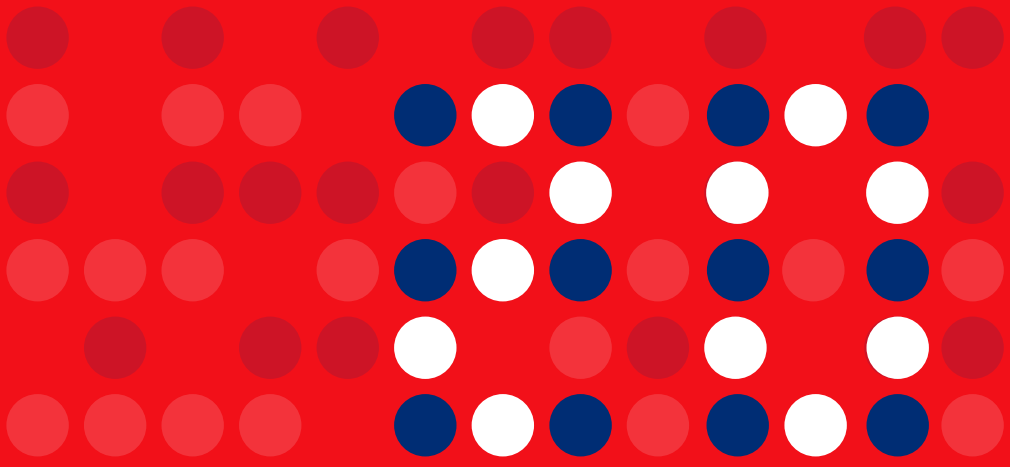
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2020



5. Distinct populations: Children living with HIV in the Netherlands

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Box 5.1: Chapter definitions

Child	An individual diagnosed with HIV and who made the first visit to a Dutch HIV treatment centre before the age of 18.
Infection	The moment a child acquires an HIV infection.
Diagnosis	The moment a child is newly diagnosed with HIV.
Registration	The moment an HIV-positive child in care is notified to SHM by their treating physician or nurse and registered in the SHM database.
In care in 2019	Clinic visit or lab measurement in 2019.
ART	Antiretroviral therapy.
cART	Combination antiretroviral therapy: a combination of at least three antiretroviral drugs from two different antiretroviral drugs classes or at least three nucleoside reverse transcriptase inhibitors.
Viral suppression	Any viral load measurements <200 copies/ml, except for time points in the past where tests were used with quantification limits higher than 200 copies/ml.

Populations described in this chapter

Vertical transmission rates of HIV remain very low in the Netherlands. Together with a decrease in the number of children with HIV being adopted by Dutch parents, this has resulted in only nine new children being registered with SHM in 2019. This chapter provides an update on the population of children in HIV care in the Netherlands, including those nine children.

Box 5.2: Outline of the paediatric ATHENA cohort in the Netherlands: HIV-positive children ever registered in the ATHENA cohort by 31 December 2019. (Children = individuals aged <18 years at the time of diagnosis who have made a first visit to a Dutch HIV treatment centre before the age of 18 years.)

1. Children who entered care in the Netherlands whilst less than 18 years of age (n=511)
2. Population in care in 2019:
   - aged <18 years in 2019 (n=199): 193 with vertically-acquired HIV, 3 with non-vertically acquired HIV, and 3 with an unknown route of transmission;
   - aged ≥ 18 years in 2019 (n=213); 118 with vertically-acquired HIV, 88 with non-vertically acquired HIV, and 7 with an unknown route of transmission.
3. Specific populations:
   - adopted children (n=140)
   - children who have transferred to adult care (n=158)

Background

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in HIV-positive children worldwide[1,2,3,4,5]. Immediate initiation of cART, regardless of CD4 cell count or percentage, is associated with a higher survival rate when compared with delayed cART initiation guided by CD4 cell count[6,7,8,9]. Studies showing a clinical benefit of early cART initiation led to a 2015 revision of the World Health Organization (WHO) guidelines on when to start cART; they now recommend initiation in everyone living with HIV, irrespective of CD4 cell count, including in all children[10].

In the Netherlands, children living with HIV generally receive health care at one of four paediatric HIV treatment centres. These children transition to adult HIV care when they reach the age of 18. However, children who acquire HIV at an older age through non-vertical transmission are more likely to enter care at an adult HIV treatment centre. Diagnosis, treatment and follow up of all these children is monitored by Stichting HIV Monitoring (SHM).

Here we report on the demographics, clinical characteristics, and long-term virological and immunological responses to treatment of HIV-positive children ever cared for in one of the paediatric and/or adult HIV treatment centres in the Netherlands, while under the age of 18 (*Box 5.2*).

Ever registered

As of 31 December 2019, SHM registered 657 individuals ever diagnosed with HIV whilst less than 18 years of age. Of these 657 children, 511 entered care in the Netherlands before 18 years of age. Those who first entered Dutch HIV care while 18 years or older (n=146) are not included in this chapter. Nine children were newly registered in 2019, and two children who had been included in the Monitoring report of 2019 were subsequently excluded from the database as they objected to further collection of their data.

Of the 511 children we report on, 393 first entered care at a paediatric HIV treatment centre and 118 at an adult treatment centre. Those who entered care at an adult HIV treatment centre were predominantly diagnosed with HIV at an older age, and had mostly acquired HIV through non-vertical transmission (*Table 5.1*).

***Table 5.1:** Demographic and HIV-related characteristics of 511 HIV-positive children ever registered by SHM and who entered care in the Netherlands below the age of 18, as of 31 December 2019.*

Characteristics	Vertically-acquired HIV infection*	Non-vertically-acquired HIV infection*	Route of transmission unknown*
Total	360	139	12
HIV treatment centre			
Paediatric care	352 (98)	31(22)	10 (83)
Adult care	8 (2)	108 (78)	2 (17)
Gender			
Male	174 (48)	50 (36)	8 (67)
Female	186 (52)	89 (64)	4 (33)
Country of origin child			
The Netherlands	111 (31)	32 (23)	0
Sub-Saharan Africa	206 (57)	81 (58)	10 (83)
Other	4 (12)	26 (19)	2(17)
Country of origin mother			
The Netherlands	32 (9)	3 (2)	1 (8)
Sub-Saharan Africa	190 (53)	13 (9)	6 (50)
Other/unknown	138 (38)	123 (8)	5 (42)
Age at HIV diagnosis	1.1 (0.2-4.0)	16.9 (16-17)	11.3 (6-14)
Adopted^	137 (38)	1 (0.7)	2 (17)
cART-treated	356 (99)	131 (94)	11 (92)
Therapy-naive at cART initiation	305(85)	124 (89)	11 (92)
CD4 at cART initiation	540 (270-1170)	310 (200-430)	315 (150-522)
CD4 Z-score at cART initiation	-0.63 (-1.04--0.15)	-0.56 (-0.96-- 0.28)	-0.60 (-0.99- -0.29)
VL (log copies/ml) at cART initiation	5.2 (4.5-5.8)	4.5 (4.0-5.2)	4.8 (4.5-5.3)

