

Combination Antiretroviral Treatment for Women Previously Treated Only in Pregnancy: Week 24 Results of AIDS Clinical Trials Group Protocol A5227

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Background: Women with HIV and prior exposure to combination antiretroviral therapy (cART) solely for prevention of mother-to-child transmission (pMTCT) need to know whether they can later be treated successfully with a commonly used regimen of efavirenz (EFV) and coformulated emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF).

Methods: Nonpregnant women with plasma HIV-1 RNA of ≥ 500 copies per milliliter, previously cART exposed for pMTCT only,

were eligible if they were off ART for ≥ 24 weeks before entry, were without evidence of drug resistance on standard genotyping, and were ready to start EFV plus FTC/TDF. The primary endpoint was virologic response (defined as plasma HIV RNA < 400 copies/mL) at 24 weeks.

Results: Fifty-four women were enrolled between October 2007 and December 2009; 52 of 54 completed 24 weeks of follow-up. Median baseline CD4⁺ T-cell count was 265/mm³ and baseline plasma HIV-1 RNA was 4.6 log₁₀ copies per milliliter. Median prior cART duration was 14 weeks, and median time elapsed from the last pMTCT dose to entry was 22 months. Virologic response at 24 weeks was observed in 42 of 52 women or 81% (exact 95% confidence interval: 68% to 90%). There were no differences in response by country, by number, or class of prior pMTCT exposures. Although confirmed virologic failure occurred in 8 women, no virologic failures were observed in women reporting perfect early adherence.

Conclusions: In this first prospective clinical trial studying combination antiretroviral retreatment in women with a history of pregnancy-limited cART, the observed virologic response to TDF/FTC and EFV at 24 weeks was 81%. Virologic failures occurred and correlated with self-reported nonadherence.

Key Words: antiretroviral therapy, postpartum women, efavirenz, adherence, pMTCT

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been shown to impact MTCT by reducing maternal viral replication, by providing effective preexposure prophylaxis of babies using antiretrovirals (ARVs) that cross the placenta, and by functioning as postexposure prophylaxis of babies after delivery.⁴

Concerns about long-term toxicities of ART and evolution of HIV-1 drug-resistance led to treatment guidelines which had recommended deferred initiation of ART until CD4⁺ T-cell counts were <350/mm³ or plasma HIV-1 RNA reached >50,000 to 100,000 copies per milliliter. In the United States, more recent guidelines⁵ have recommended ART for all HIV-infected patients following others have suggested cART be initiated regardless of CD4⁺ T-cell counts.⁶ Given the changing landscape of recommendations for initial ARV treatment, many HIV-1-infected pregnant women who received ARV drugs solely for pMTCT later intentionally discontinued their regimen at or soon after delivery but now want or need to restart therapy. These women were not considered treatment naive and thus were ineligible for clinical trials of ARV treatment initiation, which typically exclude those with >1 week history of prior ART.

Earlier studies of structured treatment interruptions (STIs) in HIV-1-infected subjects with a good response to an initial ARV regimen, suggested little risk of acquiring drug resistance mutations compromising subsequent therapy in the short term.^{7,8} Data from the Swiss-Spanish STI trial suggested that subjects with low plasma viral loads at baseline who were treated intermittently with highly active antiretroviral therapy for 8 weeks on and 2 weeks off were able to sustain virologic control without the development of significant HIV-1 drug resistance mutations.⁹ However, these data may not be directly applicable to women who received therapy solely for pMTCT, as the regimens studied in the STI trials were interrupted and reinitiated for relatively short periods of time. The risk of acquisition of drug resistance mutations may increase with recurrent treatment interruptions.^{10,11}

It is well known that selection for drug-resistant variants can occur rapidly during partially suppressive ARV regimens,¹²⁻¹⁴ and can compromise response to subsequent regimens. There is substantial risk for acquisition of nonnucleoside reverse transcriptase inhibitor (NNRTI)-associated resistance mutations in women and infants treated with single-dose nevirapine (sd-NVP) for pMTCT,¹⁵ which can be abrogated somewhat by adding combination nucleoside reverse transcriptase inhibitor (NRTI) therapy while NVP levels gradually decline.^{16,17} Whether women treated with full dose cART solely for pMTCT also acquire stable HIV-1 drug resistance mutations is unknown, as is the outcome of subsequent treatment at a later time with the same regimen. On the other hand, avoiding a well-tolerated, effective, compact single daily regimen, such as efavirenz (EFV) plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in women who have no evidence of prior virologic failure and no evidence of drug resistance mutations by standard bulk population HIV-1 genotyping (hereafter "genotyping") may unnecessarily restrict their treatment options.

