Long-Term Virological Treatment Outcomes in Adolescents and Young Adults With Perinatally and Non-Perinatally Acquired Human Immunodeficiency Virus

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Background. Long-term viral suppression on antiretroviral therapy (ART) is not established among all people with human immunodeficiency virus (PWH). Young adults (18–24 years) are recognized as a group vulnerable for suboptimal virological treatment outcomes. The aim of this study is to evaluate longitudinal virological treatment outcomes and to identify risk factors for virological failure (VF) among young adults with non-perinatally and perinatally acquired human immunodeficiency virus (HIV) in the Netherlands.

Methods. We included individuals registered in the national ATHENA observational cohort from 2000 until 2020 who had entered care before the age of 25 years, who had received ART for at least 6 months with at least 2 available HIV ribonucleic acid measurements between the age of 18 and 24 years. We compared VF between age groups 12–17, 18–24, and 25–30 years. A multivariable generalized linear mixed model was used to evaluate risk factors for VF. Analyses were stratified by HIV acquisition mode.

Results. In total, 1174 non-perinatally PWH and 157 perinatally PWH were included. In 2020, VF rate was 7% in non-perinatally PWH young adults and 19% in perinatally PWH young adults. The adjusted risk for VF was significantly higher in those aged 18–24 compared to 25–30 years in both non-perinatally PWH (odds ratio [OR], 1.27; 95% confidence interval [CI], 1.07–1.50) and perinatally PWH (OR, 2.34; 95% CI, 1.48–3.71).

Conclusions. Young adulthood is a vulnerable period, with increased risk for VF, especially for perinatally PWH. The probability of VF decreased over time, but less for perinatally PWH compared to non-perinatally PWH.

Keywords. antiretroviral therapy; HIV; longitudinal study; viral suppression; young adults.

With the availability of antiretroviral therapy (ART) for successful suppression of human immunodeficiency virus (HIV), clinical outcomes for people with HIV (PWH) have improved drastically over the last 20 years. Despite these improvements, access to treatment and long-term HIV viral suppression are still not established among all PWH [1]. One of the most vulnerable groups for suboptimal treatment of PWH are adolescents and young adults (aged 10–24 years) [2, 3]. In general, for adolescents and young adults with HIV it is hard to achieve and maintain viral suppression; a global meta-analysis showed adherence rates of only 62% [4]. These poor treatment outcomes compared to adults occur even in developed countries where ART is generally available to all PWH [5, 6]. Data from the United States as well as the United Kingdom (UK) consistently show the lowest percentage of viral suppression among 13- to 24-year-olds, compared to the high viral suppression levels in the total population (71.1%–87%) [5, 7]. Underlying developmental, social, and psychological factors related to adolescence were previously found to influence optimal treatment in adolescents and young adults with HIV [8, 9, 10]. Adolescents and young adults with HIV can historically be divided by mode of HIV acquisition: non-perinatally and perinatally PWH. Non-perinatally and perinatally PWH young adults differ in clinical characteristics like duration of HIV infection, age at diagnosis, and the likelihood of being exposed to suboptimal ART regimes, apart from differences in psychosocial events (such as parental loss) [11]. Results from studies on HIV-related outcomes of adolescents and young adults are
often not disaggregated by age or route of transmission, which hampers tailored interventions to improve these outcomes [12], although barriers towards adherence differ among groups [9]. Indeed, there are studies showing worse treatment outcomes in perinatally PWH young adults compared to non-perinatally PWH young adults [11, 13]. In the Netherlands, the HIV viral suppression rate in non-perinatally PWH young adults showed a major improvement over time, with suppression levels of 95% in 2015, like adults living with HIV in the Netherlands [14]. Previous research on virological outcomes of adolescents and young adults with perinatally acquired HIV in the Netherlands before and after transition from pediatric into adult care showed worrying results with detectable levels of viremia around the time of transition [15]. Because the follow-up period after transition was limited in this study, the question was raised regarding whether perinatally PWH young adults surviving into adulthood and non-perinatally PWH young adults would benefit equally from treatment and patient care possibilities. In an illustrative, longitudinal, New York study, researchers reported on extremely high post-transitional overall mortality rates of 10.3% during the 3-year follow-up period, 5.6% of which died within the first year after transition (82.9% due to HIV-related medical conditions) [16]. The importance of long, follow-up research of perinatally PWH as they grow old is emphasized by a large cohort study conducted in the United States that showed an increase of viremia, serious clinical events, and mortality throughout adolescence and young adulthood [17].

