Antiretroviral Therapy and Efficacy After Virologic Failure on First-line Boosted Protease Inhibitor Regimens

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Background. Virologic failure (VF) on a first-line ritonavir-boosted protease inhibitor (PI/r) regimen is associated with low rates of resistance, but optimal management after failure is unknown.

Methods. The analysis included participants in randomized trials who experienced VF on a first-line regimen of PI/r plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) and had at least 24 weeks of follow-up after VF. Antiretroviral management and virologic suppression (human immunodeficiency virus type 1 [HIV-1] RNA <400 copies/mL) after VF were assessed.

Results. Of 209 participants, only 1 participant had major PI-associated treatment-emergent mutations at first-line VF. The most common treatment approach after VF (66%) was to continue the same regimen. The virologic suppression rate 24 weeks after VF was 64% for these participants, compared with 72% for those who changed regimens (P = .19). Participants remaining on the same regimen had lower NRTI resistance rates (11% vs 30%; P = .003) and higher CD4+ cell counts (median, 275 vs 213 cells/µL; P = .005) at VF than those who changed. Among participants remaining on their first-line regimen, factors at or before VF significantly associated with subsequent virologic suppression were achieving HIV-1 RNA <400 copies/mL before VF (odds ratio [OR], 3.39 [95% confidence interval {CI}, 1.32–8.73]) and lower HIV-1 RNA at VF (OR for <10 000 vs ≥10 000 copies/mL, 3.35 [95% CI, 1.40–8.01]). Better adherence after VF was also associated with subsequent suppression (OR for <100% vs 100%, 0.38 [95% CI, .15–.97]). For participants who changed regimens, achieving HIV-1 RNA <400 copies/mL before VF also predicted subsequent suppression.

Conclusions. For participants failing first-line PI/r with no or limited drug resistance, remaining on the same regimen is a reasonable approach. Improving adherence is important to subsequent treatment success.

Keywords. first-line; protease inhibitor; virologic failure; antiretroviral therapy.

Antiretroviral therapy (ART) that includes a ritonavir-boosted protease inhibitor (PI/r) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) is among the first-line therapies recommended for human immunodeficiency virus (HIV) infection in current treatment guidelines [1, 2]. Although the effectiveness of PI/r-based regimens as initial therapy is well established, about 10%–20% of patients experience virologic failure (VF) within 2 years [3–6].

A distinctive characteristic of PI/r regimens is that those who experience VF rarely have detectable PI resistance [7–10]. As a result, clinicians theoretically have the option of continuing the same regimen or modifying the treatment by changing to a different PI/r or introducing a new drug class, such as a nonnucleoside reverse transcriptase inhibitor (NNRTI). It is important
to understand the outcome of different management strategies after failure of PI/r-based first-line therapy, but few data exist, as many first-line studies terminate follow-up soon after a participant reaches the primary VF endpoint. Furthermore, the number of participants experiencing failure in any one study is small.

This analysis evaluated therapeutic approaches and outcomes among participants in 3 large randomized clinical trials undertaken by the AIDS Clinical Trials Group (ACTG) who experienced VF on first-line PI/r-based ART.

METHODS

Study Population

The study included all 3 randomized trials of initial ART conducted by the ACTG that included a PI/r regimen and was completed by June 2013. The study population included participants who experienced VF on first-line PI/r plus 2 NRTIs while participating in ACTG A5142 [3], A5202 [4], or A5208 trial 2 [5]; A5208 trial 1 [11] was not included, as participants in that study had to have prior single-dose nevirapine exposure. The design and main results of these studies have been previously published [3–5]. The ACTG A5142 and A5202 trials enrolled men and women in the United States. A5208 trial 2 enrolled women in eastern and southern Africa without prior single-dose nevirapine exposure. These studies included randomization to lopinavir/ritonavir (LPV/r) (A5142 and A5208) or atazanavir/ritonavir (ATV/r) (A5202) as first-line PI/r, with 1 of the following combinations of 2 NRTIs: lamivudine plus either tenofovir, zidovudine, or stavudine in A5142; tenofovir plus emtricitabine or lamivudine plus abacavir in A5202; and tenofovir plus emtricitabine in A5208.

