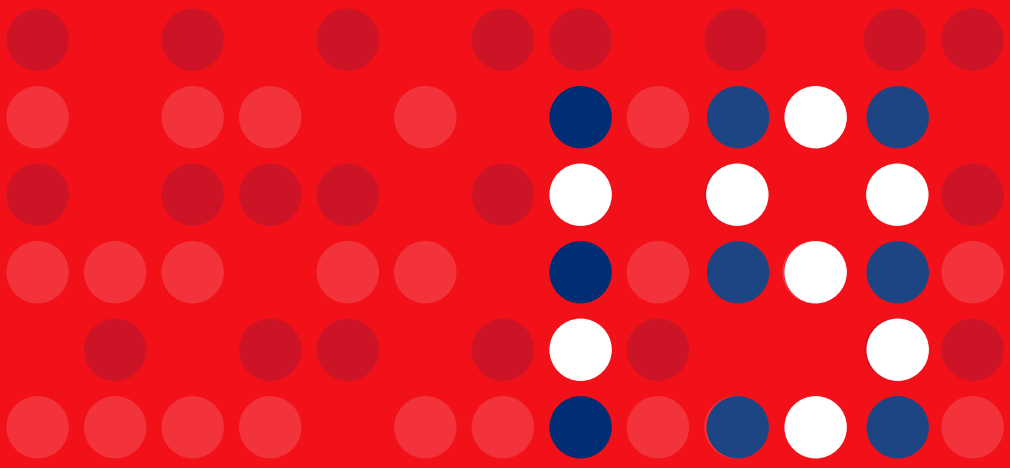
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2019

Chapter 5: Distinct populations:

Children living with HIV in the Netherlands



About Stichting HIV Monitoring

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001 and appointed by the Dutch minister of Health, Welfare and Sport as the executive organisation for the registration and monitoring of HIV-positive individuals in the Netherlands.

In collaboration with the HIV treatment centres in the Netherlands, SHM has developed a framework for systematically collecting HIV data for the long-term follow up of all registered individuals. The Netherlands is the only country in the world to have such a framework, which enables healthcare professionals to aspire to the highest standard of HIV care.

SHM contributes to the knowledge of HIV by studying the course of the infection and the effect of its treatment. To this end, SHM follows the treatment of every HIV-positive man, woman and child in care in the Netherlands and registered in the national observational HIV cohort, ATHENA. Continuous collection of data is carried out at 24 HIV treatment centres and subcentres and 4 paediatric HIV centres in the Netherlands. Patient data are collected and entered into the database in a pseudonymised form for storage and analysis. In this way SHM is able to comprehensively map the HIV epidemic and HIV treatment outcomes in the Netherlands.

Our mission

To further the knowledge and understanding of all relevant aspects of HIV infection, including comorbidities and co-infections (such as viral hepatitis), in HIV-positive persons in care in the Netherlands.

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HIV Monitoring

Monitoring Report 2019

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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Guide to buttons

Content page

Next chapter

Preceding chapter

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

Colette Smit, Tom Wolfs, Annemarie van Rossum

Box 5.1: Definitions

Child	An individual diagnosed with HIV and with a first visit in 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 2018	Clinic visit or lab measurement in 2018.
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.

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 higher survival rates of HIV-positive children when compared with children with delayed cART initiation based on CD4 cell count[6,7,8,9]. Studies showing a clinical benefit of early cART initiation led to a 2015 revision of the WHO guidelines on when to start cART, with the guidelines now recommending initiation of cART in everyone living with HIV irrespective of CD4 cell count, including all children[10].

< Back to Virological response

< Back to Chapter 6

In the Netherlands, children living with HIV generally receive healthcare at one of four paediatric HIV treatment centres. These children transition to adult HIV care when they reach 18 years of age. 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 response to treatment in 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*).

***Box 5.2:** Outline of the paediatric ATHENA cohort in the Netherlands: HIV-positive children (aged <18 years at the time of diagnosis and first visit in a Dutch HIV treatment centre) ever registered in the ATHENA cohort by 31 December 2018.*

Populations described in this chapter

1. Ever registered and in HIV care in the Netherlands before 18 years of age (n=504)
2. Population in care in 2018:
   - aged <18 years in 2018 (n=194): 189 with vertically-acquired HIV, 2 with non-vertically acquired HIV, and 3 with an unknown route of transmission.
   - aged ≥18 years in 2018 (n=214); 121 with vertically-acquired HIV, 86 with non-vertically acquired HIV, and 7 with an unknown route of transmission.
3. Specific populations:
   - adopted children (n=136)
   - children who have transferred to adult care (n=141)

Ever registered

As of 31 December 2018, 644 HIV-positive individuals diagnosed with HIV before the age of 18 years have been registered by SHM since the start of the registration in 1998. Of these 644 children, 504 children entered care in the Netherlands before 18 years of age. Those who entered Dutch HIV care only after they were 18 years or older (n=140) are not included in this chapter. Of the 504 children we report on, 387 entered care at a paediatric HIV treatment centre and 117 at an adult treatment centre. Those who entered care in 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 504 HIV-positive children ever registered by SHM and entering care in the Netherlands below the age of 18, as of 31 December 2018.

Characteristics	Vertically-acquired HIV infection*	Non-vertically-acquired HIV infection*	Route of transmission unknown*
Total	354	138	12
HIV treatment centre			
Paediatric care	346 (97)	31 (22)	10 (83)
Adult care	8 (3)	107 (78)	2 (17)
Gender			
Male	172 (49)	51 (37)	7 (58)
Female	182 (51)	87 (63)	5 (42)
Country of origin child			
The Netherlands	110 (31)	31 (22)	0
Sub-Saharan Africa	204 (58)	82 (59)	9 (75)
Other	40 (11)	25 (19)	3 (25)
Country of origin mother			
The Netherlands	32 (9)	2 (1)	1 (8)
Sub-Saharan Africa	187 (53)	13 (9)	6 (50)
Other/unknown	135 (38)	123 (89)	5 (42)
Age at HIV diagnosis	1.2 (0.3-4.0)	16.8 (16-17)	11.3 (5-14)
cART-treated	348 (98)	129 (93)	11 (92)
Therapy-naive at cART initiation	299 (84)	122 (88)	11 (92)
CD4 at cART initiation	543 (270-1190)	303 (196-412)	250 (75-522)
CD4 Z-score at cART initiation	-0.58 (-1.02–0.15)	-0.57 (-0.96–0.26)	-0.51 (-0.99–0.19)
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)

