Factors associated with time to achieve an undetectable HIV RNA viral load after start of antiretroviral treatment in HIV-1-infected pregnant women

W van Snippenburg1,*, FJB Nellen2, C Smit1, AMJ Wensing4, MH Godfried2, T Mudrikova1 for the ATHENA cohort

1 Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Netherlands
2 Department of Internal Medicine and Infectious Diseases, Academic Medical Center, Amsterdam, Netherlands
3 Stichting HIV Monitoring, Amsterdam, Netherlands
4 Virology, Department of Medical Microbiology, University Medical Center Utrecht, Netherlands

Abstract

Objective: To identify factors associated with the time to viral suppression in women starting antiretroviral treatment (ART) during pregnancy. Knowledge on duration of viral load (VL) decline could help deciding the timing of treatment initiation.

Methods: Highly active antiretroviral treatment (HAART)-naive pregnant women over 18 years of age who started treatment during pregnancy were included. The time to viral suppression was calculated and compared between subgroups.

Results: A total of 227 pregnancies matched our inclusion criteria. In 84.6% of these an undetectable VL was reached at the time of delivery. The median time to undetectable VL after initiation of treatment was 60 days (12–168 days). Only baseline VL <10,000 copies/mL showed an independent association with time to viral suppression in multivariate Cox regression analysis, with a mean time to reach a VL <50 HIV-1 copies/mL of 49 days (95% CI 44–53). No difference in time to undetectable VL was found between protease inhibitor and non-nucleoside reverse transcriptase inhibitor-based regimens. Integrase inhibitors were not part of any treatment regimen.

Conclusion: Our results suggest that in patients with baseline HIV RNA <10,000 copies/mL ART initiation might be postponed up to the twentieth week of pregnancy, thus minimising the risk of possible drug-related teratogenicity and toxicity.

Keywords: pregnancy, HIV, suppression, undetectable

Introduction

Achieving an undetectable viral load (VL) at the time of delivery is a crucial goal of antiretroviral treatment (ART) during pregnancy in order to minimise the risk of mother-to-child transmission (MTCT) of HIV [1,2]. In the past, approximately one-third of HIV-positive pregnant women in the Netherlands started highly active antiretroviral treatment (HAART) during pregnancy because they either did not have a treatment indication prior to the pregnancy, or because the infection was newly diagnosed during pregnancy [3]. Current Dutch treatment guidelines largely follow DHHS recommendations, with one exception being the recommended time for starting HAART during pregnancy. In the absence of an immunological indication for ART in the mother (i.e. CD4 cell count >350 cells/mm3), older Dutch guidelines recommended initiation of ART at 20–24 weeks’ gestation because of concerns regarding the teratogenicity of some antiretroviral agents and an increased frequency of nausea and vomiting early in pregnancy, which may compromise adequate treatment with the risk of development of resistance. The recommended time for HAART initiation has in recent years changed to 16–20 weeks’ gestation in asymptomatic women with a VL <10,000 HIV-1 copies/mL [4]. In contrast, the most recent DHHS guidelines recommend starting ART in pregnancy as soon as the HIV diagnosis has been established, although it is mentioned that this decision can be influenced by the CD4 T cell count and plasma HIV RNA levels. No further details are given concerning the CD4 T cell count or HIV RNA level at which it would be safe to postpone therapy. Regardless of the VL and CD4 T cell count, it is recommended to always start treatment before the beginning of the second trimester of pregnancy [5,6].

In this analysis, we have aimed to identify factors associated with the time to achieve an undetectable VL in pregnant women starting ART during pregnancy. Predicting which subgroup of patients might have a faster VL decline could help in the decision about the timing of treatment initiation.

