

# When Should HAART be Initiated in Pregnancy to Achieve an Undetectable Viral Load?

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## Abstract

### Background

HAART has dramatically reduced HIV mother to child transmission allowing vaginal delivery if the viral load (VL) is low or undetectable. However, the optimum timing of HAART initiation has not been established. This study aims to provide data for the timing of short course HAART in pregnancy.

### Methods

Retrospective multicentre cohort study including all pregnant women commencing boosted PI, NNRTI or triple NRTI based HAART. Demographics, gestation, drug class, CD4 count, and VL results were collated. VL data were right-censored at delivery date and regimen analyses were based on an intent-to-treat model. Survival curves for reaching a VL <50 were stratified by initial HIV VL. Cox's proportional hazards regression model adjusted for demographics and immuno-virological parameters.

### Results

439 pregnancies met the inclusion criteria of which 378 had sufficient data for analysis. Over 85% of women were of Black African origin and infected with non-B subtype. Median age at conception was 30 years (IQR 26-34). Median pre-treatment CD4 and VL was 330 cells/mm<sup>3</sup> (IQR 195-470) and 8243 copies/ml (IQR 2341-32640). 246 women (65%) commenced PI, 129 (34%) NNRTI, and 3 (1%) NRTI-based HAART, initiated at a median of 23.2 weeks gestation (IQR 20.4-26.3).

VL was <50 in 292 (77.3%) by delivery date (mean 38 weeks), following a median of 58 days of therapy. Pre-treatment VL was associated with both the time taken and the proportion achieving a VL<50 at delivery (p=<0.001) (Figure 1). A baseline VL of <10000, 10000-<50000, 50000-100000 and >100000 resulted in 91%, 73%, 54% and 37% of women <50 at delivery respectively.

In multivariate analysis, the Hazard Ratio (HR) for an NNRTI regimen achieving a VL<50 compared to a PI was 0.7 (0.52-0.94 CI 95%). However if VL >10000, 58% of PI and 66% of NNRTI regimens achieved <50.

If the baseline VL was <10000, gestation at initiation of HAART did not significantly alter the probability of a VL<50 at delivery. With a baseline VL of 10000-50000 the HR for a VL<50 reduced to 0.51 if HAART was initiated after 23.3 weeks (p<0.01) whilst if VL>100000, starting HAART before 20.4 weeks gave a HR of 0.2 (p<0.01) compared with 0.1 if started after 20.4 weeks (p<0.01).

### Conclusions

HAART fully suppresses low VL (<10000) even when initiated late in pregnancy. If VL is greater than 100000 copies HAART should be initiated as early as possible to have any chance of achieving full suppression.

## Introduction

Highly active antiretroviral therapy (HAART) during pregnancy has impacted dramatically on the rate of Mother to Child Transmission (MTCT) of HIV in the resource-rich world. Increasingly vaginal delivery is recognised as a safe option if the HIV viral load (VL) is low or undetectable. The British HIV Association

(BHIVA) guidelines permit vaginal birth if the VL is <50 copies/ml, whereas the USA (DHSS) guidelines

suggest a cut off of <1000 copies/ml. However, in women not receiving HAART at conception, and who do

not need therapy for their own health, the optimum timing for initiating short term antiretroviral therapy (START) has not been determined. Balance must be sought between the likely success of START in

reaching an undetectable VL pre-delivery and the potential toxicities of HAART, including the possibility of pre-term delivery.

The aim of this study is to provide data to aid the clinician in deciding when to commence START if vaginal birth is likely and desired.

**Table 1: Demographics of study subjects**

Variable n=378		Number	Percentage
Age at conception	Mean Range	29.9 years 14.7-49.8 years	
Ethnicity	Black African	268	70.9%
	Black Caribbean	19	5.0%
	Caucasian	24	6.4%
	Asian	6	1.6%
	Other/unknown	61	16.1%
Injection drug use	Yes	5	1.3%
Hepatitis co-infection	Hep B sAg positive	15	4.0%
	Hep C IgG positive	6	1.6%
Previous HAART	Yes	71	18.7%
Previous zidovudine monotherapy	Yes	19	5.0%
HIV clade	C	84	22.2%
	CRF_02_AG	66	17.5%
	B	33	8.7%
	G	18	4.8%
	A	15	4.0%
	Other	59	15.6%
	unknown	103	27.2%

## Method

Data from five centres across London and the South East of the United Kingdom with a significant HIV antenatal workload were collated to create a retrospective cohort of women starting HAART in pregnancy.