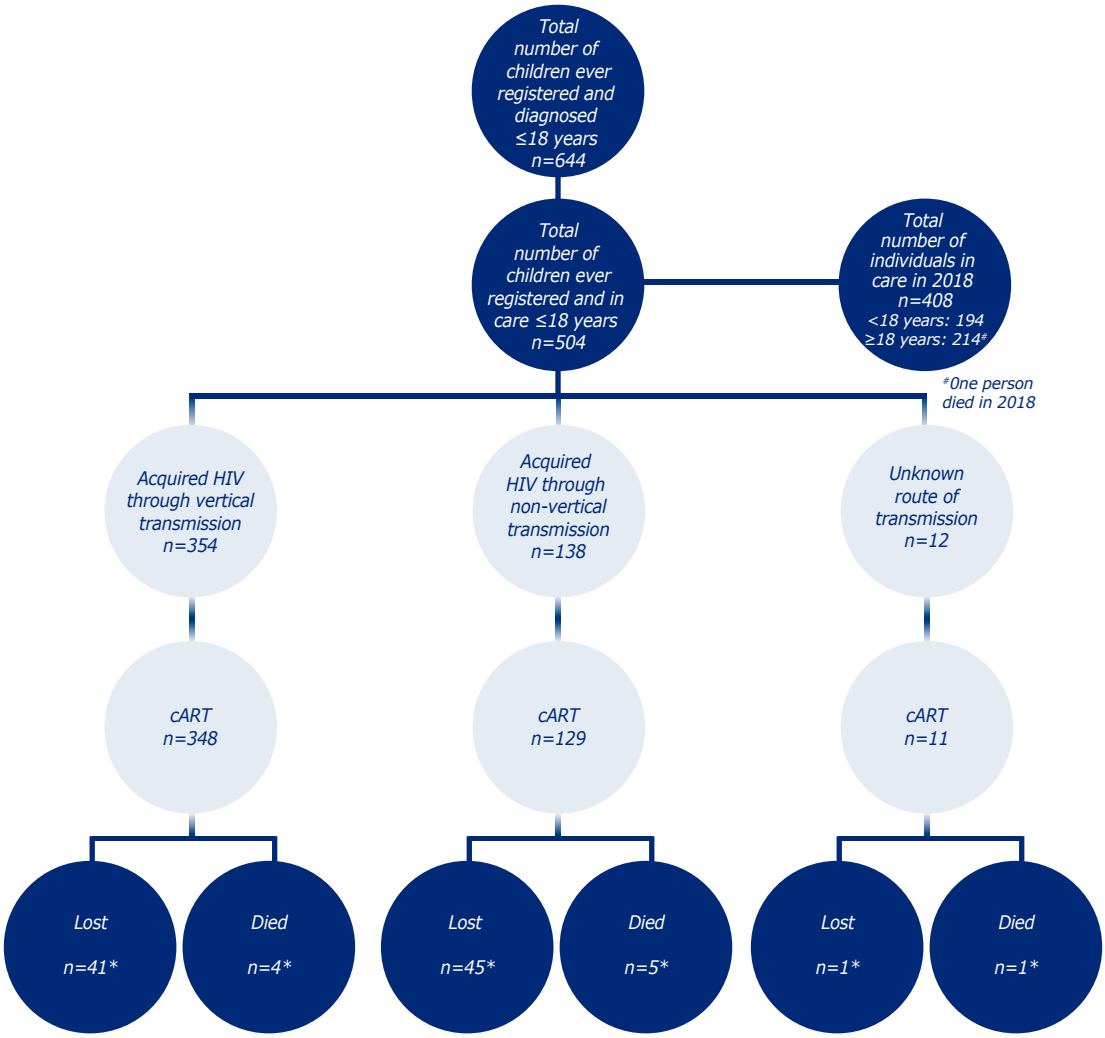
** Data are number (%) of children or median (interquartile range)*

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

Mode of transmission

The majority of the children registered had acquired HIV through vertical transmission or through sexual contact. The reported mode of HIV transmission is shown in *Figure 5.1*. *Figure 5.2* shows the number of newly-registered children per calendar year of entering care, according to the mode of HIV transmission and, for those with vertically-acquired HIV, according to 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 2018.*



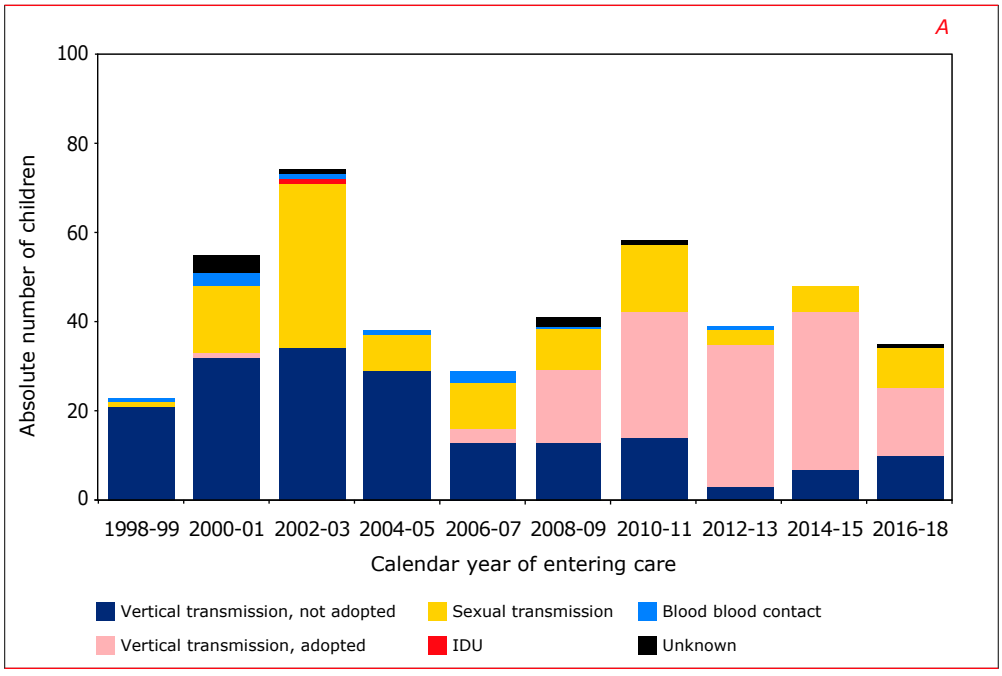
**of the total number of children who acquired HIV through vertical, non-vertical or an unknown route of transmission.*

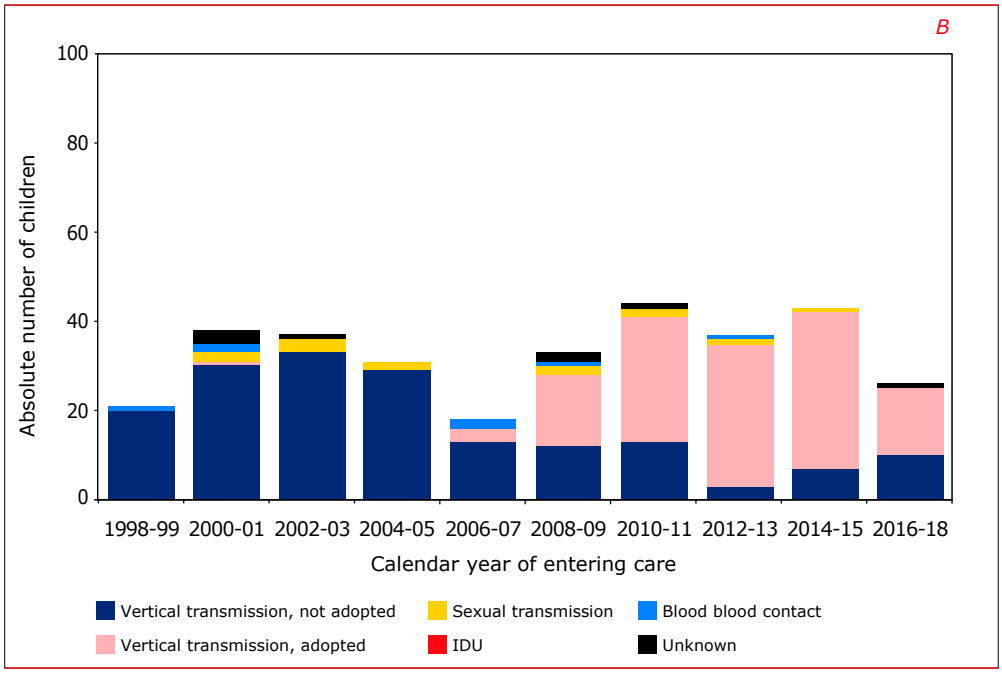
Legend: *cART=combination antiretroviral therapy.*