Materials and methods

Study cohort

Pregnant women over 18 years of age, who had no prior treatment with antiretroviral medication and who started HAART during pregnancy in the Dutch hospitals participating in the ATHENA observational cohort between 1998 and 2013, were included in this analysis. ATHENA is a national observational cohort that has collected data from all HIV-infected patients in clinical care in the Netherlands since 1996. Clinical, biological and immunological data for these patients were collected at entry and at each follow-up visit. The design of this cohort has been described previously [7]. As already mentioned, the Dutch guideline recommendations about the time of initiation of HAART have changed during the study period from 20–24 weeks to 16–20 weeks of gestation in patients with low VL. Furthermore, the recommended HAART regimen switched from nelfinavir to ritonavir-boosted lopinavir in 2007 due to the recall of nelfinavir, based on contamination concerns. At HAART initiation, plasma HIV VL had to be >50 copies/mL and at least two VL measurements during pregnancy had to be available after treatment initiation, unless an undetectable VL was reached at the time of the first measurement after the start of HAART. Plasma VL was quantified using assays with a lower detection limit of 50 copies/mL. Baseline VL was defined as the last known VL before HAART initiation. The last VL quantification, during pregnancy, was usually completed within 4 weeks prior to the expected date of delivery. Baseline HIV RNA VL was grouped into two categories: <10,000 or ≥10,000 copies/mL. This cut-off was based on a prior pilot study (data unpublished) and the results of another study [8]. Baseline CD4 T cell count was classified as ≥350 or <350 cells/mm3.
Statistical analysis

The R programming language version 3.1.0 was used for statistical analyses. Kaplan–Meier plots were used to explore associations between the maternal characteristics mentioned above and the time to a VL of <50 copies/mL after HAART initiation. Women who did not achieve full VL suppression were right censored at the date of delivery. Student’s t-test was used to test for significant difference between the mean log_{10} baseline VLs of different categories. In the subset of women achieving viral suppression during pregnancy, a univariate Cox regression analysis was used to test for significant differences in time to undetectable VL between categories of baseline VL, baseline CD4 T cell count, year of delivery, antiretroviral regimen, maternal region of birth and gestational age at initiation. These characteristics were chosen based on possible consequences for the following: interpretation of guideline recommendations (VL and CD4 T cell count); because of a change in the Dutch guidelines and possible consequence for preferred antiretroviral drug (year of delivery and HAART regimen); as a proxy for socio-economic status in absence of more suitable data (maternal region of birth); and as a proxy for possible changes in protease inhibitor (PI) pharmacokinetics in absence of the actual plasma concentrations (gestational age at start of HAART). Significant characteristics (P<0.10) were then selected and used in a multivariable Cox proportional hazards model to examine possible independent predictors of a longer time to viral suppression. Differences with P<0.05 were regarded as statistically significant. Unless stated otherwise, results are shown as median and corresponding range.

Results

There were 227 pregnancies in the ATHENA database that matched our inclusion criteria. Maternal- and pregnancy-related baseline characteristics are shown in Table 1. For newly diagnosed HIV-infected mothers median gestational age at time of diagnosis was 16.3 weeks (range 1.3–37.1 weeks). A regimen including nevirapine was initiated in 144 pregnancies (63.4%), boosted lopinavir in 55 (24.2%) and nevirapine in 26 (11.5%) pregnancies. One patient (0.4%) started both nevirapine and nevirnavir and one other patient, nevirapine and lopinavir. A backbone consisting of two nucleos(t)ide reverse-transcriptase inhibitors was used in all patients. Baseline VL was measured at a median of 25 days before the start of HAART (0–163 days). The median number of measurements during pregnancy was 4 (1–10) and the median time between any two consecutive VL samples was 28 days (1–160 days). Overall, in 200 out of 227 pregnancies (88.1%) an undetectable VL was reached during pregnancy. The percentage of women per subgroup reaching viral suppression during pregnancy is reported in Table 2. The median time to the first undetectable VL after initiation of treatment was 60 days (12–168 days). The mean time to achieving an undetectable VL for different subgroups is shown in Table 3. The median last plasma HIV RNA concentration in the women with a detectable VL prior to delivery was 151 copies/mL (52–48,800 copies/mL), with a median duration of treatment before delivery of 81 days (6–210 days).