The aim of this study is to evaluate longitudinal virological outcomes and to identify risk factors for virological failure (VF) among perinatally and non-perinatally PWH young adults in the Netherlands.

**METHODS**

Stichting HIV Monitoring (SHM) collects data from more than 97.5% of all individuals who are in care in 1 of the 24 Dutch HIV centers, comprising the AIDS Therapy Evaluation in the Netherlands (ATHENA) observational cohort [18]. Individuals were eligible for inclusion in this study if they met all of the following criteria: (1) being in care between 2000 and 2020 in 1 of the 24 Dutch HIV centers; (2) being diagnosed with HIV-1 and entered care before the age of 25 years; (3) having received ART for at least 6 months; (4) having at least 2 HIV-ribonucleic acid (RNA) viral load (VL) measurements between the age of 18 and 24 years after the minimum of 6 months ART; and (5) being registered in the ATHENA cohort.

The observation period started from the age of 12 years, an age-related marker for the start of adolescence as commonly used by the Central Bureau of Statistics in the Netherlands [19]. Data were included from the year 2000 onwards, to reduce the effect of availability of different (or less potent) ART regimes over time. Antiretroviral therapy was defined as (1) a combination of at least 3 antiretroviral drugs or (2) the use of 2 antiretroviral drugs including a combination with a protease inhibitor, integrase strand transfer inhibitor (INSTI), or non-nucleoside reverse-transcriptase inhibitor (NNRTI) [20]. In addition, prior exposure to mono or dual nucleoside reverse-transcriptase inhibitor (NRTI) is considered as pretreatment, whereas individuals without prior exposure to mono or dual NRTI were considered as ART naive. The observation period started for (1) persons already in clinical care before the age of 12 years, at the age of 12 years, or from January 1, 2000 onwards and (2) patients newly entering into care between the age 12 and 25 years, after January 1, 2000.

If individuals were diagnosed and started on ART outside the Netherlands, inclusion started at their first visit in a Dutch HIV treatment center with a minimum of 6 months of ART use. In case the moment of start ART was unknown (n = 10), individuals were excluded from the analyses. For these individuals, it was uncertain whether there were 2 HIV-RNA measurements during the young adult age. Follow up continued until the participants reached the age of 31 years, became lost to follow up, died, or at database closure on February 1, 2021. We choose to collect data until the age of 31 years, to be able to assess outcomes of young adults after they turned into adulthood with a comparable duration of observation time to the young adult age.

The following data were collected: transmission route, time-updated age, sex, country/region of birth, age at HIV diagnosis, age at start of ART, pretreatment with mono or dual ART, ART regimes, nadir CD4 counts, HIV-RNA measurements, frequency of VF and cumulative time with a detectable HIV VL, mortality, Centers for Disease Control and Prevention (CDC) B/C events, and hepatitis B and C coinfection.

We evaluated outcome measurements in 6-month blocks of follow-up time and included all plasma HIV VL measurements available during the follow-up period. Human immunodeficiency virus VL measurements were routinely collected, as part of standard HIV care according to guidelines, during outpatient clinical visits, and more often in case of medical necessity.

To account for missing values, HIV VL measurements were imputed using last observation carried forward for a maximum of 3 observation periods (eg, a maximum of 18 months). If the interval between HIV VL measurements exceeded 3 observation periods, individuals were censored and temporary excluded for the time between censoring until the date of the next available HIV RNA measurement.

