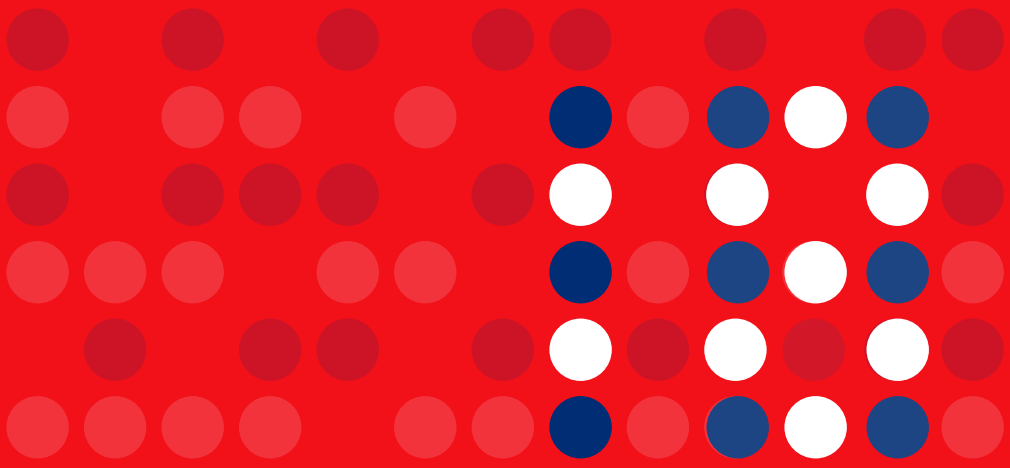
Human Immunodeficiency Virus (HIV)
infection in the Netherlands

HIV Monitoring

# HIV Monitoring Report 2018

## **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.

SHM comprehensively maps the HIV epidemic and HIV treatment outcomes in the Netherlands, thereby contributing to the knowledge of HIV. 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.

In addition to national reports, healthcare professionals are provided with treatment centre-specific reports to enable them to monitor and optimise care provided in their centres. Moreover, upon request, SHM data are also made available for use in HIV-related research, both in the Netherlands and internationally. The outcome of SHM's research and international collaborations provides tangible input into policy guidelines and further improves HIV care 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.

HIV Monitoring

# Monitoring Report 2018

## Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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

Colette Smit, Tom Wolfs and Annemarie van Rossum

*Box 5.1: Definitions*

| | |
|---|---|
| **Child** | An individual diagnosed with HIV 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 a HIV-positive child in care is notified to SHM by their treating physician or nurse and registered in the SHM database. |
| **In care in 2017** | Clinic visit or lab measurement in 2017. |
| **ART** | Antiretroviral therapy: use of an antiretroviral drug that may prevent HIV from damaging the immune system by blocking HIV replication. |
| **cART** | Combination antiretroviral therapy: a combination of three antiretroviral drugs from two different antiretroviral drugs classes. |
| **Initial virological success** | Two consecutive HIV RNA levels below 100 copies/ml, except for time points in the past where tests were used with quantification limits of 200, 400, 500 or 1000 copies/ml[1]. |
| **Viral suppression** | Any viral load measurements <200 copies/ml, at least three months after cART initiation, 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[2,3,4,5,6]. Moreover, early initiation of cART has been proven to be particularly beneficial in improving the survival of HIV-positive children[7,8,9,10]. As such, evidence from 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 at any CD4 cell count, including all children[11].

In the Netherlands, children living with HIV generally receive healthcare at one of four paediatric HIV treatment centres. These children will transition to adult HIV care upon reaching 18 years of age. However, children who acquire HIV at an older age and 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 (*Box 5.2*).

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*Box 5.2: Outline of the paediatric ATHENA cohort in the Netherlands: HIV-positive children (aged <18 years at the time of diagnosis) ever registered in the ATHENA cohort by 31 December 2017.*

**Data used in this chapter**

In 2018, Stichting HIV Monitoring launched a new data entry system, DataCapTree, which went live in February 2018 with an initial set of approved data collection protocols. The protocol for the collection of paediatric data was delayed until the second half of 2018. For this reason, data used in this chapter are based on the database lock of 31 December 2017, rather than May 2018 as in previous years. As a result, this year's earlier database lock for paediatric data may result in a certain degree of underreporting of data compared to previous years.

**Populations described in this chapter**

1. Ever registered (n=603)
2. Population in care in 2017:
   - aged <18 years in 2017 (n=183)
   - aged ≥ 18 years in 2017 (n=281)
3. Specific populations:
   - adopted children
   - children who transfer to adult care

## Ever registered

As of 31 December 2017, 603 HIV-positive children had ever been registered by SHM since 1998, representing an increase of 13 children compared with last year's report. Of the 603 ever-registered HIV positive children, 358 children entered care at a paediatric HIV treatment centre. The remaining 245 entered care at an adult HIV treatment centre. This group was predominantly diagnosed with HIV at an older age and had mostly acquired HIV through non-vertical transmission (*Table 5.1*). Both groups of HIV-positive children, i.e., those who entered care at a paediatric HIV treatment centre and those who entered care at an adult HIV treatment centre, will be discussed in this chapter.

*Table 5.1: Demographics and characteristics of 603 HIV-positive children ever registered in the Netherlands as of 31 December 2017.*

| Characteristics | Vertically-acquired HIV infection* | Non-vertically-acquired HIV infection* | Route of transmission unknown* |
|---|---|---|---|
| Total | 335 | 247 | 21 |
| HIV treatment centre | | | |
| Child care | 321 (96) | 28 (11) | 9 (43) |
| Adult care | 14 (4) | 219 (89) | 12 (57) |
| Gender | | | |
| Male | 164 (49) | 116 (47) | 13 (62) |
| Female | 171 (51) | 131 (53) | 8 (38) |
| Country of origin child | | | |
| The Netherlands | 109 (33) | 60 (24) | 1 (5) |
| Sub-Saharan Africa | 181 (54) | 121 (49) | 12 (57%) |
| Other | 45 (13) | 66 (27) | 8 (38%) |
| Country of origin mother | | | |
| The Netherlands | 23 (6) | 6 (3) | 1 (5) |
| Sub-Saharan Africa | 181 (54) | 33 (13) | 5 (24) |
| Other/unknown | 131 (39) | 208 (84) | 15 (71) |
| Age at HIV diagnosis | 1.2 (0.3-4.0) | 16.8 (16-17) | 15.7 (12-17) |
| CDC** event at HIV diagnosis | | | |
| CDC-b | 30 (9) | 10 (4) | 2 (10) |
| CDC-c | 56 (17) | 13 (5) | 2 (10) |
| cART-treated | 324 (97) | 227 (92) | 20 (95) |
| Therapy-naive at cART initiation | 281 (84) | 185 (75) | 19 (90) |
| CD4 at cART initiation | 527 (270-1,164) | 290 (162-410) | 293 (40-350) |
| CD4 Z-score at cART initiation | -0.62 (-1.05—0.16) | -0.62 (-10.4—0.26) | -0.51 (-1.12—0.24) |
| VL (log copies/ml) at cART initiation | 5.2 (4.5-5.8) | 4.4 (3.7-5.1) | 4.9 (4.7-5.3) |

