Relationship between minority nonnucleoside reverse transcriptase inhibitor resistance mutations, adherence, and the risk of virologic failure

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Objectives: To evaluate the risk of virologic failure conferred by suboptimal adherence to nonnucleoside reverse transcriptase inhibitors (NNRTIs) and minority NNRTI resistance mutations.

Design: Pooled analysis of the risk of virologic failure conferred by minority NNRTI resistance mutations and NNRTI adherence from three studies of treatment-naïve individuals initiating an NNRTI-based regimen.

Methods: Participants from each study were categorized into both adherence quartiles (Q1–Q4) and four strata: at least 95%, 80–94%, 60–79%, and below 60%. Weighted Cox proportional hazard models were used to estimate the risk of virologic failure.

Results: The majority of participants ($N = 768$) had high measured adherence, but those in the lowest adherence quartile had the highest proportion of participants with virologic failure and the risk of virologic failure increased step-wise with adherence below 95%. Detection of minority NNRTI drug resistance mutations increased the proportion of participants with virologic failure across adherence quartiles (Cochran–Mantel–Haenszel $P < 0.001$) and adherence strata [Cochran–Mantel–Haenszel $P < 0.001$; <60% adherence, hazard ratio 1.7 (1.1–2.7), $P = 0.02$; 60–79% adherence, hazard ratio 1.2 (0.5–3.2), $P = 0.67$; 80–94% adherence, hazard ratio 2.5 (0.98–6.3), $P = 0.06$; ≥95% adherence, hazard ratio 3.6 (2.3–5.6), $P < 0.001$]. On multivariate analysis, the effect of minority variants was also most prominent at higher levels of medication adherence.

Conclusions: The presence of minority NNRTI resistance mutations and NNRTI adherence were found to be independent predictors of virologic failure, but also modify each other's effects on virologic failure. In addition to the focus on medication adherence counseling, ultrasensitive HIV-1 drug resistance assays could play a role in optimizing the success rates of first-line antiretroviral therapy.

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Introduction

Nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens are recommended as first-line antiretroviral therapy (ART) and are the most commonly prescribed regimen for treatment-naive patients [1–3]. These regimens are generally well tolerated and effective, but a substantial proportion of participants treated with an NNRTI-based regimen experience virologic failure. In the AIDS Clinical Trials Group (ACTG) study A5095, virologic failure was seen in 11% of participants receiving an efavirenz-based regimen at a median of 32 weeks [4] and in 25% of participants at a median 3 years of follow-up [5]. More recently in the STARTMRK trial, 11% of participants in the efavirenz-treated arm were found not to have achieved virologic suppression by 48 weeks [6]. Despite the expanded range of available antiretroviral therapies, treatment failure of first-line regimens can have serious consequences. These include the accumulation of NNRTI or nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations, which can result in cross-resistance to second-generation NNRTI agents (e.g. etravirine and rilpivirine) and diminished effectiveness of the NRTI 'backbone' of subsequent regimens. Other potential consequences of delayed effective ART include suboptimal immunologic recovery and increased morbidity and mortality as most individuals in both developed and developing countries still enter HIV care late in the course of disease [7–9].

There are several potential causes of treatment failure for NNRTI-based ART regimens. NNRTI adherence is closely linked with the risk of virologic failure, but it is still unclear what level of NNRTI adherence is needed to maintain optimal rates of virologic suppression [10,11]. The presence of low-frequency, or minority, HIV-1 drug resistance mutations also contributes to the increased risk of virologic failure. In a recent pooled analysis of 985 participants from 10 studies, the presence of a minority HIV-1 drug resistance mutation before starting ART was associated with 2–3 times the risk of virologic failure in treatment-naïve participants initiating an NNRTI-based regimen [12].

The risk of virologic failure also increased with suboptimal medication adherence (defined as an overall adherence rate <95%), but the risk was substantially higher in the presence of both drug-resistant minority variants and suboptimal medication adherence. Using data from this pooled analysis, we report one of the largest studies evaluating the effect of NNRTI adherence on the risk of virologic failure for first-line NNRTI-based regimens. We also performed a detailed examination of the relationship between minority NNRTI resistance mutations, medication adherence (including at various adherence levels below 95%), and the risk of virologic failure.