**Statistical Analyses**

Descriptive statistics were used for demographic and clinical characteristic. All characteristics were expressed as medians with interquartile range (IQR), means with standard deviation,
or frequencies and percentages, where appropriate. Viral load measurements were based on assays in use between 2000 and 2020 using different lower limits of detection (LLD) (ranging from <500 copies/mL in the year 2000 to <20/40 copies/mL in 2020). Virological failure was defined as a measurement of an HIV VL >200 copies/mL or above the LLD where appropriate after a minimum of 6 months on ART. In case of multiple HIV RNA measurement in a 6-month time block, we used the highest value within each block to assess VF. Human immunodeficiency virus VL measurements undetectable according to LLD at the time of measurement were considered undetectable.

To evaluate the longitudinal virological outcomes and identify risk factors for VF, we used a generalized linear mixed model with a logit link function and a random intercept per person. All other variables were treated as fixed effects. The model was fit by maximum likelihood. The variables assessed for potential influence on virological failure were as follows; transmission (men who have sex with men [MSM], heterosexual men, heterosexual women, men other, women other [other includes blood transfusion or needle accident, intravenous drug use, and unknown transmission route], mother-to-child transmission), time-updated age (as a categorical variable [12 to 17 years, 18 to 24 years, or 25 to 30 years]), country or region of birth, calendar years (2000 to 2004, 2005 to 2009, 2010 to 2014, 2015 to 2020, representing time intervals with increasingly potent ART regimes), nadir CD4 count, and pretreatment with mono or dual ART.

We checked possible interaction effects between age and transmission route. Analyses were stratified by mode of transmission because of an observed interaction between age groups and transmission mode. In the stratified analyses, we observed an interaction between age and calendar time; therefore, we performed sensitivity analyses using only data from the most recent time period (2015–2020). Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical analyses were performed using R (R Core Team, 2020 Version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and SPSS (IBM SPSS Statistics for Windows, Version 26.0; Armonk, NY: IBM Corp 2019).

**Patient Consent Statement**

From 2002, ATHENA has been managed by SHM, the institute appointed by the Dutch Ministry of Public Health, Welfare and Sport for the monitoring of people with HIV in the Netherlands. People entering HIV care receive written material about participation in the ATHENA cohort and are informed by their treating physician on the purpose of data collection, thereafter they can consent verbally or elect to opt out. Data are pseudonymized before being provided to investigators and may be used for scientific purposes. A designated data protection officer safeguards compliance with the European General Data Protection Regulation.

**RESULTS**

**Demographic Characteristics**

A total of 1331 individuals were included in this study that comprised 1174 (88.2%) non-perinatally PWH and 157 (11.8%) perinatally PWH. Male sex was 64.9% in non-perinatally PWH and 51.0% in perinatally PWH. Most non-perinatally PWH and perinatally PWH originated from the Netherlands (479, 40.8% and 79, 50.3%) or sub-Saharan Africa (SSA) 337, 28.7% and 56, 35.7%). The median age at HIV diagnosis in non-perinatally PWH and perinatally PWH was 20.8 (IQR, 19.1–22.2) and 2.5 (IQR, 0.6–6.4) years, respectively. Treatment with ART started at a median age of 21.6 (IQR, 20.0–22.8) in non-perinatally PWH and 5.7 (IQR, 2.3–10.0) years in perinatally PWH. The percentage of individuals that started ART outside the Netherlands was 10.8% in non-perinatally PWH and 9.6% in perinatally PWH. Pretreatment with mono or dual ART was 2.1% in non-perinatally PWH and 20.4% in perinatally PWH. The frequency of VF and the cumulative time with a detectable VL (>200 copies/mL) was significantly higher in the perinatally PWH group (54.8% versus 42.2% and 1.8 versus 0.9 years, respectively) compared to non-perinatally PWH (Table 1).

In non-perinatally PWH 16 (1.4%), individuals died before the age of 30 years, compared to 4 (2.5%) in perinatally PWH. Causes of death in non-perinatally PWH were HIV related (n = 7), non-natural death (n = 3), and other causes (n = 6), and all deaths in perinatally PWH were HIV related (n = 4). The occurrence of mortality, CDC B/C events, and hepatitis B and C coinfection did not differ significantly between groups (Supplementary Table 1). Individuals were followed for a median time of 6.5 years in non-perinatally PWH (IQR, 3.5–8.4) and 11 in perinatally PWH (IQR, 8.0–14.1) (Table 1).

