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Early virologic response to abacavir/lamivudine and tenofovir/emtricitabine during ACTG A5202

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Abstract

Background—ACTG A5202 randomized treatment-naïve individuals to tenofovir-emtricitabine (TDF/FTC) or abacavir-lamivudine (ABC/3TC) combined with efavirenz (EFV) or atazanavir/ritonavir (ATV/r). Individuals in the high screening viral load (VL) stratum (> 100,000 copies/mL) had increased rates of virologic failure with ABC/3TC.

Objective—Compare regimen-specific early virologic response.

Methods—Using Wilcoxon rank-sum tests, we compared regimen-specific VL changes from entry to week 4 in A5202 subjects (n=1813) and from entry to week 1, 2 and 4 in a 179-patient substudy. We evaluated associations between week 4 VL change and time to virologic failure with Cox proportional-hazards models.

Results—TDF/FTC- and ABC/3TC produced similar Week 4 viral load declines in the entire study population and in the high VL stratum. EFV produced greater VL declines from baseline at week 4 than ATV/r (median −2.1 vs. −1.9 log₁₀ copies/mL; p<0.001). In the substudy of subjects with week 1, 2 and 4 VL data, there was no difference in viral load decline in those randomized to TDF/FTC versus ABC/3TC, but EFV resulted in greater VL decline from entry at each of these timepoints than ATV/r. Smaller Week 4 viral load decline was associated with increased risk of virologic failure.

Conclusions—Within all treatment arms, a less robust week 4 virologic response was associated with higher risk for subsequent virologic failure. However, between-regimen differences in week 4 VL declines did not parallel the previously reported differences in longer term virologic efficacy in A5202, suggesting that between-regimen differences in responses were not due to intrinsic differences in antiviral activity.

Keywords

Anti-HIV Agents; HIV Infections/drug therapy/*virology; Treatment Outcome

INTRODUCTION

In the randomized clinical study AIDS Clinical Trials Group (ACTG) A5202, we previously reported that in treatment-naïve HIV-1-infected individuals time to virologic failure was similar in those assigned to atazanavir/ritonavir (ATV/r) or efavirenz (EFV).¹ However, in the high screening viral load stratum (>100,000 copies/mL), there was a significantly shorter time to virologic failure in those assigned to abacavir (ABC)/lamivudine (3TC) versus tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) (hazard ratio=2.33; $p<0.001$), regardless of which third drug was used.² In contrast, this was not seen in those in the low screening viral load stratum.³

Studies have shown similar findings⁴, others have not⁵, and there remains debate regarding the optimal nucleoside/tide reverse transcriptase inhibitor (NRTI) combination for treatment-naïve HIV-1 infected individuals. The Department of Human Health Services guidelines consider TDF/FTC as the preferred NRTI combination,⁶ while the International Antiviral Society–USA Panel guidelines also include ABC/3TC as recommend components of first-line therapy for individuals with a viral load of <100,000 copies/mL.⁷

The chronic phase of untreated HIV infection is characterized by viral replication resulting in a dynamic equilibrium between viral production and clearance, with approximately one-half of the circulating virus replaced daily with newly produced virus.⁸ Combination antiretroviral therapy (ART) prevents the infection of lymphocytes and monocytes and perturbs this equilibrium. Most viral-dynamics models assume that ART results in complete inhibition of viral replication. If treatment has no effect on the death rate of infected cells or on the rate of plasma virus clearance, decay rates reflect the potency of antiretrovirals in combination. Thus, a comparison of early virologic response between different antiretroviral regimens may provide insights into a regimen's inherent antiviral activity, although antiretrovirals targeting different steps in the viral replication cycle may result in different decay rates independent of their antiviral activity.⁹ Many, but not all studies, have shown that greater early virologic response (e.g., at 1, 2, and 4 weeks) of a regimen is associated with superior longer term virologic efficacy.^{10–13} Here, in an attempt to explain the observed primary efficacy difference between TDF/FTC and ABC/3TC in the high viral load stratum, we evaluate regimen-specific early virologic response in ACTG A5202 and in its early viral load substudy.

