Initial Viral Decay to Assess the Relative Antiretroviral Potency of PI-, NNRTI- and NRTI-Sparing Regimens for First Line Therapy of HIV Infection

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Objectives: To evaluate the effects of gender and initial antiretroviral regimen on decay of HIV RNA and virologic outcome.

Methods: We conducted a viral dynamics sub-study of A5142, a trial comparing lopinavir/ritonavir+efavirenz (LPV/EFV) versus LPV+2 NRTI (LPV) versus EFV+2 NRTI (EFV) in ARV-naive subjects. HIV RNA was measured at days 2,10, and 14 in the sub-study and at weeks 1,4, and 8 in A5142 participants. Two-phase viral decay was estimated in the sub-study with bi-exponential mixed-effects modeling and compared using Wilcoxon tests. Week 1 HIV RNA change was assessed as a predictor of virologic failure (HIV RNA above 50/ 200 copies/mL) at weeks 24–96 using logistic regression.

Results: 68 subjects were enrolled in the sub-study (median HIV RNA 4.9 $\log_{10}$ copies/mL). Median rates of phase-1 viral decay by treatment were 0.61(EFV/LPV), 0.53(LPV), and 0.63(EFV) day^{-1}. Phase-1 decay was significantly faster for EFV than LPV ($P = 0.023$); other comparisons were not significant ($P > 0.11$). Viral decay did not differ by gender ($P = 0.10$). Week 1 HIV RNA change, calculated in 571 participants of A5142, was greater for the EFV (median -1.47 $\log_{10}$ copies/ml) than either the LPV/ EFV or LPV groups (-1.21 and -1.16 $\log_{10}$ copies/ml, respectively; $P < 0.001$). Week 1 HIV RNA change was associated with virologic failure above 50 copies/ mL at weeks 24 and 48 ($P < 0.018$), but not above 200 copies/mL or at week 96.

Conclusions: Phase-1 decay was faster for EFV than LPV or LPV/EFV. Week 1 HIV RNA change predicted virologic outcome to week 48, but not at week 96.

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Introduction

Treatment with combination antiretroviral therapy (ART) results in rapid decay of plasma HIV RNA. Careful measurement of the initial viral decline (phase-1 decay half-life), using multiple HIV RNA measurements in the first 7–10 days of therapy, has been useful to compare regimen potency and may be a predictor of longer term virologic response [1–5]. Efavirenz- containing regimens have been shown to have faster phase-1 decay than nelfinavir-containing regimens and this greater decay rate was associated with better viral suppression at week 24 [1]. Efavirenz plus nucleoside reverse transcriptase inhibitors (NRTI) produced faster phase I decay than a triple nucleoside combination of zidovudine, lamivudine and abacavir in AIDS Clinical Trials Group (ACTG) study 5095; a result that was consistent with the primary virologic results that showed better virologic outcome in the efavirenz-containing regimens [6]. Addition of enfuvirtide also increased viral decay when added to a four drug regimen in treatment naïve subjects [7]. Phase-1 decay with raltegravir, given as monotherapy for 10 days yielded similar viral decay to some three drug combinations (half-life between 1.1 and 1.3 days) [8]. Although many factors ultimately determine the longer term success of a regimen, some studies have suggested that early virologic changes are associated with longer-term virologic outcomes, but other studies do not find associations [2,6,9–11]. Several cohort studies have described differences in HIV-1 RNA levels between men and women [12,13]. These differences have been most apparent in early disease and have not been associated with disease progression. Few studies have evaluated gender-based differences in the observed viral decay rate after initiation of therapy.

Not all antiretroviral combinations can be tested in large randomized studies designed to assess comparable efficacy; further, some combinations that intuitively seemed acceptable have resulted in early and substantial failure (i.e., TDF/ABC/3TC) [14]. Additionally, assessment of phase 1 decay requires multiple HIV RNA levels, is inconvenient and expensive. HIV RNA changes over one week of treatment have correlated with phase 1 decay and may represent an alternative method to assess regimen potency and predict longer term virologic responses [1].

The primary objectives of this study, therefore, were to compare phase-1 viral decay rate of three regimens for initial therapy: lopinavir/ritonavir + efavirenz, lopinavir/ritonavir plus 2 NRTI versus efavirenz plus 2 NRTI; to evaluate gender differences in viral decay rates; and to evaluate the change in HIV RNA from baseline to week 1 as a potential marker of phase 1 viral decay and as a predictor of longer term virologic outcome.

Methods

Study Design and Population

ACTG A5142 was a phase III, randomized, multi-center, open label, 96-week trial that compared three class-sparing regimens for the initial treatment of HIV infection. HIV-infected, antiretroviral-naïve male and non-pregnant female subjects of at least 13 years of age with plasma HIV RNA levels $\geq$ 2,000 copies/mL, acceptable laboratory values and any CD4 cell count were enrolled into the main study. Eligible participants were randomized equally to three treatment regimens: lopinavir/ritonavir 533/133 mg BID + EFV 600 mg (LPV/EFV) or lopinavir/ritonavir 400/100 mg BID + 2 NRTI (LPV) or EFV 600 mg + 2 NRTI (EFV). Lopinavir/ritonavir was given as the soft-gel capsule and NRTI included lamivudine (3TC) plus investigator selection of zidovudine (ZDV) 300 mg twice daily or stavudine extended release (d4T XR) 100 mg once daily or tenofovir (TDF) 300 mg once daily. Details of the A5142 study design have been published [15,16]. A5160 s, the viral dynamics sub-study of A5142, aimed to accrue 66 subjects with equal numbers of men and women targeted for enrollment (11 of each for each group). HIV RNA was measured on days 2, 10 and 14 in A5160 s and on days 7, 28 and 56 in A5142.