**Virological Outcomes**

The number of individuals experiencing virological suppression (VS) and VF in different age categories is shown in Figure 1A and B. Virological failure in non-perinatally PWH during the young adult age decreased over time from 35% in 2000, to 32% in 2009, to 7% in 2020, and it decreased for perinatally PWH.

The proportion of non-perinatally PWH and perinatally PWH with a detectable VL (>200 copies/mL) was significantly higher in the perinatally PWH group (54.8% versus 42.2% and 1.8 versus 0.9 years, respectively) compared to non-perinatally PWH (Table 1).

**Treatment**

The use of different ART regimes over time for non-perinatally and perinatally PWH is shown in Figure 2A and B. In 2020, 13% of perinatally PWH versus none in the non-perinatally PWH group used an ART regime in the “other” category, which was not NRTI based, or consisted of either <2 classes or >2 classes. In this category, 3 individuals (non-perinatally PWH, n = 2; perinatally PWH, n = 1) were on a regime consisting of 1 NNRTI and 1 INSTI in 2019 and 2020, possibly an accepted form of duo therapy. Furthermore, the proportion of non-
perinatally PWH on an INSTI-based regime in 2020 was 71%, compared with 45% in the perinatally PWH group.

**Factors Associated With Virological Treatment Outcomes**

To consider the potential different effect of age on the risk of VF for both HIV transmission groups, the ORs and 95% CIs for the risk of experiencing VF are presented separately for non-perinatally and perinatally PWH (Table 2). The adjusted association with VF was significantly higher in the young adults age group compared to the oldest age group for both non-perinatally and perinatally PWH (non-perinatally PWH 12–17, OR = 1.42 and 95% CI = 0.80–2.51 and 18–24, OR = 1.27 and 95% CI = 1.07–1.50; perinatally PWH 12–17, OR = 0.88 and 95% CI = 0.46–1.66 and 18–24, OR = 2.34 and 95% CI = 1.48–3.71 [reference group 25–30]).

The probability of VF for non-perinatally PWH decreased with calendar time of being in care (2000–2004, OR = 12.48 and 95% CI = 8.38–18.59; 2005–2009, OR = 7.36 and 95% CI = 5.38–10.60; 2010–2014, OR = 3.23 and 95% CI = 2.54–4.11) compared to 2015–2020 (P < .001). In perinatally PWH, VF occurred significantly more often in the earliest period from 2000 to 2004 (OR = 5.34, 95% CI = 2.56–11.13), compared to the reference group 2015–2020 (Table 2). Limiting the analyses to the most recent time period (2015–2020), the significant effect of young adults age versus the reference group of 25–30 years was still present for non-perinatally PWH (12–17, OR = 3.97, 95% CI = 0.30–31.46 and 18–24, OR = 1.51, 95% CI = 1.02–2.25) but not for perinatally PWH (12–17, OR = 0.46, 95% CI = 0.16–1.36 and 18–24, OR = 1.36, 95% CI = 0.62–2.97). When we limited the analyses to the latest time period

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**Table 1. Demographic and Clinical Characteristics of HIV-Infected Adolescents and Young Adults in the Netherlands (2000–2020)**