This study was initiated to address the clinical question of whether HIV-1-infected women who were previously successfully treated with pregnancy-limited cART and who lack evidence of HIV-1 drug resistance by genotyping could sub-

sequently be treated successfully with a commonly used initial combination ARV regimen for their own health. Therefore, A5227 was designed to test the hypothesis that the use of short-course potent ARV drug regimens for pMTCT would not compromise subsequent treatment of HIV-1 infection with EFV plus FTC/TDF. The study outcomes through study week 24 are presented here.

METHODS

Study Population

Nonpregnant HIV-1-infected women ≥ 16 years old who were ready to start ART for their own health and who had been previously treated only for pMTCT with at least 1 cART regimen were eligible if they had *not* received any ARVs for ≥ 24 weeks before study entry, had HIV-1 RNA by polymerase chain reaction ≥ 500 copies per milliliter within 90 days of study entry, met baseline hematologic, renal and hepatic safety parameters for starting retreatment, and had no known prior or screening evidence of NRTI or NNRTI drug resistance on genotyping (see Appendix for drug resistance parameters). Women may have had drug resistance testing done outside the study at any time before study entry, but study screening included baseline bulk population genotyping, which was performed locally if available. Prior cART for pMTCT of HIV was defined as 2 or more ARV drugs, not including the combination of ZDV plus sd-NVP, for ≥ 7 days during at least 1 pregnancy. Women with documentation of confirmed virologic failure while taking cART for pMTCT (either consecutive >5,000 copies/mL after 8 weeks or >400 copies/mL after 24 weeks, if applicable) were excluded. Women of reproductive potential agreed to use 2 reliable methods of contraception. A negative pregnancy test was required within 2 days before study entry.

Sites eligible to enroll women in this study included AIDS Clinical Trials Group (ACTG) sites in the United States (starting May 2007) and starting July 2008, the RIO-FIOCRUZ ACTG site in Brazil, and the Lima ACTG site in Peru.

All women provided written informed consent, and the institutional review board for each participating site approved the study.

Study Design

A5227 was a prospective, single-arm, open-label treatment study. Women were registered to receive 48 weeks of the study treatment regimen: EFV 600 mg, plus a fixed-dose combination (FDC) of FTC 200 mg/TDF 300 mg (Truvada), each once daily by mouth.

The primary study objective was to estimate the probability of virologic response, measured as plasma HIV-1 RNA <400 copies per milliliter at week 24. Virologic failure was defined as 2 consecutive (ie, confirmed) plasma HIV-1 RNA ≥ 400 copies per milliliter at or after the week 16 study visit. If virologic failure was confirmed, samples were to be obtained for resistance testing by bulk population genotyping. This report includes data and results for follow-up through the week 24 visit. Secondary week 24 objectives

included the following: (1) summarizing safety and tolerability of EFV plus FTC/TDF, (2) estimation of the probability of virologic suppression (defined as plasma HIV-1 RNA <50 copies/mL at week 24), (3) characterization of viral drug resistance mutations in women experiencing virologic failure, (4) description of changes in CD4⁺ T-cell counts from baseline over time, (5) estimation of treatment regimen adherence, and (6) assessment of quality of life.

Study Evaluations

After screening, study evaluations were scheduled for preentry, entry, and weeks 2, 4, 8, 16, 24, 36, and 48, and before entry included a comprehensive history and clinical examination for diagnoses, signs and symptoms, hematology, blood chemistries, fasting metabolic tests, hepatitis serologies, pregnancy test, plasma HIV-1 RNA by polymerase chain reaction, and CD4⁺ T-cell subsets. Plasma for HIV-1 genotype resistance testing was collected after confirmed virologic failure, in addition to specimens collected for retrospective batched testing at entry, and at weeks 24 and 48. Samples were also collected from all women at the preentry visit, which were batched for later analysis of bulk population genotyping at the central virology laboratory.

Adherence interviews assessing the prior 4 weeks on study (or prior 2 weeks for the week 2 study visit) were conducted at the 2, 8, 24, and 48-week visits and if virologic failure or premature discontinuation of treatment occurred. Standardized questions were asked about the frequency of missed doses over the weeks before the interview and the circumstances women associated with nonadherence. Adherence interview questionnaires were structured to proceed logically so a “never missed” medication answer did not lead to questions regarding frequency of missed doses, but overall included the following questions:

1. When was the last time you missed taking your prescribed medications? Possible answers included the following: never, 1–2 weeks ago, 2–4 weeks ago, 1–3 months ago, and more than 3 months ago.
2. On how many different days did you miss taking your medications? Possible answers included the following: 0, 1, 2, 3, and 4.
3. Did you miss taking your medications on weekend days?
4. What was the total number of missed doses in the last 2 weeks?

Standardized quality of life interview was performed at entry and weeks 8, 24, and 48.