The study protocol was approved by an institutional review board or ethics committee at each participating site. All subjects provided written informed consent.

Statistical Analysis

Distributions of baseline characteristics were compared between the substudy and non-substudy participants and across gender using Kruskall Wallis tests (continuous variables) and Chi-squared tests (categorical variables). Estimation of viral decay rates used a parametric bi-exponential nonlinear mixed-effects model [17]. To ensure accurate estimation of viral decay rates, data points were excluded following treatment interruption or during documented periods of non-adherence (captured via subject diaries). Further, response profiles consistent with an undocumented treatment interruption (reflected by a non-monotonic decline in viremia defined as an HIV RNA increase of more than 0.35 $\log_{10}$ copies/mL from the previous value) were truncated at the point of rebound. HIV RNA levels below the lower level of quantification of the assay (50 copies/mL) were imputed using a hybrid Estimation-Maximization multiple imputation [18]. A grid-search was used to find the best initial values for the model-fitting. The "shoulder effect" was handled using the simple method; model fitting was repeated using the Wu-Ding method (using only on-treatment data from day 2 onwards) as a sensitivity analysis [19,20]. Wilcoxon rank sum tests were used to compare the empirical Bayes estimates of first and second phase decay parameters by treatment group and gender.

The ability of change in $\log_{10}$ HIV RNA from baseline to week 1 (week 1 change) to capture initial regimen potency (as estimated by phase-1 decay) was assessed using Spearman's rank correlation and re-evaluation of the treatment and gender group comparisons using Wilcoxon rank sum tests. Week 1 change was estimated using HIV RNA levels obtained between 5 and 8 days after starting treatment and data were excluded for treatment interruption as described above for the sub-study analyses.

In the A5142 population, associations between baseline and demographic variables and week 1 change were examined using Wilcoxon rank sum tests and censored linear regression. Associations between week 1 change and longer term outcome (HIV RNA >200 and >50 copies/mL at week 24, 48, and 96) used logistic regression models and Cox proportional hazards modeling; week 1 change was modeled as a continuous variable. These analyses were as-treated and included only treatment outcomes observed while on randomized treatment; treatment outcomes for subjects discontinuing treatment prior to the time-point of interest were imputed with the last on-treatment HIV RNA (captured after day 21) carried forward. All P values were 2-sided and were not adjusted for multiple testing. Viral dynamic model fitting was implemented using statistical software Splus version 6 (MathSoft Inc, Cambridge, Mass) (function NLME); all other statistical analysis used SAS version 9.1 (SAS Institute Inc, Cary, NC).

Results

Accrual and Subject Characteristics of the Sub-study

Of the 757 subjects participating in A5142, 68 were enrolled into the A5160 s sub-study, including 34 men and 34 women (Fig. 1). Enrollment was completed by April 2004. Approximately equal numbers of subjects (21–25) were enrolled from each of the three randomized treatment groups. Overall, sub-study subjects were predominantly black (47%) with a median age of 42 years and a median baseline HIV RNA of 4.9 $\log_{10}$ copies/mL. The median baseline HIV RNA in the sub-study subjects was marginally different in the EFV group (4.8 $\log_{10}$ copies/ mL) compared to the LPV and LPV/EFV arms (5.0 and 4.9 $\log_{10}$ copies/mL respectively; $P=0.094$). Sub-study women tended to be older (median 44 versus 40 years for men; $P=0.05$) and differed in their self-reported race/ethnicity ($P=0.02$). Baseline HIV RNA and CD4 cell counts were not significantly different between sub-study men and women ($P=0.37$ and $P=0.77$). Sub-study subjects were not different from main 5142 study subjects with the exception of age (median 42 versus 38 years, $P<0.001$) and NRTI use (a smaller proportion of sub-study subject chose to use TDF).

Phase-1 HIV RNA Decay in Sub-study Participants

Phase-1 viral decay rate was significantly faster for the 25 subjects in the EFV group compared to the 22 subjects in the LPV group ($P=0.023$); subjects in the former group had median (intra-quartile range [IQR]) decay rates of 0.63 (0.57–0.70) day^{-1} compared to 0.53 (0.38–0.66) day^{-1} in the latter group (Table 1, Fig. 2a). The faster decay for EFV corresponded to a shorter virus half-life (1.09 days) compared to LPV (1.31 days). The rate of viral decay in the LPV/ EFV group was 0.61 (0.52–0.68) day^{-1}, and was not significantly different from the other two randomized regimens ($P>0.11$). Sensitivity analyses using data collected after day 2 led to similar estimates of phase-1 parameters and similar findings for the between group comparisons (data not shown).

Overall, subjects with higher baseline HIV RNA levels tended to have larger phase-1 viral decay rates but this difference was not statistically significant ($P=0.26$; Fig. 2b), and caution is needed in interpretation because of the small number of participants in the high HIV RNA stratum. The difference in phase-1 viral decay rate between the EFV and LPV groups was observed in the stratum with lower screening HIV RNA (<100,000 copies/mL). In this stratum, the median viral decay rate was 0.64 (IQR 0.56– 0.72, $n=20$) day^{-1} for the EFV group compared to 0.50 (IQR 0.32– 0.60, $n=16$) day^{-1} for LPV group ($P=0.01$). In contrast, there was no significant difference between the viral decay rates in the EFV versus LPV groups with higher screening HIV RNA (EFV [$n=5$] median 0.62 versus LPV [$n=6$] 0.66; $P=1.0$).