| Demographic and Clinical Characteristics | All N = 1331 | Non-Perinatally PWH N = 1174 | Perinatally PWH N = 157 |
|------------------------------------------|-------------|----------------------------|------------------------|
| Sex (male)                               | 842 (63.3)  | 762 (64.9)                 | 80 (51.0)              |
| Country or Region of Birth               |             |                            |                        |
| Netherlands                              | 558 (41.9)  | 479 (40.8)                 | 79 (50.3)              |
| Sub-Saharan Africa                       | 393 (29.5)  | 337 (28.7)                 | 56 (35.7)              |
| Latin America/Caribbean                  | 208 (15.6)  | 197 (16.8)                 | 11 (7.0)               |
| Age at diagnose                          | 21.3 (18.9–22.7) | 21.6 (20.0–22.8) | 5.6 (2.3–9.8)          |
| Pretreated with mono or dual antiretroviral therapy | 57 (4.3) | 12 (2.1) | 0.6 (0.4–0.8) |
| Nadir CD4+ T-cell count (cells/µL)       | 390 (160–437) | 300 (179–440) | 0.8 (0.6–1.1) |
| HIV RNA at start ART (log copies/mL)     | 4.7 (4.1–5.2) | 4.6 (4.0–5.1) | 4.9 (4.3–5.7) |
| VF* ever (n%)                            | 581 (43.6)  | 495 (34.2)                 | 86 (54.8)              |
| Cumulative time (years) with HIV VL >200 copies/mL | 1.0 (1.7) | 0.9 (1.7) | 1.8 (2.6) |
| Age at start study data collection       | 21.8 (19.5–23.2) | 22.2 (20.6–23.3) | 12.0 (10.0–12.0) |
| Age at stop study data collection        | 28.5 (25.1–31.0) | 29.3 (25.8–31.0) | 24 (20.8–27.6) |
| Follow-up time (years)                   | 6.9 (4.0–9.0) | 6.5 (3.5–8.4) | 11.0 (8.0–14.1) |
| Moved abroad                             | 61 (4.6)    | 60 (4.5)                   | 1 (0.6)                |
| Loss to follow up                        | 109 (8.2)   | 98 (8.3)                   | 11 (7.0)               |

Abbreviations: ART, antiretroviral therapy; IDU, intravenous drug use; HIV, human immunodeficiency virus; MSM, men who have sex with men; MTCT, mother-to-child transmission; PWH, people with HIV; non-perinatally PWH, people who acquired HIV non-perinatally; perinatally PWH, people who acquired HIV perinatally; RNA, ribonucleic acid; VF, virological failure.

NOTE: Data are reported as number (%), mean (standard deviation) or median (Q1, Q3).

*European other than the Netherlands.

**Table 2. Factors Associated With Virological Treatment Outcomes**

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(2015–2020), the effect of age on the risk for VF was still significant in non-perinatally PWH but not in perinatally PWH. However, for perinatally PWH, in the unadjusted analyses, the youngest age category was associated with a significantly lower risk of VF. This difference was not observed between young adults and adults. The association with the youngest age category disappeared after adjusting for nadir CD4 count and being treated with mono or duo therapy (data not shown).

Other predictor variables for VF in non-perinatally PWH were heterosexual women (OR, 8.18; 95% CI, 4.77–14.02)

Figure 1. (A) Number and percentage of individuals experiencing viral suppression (VS) and virological failure (VF) during 3 different age categories in people who acquired human immunodeficiency virus (HIV) non-perinatally. VS is defined as an undetectable HIV viral load (VL) according to the lower limit of detection; VF is failure defined as an HIV VL > 200 copies/mL; 12–17 = 12–17 years old; 18–24 = 18–24 years old; 25–30 = 25–30 years old. (B) Number and percentage of individuals experiencing VS and VF during 3 different age categories in people who acquired HIV perinatally. VS is defined as an undetectable HIV VL according to the lower limit of detection; VF is defined as an HIV VL > 200 copies/mL; 12–17 = 12–17 years old; 18–24 = 18–24 years old; 25–30 = 25–30 years old. From the years 2000–2007, there were no perinatally PWH in the 25–30 age group.
and heterosexual men (OR, 2.82; 95% CI, 1.37–5.79) compared to MSM, and originating from Latin America or the Caribbean Islands (OR, 3.12; 95% CI, 1.74–5.61), or from other countries/regions apart from the Netherlands or SSA (OR, 2.14; 95% CI, 1.12–4.10) (Table 2).

