Time to Undetectable Viral Load after Highly Active Antiretroviral Therapy Initiation among HIV-Infected Pregnant Women

European Collaborative Study[a]

Background. There have been no clinical trials in resource-rich regions that have addressed the question of which highly active antiretroviral therapy (HAART) regimens are more effective for optimal viral response in antiretroviral-naive, human immunodeficiency virus (HIV)–infected pregnant women.

Methods. Data on 240 HIV-1–infected women starting HAART during pregnancy who were enrolled in the prospective European Collaborative Study from 1997 through 2004 were analyzed. An interval-censored survival model was used to assess whether factors, including type of HAART regimen, race, region of birth, and baseline immunological and virological status, were associated with the duration of time necessary to suppress viral load below undetectable levels before delivery of a newborn.

Results. Protease inhibitor–based HAART was initiated in 156 women (65%), 125 (80%) of whom received nelfinavir, and a nevirapine-based regimen was initiated in the remaining 84 women (35%). Undetectable viral loads were achieved by 73% of the women by the time of delivery. Relative hazards of time to achieving viral suppression were 1.54 (95% confidence interval, 1.05–2.26) for nevirapine-based HAART versus PI-based regimens and 1.90 (95% confidence interval, 1.16–3.12) for western African versus non-African women. The median duration of time from HAART initiation to achievement of an undetectable viral load was estimated to be 1.4 times greater in women receiving PI-based HAART, compared with women receiving nevirapine-based HAART. Baseline HIV RNA load was also a significant predictor of the rapidity of achieving viral suppression by delivery, but baseline immune status was not.

Conclusions. In this study, nevirapine-based HAART (compared with PI [mainly nelfinavir]-based HAART), western African origin, and lower baseline viral load were associated with shorter time to achieving viral suppression.

Plasma HIV RNA load is the preeminent risk factor for mother-to-child transmission (MTCT) of HIV infection [1, 2]. In resource-rich regions, HAART (typically composed of 3 antiretroviral agents from 2 drug classes) has substantially reduced MTCT rates through successful suppression of HIV RNA load [2, 3]. Although an increasing proportion of HIV-infected pregnant women in these regions are identified and treated before pregnancy, a substantial minority receive a diagnosis antenatally and start antiretroviral therapy (ART) for the first time during pregnancy to delay disease progression and/or to prevent MTCT [2]. In many Western European countries, these women are increasingly likely to have acquired HIV infection through heterosexual contact and to be from countries with generalized epidemics (mainly countries in sub-Saharan Africa) [4]. No clinical trials in resource-rich regions have addressed the question of which regimens are more effective for optimal viral response in ART-naive, HIV-infected pregnant women. Using data from a multicenter prospective cohort, this study was conducted to determine whether choice of initial HAART regimen for HIV-infected pregnant women is associated with the duration of time that is necessary to achieve undetectable viral load by delivery.

METHODS

The European Collaborative Study is an ongoing observational cohort study that was established in 1985,

Received 13 December 2006; accepted 18 February 2007; electronically published 2 May 2007.

[a] This article was prepared by Deven Patel, Mario Cortina-Borja, Claire Thorne, and Marie-Louise Newell (Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, London, United Kingdom). Members of the study group are listed at the end of the text.

Reprints or correspondence: Deven Patel, Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, 30 Guilford St., London WC1N 1EH, United Kingdom (d.patel@ich.ucl.ac.uk).

Clinical Infectious Diseases 2007; 44:1647–56

1058-4838/2007/4412-0019$15.00
DOI: 10.1086/518284

in which HIV-1–infected pregnant women are enrolled and their infants are prospectively observed according to standard protocols [2]. Informed consent was obtained, and local ethics committee approval was granted. Information collected included timing and type of ART, maternal CD4 cell count, HIV RNA load, and sociodemographic characteristics.

Laboratory tests were performed locally in laboratories located in tertiary care centers and university hospitals. For HIV RNA load quantification, Amplicor HIV-1 Monitor Test, versions 1.5 and ultrasensitive (Roche Diagnostic Systems); Quantiplex HIV-1 RNA (b-DNA) assay, version 3.0 (Chiron Diagnostics); or nucleic acid sequence–based amplification/nuclisens (Organon Teknika) were used. Classification of undetectable viral load (viral suppression) was based on the lower limit of quantification of the assay. Of the 759 antenatal HIV RNA load measurements available, 561 (74%) were measured with ultrasensitive assays (quantification limit, $\leqslant$50 copies/mL). HAART was defined as a regimen of $\geqslant$3 antiretroviral drugs, including a nucleoside reverse-transcriptase inhibitor backbone and nevirapine (NVP)—a nonnucleoside reverse-transcriptase inhibitor (NNRTI)—or a protease inhibitor (PI).

We restricted the analysis to HIV-infected women who were ART-naive at conception; 153 women were first identified as having HIV-infection during pregnancy, and 87 women were known to have HIV infection before pregnancy (46 of these women were known not to have previously received prophylaxis for prevention of MTCT, either because of no prior pregnancies or documented nonreceipt of ART during previous pregnancies that occurred while enrolled in European Collaborative Studies, and 41 were not receiving ART at conception and had no documented prior ART use). Other eligibility criteria were a detectable HIV RNA load measurement within 6 weeks before initiation in the study and at least 1 subsequent measurement.

Statistical methods. To determine the association of maternal factors and initial HAART regimen with viral suppression, we examined the duration of time from treatment initiation to the achievement of undetectable HIV RNA load until the time of delivery. For women not achieving an undetectable HIV RNA load, the time was right-censored at the last measurement at or before delivery. For those achieving an undetectable HIV RNA load, the end point was known only to have occurred between initiation and the first measurement (left-censoring) or between any 2 measurements following initiation (interval-censoring).

A parametric survival model based on the Weibull distribution, incorporating left-, right-, and interval-censoring, was used [5]. Estimates from Weibull models can be represented either as relative hazards (RHs) or as the acceleration factor between 2 levels of a covariate. Because most women reached viral suppression, the RH reflects the rapidity with (rate at) which viral suppression occurred, rather than solely the probability of the event occurring; larger RHs are associated with more rapid attainment of viral suppression.