There was no significant difference between men and women in the phase-1 viral decay rates (Fig. 2c). The median (IQR) decay rate for women was 0.57 (038–0.67) day^{-1} and for men was 0.63 (0.55– 0.67) day^{-1} ($P=0.10$). The treatment group differences in Phase-1 decay were observed across the subgroups of men and women.

Phase-2 HIV RNA Decay in Sub-study Participants

Phase-2 HIV RNA decay rates by treatment group (Table 1) showed an opposite pattern compared to the phase-1 decay with the LPV and LPV/ EFV groups having similar decay rates, and the EFV group having a slower decay rate (0.046, 0.045 and 0.036 day^{-1}, respectively; LPV versus EFV, $P=0.003$; others $P>0.2$). Phase-2 viral decay rates were higher across treatment groups in subjects with HIV RNA $>100{,}000$ copies/mL versus $<100{,}000$ copies/ml (median 0.048 day^{-1} compared to 0.038 day^{-1}; $P<0.001$), but because of small numbers of subjects in the high HIV RNA stratum, most of the difference in

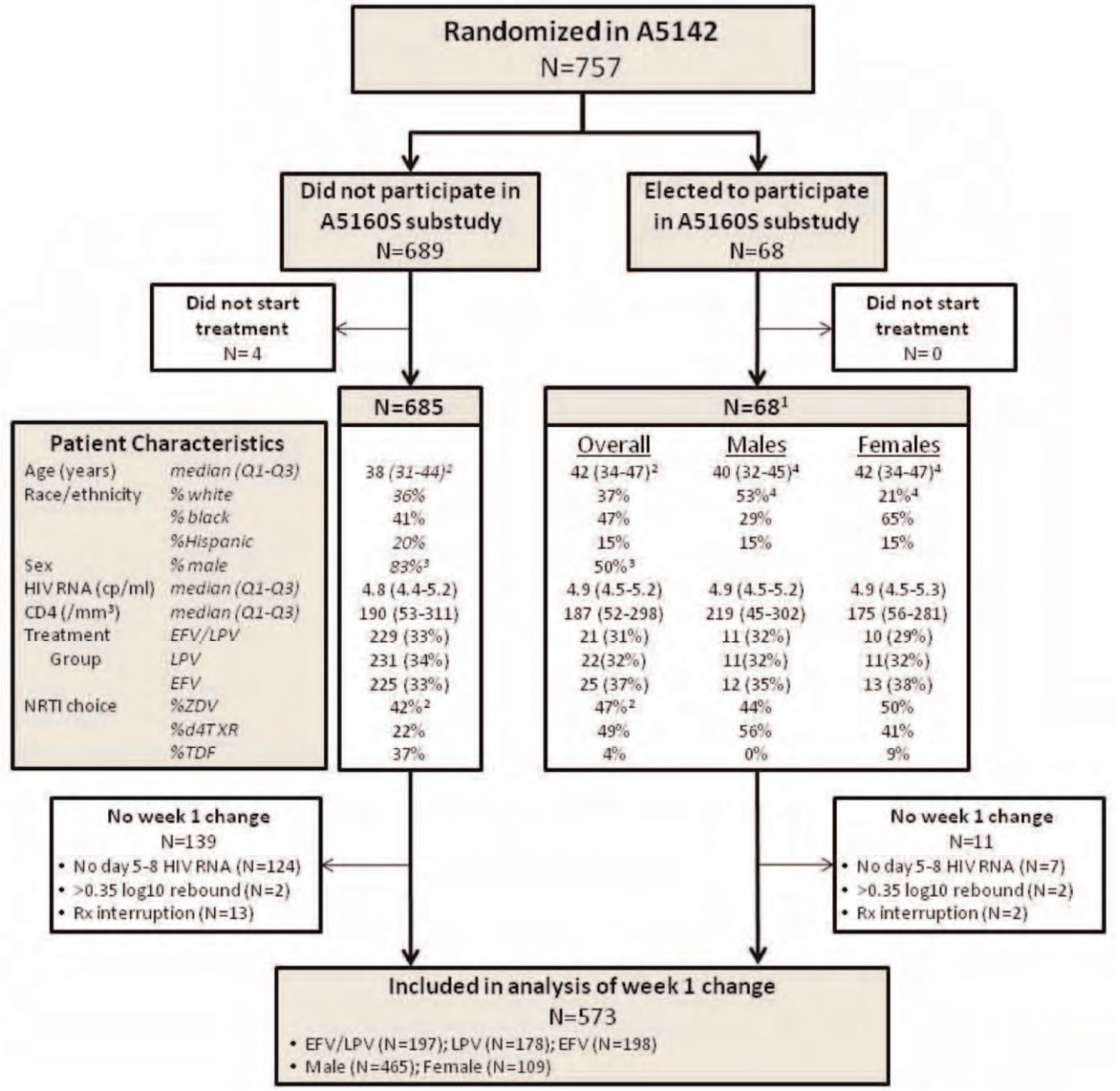

Fig. 1. Patient population. [1]26 subjects (12 females, 14 males) had data points excluded following treatment interruption, documented periods of non-adherence, or HIV RNA increase of more than 0.35 $\log_{10}$ copies/mL from the previous value (13 for treatment interruption/non-adherence, 13 due to rebound). By treatment group the subjects with excluded data were distributed 10 (EFV/LPV), 8 (LPV), and 8 (EFV). The rebound or treatment interruption occurred at week 1 (4 subjects), day 10 (3 subjects), day 14 (7 subjects); day 28 (10 subjects), and day 56 (2 subjects). [2]Significantly different from the remaining A5142 participants ($P < 0.05$). [3]Different from the remaining A5142 participants by design. [4]Significantly different between males and females in the sub-study population ($P < 0.05$). D4T XR, stavudine; EFV, efavirenz + 2 nucleoside reverse transcriptase inhibitors group; LPV, lopinavir/ ritonavir + 2 nucleoside reverse transcriptase inhibitors group; LPV/EFV, lopinavir/ ritonavir + efavirenz group; n, number in each group; Rx, treatment; TDF, tenofovir; ZDV, zidovudine.

phase-2 decay between LPV and EFV groups was in the stratum with screening HIV RNA < 100,000 copies/mL. Phase-2 values in this stratum were 0.043 and 0.034 day^{-1}, respectively ($P < 0.001$). No difference in phase-2 decay rates were detected between men and women ($P = 0.54$).