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

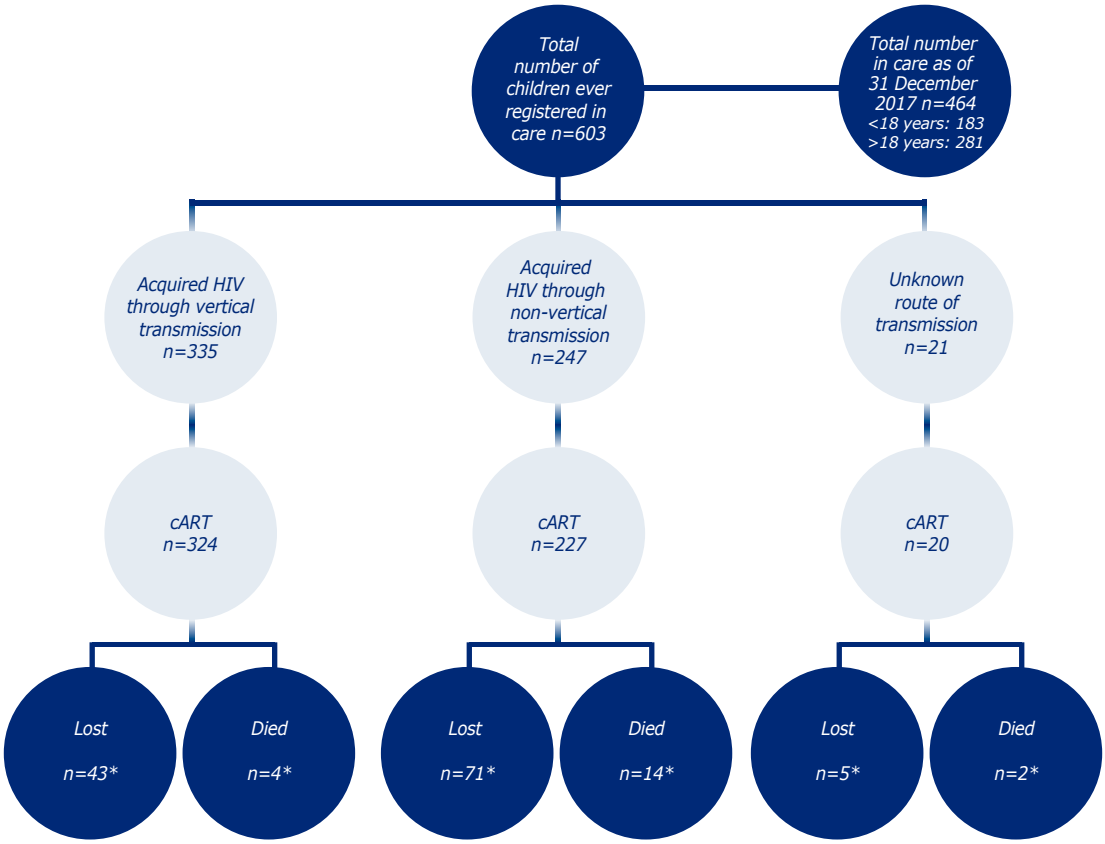
** *Categories as defined by the Centers for Disease Control and Prevention (CDC).*

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

## Mode of transmission

The majority of the children ever 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 2017.*




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

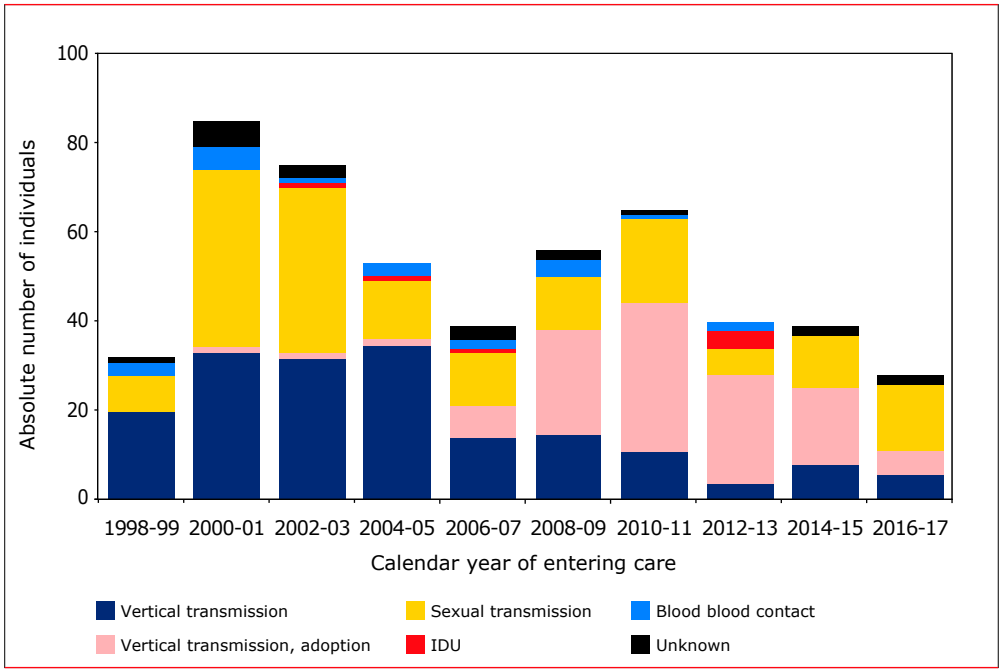
***Legend:** cART=combination antiretroviral therapy.*

### Children with vertically-acquired HIV

- In total 335 children had acquired HIV through vertical transmission, representing an increase of 5 children compared with the end of 2016. None of these 5 children were born in the Netherlands.
- 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).
- 54% (n=181) of the children were born in sub-Saharan Africa.

- 33% (n=109) of the children were born in the Netherlands.
- Only 10% of the children born in the Netherlands (11 out of 109) had parents who both originated from the Netherlands.
- Of children with vertically-acquired HIV, 96% received care in a paediatric HIV treatment centre in the Netherlands and the remaining 4% were seen in adult care.
- In total, 97% 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 1998-2017.*




*Note: low numbers in 2017 may be due to a delay in the treatment centre registering the child with SHM.*
***Legend:** IDU=transmission through injecting drug use.*

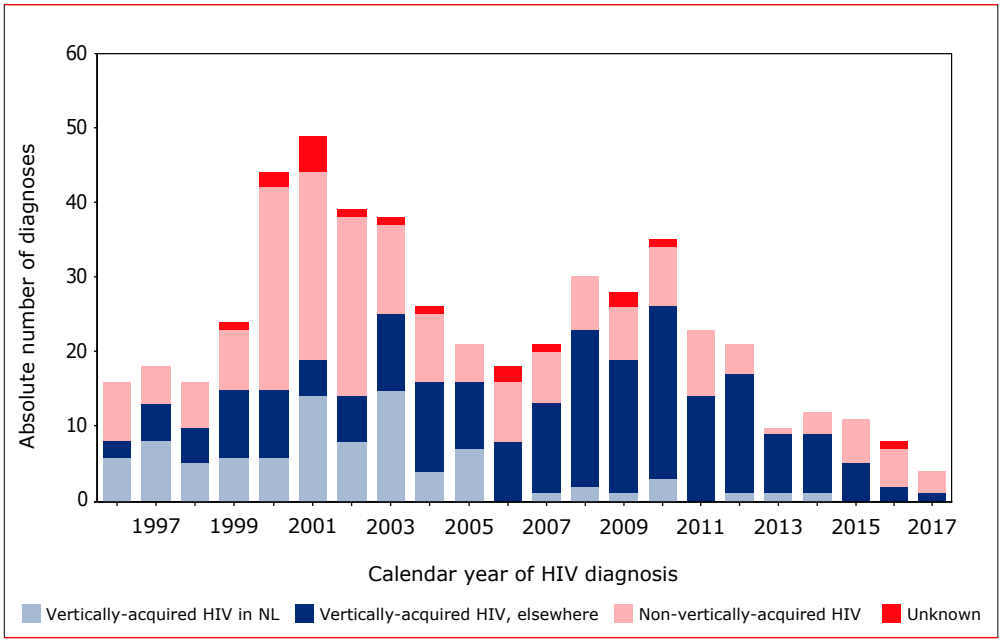
### No vertical transmission of HIV in the Netherlands since 2015

Vertical transmission of HIV has been reduced 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 (15 cases in 2003), after which it markedly declined, with a single documented case of vertical transmission in the Netherlands in 2014 and no cases since 2015.