** Data are number (%) of children or median (interquartile range)*

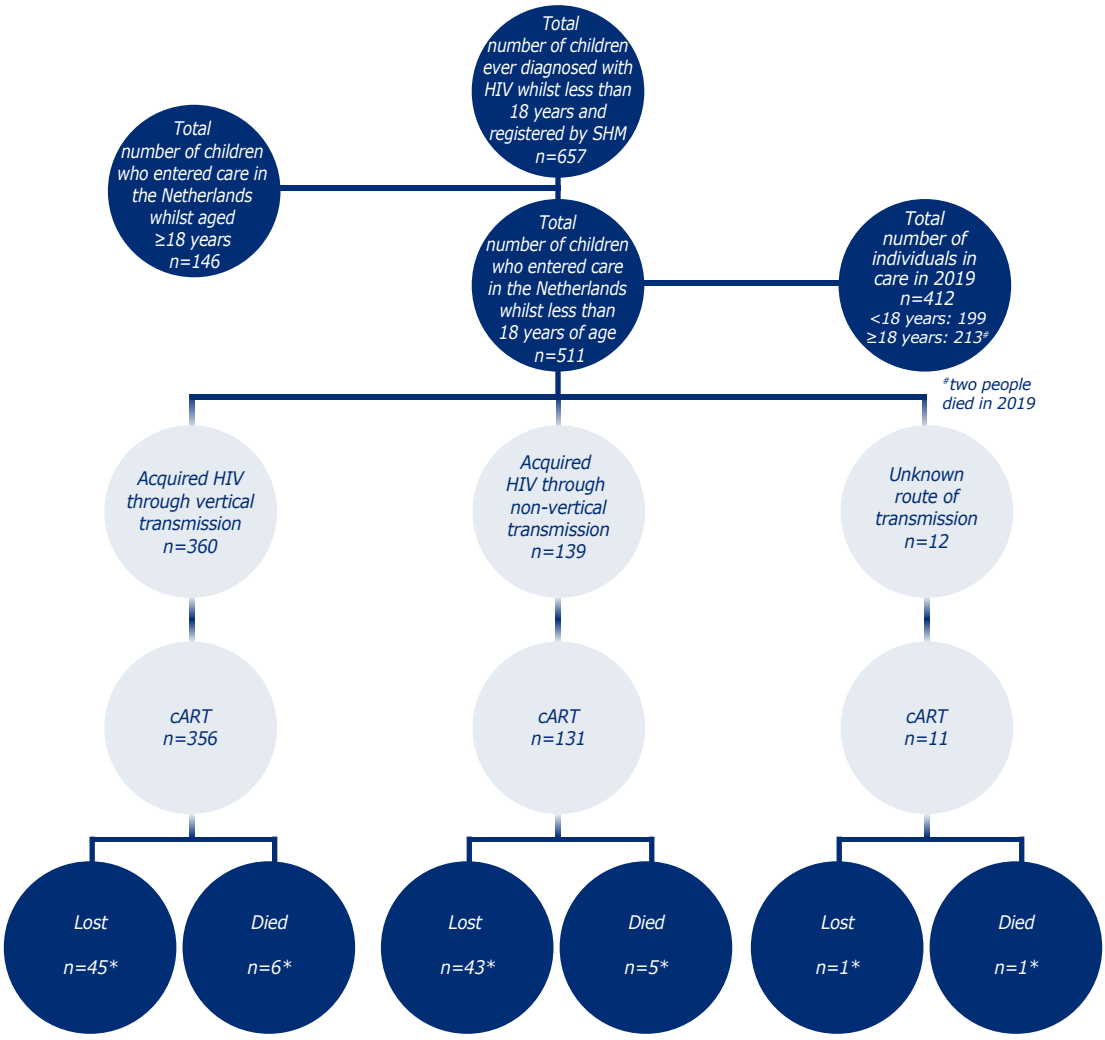
^ All adopted children were born outside the Netherlands

***Legend:** cART=combination antiretroviral therapy; VL=viral load.*

Mode of transmission

The majority of the children registered had acquired HIV through vertical transmission or, in the absence of vertical transmission, through sexual contact (*Figure 5.1*). *Figure 5.2* shows the number of newly-registered children by year of entering care in the Netherlands and the mode of HIV transmission. In addition, for those with vertically-acquired HIV, it shows whether or not they were adopted at the time of registration.

Figure 5.1: *Overview of HIV-positive children registered by Stichting HIV Monitoring as of 31 December 2019.*



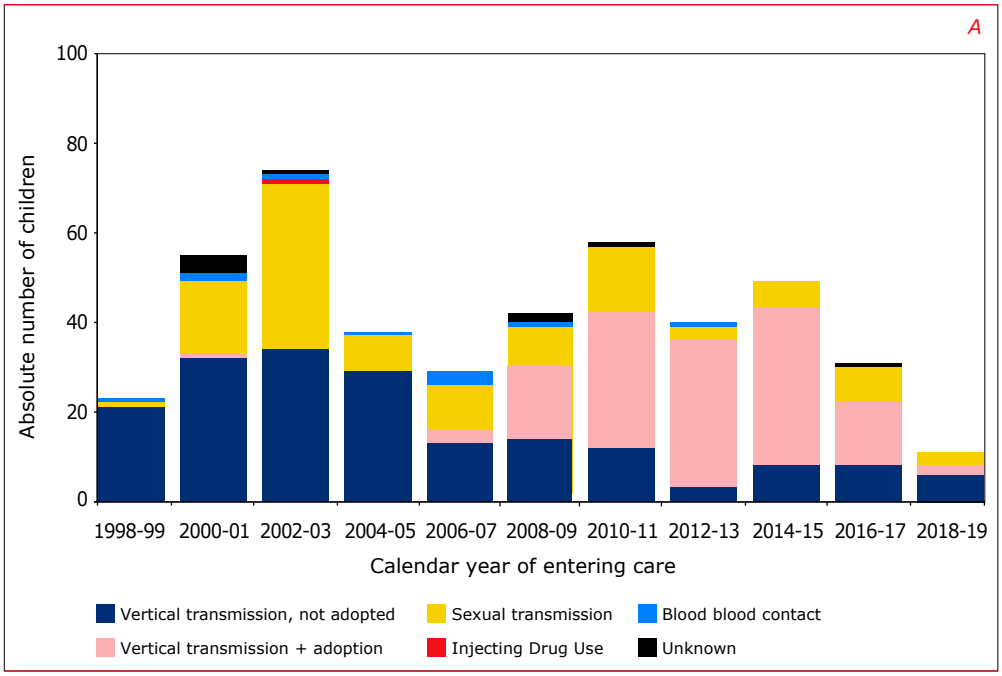
** of the total number of children who acquired HIV through a vertical, non-vertical or an unknown route of transmission.*

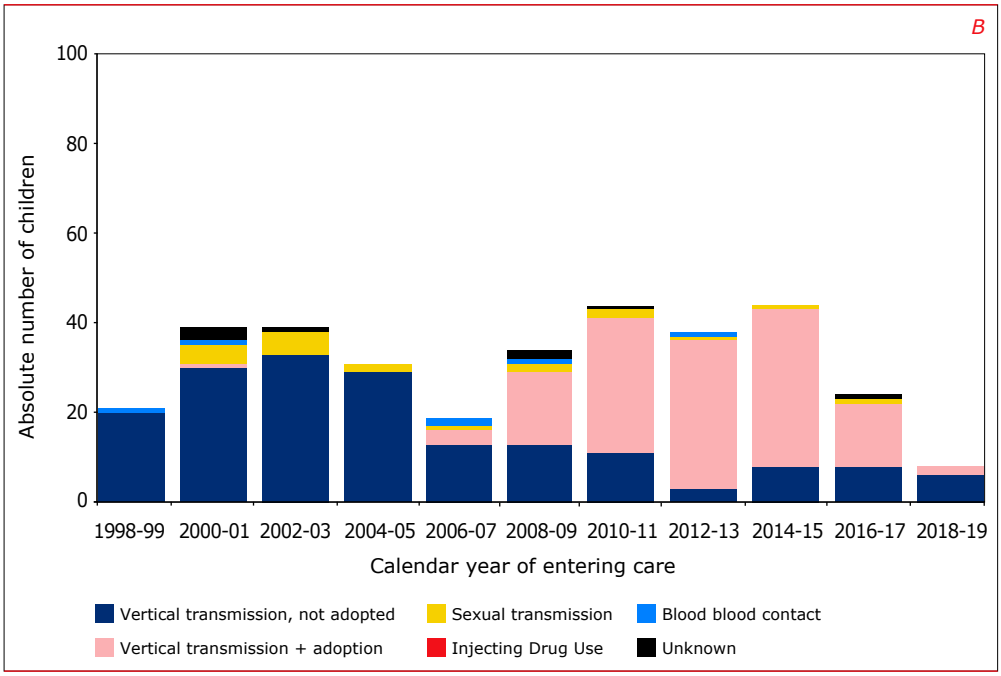
Legend: *cART=combination antiretroviral therapy.*

Children with vertically-acquired HIV

- Between 1998 and 2019, 360 children acquired HIV through vertical transmission.
- The median age at which they received their first reported HIV-positive test result (including self-reported tests performed in their country of origin), was 1.1 years (interquartile range [IQR] 0.2-4.0 years).
- 57% (n=206) of the children were born in sub-Saharan Africa.
- 31% (n=111) of the children were born in the Netherlands.
- 9% of the children born in the Netherlands (10 out of 111), had two Dutch parents.
- 98% received care in a paediatric HIV treatment centre in the Netherlands and the remaining 2% were seen in adult care.
- For 99% of the children, the date on which they started cART was documented.