Transition from First to Second Phase Decay

To explore further the treatment group differences in the phase-1 and -2 decay, the transition between phases was evaluated by identifying the HIV RNA level and day when the rate of change of the phase 2 decay processes became greater than the rate of change of the phase 1

Table 1. Phase- 1 and -2 HIV Decay Parameters by Study Regimen in the A5160 s Sub-study.

			Estimated Decay Parameter (day-1)		Half-life (day)	P-value[a]		
Regimen		n	Median	[q1, q3]	Median	EFV/ LPV vs. LPV	EFV/LPV vs. EFV	LPV vs. EFV
Phase I	EFV/LPV	21	0.61	[0.52, 0.68]	1.14	0.11	0.50	
	LPV	22	0.53	[0.38, 0.66]	1.31			0.023
	EFV	25	0.63	[0.57, 0.70]	1.09			
Phase II	EFV/LPV	21	0.045	[0.035, 0.048]	15.32	0.40	0.11	
	LPV	22	0.046	[0.043, 0.049]	15.02			0.003
	EFV	25	0.036	[0.032, 0.042]	19.49			

[a]P-values based on Wilcoxon rank sum test.
EFV, efavirenz + 2 nucleoside reverse transcriptase inhibitors group; LPV, lopinavir/ ritonavir + 2 nucleoside reverse transcriptase inhibitors group; LPV/EFV, lopinavir/ ritonavir + efavirenz group; n, number in each group; q1, first quartile; q3, 3rd quartile.