The decline of vertical transmission in the Netherlands is most likely due to HIV screening among pregnant women, which was introduced nationally in 2004[12,13]. Since the introduction of this screening programme, 9 children born with HIV in the Netherlands have been reported to SHM. These 9 children are described briefly below:

- Six children were born to mothers who only first tested positive themselves after giving birth; the mothers of four of these six children had a negative test result during the first trimester pregnancy screening and acquired HIV only later during their pregnancy.
- One child was born to a mother who was known to be HIV-positive, but who was not receiving treatment during her pregnancy for an unknown reason.
- The remaining two children were born to mothers without a known screening or known HIV status during pregnancy.

*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 2017 may be due to a delay in registration.*

### Children with non-vertically-acquired HIV

- In total, 247 children were ever registered with HIV infection acquired through non-vertical transmission, including 8 children newly-registered in 2017.
- The median age at 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*):
  - 136 children had acquired HIV through heterosexual contact,
  - 55 children had acquired HIV through homosexual contact.
- 47 children had acquired HIV through contaminated blood or blood products. This mode of transmission was no longer reported from 2002 onwards among children born in the Netherland, and from 2013 onwards among any children, regardless of country of birth.
- The remaining 9 children had acquired HIV through injecting drug use or accidentally through contaminated needles.
- Of the children with non-vertically-acquired HIV, 49% were born in sub-Saharan Africa.
- About 89% received care in an adult HIV treatment centre.
- In total, 92% of the children had started cART.

### Unknown route of HV-1 transmission

- For 21 HIV-positive children, the route of transmission was unknown.
- Their median age at diagnosis was 15.7 years (IQR 12-17).
- Nine children were in care at a paediatric HIV treatment centre.
- All children had started cART.

## Newly registered in 2017

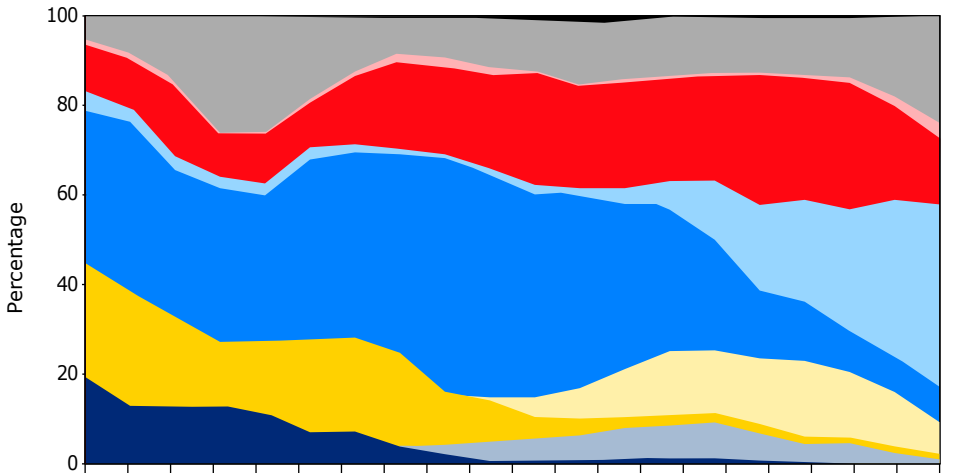
In 2017, thirteen children were newly-registered with SHM:

- Nine had entered care in 2017; the remaining 4 children had already entered care before 2017, but were only registered with SHM in 2017.
- Five had acquired HIV vertically, and 8 through sexual contact.
  - All 5 newly-registered children who had acquired HIV vertically were born outside the Netherlands; 2 of these children had been adopted by Dutch parents.
  - Five of the 8 children with non-vertically-acquired HIV were born in South America or the Caribbean and the remaining 3 children were born in various other regions outside the Netherlands.
- Four of the newly-registered children entered paediatric care and had vertically-acquired HIV. The other 9 children were in care in an adult HIV treatment centre, 8 of whom had acquired HIV through sexual contact and one who had acquired HIV vertically but had been diagnosed abroad and was older than 16 when entering care in the Netherlands.

### Age distribution

During the period from 1998 through to 2017, the proportion of children below 12 years of age decreased gradually until 2008 (*Figure 5.4*). However, from 2008 onwards, there was a slight increase in the proportion of children aged between 0 and 5 years. This is due to an increase in the rate of adoption of HIV-positive children in this age group, illustrated by the shaded areas in *Figure 5.4*. In 2017, about 85% 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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 2 | 3 | 2 | 0 | 0 | 1 | 1 | 0 | 0 | 0 |
| | 4 | 7 | 17 | 40 | 43 | 31 | 20 | 14 | 17 | 21 | 22 | 30 | 29 | 31 | 29 | 28 | 29 | 30 | 38 | 44 |
| | 0 | 1 | 1 | 1 | 1 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 3 | 4 | 6 |
| | 8 | 10 | 19 | 15 | 20 | 20 | 27 | 35 | 36 | 41 | 50 | 48 | 53 | 52 | 53 | 67 | 60 | 62 | 46 | 27 |
| | 3 | 2 | 3 | 3 | 3 | 3 | 2 | 1 | 1 | 1 | 3 | 3 | 7 | 14 | 28 | 41 | 51 | 61 | 74 | 75 |
| | 25 | 33 | 39 | 54 | 56 | 71 | 72 | 77 | 94 | 95 | 90 | 92 | 81 | 73 | 56 | 35 | 29 | 20 | 17 | 14 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 8 | 15 | 25 | 33 | 32 | 33 | 37 | 32 | 25 | 13 |
| | 18 | 22 | 24 | 22 | 27 | 37 | 36 | 35 | 21 | 19 | 11 | 8 | 4 | 5 | 4 | 5 | 4 | 3 | 4 | 2 |
| | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 4 | 7 | 8 | 12 | 14 | 16 | 18 | 13 | 8 | 8 | 5 | 2 |
| | 14 | 11 | 15 | 20 | 19 | 12 | 13 | 7 | 4 | 1 | 2 | 1 | 4 | 3 | 3 | 2 | 2 | 2 | 0 | 0 |

## Low mortality rates

The mortality rate among children ever registered between 1998 and 2017 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. Two boys died of AIDS, despite receiving cART. The third boy did not receive cART and died very short after entering care in the Netherlands.

## Treatment

Among the 603 children who were ever registered, 571 (95%) had initiated cART. Of these 571 children, 485 (85%) were treatment-naive at the start of cART and 86 (15%) had previously been exposed to monotherapy or dual therapy (i.e., pre-treated). However, the number of pre-treated children starting cART decreased over time to zero in 2016 and 2017.