Patients and methods

Study population

This is a substudy of a previously reported pooled analysis [12]. A systematic review of the literature and conference proceedings was performed through December 2010 to identify studies evaluating the impact of minority HIV-1 drug resistance mutations in ART-naive participants initiating an NNRTI-based regimen. A total of 10 studies were identified, of which 3 had available NNRTI adherence data [13–15]. Investigators from all studies agreed to provide patient-level data for this pooled analysis. Participants were excluded with any pretreatment evidence of reduced NRTI or NNRTI drug susceptibility by standard genotyping based on the Stanford Resistance DB mutation scoring system (score $\geq$10 for any antiretroviral medication). The definition of virologic failure was standardized for all patients to a plasma HIV-1 RNA level of at least 200 copies/ml at two consecutive time points at least 16 weeks after treatment initiation. Patients were also counted as virologic failures if the last available HIV-1 RNA level was at least 200 copies/ml without a confirmatory measurement. A complete description of the systematic review and pooled analysis methodologies can be found in the initial study [12].

Adherence measurements

Nonnucleoside reverse transcriptase inhibitor adherence data were available from three studies, which evaluated participants from the FIRST study [13], ACTG A5095 [14], and GS-934 [15]. In the FIRST study, NNRTI adherence measurements were based on self-reported adherence over the previous 7 days and recorded at months 1, 4, and every 4 months thereafter [16]. In ACTG A5095, NNRTI adherence was determined based on self-reported adherence over the previous 4 days at weeks 4, 12, 24, and every 24 weeks thereafter [4]. In GS-934, clinic-based pill count was performed at weeks 4, 8, every 8 weeks through week 48, and then every 12 weeks thereafter [17,18].

Minority variants

To identify NNRTI-resistant minority variants, two of the studies used allele-specific PCR [14,15] and one used 454 deep sequencing [13]. All three studies examined the frequencies of the K103N mutation; two examined the frequencies of Y181C mutation [13,14]; the study using 454 sequencing also searched for the presence of additional NNRTI mutations [13]. The study using 454 sequencing identified three participants with additional mutations associated with NNRTI resistance (G190A, K101E, and P225H); these participants were included in the analysis as harboring a minority NNRTI-resistant variant. A detailed description of the limits of detection for each assay and the NNRTI-resistant minority variants detected can be found in the original study of the pooled analysis [12]. NRTI-resistant minority variants were only evaluated in a small subset of participants and not included in this analysis.

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Table 1. Baseline characteristics of participants included in the study.

Characteristic	Simen *et al.* [13]	Paredes *et al.* [14]	Goodman *et al.* [15]	Total
Study design	Cohort	Case cohort	Cohort	
Adherence method	7-day self-report	4-day self-report	Pill count	
Virologic failure [*N* (%)]	44 (64)	148 (53)	44 (10)	236 (31)
Total participants [*N*]	69	278	421	768
Age [years, median years (IQR)]	37 (31–42)	38 (30–42)	37 (32–43)	37 (31–42)
Male sex [% (*n*/*N*)]	81 (56/69)	81 (225/278)	86 (363/421)	83 (1052/1263)
Ethnicity [% (*n*/*N*)]				
White	22 (15/69)	39 (108/277)	60 (252/420)	49 (375/766)
Black	55 (38/69)	40 (110/277)	22 (94/420)	32 (242/766)
Hispanic	20 (14/69)	19 (54/277)	14 (60/420)	17 (128/766)
Others	3 (2/69)	2 (5/277)	3 (14/420)	3 (21/766)
$CD4^+$ cell count [cells/μl, median (IQR)]	252 (38–344)	227 (127–319)	202 (68–331)	227 (127–319)
$\log_{10}$ HIV RNA [copies/ml, median (IQR)]	5.3 (4.9–5.8)	5.0 (4.7–5.4)	4.8 (4.5–5.5)	5.0 (4.7–5.4)

IQR, interquartile range.