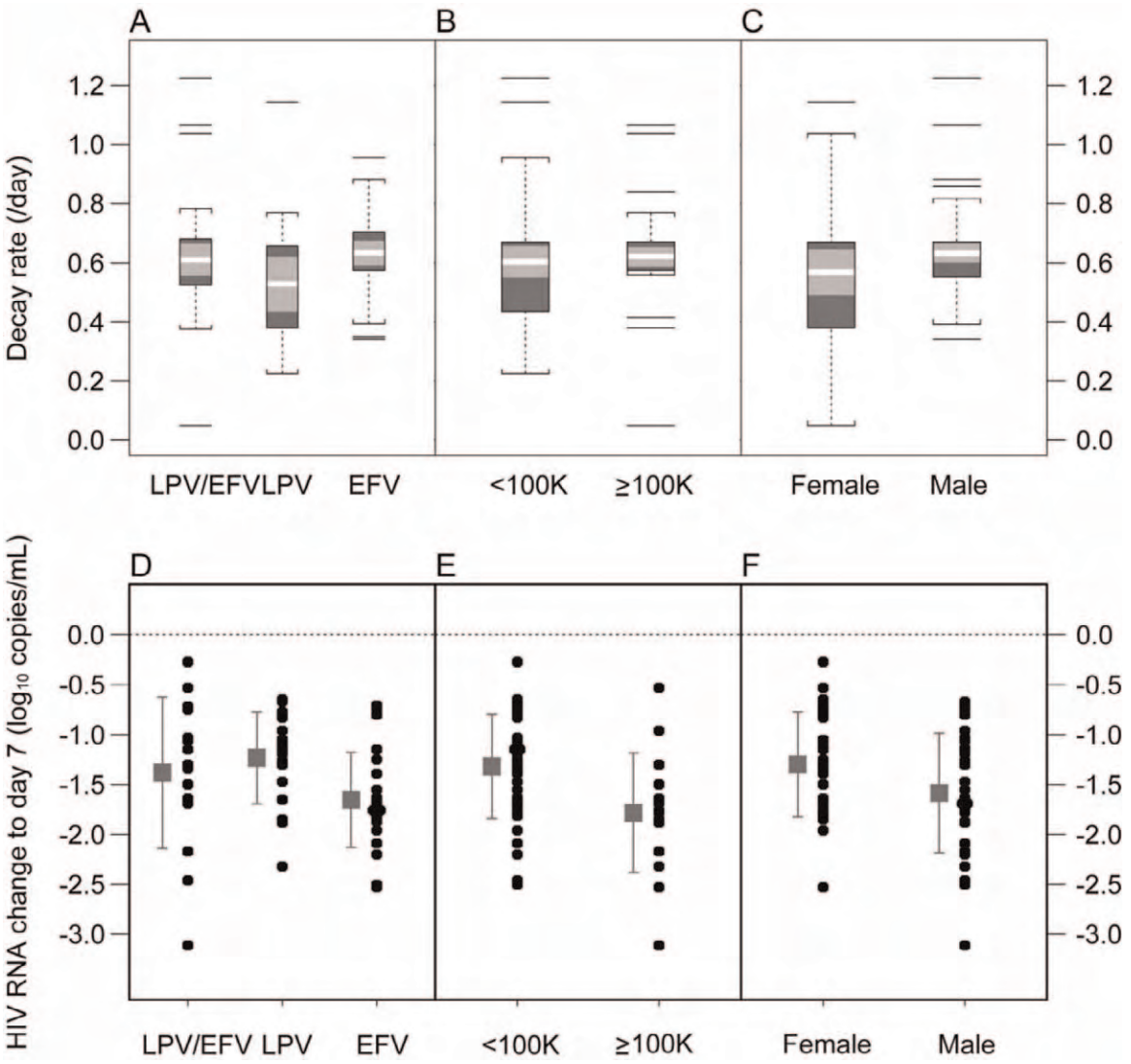

Fig. 2. Phase-1 HIV RNA decay and week 1 change in HIV RNA by regimen, baseline HIV RNA, and gender for A5160 sub-study subjects. (a-c) phase-1 decay rate, white bar is the median, the light grey is the 95% confidence interval on the median and the dark grey is the bounds of the interquartile range, horizontal lines are outliers. (d-f) week 1 change in HIV RNA; the grey boxes are the mean values, and the bars are the standard errors; black dots are individual subject values. Sub-group: A and D- by randomized treatment group; B and E- by baseline HIV RNA; C and F- by gender. EFV, efavirenz + 2 nucleoside reverse transcriptase inhibitors group; LPV, lopinavir/ ritonavir + 2 nucleoside reverse transcriptase inhibitors group; LPV/EFV, lopinavir/ ritonavir + efavirenz groups; 100K = HIV RNA at screening = 100,000 copies/ mL.

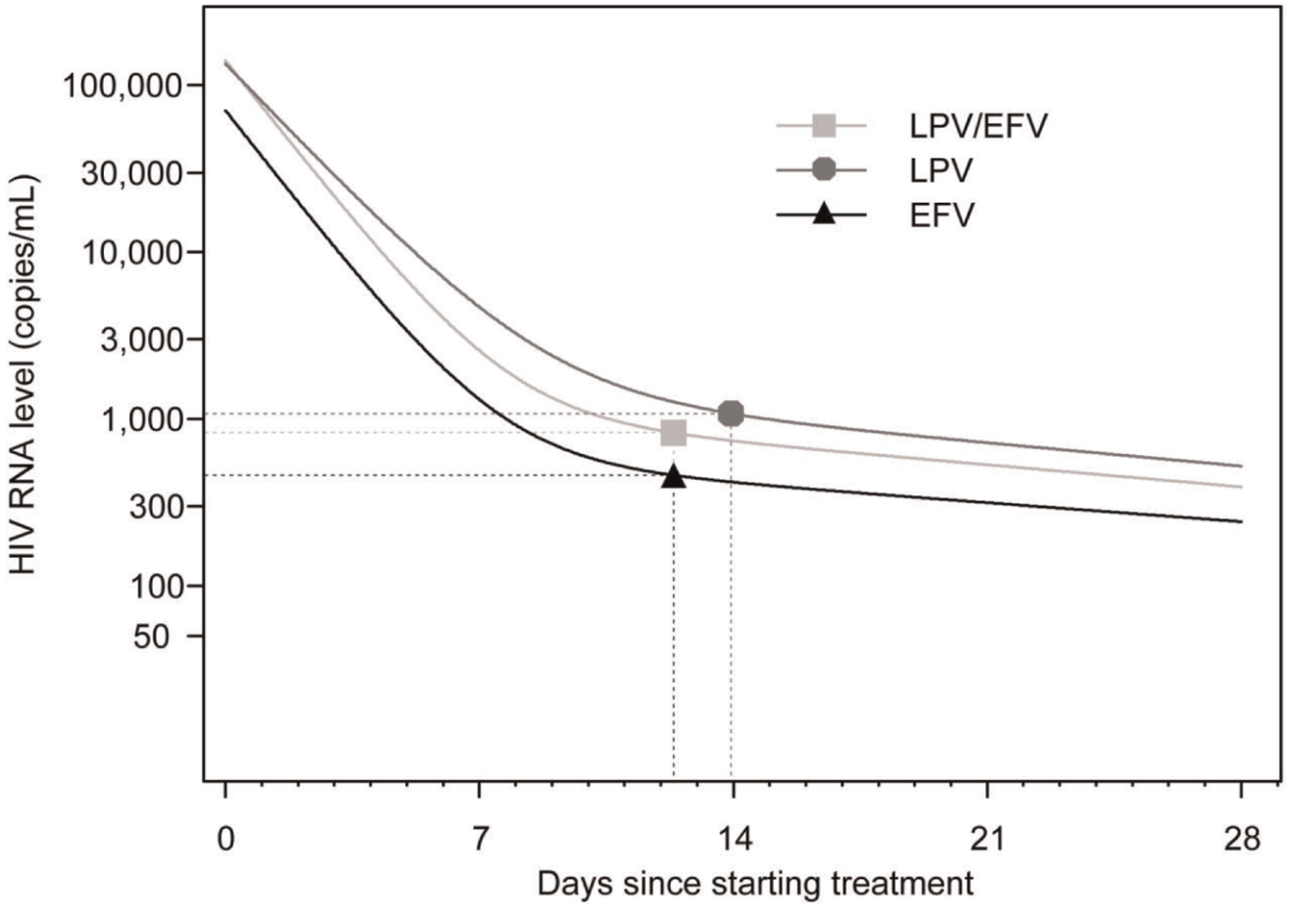

Fig. 3. Slope of the two decay processes over time by treatment group. The estimated overall bi-exponential decay in HIV RNA level over time is shown. The change point between 1st and 2nd phase is indicated by the symbol and the transition day. The day of the transition and the HIV RNA level at transition are indicated by the x- and y- intercepts, respectively. EFV, efavirenz + 2 nucleoside reverse transcriptase inhibitors group; LPV, lopinavir/ ritonavir + 2 nucleoside reverse transcriptase inhibitors group; LPV/EFV, lopinavir/ ritonavir + efavirenz groups.

