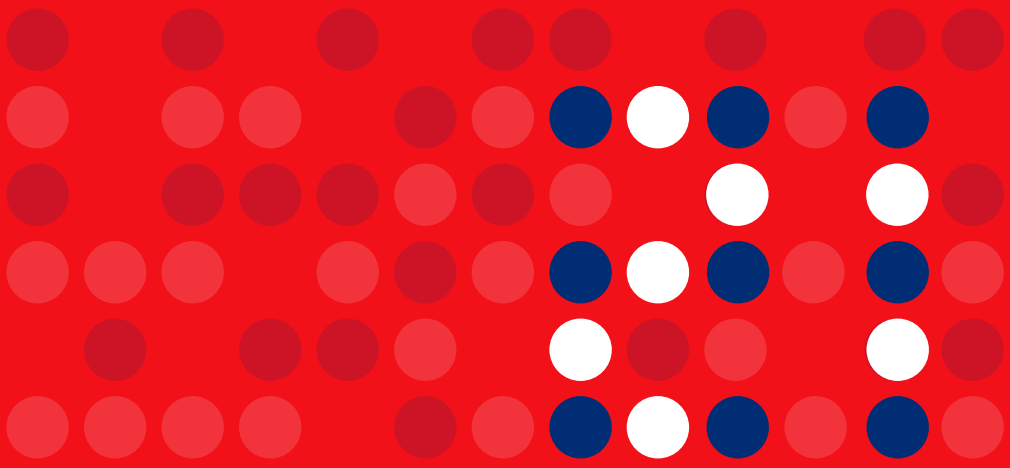
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2021

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



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

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Box 5.1: Chapter definitions.

Child living with HIV	A child diagnosed with HIV before the age of 15[1,2], whose first visit to a Dutch HIV treatment centre was before the age of 18 years.
Infection	The moment a child acquires an HIV infection.
Diagnosis	The moment a child is first diagnosed with HIV.
Registration	The moment that SHM is notified of a child living with HIV in care by their treating physician or nurse and the child is registered in the SHM database. Registration is usually within a few months of entering care, but can take longer.
In care in 2020	People are considered to be in care if they had a documented clinic visit or lab measurement in 2020.
Vertically-acquired HIV	Transmission of HIV from a woman living with the virus to a child during pregnancy, delivery, or breastfeeding.
Non-vertically-acquired HIV	Transmission of HIV through sexual contact or contact with contaminated blood or blood products.
cART	Combination antiretroviral therapy: a combination of at least three antiretroviral drugs from two different antiretroviral drug classes, or at least three nucleoside reverse transcriptase inhibitors.
Viral suppression	Any viral load measurements below 200 copies/ml, except for time points in the past where tests had quantification limits higher than 200 copies/ml.

Box 5.2: Outline of the paediatric ATHENA cohort in the Netherlands: all children living with HIV registered in the ATHENA cohort before 31 December 2020. (Children=individuals under 15 years of age at the time of diagnosis who made a first visit to a Dutch HIV treatment centre before the age of 18 years.)

1. Children who were diagnosed when younger than 15 years of age and who entered care in the Netherlands before they were 18 years (n=393).
2. Population of those who were diagnosed as a child and in care in 2020:
   - aged under 15 years in 2020 (n=152).
   - aged 15-18 years in 2020 (n=26).
   - aged 18 years or over in 2020 (n=160). Of the 160 children, 136 transferred to adult care (sometimes within the same treatment centre), five started care in an adult HIV treatment centre, and 19 were still registered as being in care at one of the paediatric HIV treatment centres.

Background

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in children living with HIV worldwide[3-7]. 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[8-11]. 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 (including children), irrespective of CD4 cell count[12].

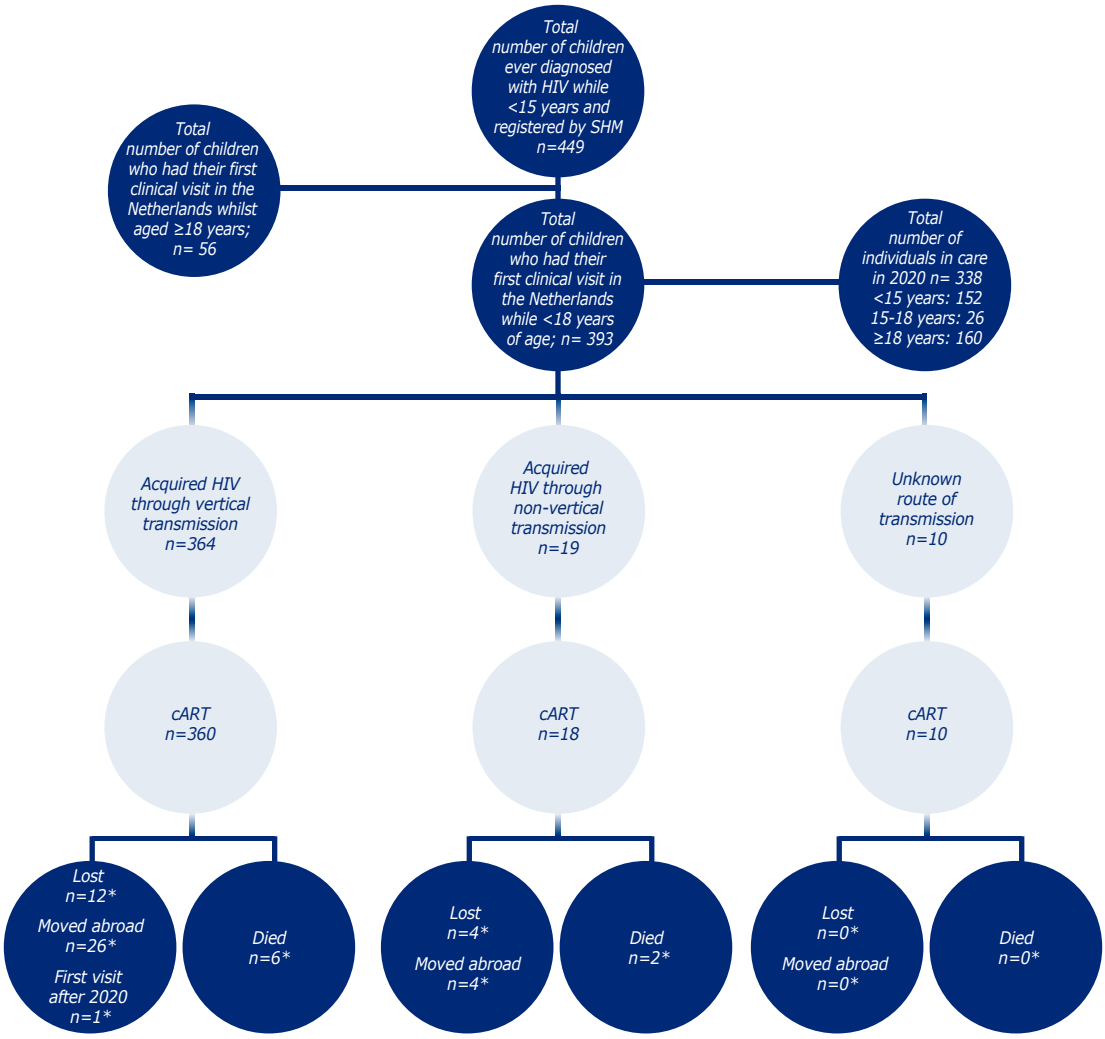
In the Netherlands, children living with HIV generally receive health care at one of four paediatric HIV treatment centres. These children transition to adult HIV care when they reach the age of 18. However, children who acquire HIV at an older age through non-vertical transmission are more likely to enter care at an adult HIV treatment centre. Accordingly, those who are diagnosed with HIV over 15 years of age are described in *Chapter 1* as part of the adult population.