After adjusting for baseline viral load, race, type of HAART, baseline CD4 cell count, maternal age, trimester at initiation of HAART, timing of HIV diagnosis, history of injection drug use, and year of delivery were considered in the Weibull model. A stepwise model selection procedure was used to choose salient prognostic variables, with a variable retained if its inclusion resulted in a significantly improved log likelihood. The propensity of being treated with NVP-based HAART was estimated by a logistic regression model that included the covariates mentioned above; the propensity score was then included in all adjusted models after stratification into quintiles [6].

Stratified survival curves and associated survival probabilities were obtained with Turnbull's generalization of the Kaplan Meier estimate, allowing for interval-censored data [5, 7], with 95% CIs calculated using the adjusted bootstrap percentile method with 1000 replications. Turnbull estimates of the proportion of women achieving undetectable viral loads, by treatment group and race, were calculated separately for women with baseline viral loads $\geqslant$4 $\log_{10}$ copies/mL or <4 $\log_{10}$ copies/mL. Skewed continuous variables were compared using the Mann-Whitney *U* test, and categorical variables were compared using the χ^2 test. Analyses were performed using Stata software, version 9.1 (StataCorp), and R, version 2.2.0 (R Development Core Team).

RESULTS

Of 1346 women receiving antenatal HAART who delivered a newborn from 1997 through 2004, 240 pregnant, HIV-infected women met our inclusion criteria. The characteristics of these women are shown in table 1. Most women (59%) were black, 90% of whom were born in sub-Saharan Africa (table 1). PI-based HAART was initiated in 156 women (65%), with the remaining 84 women (35%) receiving an NNRTI-based regimen (all including NVP). Most regimens had a zidovudine and lamivudine combination nucleoside reverse-transcriptase inhibitor backbone (table 2). One hundred twenty-five PI-based regimens (80%) included nelfinavir (NFV), with the remaining containing a lopinavir and ritonavir combination (4 regimens), ritonavir (13 regimens), indinavir (8 regimens), or saquinavir (6 regimens). The proportion of women receiving NVP-based HAART increased from 16 (25%) of 64 women during 1997–2000 to 37 (35%) of 105 women and 31 (44%) of 71 women during 2001–2002 and 2003–2004, respectively ($P = .02$). There were no differences between black and non-black women with respect to type of HAART received (48 [34%] of 141 black women vs. 34 [35%] of 96 non-black women received an NVP-based HAART regimen; $P = .94$), the distribution of baseline median HIV RNA load (4.13 $\log_{10}$ copies/mL [interquartile range (IQR), 3.54–4.60] vs. 4.20 $\log_{10}$ copies/mL [IQR, 3.76–

Table 1. Characteristics of 240 treatment-naive, HIV-infected pregnant women at initiation of HAART and the number of women acheiving the end point of an undetectable HIV RNA load by delivery.

Characteristic	All women	Women acheiving an undetectable viral load
Race		
Non-black	96 (41)	63 (66)
Black	141 (59)	110 (78)
Unknown	3	2
Region of birth[a]		
Europe	75 (32)	46 (61)
The Americas	23 (10)	18 (78)
Asia	8 (3)	7 (88)
Northern Africa	6 (2)	5 (83)
Eastern Africa	44 (19)	33 (75)
Southern Africa	2 (1)	1 (50)
Central Africa	40 (17)	31 (78)
Western Africa	39 (16)	32 (82)
Unknown	3	2
Age at delivery		
Median years (IQR)	29 (25–33)	
15–19 years	10 (4)	6 (60)
20–29 years	113 (48)	86 (76)
30–39 years	107 (45)	74 (69)
⩾40 years	8 (3)	7 (88)
Unknown	2	2
History of IDU		
Non-IDU	215 (91)	159 (74)
IDU	21 (9)	12 (57)
Unknown	4	4
Timing of diagnosis of HIV infection		
Antenatal	153 (64)	113 (74)
Prepregnancy	87 (36)	62 (71)
Stage of pregnancy at initiation of HAART		
Median weeks of gestation (IQR)	23 (18–27)	
First trimester	14 (6)	12 (86)
Second trimester	168 (70)	129 (77)
Third trimester	58 (24)	34 (59)
HIV RNA viral load, $\log_{10}$ copies/mL		
Median (IQR)	4.16 (3.62–4.58)	
⩾5	20 (8)	10 (50)
4–4.99	125 (52)	88 (70)
3–3.99	74 (31)	58 (78)
<3	21 (9)	19 (90)
CD4 cell count		
Median cells/μL (IQR)	328 (210–480)	
<200 cells/μL	48 (22)	29 (60)
200–499 cells/μL	124 (56)	95 (77)
⩾500 cells/μL	48 (22)	38 (79)
Unknown	20	13

NOTE. Data are no. (%) of patients, unless otherwise indicated. IDU, injection drug user.

[a] Regions of Africa were defined according to the United Nations groupings.

Table 2. Characteristics of study patients by HAART category.

Characteristic	PI-based HAART (n = 156)	NVP-based HAART (n = 84)	P[a]
Received NRTI backbone			
No. of patients receiving zidovudine and lamivudine (%)	139 (89)	72 (86)	
No. of patients receiving another dual combination (%)	17 (11)	12 (14)	.58
Median time of initiation of HAART, weeks of gestation (IQR)	23 (18–27)	21.5 (16–28)	.57
Median baseline HIV RNA load, $\log_{10}$ copies/mL (IQR)	4.18 (3.60–4.58)	4.08 (3.71–4.54)	.58
Median baseline CD4 cell count, cells/mm^3 (IQR)	305 (190–452)	355 (277–506)	.02
Median no. of viral load measurements (IQR)	3 (2–3)	3 (2–3)	.77
Median interval between successive HIV RNA load tests, weeks (IQR)	7.5 (4–10)	6 (4–10)	.07
Median duration of gestation at delivery, weeks (range)	38 (25–42)	37 (23–41)	<.01

NOTE. NRTI, nucleoside reverse-trascriptase inhibitor; NVP, nevirapine; PI, protease inhibitor.