Women with viral loads of <10,000 HIV-1 copies/mL and a CD4 T cell count >350 cells/mm³, having treatment with nevirapine and a gestational age of >20 weeks at initiation of HAART showed a significantly shorter time to a VL of <50 copies/mL in univariate analysis. Kaplan–Meier plots for these characteristics are shown in Figure 1. A comparison of the mean log_{10} VL before HAART initiation in different categories is shown in Table 2. The VL was significantly higher in pregnancies when HAART was started before 20 weeks compared to initiation after 20 weeks of gestation, and in pregnancies with a baseline CD4 T cell count of ≤350 cells/mm³ compared to >350 cells/mm³. The median gestational age at start of HAART was 22.2 (12.0–38.1) and 22.0 (7.9–31.0) weeks for newly diagnosed and previously known HIV-infected mothers, respectively (P=0.21). A multivariable Cox proportional hazards analysis using the above mentioned variables showed an independent association only of baseline VL <10,000 copies/mL with a shorter time to viral suppression (Table 3).

Discussion

Our retrospective analysis has shown that a baseline VL <10,000 copies/mL in pregnant women initiating HAART is associated with a shorter time to reach undetectable plasma HIV RNA. This is in line with research in other HIV-infected populations showing that the time to viral suppression is dependent on the baseline VL [5,8,9]. This finding is particularly relevant for pregnant women as these data support the consideration of postponing treatment until 20
like nausea and vomiting and guided by the CD4 cell count and can be delayed in the presence of specific maternal conditions [5]. These guidelines do indicate that the decision to start HAART transmission usually occurs late in pregnancy or during delivery of the infant, but also acknowledge that early and sustained maternal viral control might lower the risk of vertical transmission of HIV.

The decision to start HAART initiation as soon as the HIV diagnosis has been made should be weighed against the risk of vertical transmission of HIV, shortening of fetal exposure to the antiretroviral drugs. This decision should be guided by the CD4 cell count and viral load during pregnancy.

Table 2. Baseline HIV-1 viral load and the number of patients that reached an undetectable viral load during pregnancy

| Maternal region of birth          | Mean log10 baseline VL | VL <50 copies/mL during pregnancy |
|-----------------------------------|------------------------|----------------------------------|
| Sub-Saharan Africa                | 4.1                    | 117 (86.0%)                      |
| Asia                              | 4.4                    | 11 (91.7%)                       |
| Europe/USA                        | 3.7*                   | 30 (96.8%)                       |
| Latin America                     | 4.1                    | 35 (92.1%)                       |
| Other                             | 4.3                    | 7 (70.0%)                        |

| HIV diagnosis                     |                        |                                  |
|-----------------------------------|------------------------|----------------------------------|
| Known before pregnancy            | 4.1                    | 47 (92.2%)                       |
| New during pregnancy              | 4.1                    | 153 (86.9%)                      |

| Year of delivery                  |                        |                                  |
|-----------------------------------|------------------------|----------------------------------|
| 1998–2004                         | 4.0                    | 104 (88.1%)                      |
| 2005–2009                         | 4.1                    | 81 (90.0%)                       |
| ≥2010                             | 4.2                    | 15 (78.9%)                       |

| Gestational age at initiation HAART|                        |                                  |
|-----------------------------------|------------------------|----------------------------------|
| >20 weeks                         | 4.0*                   | 140 (85.9%)                      |
| ≤20 weeks                         | 4.3                    | 60 (93.8%)                       |

| HAART regimen                     |                        |                                  |
|-----------------------------------|------------------------|----------------------------------|
| Lopinavir/t                       | 4.1                    | 46 (83.6%)                       |
| Nelfinavir                        | 4.1                    | 133 (92.4%)                      |
| Nevirapine                        | 4.3                    | 21 (80.8%)                       |

| Baseline CD4 cell count(cells/mm³) |                       |                                  |
|-----------------------------------|------------------------|----------------------------------|
| >350                              | 3.8*                   | 92 (88.5%)                       |
| ≤350                              | 4.4                    | 100 (89.3%)                      |

| Baseline viral load (copies/mL)   |                        |                                  |
|-----------------------------------|------------------------|----------------------------------|
| ≥10,000                           | 4.6                    | 108 (85.0%)                      |
| <10,000                           | 3.4*                   | 79 (95.2%)                       |