decay process. Subjects in the EFV group transitioned from phase-1 to 2 at a lower HIV RNA value than the LPV group (median 398 versus 1100 copies/mL) and at an earlier time point (median 12 versus 14 days; Fig. 3). Although censoring of HIV RNA values in the EFV group could partially explain the observations (there were 5 subject in the EFV group versus 1 subject in the LPV group that were censored before day 56), the bi-exponential model includes multiple imputation methods to partially account for the greater censoring in the EFV group. Phase 1–2 transition at a lower HIV RNA in the EFV group may represent greater reduction in short-lived virus-producing cells in the EFV versus LPV group and relative enrichment for longer-lived cells manifest as slower phase-2 decay in the EFV. However, given the lower baseline HIV RNA in the EFV group and the variation in the estimated decay parameters, these data should be interpreted with caution and considered to be hypothesis generating.

Correlation between Phase-1 Decay and Week 1 change in Sub-study Participants

To evaluate the utility of using the single HIV RNA measurement at week 1 of therapy as a potential surrogate for the more detailed phase-1 decay modeling, the correlation between the phase-1 decay rate and week 1 change in HIV RNA was evaluated in the sub-study. A high degree of correlation was observed between the two measures (Spearman correlation -0.78; $P < 0.001$, Supplemental Figure 1) and were consistent across all treatment group and gender comparisons (Fig. 2). Consequently, further analyses of potential parameters influencing initial HIV decline including treatment group, gender, race/ethnicity and choice of NRTI were performed using the larger A5142 population to improve statistical power.

Week 1 HIV RNA Change in A5142 Subjects

A total of 573 subjects were evaluable for the week 1 $\log_{10}$ change in HIV RNA analysis (Fig. 4). Subjects

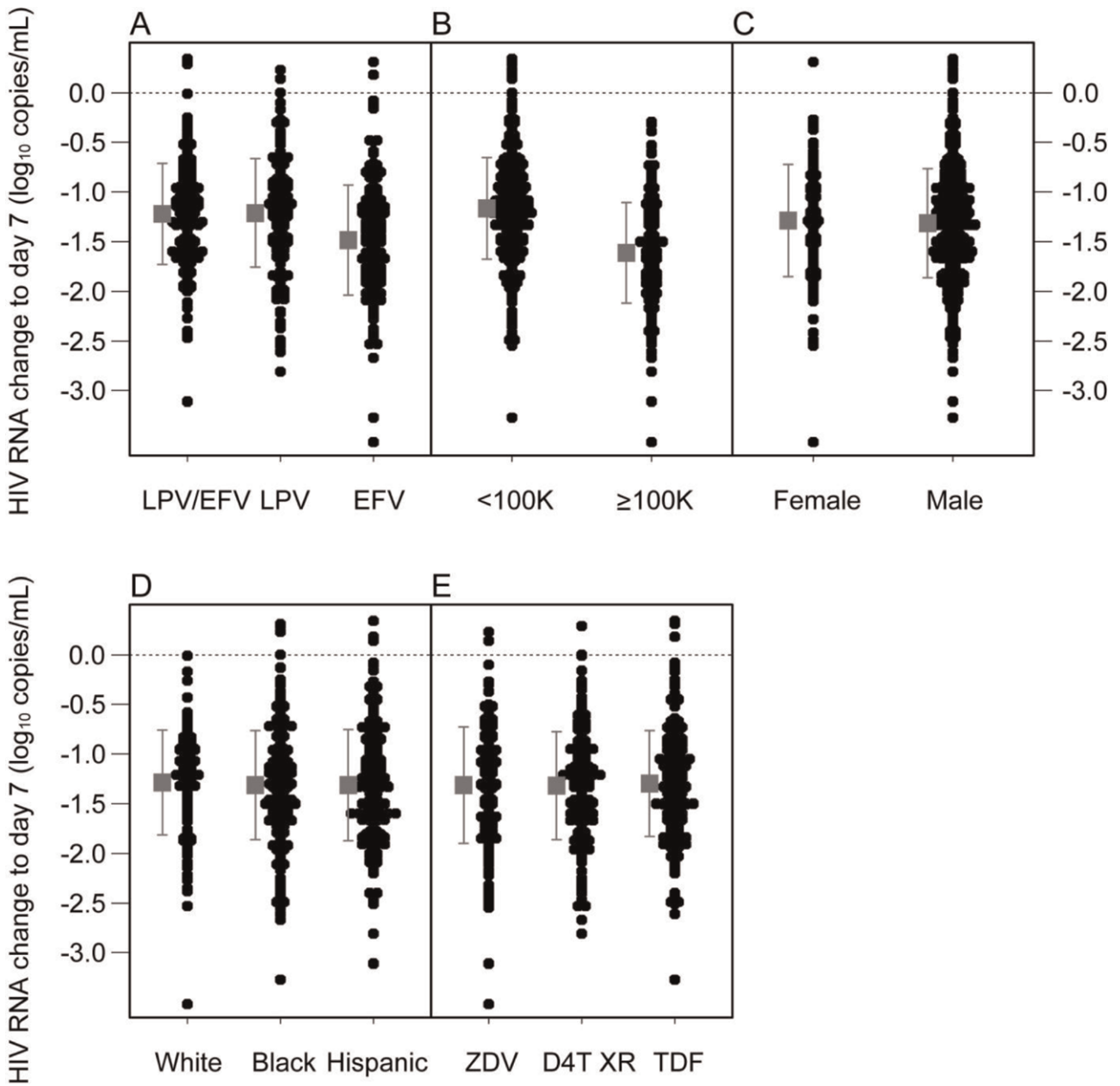

Fig. 4. Change from baseline to week 1 in HIV RNA in A5142 (N = 573) by: A. randomized study regimen; B. screening HIV RNA; C. Sex; D. Race/ Ethnicity; E. NRTI selected. The grey boxes are the mean values, and bars are standard errors; black dots are individual subject values. D4T XR, stavudine; EFV, efavirenz + 2 nucleoside reverse transcriptase inhibitors group; LPV, lopinavir/ ritonavir + 2 nucleoside reverse transcriptase inhibitors group; LPV/EFV, lopinavir/ ritonavir + efavirenz groups; TDF, tenofovir; ZDV, zidovudine.

