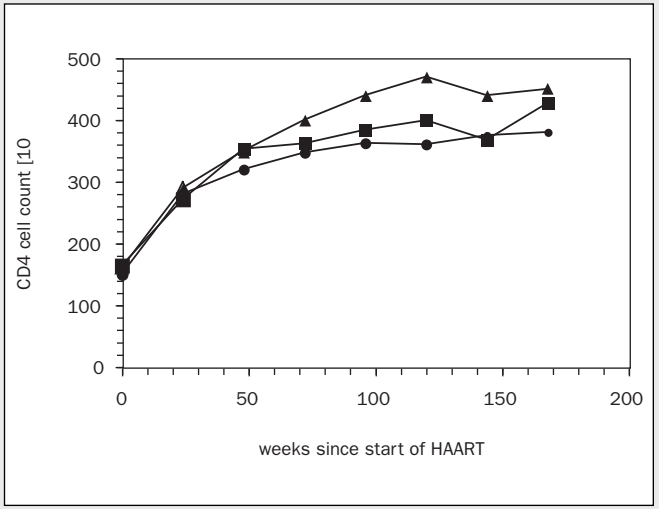


Figure 16.2: Proportion of patients still on the first HAART regimen. The solid line denotes patients in Curaçao, the long-dashed lines Surinamese in the Netherlands, and short-dashed lines Antilleans in the Netherlands.



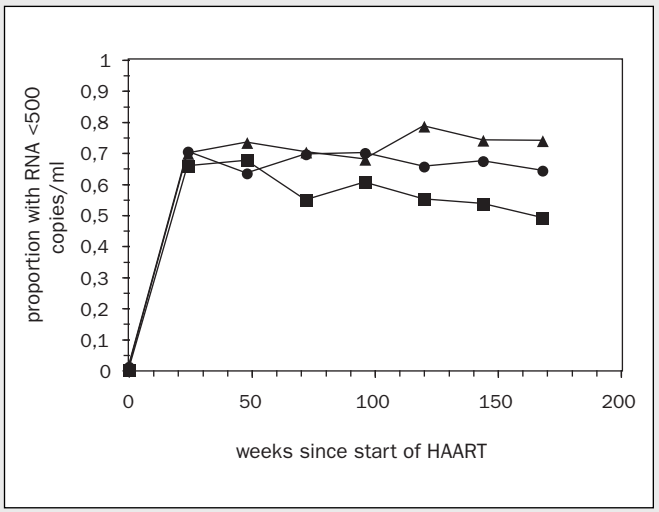


Figure 16.3: CD4 cell counts and the fraction of patients with HIV RNA levels below 500 copies/ml after the start of HAART for previously therapy-naïve patients treated in Willemstad, Curaçao (squares) and for Antilleans (dots) and Surinamese patients (triangles) in the Netherlands.

Conclusi

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Frank de Wolf

A decade of HAART: have initial benefits translated into continued declines in disease outcomes?

Large studies, including the ATHENA observational cohort[24, 124], the Swiss cohort study[21, 23, 66], and EuroSIDA[40], have convincingly shown that highly active antiretroviral therapy (HAART) restores or maintains the immune function in HIV-infected patients and reduces the short-term mortality and morbidity rates.

Results from the ATHENA observational cohort confirm results from others[23, 48] that patients who start HAART when CD4 cell counts are below 200 cells/mm^3 are at higher risk for progression to disease or death than are patients who start when counts are above 200 CD4 cells/mm^3. In the last 10 years, more than half of the patients started HAART when CD4 cell counts were below this threshold; counts were lower in patients starting HAART more recently compared to patients starting in earlier calendar years. Two factors might explain the relatively late start of HAART in half of the patients. Firstly, because the HIV-infected population is changing, patients may already be in the late stages of the infection before being diagnosed with HIV. Late diagnosis is seen especially amongst migrant populations, and these populations have added substantially to the number of new diagnoses per year since the beginning of this century[187]. Secondly, the frequency of follow-up has declined over the years since 1996 and might have resulted in a higher proportion of patients who were unaware of further deterioration of their immune system.