METHODS

ACTG A5202 Study Design

AIDS Clinical Trials Group (ACTG) A5202 was an equivalence study that randomized 1857 HIV-1-infected treatment-naïve subjects to blinded TDF/FTC or ABC/3TC combined with open-label ATV/r or EFV, stratified by screening viral load ($\geq 100,000$ or $<100,000$ copies/mL). Entry criteria for ACTG A5202 included age of ≥ 16 years, ≥ 7 days of prior ART, and no evidence of major resistance mutations.¹ Resistance testing was only required for recently infected patients and was optional for those with chronic infection. Planned study duration was 96 weeks after the last subject enrolled. The study enrolled between 2005 and 2007 and completed follow-up in 2009 with a median length of follow-up of 138 weeks. The primary efficacy endpoint was time from randomization to virologic failure. Virologic failure was defined as a confirmed viral load of ≥ 1000 copies/mL between 16 and 24 weeks after randomization or ≥ 200 copies/mL at or after 24 weeks. Screening viral load assessments prior to study entry were performed locally at each study site. From study entry onward, viral load assessments were performed centrally with the Roche Amplicor Monitor Assay Version 1.5 with a lower limit of quantification (LLQ) of 50 copies/mL.

Viral Load Change from Entry to Week 4 Analysis

All ACTG A5202 subjects with an available week 4 viral load measurement were included in this analysis. We compared the viral load change from entry to week 4 among the four different regimens (and summarized across third drug and by NRTI assignment by combining ATV/r and EFV and then ABC/3TC and TDF/FTC arms, respectively) with the Wilcoxon rank sum test. Viral load values below the Amplicor assay's lower limit of quantification (LLQ) of 50 copies/mL (occurring in 8% of patients at week 4) were set to 50 copies/mL.

Early Viral Load Substudy

An early viral load substudy was performed at five of the 59 enrolling ACTG A5202 sites. Subjects returned for phlebotomy at entry and weeks 1, 2, and 4 after randomization, and plasma samples from these visits were tested with the Roche COBAS Ampliprep/COBAS TaqMan HIV Test Version 2 with a LLQ of 20 copies/mL. To conserve sample aliquots for additional analyses, samples were diluted 1:1 (0.5mL per sample). The LLQ was therefore set to 40 copies/mL, and copy numbers reported account for this dilution. We compared the viral load changes from entry to values obtained at Weeks 1, 2, and 4 between each of the four regimens using Wilcoxon rank sum tests. Viral load values below Taqman assay's LLQ were set to 40 copies/mL (occurring in 0%, 0%, and 6% of patients at 1, 2, and 4 weeks, respectively).

Time to Virologic Failure Analysis

In the overall ACTG A5202 study population, the relationship between change in viral load from entry to week 4 and time to virologic failure was evaluated with univariate and multivariable Cox proportional hazards models. Multivariable models were adjusted for age, sex, race/ethnicity, history of intravenous drug use, whether a pre-enrollment genotype was

performed, history of AIDS, hepatitis B or C infection, baseline HIV-1 viral load, and baseline CD4+ T-cell count. Given the efficacy difference in TDF/FTC versus ABC/3TC arms in the high viral load stratum, we analyzed the associations separately in the TDF/FTC and ABC/3TC arms.

Ethics

Approval was obtained from each participating sites' institutional review board for the main study and the substudy. All subjects provided written informed consent prior to study entry.

RESULTS

The 1813 enrolled subjects included in this analysis who returned for a Week 4 viral load assessment were similar to the overall study population of ACTG A5202 (Table 1). The median age of the included subjects at baseline was 38 (IQR 31, 45) and 83% were male (Table 1). The median baseline CD4 T-cell count and viral load (by Amplicor) was 229 cells/ μ L (IQR 91, 333) and 4.7 log₁₀ copies/mL (IQR 4.3, 5.0), respectively. Forty-three percent of subjects were in the high screening viral load stratum (screening viral load of 100,000 copies/mL).

Combining the third drugs, there was no significant difference in the distribution of viral load change from entry to week 4 in those subjects randomized to TDF/FTC vs. those randomized to ABC/3TC (Figure 1; median change -2.0 vs. -2.0 log₁₀ copies/mL; $p=0.54$) without any evidence of interaction by third drug ($p=0.95$). Restricting the evaluation to subjects in the high screening viral load stratum, there was also no significant difference in change in viral load from entry to week 4 in subjects randomized to TDF/FTC versus those to ABC/3TC (Figure 1; median change -2.2 vs. -2.2 log copies/mL; $p=0.69$).