*P<0.01
HAART: highly active antiretroviral therapy

HAART initiation and time to viral suppression did not remain significant in multivariate analysis. The same pattern was observed for patients with a baseline CD4 T cell count <350 cells/mm³. There are conflicting reports in the literature on the association of baseline CD4 T cell count and the rate of viral suppression [8,9,12,13]. However, one can generally conclude that lower CD4 T cell counts (<350 cells/mm³) should prompt the start of ART during pregnancy regardless of the VL level.

A notable finding in our univariate analysis was the association of HAART initiation before 20 weeks’ gestation with a longer time to viral suppression. However, the mean baseline VL was significantly higher in this early starting group, reflecting a clinical decision of initiating HAART earlier in patients with high viraemia.

As expected, the association between early HAART initiation and time to viral suppression did not remain significant in multivariate analysis. The same pattern was observed for patients with a baseline CD4 T cell count <350 cells/mm³. There are conflicting reports in the literature on the association of baseline CD4 T cell count and the rate of viral suppression [8,9,12,13]. However, one can generally conclude that lower CD4 T cell counts (<350 cells/mm³) should prompt the start of ART during pregnancy regardless of the VL level.

When HIV is diagnosed late in pregnancy, a rapid plasma HIV RNA decline is warranted and antiretroviral agents that achieve a faster viral decay should be favoured over less potent ones. Read et al. found boosted PI regimens to be more successful in reaching an undetectable VL at the time of delivery in comparison to non-nucleoside reverse transcriptase inhibitors (NNRTIs) [8]. This is in contrast to the results from the European Collaborative Study, where no difference was seen at the time of delivery, but did show that women treated with nevirapine achieved viral suppression faster than women treated with a PI [23]. A possible explanation for this difference is the use of unboosted PIs in some participants in the latter study, as well as use of a less stringent HIV RNA quantification limit of 400 copies/mL. Katz et al. did not find a significant impact of the type of HAART on the VL at delivery [12]. In our cohort, we also did not find a significant difference in the time to an undetectable VL between patients treated with

HIV RNA levels. However, no guidance is given for a cut-off VL value [5]. In our cohort, women with a baseline VL <10,000 copies/mL had a mean time to viral suppression of 7 weeks, with a maximum of 14 weeks; women with a baseline VL ≥10,000 copies/mL had a mean time to undetectable VL of 11 weeks, with a maximum of 24 weeks. Based on our cohort data, postponing HAART initiation can be considered up to 20 weeks’ gestation for women with a baseline VL <10,000 copies/mL, even when the higher risk of preterm delivery is taken into account. Of course, treatment should be started earlier if there is a maternal indication for ART or if there are other issues that might compromise treatment efficacy, such as relevant pre-existing viral mutations or potential therapy non-adherence. However, owing to close medical follow-up by both physicians and specialist nurses, we believe adherence to be generally high in this specific patient population. Our results are in line with those of the London HIV Perinatal Research Group, which has shown the need for HAART initiation before 20 weeks of gestation if baseline VL >10,000 HIV-1 copies/mL in order to maximise the chance of full viral suppression at delivery, while in women with a VL <10,000 copies/mL no significant increase in the proportion of detectable VL at the time of delivery was seen as long as therapy was started before 26 weeks of gestation [8].
boosted lopinavir, nelfinavir or nevirapine. The number of women treated with nevirapine was small, which may have influenced this outcome. Another potential type of treatment includes integrase inhibitors, which can induce a rapid VL decline, although the experience with these drugs in pregnancy is not yet extensive. There is some experience that shows that integrase inhibitors might be an option when HIV is diagnosed late in pregnancy and that the fast VL drop may outweigh the risks to the fetus, especially since exposure will be short and organogenesis has already occurred. However, the possibility of adverse effects during pregnancy, the risk for teratogenicity and fetal toxicity when started early in pregnancy remain issues [5,24,25].