Here we report on the demographics, clinical characteristics, and long-term virological and immunological responses to treatment of children diagnosed with HIV before 15 years of age and 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*). The criteria for the age group before 15 years is aligned with the definition of children used by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO)[1,2].

Ever registered

As of 31 December 2020, the number of individuals that SHM had registered as ever being diagnosed with HIV while under 15 years of age was 449 (*Figure 5.1*). Of these, 124 were diagnosed with HIV before arrival in the Netherlands and 325 were newly diagnosed in the Netherlands. In total, 393 of the 449 children entered care in the Netherlands before 18 years of age.

Figure 5.1: *Overview of children living with HIV registered by stichting hiv monitoring as of 31 December 2020.*



** 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.*

The majority (98%) of the children reported on, entered care at a paediatric HIV treatment centre. Nine entered care at an adult HIV treatment centre at a median age of 16.7 years (IQR 16.2-17.6) (*Table 5.1*).

Table 5.1: *Demographic and HIV-related characteristics of 393 children living with HIV ever registered by SHM who were diagnosed before 15 years of age and entered care in the Netherlands below the age of 18.*

Characteristics	Vertical transmission*	Non-vertical transmission*	Route of transmission unknown*
Total	364 (93)	19 (5)	10 (3)
HIV treatment centre			
Paediatric care	361 (99)	14(74)	9 (90)
Adult care	3 (1)	5 (26)	1 (10)
Gender			
Male	173 (48)	8 (42)	7 (70)
Female	191 (52)	11 (58)	3 (30)
Child's country of origin			
The Netherlands	113 (31)	2 (11)	0
Sub-Saharan Africa	208 (57)	15 (80)	9 (90)
Other	43 (12)	2 (11)	1 (10)
Mother's country of origin			
The Netherlands	32 (9)	1 (5)	1 (10)
Sub-Saharan Africa	189 (52)	7 (37)	6 (60)
Other/unknown	143 (39)	11 (58)	3 (30)
Adopted	146 (40)	0	3 (30)
Age at HIV diagnosis	1.1 (0.25-3.6)	10.9 (6.5-14.6)	10.5 (6.3-11.8)
cART-treated	360 (99)	18 (95)	10 (100)
Therapy-naive at cART initiation	312(86)	15 (80)	10 (100)
CD4 at cART initiation	560 (286-1220)	324 (171-508)	325 (250-522)
CD4 Z-score at cART initiation	-0.58 (-1.00- -0.10)	-0.63 (-1.13- -0.08)	-0.50 (-0.91— -0.28)
VL (log copies/ml) at cART initiation	5.2 (4.5-5.8)	4.3 (4.0-5.5)	4.8 (4.3-4.9)

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

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

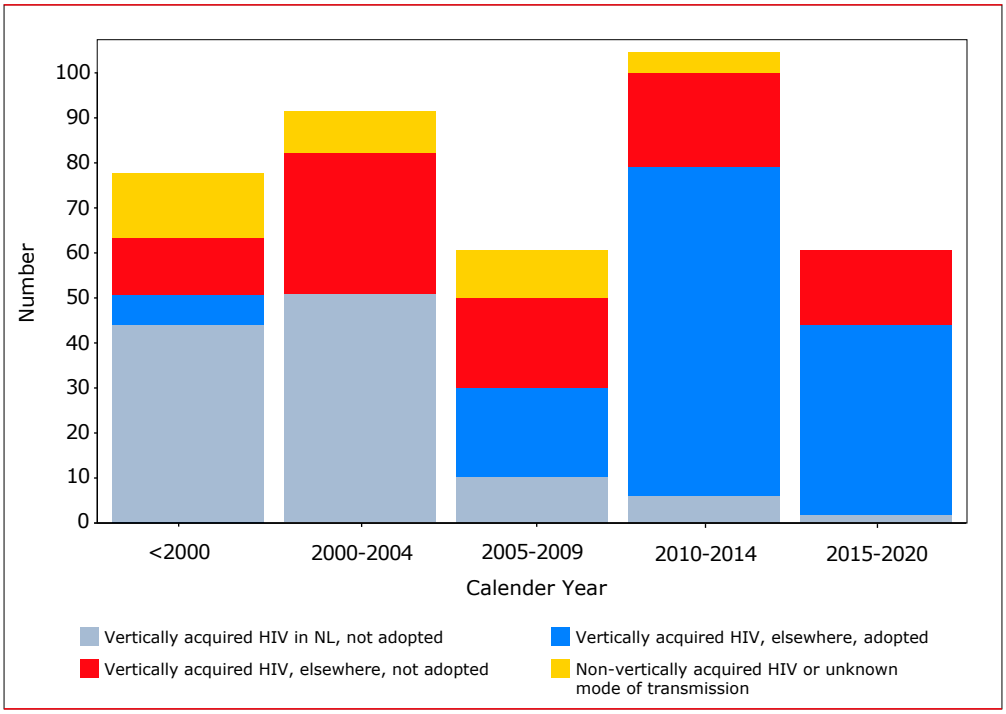
Mode of transmission

The majority (93%) of the children registered acquired HIV through vertical transmission (*Figure 5.1*).

Vertical transmission

- Between 1998 and 2020, 364 children entered care after acquiring 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] 0.3-3.6 years).
- 99% received care in a paediatric HIV treatment centre in the Netherlands.
- cART initiation was documented for 99% of the children.
- 57% (n=208) of the children were born in sub-Saharan Africa.
- 31% (n=113) of the children were born in the Netherlands.
- 9% of the children born in the Netherlands (10 out of 113), had two Dutch parents.

Figure 5.2: Number of children living with HIV by year of entering care in the Netherlands, stratified by mode of HIV transmission and adoption status.



Decline in vertical transmission of HIV in the Netherlands since 2005

Figure 5.2 shows the number of registered children by year of entering care, mode of transmission, and region of origin. The number newly entering care in the Netherlands has fallen over time from 104 in 2010-14 to 61 in 2015-20. This drop is likely linked to the declining number of adopted children newly entering care over time. Standard HIV screening among pregnant women, introduced nationally in 2004[13,14], is responsible for the strong decline in vertical transmission in the Netherlands from 2005 onwards.

Non-vertical transmission

- Between 1998 and 2020, 19 children were registered as having acquired HIV through non-vertical transmission; the reported modes were heterosexual transmission and contact with contaminated blood and blood products. Of note, contact with contaminated blood or blood products was no longer reported from 1997 onwards for children born in the Netherlands, and from 2009 onwards for all children, regardless of country of birth.
- The median age at which they received their first reported HIV-positive test result was 10.9 years (IQR 6.5-14.6). However, the median age of HIV diagnosis for those who acquired HIV by sexual transmission was higher at 14.8 years (IQR 14.1-14.8).
- In total, 95% of these children had started cART.
- 37% of children acquired HIV through heterosexual contact.
- 80% were born in sub-Saharan Africa.
- 26% received care in an adult HIV treatment centre.