Short-term outcomes, i.e., the virologic and immunologic response in the first 24 weeks following the start of HAART, has improved slightly during the first decade of HAART. HIV RNA plasma levels below 500 RNA copies/ml were measured in 89.7% of treated patients in 2002 through 2005 compared to 85.7% in 1997 through 1999. The increase in CD4 cell number during the first 24 weeks of HAART remained largely the same at approximately 130 cells/mm^3. Patients with a higher HIV RNA plasma concentration at the start had a lower chance of reaching a level below 500 copies/ml. Also, patients on a regimen including a single protease inhibitor (PI) had less chance to reach that HIV RNA level, as was true for patients originating from sub-Saharan Africa, Latin America, and the Caribbean. In addition, patients who were injecting drug users, patients who were younger in age, and those who had relatively high CD4 cell counts pre-HAART had a lower chance of achieving HIV RNA plasma levels below 500 copies/ml. Short-term increases in CD4 cell counts were seen less in women, patients from sub-Saharan Africa, and injecting drug users. Patients with low HIV RNA plasma levels when starting HAART, older patients, and those who were co-infected with HBV or HCV showed a lesser increase in CD4 cell counts. Patients treated with a boosted PI regimen had a higher increase in CD4 cells after starting HAART compared to those treated with other regimens.

Long-term responses to HAART showed an increased risk for death in patients who started treatment in 2002 through 2005 compared to those who started in 1997 through 2001. Time to death within 3 years after commencing HAART was shorter in older patients, in injecting drug users, and in those who were co-infected with HCV. Moreover, death hazards were higher amongst patients starting HAART with every 100 CD4 cells/ml less or with a CDC-C event recorded at the start of HAART.

No association between calendar year at the start of HAART and the development of a new AIDS event were found. Non-Dutch patients had a higher risk for the development of a new AIDS event, and a CDC-C diagnosis before the start of HAART or a low CD4 cell count at the start of HAART were both associated with

a shorter time to a new AIDS-defining illness. AIDS-defining illnesses most frequently found after the start of HAART were Kaposi's sarcoma, tuberculosis, oesophageal candidiasis, recurrent pneumonia, Burkitt's lymphoma, and cerebral toxoplasmosis.

Long-term virologic and immunologic responses improved over the calendar years after the start of HAART, and the incidence of virologic failure declined over time. CD4 cell increases, although highest in the first months after the start of HAART, continued, albeit at a slower pace. Increases over time were similar for the low, median, and high CD4 cell strata at the start of HAART, but for patients starting HAART at or above 500 cells/ml, the increase was less. Periods of viraemia after the start of HAART and older patient age were associated with smaller CD4 cell increases.

The improved short- and long-term virologic outcomes most probably reflect not only the change in effectiveness of more recent drugs and drug combinations[54-60] but also improved management of adherence and adverse events and toxicity[61].

The somewhat unexpected higher death rates found in later calendar years contrasts with the improved short- and long-term virologic and immunologic response to HAART. This might be the result of an incomplete death registration amongst HIV-infected patients in the years before the monitoring of HIV had started. Retrospective entry of currently missing mortality data may be of importance to correct outcomes. However, the hazard of dying was higher for patients especially in the first year after starting HAART in 1997 through 2001 compared with the hazard in 2002 through 2005; this finding could also indicate that in later years a higher number of patients were diagnosed late in the course of the infection and died shortly after the diagnosis and after the start of treatment. Such an indication might be related to the higher number of immigrant HIV-infected patients seen in the later calendar years. Patients originating from sub-Saharan Africa who were diagnosed in the Netherlands in later calendar years showed lesser short- and long-term virologic responses[62], which might result from poorer adherence. Moreover, there is a much higher prevalence of tuberculosis in these patients, which might add to the higher death rate amongst those infected with HIV from sub-Saharan Africa. Importantly, the incidence of tuberculosis is high in the first months of HAART, indicating a possible role for the immune restoration syndrome[161-165]. Closer follow-up of this particular group is needed to improve the long-term outcome.

Age plays a role in the ability to restore CD4 cell numbers to higher or even normal counts[68-71]. Consequently, the risk of a new AIDS event is higher in older patients; therefore, commencing HAART in an earlier phase of the infection in older patients should be considered.

Co-infection with hepatitis B (HBV) or C (HCV) virus in our cohort appeared to be associated with an increased risk of death. The risk of a new AIDS-defining event was higher in patients co-infected with HCV, and immune restoration in the first months after starting HAART was less. However, the long-term CD4 response to HAART did not seem to be affected. These somewhat conflicting results and their interpretation are hampered by the limited number of patients being tested for HBV and HCV. Preliminary results also indicate a shorter time to liver-related disease in patients with HCV, but not in patients co-infected with HIV and HBV. Reports on the implications of co-infection with HBV and HCV are conflicting[19, 73-77, 188]. Further studies have been initiated to determine the impact of HIV on the course of HBV and HCV infection and vice versa.