Because of the retrospective study design and small cohort size there are a number of limitations to this study. We did not have any objective data on adherence, socio-economic status, antiretroviral drug resistance and other possible confounders, which may influence the results of our Cox model. It is also important to note that the frequency of VL testing varied between patients, which may bias results in terms of the difference in the time to viral suppression between groups. A limitation regarding the generalisability of this study results from the fact that the majority of women were treated with nelfinavir, which is no longer widely used. Most of the remaining patients were treated with ritonavir-boosted lopinavir, which has been replaced by ritonavir-boosted...

### Table 3. Multivariate analysis of the time to undetectable HIV-1 viral load in women achieving an undetectable viral load before delivery

|                          | n    | Days to VL <50 (95% CI) | Univariate analysis HR (95% CI) | Multivariate analysis HR (95% CI) |
|--------------------------|------|-------------------------|---------------------------------|----------------------------------|
| **Overall**              | 200  | 64 (60–68)              |                                 |                                  |
| **Maternal region of birth** |      |                         |                                 |                                  |
| Sub-Saharan Africa       | 117  | 61 (56–66)              | 1.00                            | 1.00                             |
| Asia                    | 11   | 81 (62–100)             | 0.77 (0.42–1.44)                | 0.97 (0.50–1.90)                 |
| Europe/USA              | 30   | 56 (49–63)              | 1.72 (1.14–2.60)*               | 1.03 (0.64–1.66)                 |
| Latin America           | 35   | 72 (63–81)              | 0.99 (0.68–1.45)                | 0.83 (0.56–1.25)                 |
| Other                   | 7    | 72 (44–99)              | 0.55 (0.26–1.18)                | 0.54 (0.24–1.21)                 |
| **Year of delivery**    |      |                         |                                 |                                  |
| 1998–2004                | 104  | 61 (56–66)              | 1.00                            | 1.00                             |
| 2005–2009                | 81   | 65 (59–72)              | 0.82 (0.61–1.10)                | 0.82 (0.61–1.10)                 |
| ≥2010                   | 15   | 74 (59–89)              | 0.68 (0.39–1.17)                | 0.68 (0.39–1.17)                 |
| **Gestational age at initiation HAART** |      |                         |                                 |                                  |
| >20 weeks               | 60   | 58 (54–62)              | 1.00                            | 1.00                             |
| ≤20 weeks               | 140  | 77 (68–85)              | 1.74 (1.26–2.40)*               | 1.41 (0.97–2.04)                 |
| **Baseline CD4 cell count (cells/mm³)** |      |                         |                                 |                                  |
| ≤350                    | 100  | 71 (65–76)              | 1.00                            | 1.00                             |
| >350                    | 92   | 57 (51–62)              | 1.52 (1.14–2.02)*               | 1.02 (0.72–1.44)                 |
| **Baseline viral load (copies/mL)** |      |                         |                                 |                                  |
| ≥10,000                 | 108  | 75 (70–81)              | 1.00                            | 1.00                             |
| <10,000                 | 79   | 49 (44–53)              | 3.55 (2.58–4.87)*               | 3.29 (2.27–4.78)†                |
| **Antiretroviral regimen** |      |                         |                                 |                                  |
| Lopinavir/r             | 46   | 69 (58–79)              | 1.00                            | 1.00                             |
| Nelfinavir              | 133  | 61 (57–66)              | 1.65 (1.16–2.34)*               | 1.22 (0.82–1.82)                 |
| Nevirapine              | 21   | 67 (55–80)              | 1.27 (0.75–2.16)                | 1.18 (0.67–2.10)                 |

*P ≤ 0.10; †P ≤ 0.01

Figure 1. Kaplan–Meier plots for time to undetectable HIV-1 viral load
atazanavir and darunavir in recent years as the preferred PI for use in pregnant women. However, because our main finding was the association with baseline VL to the time of undetectable VL we believe that our results are still informative. Furthermore, our opinion is that most PIs may have a similar effect on the viral decay rate, as supported by the absence of a difference in to the time of undetectable VL between nelfinavir and lopinavir/ritonavir in our cohort, as well as the comparable viral decay rate found by Alagatnam et al. for atazanavir/ritonavir and lopinavir/ritonavir [26].