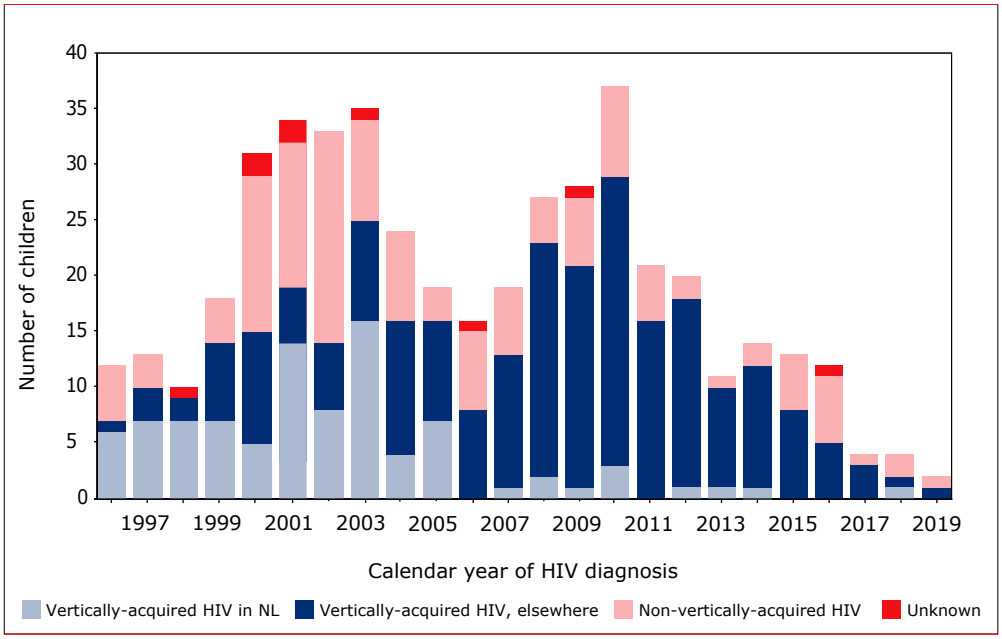
Figure 5.2: Number of HIV-positive children by year of entering care in the Netherlands, stratified by HIV transmission mode and, for those who acquired HIV through vertical transmission, by whether or not they were adopted during the period 1998-2019. Total population (A), HIV paediatric care only (B).





Note: *Low numbers in 2019 may be due to a delay in registration.*

Figure 5.3: Number of registered HIV diagnoses among children, according to year of HIV diagnosis, route of transmission, and region of origin.



Note: Registration for 2019 is not yet complete.

Vertical transmission of HIV in the Netherlands has become a rare event since 2015

Figure 5.3 shows the number of registered HIV diagnoses among children by year of diagnosis, mode of transmission, and region of origin. As shown in the figure, vertical transmission of HIV occurring in the Netherlands declined markedly after 2004 and 2005; in fact, the most recent registered case of vertical transmission in the Netherlands was in 2018. However, as reported in chapter 6 of this report - Pregnancies in HIV-infected women - a single vertical transmission did occur in 2019. The mother was newly registered in the SHM database, but as her child had yet to be formally registered at the time of database closure, it was not included in the analysis for this chapter on Children living with HIV in the Netherlands. The standard HIV screening among pregnant women, introduced nationally in 2004[11,12] is responsible for the decline in vertical transmission in the Netherlands.

Since the introduction of this screening programme, only ten children born with HIV in the Netherlands have been registered with SHM. These ten children are described briefly below:

- Seven children were born to mothers who only first tested HIV positive themselves after giving birth: the mothers of five of these seven children had had a negative test result during the first trimester pregnancy screening; they acquired HIV later during their pregnancy.
- Two children were born to mothers known to be HIV-positive; one mother did not receive treatment during her pregnancy for an unknown reason; the other mother was newly diagnosed with HIV and did start cART during pregnancy, 22 weeks after conception. Prior to initiating cART, the mother had detectable HIV RNA levels, but the last available HIV RNA measurement before delivery was undetectable (<50 copies/ml). This makes peripartum transmission highly unlikely and may suggest *in utero* transmission of HIV.
- The remaining child was born to a mother whose HIV status during pregnancy, and results of any HIV screening, remain unknown.

Children with non-vertically-acquired HIV

- Between 1998 and 2019, 139 children were registered with HIV infection acquired through non-vertical transmission.
- The median age at which they received their first reported HIV-positive test result was 16.9 years (IQR, 16-17).
- The main route of HIV transmission was sexual contact (*Figure 5.2*):
  - 92 children acquired HIV through heterosexual contact, and
  - 28 children acquired HIV through homosexual contact.
- Eighteen children acquired HIV through contaminated blood or blood products. This mode of transmission was no longer reported from 1997 onwards among children born in the Netherland, and from 2009 onwards among all children, regardless of country of birth.
- The remaining child acquired HIV either through injecting drug use or accidental contact with contaminated needles.
- 5% were born in sub-Saharan Africa.
- 78% received care in an adult HIV treatment centre.
- In total, 94% of these children had started cART.

Unknown route of HIV transmission

- For 12 HIV-positive children, the route of transmission was unknown.
- Their median age at diagnosis was 11.3 years (IQR, 6-14).
- Ten children were in care at a paediatric HIV treatment centre.
- In total, 92% of these children had started cART.

Children with HIV who were newly registered with SHM in 2019

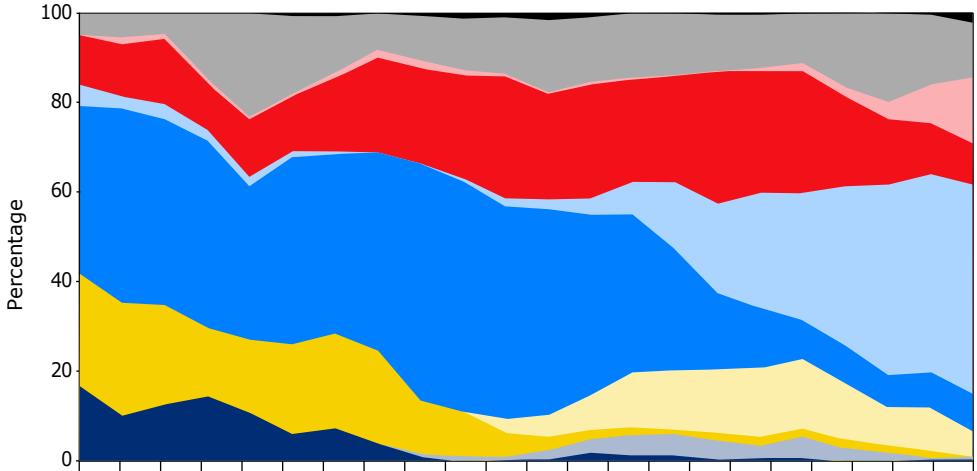
Nine children were newly registered in 2019. Two children included in earlier reports were subsequently excluded from the database as they objected to further collection of their data.

- Seven children had vertically-acquired HIV and two children acquired HIV through sexual contact.
- One child with non-vertically acquired HIV was born in the Netherlands.
- Four children were born in Sub-Sahara Africa and all had vertically-acquired HIV.
- The remaining four children were born in Europe or Latin America. All four had recently migrated to the Netherlands and had their first visit to one of the Dutch HIV treatment centres within 3.5 months of their reported date of migration.
- Eight children entered paediatric care and the remaining child entered care in an adult HIV treatment centre.

Age distribution

The age distribution of children receiving HIV care shifted between 1998 and 2008 (*Figure 5.4*). From 2008 onwards, there has been an increase in the proportion of children aged 0 to 5 years. This is due to an increase in the rate of adoption of HIV-positive children in these age groups, as illustrated by the shaded areas in *Figure 5.4*. In 2019, about 86% of the children aged 12 years or younger living with HIV were adopted.

Figure 5.4: Time-dependent age distribution of HIV-positive children in care over time.