[a] P values were calculated with the χ^2 test or Mann-Whitney U test, as appropriate.

4.56]; $P = .18$), and baseline median CD4 cell count (313 cells/mm^3 [IQR, 210–449] vs. 370 cells/mm^3 [IQR, 231–528]; $P = .12$). However, black women tended to start treatment later than non-black women (median of 24 weeks of gestation [IQR, 20–28] vs. median of 20.5 weeks of gestation [IQR, 15–27]; $P \leqslant .01$).

The median number of virological measurements per woman was 3 (range, 2–7 measurements), with a similar interval between successive tests for the 2 treatment groups (table 2). Figure 1 shows the distribution of HIV RNA load measurements at initiation, by weeks of gestation, together with baseline median viral load and baseline median CD4 cell count. Thirty-nine (24%) of 165 women starting HAART during the first or second trimester had a CD4 cell count <200 cells/mm^3, compared with 9 (16%) of 55 women starting HAART during the third trimester ($P = .35$).

Although time of HAART initiation and baseline HIV RNA loads were similar between treatment groups, the PI-based group had significantly lower baseline CD4 cell counts (table 2). Among the NVP group, 61 women (73%) had a CD4 cell count >250 cells/mm^3 at initiation; of these women, 57 (93%) delivered a newborn before February 2004 (when NVP prescribing information changed [8]).

The median gestational age at delivery was 38 weeks (range, 23–42 weeks), and 175 (73%) of 240 women had undetectable viral loads by this time; table 1 shows the number of women reaching this outcome, by maternal characteristics. The proportion of women achieving an undetectable viral load did not differ between treatment groups (111 [71%] of 156 women receiving PI-based regimens and 64 [76%] of 84 women receiving NVP-based HAART regimens; $P = .49$). Figure 2 displays estimated proportions of women achieving undetectable viral loads—beginning at the time of initiation of therapy—stratified by HAART category and baseline viral load. For women with a baseline HIV RNA load $\geqslant 4$ $\log_{10}$ copies/mL, 35.2% (95% CI, 20%–51.1%) of the PI group and 53.0% (95% CI, 20%–94%) of the NVP group achieved an undetectable HIV RNA load by 5 weeks, 56.4% (95% CI, 45%–71%) of the PI group and 76.4% (95% CI, 56%–94%) of the NVP group achieved an undetectable viral load by 10 weeks, and 59.4% (95% CI, 43%–755) in the PI group and 93.4% (95% CI, 66%–99.0%) of the NVP group achieved an undetectable viral load by 15 weeks, indicating a differing response by treatment category (figure 2*B*). Stratifying by race and baseline viral load, 58.7% (95% CI, 44%–75%) of non-black women and 66.3% (95% CI, 53%–79%) of black women with baseline HIV RNA loads $\geqslant 4$ $\log_{10}$ copies/mL achieved an undetectable viral load at 10 weeks, and 64.1% (95% CI, 38%–85%) of non-black women and 79.3% (95% CI, 65%–93%) of black women achieved an undetectable viral load at 15 weeks, suggesting possible race-associated differences.

RHs from univariable survival analyses adjusting for baseline viral load confirmed the race differences described above (RH for black women vs. non-black women, 1.40; 95% CI, 1.00–1.97) and were explored in further models through examination of region of birth. Table 3 shows the RHs for time from initiation of HAART to achievement of an undetectable viral load for the full-adjusted model. Twenty-three women with information missing on race or CD4 cell count were excluded from the model; these women had characteristics that were similar to those of women who were included (data not shown). Including 2-way interaction terms between any of the variables in the final model did not significantly improve the fit. The rate of women achieving an undetectable viral load in the NVP group was estimated to be almost 1.5 times than that in the PI group (table 3). Baseline viral load and being of Western African origin were also significant factors affecting the rate of achieving undetectable viral load by delivery. A sensitivity analysis including women receiving a PI-based regimen including NFV only revealed similar RHs among women receiving NVP-

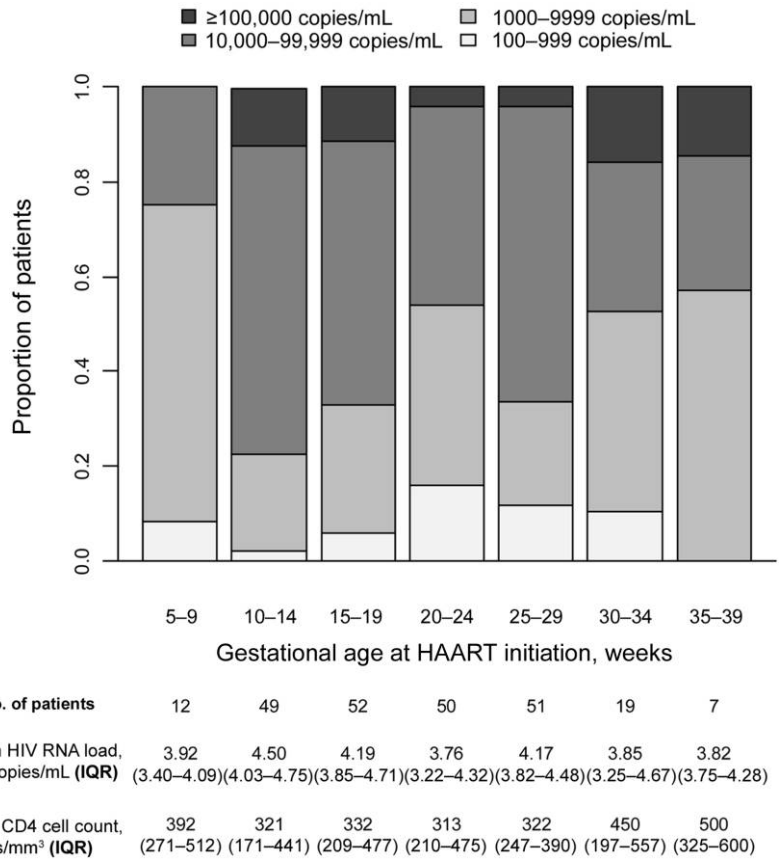

Figure 1. Distribution of baseline HIV RNA load measurements, median baseline HIV RNA load, and median CD4 cell count, by timing of initiation of HAART during pregnancy. IQR, interquartile range.

based HAART (RH, 1.56; 95% CI, 1.05–2.32), as did including only women initiating therapy in the first and second trimesters (RH, 1.82; 95% CI, 1.18–2.84).