All available data from the year 2000 onwards were included if the women: commenced ritonavir-boosted Protease inhibitor (PI)-based HAART, non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART or triple nucleoside reverse transcriptase inhibitor (NRTI) based HAART; were assessed using a Viral load (VL) assay with a lower limit of detection of <50 copies/ml or less; and had sufficient baseline data for analysis

Data were collected for demographics and baseline variables of CD4 count, viral load, previous HIV therapy, known HIV drug resistance, HIV clade, hepatitis B & C status, and choice and timing of HAART.

Additionally, dates and values of subsequent VL on HAART, VL at the time of delivery and date of delivery were retrieved from hospital databases and medical note review.

Viral load data were right-censored at the date of delivery and analyses were based on an intent-to-treat model with regards to drug regime. Data were analysed by both baseline viral load, gestational weeks at

initiation of HAART and type of HAART regimen. Survival curves for reaching a VL<50 were stratified by starting viral load. We assessed the impact of baseline VL using pre-planned clinical strata of <10,000 copies/ml, 10,000-<50,000 copies/ml, 50,000-100,000 copies/ml and >100,000 copies/ml as well as by data-driven quartiles. Primary analyses were based on the VL at delivery, however, the VL at 36 weeks of gestation was also included as this is often when mode-of-delivery decisions are made.

Hazard ratios with respect to the lowest VL strata were calculated and Cox's proportional hazards regression model adjusted for demographics and immuno-virological parameters.

Finally, in order to determine if VL decay differs as women move into the 3<sup>rd</sup> trimester, we paired all women starting boosted PI-based HAART after 28 weeks of gestation, in whom a VL was available from 12-16 days on HAART (cases), with a woman starting boosted PI-based HAART before the 3<sup>rd</sup> trimester (matches). Potential matches with a VL taken after the same duration (days) on HAART were reviewed, and the match with a baseline VL closest to the case were chosen for analysis. The starting VL, value of first VL on HAART, and duration of therapy were used to calculate the HIV viral plasma half life in days.

## Results

439 pregnancies met the inclusion criteria, of which 378 had enough data for analysis. The baseline demographic parameters for these 378 pregnancies are summarised in Table 1. Median pre-treatment VL was 8243 copies/ml (IQR 2341-32640), and median pre-treatment CD4 was 330 cells/mm<sup>3</sup>. Boosted PI-based HAART was initiated in 246 (65%) women, NNRTI-based HAART in 129 (34%) and 3 (1%)

commenced triple NRTI-based therapy.

In total, 292 women (77.2%) achieved a documented VL<50 copies/ml prior to delivery, after a median of 58 days of HAART. This overall success rate is stratified into clinical VL categories in Figure 1.