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
16-18*, adopted	0	0	0	0	0	1	1	0	1	2	2	3	2	0	0	1	1	0	0	0	1	4
16-18*	3	4	4	18	35	28	20	13	16	20	22	30	27	29	28	26	25	25	38	45	32	23
12-16*, adopted	0	1	1	1	1	1	2	3	3	2	1	1	1	1	1	0	1	4	5	9	18	28
12-16*	7	9	14	13	20	20	27	35	36	41	49	45	49	47	49	63	59	63	47	34	24	18
5-12*, adopted	3	2	3	3	3	2	1	0	0	1	3	4	7	15	31	43	56	66	84	98	93	89
5-12*	24	33	39	52	53	68	66	73	89	91	86	88	78	73	56	36	29	20	18	17	17	16
2-5*, adopted	0	0	0	0	0	0	0	0	0	0	5	9	15	25	28	30	33	36	31	19	20	11
2-5*	16	19	22	19	25	33	35	34	20	18	10	6	4	4	2	4	4	4	5	4	3	0
0-2*, adopted	0	0	0	0	0	0	0	0	1	2	1	4	6	9	10	9	6	11	7	5	1	1
0-2*	11	8	13	18	17	10	12	7	2	0	1	1	5	3	3	1	2	2	0	1	1	1

** age in years*

Low mortality rates

The mortality rate among children registered with SHM between 1998 and 2019 is very low. Three children (0.5%) under the age of 18 years have died since the start of registration. These three boys were born outside the Netherlands and died before 2010. AIDS was the reported cause of death for each of them, despite the fact that two of the boys were receiving cART. One boy had very low CD4 cell counts while using cART, and the other boy died shortly after the start of cART; he had a high HIV RNA and low CD4 cell count.

Antiretroviral treatment

Of the 511 children who entered care in the Netherlands before 18 years of age, 498 (97%) started cART. Of these 498 children, 440 (88%) were treatment-naive at the start of cART and 58 (12%) had previously been exposed to monotherapy or dual therapy (i.e., were pre-treated).

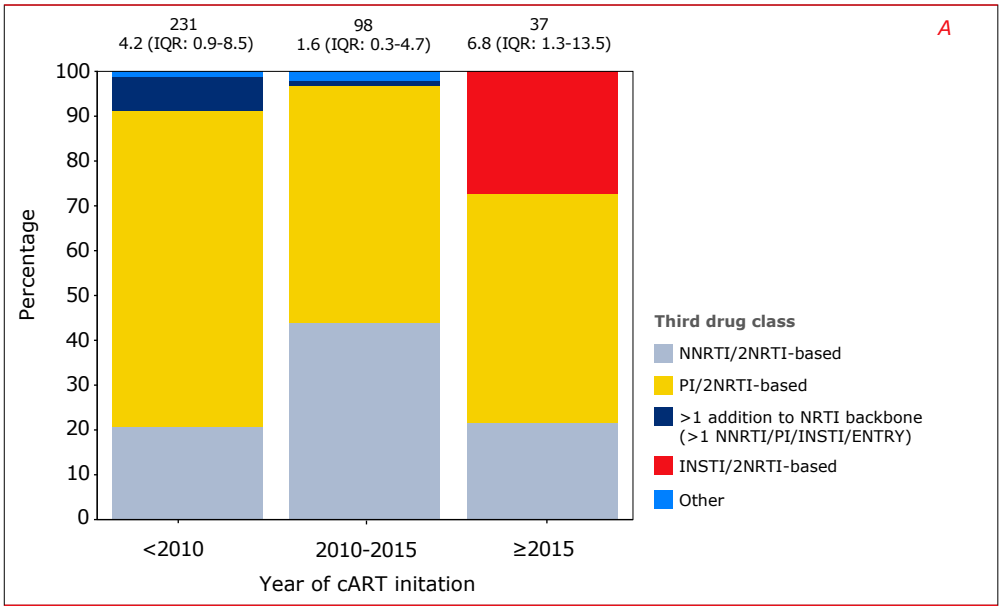
For the purposes of this analysis, we included both pre-treated and treatment-naive children, and grouped them according to calendar year of starting cART: 311 children started a cART regimen before 2010, 134 between 2010 and 2015, and 53 children from 2015 onwards.

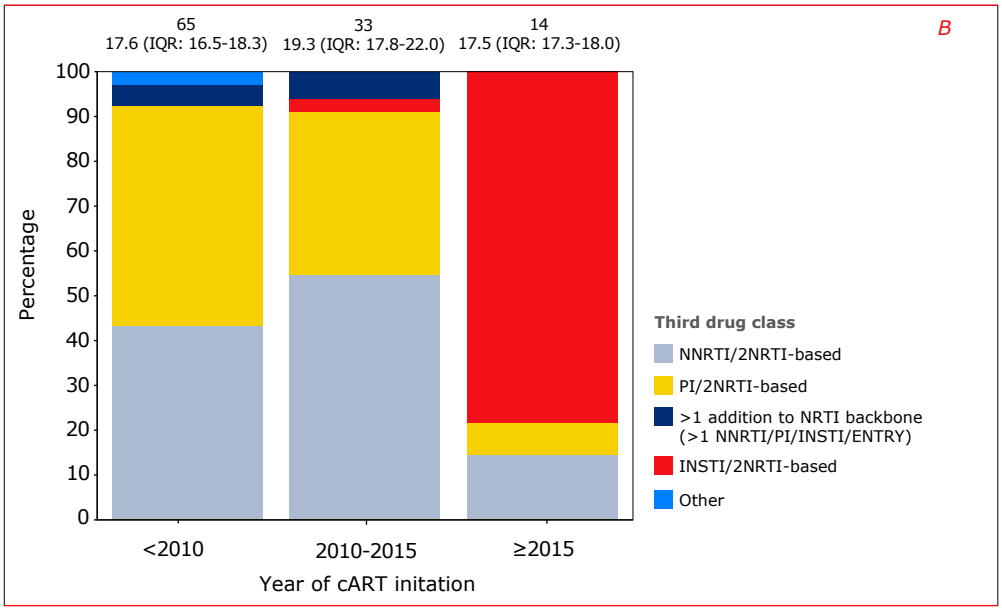
Of the 13 children not treated with cART, one died shortly after entering care, eight were lost to follow up, and another two moved abroad. The reason the remaining two children did not start cART was recorded as 'own decision', and in the second child, cART initiation was delayed because of persistent low HIV RNA levels and high CD4 cell counts in the absence of treatment.

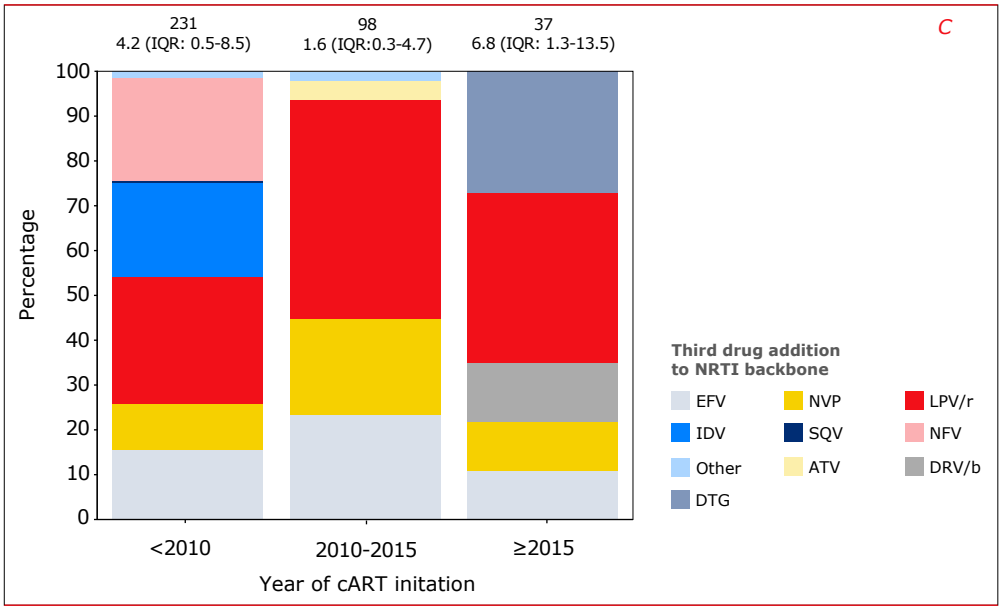
Initial combination antiretroviral regimen