Using the acceleration factor format, the median time to achievement of an undetectable viral load for a woman receiving PI-containing HAART was estimated to be 1.38 times (95% CI, 1.04–1.83 times) that for a woman receiving NVP-containing HAART. The predicted median time to achievement of an undetectable viral load for non-African women with baseline CD4 cell counts of 200–499 cells/mm^3 and HIV RNA viral loads of 3.81–4.39 $\log_{10}$ copies/mL who initiated treatment during the second trimester was 7.1 weeks (95% CI, 3.60–10.53 weeks) for the NVP group and 9.8 weeks (95% CI, 5.38–14.16 weeks) for the PI group; for Western African women with similar characteristics, these times were 4.4 weeks (95% CI, 2.1–6.7 weeks) and 6 weeks (95% CI, 3.2–8.9 weeks), respectively.

Viral response in 70 women eligible for NVP, according to current prescribing advice [8] (i.e., with baseline CD4 cell counts <250 cells/mm^3) was explored; the median baseline viral load was 4.35 $\log_{10}$ copies/mL (IQR, 4.05–4.69), the median duration of gestation at initiation of HAART was 22 weeks, and 16 women (24%) received NVP. The percentage of women reaching an undetectable viral load at 5 weeks was 34.8% (95% CI, 20.4%–46.7%) for those receiving PI-based regimens and 52.9% (95% CI, 22.1%–71.6%) for those receiving NVP regimens; the percentages increased to 50.4% (95% CI, 34.0%–62.8%) and 82.4% (95% CI, 50.7%–93.7%), respectively, at 8.5 weeks. In adjusted analyses, these treatment group differences were not statistically significant (RH for NVP-containing HAART, 1.89; 95% CI, 0.87–4.12).

The 65 women (27%) who delivered with a detectable viral load were similar to those achieving undetectable viral loads with regard to regard to race and type and timing of HAART (data not shown). However, more of the women with detectable viral loads at delivery were severely immunosuppressed (defined as a CD4 cell count <200 cells/mm^3; 19 [33%] of 58 women with a detectable viral load vs. 29 [18%] of 162 women with an undetectable viral load; $P = .03$), and more of these women had baseline viral loads >5 $\log_{10}$ copies/mL (10 [15%] of 65 women with a detectable viral load vs. 10 [6%] of 175 with an undetectable viral load; $P = .03$); the median viral load at delivery for women with a detectable viral load was 2.48 $\log_{10}$ copies/mL (IQR, 2.26–3.11), and only 20 of these women (31%) had a viral load >1000 copies/mL.

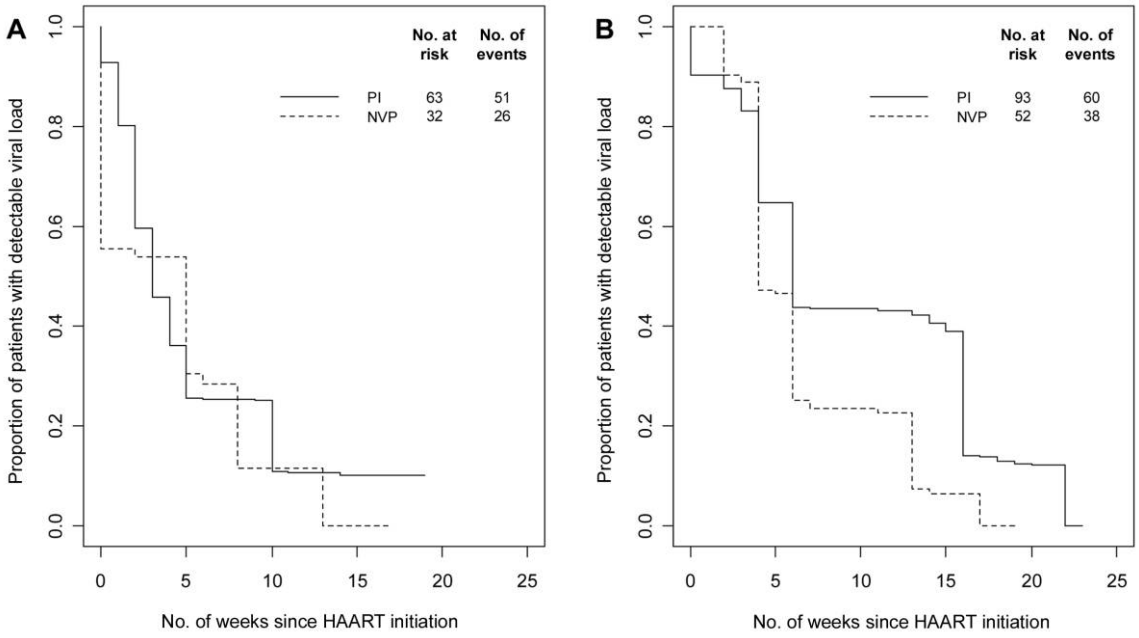

Figure 2. Survival curves for the time from initiation of HAART to achievement of an undetectable viral load, by initial treatment category: *(A),* women with a baseline viral load <4 $\log_{10}$ copies/mL, and *(B),* women with a baseline viral load ⩾4 $\log_{10}$ copies/mL. NVP, nevirapine; PI, protease inhibitor.