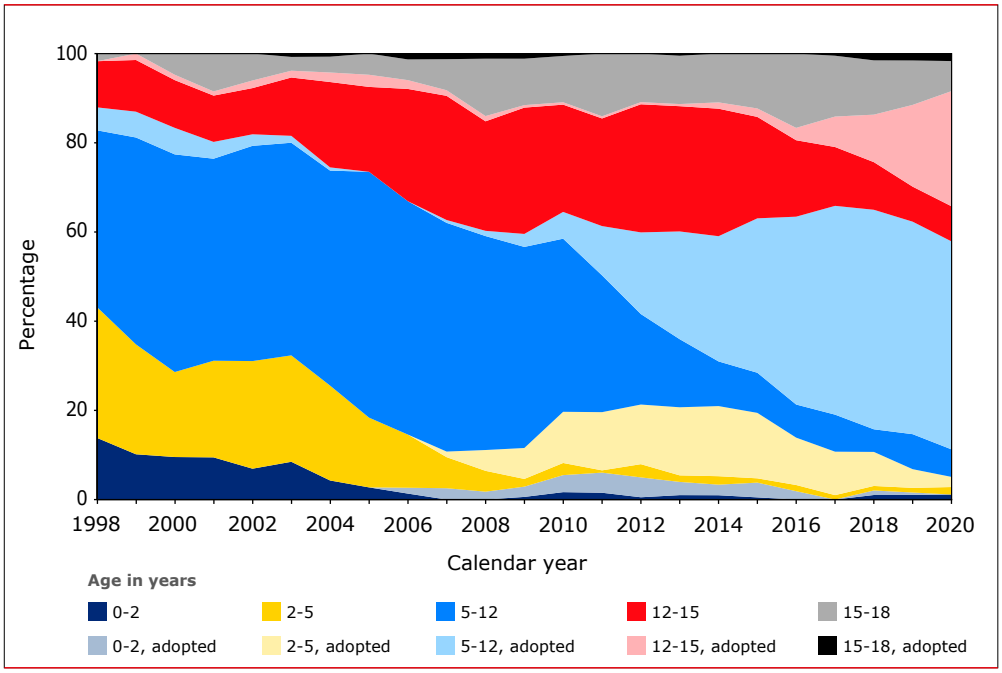
Unknown route of HIV transmission

- For 10 children living with HIV, the route of transmission remains unknown.
- Their median age at diagnosis was 10.5 years (IQR 6-12).
- All children had started cART.

Age distribution

The age distribution of children receiving HIV care shifted between 1998 and 2009 (*Figure 5.3*). From 2009 onwards, there was an increase in the proportion of children aged 0 to 5 years. This was due to a rise in adoption rates of children living with HIV in those age groups. In 2020, about 82% of children living with HIV aged 15 years or younger were adopted.

Figure 5.3: Time-dependent age distribution of children living with HIV in care over time. The shaded areas represent the proportion of adopted children.



Low mortality rates

The mortality rate between 1998 and 2020 for children registered with SHM was very low. In total, two children (0.5%) under the age of 18 years have died since the start of registration. Both children died from AIDS before 2010. Another six (1.5%) young adults diagnosed with HIV as children died when over the age of 18 years; their median age of death was 27 years (IQR 24-30) and all died before the age of 35 years. Four of these young adults died from AIDS and two of a non-AIDS related cause.

Antiretroviral treatment

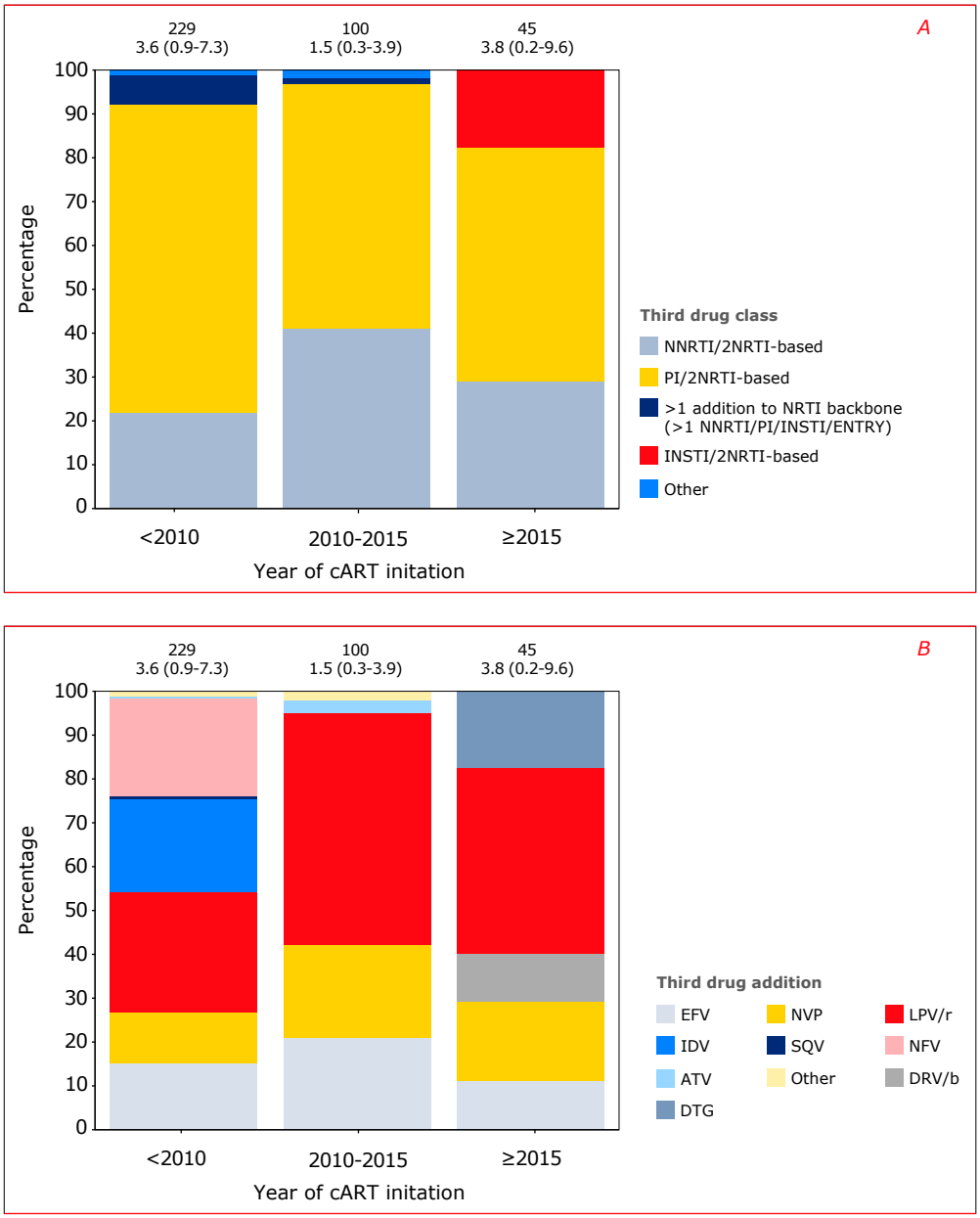
Of the 393 children who entered care in the Netherlands before 18 years of age, 388 (99%) started cART; 337 (87%) of them were treatment-naive at the start of cART and 51 (14%) had previously been exposed to monotherapy or dual therapy (i.e., were pre-treated).

For the purposes of this analysis, we have included both pre-treated and treatment-naive children, and grouped them by calendar year of cART initiation: 229 children started a cART regimen before 2010, 100 in 2010-15, and 45 children after 2015. For 14 children, the year of cART initiation is not known. In total, five children were not treated with cART, of whom four are no longer in care.

Initial combination antiretroviral regimen

Of the 388 registered children known to have initiated cART, 64% were treated with a first-line regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs). Another 28% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with two or more NRTIs. *Figure 5.4* shows the trends over time for the third-drug additions to the NRTI backbone as part of the initial cART regimens, stratified by calendar period of starting cART. Among children, lopinavir was the most commonly-used PI (36%). Following its introduction in 2014, the integrase inhibitor dolutegravir was included in the initial cART regimen given to 18% of the children; only one of those children was under 12 years of age.

Figure 5.4: 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, and (B) specific third drugs. Numbers above the bars represent the total number of individuals initiating cART in that calendar year period. Median ages and interquartile ranges above the bars represent the ages of individuals at the 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 388 children who had ever started cART spent on an initial regimen was 22.6 months (IQR 7-56). Discounting weight-related dose changes, 327 children (84%) discontinued their first-line treatment regimen. The most important reasons for changing included simplification (38%) and toxicity (15%). Virological failure was the reason given in 14% of cases, and lack of adherence in 4%. Other reasons included decision by parents or child, blood level-related, or difficulties taking medication.