Any laboratory abnormalities or clinical events that led to a change in treatment, regardless of grade, and any grade ≥ 3 signs/symptoms or laboratory results were recorded and graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.¹⁸

Laboratory Testing

Plasma for HIV-1 RNA levels and for HIV-1 drug resistance genotyping was separated and frozen at -85°C . Roche COBAS Amplicor HIV-1 Monitor (version 1.5;

Roche Molecular Systems, Alameda CA, and Branchburg, NJ) was used to quantify HIV-1 RNA in plasma; the ultrasensitive version (lower limit of quantification = 50 copies/mL) was employed at a centralized contract laboratory (Johns Hopkins University, Baltimore, MD) for US ACTG sites. At international sites, both ultrasensitive and standard versions (lower limit of quantification = 400 copies/mL) were used. Additional plasma was prospectively collected to allow for retrospective, batched retesting of specimens with results <400 HIV-1 RNA copies per milliliter to assess whether these specimens were also <50 copies per milliliter. Plasma HIV-1 reverse transcriptase (RT) and protease genotyping by standard bulk population sequencing was performed using HIV-1 TruGene (Siemens Healthcare Diagnostics, Deerfield, IL). Only the central virology laboratory HIV-1 bulk population genotyping results are presented here.

Statistical Methods

Sample Size

Since the primary study objective was the estimation of the probability of plasma HIV-1 RNA <400 copies per milliliter at week 24, the study sample size was justified by the precision (length of 2 sided, exact 95% confidence interval or CI) of the estimated virologic response. A planned sample size of 47 women provided precision of ≤ 25 percentage points, assuming at least 80% of the study sample had a virologic response at week 24, and a 5% inflation rate due to losses to follow-up.

Statistical Analyses

Evaluation for the primary endpoint of virologic response, which could occur from 20 to 30 weeks after enrollment, used the result closest to week 24. The primary analysis was intent-to-treat (treatment history and status ignored) and estimation used only available data. Exact 95% CIs were calculated. Secondary (sensitivity) analyses included imputing missing values as nonresponses and using the highest observed RNA within the evaluation window. Prespecified subgroup comparisons by country and pMTCT exposure used Fisher exact test. Exploration of baseline covariate association with the primary endpoint used univariate exact logistic regression.

Virologic failure was time to confirmed plasma HIV-1 RNA >400 copies per milliliter, starting at the week 16 study visit. Survivor distributions were estimated with the method of Kaplan–Meier and used Greenwood formula for CI estimation on cumulative probability of outcome by week 24.

Adherence was a dichotomous outcome formulated as any nonadherence to the prescribed regimen in the previous 4 weeks versus an absence of self-reported nonadherence. Changes in quality of life measures from baseline to follow-up used paired *t* test. Association of adherence to primary outcome and virologic failure used Fisher exact test.

RESULTS

Enrollment/Participant Characteristics/Disposition

Fifty-four women enrolled between October 2007 and December 2009: 22 from Brazil, 20 from Peru, and 12 from the United States. The median baseline characteristics and interquartile ranges are presented in Table 1 and included the following: age 29 years, CD4⁺ T-cell count 265/mm³, and plasma HIV-1 RNA 4.6 log₁₀ copies per milliliter. Forty-six women had prior cART exposure in only 1 pregnancy, 8 had prior exposure in 2 pregnancies; the median total prior cART exposure was 13.9 weeks, and the median time from the last pMTCT dose to entry was 22 months. In 38 of 54 women, the last pMTCT cART regimen consisted of a protease inhibitor and 2 NRTIs, 2 of these also had prior exposure in pregnancy to a dual nucleoside only regimen and 4 of these also had prior exposure in pregnancy to ZDV monotherapy. In 11 of 54 women, the last pMTCT cART regimen was an NNRTI with 2 NRTIs, of these 1 also had prior dual nucleoside only therapy and 2 also had prior ZDV monotherapy. In 5 of 54 women, cART in their last pregnancy had consisted of only dual NRTIs. The last clinical peripartum HIV-1 RNA copy number was available for 19 of 22 women in Brazil, for only 2 of 20 women in Peru, and for only 8 of 12 women in the

United States, ranging overall from 40 copies per milliliter to 23,000, with a median of 280.

A total of 52 of 54 (96%) women completed 24 weeks of follow-up. Figure 1, a CONSORT diagram, describes the participant flow through week 24. Four women had prolonged time off treatment while on study, ranging from 12 to 57 days, for a variety of personal reasons (family issues, travel, unable to return to pick up medications); none of these 4 women reported any adverse events (AEs) through 24 weeks.