DISCUSSION

Suppressing plasma HIV RNA load below detectable limits is one of the goals for effective treatment of HIV-infected women during pregnancy and for prevention of MTCT [9, 10]. In our study, most pregnant women (73%) initiating HAART antenatally delivered with an undetectable viral load, and the remaining women delivered with a detectable but generally very low viral load. Less than one-quarter of the women had immunological indications for treatment [9, 10]. Most women were prescribed PI-containing HAART, with a highly homogenous approach, with 76% of these women receiving a combination of NFV, zidovudine, and lamiduvine. NFV has the most extensive data on pharmacokinetics and safety during pregnancy among all of the PIs and is currently preferred for use in antenatal HAART, especially in patients in whom there are no maternal indications for treatment [11]. One-third of women received NVP-containing HAART, with increasing use over time; this trend is unlikely to continue because of updated NVP prescribing advice [8]. The predominance of zidovudine- and lamiduvine-containing regimens in our study reflects current recommendations for this nucleoside reverse-transcriptase inhibitor combination to be the backbone treatment for pregnant women [10, 11] and is consistent with prescribing patterns in Europe for nonpregnant individuals [12].

To our knowledge, this study is the first to suggest that choice of initial HAART regimen has implications for timely achievement of undetectable viral load during pregnancy. Adjusting for baseline prognostic factors, the hazard of achieving an undetectable viral load was greater for women receiving NVP-containing HAART, with women in the PI group requiring an average of 1.4 times longer to achieve viral suppression. Findings conflict with regard to the relative effectiveness of PI-containing versus NNRTI-containing HAART regimens in nonpregnant adults. A recent direct meta-analysis of "head-to-head" randomized trials suggested that NNRTI-based HAART (predominated by efavirenz) was 60% more effective for virological suppression than was PI-based HAART (50% boosted PIs), although no difference in clinical outcomes was reported [13]. However, an indirect meta-analysis yielded contradictory results (i.e., NNRTI-based HAART was less effective than PI-based HAART for virological suppression [13]); these discordant results may be a result of differences in population, study design, or type of nucleoside reverse-transcriptase inhibitor backbone, highlighting the difficulties of translating trial findings into clinical recommendations and the importance of direct comparisons [13].

Therapeutic decision-making during pregnancy is complicated by unique factors, including the need to consider prevention of MTCT, safety and toxicity, and physiological changes, which may affect pharmacokinetics [8, 14]. Accumulating data on NFV pharmacokinetics suggest that drug levels during the third trimester may frequently be subtherapeutic [15–17]. This may explain why we found a superior virologic response with NVP-containing versus PI-containing (mostly

Table 3. Factors associated with time to achieving undetectable HIV RNA load after initiation of HAART during pregnancy among 217 study women.

Variable	No. of patients	Univariate analysis		Multivariable analysis	
		RH (95% CI)	*P*	RH (95% CI)	*P*
Region of birth					
Non-African	96	1.00		1.00	
Eastern Africa	42	1.15 (0.73–1.83)	.55	1.61 (0.84–3.11)	.15
Central Africa	33	1.58 (0.96–2.60)	.07	1.24 (0.70–2.21)	.46
Northern or southern Africa	7	0.82 (0.31–2.13)	.68	1.25 (0.38–4.07)	.72
Western Africa	39	1.58 (1.0–2.50)	.05	1.90 (1.16–3.12)	.01
HAART regimen					
PI-based	141	1.00		1.00	
NVP-based	76	1.62 (1.14–2.31)	<.01	1.54 (1.05–2.26)	.02
Baseline HIV RNA load, $\log_{10}$ copies/mL[a]					
⩾4.40	72	1.00		1.00	
3.81–4.39	73	1.75 (1.15–2.66)	<.01	1.70 (1.08–2.68)	.02
<3.81	72	2.54 (1.69–3.80)	<.001	2.76 (1.68–4.52)	<.001
Baseline CD4 cell count, cells/mm^3					
<200	47	1.00		1.00	
200–499	123	1.39 (0.89–2.15)	.14	1.25 (0.69–2.24)	.46
⩾500	47	1.42 (0.83–2.43)	.20	1.40 (0.71–2.76)	.33

NOTE. Univariate and multivariable estimates were adjusted for baseline viral load. Multivariable estimates were adjusted for all covariates listed in the table, with the addition of the treatment propensity score and trimester of initiation during pregnancy. NVP, nevirapine; PI, protease inhibitor; RH, relative hazard.

[a] Baseline HIV RNA load was categorized according to their tertiles.

NFV) HAART—in contrast to the Combine Study, in which an equivalent response was reported among ART-naive nonpregnant individuals randomized to a zidovudine and lamiduvine backbone with NVP or NFV [18].

African and non-African pregnant women had similar baseline immune and virological status—in contrast to previous findings based on the whole cohort [4]—probably reflecting eligibility criteria for this analysis. The median baseline CD4 cell count among black women in our study was marginally lower than those reported in African prevention of MTCT trials (335–363 cells/mm^3 among ART-naive pregnant women) [19, 20]. Univariably, black women in our study responded to HAART more favorably than did non-black women; further investigation, stratifying by region of birth, revealed that this effect was limited to women of western African origin. Limited information is available regarding response to HAART among African populations, and even less is available for pregnant African women. In the Drug Resource Enhancement against AIDS and Malnutrition pilot in Mozambique, 26 (65%) of 40 pregnant women starting HAART, with a median baseline HIV RNA load of 4.2 $\log_{10}$ copies/mL, achieved viral suppression (viral load, <400 copies/mL) by delivery after an average of 12 weeks [21]; these data are consistent with our results. An impact of race on disease progression or response to HAART has been suggested by several studies of pregnant and nonpregnant individuals, which generally revealed poorer virological responses among black and/or African groups; these findings were suggested to be a result of coinfections or adherence [22–24]. We did not have adherence data available, but it seems unlikely that differing adherence levels could explain our findings, because the better virological response to HAART was limited to the western African group only. Little is known about the impact of different HIV subtypes on the effectiveness of HAART [25, 26]. Differences in underlying maternal subtype may possibly explain our findings, although host biological and genetic differences may also play a part [27].