Conclusions

Our analysis has shown that a baseline VL of <10,000 HIV-1 copies/mL is associated with a shorter time to viral suppression after initiation of a non-integrase inhibitor-containing HAART regimen during pregnancy. This suggests that in patients with HIV RNA <10,000 copies/mL, postponing ART initiation until the twentieth week of pregnancy can be considered, thus minimising the risk of potential drug-related teratogenicity and toxicity. In pregnant patients with a baseline VL ≥10,000 copies/mL, our data support the recommendation by the current DHHS guidelines that HAART should be initiated as early as possible to achieve optimal HIV suppression of HIV at the time of delivery.

Acknowledgments

The ATHENA database is maintained by Stichting HIV Monitoring and supported by a grant from the Dutch Ministry of Health, Welfare and Sport through the Centre for Infectious Disease Control of the National centre for Public Health and the Environment.

Clinical centres

*Denotes site coordinating physician.

Academic Medical Centre of the University of Amsterdam: HIV treating physicians: JM Prins*, TW Kuijpers, HJ Scherpbier, JTM van der Plas, AM Weijsenfeld. Erasmus MC, Rotterdam: HIV treating physicians: S Baas, L Hage de Looff. HIV nurse consultants: N Hulshoff, LMM van der Prijt, J van der Velden. St Elisabeth Ziekenhuis, Tilburg: HIV treating physicians: MEE van der Burg-van de Plas, H Heins. Data collection: E Witte.

Data collection: Ad van HagaZiekenhuis, Den Haag: HIV treating physicians: EMS Leyten*, LBS Gelinc. HIV nurse consultants: A van Hartingsveld, C Meeker, CS Wilderenbeest. HIV clinical virologists/chemists: JAEM Mutsaers, CL Jansen. MC Slotervaart, Amsterdam: HIV treating physicians: JW Mulder, SME Vrouenraets, FNLauw. HIV nurse consultants: MC van Broekhuizen, H Paap, DJ Vlasbloem. HIV clinical virologists/chemists: PSME Smits. MC Zuiderzee, Lelystad: HIV treating physicians: S Weijer*, REI Moussiaoui. HIV nurse consultant: AS Bosma. Medisch Centrum Leeuwarden, Leeuwarden: HIV treating physicians: MGA VanVonderen*, DP van Houte, LM Kampschreur. HIV clinical virologists/chemists: K. Dijkstra, S. Faber. HIV clinical virologists/chemists: J Weel. Medisch Spectrum Twente, Enschede: HIV treating physicians: GJ Kootstra*, CE Delsing. HIV nurse consultants: M van der Burg-van de Plas, H Heins. Data collection: E. Lucas. NoordwestZiekenhuisgroep, Alkmaar: HIV treating physicians: W Kortmann*, G van Twillert*, JNT Cohen Stuart, BMW Diedereren. HIV nurse consultant and data collection: D Pronk, FA van Truijen-Oud.HIV clinical virologists/chemists: WA van der Reijden, R Jansen. OLVG, Amsterdam: HIV treating physicians: K Brinkman*, GEL van den Berk, WL Blok, PHJ Fruissen, KD Lettinga, WEM Schouten, J Veenstra. HIV nurse consultants: CJ Brouwer, GF Geerdes, K Hoekema, MJ Kleene, IB van der Meché, M Spellbirk, H Sulman, AJM Toonen, S Wijnands. HIV clinical virologists: M Damen, D Kwa. Data collection: E Witters.