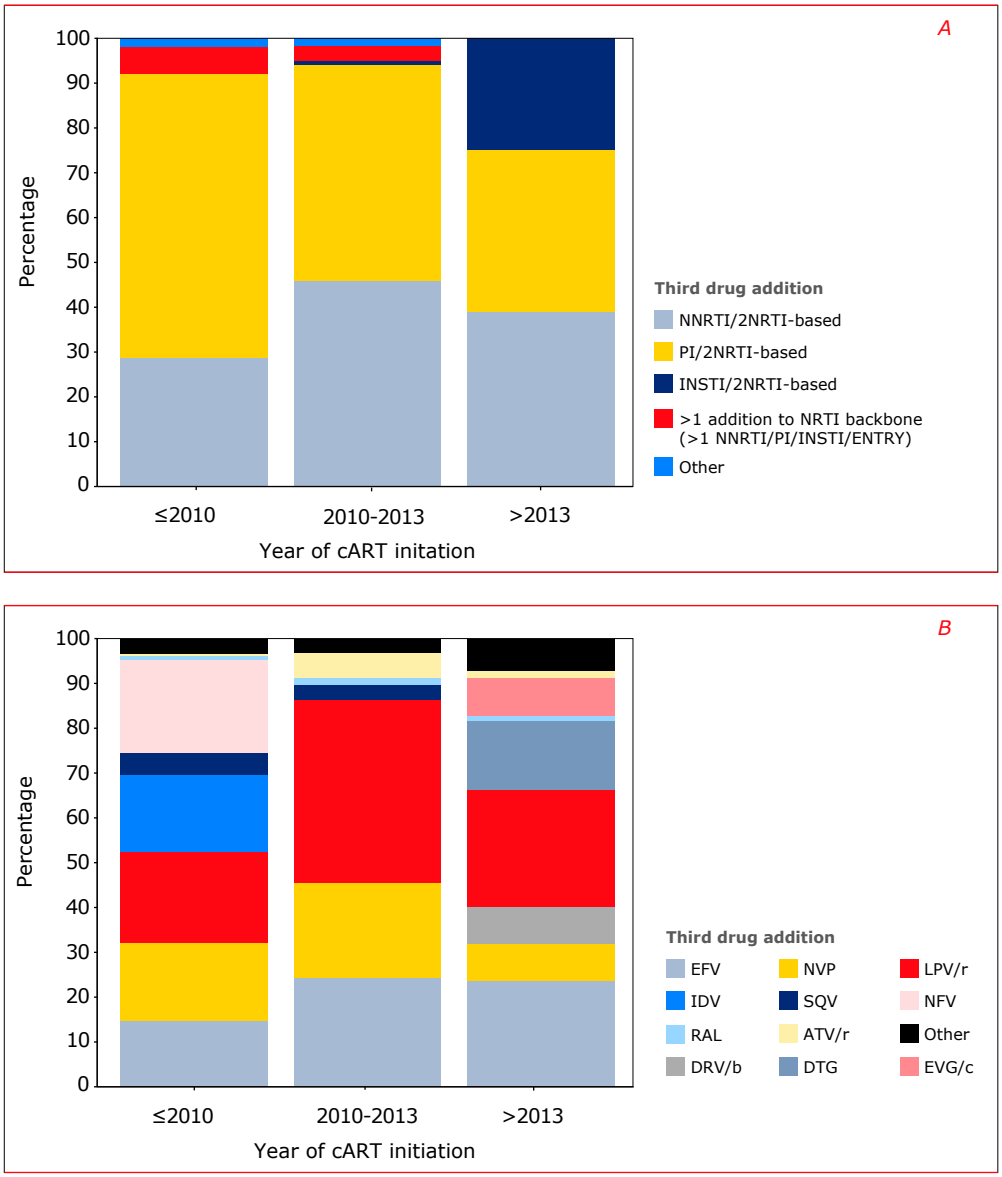
When assessing treatment, we included both pre-treated and treatment-naive children, grouped according to calendar year of starting cART: 399 had started a cART regimen before 2010, 97 had started between 2010 and 2013, and 75 had started cART from 2013 onwards.

Among those children not treated with cART, 6 had recently entered care, one had died shortly after entering care, and another 9 had been in care for less than one year.

### Initial combination antiretroviral therapy regimen use

Overall, out of the 571 ever-registered children who were known to have initiated cART, 57% were treated with a first-line cART regimen that included a protease inhibitor (PI) and two or more nucleoside analogue reverse transcriptase inhibitors (NRTIs) and another 34% were treated with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with two or more NRTIs. *Figures 5.5A* and *5.5B* show the trends over time for the third-drug additions to the NRTI backbone as part of the initial cART regimens. The protease inhibitors nelfinavir and (boosted) indinavir were used when cART was initiated before 2000[14], but have since been replaced by improved regimens that include ritonavir-boosted lopinavir or efavirenz as the most-frequently used NNRTI, in line with current guidelines[1,15,16,17]. With the introduction of dolutegravir and elvitegravir in 2013 and 2014, these integrase inhibitors have also become part of the initial cART regimens.

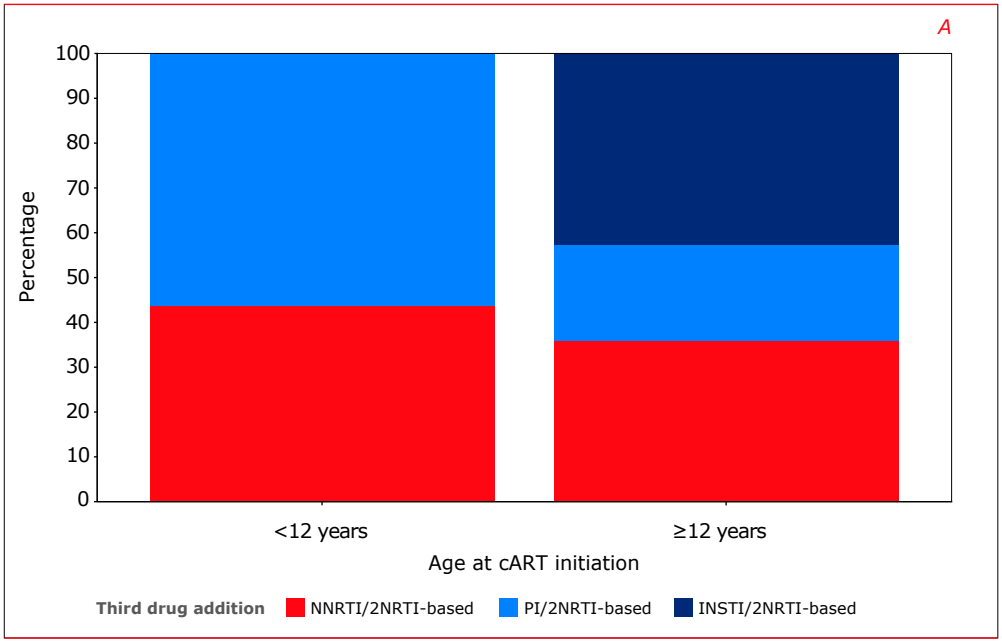
*Figure 5.5: Third-drug additions to the nucleoside analogue reverse transcriptase backbone used as part of the initial cART regimen, stratified by calendar year period, according to (A) antiretroviral class and (B) specific drug.*

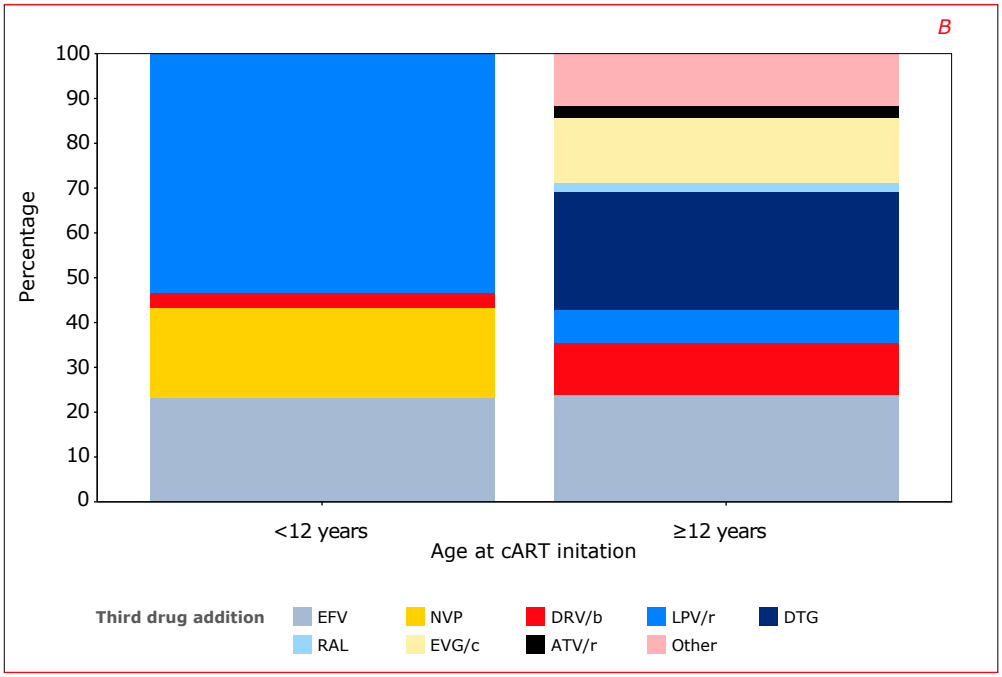



*Legend: cART=combination antiretroviral therapy; ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI= nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; EFV=efavirenz; NVP= nevirapine; LPV/r=ritonavir-boosted lopinavir;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