Children with vertically-acquired HIV

- In total 354 children had acquired HIV through vertical transmission.
- The median age at the first reported HIV-positive test result, including self-reported tests in the country of origin, was 1.2 years (interquartile range (IQR) 0.3-4.0 years).
- 58% (n=204) of the children were born in sub-Saharan Africa.
- 31% (n=110) of the children were born in the Netherlands.
- In 9% of the children born in the Netherlands (10 out of 110), both parents originated from the Netherlands.
- Of children with vertically-acquired HIV, 97% received care in a paediatric HIV treatment centre in the Netherlands and the remaining 3% were seen in adult care.
- In total, 98% of the children had a documented cART start date.

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 had acquired HIV through vertical transmission, by whether or not they had been adopted during the period 1998-2018. A) total population, B) HIV paediatric care only.





Note: *low numbers in 2018 may be due to a delay in the treatment centre registering the child with SHM.*

Legend: *IDU=transmission through injecting drug use.*

Only a single case of HIV vertical transmission in the Netherlands since 2015

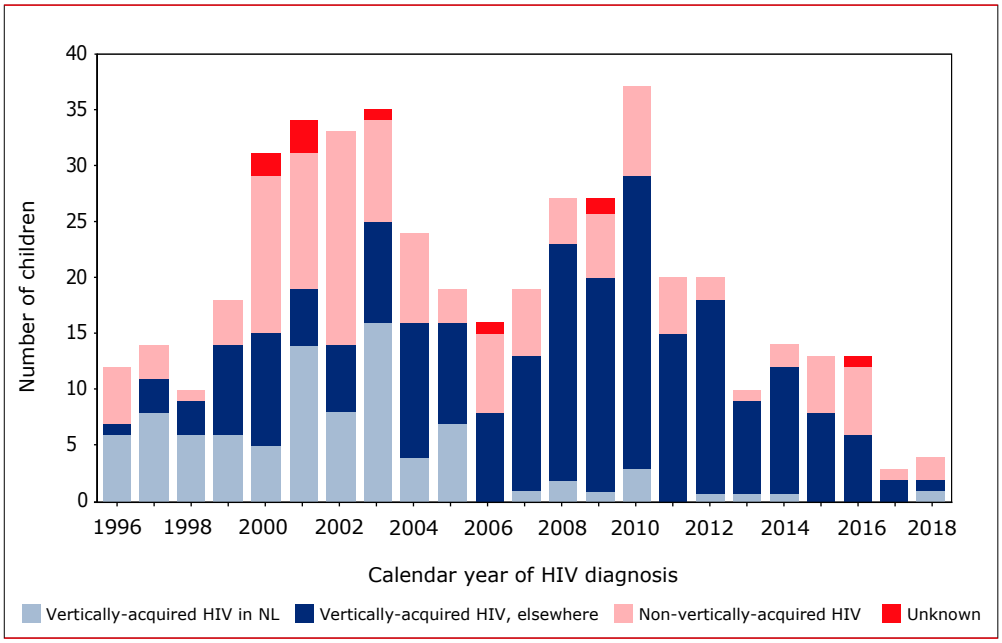
Vertical transmission of HIV has been reduced to close to zero in the Netherlands since 2015. *Figure 5.3* shows the number of newly-registered HIV diagnoses among children by year of diagnosis, according to mode of transmission and region of origin. As shown in the figure, vertical transmission of HIV in the Netherlands was relatively frequent prior to 2004 (16 cases in 2003), after which it markedly declined, with a single documented case of vertical transmission in the Netherlands in 2018.

The decline of vertical transmission in the Netherlands resulted from standard HIV screening among pregnant women, which was introduced nationally in 2004[11,12]. Since the introduction of this screening programme, 10 children who were born with HIV in the Netherlands have been reported to SHM. These 10 children are described briefly below:

- Seven children were born to mothers who only first tested 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 and only acquired HIV later during their pregnancy.

- One child was born to a mother who was known to be HIV-positive, but who did not receive treatment during her pregnancy for an unknown reason.
- In one case, the 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 could suggest *in utero* transmission of HIV in this pregnancy.
- The remaining child was born to a mother whose HIV status during pregnancy was unknown, including any result of screening for HIV.

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



Note: *low numbers in 2018 may be due to a delay in registration.*

Children with non-vertically-acquired HIV

- In total, 138 children were registered with HIV infection acquired through non-vertical transmission, including 2 children newly-registered in 2018.
- The median age at their first reported HIV-positive test result was 16.8 years (IQR 16-17).

- The main route of HIV transmission was sexual contact (*Figure 5.2*):
  - 90 children had acquired HIV through heterosexual contact,
  - 28 children had acquired HIV through homosexual contact.
- Nineteen children had 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 had acquired HIV through injecting drug use or accidentally through contaminated needles.
- Of the children with non-vertically-acquired HIV, 59% were born in sub-Saharan Africa.
- 81% received care in an adult HIV treatment centre.
- In total, 93% of the children had started cART.

Unknown route of HV-1 transmission

- For 12 HIV-positive children, the route of transmission was unknown.
- Their median age at diagnosis was 11.3 years (IQR 5-14).
- Ten children were in care at a paediatric HIV treatment centre.
- In total, 92% of these children had started cART.

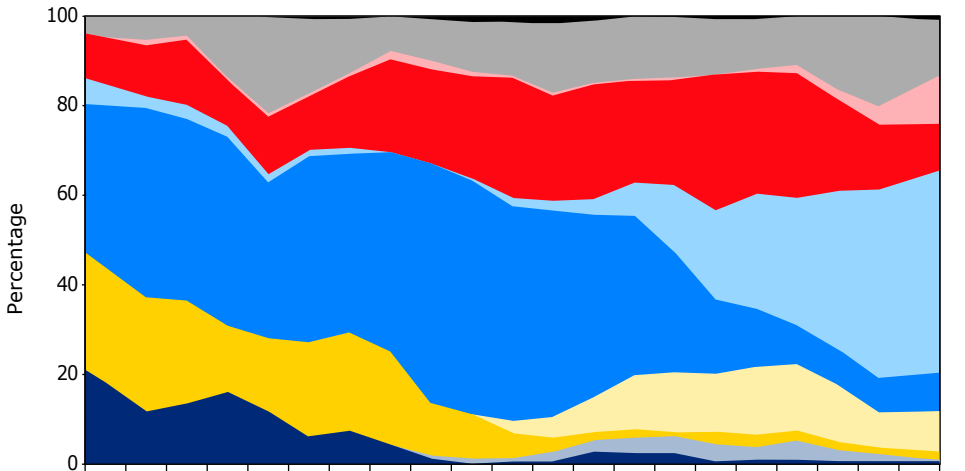
Newly registered in 2018

- 6 children first entered care in 2018.
- 4 of these children had vertically-acquired HIV and entered paediatric care.
- The other 2 children had acquired HIV through sexual contact and entered care in an adult HIV treatment centre; at that time they were older than 17 years.
- 3 children were born in the Netherlands; 1 child had acquired HIV through vertical transmission and 2 children through non-vertical transmission.
- 3 children were born in sub-Sahara Africa and all had vertically-acquired HIV. Two of these children had been adopted by Dutch parents.