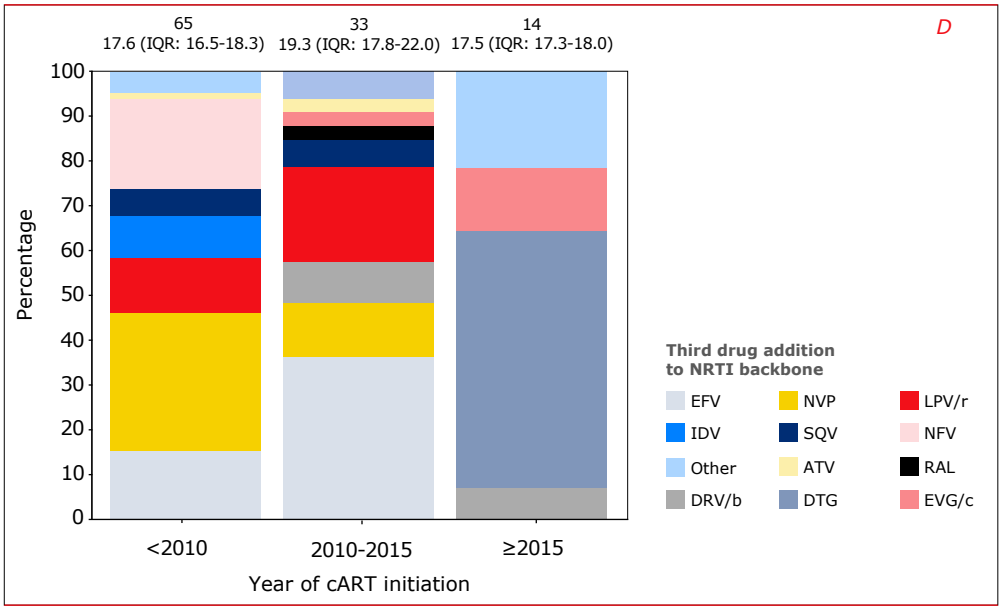
Of the 498 registered children known to have initiated cART, 58% were treated with a first-line regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs). Another 31% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with two or more NRTIs. *Figure 5.5* show the trends over time for the third-drug additions to the NRTI backbone as part of the initial cART regimens, stratified by calendar year of starting cART, and by being in care in a paediatric or adult HIV treatment centre. Among children in paediatric care, lopinavir was the most commonly-used protease inhibitor. Following their introduction in 2013 and 2014, the integrase inhibitors dolutegravir and elvitegravir have also become part of an initial cART regimen in children, but were mainly prescribed to children older than 12 years of age and to only one child younger than 12.

Figure 5.5: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial cART regimen, stratified by calendar year period, according to (A) antiretroviral class among children in paediatric care, (B) antiretroviral class among children in adult care and (C) specific third drugs among children in paediatric care and (D) specific third drugs among children in adult care. Numbers above the bars represent the total number of individuals initiating cART in that particular calendar year period. Median age and interquartile range above the bars represents the age of individuals at time of cART initiation.









Legend: cART=combination antiretroviral therapy; ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI=protease inhibitor; EFV= efavirenz; NVP=nevirapine; LPV/r=ritonavir-boosted lopinavir; IDV=indinavir; SQV=saquinavir; NFV=nelfinavir; RAL=raltegravir; DRV/b=cobicistat- or ritonavir-boosted darunavir; ATV/r=ritonavir-boosted atazanavir; DTG=dolutegravir; EVG/c=cobicistat-boosted elvitegravir.

Discontinuation of the initial cART regimen

The median time the 498 children who had ever started cART spent on an initial regimen was 19.4 months (IQR, 5-50). Discounting weight-related dose changes, 423 children (90%) discontinued their first-line treatment regimen. The most important reasons for changing first-line cART included toxicity (18%) and simplification (23%). Virological failure accounted for changing first-line cART therapy in 9% of cases. Other reasons were low drug concentrations, decision by parents and/or child, research protocol-driven reasons, or unknown.

Immunological response

Earlier reports have shown that the clinical benefit of cART is strongly related to the degree to which the CD4 cell count recovers[13]. Long-term CD4 cell count changes were assessed among the 498 children who had ever started cART. Children with vertically-acquired HIV were stratified according to age at the time of cART initiation, resulting in the following categories:
(1) vertically-acquired, 0-1 year,
(2) vertically-acquired, 2-5 years,
(3) vertically-acquired, 5-18 years,
(4) non-vertically-acquired or unknown mode of HIV transmission[a], 5-18 years.

Given that normal CD4 cell counts in younger children are highly age-dependent[14], it is more appropriate to analyse time-dependent CD4 count trajectories, expressing CD4 counts as Z-scores, in which counts are standardised in relation to age. CD4 Z-scores, which represent the standard deviation from the reference values for HIV-negative children, were calculated for CD4 cell counts to correct for age-related differences. All absolute CD4 T-cell counts were transformed into Z-scores by subtracting the age-related reference value for the age at the time of the CD4 measurement[15] and dividing the outcome by the age-related standard deviation. A Z-score of zero represents the age-appropriate median. A CD4 Z-score of minus 1 indicates that a child's CD4 cell count is 1 standard deviation below the age-specific median of the HIV-negative population.

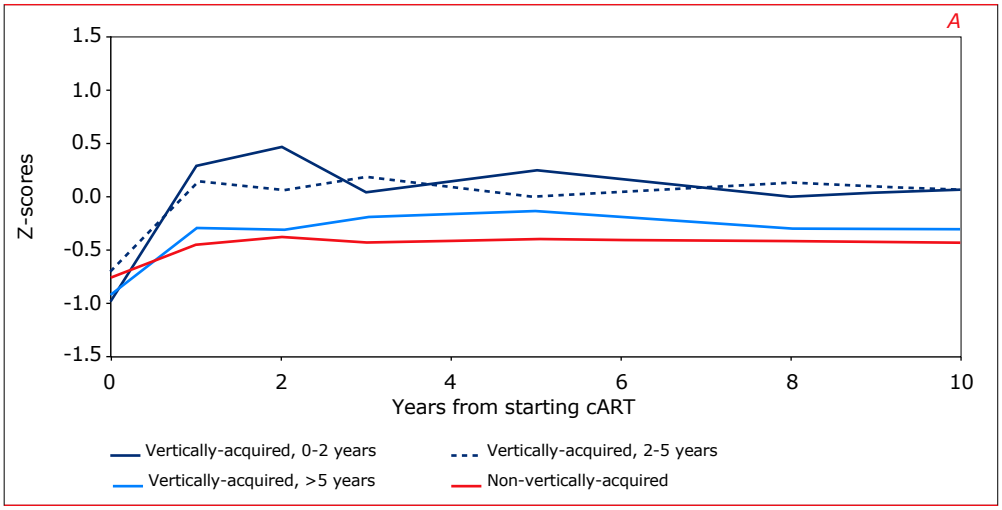
Figures 5.6A and 5.6B show the changes in CD4 T-cell Z-scores among HIV-positive children stratifying those with vertically-acquired HIV by age at initiation of cART, and by calendar year of cART initiation. The youngest children (less than two years of age at cART initiation), as expected, had the highest absolute CD4 cell counts at cART initiation (*Table 5.1*), but the age-adjusted CD4 Z-scores did not differ significantly between groups.

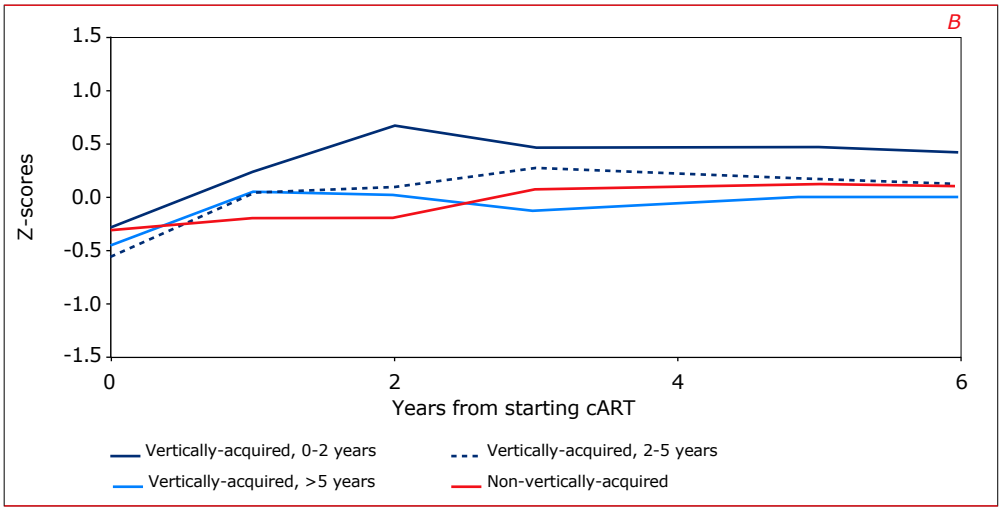
a *The number of children with an unknown route of HIV transmission is too small to include as a separate category in this analysis. As these children had the same age distribution as those with non-vertically-acquired HIV, these two groups were jointly analysed in a shared category.*

Among those initiating cART between 1998 and 2009, CD4 Z-scores increased significantly in the year following cART initiation in all children with vertically-acquired HIV. The increase in CD4 Z-scores was less strong among children with non-vertically-acquired HIV. However, the youngest children (below 5 years of age at the time of cART initiation), had higher CD4 Z-scores compared to children who were over 5 years of age at the time of cART initiation, and CD4 Z-scores remained consistently higher among the youngest children (*Figure 5.6A*).