*Figures 5.6A* and *5.6B* further specify these third-drug additions to the NRTI backbone according to the age of starting cART in 2013-2016. Between 2013 and 2016, more than 50% of children below 12 years of age at the time of cART initiation used lopinavir/ritonavir and none of the children used an integrase inhibitor in their initial regimen. Among older children (≥12 years), there was more variation in the third-drug additions of the initial regimen, including the use of integrase inhibitors (24% dolutegravir and 14% elvitegravir).

***Figure 5.6:*** *Third-drug additions to the nucleoside analogue reverse transcriptase backbone used as part of the initial cART regimen in 2013–2016, stratified by age at cART initiation, according to (A) antiretroviral class and (B) specific drug.*






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

### Discontinuation of the initial cART regimen

We assessed the time spent on the initial regimens among the 571 children who ever started cART. The median time spent on an initial regimen was 14 months (IQR 3.1-33.9). Discounting weight-related dose changes, 451 children (79%) discontinued their first-line treatment regimen. The most important reasons for changing first-line cART regimens included toxicity (20%), simplification (18%), and parental non-adherence (2%). Virological failure accounted for 10% of the reasons for changing first-line cART therapy. Other reasons were low drug concentrations, decisions 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[18]. To investigate long-term CD4 cell count changes among the 571 children who ever started cART, we stratified the children with vertically-acquired HIV according to age at the time of cART initiation.

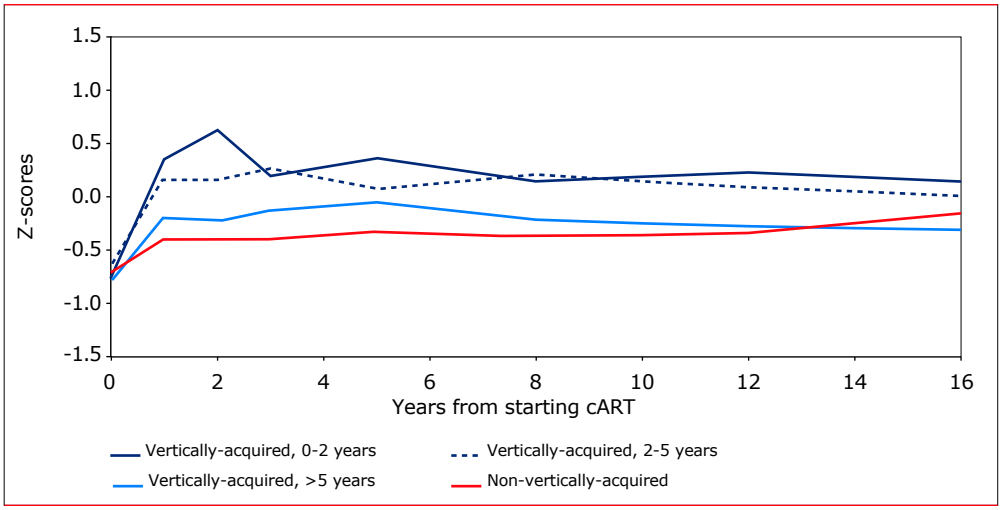
These categories were as follows:
(1) vertically-acquired, 0-2 year,
(2) vertically-acquired, 2-5 years,
(3) vertically-acquired, 5-18 years,
(4) non-vertically-acquired or unknown mode of HIV transmission[c], 5-18 years.

Given that normal CD4 cell counts in younger children are highly age-dependent[19], 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[20] 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.

*Figure 5.7* shows the changes in Z-scores for CD4 T-cell counts among HIV-positive children stratified 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. This increase was lower in the groups of children aged 5-18 years at cART initiation with both vertically and non-vertically-acquired HIV than in the group of children less than two years of age with vertically-acquired HIV.

*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 who with non-vertically-acquired HIV, these two groups were jointly analysed in a shared category.*

*Figure 5.7: 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 virological outcomes used in this chapter are described in *Box 5.1*. Virological response to cART was assessed in two ways: firstly, based on initial virological success (i.e., two consecutive HIV RNA levels below 100 copies/ml), and secondly, based on viral suppression (i.e., viral load <200 copies/ml) over a longer period of time (1-10 years).

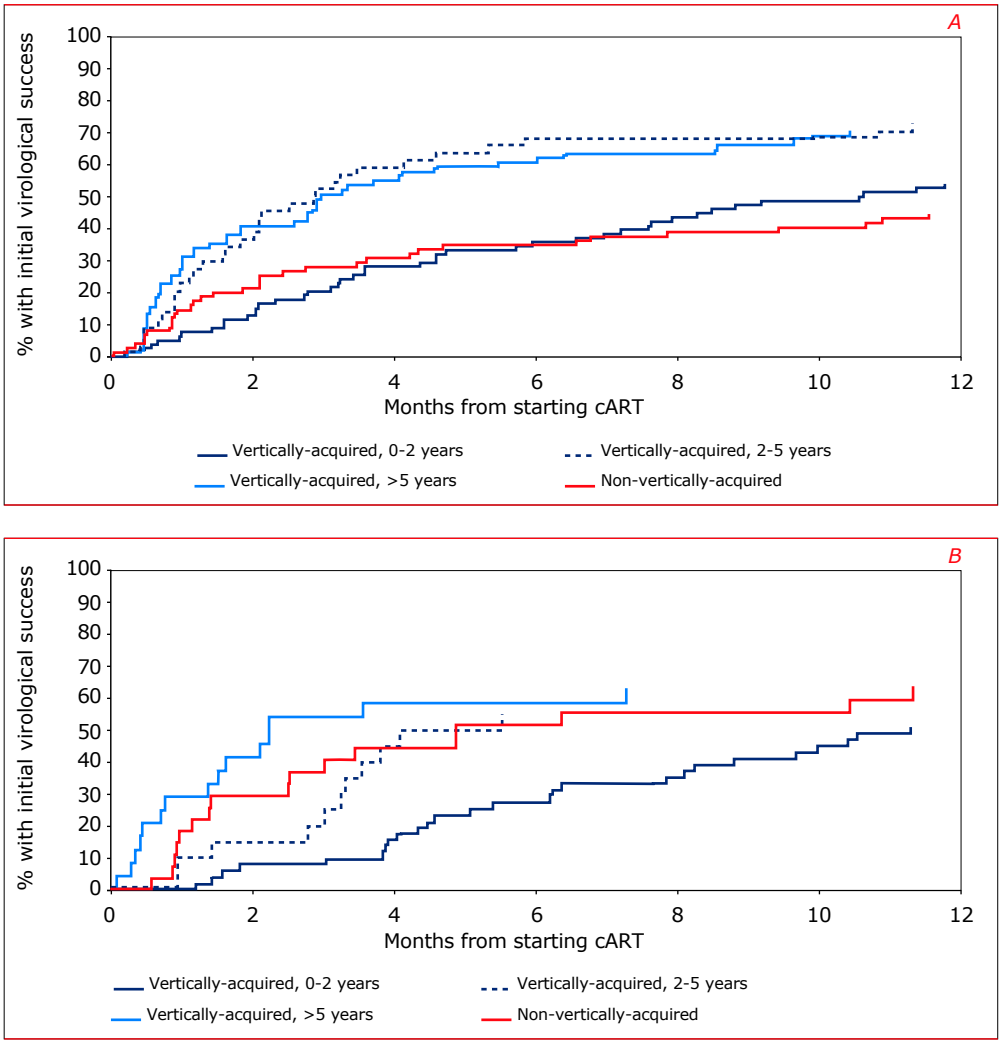
For the current analysis, we included data from the 571 children ever registered and who had ever started cART. Children were stratified by age at cART initiation (these are the same groups as those presented in the paragraph on immunological response to cART).

