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

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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/mm^3), 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.

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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/mm^3.

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 HAART 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 nelfinavir 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 nelfinavir 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/mm^3, having treatment with nelfinavir 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/mm^3 compared to >350 cells/mm^3. 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).

Table 1. Baseline and treatment characteristics

Maternal region of birth	
Sub-Saharan Africa	136 (60.4%)
Asia	12 (5.3%)
Europe/USA	31 (13.7%)
Latin America	38 (16.7%)
Other	10 (4.4%)
Newly diagnosed HIV during pregnancy	176 (77.5%)
Year of delivery	
1998–2004	118 (52.0%)
2005–2009	90 (39.6%)
≥2010	19 (8.4%)
Maternal age at delivery	29 years (17–43)
Gestational age at delivery	40 weeks (25–46)
<30 weeks	3 (1.3%)
30–36 weeks	19 (8.4%)
37–42 weeks	200 (88.1%)
>42 weeks	5 (2.2%)
Baseline CD4 cell count	346 cells/mm^3 (50–1180)
<200	46 (20.3%)
200–350	66 (29.1%)
>350	104 (45.8%)
Baseline viral load	4.2 log copies/mL (1.8–5.9)
<10,000	83 (36.6%)
10,000–100,000	110 (48.5%)
>100,000	17 (7.5%)
Gestational age at initiation HAART	22 weeks (8–38)
<10 weeks	3 (1.3%)
10–19 weeks	57 (25.1%)
20–29 weeks	141 (62.1%)
≥30 weeks	26 (11.5%)
Antiretroviral regimen	
Lopinavir/ritonavir	56 (24.7%)
Nelfinavir	145 (63.9%)
Nevirapine	28 (12.3%)

Reported as number of pregnancies (proportion of cohort) or as median (range)

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

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

	Mean log_{10} baseline VL	VL <50copies/mL during pregnancy
Maternal region of birth		
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/r	4.1	46 (83.6%)
Nelfinavir	4.1	133 (92.4%)
Nevirapine	4.3	21 (80.8%)
Baseline CD4 cell count(cells/mm^3)		
>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%)

*$P \leq 0.01$
HAART: highly active antiretroviral therapy

weeks' gestation in selected patients, without jeopardising the goal of achieving viral suppression before delivery. In high-income countries the proportion of women who ultimately achieve full viral suppression is generally high, [10–15] but pregnant women and their physicians are generally concerned about the possible teratogenicity and side effects of antiretroviral drugs. Antiretroviral therapy has been associated with adverse pregnancy outcomes such as small-for-gestation-age, preterm delivery [16,17], low birth weight [18], pre-eclampsia [19,20] and impaired glucose tolerance or gestational diabetes [21,22]. Furthermore, hyperemesis gravidarum in the first trimester may pose a risk for insufficient drug exposure and development of resistance. For these reasons, identification of characteristics associated with the time to viral suppression can play a role in the decision making regarding the timing of ART initiation during pregnancy, resulting in a potential shortening of fetal exposure to the antiretroviral drugs. This decision should be weighed against the risk of vertical transmission of HIV and discussed with the patient. Current DHHS guidelines advocate HAART initiation as soon as the HIV diagnosis has been made because early and sustained maternal viral control might lower residual perinatal virus transmission, but also acknowledge that transmission usually occurs late in pregnancy or during delivery [5]. These guidelines do indicate that the decision to start HAART can be delayed in the presence of specific maternal conditions like nausea and vomiting and guided by the CD4 cell count and 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].

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/mm^3. There are conflicting reports in the literature on the association of baseline CD4 T cell count and the rate of viral suppression [8,9,12,13,23]. However, one can generally conclude that lower CD4 T cell counts (<350 cells/mm^3) 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

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/mm^3)				
≤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)

*$P \leq 0.10$; †$P \leq 0.01$

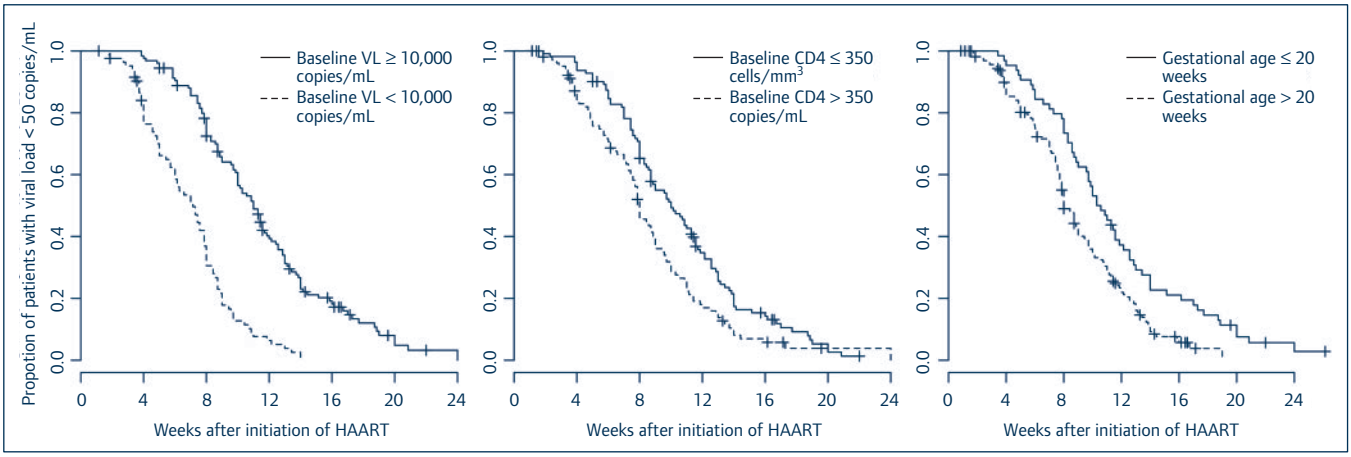

Figure 1. Kaplan–Meier plots for time to undetectable HIV-1 viral load

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

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 Alagaratnam *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.

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