Radboudumc, Nijmegen: HIV treating physicians: R van Crevel*, PP Koopmans, M Keuter, AJAM van der Ven, HJM ter Hofstede, ASM Dofferhoff. HIV nurse consultants: M Albers, MWE Bosch, KJT Grintjes-Huisman, BJZomer. HIV clinical virologists/chemists: MGA VanVonderen*, DP van Houte, LM Kampschreur. HIV clinical virologists/chemists: WS van der Reijden, R Jansen. OLVG, Amsterdam: HIV treating physicians: K Brinkman*, GEL van den Berk, WL Blok, PHF Fruissen, KD Lettinga, WEM Schouten, J Veenstra. HIV nurse consultants: CJ Brouwer, GF Geerdes, K Hoekema, MJ Kleene, IB van der Meché, M Spellbirk, H Sulman, AJM Toonen, S Wijnands. HIV clinical virologists: M Damen, D Kwa. Data collection: E Witte.

ORIGINAL RESEARCH

Journal of Virus Eradication 2017; 3: 34–39
Groningen: HIV treating physicians: WFW Bierman*, H Scholvinck, KR Wilting, Y Stienstra. HIV nurse consultants: H de Groot-de Jonge, PA van der Meulen, DA de Weerd, J Ludwig-Roukema. HIV clinical virologists/chemists: HCM Niesters, A Riezebos-Brilman, CC van Leer-Buter, PM Knoester. Universiteit Medisch Centrum Utrecht, Utrecht: HIV treating physicians: AIM Hoepelman*, T Mudrikova, PM Ellerbroek, JJ Oosterheert, JE Arends, RE Barth, MWM Wassenberg, EM Schadd, VHmc, Amsterdam: HIV treating physicians: EJG. Peters*, MA van Agtmael, M Bomers, J de Vocht. HIV nurse consultants: M Heitmuller, LM Laan. HIV clinical virologists/chemists: R Schuurman, F Verduyn-Lunel, AMJ Wensing. VUmc, Amsterdam: HIV treating physicians: SPM Geelen, TFW Wolfs, LJ Bont. HIV nurse consultants: N Nauta.

Coordinating centre

Director: P. Reiss. Data analysis: DO Bezemer, AI van Sighem, C Smit, FWMN. Wit, TS. Boender. Data management and quality control: S Zaheri, M Hillebregt, A de Jong. Data monitoring: D Bergsma, P Hoekstra, A de Lang, S Grivell, A Jansen, MJ Rademaker, M Raethke, R Meijering, S Schnör. Data collection: Lde Groot, M van den Akker, Y Bakker, E Claessen, A El Berkouzi, J Koops, E Krujine, C Lodewijk, L Munjishvili, B Pecck, C Ree, R Regtop, Y Ruijs, T Rutkens, L van de Sande, M Schoorl, A Timmerman, E Tujin, L Veenenberg, S van der Vliet, A Wisse, T Woudstra. Patient registration: B Tuk.

Declaration of interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors received no financial support for the research, authorship and/or publication of this article.