Statistical analysis

Fisher's exact tests and Cochran–Mantel–Haenszel statistics (stratified by study) were used to compare the risk of virologic failure by adherence categories. Cox proportional hazard models stratified by study were used to estimate the risk of virologic failure across multiple factors: the presence of baseline minority NNRTI resistance mutations, NNRTI adherence, ethnicity, baseline CD4 cell count, and viral load. To avoid bias induced by targeted sampling, nonrandomly sampled cases (virologic failures) in the analysis of A5095 contributed to the Cox proportional hazard models only at their time of failure and were not included in the calculation of virologic failure prevalence. The resulting analysis framework may be considered analogous to a Prentice-weighted analysis for a case-cohort study [19,20]. Cox proportional hazard models were evaluated using time-updated recent adherence, which was defined as the average adherence in the most recent 60 days. Missing values were imputed from the most proximal adherence measurement. Only documented adherence data to the time of virologic failure or censoring were used to categorize participants into adherence quartiles and strata. The presence of an interaction between recent adherence and baseline NNRTI resistance was also evaluated. Statistical analysis was performed using SAS 9.2 (SAS Institute, Cary, North Carolina, USA) and PASW Statistics 18 (IBM SPSS, Chicago, Illinois, USA). Figures were created using GraphPad Prism 5 (GraphPad Software, La Jolla, California, USA). Findings with a P value less than 0.05 were considered to be statistically significant except for the test of interaction for which a P value less than 0.10 was considered to be statistically significant.

Results

Patient and study characteristics

Of the 10 studies included in the original pooled analysis [12], medication adherence data were available from three studies constituting 78% (768/985) of the total participants [13–15]. The baseline characteristics of the participants are described in Table 1. Low-frequency NNRTI resistance mutations were detected by 454 deep sequencing in one study [13] and by allele-specific PCR in two studies [14,15]. The median follow-up time was 32 months [interquartile range (IQR) 12–34 months].

Risk of virologic failure by NNRTI adherence levels

The overall level of NNRTI adherence was high within all three studies with a median adherence rate of 93% (IQR 84–100%) for participants of the FIRST study [13], 98% (IQR 94–99%) for participants of GS-934 [15], and 94% (IQR 81–100%) for participants of ACTG A5095 [14]. To account for potential differences in adherence measurement methodologies between studies (clinic-based pill count versus 4 or 7-day recall), an initial analysis was performed by stratifying participants from each study into NNRTI adherence quartiles. The combined adherence data from the three studies showed excellent adherence within the top three quartiles, all of which had median NNRTI adherence at least 95% (Fig. 1a). Individuals in the lowest adherence quartile were found to have the highest virologic failure rate: 38% (Q1), 15% (Q2), 11% (Q3), and 17% (Q4) (Fisher's exact $P < 0.001$ for Q1 virologic failure rate compared to virologic failure rates of either Q2, Q3, or Q4, Fig. 1b).

Participants were also categorized by NNRTI adherence strata: below 60%, 60–79%, 80–94%, and at least 95%. An increased risk of virologic failure was seen at every NNRTI adherence stratum below 95% (Fisher's exact and Cochran–Mantel–Haenszel $P < 0.001$, Fig. 2a). Using the Cox proportional hazard model and at least 95% NNRTI adherence as the reference category, the risk of virologic failure at lower strata of adherence were: 80–94% hazard ratio 2.0 [95% confidence interval (CI) 1.3–3.2], $P = 0.004$; 60–79% hazard ratio 3.1 (1.9–5.0), $P < 0.001$; and below 60% hazard ratio 12.6 (9.4–17.0), $P < 0.001$. This trend was also observed within each of the three studies (data not shown).