Virological response

Virological response to cART was assessed based on viral suppression (i.e., viral load below 200 copies/ml, [*Box 5.1*]). Initial virological response is reported for the first two years after starting cART and stratified by calendar year of cART initiation. Long-term virological response is reported by time-updated age for those who used cART for at least 24 months.

Initial response to cART

This analysis used data from the 388 children who were registered with SHM and had ever started cART. Children who acquired HIV through vertical transmission were stratified by age at cART initiation, resulting in the following categories:
(1) vertical transmission, 0-1 year
(2) vertical transmission, 2-5 years
(3) vertical transmission, 5-18 years
(4) non-vertical transmission or unknown mode of HIV transmission[a], 5-18 years

Among the children who ever started cART, we assessed their viral suppression rates at 24-week intervals while they were on cART. Viral load measurements closest to each 24-week time point (plus or minus 8 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.
Figures 5.5A and *5.5B* shows viral suppression rates by calendar period of cART initiation: 1998-2009 and 2010-20.

cART initiation between 1998 and 2009:

- Among children with vertically-acquired HIV who were aged 0-2 years at the time of cART initiation, viral suppression rates increased from 78% after one year of cART, to 81% after two years.
- Among children with vertically-acquired HIV who were aged 2-5 years at cART initiation, viral suppression rates increased from 95% after one year of cART, to 93% after two years.

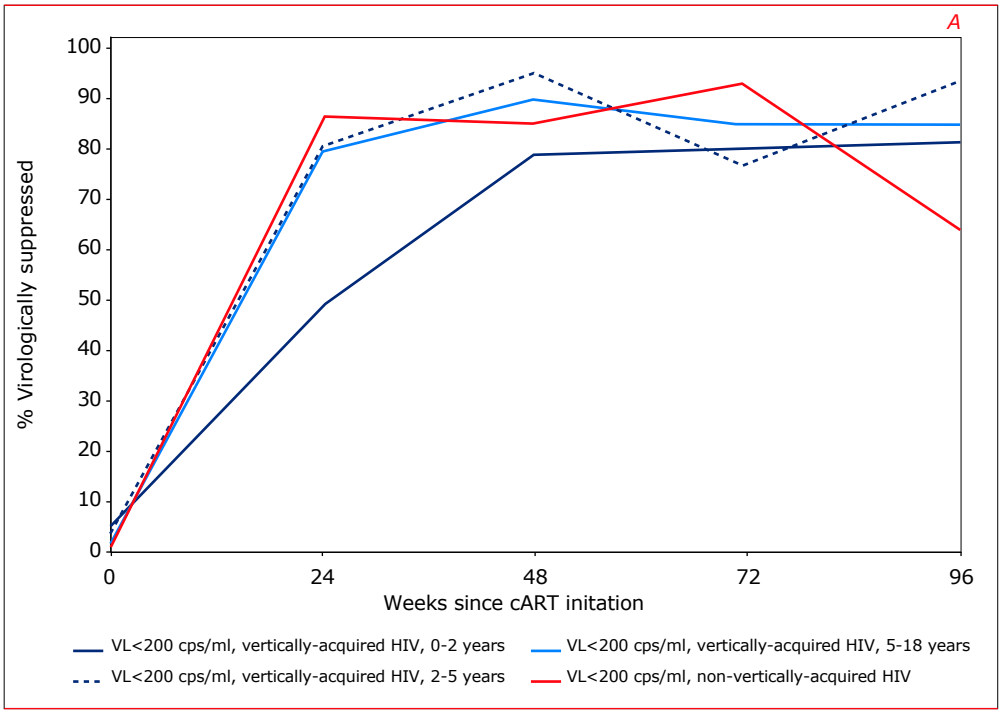
a *The number of children with an unknown route of HIV transmission is too small to include as a separate category in this analysis. As these children had the same age distribution as those with non-vertically-acquired HIV, these two groups were jointly analysed in a shared category.*

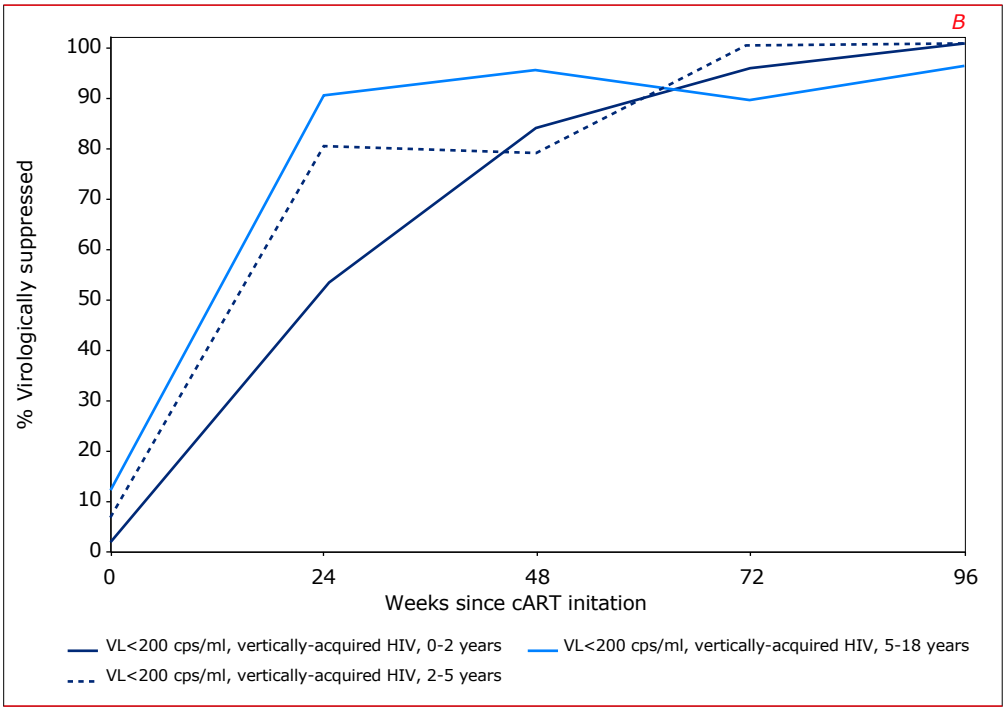
- Among children with vertically-acquired HIV who were over 5 years of age at cART initiation, viral suppression rates increased to 89% after one year of cART use. However, two-year viral suppression rates (85%) were lower than those seen among children aged 2-5 years of age at the time of cART initiation.
- Among children with non-vertically-acquired HIV, the one-year viral suppression rate was 80% and the two-year viral suppression rate was the lowest seen among all groups at 64% (*Figure 5.5A*).