*I. Initial virological success*

Among children who started cART before 2010, the poorest virological responses were observed in those less than two years of age (54% reached initial virological success 12 months after the start of cART) and in those with non-vertically acquired HIV (55%). The best responses were among children aged two to four years old (75%) and those aged five years old or above who had vertically-acquired HIV (72%) (*Figure 5.8A*).

*Figure 5.8B* shows the time to initial virological success among children who initiated cART in or after 2010. In this group, 53% of the children less than two years of age and 60% of those aged between 2 and 5 years of age achieved an undetectable HIV RNA within 12 months. Higher initial virological success rates were observed among children aged five years or above with vertically-acquired HIV (63%).

***Figure 5.8:*** *Kaplan-Meier estimates of the percentage of HIV-positive children with initial virological success (<100 copies/ml) during the first year after starting combination antiretroviral therapy (cART) by age at cART initiation and HIV transmission mode: (A) initiation of cART between 1998-2010 and (B) initiation of cART between 2010-2017.*




***Legend:*** *cART=combination antiretroviral therapy.*

*II. Long term viral suppression*

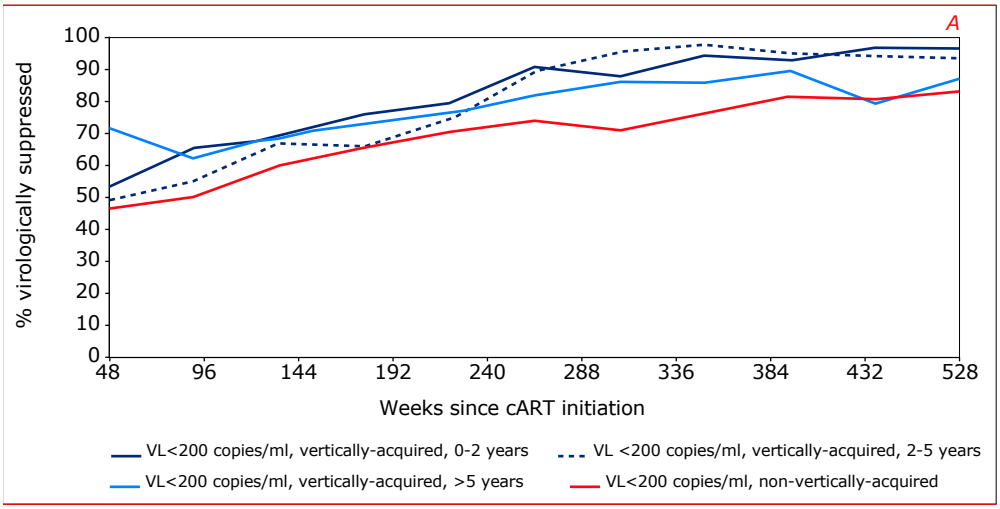
Among the 571 children who ever started cART, we assessed longitudinal viral suppression rates over time on cART during 24-week intervals. Viral load measurements closest to each 24-week time point (±12 weeks) were included in the analysis. Viral suppression rates were stratified by calendar year of cART initiation, to account for changes in the use of cART regimens.

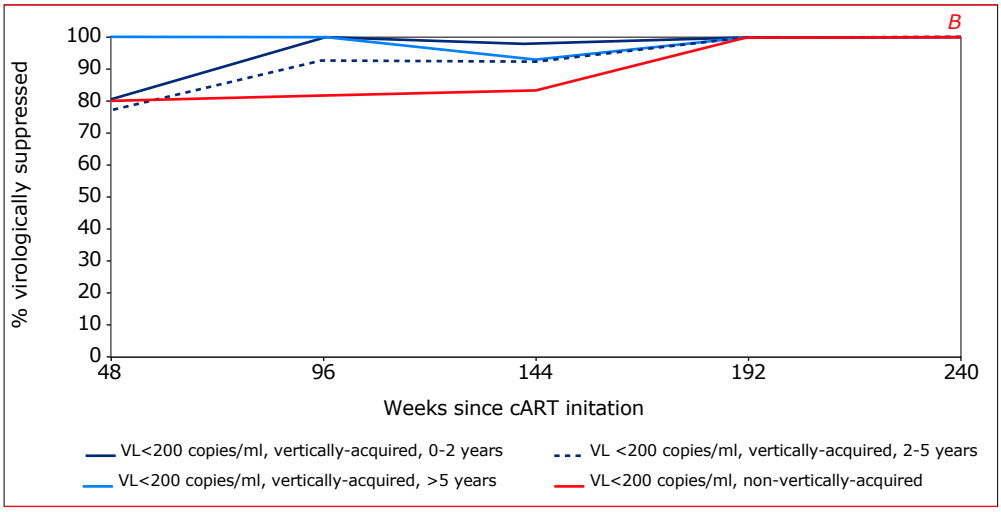
*Figure 5.9* shows viral suppression rates by calendar period of cART initiation: 1998-2009 and 2010-2017.

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 from 53% after one year of cART use to 79% and 97% after 5 and 10 years, respectively.
- Among children with vertically-acquired HIV and aged 2-5 years at cART initiation: viral suppression increased from 49% after one year of cART use to 74% and 94% after 5 and 10 years, respectively.
- Ten-year viral suppression rates were lower for children with vertically-acquired HIV and aged over 5 years of age and for those with non-vertically acquired HIV (79% and 80%, respectively [*Figure 5.9A*]).
- Long-term viral suppression rates improved over time. Among those who started cART in or after 2010 the viral suppression rates were 100% in all groups after 5 years of cART use (*Figure 5.9B*).

*Figure 5.9: Viral suppression since combination antiretroviral therapy initiation, by calendar period of therapy initiation: (A) 1998–2010 and (B) 2010–2017.*




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

The less favourable initial virological success among the youngest children that has also previously been described by others[18] might be due to difficulties in performing regular dosing adjustments in young children[19], but also due to the higher pre-cART viral loads in younger children[20]. Although we observed a poorer initial virological success during the first year of treatment among children who were aged less than 2 years at the time of cART initiation, their long-term viral suppression rate improved over time and most of these children had suppressed HIV RNA after 10 years of cART use.

## Currently in clinical care

Of the 603 HIV-positive children ever registered by SHM, 464 (77%) were still in clinical care at the end of 2017 (*Figure 5.1*). Of the remaining 139 children no longer in care, 20 had died, 49 had moved abroad, and 70 were lost to follow up.

### Currently in care and less than 18 years old

- Of the 464 children still in care, 183 were aged <18 years at the end of 2017.
- Their median age as of 31 December 2017 was 11 years (IQR 7-15).