Combining the NRTIs, subjects randomized to EFV-containing regimens had a significantly greater decline in viral load from entry to 4 weeks than those randomized to ATV-containing regimens (Figure 1; median change -2.1 vs. -1.9 log₁₀ copies/mL; $p<0.001$) without evidence of an interaction by assigned NRTIs ($p=0.78$).

In the early viral load substudy, 179 subjects enrolled. Table 1 displays the baseline characteristics of these subjects. The subjects differed from those ACTG A5202 subjects not enrolled in the substudy in that they were more frequently male and White non-Hispanic, had a lower median baseline CD4+ T-cell count, and less frequently had a pre-enrollment genotype performed. Baseline characteristics were balanced between subjects randomized to each of the four study regimens within the substudy (data not shown).

Patterns of viral load changes in the early viral load substudy mirrored the patterns observed in the overall study. Viral load change from entry to weeks 1, 2, and 4 were similar between those subjects randomized to TDF/FTC versus those randomized to ABC/3TC, whether paired with EFV or ATV/r (Table 2). In the high viral load stratum, there also was no significant difference in viral load change between subjects randomized to TDF/FTC compared to those randomized to ABC/3TC when paired with EFV, although with ATV/r there appeared to be a trend toward a smaller decline in viral load from entry to weeks 1, 2

and 4 in subjects randomized to ABC/3TC compared to those randomized to TDF/FTC (Table 3).

In the early viral load substudy, subjects randomized to EFV-containing regimens had greater decreases from entry in viral load than those assigned to ATV/r-containing regimens. This difference was apparent by week 1 (median change $-1.5 \log_{10}$ vs. $-1.2 \log_{10}$; $p<0.001$) and was maintained at both week 2 (median change $-2.0 \log_{10}$ vs. $-1.8 \log_{10}$; $p<0.001$) and week 4 (median change $-2.4 \log_{10}$ vs. $-2.2 \log_{10}$; $p=0.003$).

In the overall ACTG A5202 study, combining across the third drugs, a smaller viral load decline from entry to week 4 was associated with increased risk of study-defined virologic failure in individuals on both TDF/FTC- and ABC/3TC-containing regimens with a hazard ratio (HR) for virologic failure per 1 $\log_{10}$ copies/mL less decline in viral load of 1.8 (95% CI: 1.4, 2.3) and of 1.3 (95% CI: 1.1, 1.7), respectively. There was no evidence that this association differed by third drug assignment (p -value for interaction of 0.66 for TDF/FTC-containing arms and of 0.53 for ABC/3TC-containing arms). After adjusting for baseline covariates, the relationship between viral load change from entry to week 4 and virologic failure was maintained in both TDF/FTC- and ABC/3TC-containing regimen arms with adjusted HR of virologic failure per 1 $\log_{10}$ copies/mL less decline in viral load of 1.8 (95% CI: 1.4, 2.3) and of 1.9 (95% CI: 1.5, 2.4), respectively.

DISCUSSION

In this protocol-specified secondary analysis of ACTG A5202 and its viral load substudy, we found no significant difference in early viral load change between the NRTI arms, including in the high viral load stratum. In contrast, assignment to EFV resulted in a small but significantly greater early viral load decline than ATV/r. We found a smaller week 4 virologic response was associated with an increased risk for subsequent virologic failure.

Our findings are consistent with a study from Haubrich and colleagues in ACTG A5142, which found a small, but significantly greater early viral load decline in individuals on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy compared to individuals on ritonavir-boosted protease inhibitor (PI/r)-based therapy.¹³ In this previous study, NNRTI-based therapy resulted in faster Phase 1 viral decay than PI/r-based therapy.¹³ Our results support this observation as a significantly greater viral load decline from entry between those on EFV compared to ATV/r was already apparent at week 1 - a timepoint that can be used as a surrogate for Phase 1 decay.¹³ It has been postulated that the slower early decrease in viral load with PI- versus NNRTI-based regimens may be due to PIs acting later in the virus replication cycle than NNRTIs, resulting in slower inhibition of productive virus replication. More importantly and somewhat paradoxically, the diminished early response to PI-based therapy as compared to NNRTI-based therapy did not result in an increased rate of subsequent virologic failure with the PI/r-based regimen in ACTG A5202, as was seen in ACTG A5142.¹⁴