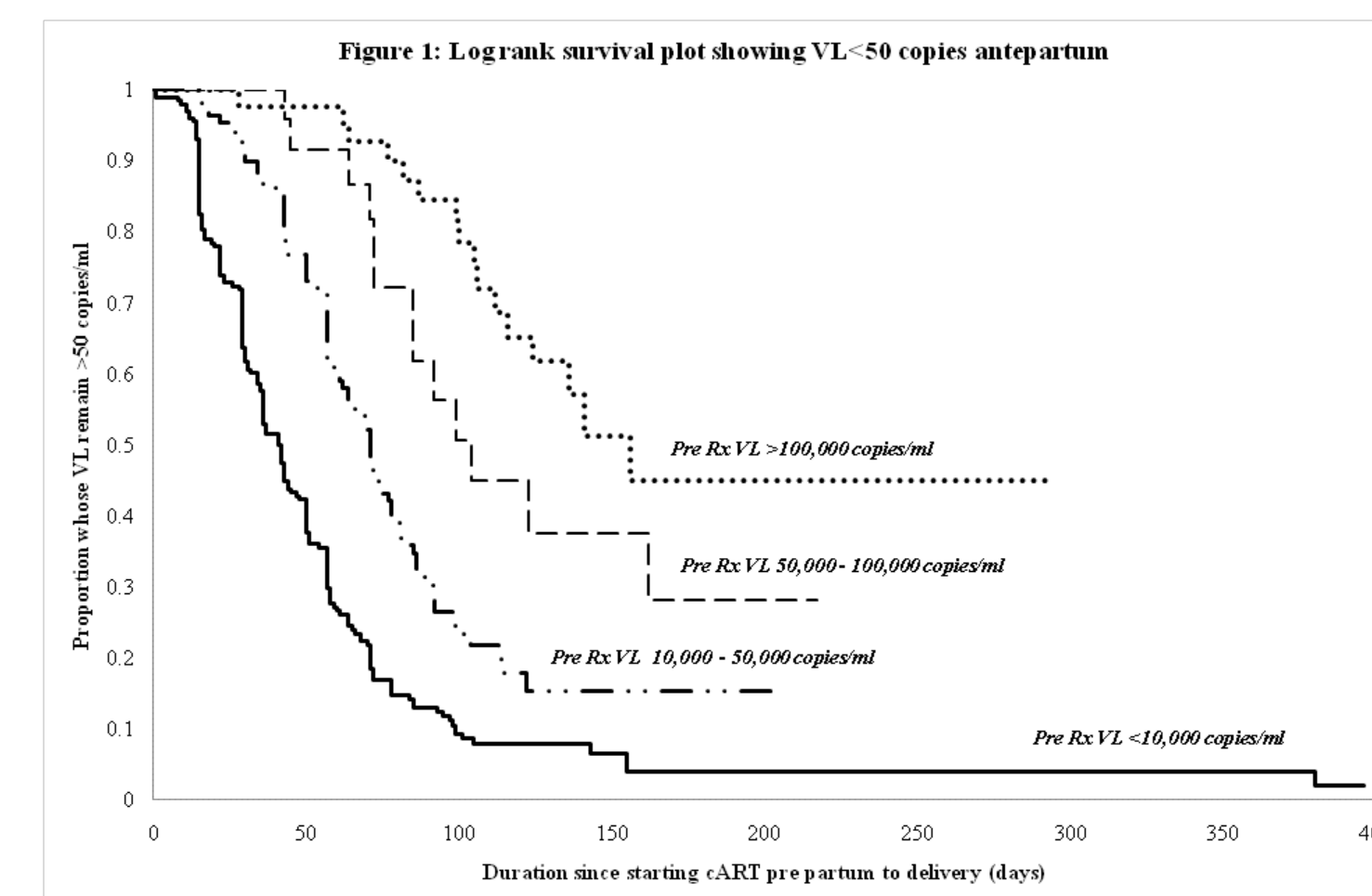


Table 2 (below) demonstrates the proportion of women achieving a VL of <50 and <1000 by delivery, and by 36 weeks of gestation when mode of delivery decisions are usually finalised.

Pre treatment Viral load copies/ml N=378	% & No. <50 copies/ml at delivery	% & No. <50 copies/ml at 36 weeks gestation	Hazard ratio for <50 at delivery	% & No. <1000 copies/ml at delivery	Hazard ratio for <1000 at delivery
<10,000 N=200	91% 182	80% 159	1	98% 195	1
10,000-<50,000 N=111	73% 81	60% 67	0.86	93% 103	0.82
50,000-100,000 N=24	54% 13	50% 12	0.68	88% 21	0.73
>100,000 N=43	37% 16	30% 13	0.31	84% 36	0.53

Multivariable analysis of the natural inter-quartile range (2341-32640 copies/ml) reveals that any VL in the 4<sup>th</sup> quartile ( $\geq 32641$  copies/ml) is associated with the greatest reduction in the likelihood of a VL<50 by delivery. Combining the lower 3 quartiles shows 87% of those with a pre-treatment VL of <32641 copies/ml were <50 copies/ml by delivery, compared to only 46% when the VL is >32641. (HR 0.68).