HAART induces adverse events and toxic responses that may result in poor adherence or even therapy interruption, causing suboptimal drug levels and subsequent failure of therapy and resistance to it. The incidence of therapy changes after toxic responses was highest in the first 3 months of HAART and became less amongst patients starting HAART between 2002 and 2005 compared to patients commencing before 2002. This result is largely explained by the introduction of new combinations of antiretroviral drugs with improved toxicity profiles.

Virologic failure (2 consecutive measures of HIV RNA plasma concentration above 500 copies/ml) amongst antiretroviral therapy-naïve patients receiving HAART increased from 6% in 1997 to 11% in 2004 and declined to 8% in 2006. The proportion of antiretroviral drug-experienced patients failing on HAART decreased from 50% in 1997 to 16% in 2006. The fraction of patients failing HAART and having drug resistance measured, has remained at approximately 10% per year since 1997 for those who were therapy-naïve and 15% per year for the pre-treated patients. Resistance was found in 97% of the pre-treated patients, and 79% of the therapy-naïve patients. These prevalences are in accordance with those reported by others[104]. As reported previously[26], the prevalence of resistance to specific antiretroviral drugs changes over time in correlation with the changes in drug use[121]. Of the patients still in follow-up in the ATHENA observational cohort, 11% harbour viruses with high-level resistance to at least 1 anti-retroviral drug. Percentages reported by others are between 25% and 27%[103, 122]. This indicates that the prevalence of resistance found in the ATHENA cohort is an underestimation, which is not surprising given the fact that resistance is measured in, at most, a quarter of the patients failing therapy. It may be worthwhile to design a specific study to improve insight into the true prevalence of resistance and the source population for transmission of drug-resistant virus in the Netherlands.

A decade of HAART: has it changed the HIV epidemic in the Netherlands?

In 1996, the year HAART was introduced for routine HIV patient care, the majority of HIV diagnoses were amongst men having sex with men (MSM). This changed rapidly, and by 2000, the annual number of new HIV diagnoses included an equal number of cases of heterosexually and homosexually acquired infection. From the data presented in this report, it appears that the epidemic in the Netherlands has changed again in the last few years; today, as in 1996, the majority of new HIV diagnoses are in MSM. Since 1998, the annual number of MSM newly diagnosed with HIV increased from 300 patients to almost 500 in 2005.

However, there are a few differences compared to the numbers for 1996. The annual number of patients who acquired HIV through injecting drug use declined from 47 in 1996 to 10 in 2005. In the first half of 2006, no new diagnoses amongst injecting drug users have been registered. This is most probably the result of injecting drug use becoming less fashionable compared to other ways of taking hard drugs[30]. In contrast to 1996, injecting drug users have now become a small fraction of the annual number of new diagnoses. Another difference concerns heterosexual transmission. The absolute number of new diagnoses of heterosexually transmitted HIV has remained stable at approximately 300 cases per year since 2000. Previously, we reported that heterosexually acquired HIV was mainly being driven by the importing of HIV from endemic areas[26, 187]. Recent figures, however, show an upward shift in the number of new HIV diagnoses amongst heterosexual men and women who originate from the Netherlands.

The total annual number of new diagnoses has increased from 621 in 1996 to 1028 in 2004, with a decrease to 950 in 2005. This growing number might be explained partly by HIV-infected individuals who were

unaware of their infection[31], but who decided, with the introduction of effective treatment, to accept a test for HIV. In accordance with the rise of new HIV diagnoses since 2000 amongst MSM are reports of behaviour showing increasing sexual risk[32, 33]. Together with the increasing proportion of MSM with relatively high CD4 cell counts at diagnosis, this indicates that part of the increase of new diagnoses stems from more recently infected individuals. Preliminary results of a study on the effect of HAART on HIV transmission amongst MSM show that improved reduction of risk behaviour, together with HAART, would reduce transmission of HIV to levels below sustainability of the epidemic. However, at present, despite the widespread use of HAART, the epidemic amongst MSM is not under control because increasing risk behaviour counterbalances HAART interventions (Bezemer 2006, submitted). Given the variability regarding age, origin, and sexual preference and practices, tailored intervention and prevention strategies are needed.

The number of HIV-infected patients originating from sub-Saharan Africa has declined. This is due to a decrease in the number of immigrants from sub-Saharan African countries since 2002. In 2002, 14,980 people from these countries entered the Netherlands compared to 6207 in 2005 (Statistics Netherlands). Most of the immigrants were already infected in their country of origin, and accordingly, the distribution of HIV-1 subtypes found in the immigrant population corresponded with that found in sub-Saharan Africa. Only a small proportion of sub-Saharan Africans with HIV-1 subtype B were infected in the Netherlands, indicating that sub-Saharan Africans in the Netherlands are a closed group in terms of HIV transmission.