We found no significant difference in time to attaining undetectable viral load between severely immunosuppressed women and those with greater immunocompetence. This is consistent with other studies that have found a significant association between baseline viral load and subsequent virological response after HAART initiation but not an association between baseline CD4 cell count and virological response [28, 29]. Few studies have examined the latter association among ART-naive pregnant women, in whom treatment effect and the relationship between baseline CD4 cell count and viral load may differ from that in nonpregnant adults [30, 31].

Our data are limited by their observational nature [32]; however, we allowed for interval-censoring [5], adjusted for timing of initiation of therapy during pregnancy, and minimized confounding by ART experience through our selection criteria. Additionally, we used a treatment propensity score to reduce

bias in the comparison of a treatment group to a nonrandomized control group [6]. We could not account for additional factors potentially influencing response to HAART, such as adherence, biological differences in drug activity arising from variations in body weight and pharmacokinetics between groups, HIV subtypes, and other genetic factors [14, 33, 34]. A disadvantage of cohort data is their limited contemporary relevance when therapeutic practices have changed over time. A case-in-point is the NVP prescribing changes after the association of the drug with hepatotoxicity in women with moderate to high CD4 cell counts [8]. If clinicians comply with prescribing advice, one would expect the future group of ART-naive women starting NVP-containing HAART to have lower CD4 cell counts than the women in our study. However, our subanalysis of women with CD4 cell counts <250 cells/mm^3 indicates that our results may be generalizable but had limited statistical power.

Although guidelines state that pregnancy should not preclude use of optimal ART regimens [11], in reality, there are limited options. For nonpregnant adults, NNRTI-containing HAART is recommended as a first-line regimen, preserving PI-containing HAART for later treatment, with efavirenz as the preferred agent. Because efavirenz is contraindicated during the first trimester of pregnancy, NVP-containing HAART has been increasingly used for ART-naive pregnant women in Europe, but this is no longer recommended for women with relatively good immune functioning. The potential option of initiating efavirenz-based HAART during the second or third trimester, if contraception can be assured after delivery, has been suggested in current World Health Organization recommendations for resource-limited countries [35], but whether this approach will be used in Europe is uncertain.

To date, NFV has been the overwhelming choice to accompany zidovudine and lamivudine in the treatment of ART-naive women in our study, but was less effective with regard to virological suppression than NVP-containing HAART. Boosted PI regimens appear to offer superior virological suppression in ART-naive adults, compared with PI alone [36], and lopinavir and ritonavir combination therapy is identified as a preferred PI regimen for initial HAART during pregnancy in current US guidelines—albeit, with limited pharmacokinetic and safety data [11, 37]. As more information becomes available, including boosted PIs in initial HAART regimens during pregnancy may become increasingly common, and the question of the equivalence of such regimens to other HAART regimens warrants investigation (in addition to research of new agents, such as integrase inhibitors). In the absence of clinical trials of HAART among pregnant women, our findings add to the evidence base to assist therapeutic decision-making for ART-naive, HIV-infected pregnant women. Our results strongly suggest that an ART-naive pregnant woman with a CD4 cell count <250 cells/mm^3 should begin receiving NVP-containing HAART rather than NFV-containing HAART. In addition, our results highlight the urgent need for further research of the pharmacokinetics, efficacy, and safety of ART during pregnancy.

EUROPEAN COLLABORATIVE STUDY COLLABORATORS

Dr. C. Giaquinto, Dr. O. Rampon, Dr. R. D'Elia, and Prof. A. De Rossi (Universita degli Studi di Padova, Padua, Italy); Prof. I. Grosch-Wörner (Charite Virchow-Klinikum, Berlin, Germany); Dr. J. Mok (Royal Hospital for Sick Children, Edinburgh, Scotland); Dr. I. de José, Dra. Laarú, Dr. I. Bates, Dr. A. Salas, Dr. J. Ma Peña, Dr. J. Gonzalez Garcia, Dr. J. R. Arribas Lopez, and Dr. M. C. Garcia-Rodriguez (Hospital Infantil La Paz, Madrid, Spain); Prof. F. Asensi-Botet, Dr. M. C. Otero, and Dr. D. Pérez-Tamarit (Hospital La Fe, Valencia, Spain); Dr. H. J. Scherpbier, M. Kreyenbroek, Dr. M. H. Godfried, Dr. F. J. B. Nellen, and Dr. K. Boer (Academisch Medisch Centrum, Amsterdam, The Netherlands); Dr. A. B. Bohlin, Dr. S. Lindgren, Dr. B. Anzén, Dr. K. Lidman, Dr. K. Elfgren, Dr. K. Gyllensten, and Dr. P. O. Pehrson (Karolinska University Hospital, Huddinge and Solna, Sweden); Prof. J. Levy, Dr. P. Barlow, Dr. Y. Manigart, Dr. M. Hainaut, Dr. A. Peltier, and Dr. T. Goetghebuer (Hospital St. Pierre, Brussels, Belgium); Dr. A. Ferrazin (Infectious Diseases Clinic, University of Genoa, Genoa, Italy); Prof. A. De Maria (Department of Internal Medicine, University of Genoa, Genoa, Italy) Prof. G. Bentivoglio, Dr. S. Ferrero, and Dr. C. Gotta (Department of Obstetrics and Gynecology-Neonatology Unit, University of Genoa, Genoa, Italy); Prof. A. Mûr, Dr. A. Payà, Dr. M. A. López-Vilchez, and Dr. R. Carreras (Hospital del Mar, Universidad Autonoma, Barcelona, Spain); Dr. N. H. Valerius and Dr. V. Rosenfeldt (Hvidovre Hospital, Hvidovre, Denmark); Dr. J. Jimenez (Hospital 12 De Octubre, Madrid, Spain); Dr. O. Coll, Dr. A. Suy, and Dr. J. M. Perez (Hospital Clínic, Barcelona, Spain); Dr. C. Fortuny and Dr. J. Boguña (Hospital Sant Joan de Deu, Barcelona, Spain); Dr. M. Casellas Caro (Hospital Vall D'Hebron, Barcelona, Spain); Dr. Y. Canet (Hospital Parc Tauli de Sabadell, Barcelona, Spain); Prof. G. Pardi and Dr. M. Ravizza (Ospedale San Paolo, Milan, Italy); Dr. B. Guerra, Dr. M. Lanari, Dr. S. Bianchi, and Dr. L. Bovicelli (Policlinico S Orsola, Bologna, Italy); Dr. E. Prati and Prof. M. Duse (Universita di Brescia, Brescia, Italy); Dr. G. Scaravelli and Dr. M. Stegagno (Universita La Sapienza, Rome, Italy); Dr. M. De Santis (Universita Cattolica, Rome, Italy); Dr. V. Savasi, Dr. S. Fiore, Dr. M. Crivelli, and Prof. E. Ferrazzi (Ospedale L. Sacco, Milan, Italy); Dr. A. Viganò, Dr. V. Giacomet, Dr. D. Frasca, and Prof. G. Zuccotti (Department of Pediatrics, L. Sacco Hospital, University of Milan, Milan, Italy); Dr. F. Ravagni Probizer and Prof. A. Maccabruni (Policlinico S. Matteo, Pavia, Italy); Dr. A. Bucceri and Dr. L. Rancilio (Clinica Mangiagalli and Clinica De Marchi,