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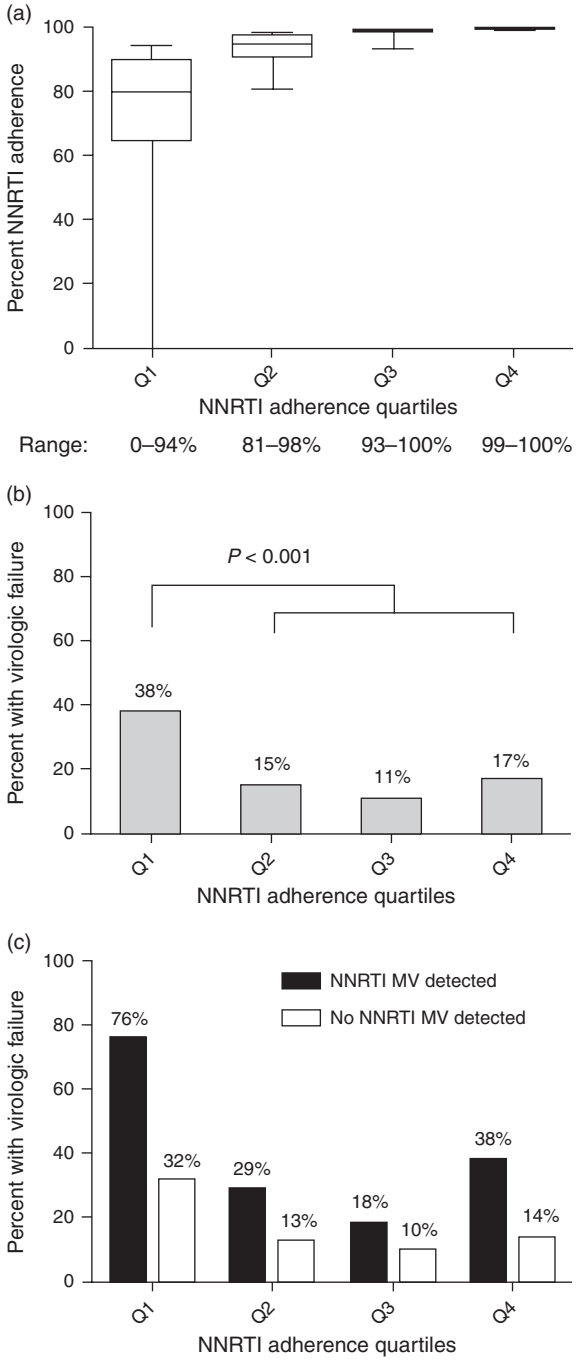

Fig. 1. Nonnucleoside reverse transcriptase inhibitor adherence and virologic failure rates by adherence quartiles. (a) Box plot of NNRTI adherence by adherence quartiles. Participants from each study were stratified into quartiles by adherence and participants from each quartile then combined. (b) Rates of virologic failure by adherence quartiles. *P* values represent Fisher's exact test comparing virologic failure rate for quartile 1 versus each of the other quartiles. (c) Virologic failure rates by adherence quartile stratified by presence of NNRTI minority variants. MV, minority variants; NNRTI, nonnucleoside reverse transcriptase inhibitor.