Antiretroviral drug-resistant virus may be transmitted to uninfected patients, and prevalences of resistant virus found in newly infected patients vary from 5% to 25%[107, 108]. Transmission of resistant HIV was reported in 6% of newly infected patients in the Netherlands[109]. The rate of transmission of drug-resistant HIV found in the ATHENA observational cohort is currently 4.8% amongst newly infected patients and is similar to previously reported rates[26, 187, 189] comparable to those observed in other countries where HAART is routinely used for treatment of HIV[107, 108, 116, 117]. Resistance is found in 7.4% of the newly diagnosed patients. The stable low level of transmission of drug-resistant virus, despite the increase in the number of patients treated with HAART since 1996, may be explained by the decreasing proportion of patients who have become infectious after therapy failure, together with the possibly higher contribution to transmission rates by patients who are not being treated (around 20% of the registered population) or who are unaware of their HIV status. However, the transmission rate of resistant HIV might also be underestimated, since the determination of resistance amongst newly diagnosed patients or amongst patients failing therapy is still not the standard of care in the Netherlands. Because the risk of transmission of resistant HIV will increase and because there will be widespread treatment in areas such as Africa where the disease is endemic, the HMF should implement a prognostic longitudinal study amongst both the source population of infected individuals receiving treatment and the population of newly and recently diagnosed individuals, in collaboration with a limited number of HIV Treatment Centres.

Since 1996, the overall mortality in the HIV-infected population in the Netherlands has remained stable at a level between 1 and 2 cases per 100 person-years of follow-up. There has been a shift in the causes of death from the majority being HIV-related in 1996 to half not being directly related to HIV in 2005. However, patients with an AIDS event at diagnosis have a higher risk of death, especially those who are more than 50 years of age, and HIV-related death amongst HAART-treated patients is associated with being diagnosed with AIDS

at the start of treatment. An incidence of 2 cases of AIDS per 100 person-years after the start of HAART has been found since 2000, without a difference between previously treated patients and those who had no experience with antiretroviral drugs.

Finally, we have reported specifically on HAART in women and children. HAART reduces the risk of mother-to-child transmission of HIV[141, 142] to approximately 2%, and pregnant women in the Netherlands are now routinely screened for HIV as partof prenatal care. The number of pregnancies amongst HIV-infected women has increased since 2000, especially amongst Dutch women who were also more often aware of their HIV status before becoming pregnant. Together with a reduced proportion of induced abortions since the introduction of HAART[145], this increase may indicate that HIV-infected women are now better prepared for becoming pregnant.

Most of the children with HIV in the Netherlands are infected through mother-to-child transmission. Almost all are born in the Netherlands, but only a few have both parents originating from the Netherlands; a large majority have one parent from sub-Saharan Africa. The number of children infected by mother-to-child transmission has decreased over time, and since 2000, children have been treated with HAART in an earlier phase of the infection and therefore, at a younger age than before. Currently, 132 children, 72 boys and 61 girls, with a median age at HIV diagnosis of 1.2 years, are registered. Continued monitoring of these children is important to measure outcomes of HIV infection and HAART initiated so early in life.

Curaçao

In collaboration with the Red Cross Blood Transfusion Service and St. Elisabeth Hospital in Willemstad, Curaçao, HMF started monitoring of HIV in the Netherlands Antilles by the end of last year. The first results were presented in May 2006, and further analyses of the effect of HAART amongst patients diagnosed and treated in Curaçao and patients of Antillean or Surinamese origin diagnosed and treated in the Netherlands are part of the present report. The immunologic and initial virologic response to HAART is similar in all 3 groups; however, the longer-term virologic response amongst patients treated in Curaçao was less compared to the Surinamese and Antillean groups treated in the Netherlands. This might reflect a difference in patient adherence, but it might also reflect limitations in the number of different antiretroviral drugs available for treatment of patients in Curaçao. The finding that patients in Curaçao do not switch their initial HAART regimen as often as the patients treated in the Netherlands confirms the influence of limited drug availability. The inferior suppression of HIV in patients treated in Curaçao may result in development of drug resistance and thus, an increasing number of infectious patients. In turn, these patients form a growing reservoir for transmission of HIV not only in the Netherlands Antilles but also in the Netherlands. For the benefit of individual patients and the populations at risk, availability of all HIV treatment options in the Netherlands Antilles is of the utmost importance.

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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 treated and untreated HIV infection.

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