Milan, Italy); Dr. S. Alberico, Dr. M. Rabusin, and M. Bernardon (IRCCS Burlo Garofolo, Trieste, Italy); Dr. G. P. Taylor and Dr. E. G. H. Lyall (St. Mary's Hospital, London,United Kingdom); Z. Penn (Chelsea and Westminster Hospital, London, United Kingdom); Drssa. W. Buffolano and Dr. R. Tiseo (Pediatric Dept, Federico II University, Naples, Italy), Prof. P. Martinelli, Drssa. M. Sansone, Dr. G. Maruotti, and Dr. A. Agangi (Obstetric Dept, Federico II University, Naples, Italy); Dr. C. Tibaldi, Dr. S. Marini, Dr. G. Masuelli, and Prof. C. Benedetto (University di Torino, Turin, Italy); Dr. T. Niemieç (National Research Institute of Mother & Child, Warsaw, Poland), Prof. M. Marczynska, Dr. S. Dobosz, Dr. J. Popielska, and Dr. A. Oldakowska (Medical University of Warsaw, Infectious Diseases Hospital, Warsaw, Poland); Dr. R. Malyuta, Dr. I. Semenenko, and T. Pilipenko (ECS Ukraine coordinating centre, Odessa, Ukraine); Dr. S. Posokhova and Dr. T. Kaleeva (Odessa, Ukraine); and Dr. A. Stelmah and Dr. G. Kiseleva (Simferopol, Ukraine).

Acknowledgments

We thank Kirsty England at the European Collaborative Study coordinating centre (London, United Kingdom); Prof. L. Chieco-Bianchi, Prof. F. Zacchello, Dr. E. Ruga, Dr. A. M. Laverda, Dr. A. Mazza, and S. Oletto (Padua, Italy); Dr. T. Schmitz, Dr. R. Weogel, Dr. Karen Seel, and Dr. S. Casteleyn (Berlin, Germany); Dr. S. Burns, Dr. N. Hallam, Dr. P. L. Yap, and Dr. J. Whitelaw (Edinburgh, Scotland); Dra. B. Sancho and Dr. G. Fontan-Casanego (Madrid, Spain); Dr. A. Gonzalez Molina, Dr. M. Gobernado, Dr. J. L. Lopez, and Dr. J. Cordoba (Valencia, Spain); A. van der Plas and E. M. Lepoole (Amsterdam, The Netherlands); Dr. E. Belfrage, Dr. L. Navér, Dr. A. Kaldma, and Dr. A. C. Lindholm (Sweden); Dr. G. Di Siena, G. Mantero, Prof. S. Trasino, and Dr. J. Nicoletti (Genoa, Italy); Dr. A. Mur (Barcelona, Spain); Dr. B. Martinez de Tejada, Dr. L. Zamora, and Dr. R. Vidal (Barcelona, Spain); Dr. G. Zucotti (Milan, Italy); Dr. M. Carla Re (Bologna, Italy); Prof. P. A. Tovo and Dr. C. Gabiano (Turin, Italy); Dr. A. Maccabruni (Pavia, Italy); Dr. G. Ferraris (Clinica Mangiagalli, Milan, Italy); Dr. T. Bruno (Naples, Italy); The Regional Health Office and RePuNaRC (Naples, Italy); G. Mantero, Dr. A. Nicoletti, Dr. B. Bruzzone, Dr. R. Rosso, and Dr. M. Setti (Genoa, Italy); and M. Kaflik (Medical University of Warsaw, Warsaw, Poland). We also thank the anonymous referees for their helpful comments.

Financial support. The European Collaborative Study (ECS) is a coordination action of the European Commission (PENTA/ECS 018865), and the coordinating center receives support from the UK MRC Sexual Health and HIV Strategy Committee.

Potential conflicts of interest. All authors: no conflicts.