Age distribution

The age distribution of children reveals some shifts between 1998 and 2008 (*Figure 5.4*). From 2008 onwards, there was an increase first in the proportion of children aged 0 to 5 years, and subsequently in thosed aged 5 to 12 from 2011 onwards. 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 2018, about 83% of the children aged 12 years or below were adopted.

Figure 5.4: Time-dependent age distribution of HIV positive children in care over time. The shaded areas represent the proportion of adopted children.



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
	0	0	0	0	0	1	1	0	1	2	2	3	2	0	0	1	1	0	0	0	1
	3	4	4	17	34	28	20	13	16	20	22	30	27	29	29	27	25	25	38	46	31
	0	1	1	1	1	1	1	3	3	2	1	1	1	1	1	0	1	4	5	9	18
	7	9	14	13	20	20	27	35	36	41	49	46	50	48	50	65	60	65	48	34	24
	3	2	3	3	3	2	2	0	0	1	3	4	7	15	31	43	56	66	82	96	91
	24	33	39	53	54	69	67	75	92	94	88	90	80	75	57	36	29	20	19	18	17
	0	0	0	0	0	0	0	0	0	0	5	9	15	25	28	28	33	34	30	18	18
	17	20	22	19	26	35	37	35	20	18	10	6	4	4	2	6	6	5	4	3	4
	0	0	0	0	0	0	0	0	1	2	1	4	5	7	8	8	6	10	6	4	1
	12	9	13	20	18	10	12	7	2	0	1	1	5	5	5	1	2	2	1	1	1

Low mortality rates

The mortality rate among children registered between 1998 and 2018 is very low. Three children (0.5%) have died at less than 18 years of age 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 these boys, despite the fact that two of the boys were receiving cART. One boy had very low CD4 cell counts,

despite the use of cART and one boy died shortly after the start of cART with high levels of HIV RNA and low CD4 cell counts.

Treatment

Of the 504 children who were registered, 488 (98%) started cART. Of these 488 children, 439 (88%) were treatment-naive at the start of cART and 61 (11%) had previously been exposed to mono- or dual therapy (i.e., were pre-treated).

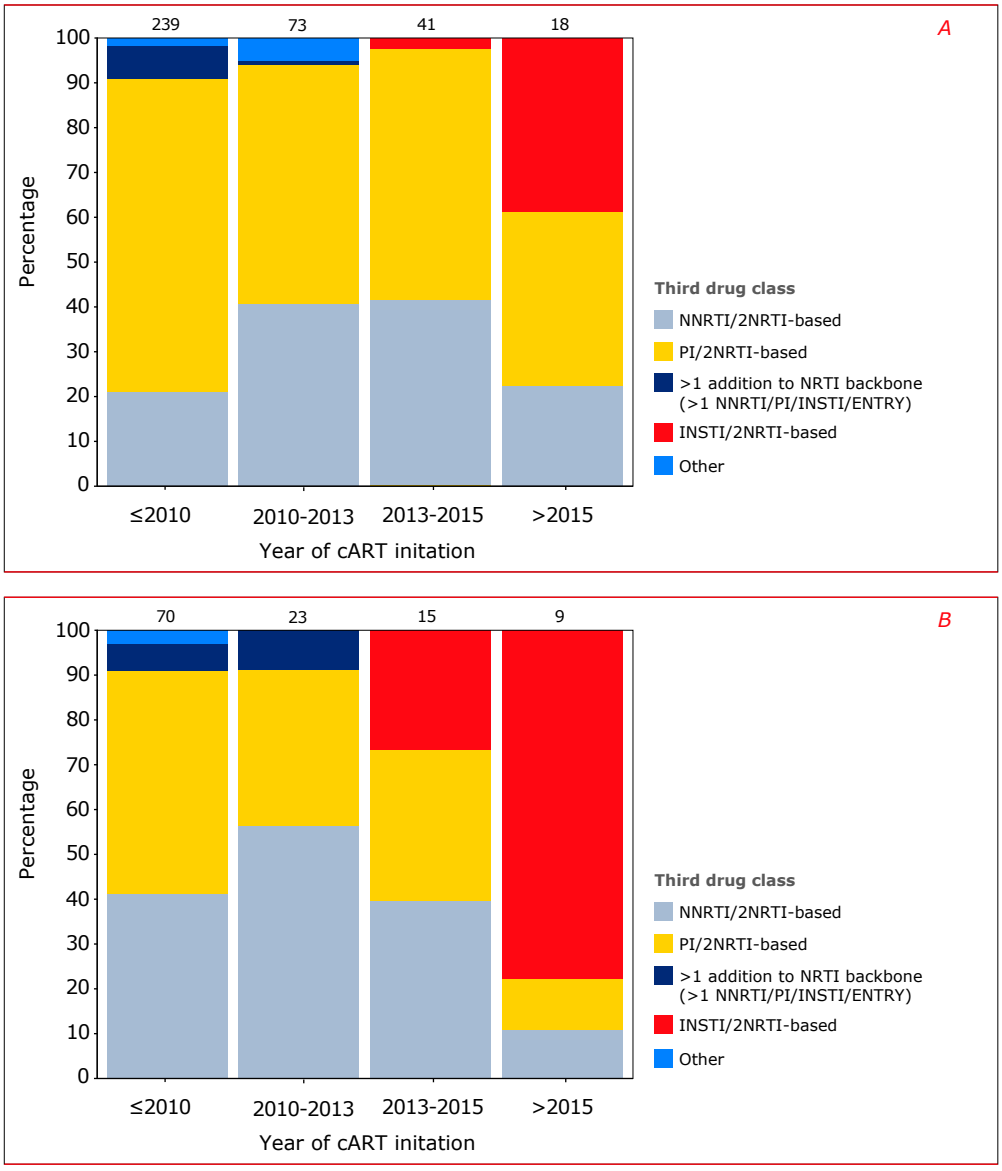
When assessing treatment, we included both pre-treated and treatment-naive children, grouped according to calendar year of starting cART: 309 children started a cART regimen before 2010, 96 started cART between 2010 and 2013, 83 started from 2013 onwards.