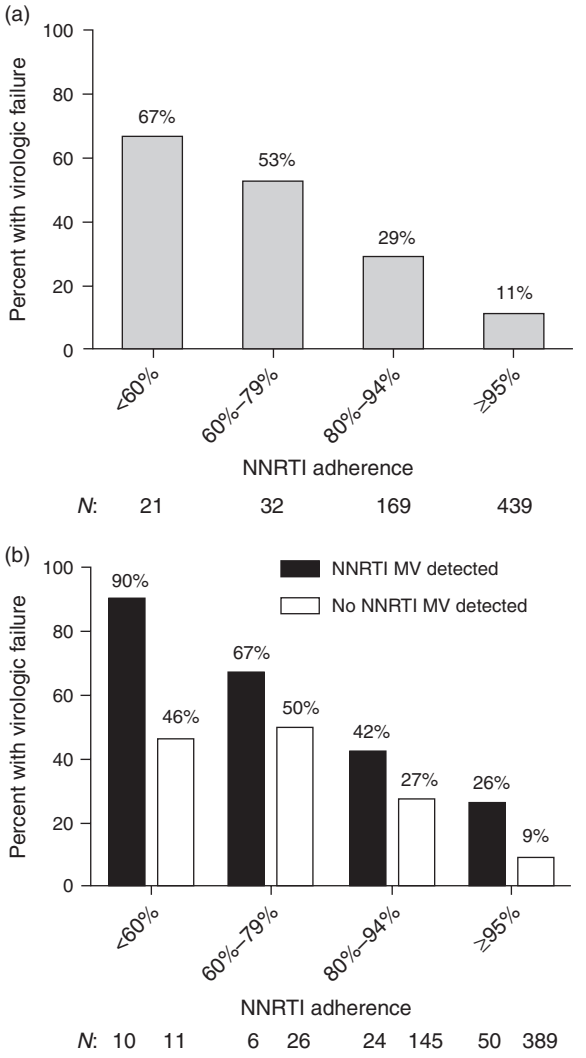

Fig. 2. Virologic failure rates by nonnucleoside reverse transcriptase inhibitor adherence strata. (a) Rates of virologic failure by adherence categories. (b) Virologic failure rates by adherence categories stratified by presence of NNRTI minority variants. MV, minority variants; NNRTI, nonnucleoside reverse transcriptase inhibitor.

Baseline minority variants increase the proportion of participants with virologic failure across adherence categories

Participants with detectable baseline minority NNRTI resistance mutations had a higher rate of virologic failure across adherence quartiles (Cochran–Mantel–Haenszel $P < 0.001$ and Breslow–Day test for homogeneity $P = 0.45$, Fig. 1c). The detection of baseline minority NNRTI resistance mutations also increased the proportion of participants with virologic failure across adherence stratum (Cochran–Mantel–Haenszel $P < 0.001$ and Breslow–Day test for homogeneity $P = 0.49$, Fig. 2b). The increased risk of virologic failure in the presence of minority variants was reflected in the Cox proportional hazard models: less than 60%

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Table 2. Multivariate Cox proportional hazard models using two methods of analyzing NNRTI adherence.

	Overall average adherence			Time-updated adherence (last 60 days)		
	HR	95% CI	*P* value	HR	95% CI	*P* value
MV present (NNRTI)	2.3	1.7–3.2	<0.0001	2.2	1.6–3.1	<0.0001
Adherence (per 5% decrease)	1.15	1.13–1.18	<0.0001	1.14	1.13–1.17	<0.0001
Ethnicity						
Black	2.8	2.1–3.9	<0.0001	2.7	1.9–3.6	<0.0001
Hispanic	2.0	1.4–2.9	0.0004	1.9	1.3–2.8	0.001
Other	2.6	1.0–6.5	0.046	2.2	0.9–5.6	0.10
CD4 cell count (per 50 cells/μl increase)	1.0	0.98–1.04	0.67	1.0	0.96–1.02	0.46
Baseline pVL (log_{10} copies/ml increase)	1.0	0.88–1.33	0.44	1.1	0.90–1.36	0.33

CI, confidence interval; HR, hazard ratio; MV, minority variant; NNRTI, nonnucleoside reverse transcriptase inhibitor.

adherence, hazard ratio 1.7 (1.1–2.7), $P = 0.02$; 60–79% adherence, hazard ratio 1.2 (0.5–3.2), $P = 0.67$; 80–94% adherence, hazard ratio 2.5 (0.98–6.3), $P = 0.06$; at least 95% adherence, hazard ratio 3.6 (2.3–5.6), $P < 0.001$.

Multivariate analysis

In the multivariate Cox proportional hazard model reported in our initial pooled analysis, an overall average adherence value was included in the model [12]. We utilized an additional method of incorporating adherence data in the Cox model that involved a time-updated analysis of the most recent NNRTI adherence within the past 60 days as a reflection of recent adherence. The results from the additional Cox proportional hazard model closely mirror the results of the original multivariate analysis and support the original findings (Table 2). In addition, the effect estimates of NNRTI adherence on the risk of virologic failure were concordant between the Cox proportional hazard models for each of the three studies and ranged from a hazard ratio of 1.13 to 1.18 (per 5% lower adherence) using the time-updated most recent 60-day adherence analysis. Limiting the analysis to K103N minority variants only did not significantly alter the results.