Virologic Outcomes

Virologic response (plasma HIV-1 RNA <400 copies/mL) at week 24 was observed in 42 of 52 women; the estimated primary response probability is 81% (95% CI: 68% to 90%). If the 2 women not evaluated at week 24 due to premature study discontinuation are imputed as nonresponders, the estimated response probability is 78% (42/54). Figure 2 shows virologic response (plasma HIV-1 RNA <400 copies/mL) and virologic suppression (plasma HIV-1 RNA <50 copies/mL) and the number of observations during the first 24 weeks. Of the 10 nonresponders for the primary endpoint of virologic response through the week 24 study interval, 7 had been previously identified as virologic failures. The 3 remaining nonresponders had their first elevated RNA at the

TABLE 1. Baseline Characteristics

Characteristics	Brazil (N = 22)	Peru (N = 20)	United States (N = 12)	Total (N = 54)
Age (yrs), median (Q1, Q3)	29 (25, 33)	24.5 (22.5, 31.5)	34 (28, 39)	28.5 (24.0, 33.0)
Minimum, maximum	19, 45	19, 39	19, 43	19, 45
Race				
White non-Hispanic (%)	0 (0)	0 (0)	1 (8)	1 (2)
Black non-Hispanic (%)	0 (0)	0 (0)	9 (75)	9 (17)
Hispanic (regardless of race) (%)	22 (100)	19 (95)	2 (17)	43 (80)
Unknown/missing (%)	0 (0)	1 (5)	0 (0)	1 (2)
Body mass index (kg/m ²), median (Q1, Q3)	22.2 (20.2, 29.9)	24.8 (22.6, 26.7)	30.8 (27.0, 39.1)	25.2 (21.7, 30.1)
Minimum, maximum	15.4, 40.6	20.1, 30.9	20.3, 48.5	15.4, 48.5
No IV drug use history, n (%)	22 (100)	19 (95)	12 (100)	53 (98)
Prior IV drug use history, n (%)	0 (0)	1 (5)	0 (0)	1 (2)
CD4 ⁺ (cell/mm ³), median (Q1, Q3)	317.3 (263.5, 373.5)	231.8 (164.0, 281.5)	226.0 (161.5, 297.8)	265.3 (176.5, 325.0)
Minimum, maximum	131.5, 566.5	122.5, 404.0	26.5, 338.5	26.5, 566.5
HIV-1 RNA (log ₁₀ copies/mL), median (Q1, Q3)	4.9 (4.5, 5.1)	4.5 (4.2, 4.8)	4.5 (3.9, 4.7)	4.6 (4.2, 4.9)
Minimum, maximum	2.9, 5.9	3.8, 5.0	3.3, 4.9	2.9, 5.9
Total pMTCT ARV exposure (wks)				
Median (Q1, Q3)	13.5 (7.7, 23.8)	13.6 (10.2, 20.9)	14.4 (4.5, 25.5)	13.9 (8.0, 22.0)
Minimum, maximum	2.7, 31.7	1.4, 26.9	2.1, 52.1	1.4, 52.1
Time since last dose of pMTCT ARV (mo)				
Median (Q1, Q3)	25.5 (13.0, 31.0)	17.5 (9.0, 24.0)	53.0 (19.0, 80.5)	22 (13, 34)
Minimum, maximum	6, 53	7, 58	9, 118	6, 118
Parity median (range)	2 (1–5)	2 (1–4)	3.5 (1–10)	2 (1–10)
Last pMTCT regimen class,* n (protease inhibitor/NNRTI/dual NRTI)	21/1/0	10/8/2	7/2/3	38/11/5
Duration last pMTCT regimen (wks), median (range)	12.8 (0.4–25.7)	2.3 (1.2–22.1)	14.3 (2.1–28.9)	13.05 (0.4–28.9)
Last peripartum HIV-1 RNA (copies/mL), median (range), n = available	280 (50–23,000), n = 19	400–554, n = 2	142 (40–528), n = 8	280, (40–23,000), n = 29

*Combination antiretroviral class = protease inhibitor + 2 NRTI, NNRTI + 2 NRTI or dual NRTI.