Randomized comparisons between TDF/FTC and ABC/3TC show conflicting results, depending on the third drug used.^{2,4,5,15} In the ASSERT study with EFV as the third drug

among 385 treatment-naïve subjects, a significantly lower proportion achieved a viral load of <50 copies/mL at 48 weeks in the ABC/3TC arm (59%) compared to in the TDF/FTC arm (71%).⁴ Alternatively, in the HEAT study with lopinavir/ritonavir as the third drug among 688 treatment-naïve subjects, ABC/3TC was shown to be non-inferior to TDF/FTC with 68% and 67% of subjects, respectively, achieving a viral load of <50 copies/mL at 48 weeks, with similar outcomes also seen in individuals with a viral load of 100,000 copies/mL.⁵ In a small study of 109 subjects with ATV/r as the third drug, the time to virologic failure was not significantly different in those randomized to ABC/3TC versus TDF/FTC (HR=2.1; 95% CI: 0.7, 6.1), although nearly 100% of patients had a baseline viral load of <100,000 copies/mL.¹⁵ Additionally, subgroup analyses from the randomized THRIVE and SPRING-2 studies did not show a difference in efficacy between subjects given ABC/3TC vs. TDF/FTC, although the NRTIs were investigator-selected in these studies and not allocated through randomization.^{16,17}

The early decline in plasma HIV-1 RNA from baseline does not appear to explain the difference in primary efficacy outcomes observed in ACTG A5202 between the NRTIs. In fact, we found no significant differences in the early virologic responses to TDF/FTC and ABC/3TC, including in the high viral load stratum. This suggests that the increased rates of virologic failure with ABC/3TC in the high viral load stratum may not have been primarily due to differences in antiviral activity between ABC/3TC and TDF/FTC, but by factors such as long-term adherence, pharmacokinetics/pharmacodynamics, and toxicity. Our study results call into question the value of using early virologic response as a surrogate for expected longer term virologic outcome when comparing the efficacy of different regimens. Indeed, in ACTG A5202, early virologic responses were the converse of the overall study outcome: TDF/FTC and ABC/3TC had comparable early VL responses, yet ABC/3TC had a higher rate of virologic failure; by contrast, EFV had a greater VL response than ATV/r, yet the two strategies had similar rates of virologic failure in this equivalence study. Similarly, clinical trials that compare integrase inhibitor- to non-integrase inhibitor-based regimens invariably show a faster viral load decline in the integrase treatments, yet the ultimate study outcomes may be comparable.^{18–20}

In monotherapy studies, TDF and ABC produced 1.5 and 1.1 log₁₀ copies/mL reductions in viral load, respectively.^{21,22} In vitro, FTC has been shown to be more potent than 3TC.²³ However, the most clinically relevant difference between the medications may be the longer intracellular half-life of TDF/FTC versus ABC/3TC.⁶ Pharmacokinetic differences in regimens have manifested as higher rates of virologic failure in only the subset of subjects with high viral loads in a number of recent clinical trials,^{16,24,25} suggesting that the shorter half-life of ABC/3TC could be a plausible mechanism for the overall findings of ACTG A5202.

Some limitations of this study should be noted. Subjects were not directly observed taking medication and baseline genotypes were not performed for all individuals in the study, possibly obscuring any potential differences in regimen potencies; however, these limitations would presumably apply similarly across all randomized treatment arms. The association analysis is based on data collected post-randomization and restricted to those who were able to return for their Week 4 viral load sample. The virologic failure definition

for A5202 included the relatively atypical criteria of a viral load of 1000 copies/mL between 16 and 24 weeks after randomization, as well as the more typical threshold of 200 copies/mL at or after 24 weeks. We did not separately assess the relationship between week 4 virologic response and early or late virologic failure. Additionally, for the early viral load substudy, the sample size was relatively small and we did not sample sufficient timepoints to calculate Phase 1 and Phase 2 decay rates. However, previous studies have shown that single early viral load measurements can be used as surrogates for the more complex sampling and modeling involved in estimating the phases of decay.¹³

CONCLUSION

In summary, we have shown that smaller four-week decline in viral load was associated with a higher rate of subsequent virologic failure. EFV resulted in a slightly greater decline in early viral loads than ATV/r, but this did not parallel a difference in virologic failure in individuals on these medications. By contrast, there was no significant difference observed in early response between the TDF/FTC and ABC/3TC arms, including in the high viral load stratum. This would suggest that differences in intrinsic antiviral potency alone do not explain the increased rates of virologic failure in those assigned ABC/3TC versus TDF/FTC in the high viral load stratum of ACTG A5202, raising the possibility that other factors, such as pharmacokinetics, barrier to resistance, and tolerability may have contributed.