Participants who changed to a regimen other than PI/r plus 2 NRTIs prior to first-line VF and those who had <24 weeks of follow-up after failure were excluded from the analysis.

First-line Virologic Failure and ART Management

HIV type 1 (HIV-1) RNA was measured in plasma using the Ultrasensitive Roche Amplicor Monitor V1.5 in A5142 and A5202, and the standard Roche Amplicor Monitor V1.5 in A5208. First-line VF was defined similarly with little variation among the 3 studies (Table 1). Decisions regarding ART management after first-line VF were made by site clinicians and participants. Real-time drug resistance testing at VF was available in A5142 and A5202, but was done retrospectively using stored samples at the end of A5208; pretreatment drug resistance testing using stored samples was performed retrospectively for participants experiencing VF in all 3 studies. Major resistance mutations were defined mainly based on International Antiviral Society (IAS)–USA [12, 13], and the details are shown in Table 1 along with the protocol-suggested management on first-line virologic failure and study-provided ART.

Table 1. Definition of First-line Virologic Failure, Protocol-Suggested Postvirologic Failure Management, and Available Antiretroviral Therapy and Major Resistance Mutation by ACTG Study

<table>
<thead>
<tr>
<th>Definition</th>
<th>A5142</th>
<th>A5202</th>
<th>A5208</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of first-line virologic failure</td>
<td>HIV-1 RNA &lt;1 log_{10} copies/mL below baseline at/after 8 wk of ART or ≥200 copies/mL at/after 32 wk confirmation of VF was required in a subsequent plasma sample</td>
<td>HIV-1 RNA ≥1,000 copies/mL at/after 16 wk or ≥200 copies/mL at/after 24 wk; confirmation of VF was required in a subsequent plasma sample</td>
<td>HIV-1 RNA &lt;1 log_{10} copies/mL below baseline at/after 12 wk or ≥400 copies/mL at/after 24 wk; confirmation of VF was required in a subsequent plasma sample</td>
</tr>
<tr>
<td>Protocol suggested management on first-line virologic failure</td>
<td>Suggested second-line regimen is EFV + additional agents selected by genotypic resistance result Alternatively, any regimen may be chosen based on the genotypic resistance test results</td>
<td>Subjects may remain on their study regimen in consultation with their primary care provider. If the CD4 count or the HIV-1 RNA returns to the baseline level, subjects will be strongly advised to change therapy according to resistance test result</td>
<td>Suggested second-line regimen is NVP-containing regimen, but switching to a second-line regimen is not mandatory. Participants may remain on the step 1 regimen at the discretion of the participant and site investigator</td>
</tr>
<tr>
<td>Study-provided ART</td>
<td>EFV, LPV/r, d4T, TDF</td>
<td>ABC/3TC, FTC/TDF, 3TC/ZDV, LPV/r, ABC, ATV, ddI, EFV, FTC, FPV, 3TC, d4T, RTV, TDF, ZDV</td>
<td>NVP, LPV/r, FTC, TDF, FTC/TDF, ddI, and ZDV</td>
</tr>
</tbody>
</table>

Abbreviations: 3TC, lamivudine; ABC, abacavir; ACTG, AIDS Clinical Trials Group; ART, antiretroviral therapy; ATV, atazanavir; d4T, stavudine; ddI, didanosine; EFV, efavirenz; FPV, fosamprenavir; FTC, emtricitabine; HIV-1, human immunodeficiency virus type 1; IAS, International AIDS Society; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RTV, ritonavir; TDF, tenofovir; ZDV, zidovudine.
Statistical Methods

The primary endpoint of the analysis was virologic suppression, defined as HIV-1 RNA <400 copies/mL, at 24 weeks after confirmation of first-line VF. Missing values were considered as lack of suppression unless the last HIV-1 RNA before 24 weeks was <400 copies/mL. For participants who changed ART within 24 weeks after first-line VF confirmation, virologic suppression at 24 weeks after regimen change was also examined.