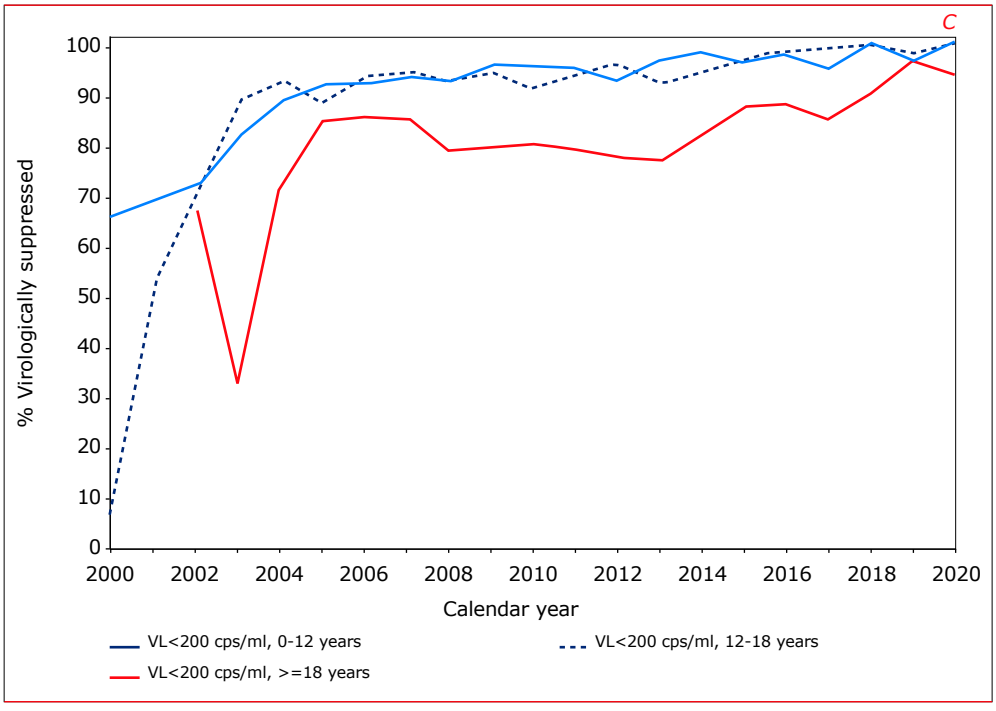
cART initiation in or after 2010:

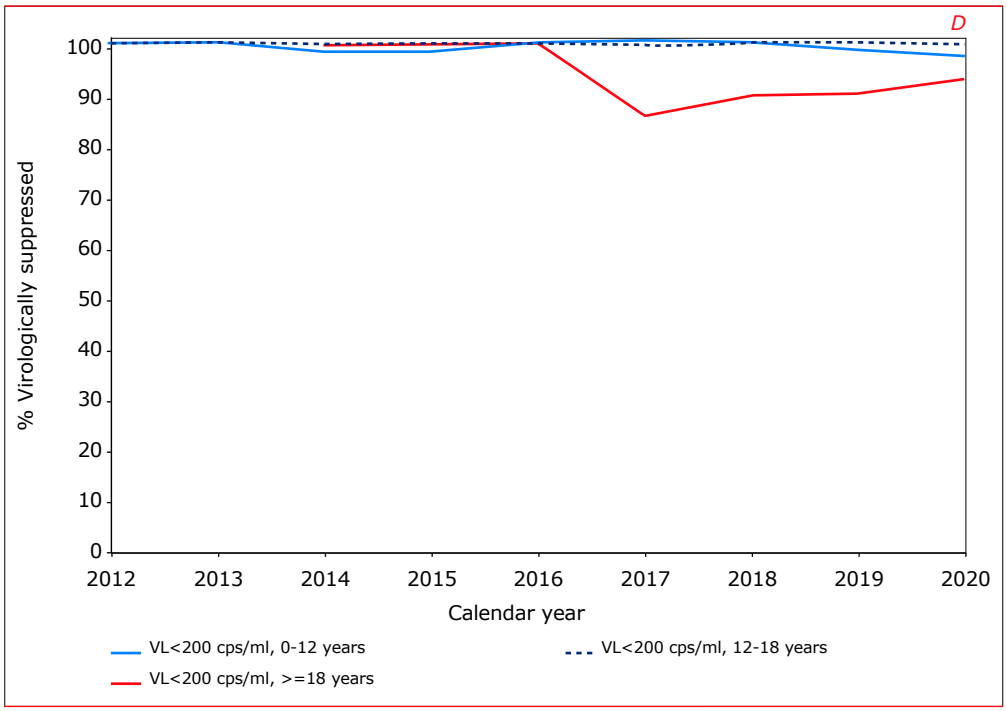
- Two years after treatment initiation, the viral suppression rates were 100% in all children who acquired HIV through vertical transmission below the age of 5 years. However, children with vertically-acquired HIV who were aged over 5 years at the time of cART initiation, reached a somewhat lower viral suppression rate of 96% over the same period. 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 5.5B*).

Figure 5.5: *Viral suppression following combination antiretroviral therapy (cART) initiation, by calendar period of therapy initiation: (A) during the first two years of cART 1998–2009, (B) during the first two years of cART 2010–2020, (C) time-dependent and age-dependent viral suppression rates after two years of cART for children who initiated cART in 1998–2010, and (D) time-dependent and age-dependent viral suppression rates for children after two years of cART who initiated cART in 2010–2020.*
Viral suppression is defined as any viral load measurements below 200 copies/ml, except for time points in the past where tests were used with quantification limits above 200 copies/ml.




B
% Virologically suppressed
100
90
80
70
60
50
40
30
20
10
0
0
24
48
72
96
Weeks since cART initation
VL<200 cps/ml, vertically-acquired HIV, 0-2 years
VL<200 cps/ml, vertically-acquired HIV, 5-18 years
VL<200 cps/ml, vertically-acquired HIV, 2-5 years


C
% Virologically suppressed
100
90
80
70
60
50
40
30
20
10
0
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
Calendar year
VL<200 cps/ml, 0-12 years
VL<200 cps/ml, 12-18 years
VL<200 cps/ml, >=18 years



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

Long term virological response

Among the children who were using cART for more than 24 months, we assessed viral suppression rates by calendar year of follow-up. The latest viral load measurement in each calendar year was 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.

Time-updated age of HIV RNA measurements was calculated, and children were stratified by the following time-updated age ranges:
(1) 0-12 years
(2) 12-18 years
(3) 18 years or older

Age and time-updated HIV RNA viral suppression rates slightly improved over calendar time among those who initiated cART before 2010. However, viral suppression was lowest among those aged 18 years or older (*Figure 5.5C*). Consistently high viral suppression rates over calendar time were seen among children who initiated cART after 2010. Still, viral suppression rates decreased when the age of 18 years was reached (*Figure 5.5D*).

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[15]. Long-term CD4 cell count changes were assessed among the 388 children who had ever started cART. Children with vertically-acquired HIV were stratified according to their age at the time of cART initiation, as described earlier in this chapter.

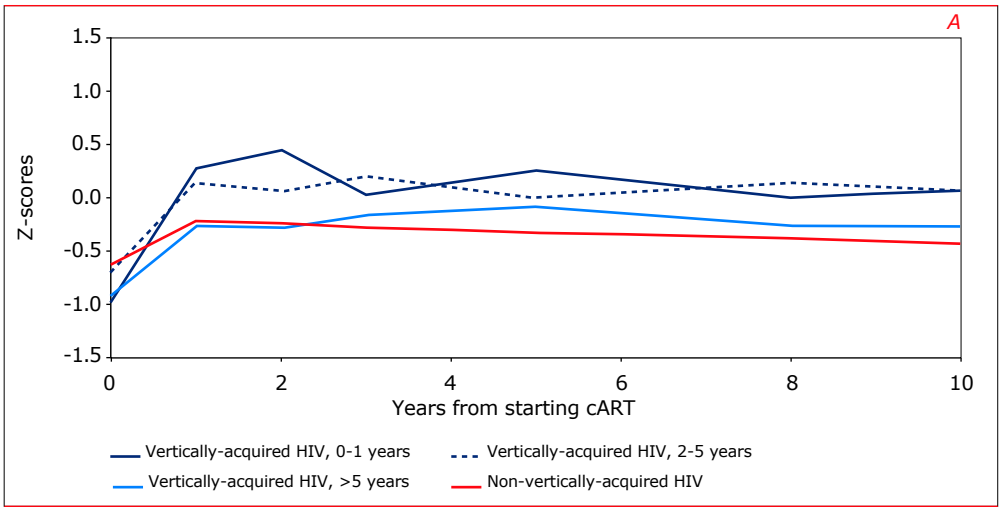
Given that normal CD4 cell counts in younger children are highly age-dependent[16], it is more appropriate to analyse time-dependent CD4 count trajectories, expressing CD4 counts as Z-scores, in which counts are standardised in relation to age. CD4 Z-scores, which represent the standard deviation from 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[17] 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.