References

1. European Collaborative S. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clin Infect Dis 2005; 40: 458–465.
2. Tubiana R, Le Chenedec J, Rouzioux C et al. Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: a case-control study nested in the French perinatal cohort (EPF-ANRS C01). Clin Infect Dis 2012; 50: 585–596.
3. Stichting HIV Monitoring. Monitoring report 2014: human immunodeficiency virus (HIV) infection in the Netherlands. Available at: www.hiv-monitoring.nl/english/research/monitoringreports/ (accessed December 2016).
4. Nederlandse Vereniging voor HIV Behandelaren. HIV richtlijn: hoofdstuk 7. 2015.
5. Panel on Treatment of HIV Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. Section Antepartum care. Rockville (MD): Public Health Service Task Force, 2016 (Last updated: April 29, 2016).
6. European ACS. The European Guidelines for treatment of HIV-infected adults in Europe. 2015.
7. van Sighem AI, van de Wiel MA, Chani AC et al. Mortality and progression to AIDS after starting highly active antiretroviral therapy. AIDS 2003; 17: 2227–2236.
8. Read PJ, Mandalia S, Khan P et al. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? AIDS 2012; 26: 1095–1103.
9. Philipsen AN, Staszewski S, Weber R et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. JAMA 2001; 286: 2560–2567.
10. Louis JM, Buhan MA, Blackwell SC et al. Characteristics associated with suboptimal viral suppression at delivery in human immunodeficiency virus-1-infected pregnant women. Am J Obstet Gynecol 2005; 193: 1266–1269.
11. Weinberg A, Harwood JF, McFarland EJ et al. Kinetics and determining factors of the virologic response to antiretrovirals during pregnancy. Infect Dis Obstet Gynecol 2009; 2009: 621789.
12. Katz IT, Shapiro R, Li D et al. Risk factors for detectable HIV-1 RNA at delivery among women receiving highly active antiretroviral therapy in the women and infants transmission study. J Acquir Immune Defic Syndr 2010; 54: 27–34.
13. Izzo I, Forleo MA, Carani S et al. Maternal characteristics during pregnancy and risk factors for positive HIV RNA at delivery: a single-cohort observational study (Brescia, Northern Italy). BMC Public Health 2011; 11: 124.
14. Westreich D, Cole SR, Nagar S et al. Pregnancy and virologic response to antiretroviral therapy in South Africa. PLoS One 2013; 6: e23778.
15. Jouo EC, Couvéda MI, Menezes JA et al. Factors associated with viral load suppression in HIV-infected pregnant women in Rio de Janeiro, Brazil. Int J STD AIDS 2012; 23: 44–47.
16. Townsend CL, Cortina-Boja M, Peckham CS, Tooke PA. Antiretroviral therapy and premature delivery in diagnosed HIV-infected women in the United Kingdom and Ireland. AIDS 2007; 21: 1019–1026.
17. Kakkar F, Boucorian I, Lamare V et al. Risk factors for pre-term birth in a Canadian cohort of HIV-positive women: role of ritonavir boosting? J Int AIDS Soc 2015; 18: 19933.
18. Hernández S, Morén C, López M et al. Perinatal outcomes, mitochondrial toxicity and apoptosis in HIV-treated pregnant women and in-utero-exposed newborns. AIDS 2012; 26: 419–428.
19. Wimalasundera RC, Larbalestier N, Smith JH et al. Pre-eclampsia, antiretroviral therapy, and immune reconstitution. Lancet 2003; 360: 1152–1154.
20. Suy A, Martínez E, Coll O et al. Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. AIDS 2006; 20: 59–66.
21. Watts DH, Balazsabramanian R, Maupin RT, Jr et al. Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316. Am J Obstet Gynecol 2004; 190: 506–516.
22. Tuomala RE, Watts DH, Li D et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. J Acquir Immune Defic Syndr 2005; 38: 449–473.
23. European Collaborative S, Patel D, Cortina-Boja M et al. Time to undetectable viral load after highly active antiretroviral therapy initiation among HIV-infected pregnant women. Clin Infect Dis 2007; 44: 1647–1656.
24. Blokh M, Colbers APH, Hidalgo-Tenorio C et al. Raltegravir in HIV-1-Infected Pregnant Women: Pharmacokinetics, Safety, and Efficacy. Clin Infect Dis 2015; 61: 809–816.
25. Mulligan N, Best BM, Capparelli E et al. 2016. Dolutegravir pharmacokinetics in HIV-infected pregnant and postpartum women. Conference on Retroviruses and Opportunistic Infections. Boston, MA, USA. Abstract 438.
26. Alagaratnam J, Chitty S, de Ruiter A et al. Initiating CART in pregnancy: impact on HIV RNA decay. Conference on Retroviruses and Opportunistic Infections. Boston, MA, USA. Abstract 794.