In those who initiated cART in or after 2010, the youngest children (below two years of age at cART initiation) had the highest CD4 Z-scores at the time of cART initiation. In the first year following cART initiation, CD4 Z-scores increased significantly in all children with vertically-acquired HIV. During the first two years, increases in CD4 Z-scores were slowest in children with non-vertically-acquired HIV. CD4 Z-cores remained consistently highest among the youngest children (aged below 2 years at the time of cART initiation) (*Figure 5.6B*).

Figure 5.6: Changes in Z-scores for CD4 T-cell counts among HIV-positive children, stratified by age at initiation of combination antiretroviral therapy (cART: (A) cART initiation between 1998 and 2009 and (B) cART initiation between 2010 and 2019.





Legend: *cART=combination antiretroviral therapy.*

Virological response

The main definition for viral suppression used in this chapter is described in *Box 5.1*. Virological response to cART was assessed based on viral suppression (i.e., viral load <200 copies/ml) over a longer period of time (0-10 years).

The current analysis uses data from the 498 children who were registered with SHM and had ever started cART. Children with vertically-acquired infection were stratified by age at cART initiation, as described earlier in this chapter.

Among the children who ever started cART, we assessed viral suppression rates over time on cART during 24-week intervals. Viral load measurements closest to each 24-week time point (±12 weeks) were included in the analysis. Viral suppression rates were stratified by calendar period of cART initiation, to account for changes in the use of cART regimens.

Figure 5.7 shows viral suppression rates by calendar period of cART initiation: 1998-2009 and 2010-2019.

cART initiation between 1998 and 2009:

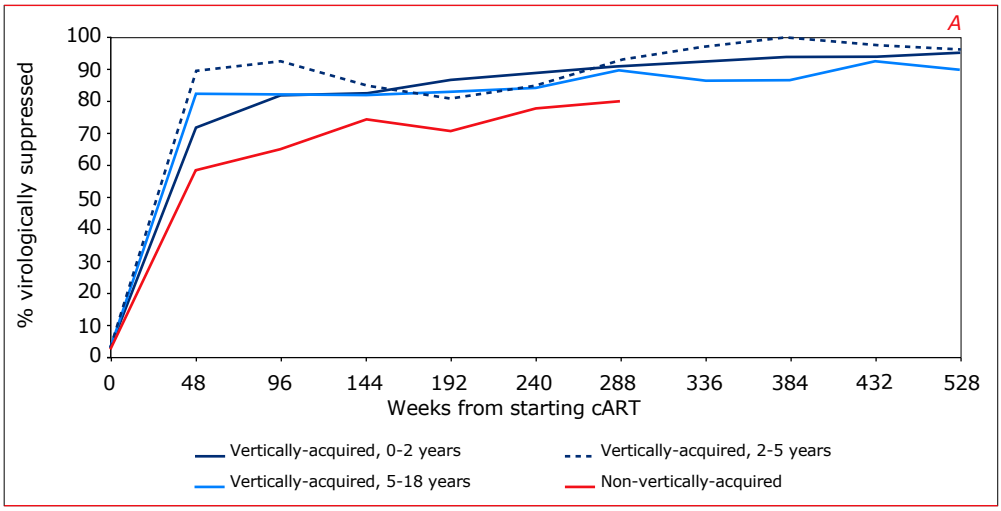
- Among children with vertically-acquired HIV who were aged 0-2 years at time of cART initiation, viral suppression rates increased from 72% after one year of cART, to 88% and 95% after five and ten years, respectively.
- Among children with vertically-acquired HIV who were aged 2-5 years at cART initiation, viral suppression rates increased from 90% after one year of cART, to 85% and 97% after five and ten years, respectively.
- Among children with vertically-acquired HIV who were aged over 5 years at cART initiation, viral suppression rates increased to 82% after one year of cART use. However, ten-year viral suppression rates were somewhat lower (90%) compared with children who were aged under 5 years of age at the time of cART initiation.
- Among children with non-vertically-acquired HIV, the five-year viral suppression rate was 78%. The ten-year viral suppression rate is not shown, due to the small number of children for whom such long-term data could be calculated [*Figure 5.7A*].

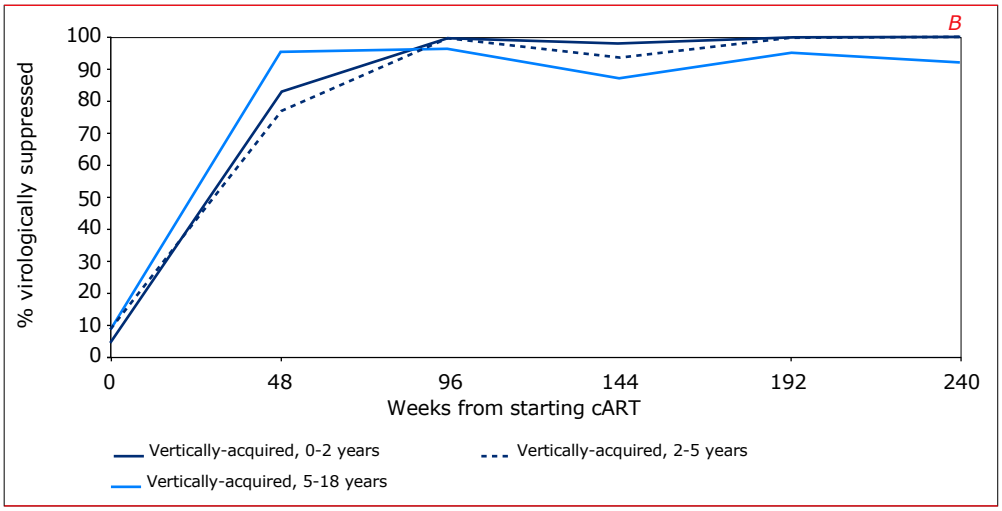
cART initiation in or after 2010:

- The viral suppression rates were 100% in children with vertically-acquired HIV who initiated cART before the age of 5 years. However, among children with vertically-acquired HIV who were aged over 5 years at the time of cART initiation, the viral suppression rate was 92% after five years of cART use. Note: Viral

suppression rates are not presented for those with non-vertically-acquired HIV, due to the limited follow-up time between age at cART initiation and reaching 18 years of age (*Figure 5.7B*).

Figure 5.7: *Viral suppression since combination antiretroviral therapy initiation, by calendar period of therapy initiation: (A) 1998-2010 and (B) 2010-2019. Viral suppression is defined as any viral load measurements <200 copies/ml, except for time points in the past where tests were used with quantification limits higher than 200 copies/ml.*





Legend: *cART=combination antiretroviral therapy.*

Currently in clinical care

Of the 511 HIV-positive children ever registered by SHM who entered care in the Netherlands before the age of 18 years, 412 (81%) were still in care in 2019 (*Figure 5.1*). Of the remaining 99 children no longer in care, ten had died, 39 had moved abroad, and a substantial number of children (50 children) were lost to follow up.

Currently in care and less than 18-years-old

- Of the 511 individuals with HIV who entered care before the age of 18 years, 199 were still aged under 18 at the end of 2019.
- 196 of these 199 children were in care in one of the paediatric HIV treatment centres, and the remaining three children were in care in one of the adult HIV treatment centres. As of 31 December 2019, their median age was 11 years (IQR, 8-14).