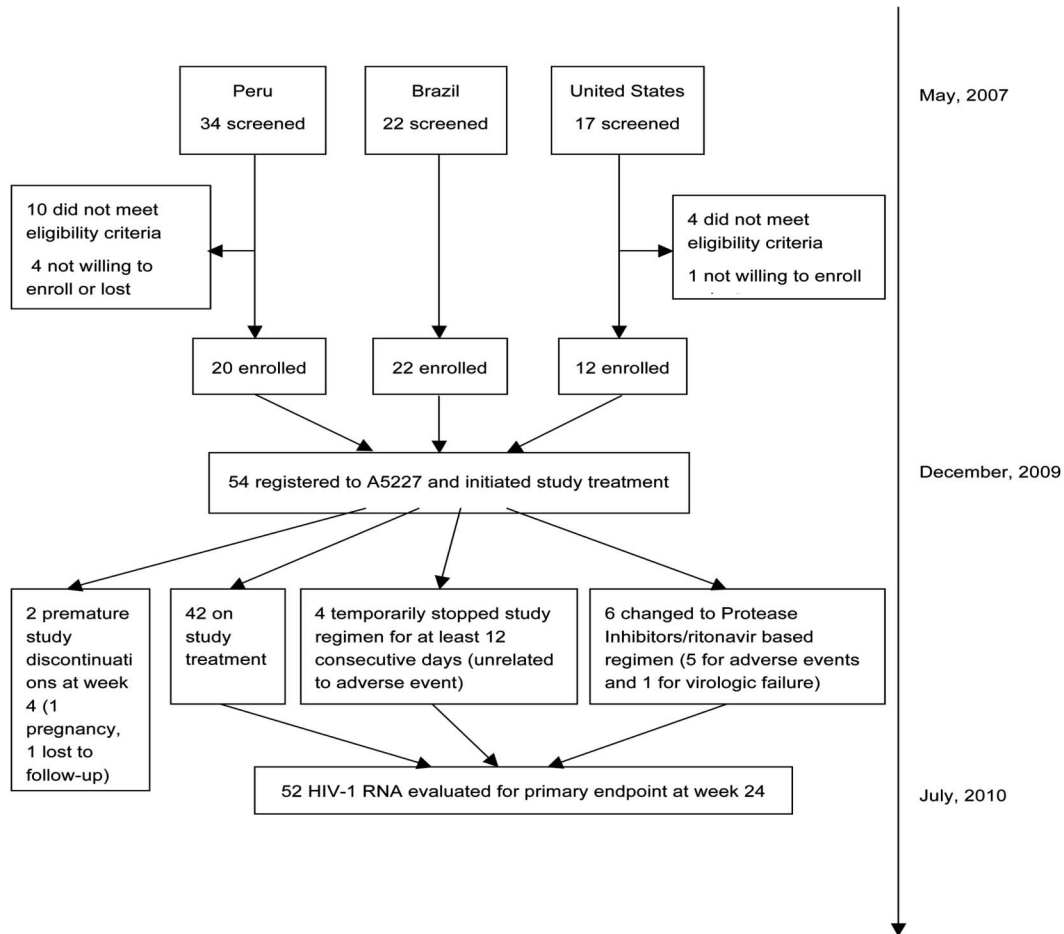


FIGURE 1. CONSORT diagram of A5227 women.

week 24 study visit. *None* of the following baseline characteristics (examined independently) were significantly associated with virologic response at week 24 (data not shown): country of participant, self-reported ethnicity (Hispanic versus not Hispanic), pMTCT NNRTI exposure (versus no NNRTI exposure), pMTCT ZDV monotherapy or dual-NRTI exposure (versus no such exposure), participant age, participant body mass index, baseline CD4⁺ T-cell count, or baseline plasma HIV-1 RNA levels.

Virologic Failure and HIV-1 Drug Resistance Genotyping Results

A total of 8 women experienced confirmed virologic failure (plasma HIV-1 RNA ≥ 400 copies/mL on 2 consecutive measurements starting at study week 16). By definition, as noted above, 7 of these were identified as virologic failures and subsequently met criteria as virologic nonresponders at week 24 as well. The other virologic failure at week 16 subsequently became a virologic responder with suppressed RNA by the primary outcome evaluation at week 24. Bulk population genotyping at baseline and at virologic failure was successful in samples from 6 of 8. The estimated probability of virologic failure by week 24 is 15.4% (95% CI: 8% to 28.4%).

As shown in Table 2, 5 of the 6 HIV-1 isolates from women failing therapy and having genotype data available showed evolution of NNRTI resistance mutations (K103N in all 5; also G190A and P225H in 1); in 2 of these, a new NRTI M184V mutation was also identified.

Other Secondary Outcomes Through Study Week 24

Safety/Tolerability

Occurrence of severe or life-threatening signs/symptoms or laboratory abnormalities was rare and no women died. Though rash was the most common AE, only 1 grade ≥ 3 rash occurred. One participant exhibited \geq grade 3 CNS symptom (suicidal ideation). A total of 9 AEs \geq grade 3 occurred in 6 women, 3 of these were not thought related to study drugs. Four women had \geq grade 3 laboratory abnormalities: 1 elevation of alkaline phosphatase, 1 bilirubin elevation, and 2 women had neutropenia. Six women had study treatment modifications based on AEs before primary outcome evaluation; another 2 modified after the primary outcome evaluation but within the week 24 study visit interval. Figure 1, the CONSORT diagram, characterizes participant changes in the study regimen for any reason, including AEs.