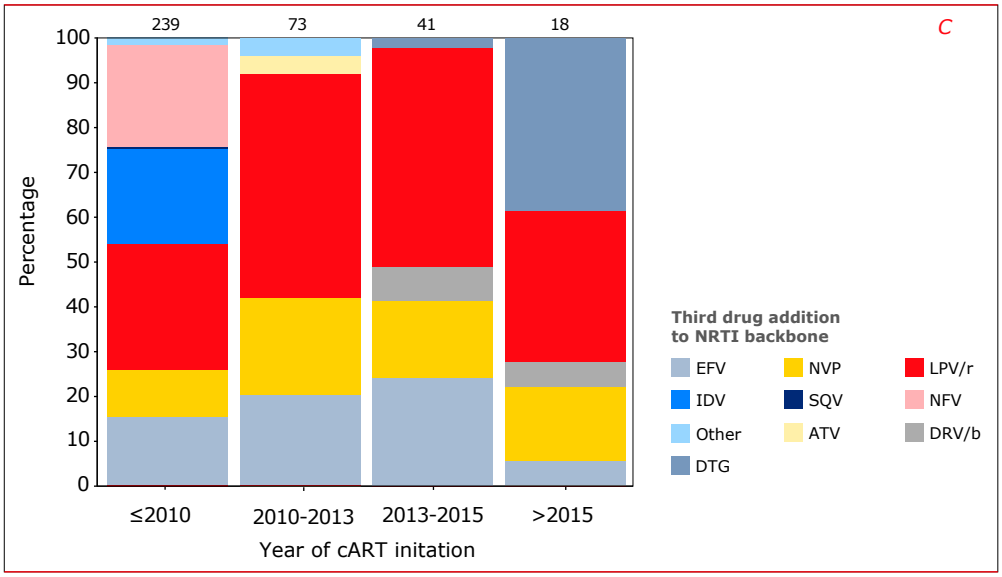
Of the children not treated with cART, 2 had only recently entered care, one had died shortly after entering care, 8 were lost to follow up and another 2 moved abroad. For another child the reason for not starting cART was recorded as being their one own decision and in another child who had low HIV RNA levels cART initiation was delayed until after transfer to adult care. Finally, for the remaining child, the reason for not initiating cART was unknown.

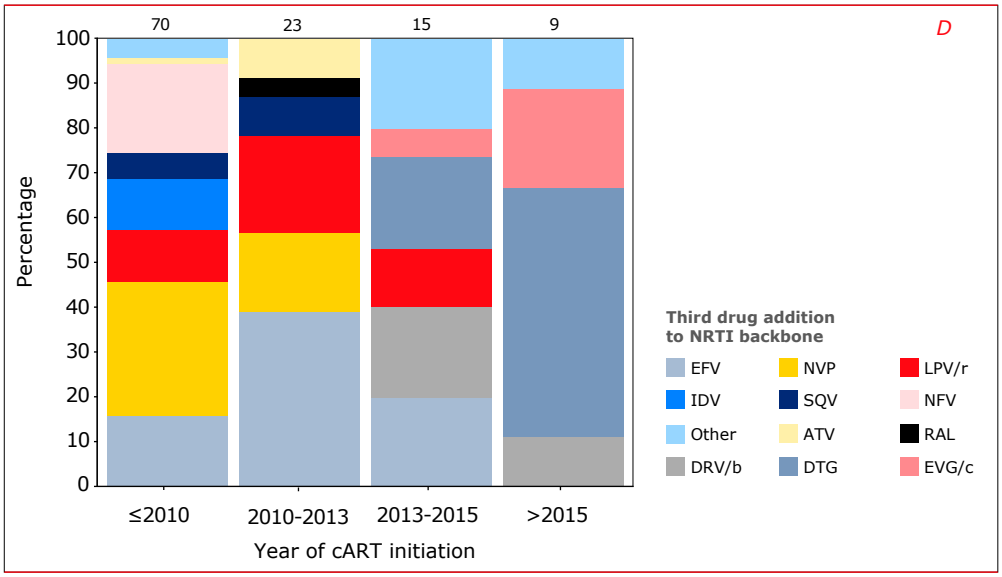
Initial combination antiretroviral regimen used

Overall, out of the 488 registered children who were known to have initiated cART, 58% were treated with a first-line cART regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs) and 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. In addition, 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 only prescribed to children older than 12 years of age.

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 drug among children in paediatric care and (D) specific drug among children in adult care.







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 spent on an initial regimen among the 488 children who ever started cART was 17 months (IQR 4-41). Discounting weight-related dose changes, 433 children (88%) discontinued their first-line treatment regimen. The most important reasons for changing first-line cART included toxicity (15%) and simplification (22%). Virological failure accounted for 9% of the reasons for changing first-line cART therapy. Other reasons were low drug concentrations, decision by parents and/or child, research protocol-driven reasons, or unknown. The duration of time spent on an initial regimen was shorter for children who initiated cART in or after 2013 (median 14 months (IQR 6-25), likely the result of dolutegravir and elvitegravir becoming available as more attractive treatment options in 2013 and 2014.

Immunological response

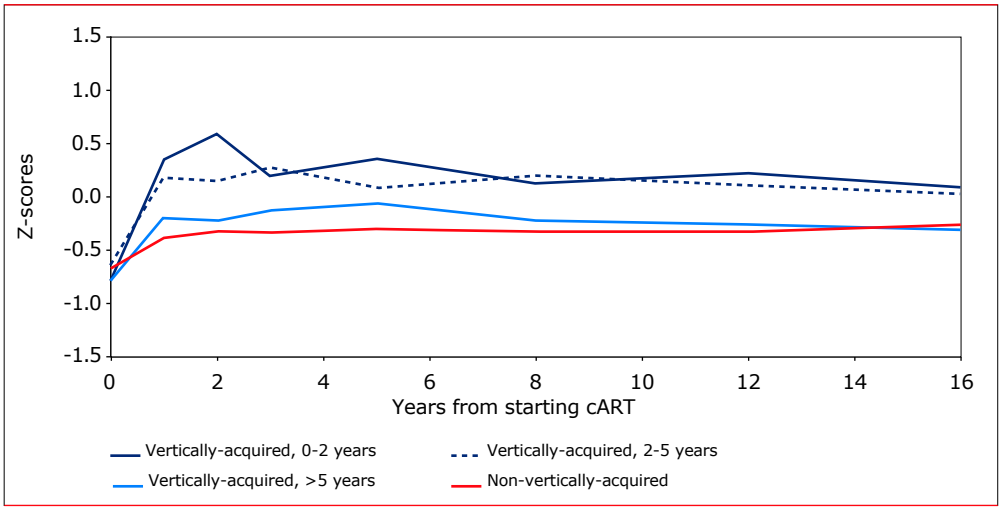
Earlier reports have shown that the clinical benefit of cART is strongly related to the degree to which the CD4 cell count recovers[13]. Long-term CD4 cell count changes were assessed among the 488 children who ever started cART. Children with vertically-acquired HIV were stratified according to age 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[c], 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.

c *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.*

Figure 5.6 shows the changes in Z-scores for CD4 T-cell counts among HIV-positive children stratifying those with vertically-acquired HIV by age at initiation of cART. The youngest children (less than two years of age at cART initiation) had the highest absolute CD4 cell counts at cART initiation, but the age-adjusted CD4 Z-scores did not differ significantly between groups. In the first two years after cART initiation, CD4 Z-scores increased significantly in all children. However, the youngest children (aged below 5 years at time of cART initiation) had higher CD4-Z scores compared to children who were >5 years of age at time of cART initiation, and the CD4 Z-scores remained consistently higher among the youngest children.