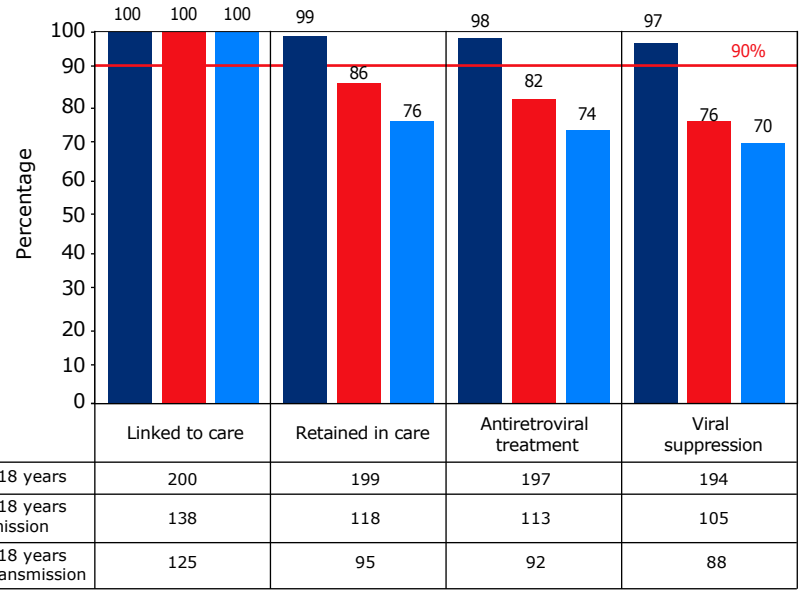
Currently in clinical care and 18 years or older

- The remaining 213 HIV-positive individuals who were first registered when still a child, were in care and older than 18 at the end of 2019.
- Their median age was 23 years (IQR, 20-28) for those who had vertically-acquired HIV, and 33 years (IQR, 26-36) for those with non-vertically-acquired HIV.

Continuum of care

A 'continuum of care' was constructed, based on the total number of HIV-positive children ever registered by SHM that were still alive on 31 December 2019, and not reported to have moved abroad or to have died. This continuum of care depicts engagement in HIV care across a number of key indicators, the last one being the number of children whose most recent HIV RNA measurement was below 200 copies/ml (*Figure 5.8*).

Figure 5.8: Continuum of care by age, as of 31 December 2019, and by mode of HIV acquisition. The numbers above the bars indicate the proportion of individuals.



Individuals were stratified by age on 31 December 2019 and categorised as:

I. current age <18 years; in this age group, the number of children with non-vertically-acquired HIV was too small (n=6) for stratification by mode of acquisition;
II. current age ≥18 years with vertically-acquired HIV;
III. current age ≥18 years with non-vertically-acquired HIV.

I Continuum of care: current age <18 years

- In total, 200 children under 18 years of age on 31 December 2019 were linked to care, registered by SHM, still alive, and not reported as having moved abroad.
- Of these children, 99.5% were retained in care (199/200); 196 children were receiving paediatric care. The single child lost to follow up was born outside the Netherlands.
- During their last clinical visit in 2019, 98% (197/200) were using antiretroviral therapy.
- Overall, 97% had a most recent HIV RNA measurement below 200 copies/ml (194/200).

II Continuum of care: current age ≥18 years with vertically-acquired HIV

- 138 individuals who acquired HIV through vertical transmission and were over 18 years of age on 31 December 2019 were linked to care.
- Of these 138 individuals, 86% (118) were still in care as of 31 December 2019. The remaining 20 individuals were lost to follow up - 11 of these were born in the Netherlands.
- 82% (113/138) were using antiretroviral therapy during their last registered clinical visit.
- Overall, 76% (105/138) had a most recent HIV RNA measurement below 200 copies/ml.

III Continuum of care: current age ≥18 years with non-vertically-acquired HIV

- 125 individuals were older than 18 by 31 December 2019 and acquired HIV through non-vertical-transmission.
- Of these, 95 (76%) were still in care as of 31 December 2019; 30 individuals were lost to follow up, including 18 women originating from sub-Saharan Africa.
- 74% (92/125) were using antiretroviral therapy during their last registered clinical visit.
- Overall, 70% (88/125) had a most recent HIV RNA measurement below 200 copies/ml.

In care and on cART in 2019

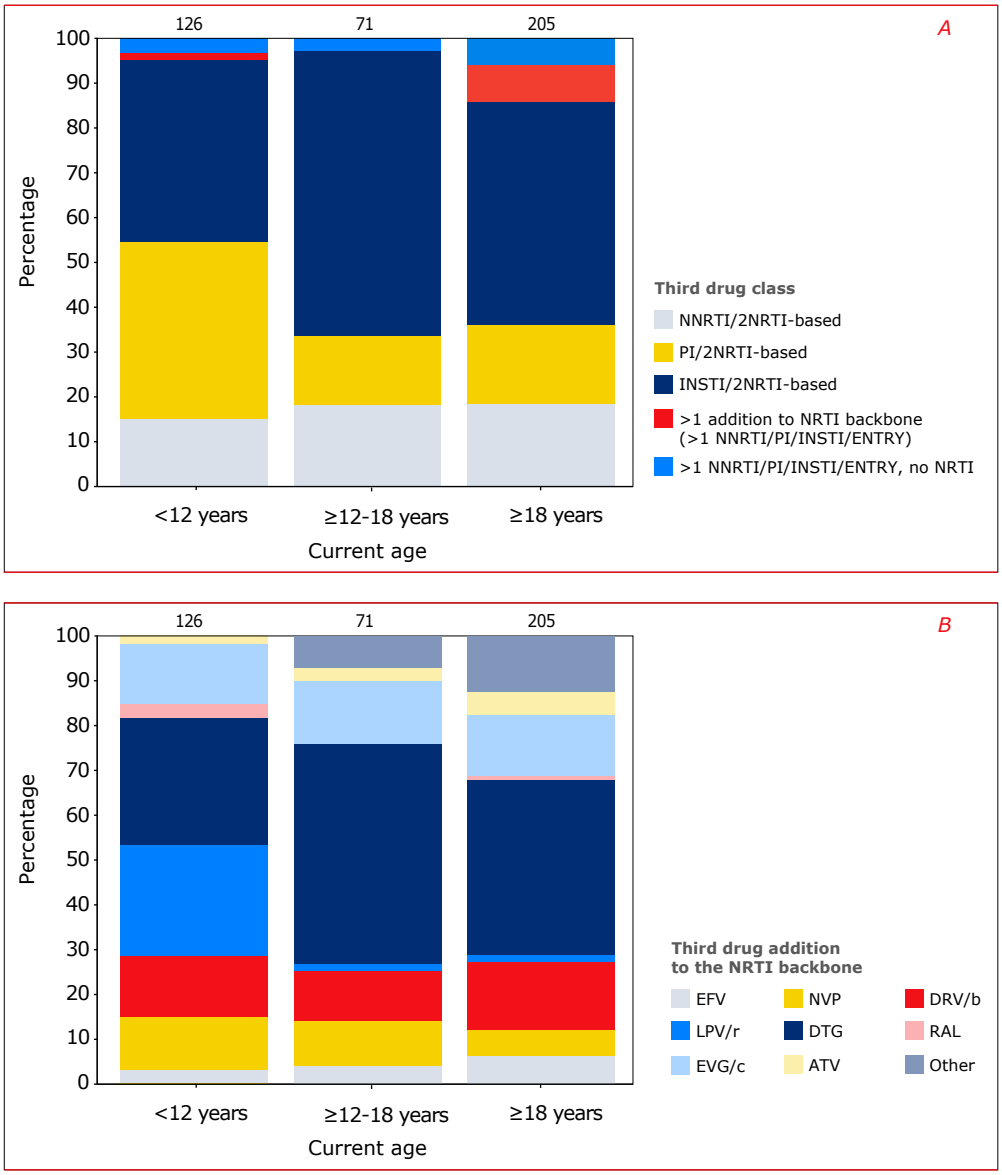
Of the 199 children known to be in care in 2019 and under 18 years of age, 197 (97%) were on cART during their last reported clinical visit. The distribution of current cART use is shown in *Figure 5.9*, according to age on 31 December 2019.

Among those aged <12 years, PI-containing and INSTI-based regimens were currently most often used (both categories are 40%), with dolutegravir (29%) and lopinavir/ritonavir (25%) the most common individual third agents.

In children aged between 12 and 18 years, 18% were using an NNRTI-based regimen, 15% a PI-based regimen, and 63% an INSTI-based regimen. Among those using an INSTI-based regimen, dolutegravir was the most commonly used (49%).

Among individuals diagnosed with HIV during childhood who are currently over 18 years of age, 50% were using an INSTI-based regimen, mainly dolutegravir.

Figure 5.9: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the current regimen, stratified by current age: (A) antiretroviral class and (B) specific drug. Numbers above the bars represent the total number of individuals initiating cART in that particular calendar year period.