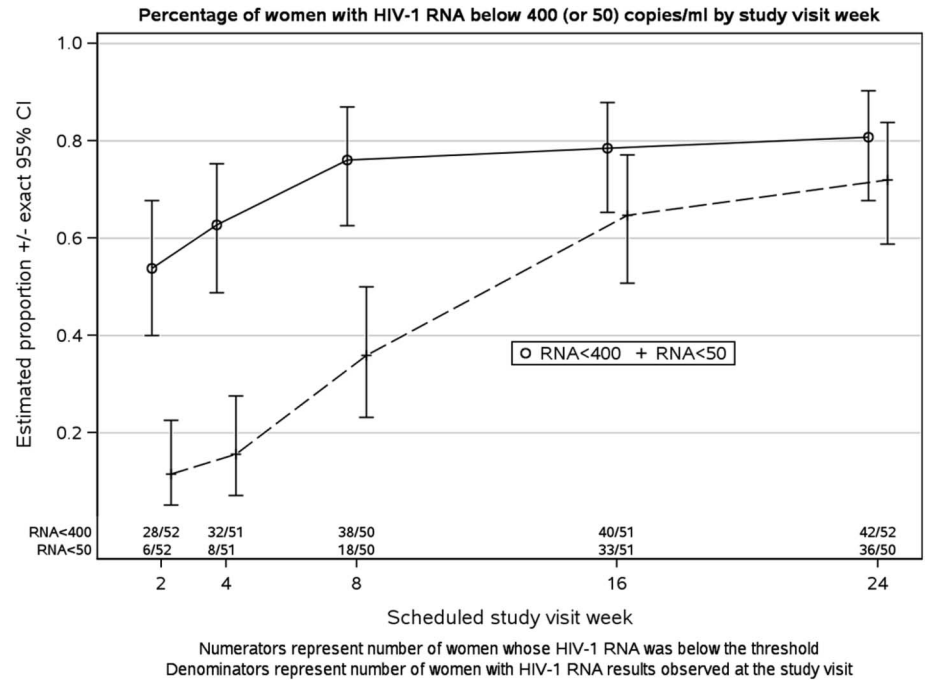


FIGURE 2. Percentage of women with HIV-1 RNA below 400 (or 50) copies per milliliter by study visit week. Numerators represent number of women whose HIV-1 RNA was below threshold and denominators represent number of women with HIV-1 RNA results observed at the study visit.

The estimated probability of permanently stopping EFV by week 24 was 19% and for stopping FTC/TDF was 11%.

Immunologic Response

CD4⁺ T-cell counts and percentages rose over time after ARV initiation, with median increases of 82 cells per cubic millimeter at week 4, 91 cells per cubic millimeter at week 8, 111 cells per cubic millimeter at week 16, and 115 cells per cubic millimeter at week 24.

Study Regimen Adherence and Virologic Responses

Adherence to the study regimen was based on the prior 4 weeks at each assessment (or the prior 2 weeks for the week 2 assessment) and was observed to be lower at week 8 (67% reported perfect adherence) than at week 2 (82%) or at week 24 (76%). Of women reporting perfect adherence in the first 24 weeks of follow-up, 25 of 26 (96%) were virologic responders. Conversely, 14 of 25 (56%) of women reporting some nonadherence were virologic responders (and the remaining 3 women for whom adherence data are not available were also virologic responders). No baseline correlates of adherence outcome were identified.

Virologic failure was similarly associated with early self-reported measures of adherence. There were no virologic failures observed in 31 women reporting perfect adherence at both weeks 2 and 8. Of 20 women reporting some non-adherence within the first 8 weeks on study, 7(35%) experienced virologic failure at week 16 (The additional woman experiencing virologic failure did not report adherence information.). Although the reasons listed for nonadherence varied, reasons cited at week 8 included illness, fear of side effects, and pill burden rather than transportation problems or running

out of pills. No baseline correlates of early adherence were identified, including demographic factors, binge drinking, or substance use.

There were no significant changes in quality of life indices reported by the study women between study entry and weeks 8 and 24 (data not shown).