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).*



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).

For the current analysis, we included data from the 488 children registered and who 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 longitudinal 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, from 1998-2009 and 2010-2018.

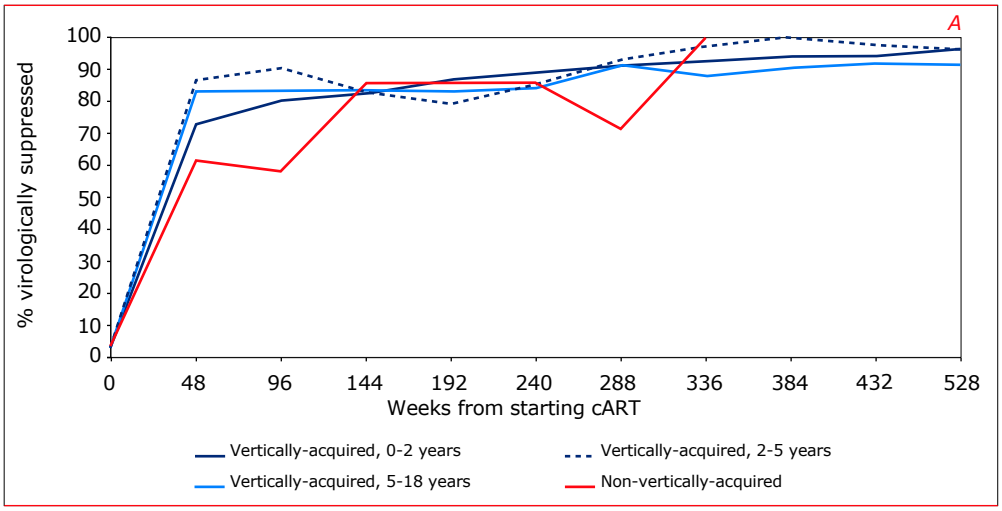
In those initiating cART between 1998 and 2009:

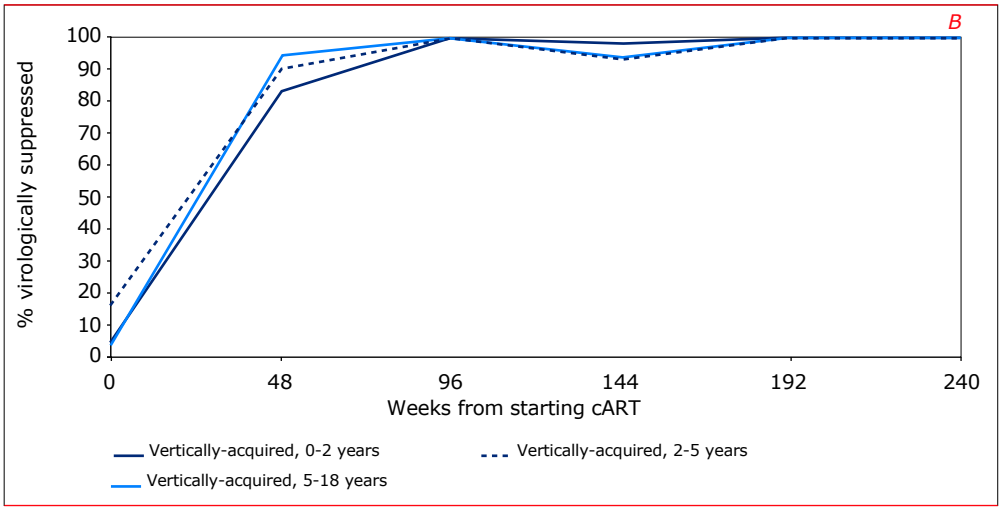
- Among children with vertically-acquired HIV and aged 0-2 years at time of cART initiation, viral suppression rates increased to 73% after one year of cART use, to 86% and 96% after 5 and 10 years, respectively.
- Among children with vertically-acquired HIV and aged 2-5 years at cART initiation, viral suppression rates increased to 87% after one year of cART use, to 85% and 96% after 5 and 10 years, respectively.
- Among children with vertically-acquired HIV and aged over 5 years at time of cART initiation, viral suppression rates increased to 87% after one year of cART use. However, ten-year viral suppression rates were lower (89%) compared with children less than 5 years of age at time of cART initiation.
- Among children with non-vertically-acquired HIV the five-year viral suppression rate was 86%. The 10-year viral suppression is not shown, due to the small number of children for whom such long term data could be calculated [*Figure 5.7A*].

In those initiating cART in or after 2010:

- Among those who started cART in or after 2010, the viral suppression rates were 100% in all groups after 5 years of cART use. However, among children with vertically-acquired HIV and aged 0-2 years at time of cART initiation, viral suppression rate after one year of cART use was 83% and lower than that in older children with vertically-acquired HIV. Importantly, due to the limited follow-up time between age at cART initiation and reaching 18 years of age for those with non-vertically acquired HIV, viral suppression rates are not presented for these children (*Figure 5.7B*).

Figure 5.7: Viral suppression since combination antiretroviral therapy initiation, by calendar period of therapy initiation: (A) 1998-2009 and (B) 2010-2018. 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 504 HIV-positive children ever registered by SHM, 408 (76%) were still in clinical care in 2018 (*Figure 5.1*). Of the remaining 96 children no longer in care, 9 had died, 35 had moved abroad, and 52 were lost to follow up.

Currently in care and less than 18 years old

- Of the 408 individuals with HIV who entered care before the age of 18 years, 194 were still younger than 18 at the end of 2018.
- 192 children were in care in one of the paediatric HIV treatment centres.
- Their median age as of 31 December 2018 was 11 years (IQR 8-14).

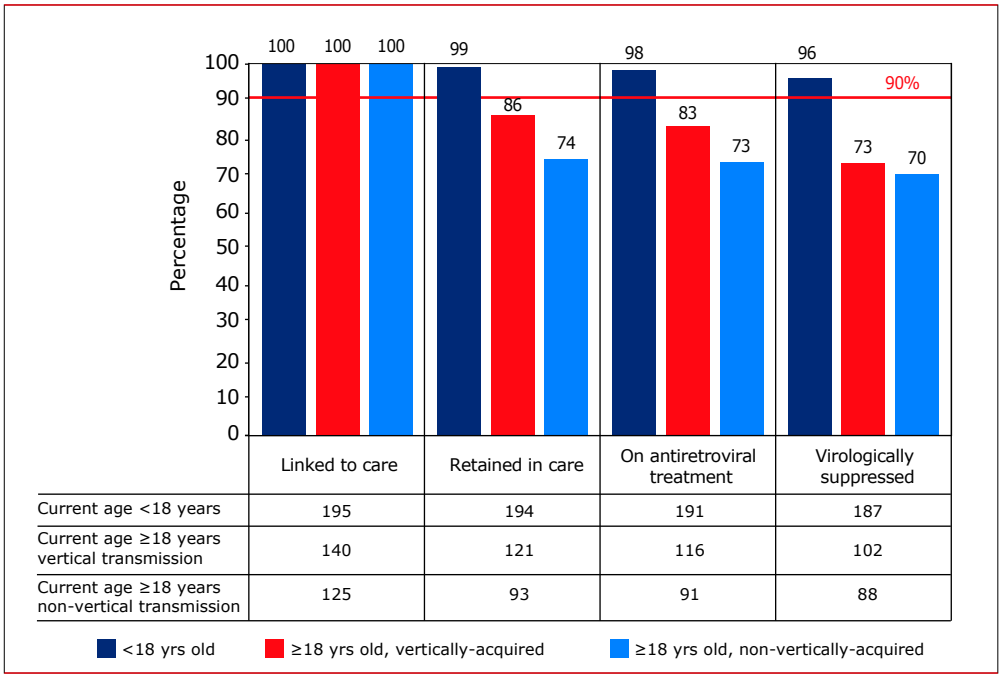
Currently in clinical care and 18 years or older

- The remaining 214 HIV-positive individuals who were first registered as a child were in care and older than 18 at the end of 2018.
- Their median age was 22 years (IQR 20-27) for those who had vertically-acquired HIV and 32 years (IQR 26-36) for those with non-vertically-acquired HIV.

