



Time to undetectable viral load after HAART initiation in HIV-infected pregnant women in Europe

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Introduction

- Plasma HIV RNA viral is the pre-eminent risk factor for mother-to-child transmission (MTCT) of HIV infection.
- Highly active antiretroviral therapy (HAART) in resource-rich settings has substantially reduced MTCT rates through successful suppression of maternal HIV-RNA viral load.
- A substantial minority of HIV-infected pregnant women in these settings are diagnosed antenatally and start antiretroviral drugs to delay disease progression and/or to prevent MTCT for the first time in pregnancy
- In many Western European countries, these women are increasingly likely to have acquired HIV heterosexually and to be from countries with generalised epidemics, mostly in sub-Saharan Africa.
- There have been no clinical trials to address the question of which HAART regimens are more effective for optimal viral response in HIV-infected women starting treatment for the first time in pregnancy.

Methods

- The European Collaborative Study (ECS) is an ongoing cohort study covering 10 European countries, in which HIV-1 infected pregnant women are enrolled and their children followed from birth with a standard clinical and laboratory protocol.
- Two HAART regimens were compared – PI-based vs. NNRTI-based (all Nevirapine [NVP]).
- The analysis was restricted to women identified for the first time in pregnancy or who had documented non-receipt of prior therapy.
- The primary endpoint was the time taken from treatment initiation to achieving undetectable HIV RNA viral load, through to the time of delivery.
- Classification of undetectable HIV RNA viral suppression was based on the lower limit of quantification of the assay. Seventy-four percent (561/759) of the viral load measurements were measured with ultra-sensitive assays (quantification limit ≤ 50 copies/ml).
- A parametric survival model using a Weibull distribution, incorporating left, right and interval censoring was used.
- Race, type of HAART regimen, time of initiation, baseline HIV RNA viral load and CD4 cell count, maternal age, history of injecting drug use and year of delivery were considered for inclusion in the model
- Scores for the propensity of being treated with NVP-based HAART were included in all adjusted models after stratification into quintiles
- Stratified survival curves were obtained with Turnbull's generalisation of the Kaplan-Meier estimate.

Results (1)

- Two-hundred and forty treatment-naïve HIV-infected women met our inclusion criteria:
 - 156 (65%) initiated PI-based HAART (80% nelfinavir)
 - 84(35%) initiated NVP-based HAART.
- Most women were black (59%) (90% born in Africa) and were identified with HIV during pregnancy (64%).
- Figure 1 shows the distribution of baseline HIV RNA viral load (red bars) and timing of treatment-initiation (blue bars).
- There were no differences between treatment groups regarding time of HAART initiation ($p=0.6$) or baseline viral load ($p=0.6$)
- Median gestational age at delivery was 38 weeks (range 23-42) and 73% of women had achieved viral suppression by this time
- The proportion of women achieving viral suppression by delivery did not differ by treatment group ($p=0.49$)
- However, by 15 weeks 93.4% of the NVP-based HAART group (red line) had achieved viral suppression compared to only 59.4% of the PI-based group (black line) (Figure 2)

Figure 1: Bivariate scatterplot and histogram of HIV RNA viral load and time of initiation

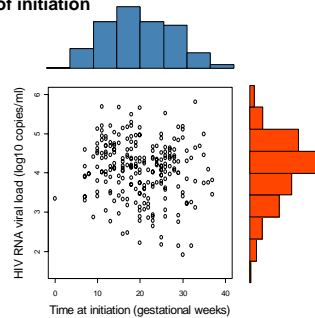


Figure 2: Time to achieving viral suppression, by HAART type and baseline viral load

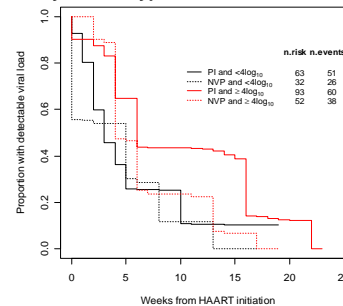


Table: Factors associated with time to achieving undetectable HIV RNA viral load after initiation of HAART in pregnancy

Variable	N	Adjusted Hazard Ratio (95%CI)
Region of birth		
Non-African	96	1.00
Eastern Africa	42	1.61 (0.84-3.11)
Central Africa	33	1.24 (0.70-2.21)
North /Southern Africa	7	1.25 (0.38-4.07)
Western Africa	39	1.90 (1.16-3.12)
HAART regimen		
PI-based	141	1.00
NVP-based	76	1.54 (1.05-2.26)
Baseline HIV RNA		
$\geq 4.40 \log_{10}$ copies/ml	72	1.00
$3.81-4.39 \log_{10}$	73	1.70 (1.08-2.68)
$<3.81 \log_{10}$	72	2.76 (1.68-4.52)

* adjusting for baseline CD4, trimester of HAART initiation and treatment propensity score

Results (2)

- Using an alternative representation for the Weibull model estimates (the acceleration factor), the median time to viral suppression for a woman receiving PI-based HAART was 1.38 (95% CI 1.04-1.83) times that of a woman receiving NVP-based HAART
- Viral response in women eligible for NVP-containing HAART according to current prescribing advice (i.e. with baseline CD4 counts <250 cells/mm³) was explored: by 8.5 weeks an estimated 82.4% (95% CI 50.7-93.7) of women on NVP-based HAART will have reached viral suppression versus 50.4% (95% CI 34.0-62.8) on PI-based HAART.
- The 65 (27%) of women delivering with detectable viral load were similar to those achieving undetectable levels with respect to race and type/timing HAART, but had lower CD4 counts and higher viral load at initiation

Conclusions

- NVP-based HAART versus PI (mainly nelfinavir)-based HAART, Western African origin and lower baseline viral load were associated with shorter time to achieving viral suppression
- Our findings suggest that NVP should be used in preference over PI in HAART for treatment-naïve women with CD4 cell counts <250 mm³
- Accumulating data on NFV pharmacokinetics suggest that drug levels in the third trimester may frequently be sub-therapeutic, which could explain the differences observed
- The finding that West African women responded more favourably to HAART may be explained by differences in underlying maternal sub-type, or by host biological and genetic differences

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