DISCUSSION

In this first prospective clinical trial studying cART retreatment in HIV-1–infected women previously treated with cART only in pregnancy, the observed virologic response to EFV and TDF/FTC at 24 weeks was 81% (95% CI: 68% to 90%). To put these results in context, Figure 3 plots the virologic responses (and CIs) to EFV plus FTC/TDF observed at 24 weeks in women participating in 3 other studies: ACTG A5175, ACTG A5202, and Gilead 934^{19–21} in comparison with the women of A5227. The upper panel shows the data analyzed as missing = excluded from the primary endpoint analysis, whereas the lower panel shows the data analyzed as missing = nonresponders (eg, HIV-1 RNA ≥400 copies/mL) in the primary endpoint analysis. The hypothesis of A5227, namely, that virologic response in HIV-1–infected women to a commonly used initial cART regimen, consisting of EFV, FTC, and TDF, would not be compromised by prior pMTCT with cART is supported when compared with the more demographically similar population of women in A5175 as shown in the figure, in which the CIs for estimated virologic responses in these 2 studies overlap. Like A5175, the women in A5227 were primarily enrolled and studied outside the United States so these study populations may be more similar and one might expect more similar outcomes. When compared with United States women

TABLE 2. Nonresponders at week 24 (HIV-1 RNA by polymerase chain reaction >400 copies/mL) and virologic failures at week 16 (confirmed HIV-1 RNA by polymerase chain reaction >400 copies/mL) by prior pregnancy-limited ART

ID	Country	VF?	Parity	Most Recent Pregnancy Limited cART Regimen	Last Peripartum HIV-1 RNA (copies/mL)	Delivery HIV-1 RNA Result (d)	Time Since Last cART (mo)	Prior Dual Nucleoside and/or Mono ZDV?	Regimen at Virologic Failure or Primary Endpoint	New NRTI* or NNRTI Mutation
1	United States	Yes	4	NVP/ZDV/3TC × 16 wks	40	36 d pre	81	ZDV/3TC × 22 wks	EFV/FTC/TDF	K103N
2	United States	Yes	4	LPV/r ZDV/3TC × 2.4 wks	186	3 d post	67	No	EFV/FTC/TDF	K103N, G190AG, P225HP, M184V
3	Peru	Yes	3	NVP/ZDV/3TC × 15 wks	na	na	20	No	LPV/r/FTC/TDF	None
4	Peru	Yes	2	NVP/ZDV/3TC × 2.6 wks	554	19 d post	7	No	NVP/FTC/TDF	K103N, M184V
5	Brazil	Yes	1	LPV/r/ZDV/3TC × 7 wks	14571	10 d pre	7	No	EFV/FTC/TDF	K103N
6	Brazil	Yes	4	NVP/ZDV/3TC × 3.4 wks	280	31 d pre	22	No	LPV/r/ZDV/3TC	na
7	Brazil	Yes	3	NFV/ZDV/3TC × 12.7 wks	na	na	16	ZDV × 13 wks	EFV/FTC/TDF	K103N
8	Brazil	No	5	NFV/ZDV/3TC × 11 wks	900	37 d pre	27	No	EFV/FTC/TDF	na
9	Brazil	No	3	NVP/3TC/d4T × 17.6 wks	na	na	7	ZDV × 9 wks	EFV/FTC/TDF	na
10	Brazil	No	4	NFV/ZDV/3TC × 3.7 wks	5100	34 d pre	31	ZDV/3TC × 1 wk	EFV/FTC/TDF	na
11	Brazil	Yes	4	LPV/r/ZDV/3TC × 14.7 wks	59	31 d pre	10	No	EFV/FTC/TDF	na

Subject no 3 changed ARV regimen to TDF/FTC + LPV/r before virologic failure, no resistance mutations were found to LPV on the VF sample. Subject no 4 suppressed to <400 copies by week 24. NNRTI-associated mutations: L100I, K103N, V106A/M, V108I, Y181C/I, Y188C/H/L, G190A/S, P225H, and P236L. NRTI-associated mutations: M41L, K65R, D67N, 69 insertion complex, K70R, L74V, Q151M, M184V, L210W, T215A/C/D/E/F/G/H/I/L/N/S/V/Y/I, K219Q/E, and Y115F.

VF, virologic failure; pre, prepartum; post, postpartum; 3TC, lamivudine; LPV/r, lopinavir/ritonavir fixed dose combination tablet; na = not available.

*Refer to Appendix for interpretation of resistance mutations.

(A5202) treated with the same regimen, in which the subgroup of women had an extremely high response rate, there was almost no overlap in CIs.

Despite careful selection to minimize known risks of virologic failure in A5227, confirmed virologic failures by 24 weeks (assessed starting with study visit week 16) nonetheless occurred in 8 women. Not surprisingly, none of these 8 reported early perfect adherence at their week 2 and/or week 8 interviews. There were statistically significant associations described between virologic response and self-reported adherence and between lack of virologic failure and self-reported adherence.

Earlier studies of pMTCT suggest that although adherence may peak during pregnancy in some women, it declines during the postpartum period. This may result from burgeoning maternal responsibilities but has also correlated with aversion to risk of side effects.^{22,23} Perhaps once the risk of HIV-1 transmission to an unborn child has passed, the tolerance for side effects may diminish. In 1 study using MEMS caps to track adherence, the overall adherence rate in the postpartum period was 34%.²⁴ Bardeguet et al found that adherence rates fell by 10% from prepartum to 48 weeks postpartum.²⁵ Even outside the research environment, many women find it difficult to attend doctor visits in the postpartum period. Rana et al found that only 37% of women are able

to keep 2 or more visits with their HIV provider during the postpartum year.²⁶ In contrast, the women in A5227 were generally presenting for retreatment well after the first postpartum year.