Continuum of care

On the basis of the total number of HIV-positive children ever registered by SHM, still alive on 31 December 2018, and not reported to have moved abroad or to have died, a 'continuum of care' was constructed. This continuum of care depicts engagement in HIV care across a number of key indicators, the last one being the number of children with a most recent HIV RNA measurement below 200 copies/ml (*Figure 5.8*).

Figure 5.8: Continuum of care by age and mode of HIV acquisition, as of 31 December 2018. The numbers above the bars indicate the proportion of individuals.



Individuals were stratified by age on 31 December 2018 and categorised as:

I. current age <18 years; in this age group, the number of children with non-vertically acquired of HIV was too small (n=5) 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, 195 children less than 18 years old on 31 December 2018 were linked to care, registered by SHM, still alive, and not reported as having moved abroad.
- Of these children, 99% were retained in care (194/195); 192 children were receiving paediatric care. The single child that had been lost to follow up was born outside the Netherlands.
- During their last clinical visit in 2018, 98% (191/195) were using antiretroviral therapy.
- Overall, 96% of those linked to care and less than 18 years old had a most recent HIV RNA measurement below 200 copies/ml (187/195).

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

- 140 individuals who had acquired HIV through vertical transmission and who were over 18 years of age on 31 December 2018 were linked to care.
- Of these 140 individuals, 86% (121) were still in care as of 31 December 2018. The remaining 19 individuals had been lost to follow up, 11 of whom were born outside the Netherlands.
- 83% (116/140) were using antiretroviral therapy at their most recent clinical visit.
- 73% (102/140) 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 2018 and had acquired HIV through non-vertical transmission.
- Of these, 93 (74%) were still in care as of 31 December 2018; 32 individuals had been lost to follow up, including 18 women originating from sub-Saharan Africa.
- 73% (91/125) were using antiretroviral therapy during their last registered clinical visit.
- and 70% (88/125) had a most recent HIV RNA measurement below 200 copies/ml.

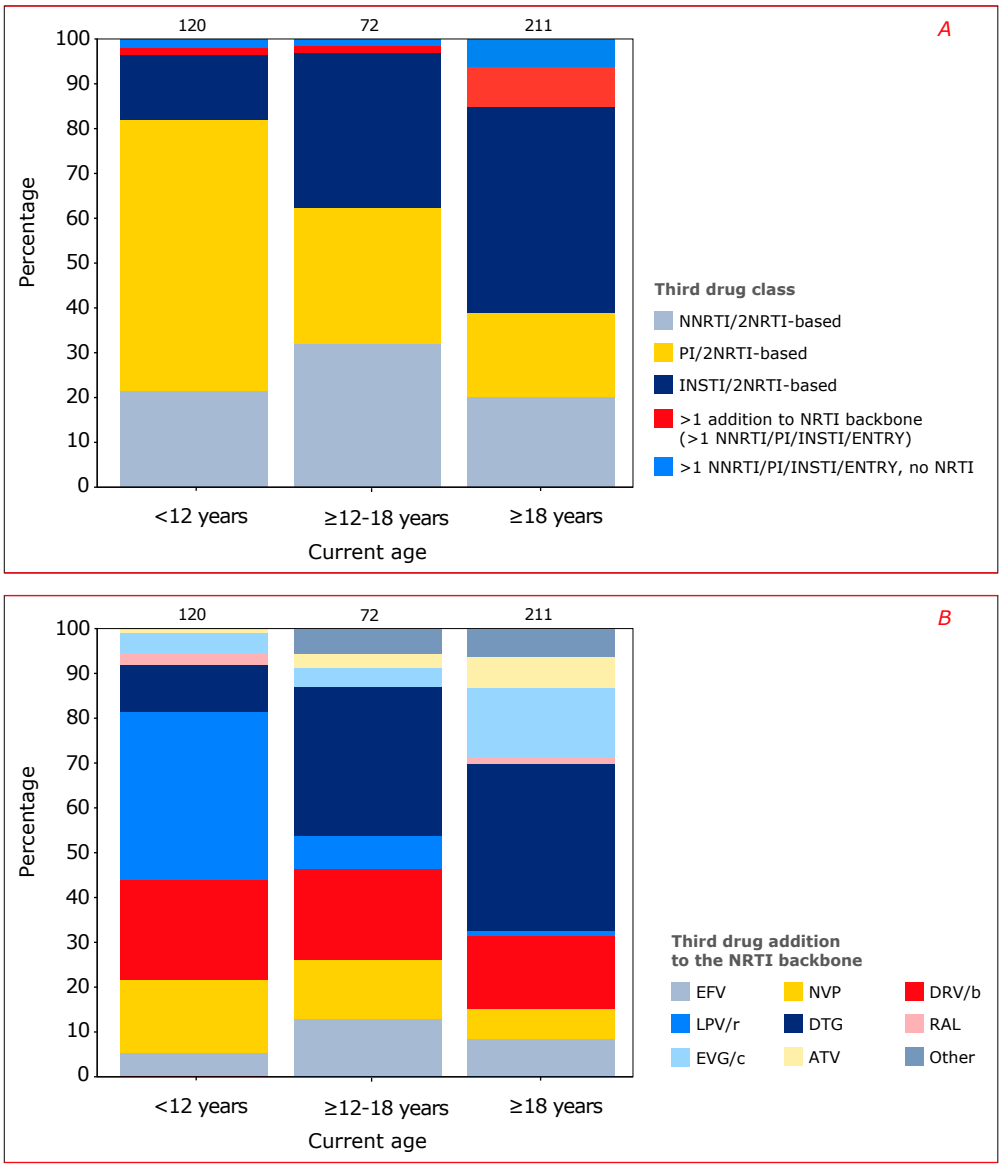
In care and on cART in 2018

Of the 408 people known to be in care in 2018 and aged less than 18 years, 396 (97%) were on cART by the end of 2018. The distribution of current cART use is shown in *Figure 5.9*, according to age on 31 December 2018.

Among those aged <12 years, a PI-containing regimen is currently used most often (61%), with lopinavir/ritonavir being the most common (37%). In children aged between 12 and 18 years, 32% are currently using an NNRTI-based regimens, 30% are using a PI-based regimen, and 35% are using an INSTI-based regimen. Among those who are currently using an INSTI-based regimen, dolutegravir was most commonly used (33%).