The following variables were evaluated for their association with ART management following VF and with subsequent virologic suppression: first-line ART regimen, HIV-1 RNA, and CD4 cell count at ART initiation and at VF, HIV-1 RNA <400 copies/mL at any time prior to VF, weeks from ART initiation to VF, change in CD4 count from ART initiation to VF, age and drug resistance at VF, and last available self-reported adherence (in the prior 4 days) within 24 weeks prior to VF. Sex and race were only examined among A5142 and A5202 participants because A5208 only included African women, and all were black. The association between resistance and ART management was also only examined among A5142 and A5202 participants, as real-time resistance results were not available in A5208 to guide ART management. Participants who switched to a nonstandard second-line regimen after VF (including a nonboosted PI or both an NNRTI and a PI/r) were included in analyses of ART management after VF but were excluded from analyses examining subsequent suppression.

All analyses were stratified by ACTG study. To compare characteristics and virologic suppression rates between participants

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**Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) diagram for inclusion and exclusion criteria. Among the 21 patients with some follow-up, 16 stayed on their first-line ritonavir-boosted protease inhibitor (PI/r)-based regimen; 13 of the 21 (62%) had HIV-1 RNA <400 copies/mL at their last available measurement after initial virologic failure. The 5 participants who changed to a nonstandard regimen included 3 who changed to an unboosted protease inhibitor–containing regimen and 2 who changed to a PI/r + nonnucleoside reverse transcriptase regimen. Abbreviations: ART, antiretroviral therapy; HIV-1, human immunodeficiency virus type 1; NRTI, nucleoside reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitor.
remaining on the same regimen vs changing regimen, and among different regimens for those who changed regimens, van Elteran and Cochran-Mantel-Haenszel tests were used for continuous and categorical variables, respectively. To evaluate factors associated with subsequent virologic suppression, multivariable logistic regression was constructed by stepwise variable selection with \( P < .05 \) required for entry and subsequent retention. The following sensitivity analyses were conducted: excluding participants whose HIV-1 RNA at VF was <400 copies/mL for both initial and confirmatory measurements; excluding participants from resource-limited settings (A5208); and defining virologic suppression as HIV-1 RNA <200 copies/mL (limited to A5142 and A5202 because A5208 used the assay with lower limit of quantification of 400 copies/mL). All analyses were performed using SAS software, version 9.2.
RESULTS

Characteristics at Pretreatment and at First-line Virologic Failure

Among the 1429 participants randomized to receive a first-line PI/r-based regimen, 277 (19%) experienced study-defined VF. Seven were not eligible for this analysis because they switched to a regimen other than PI/r + 2 NRTIs prior to VF. Sixty-one were excluded from the analysis because they were not followed (n = 40) or had <24 weeks of follow-up (n = 21) after VF, either because of study closure or because of loss to follow-up (Figure 1).

Among the 209 participants included, 67 (32%) were from A5142 and 107 (51%) were from A5202 (thus 83% enrolled in the United States), and 35 (17%) were from A5208 (enrolled in Africa). Overall, 43% of participants were female, the median pretreatment HIV-1 RNA was 4.8 log10 copies/mL, and median CD4 count was 118 cells/µL; 49% received LPV/r and 51% received ATV/r as the PI/r component of first-line ART (Table 2).

Median time from ART initiation to confirmation of VF was 39 weeks, and 78% of participants achieved HIV-1 RNA <400 copies/mL at some time prior to VF. At VF, the median HIV-1 RNA was 3.9 log10 copies/mL, the median CD4 count was 246 cells/µL, and the median CD4 count increase from pretreatment was 96 cells/µL. Self-reported ART adherence within the 4 days prior to VF was 100% for 62% of participants and <100% for 23% (9% reported not being on ART, and 6% had no report).