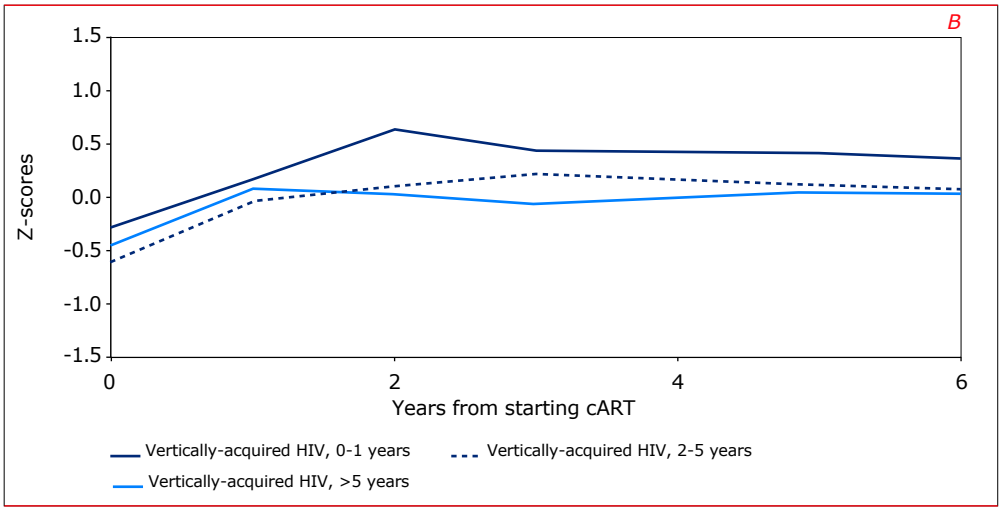
Figures 5.6A and *5.6B* show the changes in CD4 T-cell Z-scores among children living with HIV stratifying those with vertically-acquired HIV by age at initiation of cART, and by calendar year of cART initiation. As expected, the youngest children (under two years of age at cART initiation), had the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

For those who initiated cART between 1998 and 2009, CD4 Z-scores increased significantly in the year following cART initiation, whether HIV transmission was non-vertical or vertical. However, the increase in CD4 Z-scores was less strong among children with non-vertical transmission. The youngest children (under 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 in the vertical transmission group. CD4 Z-scores remained consistently higher among the youngest age group (below 2 years of age at cART initiation) (*Figure 5.6B*). Note: CD4 Z-scores are not presented for those in the non-vertical transmission group, due to the low number of children who started cART after 2010.

Figure 5.6: *Changes in Z-scores for CD4 T-cell counts among children living with HIV, stratified by age at initiation of combination antiretroviral therapy (cART): (A) cART initiation between 1998 and 2009, and (B) cART initiation between 2010 and 2020.*





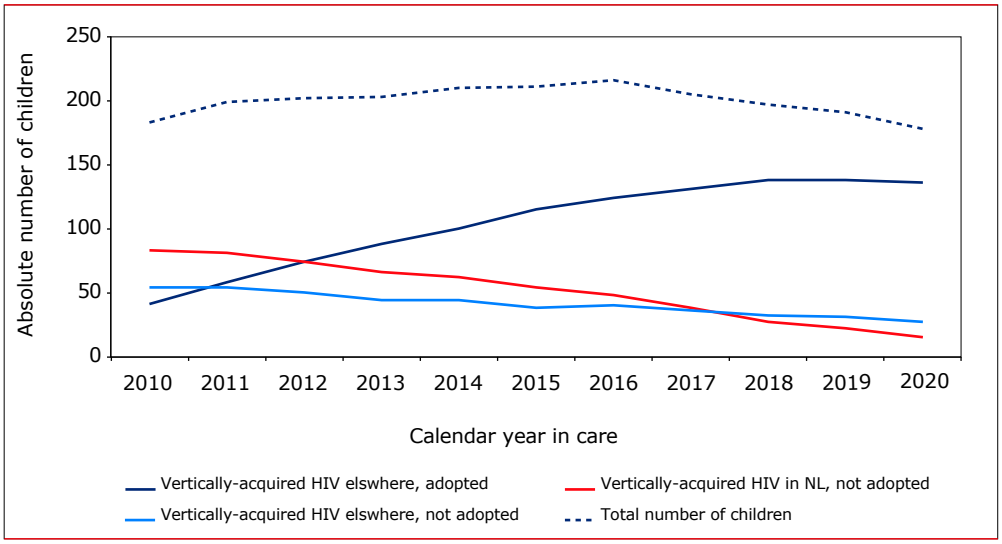
Legend: *cART=combination antiretroviral therapy.*

Currently in clinical care

Of the 393 children living with HIV ever registered by SHM who entered care in the Netherlands before the age of 18 years, 338[b] (86%) were still in care in 2020, 178 of whom were under 18 years of age (*Figure 5.1*). Of the 54 children no longer in care, eight had died, 30 had moved abroad, and 16 children, a substantial number, were lost to follow up.

Figure 5.7 shows the number of children under 18 years of age in care in each calendar year; the number was highest in 2016, with 216 children. However, by 2020, this figure had declined to 178, mainly due to the fact that more children with vertically-acquired HIV who are not adopted are reaching the age of 18 years and, at the same time, fewer children are newly entering care. The number of adopted children in care increased from 41 in 2010 to 138 in 2018, a figure that has remained more or less stable over the last three years.

Figure 5.7: *Number of children aged <18 years known to be in care at the end of each calendar year shown by mode of HIV transmission and adoption status.*



Note: *Children with non-vertically-acquired HIV are not reported as a separate category due to their small numbers, but they are included in the total number of children in care.*

b *One child had a first clinical visit after 2020.*

Currently in care and under 18 years of age

- Of the 393 individuals with HIV who entered care before the age of 18 years, 178 were still aged under 18 at the end of 2020 and 152 were younger than 15 years.
- As of 31 December 2020, their median age was 11 years (IQR 8-14).

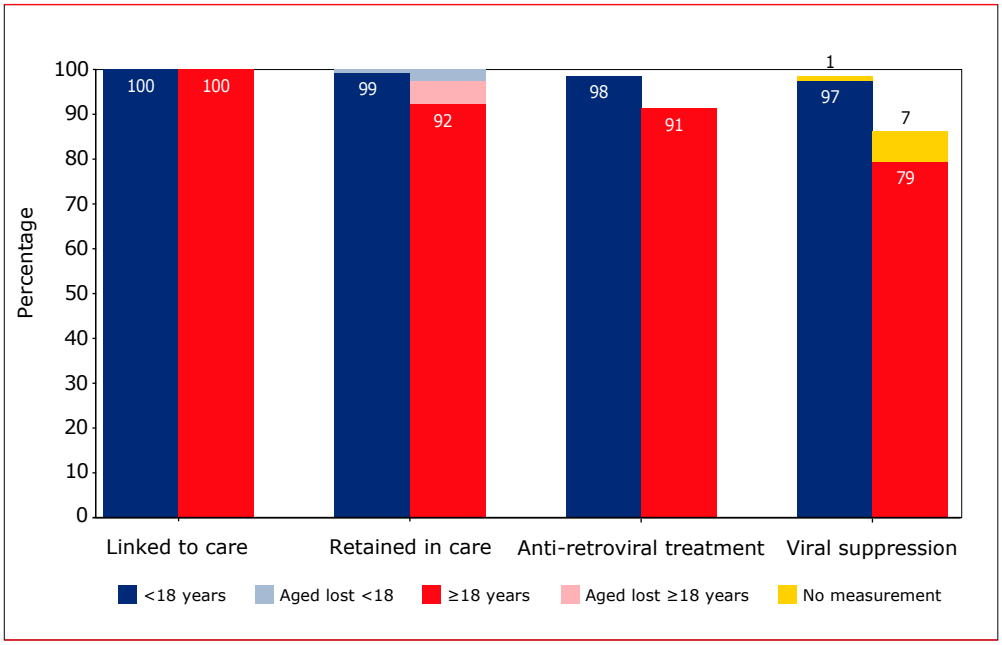
Currently in clinical care and 18 years or older

- The remaining 160 individuals living with HIV who were first registered when still a child, were in care and older than 18 years at the end of 2020.
- As of 31 December 2020, their median age was 24 years (IQR 21-28).