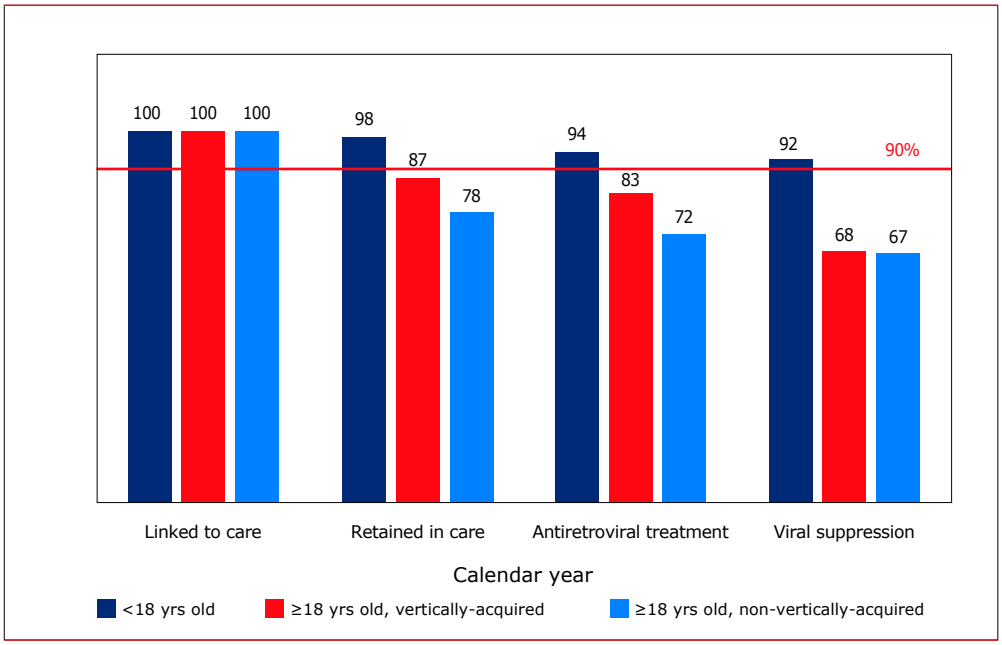
### Currently in clinical care and 18 years or older

- 281 individuals who were registered as a child were in care and over 18 at the end of 2017.
- Their median age was 23 years (IQR 20-26) for those who had vertically acquired HIV and 32 years (IQR 26-35) 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 2017, 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 5.10*).

*Figure 5.10: Cascade of care by age and mode of HIV acquisition, as of 31 December 2017. The numbers above the bars indicate the proportion of individuals.*




Individuals were stratified by age on 31 December 2017 and further categorised as:

I. current age <18 years (the number of children currently less than 18 years old with non-vertical acquisition of HIV was too small (n=5) for stratification by mode of acquisition in this age group).
II. current age ≥18 years and vertically-acquired HIV; and
III. current age ≥18 years and non-vertically-acquired HIV.

**I. Continuum of care: current age <18 years**

- In total, 187 children less than 18 years old on 31 December 2017 were linked to care, registered by SHM, still alive, and not reported as having moved abroad.
- Of these 187 children, 98% were retained in care (183/187). The remaining 4 children had been lost to follow up, all of whom were born outside the Netherlands.
- During their last clinical visit in 2017, 94% (176/183) were using antiretroviral therapy.
- Overall, 92% of those linked to care and less than 18 years old had a most recent HIV RNA measurement below 200 copies/ml (172/187).

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

- 127 individuals who had acquired HIV through vertical transmission and who were over 18 years of age on 31 December 2017 were linked to care.
- Of these 127 individuals, 87% (110) were still in care as of 31 December 2017. The remaining 17 individuals had been lost to follow up, 10 of whom were born outside the Netherlands.
- 83% (106/127) were using antiretroviral therapy at their most recent clinical visit.
- 68% (86/127) had a most recent HIV RNA measurement below 200 copies/ml.

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

- 219 individuals were older than 18 by 31 December 2017 and had acquired HIV through non-vertical transmission.
- Of these 219 individuals, 171 (78%) were still in care as of 31 December 2017; 48 individuals had been lost to follow up, including 24 women originating from sub- Saharan Africa.
- 72% (157/219) were using antiretroviral therapy during their last registered clinical visit.
- and 67% (147/219) had a most recent HIV RNA measurement below 200 copies/ml.