A significant interaction was found in the Cox model between the presence of baseline minority variants and recent medication adherence ($P = 0.09$). When NNRTI adherence was stratified into previously defined categories, the effect of minority variants on virologic failure was greatest with higher levels of medication adherence (Fig. 3). The association between minority variants and virologic failure was significantly greater in participants with at least 95% recent adherence than in those with less than 60% recent adherence ($P = 0.03$).

Discussion

In this study, we evaluated the relationship between NNRTI-resistant minority variants, medication adherence, and the risk of virologic failure in a subset of participants from three randomized HIV-1 treatment trials. The majority of participants had high measured NNRTI adherence and an increased proportion of participants were found to have virologic failure in the lowest quartile of measured adherence and at every adherence stratum below 95%. Minority NNRTI drug resistance mutations increased the risk of virologic failure across adherence categories. We also detected a significant interaction between the presence of minority variants and medication adherence and found that the effect of minority variants on virologic failure appeared to be most pronounced with higher levels of adherence.

It is clear that there are ART class-specific relationships between adherence and virologic failure. In contrast to

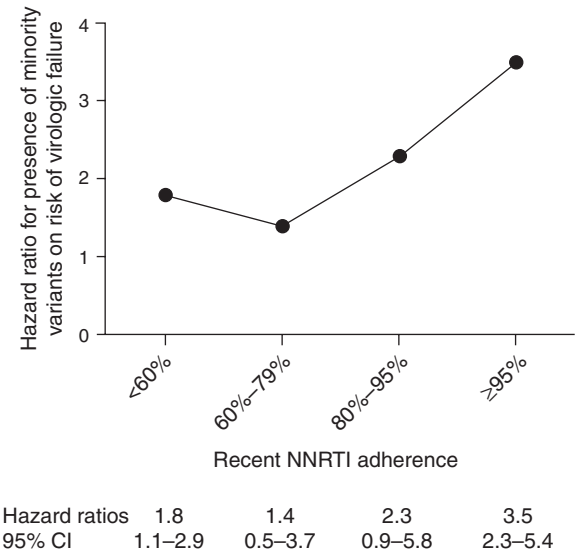

Fig. 3. Relationship between the presence of nonnucleoside reverse transcriptase inhibitor-resistant minority variants and risk of virologic failure differs by levels of medication adherence. Hazard ratios are from the Cox proportional hazard model using NNRTI adherence over the most recent 60 days in a time-updated analysis. NNRTI, nonnucleoside reverse transcriptase inhibitor.

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the adherence–failure relationship for protease inhibitors, there is evidence that less than 95% adherence to NNRTI therapy may be sufficient for virologic suppression [10,11]. In this analysis, we found that most participants had excellent adherence, but that there was an increased risk of virologic failure at every adherence stratum below 95%. One possible explanation for the discrepancy lies in the method used for measuring adherence. Whereas one of the prior studies analyzed self-reported adherence [11], another study used both electronic bottle cap monitoring and unannounced pill counts [10]. The use of self-report and clinic-based pill counts for adherence measurements may overestimate the levels of medication adherence [21]. However, there is also evidence that patient self-report and electronic medication monitoring may yield similar results [22,23] and that electronic medication monitoring may underestimate actual adherence [21]. Although unannounced pill counts or electronic medication monitoring are likely optimal methods of measuring adherence, the cost associated with these methods also limits the number of participants who can be evaluated.