In 5 of the women experiencing virologic failure who had genotype data available, there was evidence for evolution of HIV-1 drug resistance on study. Table 2 presents summary data on virologic failures and nonresponders by prior regimens. There does not seem to be a clear pattern of predictable emergence of resistance on treatment. As noted earlier, there were no statistical associations between prior regimen(s) and outcomes and no association with prior mono or dual nucleoside therapy. A number of clinical trials have evaluated retreatment with an NNRTI-based triple combination therapy regimen in women previously treated with sd-NVP,^{14,27,28} which is known to be associated with high-level NNRTI resistance.^{12,13} Despite the evidence for high prevalence and persistence of NNRTI resistance mutations by highly sensitive assays after such exposure,^{29,30} the risk of virologic failure with retreatment on an NNRTI-based regimen declines with time from last dose.^{27,28} Such sensitive assays have now also identified a variety of drug resistance mutations in early postpartum samples from women previously treated with combination therapy in pregnancy.³¹

(a) Week 24 Plasma HIV-1 Results from ACTG A5227 and (TDF/FTC+EFV arms of) other naive studies

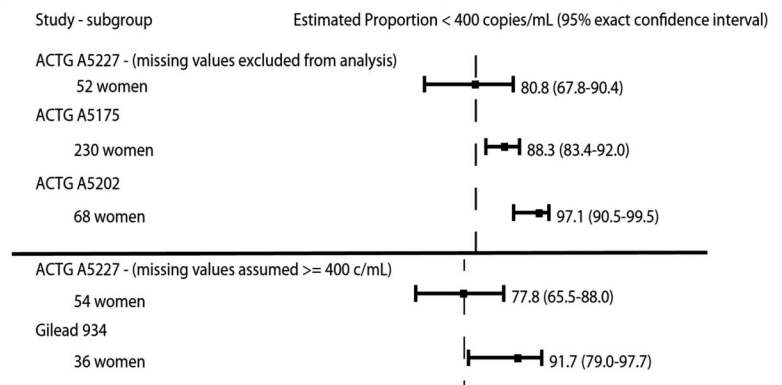


FIGURE 3. Week 24 plasma HIV-1 results from ACTG A5227 and (TDF/FTC + EFV arms of) other naive studies.

The clinical problem generating our study hypothesis was how to reinstate ARV treatment in women previously treated in pregnancy who often were treated long ago and currently show no evidence of HIV-1 drug resistance by genotyping. In other words, are these women with a history of pregnancy limited ART approximately equivalent virologically to women who have never been treated with ARVs for any reason and so could expect the same virologic response to the same regimen as that seen in ARV naive women? Our results suggest that virologic response to a commonly used initial combination ARV treatment regimen in women with a history of pregnancy limited cART and in women with no history of ART are comparable in more demographically similar populations, and, in women with a history of pregnancy limited cART, perfect adherence is a statistically significant correlate of virologic response at 24 weeks.

In terms of virologic nonresponders at 24 weeks and virologic failures, there was no clear correlation with any baseline measures, prior regimen type or duration. The standard HIV-1 bulk population genotyping employed for entry participation in A5227 (either by review of previous HIV-1 drug resistance mutation reports or by screening HIV-1 drug resistance testing) was analogous to what is commercially available worldwide in nonclinical trials settings. This HIV-1 drug resistance testing approach may miss detection of drug resistance in minority variants present at baseline. Moreover, because these A5227 women were off ARV therapy for more than 6 months before study entry, they may have been more likely to demonstrate “fading” of HIV-1 drug resistance mutations by standard bulk population genotyping,¹² so attempts to optimize therapy using preretreatment genotyping might fail. Pharmacokinetic analyses and drug resistance minority variant analyses are planned and may help to understand some of the mechanism(s) of treatment failure in HIV-1-infected women previously treated with cART during pregnancy.

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APPENDIX. A5227 Exclusionary HIV-1 Drug Resistance-Associated Mutations* at Study Entry

NRTI-associated mutations:	M41L, K65R, D67N, 69 insertion complex, K70R, L74V, Q151M, M184V, L210W, T215A/C/D/E/F/G/H/I/L/N/S/V/Y, K219Q/E, Y115F
NNRT-associated mutations	L100I, K103N, V106A/M, V108I, Y181C/I, Y188C/H/L, G190A/S, P225H, P236L

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