Among people who were diagnosed with HIV in childhood, but who are currently over 18 years of age, 46% are using an INSTI-based regimen, comprising mainly dolutegravir. There were no differences between those who started care in a paediatric HIV treatment center and those who did not.

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.



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.*

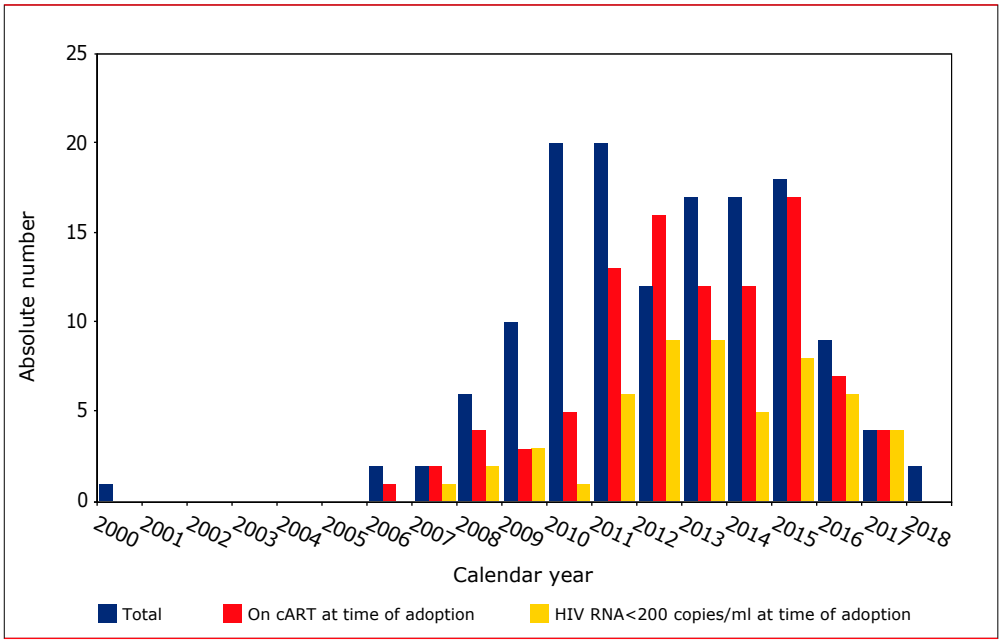
Special populations

Adopted children

Of the 504 children ever registered, 136 (27%) children were adopted by Dutch parents. The absolute number of children being adopted varied between 2 in 2006 and a maximum of 18 in 2015, with a decrease from 2016 onwards to 4 children in 2017 and 2 children in 2018 (*Figure 5.10*):

- Their median age at time of entering care in the Netherlands was 2.8 years (IQR 1.7-5.1).
- All but one child used cART during follow up in clinical care in one of the Dutch HIV treatment centres.
- In total, 96 (71%) children were already receiving cART before being adopted.
- 17 (13%) children had been treated with monotherapy or dual therapy before the start of cART.
- The proportion of children receiving treatment prior to adoption increased over time, and was 100% for children adopted in 2017. However, the 2 children who were adopted in 2018 had no documented cART use at time of adoption. At the moment of entering care in the Netherlands, only 54 (40%) of the 136 children had a viral load <200 copies/ml, and this proportion did not increase substantially over time.
- All children are currently alive and in care, and their median current age is 8.4 years (IQR 6.2-10.8).
- All children who started cART are still on treatment, and 134/135 (99%) had an undetectable viral load (≤200 copies/ml) at the last known time point. The only individual with a detectable HIV RNA level was currently older than 18 and had transferred to an adult HIV treatment centre.

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



Legend: cART=combination antiretroviral therapy.

Transfer to adult care

Of the registered 504 children, 387 children initially received HIV care in one of the paediatric HIV treatment centres. As of 31 December 2018, 141 (36%) of these 387 children had transferred from paediatric to adult care because they had reached the age of 18.

The number of children who transferred to an adult centre varied from one child in 2000 to 20 in 2011, 11 in 2016, and 9 in 2018. The median age at transfer was 19.0 years (IQR 18.4-19.7). The median time in care after transfer is currently 5.1 years (IQR 2.5-8.0). Of the children who have transferred to adult care, 22 (16%) have been lost to follow up, six (4%) have since moved abroad, and 3 (2.1%) have died. The remaining 119 are currently alive and in care.

At their most recent clinical visit in 2018, 13 of the 119 individuals still in care (12%) had an HIV RNA level >200 copies/ml (median 2794; IQR 497-63,600).

At the time of transfer to an adult HIV treatment centre, 94 (80%) of the 117 children with an available HIV RNA measurement had an HIV RNA ≤200 copies/ml and 23 (20%) had an HIV RNA level>200 copies/ml. These rates are comparable to results from the UK, which found that three quarters of the adolescents were virologically suppressed at 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 children had an HIV RNA level ≤200 copies/ml, compared to 80% of the young adults one year after their transfer. Of the 23 adolescents without viral suppression at time of transfer, 2 had died, 6 were no longer in care and 5 had a most recent HIV RNA >200 copies/ml. The remaining 10 adolescents were 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 504 children diagnosed with HIV before the age of 18 and registered by SHM, 81% are still in care. 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.

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 one case reported since 2015. This reflects the success of standardised HIV screening during the first trimester of pregnancy[11]. This measure does not, however, completely prevent vertical transmission from occurring. Physicians should therefore remain alert to the possibility of incident HIV acquisition later during pregnancy in women who tested HIV-negative during the first trimester and 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. Ninety-seven percent of HIV-positive children ever in care in the Netherlands have received cART. Over time, the initial cART regimens have changed and, in more recent years, mostly include the protease inhibitors lopinavir/ritonavir and

darunavir, as well as the integrase inhibitors dolutegravir and elvitegravir in children 12 years of age or older.

Long-term immunological outcomes after initiating cART were poorer in children who started cART when they were five years of age or older. Moreover, although a less favourable initial virological response was seen in the youngest children, the viral suppression rate after 5 years of cART use in HIV-positive children who initiated cART in or after 2010 cART is high (99% 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, young people who have reached 18 years of age or above are more likely to be lost to follow up. Moreover, compared with children who are still below 18 years of age, a substantially lower proportion of those aged 18 years or above had suppressed HIV RNA levels by the end of 2018 (96% versus 72%). Another important point is that almost all children (99%) who were adopted by Dutch parents had currently suppressed HIV RNA levels.

Of those individuals who were originally registered as a child and were still in care in 2018, 52% were older than 18 on 31 December 2018. The high rate of detectable HIV viral load in HIV-positive individuals around the time of transitioning to adult care is of concern. Although viral suppression rates have improved over time resulting in relatively more young people being virally suppressed during their most recent clinical visit, 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 have reached the age of 18 or older 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 universal screening for HIV early during pregnancy has resulted in vertical transmission of HIV having been reduced to close to zero in the Netherlands, health care providers should remain vigilant for the occasional incident maternal HIV infection which may occur later during pregnancy, and which, unnoticed, could result in vertical transmission.

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