Of the 209 participants, 188 had drug resistance results available at VF, excluding the 5 on nonstandard regimens (Table 2). Only 1 participant selected a new major PI-associated mutation since ART initiation (0.5%), although another 4 participants had such mutations at baseline; 15 (9%) selected new NRTI-associated mutations, with 23 having these at baseline; and 7 (4%) had NNRTI-associated mutations, all present at baseline. Among the 61 participants who were excluded, resistance was also infrequent at VF: none had major PI-associated resistance and 7% and 4% had NRTI and NNRTI resistance, respectively. Compared with the 209 participants included, the participants excluded did, however, have significantly higher median pretreatment CD4 counts (277 vs 165 cells/µL; P < .001) and lower median pretreatment HIV-1 RNA (4.66 vs 4.84 log10 copies/mL; P = .006).

ART Regimen After First-line Virologic Failure

Participants who did not change ART regimen through 24 weeks after first-line VF confirmation were defined as remaining on their first-line regimen, whereas participants who changed regimens within 24 weeks were classified by the type of their first regimen change. Among the 209 participants, 137 (66%) remained on their first-line regimen and 61% for those who remained on their first-line ART and 61% for those who changed (OR, 0.97 [95% CI, .61–1.54]; P = .89). Among participants from A5142 and A5202 (which used a more sensitive HIV-1 RNA assay), 62 participants (57%) who

Table 3. Antiretroviral Therapy Regimen Within 24 Weeks After First-line Virologic Failure Confirmation

<table>
<thead>
<tr>
<th>Regimen</th>
<th>A5142 (N = 67)</th>
<th>A5202 (N = 107)</th>
<th>A5208 (N = 35)</th>
<th>Overall (N = 209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change in ART</td>
<td>34 (51%)</td>
<td>74 (69%)</td>
<td>29 (83%)</td>
<td>137 (66%)</td>
</tr>
<tr>
<td>Changed to an NNRTI-containing regimen</td>
<td>15 (22%)</td>
<td>9 (8%)</td>
<td>4 (11%)</td>
<td>28 (13%)</td>
</tr>
<tr>
<td>Changed to ART including a different PI/r</td>
<td>6 (9%)</td>
<td>8 (7%)</td>
<td>0 (0%)</td>
<td>14 (7%)</td>
</tr>
<tr>
<td>Changed NRTI(s) only</td>
<td>8 (12%)</td>
<td>15 (14%)</td>
<td>2 (6%)</td>
<td>25 (12%)</td>
</tr>
<tr>
<td>Changed to nonstandard second-line regimen*</td>
<td>4 (6%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

*The 5 participants who changed to a nonstandard second-line regimen included 2 who changed to a ritonavir-boosted PI + NNRTI-based regimen and 3 who changed to a PI regimen without ritonavir boosting.

Virologic Suppression After First-line Virologic Failure

At 24 weeks after confirmation of first-line VF, 136 of 204 participants (67%) had HIV-1 RNA <400 copies/mL (excluding the 5 on nonstandard regimens; Table 4): 88 (64%) of those who remained on their first-line regimen and 48 (72%) of those who changed (odds ratio [OR], 0.74 [95% confidence interval [CI], .48–1.16]; P = .19; if adjusted for CD4 count and presence of NRTI resistance mutations at VF: OR, 0.75 [95% CI, .36–1.58]; P = .45). Among the 146 participants without NRTI-, NNRTI-, or major PI-associated resistance mutations detected, the proportion with virologic suppression was 62% for those who remained on their first-line ART and 61% for those who changed (OR, 0.97 [95% CI, .61–1.54]; P = .89).
remained on their first-line ART and 40 participants (69%) who changed had HIV-1 RNA <200 copies/mL at 24 weeks after first-line VF confirmation \( (P = .34) \) (Table 4).