In perinatally PWH, having a nadir CD4 count <200/×10⁶/L was associated with an increased probability of experiencing VF (200–500, OR = 0.27 and 95% CI = .11–.63; 500+, OR = 0.08 and 95% CI = .02–.31). Further, being pretreated with mono or dual ART increased the probability of experiencing VF (OR, 4.25; 95% CI, 1.62–11.15) (Table 2).

**Sensitivity Analyses**

In sensitivity analyses in which VF was defined as 2 consecutive viral load measurements >200, there was no change on the effect of age or calendar time on VF in both groups (data not shown).
**DISCUSSION**

Young adults (aged 18–24 years) living in the Netherlands were more likely to experience virological failure compared to other age categories. This result confirms that, as showed in other studies, young adulthood is a period of vulnerability to suboptimal HIV treatment [7, 21]. As hypothesized, we observed considerable differences between perinatally PWH and non-perinatally PWH young adults regarding current treatment success. In 2020, 19% of perinatally PWH young adults were not virologically suppressed compared to 7% in non-perinatally PWH young adults. Similar high nonsuppression rates (19.6%) in perinatally PWH young adults were recently reported in the UK [22]. In a previously published study from Florida, researchers assessed outcomes of youth separately for multiple transmission routes and showed that although retention in care of perinatally PWH was high, the rate of VS was low [21]. The high percentage of nonsuppressed perinatally PWH in the young adult age is in line with our previous research, in which we observed an increase of VF after transition [15]. It is remarkable that, in a Spanish cohort of perinatally PWH (1997–2016), the high nonsuppression rates of individuals at transition improved over time after transition to adult care [23]. The researchers mentioned the possible role of the availability of improved ART regimes initially available only for adults. A New York study reported an improvement of suppression rates posttransition, although the median age at transition was 22 years, and suppression rates were still only 51.9% at 3 years posttransition with high posttransitional mortality rates [16]. In a US study that compared different stages of adolescence in perinatally PWH comparable to our data, researchers observed an increase of nonsuppression from early adolescence to young adulthood (16% to 40%) [24].

In non-perinatally PWH, HIV suppression rates of 93% during the young adult age (18–24 years) in non-perinatally PWH in 2020 approach HIV suppression rates of 95% in adult people with HIV on ART in the Netherlands [25]. Our outcomes are in line with a Canadian study reporting on differences between young adults (<19 years) and older adults regarding achievement of VS (90% versus 93%) and experiencing viral rebound (28% versus 26%) [26]. Non-perinatally PWH young adults in the Netherlands seem to reach optimal HIV suppression more often in recent years (93% in 2020) compared to other

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**Table 2. Multivariable Associations With Virological Failure Among Non-Perinatally PWH and Perinatally PWH**