References

1. Mofenson LM, Lambert JS, Stiehm ER, et al. Risk factors for perinatal transmission of human immunodeficiency virus type 1 in women treated with zidovudine. Pediatric AIDS Clinical Trials Group Study 185 Team. N Engl J Med **1999**; 341:385–93.
2. European Collaborative Study. Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy. Clin Infect Dis **2005**; 40:458–65.
3. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1–infected women and prevention of perinatal HIV-1 transmission. J Acquir Immune Defic Syndr **2002**; 29:484–94.
4. European Collaborative Study. The mother-to-child HIV transmission epidemic in Europe: evolving in the East and established in the West. AIDS **2006**; 20:1419–27.
5. Lindsey JC, Ryan LM. Tutorial in biostatistics methods for interval-censored data. Stat Med **1998**; 17:219–38.
6. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med **1998**; 17:2265–81.
7. Giolo SR. Turnbull's nonparametric estimator for interval-censored data. Technical report **2004**. Available at: http://www.est.ufpr.br/rt/suely04a.pdf. Accessed 9 October 2006.
8. Public Health Service Taskforce. Safety and toxicity of individual antiretroviral agents in pregnancy. Available at: http://aidsinfo.nih.gov/. Accessed 9 October 2006.
9. British HIV Association. Guidelines for the management of HIV infection in pregnant women and the prevention of mother-to-child transmission of HIV. http://www.bhiva.org/guidelines/2005/pregnancy/. Accessed 9 October 2006.
10. Public Health Service Taskforce. Recommendations for use of antiretroviral drugs in pregnant HIV-1–infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Available at: http://aidsinfo.nih.gov/. Accessed 9 October 2006.
11. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents. Available at: http://aidsinfo.nih.gov/. Accessed 9 October 2006.
12. Mocroft A, Phillips AN, Ledergerber B, et al. Relationship between antiretrovirals used as part of a cART regimen and CD4 cell count increases in patients with suppressed viremia. AIDS **2006**; 20:1141–50.
13. Chou R, Fu R, Huffman LH, Korthuis PT. Initial highly-active antiretroviral therapy with a protease inhibitor versus a non-nucleoside reverse transcriptase inhibitor: discrepancies between direct and indirect meta-analyses. Lancet **2006**; 368:1503–15.
14. Mirochnick M, Capparelli E. Pharmacokinetics of antiretrovirals in pregnant women. Clin Pharmacokinet **2004**; 43:1071–87.
15. Villani P, Floridia M, Pirillo MF, et al. Pharmacokinetics of nelfinavir in HIV-1–infected pregnant and nonpregnant women. Br J Clin Pharmacol **2006**; 62:309–15.
16. Nellen JF, Schillevoort I, Wit FW, et al. Nelfinavir plasma concentrations are low during pregnancy. Clin Infect Dis **2004**; 39:736–40.
17. van Heeswijk RP, Khaliq Y, Gallicano KD, et al. The pharmacokinetics of nelfinavir and M8 during pregnancy and post partum. Clin Pharmacol Ther **2004**; 76:588–97.
18. Podzamczer D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). Antivir Ther **2002**; 7:81–90.
19. Taha TE, Brown ER, Hoffman IF, et al. A phase III clinical trial of antibiotics to reduce chorioamnionitis-related perinatal HIV-1 transmission. AIDS **2006**; 20:1313–21.
20. Shapiro RL, Thior I, Gilbert PB, et al. Maternal single-dose nevirapine versus placebo as part of an antiretroviral strategy to prevent mother-to-child HIV transmission in Botswana. AIDS **2006**; 20:1281–8.
21. Giuliano M, Guidotti G, Andreotti M, et al. Triple antiretroviral therapy administered during pregnancy and after delivery significantly reduces breast milk viral load [abstract 727]. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections (Denver). **2006**.
22. Frater AJ, Dunn DT, Beardall AJ, et al. Comparative response of African HIV-1–infected individuals to highly active antiretroviral therapy. AIDS **2002**; 16:1139–46.
23. Cunningham CK, Balasubramanian R, Delke I, et al. The impact of race/ethnicity on mother-to-child HIV transmission in the United States in Pediatric AIDS Clinical Trials Group Protocol 316. J Acquir Immune Defic Syndr **2004**; 36:800–7.
24. Anastos K, Gange SJ, Lau B, et al. Association of race and gender with HIV-1 RNA levels and immunologic progression. J Acquir Immune Defic Syndr **2000**; 24:218–26.

25. Bocket L, Cheret A, Deuffic-Burban S, et al. Impact of human immunodeficiency virus type 1 subtype on first-line antiretroviral therapy effectiveness. Antivir Ther **2005**; 10:247–54.
26. Geretti AM. HIV-1 subtypes: epidemiology and significance for HIV management. Curr Opin Infect Dis **2006**; 19:1–7.
27. Brumme ZL, Harrigan PR. The impact of human genetic variation on HIV disease in the era of HAART. AIDS Rev **2006**; 8:78–87.
28. Phillips 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**; 286:2560–7.
29. Matthews GV, Sabin CA, Mandalia S, et al. Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naive patients: a cohort study. AIDS **2002**; 16:53–61.
30. Melvin AJ, Burchett SK, Watts DH, et al. Effect of pregnancy and zidovudine therapy on viral load in HIV-1–infected women. J Acquir Immune Defic Syndr Hum Retrovirol **1997**; 14:232–6.
31. Burns DN, Landesman S, Minkoff H, et al. The influence of pregnancy on human immunodeficiency virus type 1 infection: antepartum and postpartum changes in human immunodeficiency virus type 1 viral load. Am J Obstet Gynecol **1998**; 178:355–9.
32. Phillips AN, Grabar S, Tassie JM, Costagliola D, Lundgren JD, Egger M. Use of observational databases to evaluate the effectiveness of antiretroviral therapy for HIV infection: comparison of cohort studies with randomized trials. EuroSIDA, the French Hospital Database on HIV and the Swiss HIV Cohort Study Groups. AIDS **1999**; 13:2075–82.
33. Stebbing J, Bower M. Comparative pharmacogenomics of antiretroviral and cytotoxic treatments. Lancet Oncol **2006**; 7:61–8.
34. Lowe SH, Prins JM, Lange JM. Antiretroviral therapy in previously untreated adults infected with the human immunodeficiency virus type I: established and potential determinants of virological outcome. Neth J Med **2004**; 62:424–40.
35. World Health Organization. Anitretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access. Geneva, Switzerland: World Health Organization, **2006**.
36. Bartlett JA, Fath MJ, Demasi R, et al. An updated systematic overview of triple combination therapy in antiretroviral-naive HIV-infected adults. AIDS **2006**; 20:2051–64.
37. Stek AM, Mirochnick M, Capparelli E, et al. Reduced lopinavir exposure during pregnancy. AIDS **2006**; 20:1931–9.