Among the 137 participants remaining on their first-line regimen, the following factors were significantly associated with higher odds of virologic suppression at week 24 after first-line VF in univariate analysis: greater increase in CD4 count and longer time from ART initiation to VF, HIV-1 RNA <400 copies/mL at any time prior to VF, and HIV-1 RNA <10,000 copies/mL at VF confirmation. Two variables remained significantly associated in multivariate analysis: HIV-1 RNA <400 copies/mL at any time prior to VF (OR, 3.39 vs ≥400 copies/mL; \( P = .011 \)), and HIV-1 RNA <10,000 copies/mL at VF (OR, 3.35 vs ≥10,000 copies/mL; \( P = .007 \)) (Table 5). No significant interaction was detected between these 2 variables.

Among the 137 participants remaining on their first-line regimen, 126 (92%) had self-reported adherence data available after VF: 84 (67%) reported 100% adherence during the 4 days prior to evaluation, 35 (28%) reported <100% adherence, and 7 (6%) were not on ART at the evaluation. The virologic suppression rate was 75% for participants who reported 100% adherence, compared with 54% for participants reporting <100% adherence (OR, 0.38; \( P = .044 \)), and 15% for participants not on ART (OR, 0.06; \( P = .007 \)) (Table 6). Similar results were found when adjusted for whether or not a participant achieved HIV-1 RNA <400 copies/mL prior to VF and for HIV-1 RNA at VF.

For the 67 participants who changed ART within 24 weeks after first-line VF, the median time from VF confirmation to regimen change was 10 weeks. Forty-three (64%) had HIV-1 RNA <400 copies/mL at 24 weeks after regimen change, including 20 (71%) of 28 participants who switched to a NNRTI-containing regimen, 6 (44%) of 14 who changed to a different PI/r, and 18 (72%) of 25 who only changed 1 or more NRTIs \( (P = .39) \). Achieving HIV-1 RNA <400 copies/mL prior to VF was the only significant factor associated with higher suppression rate at 24 weeks after regimen change \( (OR, 6.50 \ [95\% CI, 1.91–22.11]; \ P = .003) \).

Results consistent with those reported above were observed in sensitivity analyses, with the exception that, in the analysis restricted to A5142 and A5202 participants in which virologic suppression was defined as HIV-1 RNA <200 copies/mL, virologic suppression rates at 24 weeks after regimen change differed significantly by type of change (67% of the 15 participants who changed to a NNRTI-based regimen, 33% of the 6 participants who changed to another PI/r, and 57% of the 7 participants who only changed NRTIs; \( P = .028) \).

### DISCUSSION

This study provides important information that adds to the current knowledge regarding management of ART after VF on
first-line PI/r plus 2 NRTIs. Of note, our study suggests that a large proportion of patients failing these regimens can subsequently achieve virologic suppression without changing their ART regimen, particularly if no resistance is detected, if virologic suppression was ever achieved prior to VF, and if self-reported treatment adherence is good.

Our study included participants in randomized trials who experienced VF on PI/r-based regimens. The proportion of...
participants with treatment-emergent mutations at VF was low—0.5% for major PI-associated and 9% for NRTI-associated mutations. The most common therapeutic strategy within 24 weeks after VF (66%) was to continue the same first-line regimen; 64% of participants doing this achieved HIV-1 RNA <400 copies/mL after 24 weeks. This did not differ significantly from the rate (72%) among those who changed regimen. Because the proportion of participants with resistance-associated mutations was higher among those who changed regimen vs those who did not, we also evaluated virologic suppression rates among the subgroup of participants with no such mutations detected at first-line VF; subsequent suppression rates were almost identical in those who remained on their initial ART regimen vs those who changed (62% vs 61%).