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Figure 1.
Box Plot of 4 Week Viral Load Change from Entry by Regimen and Screening Viral Load Strata

Table 1

Baseline Characteristics of Included Subjects in ACTG A5202 and the Early Viral Load Substudy

Characteristic	A5202 with Week 4 RNA Data (n=1813)	All A5202 (n=1857)	Early Viral Load Substudy (n=179)
Median Age - Years (IQR)	38 (31, 45)	38 (31, 45)	38 (31, 45)
Gender			
Male	1500 (83%)	1535 (83%)	159 (89%)
Female	313 (17%)	322 (17%)	20 (11%)
Race/Ethnicity			
White Non-Hispanic	734 (41%)	746 (40%)	93 (52%)
Black Non-Hispanic	599 (33%)	615 (33%)	39 (22%)
Hispanic	417 (23%)	429 (23%)	39 (22%)
Other	58 (4%)	62 (4%)	7 (5%)
Median CD4+ Count -cells/μL (IQR)	229 (91, 333)	230 (90, 334)	185 (56, 287)
Screening Viral Load			
100,000 copies/mL	783 (43%)	797 (43%)	80 (45%)
<100,000 copies/mL	1030 (57%)	1060 (57%)	99 (55%)
Entry Viral Load (Amplicor) – copies/mL (IQR)	4.7 (4.3, 5.0)	4.7 (4.3, 5.0)	4.7 (4.4, 5.3)
Entry Viral Load (Taqman) - copies/mL (IQR)	-	-	5.2 (4.8, 5.6)
Genotype at Entry			
Yes	814 (45%)	830 (45%)	38 (21%)
No	999 (55%)	1027 (55%)	141 (79%)

Table 2

Median Log₁₀ Viral Load Change from Entry by NRTI Arm in the Early Viral Load Substudy (IQR)

Visit Week	EFV			ATV/r		
	TDF/FTC (n=48)	ABC/3TC (n=44)	p-value [†]	TDF/FTC (n=46)	ABC/3TC (n=41)	p-value [†]
1	-1.6 (-1.7, -1.2)	-1.5 (-1.8, -1.3)	0.92	-1.2 (-1.5, -1.0)	-1.2 (-1.4, -0.9)	0.39
2	-2.1 (-2.2, -1.8)	-2.0 (-2.3, -1.8)	0.98	-1.9 (-2.1, -1.6)	-1.8 (-2.0, -1.7)	0.80
4	-2.4 (-2.6, -2.1)	-2.4 (-2.6, -2.1)	0.71	-2.3 (-2.4, -1.9)	-2.2 (-2.4, -1.9)	0.78

EFV=efavirenz; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; ABC=abacavir; 3TC=lamivudine; ATV/r=atazanavir/ritonavir;

[†] Calculated with Wilcoxon rank sum test.

Table 3

Median Log₁₀ Viral Load Change from Entry among Individuals in High Viral Load Stratum (> 100,000 copies/mL) in the Early Viral Load Substudy (IQR)

Visit Week	EFV		ATV/r	
	TDF/FTC (n=26)	ABC/3TC (n=18)	TDF/FTC (n=18)	ABC/3TC (n=18)
1	-1.5 (-1.7, -1.2)	-1.5 (-1.8, -1.3)	-1.4 (-1.6, -1.1)	-1.1 (-1.5, -0.9)
2	-2.1 (-2.3, -1.8)	-2.1 (-2.4, -1.8)	-2.0 (-2.2, -1.8)	-1.8 (-1.95, -1.6)
4	-2.6 (-2.9, -2.3)	-2.5 (-2.8, -2.2)	-2.4 (-2.6, -2.2)	-2.1 (-2.4, -1.9)
		p-value [†]		p-value [†]
		0.64		0.18
		0.58		0.11
		0.63		0.08

EFV=efavirenz; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; ABC=abacavir; 3TC=lamivudine; ATV/r=atazanavir/ritonavir;

[†] Calculated using Wilcoxon rank sum test.