randomized to the EFV group had a significantly greater median week 1 $\log_{10}$ change in HIV RNA (−1.47, interquartile range [IQR] −1.83 to −1.15) than those in either the LPV/EFV (−1.21, −1.58 to −0.90) or the LPV group (−1.16, −1.52 to −0.87; $P < 0.001$ for each pairwise comparison with EFV; Fig. 4). Across all treatment groups combined, subjects with baseline HIV RNA > 100,000 copies/mL had larger week 1 change compared to those with lower baseline HIV RNA ($P < 0.001$); the median change was −1.62 copies/mL (IQR −1.92 to −1.29) compared to −1.15 copies/mL (IQR −1.48 to −0.85; $P < 0.001$). After adjusting for initial HIV RNA level, the week 1 change associated with the EFV group remained greater than both the LPV and LPV/EFV groups ($P < 0.001$). There was no interaction between treatment and initial HIV RNA ($P = 0.11$ overall, pairwise interaction terms > 0.26). No differences in week 1 change were detected between men and women ($P = 0.51$), by self-reported race/ethnicity ($P = 0.60$), or by choice of NRTI ($P = 0.82$).

Table 2. Predictors of Virologic Failure after 24–96 Weeks on Study.

Predictors of Virologic failure	Analysis sample size (# events)		Odds ratio (95% confidence interval)		P-value
At Week 24					
HIV RNA > 50 copies/ mL					
Change to week 1 (per 1$\log_{10}$ decrease)	530	(170)	0.22	(0.14, 0.35)	< 0.001
Baseline HIV RNA (per 1$\log_{10}$)	530	(170)	4.21	(2.95, 6.14)	<0.001
HIV RNA > 200 copies/ mL					
Change to week 1 (per 1$\log_{10}$ decrease)	530	(55)	0.68	(0.38, 1.19)	0.18
Baseline HIV RNA (per 1$\log_{10}$)	530	(55)	1.92	(1.24, 3.01)	0.004
At Week 48					
HIV RNA > 50 copies/ mL					
Change to week 1 (per 1$\log_{10}$ decrease)	535	(127)	0.61	(0.40, 0.91)	0.018
Baseline HIV RNA (per 1$\log_{10}$)	535	(127)	2.05	(1.48, 2.86)	<0.001
HIV RNA > 200 copies/ mL					
Change to week 1 (per 1$\log_{10}$ decrease)	535	(60)	0.67	(0.39, 1.15)	0.15
Baseline HIV RNA (per 1$\log_{10}$)	535	(60)	1.40	(0.92, 2.14)	0.12
At Week 96					
HIV RNA > 50 copies/ mL					
Change to week 1 (per 1$\log_{10}$ decrease)	524	(136)	0.76	(0.51, 1.13)	0.18
Baseline HIV RNA (per 1$\log_{10}$)	524	(136)	1.46	(1.08, 2.00)	0.015
HIV RNA > 200 copies/ mL					
Change to week 1 (per 1$\log_{10}$ decrease)	524	(84)	0.89	(0.56, 1.41)	0.62
Baseline HIV RNA (per 1$\log_{10}$)	624	(84)	1.04	(0.73, 1.50)	0.81

The Odds Ratio (OR) represents the odds of virologic failure per 1 $\log_{10}$ HIV RNA reduction to week 1. HIV RNA outcome is defined by HIV RNA above 200 or 50 copies/mL at weeks 24, 48 and 96. Analyses are presented for the as-treated population and use a last on-treatment observation carried forward for subjects discontinuing randomized treatment. An OR below 1 suggests a reduction in risk of virologic failure for greater HIV RNA reductions at week 1.

HIV RNA week 1 $\log_{10}$ Change from Baseline as a Predictor of Longer Term Viral Suppression

The ability of week 1 change in HIV RNA to predict longer term virologic outcome was studied in multivariate logistic regression models adjusted for baseline HIV RNA with virologic failure defined by levels above 50 and 200 copies/mL at weeks 24, 48, and 96 (Table 2). Each additional $\log_{10}$ decrease in HIV RNA at week 1 was associated with a reduction in the odds of week 24 HIV RNA > 50 copies/mL (odds ratio 0.22, 95% confidence interval 0.14, 0.35; $P < 0.001$) but not significantly with virologic failure above 200 copies/mL ($P = 0.18$). There was no evidence of an interaction between baseline HIV RNA and week 1 change ($P = 0.80$) with respect to their association with week 24 outcomes. Similarly, after accounting for baseline HIV RNA, the week 1 change was associated with a lower odds of week 48 HIV RNA > 50 copies/mL (0.61, 95% CI, 0.40, 0.91, $P = 0.018$), but not with the virologic failure above 200 copies/mL ($P = 0.15$). There were no significant associations between week 1 change and virologic failure at week 96 using either the 50 or 200 copies/mL failure thresholds.