Continuum of care

A 'continuum of care' was constructed, based on the total number of children living with HIV ever registered by SHM that were still alive on 31 December 2020, and not reported to have moved abroad or 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 2020. The numbers in and above the bars indicate the proportion of individuals.*



Individuals were stratified by age on 31 December 2020 and categorised as:
I. current age, under 18 years
II. current age, 18 years or older

Note: The numbers of children with non-vertically-acquired HIV or unknown mode of HIV transmission in care in 2020 were too small (n=19) for stratification by mode of acquisition.

I Continuum of care: current age under 18 years:
- In total, 180 children under 18 years of age on 31 December 2020 were linked to care, registered by SHM, still alive, and not reported as having moved abroad.
- Of these children, 99% (178/180) were retained in care. Two children, both born outside the Netherlands, were lost to follow up.
- During their last clinical visit in 2020, 98% (177/180) were using antiretroviral therapy.
- Overall, 97% (164/180) had a most recent HIV RNA measurement below 200 copies/ml. Note: one child did not have an HIV RNA measurement in 2020, however, the last HIV RNA measurement in 2019 was below 200 copies/ml.

II Continuum of care: current age 18 years or older:
- 174 individuals over 18 years of age on 31 December 2020 were linked to care.
- 92% (160/174) were still in care as of 31 December 2020. The remaining 14 individuals (six of whom were born outside the Netherlands), were lost to follow up; six before they were 18 years and the remaining eight when they were older than 18 years. Four of these 14 adolescents, who were aged between 17 and 19 years at the time of their last clinical contact at a paediatric HIV treatment centre, were signed off in the registration; they may have been lost during transition to adult care or may be waiting to be re-registered by the adult treatment centre.
- 91% (159/174) were using antiretroviral therapy during their last registered clinical visit.
- Overall, 79% (138/174) had a most recent HIV RNA measurement below 200 copies/ml. Note: 12 young adults did not have an HIV RNA measurement in 2020. For this group, a non-physical consultation was often reported (i.e., via web camera or telephone). The COVID-19 pandemic has shifted how consultations are conducted for adults in care in an HIV treatment centre (see *Chapter 7: Quality of care*). For ten of these 12 young adults, there was a 2019 HIV RNA measurement available; all were below 200 copies/ml.

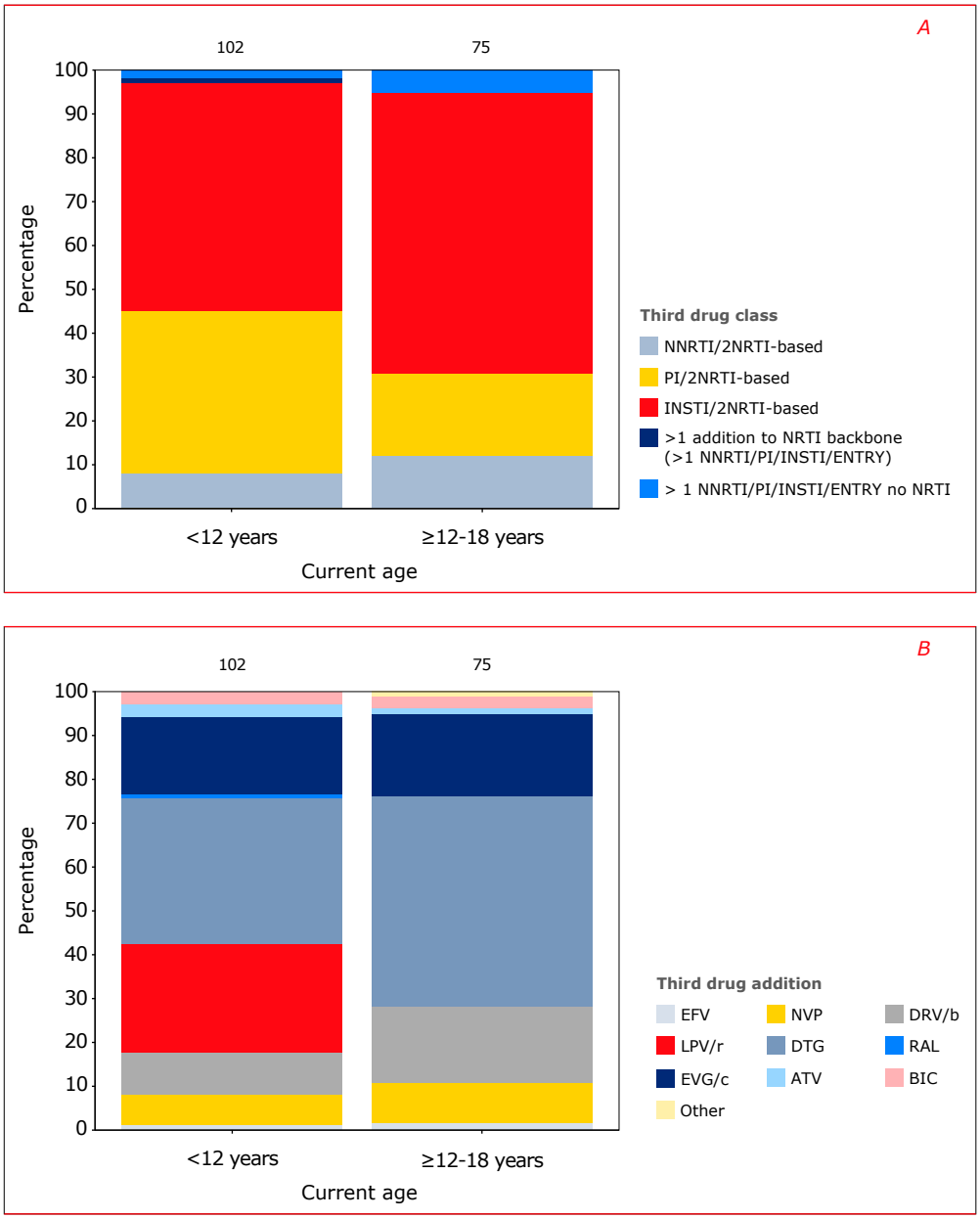
In care and on cART in 2020

Of the 178 children known to be in care in 2020 and under 18 years of age, 177 (99%) 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 2020.

Among those under 12 years of age, PI-containing and INSTI-based regimens were the most commonly-used (37% and 52%), with dolutegravir (33%) and lopinavir/ritonavir (25%) the most common individual third agents.

In children aged between 12 and 18 years, 12% were using an NNRTI-based regimen, 19% a PI-based regimen, and 64% an INSTI-based regimen. Among those using an INSTI-based regimen, dolutegravir was most common (48%), followed by elvitegravir (19%). Overall, five children used bictegravir.