Hepatitis co-infection, ethnicity, injection drug use, maternal age, previous HAART or zidovudine monotherapy were not significantly associated with reaching a VL<50 by delivery in univariate analysis.

Baseline CD4 count was also associated with success in univariate analyses. CD4 in the lower quartile (<195 cells/mm<sup>3</sup>) resulted in 69% <50 by delivery (HR=1) compared to 85% for those in the upper quartile (>470 cells/mm<sup>3</sup>) (HR=2.5, 1.8-3.49 CI 95% p=<0.01)

Table 3 demonstrates that the hazard ratio for reaching a VL of <50 copies/ml by delivery is not affected by gestation at initiation of HAART if the baseline VL is <10,000 copies/ml. However, the HR rapidly reduces as the viral load increases, so for a VL of over 100,000 copies/ml there is little likelihood of achieving an undetectable VL by delivery if HAART is started after 20 weeks of gestation.

Baseline VL (copies/ml)	Table 3	Weeks gestation at initiation on HAART (quartiles)							
		<20.3		20.3-23.3		23.4-26.3		>26.3	
		%<50	HR	%<50	HR	%<50	HR	%<50	HR
<10000	97	1	93	0.86	94	1.18	82	1.43	
10000-50000	82	0.61*	78	0.51*	64	0.39*	65	0.6*	
50000-100000	72	0.26*	33	0.12*	66	0.53	0	n/a	
>100000	55	0.2*	29	0.1*	33	0.12*	0	n/a	

In the multivariate analysis, boosted PI-based HAART resulted in 80% of women reaching <50 copies/ml (n=246) compared to 72% of those receiving NNRTI therapy (n=129). The hazard ratio for PI versus NNRTI was 0.7 (0.52-0.94 CI 95% p=0.016). However, in those with a baseline VL of >10,000 copies/ml, NNRTI therapy resulted in 66% <50 compared to 58% with PI-based HAART.

Seventeen women starting PI-based HAART after 28 weeks (mean 29.8 weeks) were matched with similar women starting the same therapy before 28 weeks (Mean 20.3 weeks). No statistically significant difference in the HIV viral half life was observed between the groups (Post 28 weeks: 3.17 days vs pre-28 weeks 3.24 days p=0.89 Wilcoxon signed rank test).

## Conclusions

These data indicate the key determinants of achieving a viral load low enough to permit safe vaginal delivery according to clinical guidelines are baseline viral load, gestational age at initiation of HAART and the class of therapy. If the baseline VL is <10,000 copies/ml then there is no significant advantage to starting START before 26 weeks. However, patients with a baseline VL >100,000 copies/ml should commence START as early in pregnancy as possible, rather than the widely practiced recommendation of delaying until after 20 weeks gestation as the median time to <50 copies/ml was 156 days. In addition, our data suggest that if patients with a VL>10,000 copies/ml delay START beyond 20.4 weeks, the likelihood of achieving a vaginal birth is compromised. Final decisions on mode of delivery often depend on the VL at 36 weeks gestation and this needs to be taken into account when starting HAART based on these data. Furthermore, when considering the definition of a high viral load in the context of aiming for vaginal birth after START, the threshold of 32000 copies/ml should be considered the lower limit of this "high viral load" stratum. Protease inhibitor-based HAART performed well overall, but when appropriate, NNRTI-based therapy may be preferred if the VL is >10,000 copies/ml.

The impact of viral load on delivery management is likely to be influenced by local guidelines and policies, and the timing of START will have less impact on the probability of successful vaginal delivery if the threshold for vaginal birth is <1000 copies per ml compared to <50 copies/ml.

## Key messages:

- Women with a VL >10,000 copies/ml should commence START by 20.4 weeks
- Women with a VL >100,000 copies/ml should commence START without delay
- If the VL is <10,000 copies/ml, START may be deferred to 26 weeks
- If the VL is >10,000 copies/ml NNRTI-based HAART, where appropriate, may be more successful