Discussion

Initial viral clearance, as evaluated by phase-1 HIV RNA decay, was significantly greater for subjects treated with EFV + 2 NRTI than LPV + 2NRTI. The NRTI-sparing regimen of LPV-EFV had initial viral clearance similar to that for EFV + 2 NRTI. These results are concordant with the overall results of 5142, which found that subjects randomized to the EFV group reached HIV RNA < 50 copies/mL faster (78% for the EFV and 62% for the LPV groups at week 24) and had significantly longer time to virologic failure than those in the LPV group [16]. The viral decay rate for the LPV/EFV arm was also consistent with the overall results of A5142 suggesting that phase-1 decay on this regimen is driven by EFV. As with other reports, phase-1 decay was not significantly different for subjects by gender and race/ethnicity [1,6,11].

Importantly, we found that modeled phase-1 decay in the A5160 s sub-study population was strongly correlated week 1 HIV RNA reduction (Spearman correlation −0.78; $P < 0.001$), indicating that HIV-1 RNA change after the first week of therapy can be used as a simpler surrogate for the more complex sampling and modeling involved in estimating phase-1 decay. Furthermore, week 1 HIV RNA decline was greatest in the EFV + 2 NRTI arm of A5142 and that greater week 1 HIV RNA reductions were predictive of lower odds of virologic failure at weeks 24 and 48 (but not 96) defined by HIV RNA values above 50 copies/mL. Taken together, these observations support the use of week 1 HIV RNA change as an indicator of initial regimen activity and durability of suppression up to 48 weeks. The waning of the predictive effect of week 1 HIV RNA change over time is not surprising given the many other factors, such as adherence, side effects, and pill burden that influence longer-term virologic outcome. Furthermore, week 1

HIV RNA change was not predictive of virologic failure >200 copies/mL suggesting that other factors are involved in the extent of virologic failure including emergence of HIV drug resistance.

Some limitations of this study should be noted, particularly for the sub-study. Censoring of HIV RNA values below 50 copies/ mL could affect estimates of phase-2 decay in the sub-study, although we used multiple imputation methods to partially address this issue. Differences, although minor, in pre-therapy HIV RNA levels between sub-study treatment groups could have impacted decay estimates, and the relatively small number of sub-study subjects in the high HIV RNA stratum make complicates interpretation, as we have cautioned. In addition, the relationship between week 1 HIV RNA changes and week 24–96 HIV RNA suppression in A5142 could be confounded by factors such as drop out and differential regimen adherence. This is, in fact, suggested by stronger correlations with week 24 than week 96 results. Despite these limitations, this study provides important new insight into the relations between phase-1 decay, week 1 HIV RNA change, and longer-term virologic outcome.

These findings add to the body of evidence that early viral decay after initiation of combination ART can be useful to evaluate the likelihood of longer term viral suppression. Potentially, novel combinations of 2 or more antiretroviral agents could be assessed in short term studies of 7–14 days; and, if adequate phase-1 decay or week 1 HIV RNA reductions are achieved, then further testing of the combinations could be pursued and combinations that have inadequate potency could be avoided. However, these findings do not guarantee a link between early viral decay and longer term suppression for combinations other than the ones evaluated here. Early response to new drug combinations having different mechanisms of action may be less predictive.

Phase-2, and to a lesser extent phase-1, HIV RNA decay correlated directly with pre-therapy HIV RNA. Specifically, phase-2 decay was greater in subjects with pre-therapy HIV RNA >100,000 copies/mL than those with < 100,000 copies/mL. The reason for greater phase-2 decay with higher pre-therapy viremia is unknown, but may be the consequence of a larger, pre-therapy infected cell population such that more cells with relatively short half-lives contribute to decay after the modeled transition between phase-1 and phase-2. The transition between phase-1 and -2 is postulated to be the time when the slope of decay becomes dominated by long-lived productively infected cells as opposed to short-lived cells [21–23]. Phase-2 decay was significantly slower in the EFV group, which had the highest phase-1 decay rate, compared to the LPV-containing treatment groups. This inverse relationship was observed in subjects with HIV RNA below 100,000 copies/mL. There are several potential explanations for this observation including: greater censoring at the 50 copies/mL detection limit in the EFV group with greater reliance on imputation for modeling of phase-2 decay or intrinsic differences in the mechanism of action of the ARV studied (protease inhibitors act later in the virus life cycle and potentially could have activity against the chronically-infected cell populations that may contribute to phase-2 viral decay) [24,25]. Alternatively, greater inhibition of productive infection of short-lived cells by EFV, which acts before HIV integration could enrich for infected cells with

In summary, we have shown that faster phase-1 viral decay rate, as assessed either by modeled dynamics in A5160 s or by week 1 change in HIV RNA in A5142, was greater in subjects who received 2 NRTI plus EFV compared with LPV, and that greater initial HIV RNA decline was predictive of longer term virologic outcome to week 48, but not at week 96. Regimen potency, as assessed by these measures, was not influenced by demographic factors. These findings add to the literature supporting the use of initial viral decay rate to assess new combinations of antiretrovirals for initial activity and durability of HIV suppression up to 48 weeks.

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Potential Conflicts of Interest

R.H. reports having received honoraria or consultant fees from Abbott, Bristol-Myers Squibb, Gilead Sciences, GSK, Merck, Monogram, Pfizer, Roche, Tibotec and ViiV and research support (to UCSD) from Abbott, GlaxoSmithKline, Merck, Pfizer and ViiV.

JM reports being a consultant for Merck, Gilead Sciences, and RFS Pharma, and owning share options in in RFS Pharma.

DH is the principal investigator of a NIH sponsored study where Abbott pharmaceuticals provides study drug.

KG is an employee of Abbott Laboratories.

DB is an employee of Bristol-Myers Squibb.

JR is an employee of Gilead Sciences.

SR, HR, KK and GDR report no conflicts.

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