| Determinant                          | Non-Perinatally PWH | Perinatally PWH |
|--------------------------------------|---------------------|-----------------|
|                                      | OR                  | 95% CI          | P Value | OR                  | 95% CI          | P Value |
| Transmission and Sex                 |                     |                 |         |                     |                 |         |
| MSM (reference)                      | 1                   | —               |         | 1                   | —               |         |
| Heterosexual men*                    | 2.82                | 1.37/5.79       | .005    | 1                   | —               |         |
| Heterosexual women*                  | 8.18                | 4.77/14.02      | <.001   | 1                   | —               |         |
| Men other*                           | 2.30                | 0.94/5.59       | .067    | 2.30                | 0.80/9.10       | .022    |
| Women other*                         | 2.34                | 0.80/9.10       | .022    | 2.34                | 0.80/9.10       | .022    |
| Sex                                  |                     |                 |         |                     |                 |         |
| Male (reference)                     | 1                   | —               |         | 1                   | —               |         |
| Female                               | .65                 | .29/1.41        | .27     | .65                 | .29/1.41        | .27     |
| Age Group                            |                     |                 |         |                     |                 |         |
| 12–17                                | 1.42                | .80/2.51        | .23     | 1.42                | .80/2.51        | .23     |
| 18–24                                | 1.27                | 1.07/1.50       | .007    | 2.34                | 1.48/3.71       | <.001   |
| 25–30 (reference)                    | 1                   | 1               |         | 1                   | 1               |         |
| Birth Country or Region              |                     |                 |         |                     |                 |         |
| Netherlands (reference)              | 1                   | 1               |         | 1                   | 1               |         |
| Sub Saharan Africa                   | 1.50                | .85/2.64        | .16     | 1.50                | .85/2.64        | .16     |
| Latin America or Caribbean           | 3.12                | 1.74/5.61       | <.001   | 3.12                | 1.74/5.61       | <.001   |
| Other*                               | 2.14                | 1.12/4.10       | .02     | 2.14                | 1.12/4.10       | .02     |
| Nadir CD4+ T-Cell Count (x10^3/LL)  |                     |                 |         |                     |                 |         |
| <200 (reference)                     | 1                   | 1               |         | 1                   | 1               |         |
| 200–500                              | .75                 | .48/1.17        | .21     | .75                 | .48/1.17        | .21     |
| >500                                 | .58                 | .29/1.15        | .12     | .58                 | .29/1.15        | .12     |
| Calendar Years                       |                     |                 |         |                     |                 |         |
| 2000–2004                            | 12.48               | 8.38/18.59      | <.001   | 12.48               | 8.38/18.59      | <.001   |
| 2005–2009                            | 7.36                | 5.38/10.06      | <.001   | 7.36                | 5.38/10.06      | <.001   |
| 2010–2014                            | 3.23                | 2.54/4.11       | <.001   | 3.23                | 2.54/4.11       | <.001   |
| 2015–2020 (reference)                | 1                   | 1               |         | 1                   | 1               |         |
| Pretreated With Mono or Dual         |                     |                 |         |                     |                 |         |
| Antiretroviral Therapy               | No (reference)      | 1               |         | Yes                 | .90              | .27/2.96 |
|                                      | .90                 | .27/2.96        | .86     | 4.25                | 1.62/11.15      | .003    |

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MSM, men who have sex with men; non-perinatally PWH; people who acquired HIV non-perinatally; OR, odds ratio; perinatally PWH, people who acquired HIV perinatally.

NOTE: The table shows which factors were associated with virological failure, defined as an HIV VL measurement >200 copies/mL, analyzed using a general linear mixed model. Bold text refers to statistical significant findings.

*aHeterosexuals who acquired HIV through heterosexual contact.

*bOther includes the following: blood transfusion or needle accident, intravenous drug use, and unknown transmission route.

*Europe other than the Netherlands, North America, North Africa and Middle East, Oceania and Pacific, and unknown.

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Western cohorts such as the UK, where suppression rates are markedly worse (87% in 2018) in comparison to the general adult population of PWH (97% in 2018) [8]. Comparison with other national cohorts has some limitations. Virological suppression is not always determined in adolescents and young adults who were prescribed ART, and there is no international consensus on the use of age ranges in youth [3, 19]. More specifically, in those who had access to ART through the Ryan White HIV/AIDS program, 79.1% of young adults (20–24) attending were virally suppressed in 2019. Numbers differ by race/ethnicity as seen in our cohort and are generally worse for non-Whites and non-Asians [27].

It is possible that the origin of differences in viral outcomes between non-perinatally PWH young adults living in the Netherlands and United States lies in the socioeconomic background of individuals. Non-perinatally PWH adolescents and young adults (16–24) from a US cohort who were linked to care, with suppression rates of 89%, were mostly of Black/non-Hispanic origin (71%), and 40% had a history of incarceration [28]. The subgroup of non-perinatally PWH in our study, who originated from countries or regions other than the Netherlands or SSA, were more likely to experience VF. It is arguable that socioeconomic circumstances are worse for this group, because there are known disparities in access and use of HIV-related healthcare services for migrant men, women, and MSM in the Netherlands. In addition, they experience uncertainty about their rights to healthcare, language barriers, and are more likely to have experienced HIV discrimination [29].