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; BIC=bictegravir.*

Special Populations

Adopted children

Of the 393 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 149 (38%) had been adopted by Dutch parents. The percentage of adopted children newly entering care increased from 3% in 2000 and 2001 to 89% in 2012 and 2013:

- Their median age at the time of entering care in the Netherlands was 2.7 years (IQR 1.5-5.0).
- All children used cART during follow up in clinical care in one of the Dutch HIV treatment centres.
- In total, 104 (70%) children were already receiving cART before they were adopted.
- 19 (13%) had been treated with monotherapy or dual therapy before the start of cART.
- At the moment of entering care in the Netherlands, only 64 (43%) of the 149 children had a viral load below 200 copies/ml.
- *Figure 5.7* shows the number of adopted children still in care and under 18 years of age. As of 31 December 2020, 146 children were alive and in care and 136 of them were aged below 18 years. Their median age was 10.5 years (IQR 8.7-13.1).
- Three adopted children are no longer in care.
- All children who started cART and who are known to be in care, were still receiving treatment in 2020, and 99% had an undetectable viral load (equal to or below 200 copies/ml) at the last known time point.

Transfer to adult care

Of the 393 children ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 150 children were aged over 18 years and had transferred from paediatric care to adult care by 31 December 2020.

The number of adolescents transferring to an adult centre each year varied between one and 20. The median age for their last visit in paediatric care was 18.3 years (IQR 18.0-19.0). The median time between their last visit in paediatric care and their first visit in adult care was 3.7 months (IQR 2.5-5.2). Time in care after transfer until last documented visit was 6.0 years (IQR 2.7-9.3). Of the 150 individuals who transferred to adult care, four (3%) were lost to follow up, two were signed off registration in the paediatric centre but have not yet been re-registered in an adult treatment centre (which could be down to an administrative delay in re-registration), two (3%) moved abroad, and five (3%) died. The remaining 137 are alive and in care.

At the time of their last clinical visit in paediatric care, 30/150 (20%) had an HIV RNA level above 200 copies/ml (median 3443; IQR 1220-27065). These rates are comparable to results from the UK, which found that three quarters of adolescents were virologically suppressed at the time of transition[18]. We also observed lower proportions of undetectable HIV RNA levels in the year before transfer to adult care, but higher levels one year after transfer: one year before transfer to adult care, 14% of the adolescents had a detectable HIV RNA level, compared to 25% one year after their transfer.

In 2020, 126 of the 137 young adults who were still in care after transfer had an HIV RNA measurement; in 6% of cases it was above 200 copies/ml.

During their last visit in paediatric care, 91% of the adolescents were using cART, while nine percent had discontinued cART: reported reasons for discontinuation were decision by adolescents or parents, low adherence, or decision by physician or nurse. Among adolescents using cART, 29% used a NNRTI-based regimen, 24% a PI-based regimen and 22% an integrase-containing regimen. Of the 137 children who transferred to adult care and who were still in care in 2020, 99% used cART. The majority of them used an integrase inhibitor-based regimen (53%).

Summary

Of the 393 children with HIV ever registered by SHM who were under 18 years of age when they entered care in the Netherlands, 86% remain in care in the Netherlands. A substantial proportion of the children newly registered since 2010 are children who were adopted by Dutch parents. This has driven the observed increase in the proportion of children in care who are aged 0-12 years. 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 rare. This reflects the success of standardised HIV screening during the first trimester of pregnancy[13]. 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 children living with HIV in care in the Netherlands, however the mortality rate was higher among young adults who were diagnosed with HIV as a child, and it included AIDS-related causes of death.

In total, 99% of children living with HIV ever in care in the Netherlands have received cART. The cART regimens have changed over time. Current regimens in use include dolutegravir and lopinavir/ritonavir for younger children, and 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, long-term viral suppression rates in children living with HIV who initiated cART in or after 2010, have improved over time, including among that young age group. However, those response rates are lower when children reach the age of 18 years; for example, detectable HIV RNA rates were 20% at the time of transition to adult care, which generally happens around the age of 18.

The continuum of care showed a high retention-in-care rate among children under 18 years of age. 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 2020 (97% versus 79%). A small number of young adults had no available HIV RNA measurement in 2020 after the start of the COVID-19 pandemic, but most of them had suppressed HIV RNA levels in 2019.

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 among those under 18 years of age. 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 and treatment interruptions.

References

1. UNAIDS. Start Free, Stay Free, AID Free. Final report on 2020 targets. https://www.unaids.org/sites/default/files/media_asset/2021_start-free-stay-free-aids-free-final-report-on-2020-targets_en.pdf. Published 2021.
2. WHO. HIV/AIDS. https://www.who.int/news-room/fact-sheets/detail/hiv-aids. Published 2021.
3. Goetghebuer T, Haelterman E, Le Chenadec J, et al. Effect of early antiretroviral therapy on the risk of AIDS/death in HIV-infected infants. *AIDS*. 2009;23(5):597-604. doi:10.1097/QAD.0b013e328326ca37
4. Judd A, Chappell E, Turkova A, et al. Long-term trends in mortality and AIDS-defining events after combination ART initiation among children and adolescents with perinatal HIV infection in 17 middle- and high-income countries in Europe and Thailand: A cohort study. Deeks SG, ed. *PLOS Med*. 2018;15(1):e1002491. doi:10.1371/journal.pmed.1002491
5. Gibb DM. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland. *BMJ*. 2003;327(7422):1019-0. doi:10.1136/bmj.327.7422.1019
6. Gortmaker SL, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. *N Engl J Med*. 2001;345(21):1522-1528. doi:10.1056/NEJMoa011157
7. de Martino M, Tovo PA, Balducci M, et al. Reduction in mortality with availability of antiretroviral therapy for children with perinatal HIV-1 infection. Italian Register for HIV Infection in Children and the Italian National AIDS Registry. *JAMA*. 2000;284(2):190-197.
8. Foster C, Pace M, Kaye S, et al. Early antiretroviral therapy reduces HIV DNA following perinatal HIV infection. *AIDS*. 2017;31(13):1847-1851. doi:10.1097/QAD.0000000000001565
9. Shiau S, Strehlau R, Technau KG, et al. Early age at start of antiretroviral therapy associated with better virologic control after initial suppression in HIV-infected infants. *AIDS*. 2017;31(3):355-364. doi:10.1097/QAD.0000000000001312
10. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *N Engl J Med*. 2008;359(21):2233-2244. doi:10.1056/NEJMoa0800971
11. Newell M-L, Patel D, Goetghebuer T, Thorne C. CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: is it associated with age at initiation? *J Infect Dis*. 2006;193(7):954-962. doi:10.1086/500842
12. World Health Organization. Guidelines Guideline on When To Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. *World Heal Organ*. 2015;(September):78. doi:978 92 4 150956 5

13. Boer K, Smit C, Van Der Flier M, De Wolf F. The comparison of the performance of two screening strategies identifying newly-diagnosed HIV during pregnancy. *Eur J Public Health*. 2011;21(5):632-637. doi:10.1093/eurpub/ckq157
14. Op de Coul ELM, Hahné S, van Weert YWM, et al. Antenatal screening for HIV, hepatitis B and syphilis in the Netherlands is effective. *BMC Infect Dis*. 2011;11(1):185. doi:10.1186/1471-2334-11-185
15. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372(9635):293-299. doi:10.1016/S0140-6736(08)61113-7
16. Bunders M, Cortina-Borja M, Newell M-L, European Collaborative Study. Age-related standards for total lymphocyte, CD4+ and CD8+ T cell counts in children born in Europe. *Pediatr Infect Dis J*. 2005;24(7):595-600. http://www.ncbi.nlm.nih.gov/pubmed/15998999. Accessed September 16, 2016.
17. Comans-Bitter WM, De Groot R, Van den Beemd R, et al. Immunophenotyping of blood lymphocytes in childhood: Reference values for lymphocyte subpopulations. *J Pediatr*. 1997;130(3):388-393. doi:10.1016/S0022-3476(97)70200-2
18. Collins IJ, Foster C, Tostevin A, et al. Clinical Status of Adolescents with Perinatal HIV at Transfer to Adult Care in the UK/Ireland. *Clin Infect Dis*. 2017;64(8):1105-1112. doi:10.1093/cid/cix063