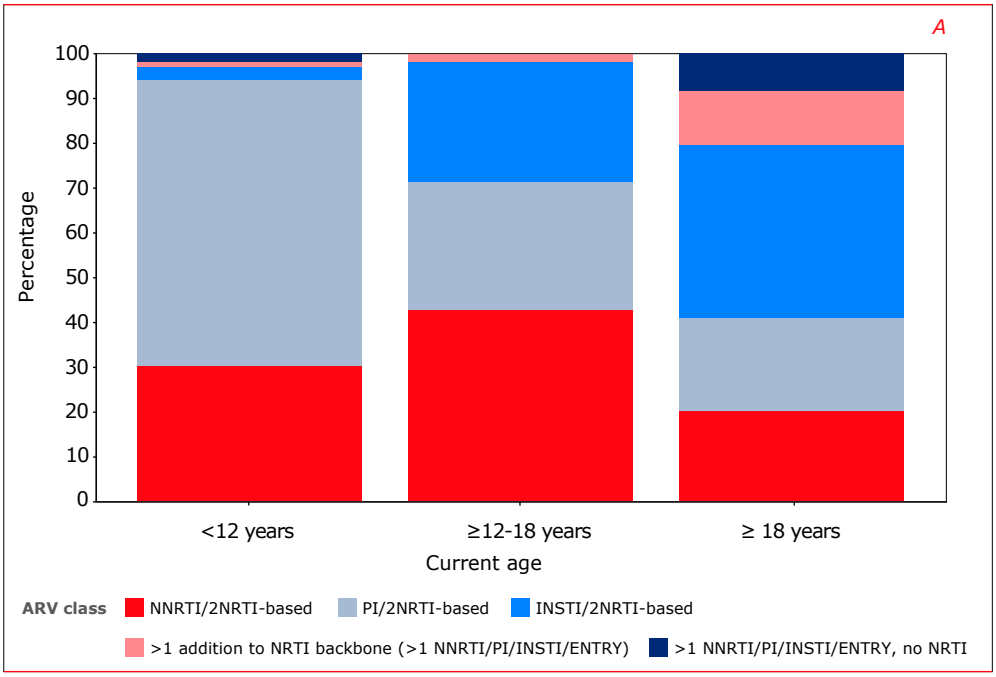
### In care and on cART in 2017

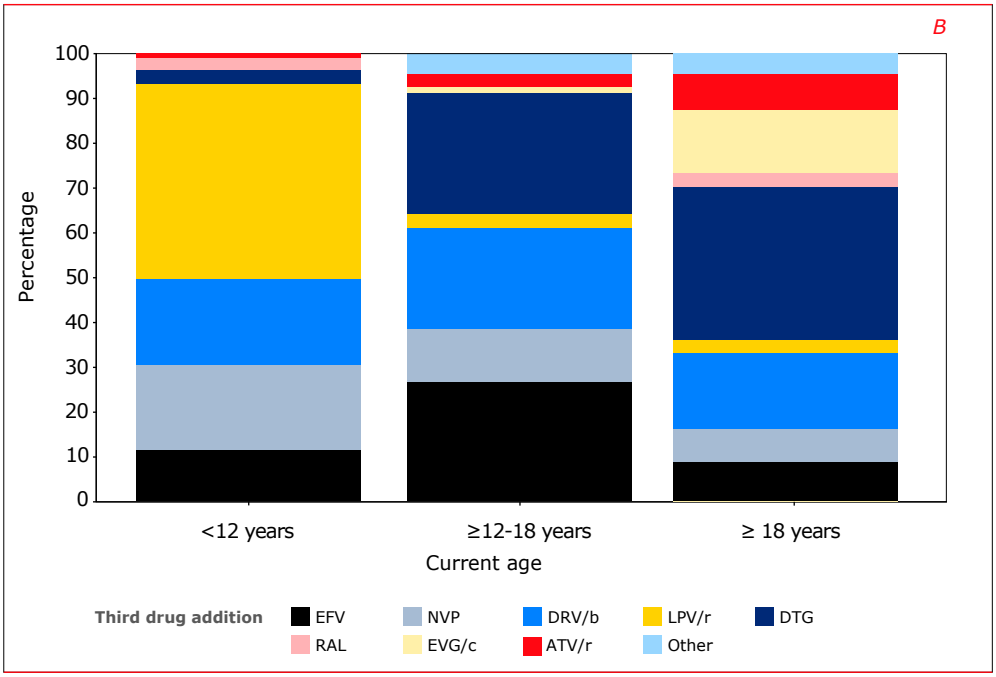
Of the 464 people known to be in care in 2017, 439 (95%) received cART in 2017. The distribution of current cART use is shown in *Figure 5.11*, according to age on 31 December 2017. Among those aged <12 years, a PI-containing regimen is currently used most often (64%), with lopinavir/ritonavir being the most common (43%).

In children aged between 12 and 18 years, 43% are currently using an NNRTI-based regimens, 28% are using a PI-based regimen, and 27% are using an INSTI-based regimen. Among those who are currently using an INSTI-based regimen, 27% use dolutegravir and another 27% use efavirenz.

Among people who were diagnosed with HIV in childhood, but who are currently over 18 years of age, 38% are using an INSTI-based regimen, comprising mainly dolutegravir.

*Figure 5.11: 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:*** *ARV=antiretroviral drug; ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI=nucleoside analogue reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; 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

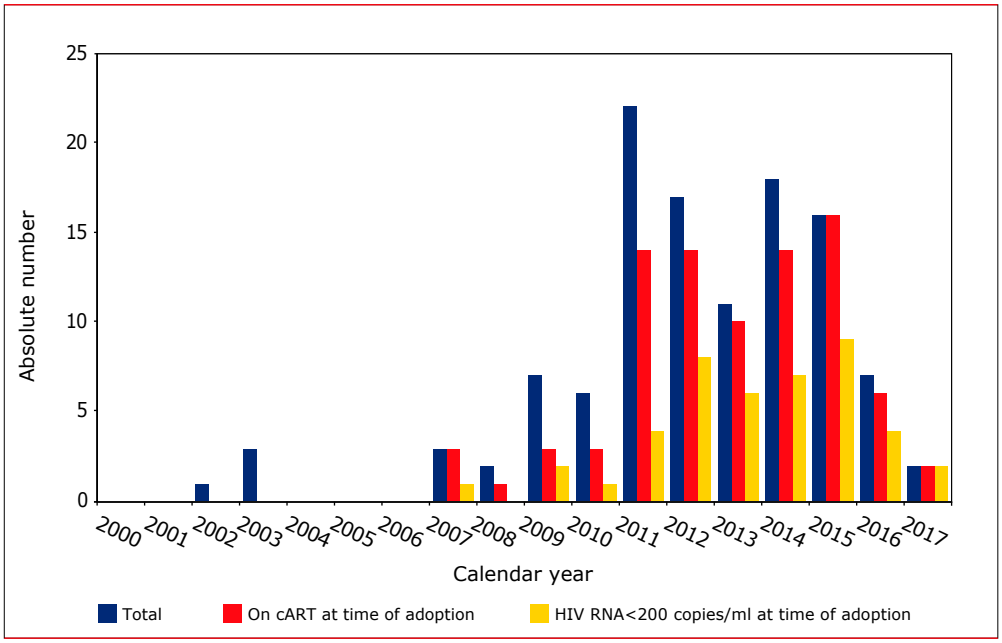
### Adopted children

Of the 603 children ever registered, 115 children were adopted by Dutch parents (*Figure 5.12*):

- Their median age at time of entering care in the Netherlands was 2.7 years (IQR 6.4-4.7).
- 113 children ever used cART during follow up in clinical care in one of the Dutch HIV treatment centres.
- In total, 88 children were already receiving cART before being adopted.
- 9 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.

- At the moment of entering care in the Netherlands, only 44 (38%) of the 115 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 8.8 years (IQR 6.4-10.9).
- All children who started cART are still on treatment, and all 113 (100%) had an undetectable viral load (≤200 copies/ml) at the last known time point.

*Figure 5.12: Number of HIV-positive children who entered paediatric care through adoption, by calendar year.*




*Legend: cART=combination antiretroviral therapy.*

## Individuals who transfer to adult care

Of the ever-registered 603 children, 358 children initially received HIV care in one of the paediatric HIV treatment centres. As of 31 December 2017, 128 (36%) of these 358 children had transferred from paediatric to adult care because they had reached 18 years of age.

The number of children who transferred to an adult centre varied from one child in 2000 to 20 in 2011, 11 in 2016, and 5 in 2017. The median age at transfer was 19.0 years (IQR 18.4-19.8). The median time in care after transfer was 4.8 years

(IQR 2.5-7.3). Of the children who transferred to adult care, 13 (10%) were lost to follow up, seven (5%) have since moved abroad, and two (1.6%) have died. The remaining 106 are currently alive and in care.

At their most recent clinical visit in 2017, 18 of the 106 individuals still in care (17%) had an HIV RNA level >200 copies/ml (median 5,180, IQR 1,740-60,000). The majority of these people were young women (58%) with vertically-acquired HIV (89%) and who were not originally from the Netherlands.

At the time of transfer to an adult HIV treatment centre, 89 (79%) of the 113 children with an available HIV RNA measurement had an HIV RNA ≤200 copies/ml and 24 (21%) 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[21]. 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, 83% of the children had an HIV RNA level ≤200 copies/ml, compared to 80% of the young adults one year after their transfer.

Of those 24 adolescents without viral suppression at time of transfer, 1 had died, 6 were no longer in care and 7 had a most recent HIV RNA >200 copies/ml. The remaining 10 individuals had suppressed HIV RNA levels at their most recent HIV RNA measurement.

The virological and social outcomes of HIV-positive adolescents and young adults in the Netherlands before and after transition to adult care have been explored in more detail by Weijsenfeld *et al.,* who confirmed 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. Characteristics found to be significantly associated with virological failure were a low level of education and a lack of autonomy regarding medication adherence at the time of transitioning to adult care[22].

## Summary

Among the 603 children diagnosed with HIV before the age of 18 and ever registered by SHM, 77% are still in care. A substantial proportion of the children newly registered since 2010 are children who have been adopted by Dutch parents, and this drives the small increase observed in the proportion of children in care aged between 0 and 5 years old.

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 no cases reported since 2015. This reflects the success of standardised HIV screening in the first trimester of pregnancy[12]. 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. Given the low prevalence (between 0.04% and 0.08%)[13] of primary HIV infection among pregnant women in the Netherlands, standardised repeat screening during pregnancy is not likely to be cost effective.

We observed low mortality rates in HIV-positive children in care in the Netherlands. The majority 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 lopinavir/ritonavir, and efavirenz, 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 overall viral suppression rate of HIV-positive children receiving cART is high and continues to improve over time, 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 2017. It is also worth noting that all children 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 2017, 61% were older than 18 on 31 December 2017. The majority of these young

people are on cART. The high rate of detectable HIV viral load in these 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 seems to be associated with an increased risk of virological failure. Although no cases of vertical HIV transmission within the Netherlands have been documented since 2015, there remains a need for awareness of the potential for incident HIV infections during pregnancy to ensure vertical transmission of HIV remains at zero.

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