In the analysis of A5095, the increased risk of virologic failure associated with baseline NNRTI-resistant minority variants was only statistically significant for those individuals with high medication adherence [14]. In this larger pooled analysis, which includes participants from A5095, we found that the presence of baseline NNRTI-resistant minority variants increased the risk of virologic failure across adherence strata. We also detected an interaction between the presence of minority variants and adherence and showed that the minority variant effect on the risk of virologic failure was most prominent in individuals with higher rates of recent medication adherence. The most likely explanation for this observation is that the effect of drug-resistant minority variants on risk of treatment failure is partly masked in nonadherent patients, who have a substantial risk of virologic failure whether or not drug-resistant mutants are present in the virus population.

This analysis has some limitations. First, we combined three studies using different methods of measuring adherence: clinic-based pill count, 4-day, and 7-day recall. We were conscious of possible method-dependent measurement differences that could introduce heterogeneity to the results. Our primary analysis was therefore based on stratifying participants into adherence quartiles within each study prior to combining the data across studies to minimize heterogeneity. Reassuringly, the effect estimates of NNRTI adherence on the risk of virologic failure in the Cox proportional hazard models were nearly identical between the three studies. Another limitation involves the pooling of data from three studies that used different minority variant assay methodologies with different sensitivities for variant detection. These issues were discussed in detail in the primary pooled analysis and a number of sensitivity analyses were performed to confirm the robustness of the findings [12]. Since only a subset of participants in this analysis were tested for Y181C mutation (Goodman *et al.* [15] only tested for the presence of K103N mutation) and only participants in the FIRST study were tested for NNRTI mutations other than K103N and Y181C [13], our results most likely underestimate the effect of minority NNRTI resistance mutations on the risk of virologic failure as a significant proportion of those with no detectable minority variants may have had unmeasured Y181C or other NNRTI resistance mutations. Finally, we used two methods of analyzing adherence in the Cox proportional hazard model, both of which have some limitations. The use of average adherence for each participant is insensitive to variations in adherence over time, but the use of a time-dependent analysis requires imputing adherence for missing values using the most proximal adherence measurement. The effect estimates for baseline minority variants, adherence, and the other variables in the multivariate model are relatively unchanged, however, when results of the two models are compared.

In this study, we report the largest and most in-depth analysis of the relationship between baseline NNRTI-resistant minority variants, NNRTI adherence, and the risk of virologic failure. We found that the presence of minority drug resistance mutations and suboptimal NNRTI adherence were independent predictors of virologic failure, but also modify each other's effects on virologic failure. Not only was optimal NNRTI adherence not sufficient to overcome the effect of NNRTI-resistant minority variants, the risk associated with these minority variants was actually greatest in those individuals with the highest levels of adherence. In addition to the continued focus on medication adherence counseling, the use of ultrasensitive HIV-1 drug resistance assays could play a role in optimizing the success rates of first-line antiretroviral therapy.

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Contributions: J.Z.L., R.P., H.R., and D.R.K. provided scientific input into the study design. J.Z.L. and H.R. performed the statistical analysis. All authors were involved in data collection, data analysis, and the editing of the manuscript.

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Conflicts of interest

Financial disclosures and conflicts of interest: J.Z.L. has received research support from Bristol-Myers Squibb and has served as a consultant for Tibotec. R.P. has received consulting fees from Pfizer, Merck, Roche Diagnostics; the IrsiCaixa AIDS Research Institute and the Lluita contra la SIDA Foundation have received grant support from Pfizer, ViiV Healthcare, Siemens, Merck, and Boehringer Ingelheim for studies that R.P. serves as principal investigator. E.S.S. and M.D.M. are employees and stock-holders of Gilead Sciences, Inc. Yale University receives grant support from Merck, Pfizer, Gilead, Abbott, ViiV and Bristol-Myers Squibb for studies that M.J.K. serves as the principal investigator. M.J.K. receives royalties from patents owned by Stanford University for some HIV diagnostic tests. D.R.K. has served as a consultant to and/or has received research grant support from Abbott, Avexa, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Glaxo-SmithKline, Merck, Oncolys, Pfizer, Roche, Tobira, Vertex, ViroStatistics, and ViiV Healthcare. No other potential conflicts of interest relevant to this article were reported.

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