Because calendar time represents the availability of improved ART therapy, it is possible that perinatally and non-perinatally PWH do not profit equally from the availability of these more potent regimes. This might partly be explained by the later introduction of integrase inhibitor (INSTI)-based treatment regimes in perinatally PWH (2013) compared with non-perinatally PWH (2009) in our cohort, due to the later US Food and Drug Administration approval of INSTIs in children and adolescents [30]. Furthermore, there is a risk of therapy fatigue for perinatally PWH who generally started ART at a young age. Maintaining life-long adherence can be challenging for them, especially in combination with transition to adult care [9, 11].

When we limited the analyses to the latest time period (2015–2020), the effect of age on the risk for VF is still significant in non-perinatally PWH but not in perinatally PWH. However, for perinatally PWH, in care in 2015–2020, the youngest age category was less likely to experience VF. This difference was not observed between young adults and adults, indicating that the virological outcomes do not improve with aging, as seen in non-perinatally PWH. The association with the youngest age category disappeared after adjusting for nadir CD4 count and being treated with mono- or duo therapy, characteristics that present more often in the older age category compared to the youngest age category. The latter were diagnosed more recently and were more likely to profit from potent ART regimes and earlier treatment initiation as recommended by recent guidelines.

Both a low nadir CD4 count (<200 × 10⁹/L) and pretreatment with mono or dual therapy are associated with VF in our cohort for perinatally PWH, but not non-perinatally PWH. The latter could be explained by the higher percentage of perinatally PWH who were pretreated with mono or dual therapy compared to non-perinatally PWH. Having started directly with ART can partly explain the overall better outcomes of non-perinatally PWH, because it lowers the possibility of drug-resistant mutations and subsequently more complicated treatment regimens that may hamper treatment adherence. Our outcomes show that in the Netherlands, the cumulative time spent with a detectable VL is higher in perinatally PWH compared to non-perinatally PWH. An expert review on treatment in adolescents and young adults with early-acquired HIV in the United States highlights specific challenges such as development of drug-resistant mutations due to exposure to suboptimal treatment regimens or nonadherence [31]. Although we do not report on the occurrence of drug-resistant mutations, higher rates of triple-class VF were found in teenagers who acquired HIV perinatally compared to young adults who acquired HIV heterosexually in Europe [13].

In our cohort, perinatally PWH individuals are prescribed complex ART regimes more often during the follow-up period compared to their non-perinatally PWH peers, indicating the presence of drug-resistant mutations. With the growing availability of injectable, long-acting ARTs, and the high interest of young people for these alternative strategies [32], this is of great concern. Moreover, there are consequences of ongoing viremia and long-standing infection (ie, inflammation and its sequelae including malignancy) [33, 34].

In non-perinatally PWH, VF was more probable in heterosexual men and women compared to the MSM group, in line with data of the total HIV population from the Netherlands [25]. Better outcomes in MSM compared with heterosexuals were also described in the earlier mentioned Canadian and Florida study [21, 26], as well as in our previous study on outcomes on young adults with behaviorally acquired HIV [14]. For the discussion of underlying characteristics that possibly drive these better outcomes, we refer to that study, but it is not the main focus of our current study.

Together with demographic differences and differences regarding HIV disease history and ART characteristics, our findings support the recommendation to disaggregate not only by age but by perinatal and behavioral-acquired infection as well when assessing outcomes in adolescents and young adults with HIV [11]. Furthermore, researchers should consider reporting on risk of VF for different subgroups within the non-perinatally PWH group, because large differences are observed between young people with heterosexual versus MSM transmission.
CONCLUSIONS
As in other Western cohorts, young adults in the Netherlands represent a relatively small amount (approximately 1%) of the total population of PWH [25]. Therefore, the specific problems regarding adherence and sustained viral suppression may be underestimated once in care at an adult treatment center. Our study shows that even in the Netherlands where excellent HIV care is accessible to all PWH, young adults age is a period with increased risk for VF for both non-perinatally and perinatally PWH. Tailor-made interventions developed in cooperation with young people are essential to improve the outcomes of those at risk. Interventions to support adherence in young adults should consider the possible specific developmental and psychosocial problems that drive nonadherence, because those might differ between risk groups.

Supplementary Data
Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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