Legend: *ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI=protease inhibitor; EFV= efavirenz; NVP=nevirapine; DRV/b=cobicistat/ritonavir-boosted darunavir; LPV/r=ritonavir-boosted lopinavir; DTG=dolutegravir; RAL=raltegravir; EVG/c=cobicistat-boosted elvitegravir; ATV/r= ritonavir-boosted atazanavir.*

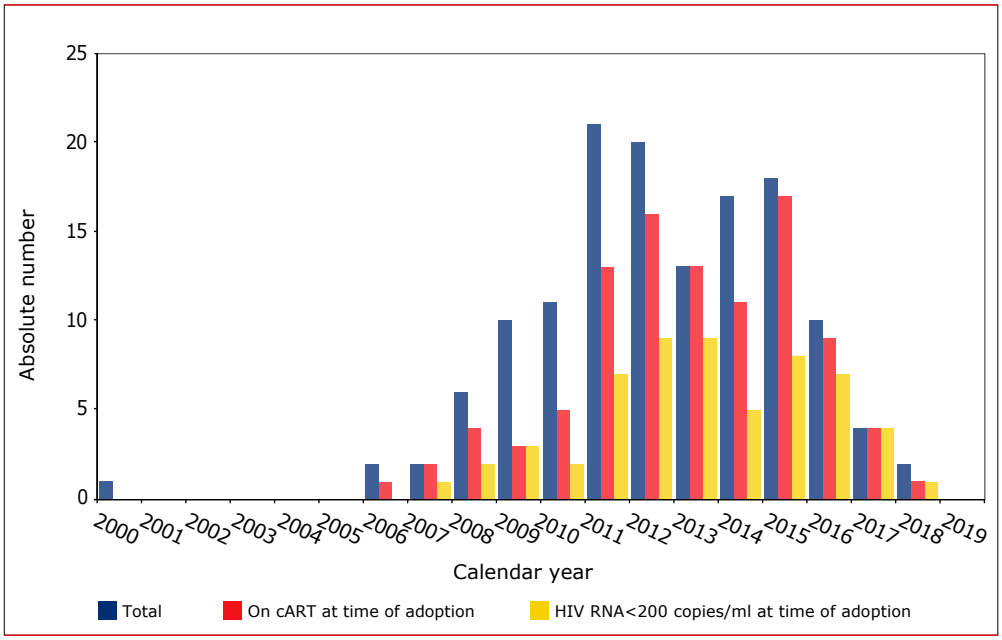
Special Populations

Adopted children

Of the 511 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 140 (27%) had been adopted by Dutch parents. The absolute number of child adoptions varied between two in 2006 and a maximum of 21 in 2011, with a decrease from 2016 onwards to four children in 2017, two children in 2018 and no adopted children being registered in 2019(*Figure 5.10*):

- Their median age at the time of entering care in the Netherlands was 2.7 years (IQR, 1.5-5.1).
- All children used cART during follow up in clinical care in one of the Dutch HIV treatment centres.
- In total, 99 (71%) children were already receiving cART before they were adopted.
- 18 (13%) children had been treated with monotherapy or dual therapy before the start of cART.
- The proportion of children already receiving HIV treatment prior to adoption varied over time, and was 100% for children adopted in 2017 and 2018. At the moment of entering care in the Netherlands, only 58 (41%) of the 140 children had a viral load <200 copies/ml, and this proportion did not increase substantially over time.
- As of 31 December 2019, all children were currently alive and in care, and their median current age was 9.3 years (IQR, 7.1-11.7).
- All children who started cART were still receiving treatment in 2019, and all (100%) had an undetectable viral load (≤200 copies/ml) at the last known time point.

Figure 5.10: Number of HIV-positive adopted children who entered paediatric care, by calendar year.



Legend: cART=combination antiretroviral therapy.

Transfer to adult care

Of the 511 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 393 initially received that care in one of the paediatric HIV treatment centres. As of 31 December 2019, 158 (40%) of these 393 children were aged over 18 years and had transferred to adult care

The number of adolescents who transferred to an adult centre each year varied; it was one in 2000, 20 in 2011, 11 in 2016, and 16 in 2019. The median age at the time of transfer was 19.0 years (IQR, 18.4-19.8). The median time in care after transfer until last documented visit is 5.6 years (IQR, 1.3-8.0). Of the 158 individuals who transferred to adult care, 11 (7%) have been lost to follow up, six (4%) have moved abroad, and five (3%) have died. The remaining 136 are alive and in care.

At the time of their last clinical visit in 2019, eight of the 136 individuals still in care (6%) had a last known HIV RNA level >200 copies/ml (median 4501; IQR 3957-162,869), a decline from the 12% described in the 2019 SHM Monitoring report.

At the time of transfer to an adult HIV treatment centre, 139 out of the 158 adolescents had a documented HIV RNA level; 24(17%) had an HIV RNA level >200 copies/ml and 115 (83%) of these 139 adolescents with an available HIV RNA measurement had an HIV RNA ≤200 copies/ml. These rates are comparable to results from the UK, which found that three quarters of the adolescents were virologically suppressed at the time of transition[16]. We also observed comparable proportions of undetectable HIV RNA levels in the year before and after transfer to adult care: one year before transfer to adult care, 84% of the adolescents had an HIV RNA level ≤200 copies/ml, compared to 79% of the young adults one year after their transfer.

Of the 24 adolescents without viral suppression at the time of transfer, three have died, seven are no longer in care, and three had a most recent HIV RNA >200 copies/ml. The remaining 11 adolescents are virally suppressed, according to their last available HIV RNA measurement.

Weijsenfeld *et al.* explored the data on transition to adult care in our registry in more detail[17], and reported an increased risk of virological failure between 18-19 years of age, with this risk being concentrated around the time of transitioning to adult care. Virological failure was associated with a low level of education and a lack of autonomy regarding medication adherence at the time of transitioning to adult care.

Summary

Of the 511 children with HIV ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 81% remain in care in the Netherlands. A substantial proportion of the children newly registered since 2010 are children who have been adopted by Dutch parents. This has driven the observed increase in the proportion of children in care aged between 0 and 12 years old. It is worth noting that the annual number of newly-registered children who were adopted by Dutch parents has been decreasing since 2016. This decrease contributes to the drop in the overall number of newly-registered children with HIV in the Netherlands since 2016.

The majority of children with vertically-acquired HIV were born outside the Netherlands. Vertical transmission of HIV within the Netherlands has become extremely rare, with two cases reported since 2015. This reflects the success of standardised HIV screening during the first trimester of pregnancy[11]. This screening does not, however, completely prevent vertical transmission from occurring. Physicians should therefore remain alert to the possibility of HIV acquisition later during pregnancy in women who tested HIV-negative during the first trimester. They should also be aware of possible signs of primary HIV infection. We observed low mortality rates in HIV-positive children in care in the Netherlands. In total,

97% of HIV-positive children ever in care in the Netherlands have received cART. The cART regimens have changed over time and, in more recent years, mostly include the protease inhibitors lopinavir/ritonavir and darunavir in the younger children, as well as the integrase inhibitors dolutegravir and elvitegravir in children 12 years of age or older.

Although a less favourable initial virological response was seen in the youngest children, the viral suppression rate after five years of cART in HIV-positive children who initiated cART in or after 2010, was high (97% HIV-RNA < 200 copies/ml), including among the youngest children.

The continuum of care shows a high retention-in-care rate among children currently aged less than 18 years. However, once young people reach the age of 18 they become more likely to be lost to follow up. Moreover, compared with children younger than 18, a substantially lower proportion of those aged 18 years or older had suppressed HIV RNA levels by the end of 2019 (97% versus 73%). Another important point is that all children who were adopted by Dutch parents have suppressed HIV RNA levels, based on their last available HIV RNA measurement.

Of those individuals originally registered as a child who were still in care in 2019, 52% were older than 18 on 31 December 2019. The high rate of detectable HIV viral load in HIV-positive individuals around the time of transitioning to adult care is of concern. Viral suppression rates have improved over time, resulting in relatively more young people being virally suppressed during their most recent clinical visit. However, there remains a group of young people who are unable to achieve HIV RNA suppression, despite cART use.

Recommendations

The provision of care for children living with HIV in the Netherlands has resulted in generally favourable outcomes, with a low mortality rate and good long-term virological and immunological responses to treatment. An increasing proportion of the children registered with SHM have now reached the age of 18 and have transitioned to adult care. Special attention is needed for this group, as this period of transition is associated with an increased risk of virological failure.

Although the occurrence of vertical transmission of HIV in the Netherlands has become very rare due to universal HIV screening during the first trimester of pregnancy, healthcare providers should remain vigilant for the occasional incident maternal HIV infection later during pregnancy, which, if unnoticed, can result in vertical transmission.

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