The rarity of major PI-associated resistance mutations following VF on PI/r regimens in this study is consistent with findings in other studies [7–10], resulting from several possible mechanisms: one is a high genetic barrier to resistance and the higher drug concentration achieved with ritonavir boosting [7]; another is that PIs have inhibitory effects in multiple steps in the viral life cycle and act like multiple drugs in one [14]; and a third one is the limited time period during which resistance can be selected due to the short pharmacokinetic half-lives of PI/r regimens allowing rebound of susceptible virus [15]. This raises the possibility, as seen in our study, for subsequent virologic suppression with continued use of the same regimen. Other studies have also shown that delay in treatment switch after failing first-line PI/r does not have substantial impact on subsequent outcome [16, 17]. In the absence of measurable drug resistance, continuing a first-line PI/r regimen might therefore be a reasonable approach, especially for those with lower HIV-1 RNA at VF and successful suppression of HIV-1 RNA prior to VF, as suggested by our multivariate analysis (Table 5). However, these findings should not undermine the importance of resistance testing at the time of VF on a first-line PI/r-based regimen; although the rate of PI resistance was low in our study, there was a higher rate of NRTI resistance. Our study was not able to examine the impact that NRTI resistance had on outcome because these participants were more likely to have regimen changes following VF, and the number with NRTI resistance who remained on the same PI/r-based regimen was small.

For participants who changed ART regimens after first-line VF, no difference in rates of virologic suppression to <400 copies/mL after regimen change was detected among different regimens. However, our study had limited sample size for participants who changed regimens after failing first-line PI/r, restricting the power to detect possible differences among regimens. A sensitivity analysis did, however, suggest that changing to a different PI/r-containing regimen gave a lower rate of suppression to <200 copies/mL than other regimen changes. The latter is similar to the findings in a German cohort, which suggested that switching to a NNRTI-based regimen had improved durability compared with switching to a different PI after VF [18]. However, the newer PI darunavir was not used in these studies, and its use might give better outcomes. As for participants who did not change regimen, achieving an HIV-1 RNA <400 copies/mL prior to initial VF was a significant predictor of subsequent suppression among those who changed regimens. Such prior suppression may be a marker of adequate adherence that is realizable again following VF whether or not a regimen is changed. This is consistent with other studies that have shown that improved adherence after first-line VF is important for the subsequent virologic suppression with or without regimen change [17,19,20], and emphasizes the need for ongoing efforts to promote good adherence following VF.

Our study has some limitations, and the findings need to be interpreted with caution. First, our study was observational and involved follow-up of participants in clinical trials. Hence, ART management after first-line VF was not randomized, and treatment options as well as the definition of VF and assays used varied among the 3 studies and between study sites. Identification of VF and subsequent treatment management may have been quicker in these trials than would occur in practice. Also, data were not collected to allow an evaluation of the extent to which a physician’s assessment of a patient’s adherence to treatment and low-grade PI/r-related toxicity might have determined the approach to treatment management following VF. Second, despite the fact that we combined data from >200 participants from 3 large clinical trials who experienced first-line VF, this sample size likely provides inadequate power to identify some factors that might be associated with clinically relevant differences in outcome. Third, 23% of participants who experienced VF on a PI/r-based regimen were excluded because of limited or no follow-up after VF. The excluded participants had higher CD4 count and lower HIV-1 RNA prior to starting ART than those included but, like those included, had limited resistance at first-line VF. Although we cannot fully assess the impact of these exclusions on our results, among the 21 excluded who had some follow-up, a similar percentage (62%) achieved HIV-1 RNA <400 copies/mL at their last available measurement after initial VF as among included participants at 24 weeks after VF (67%).

CONCLUSIONS

Our findings suggest that if no or limited drug resistance is detected at VF on a first-line PI/r-containing regimen, remaining on the same regimen after VF coupled with strategies to improve adherence could be a reasonable and effective approach to achieving virologic suppression. Further evaluation of approaches to
treatment management following VF on a first-line PI/r-containing regimen is warranted.

Notes

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