Genotypic Resistance and Immunologic Outcomes Among HIV-1–Infected Women With Viral Failure

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Objectives: To describe the prevalence of specific protease inhibitor (PI) and nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations and the relationship between the presence of these mutations and immunologic outcomes following PI/NNRTI initiation among a cohort of HIV-1–infected women.

Methods: Viral genotypic resistance testing was done for 366 women enrolled in the Women's Interagency HIV Study at the visit immediately prior to 1st reported use of PI or NNRTI (baseline) and at the visit approximately 1 year after PI/NNRTI initiation. We modeled the changes in $CD4^+$ T-cell counts and HIV RNA levels approximately 1 year after therapy initiation as a function of baseline and follow-up markers, type of antiretroviral therapy used, and resistance mutations.

Results: At baseline, 52% of women showed only nucleoside reverse transcriptase inhibitor (NRTI) mutations, 38% showed no mutations, and 10% showed PI or NNRTI mutations. Only 40% of women showed viral response (HIV-1 RNA $\leq$ 80 copies/mL) 1 year after initiating a PI or NNRTI. Among those without a viral response, 54% developed PI or NNRTI mutations. NNRTI (among those with baseline NRTI mutations) and PI resistance mutations were associated with better $CD4^+$ cell count changes (mean increase of 118 cells/mm^3 and 64 cells/mm^3, respectively, as compared with viral nonresponders with no PI or NNRTI mutations).

Conclusions: In this population-based cohort, virologic failure with PI or NNRTI resistance was common. Viremia with these resistance mutations was associated with preserved $CD4^+$ T-cell count responses, providing evidence of reduced virulence or viral fitness.

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The use of highly active antiretroviral therapy (HAART) has resulted in dramatic improvements in immunologic function and reductions in morbidity and mortality among HIV-1–infected individuals in North America and Europe.[1–4] Complete viral suppression has been shown to be associated with more durable response,[5] and evidence of favorable clinical outcomes with on-treatment viral replication is accumulating.[6] Achievement of undetectable HIV-1 RNA levels in plasma outside of clinical trial settings is much more variable.[7–9] Even in patients who achieve optimal initial responses to antiretroviral therapy, viral failure is often detected at some time during therapy[10] and the rate of detection increases with the duration of surveillance and the sensitivity of the assays.[11,12]

On-treatment viral failure occurs both in individuals with HIV-1 genetic mutations that confer resistance to therapeutic levels of antiretroviral drugs, and in individuals with wild-type (WT) virus that is able to replicate during treatment due to inadequate drug activity or inadequate drug exposure associated with nonadherence or pharmacodynamic factors. Despite ongoing viral failure, some individuals with HIV-1 protease gene mutations demonstrate continued improvements in $CD4^+$ cell counts; yet patients with strains resistant only to nucleoside reverse transcriptase inhibitors (NRTIs) do not fare as well.[7,13–20] Limited information is available on the relationship between on-treatment viral failure with nonnucleoside reverse transcriptase inhibitor (NNRTI)-resistant mutations and immunologic outcomes, even though the use of NNRTI-based regimens is increasingly prevalent.

The purpose of this analysis was to describe the prevalence of specific protease inhibitor (PI) and NNRTI resistance mutations and to examine immunologic outcomes of on-treatment viremic participants in the Women's Interagency HIV Study (WIHS), a cohort that reflects the epidemiology of HIV-1 infection among women in the United States. Using the extensive clinical data and repository specimens collected for this study, we were able to measure HIV-1 resistance mutations before and after initiating PI or NNRTI antiretroviral therapy (ART). We were also able to evaluate how resistance mutations were associated with short-term (1-year) $CD4^+$ cell count changes among women whose HIV-1 RNA level remained $>$1000 copies (cps)/mL after initiating a PI or an NNRTI.

METHODS

Study Population

The WIHS is conducted in 5 locations within the United States: New York City (Bronx and Brooklyn sites), Washington, DC, Chicago, southern California, and the San Francisco Bay area. The WIHS methods and baseline characteristics of the original recruits have been described previously.[21] Briefly, from October 1994 through November 1995, 2059 HIV-1–seropositive women were recruited from HIV primary care clinics, hospital-based programs, research programs, community outreach sites, women's support groups, drug rehabilitation programs, HIV testing sites, and referrals from enrolled participants. Every 6 months, WIHS participants were interviewed using a structured questionnaire, received physical and gynecologic examinations, and provided multiple laboratory specimens. To help participants correctly recall and identify their antiretroviral medication usage, photo medication cards were used that identified all antiretroviral drugs by photograph, brand, and generic drug names. Adherence measures were implemented in the study questionnaire in October 1998 after the majority of women in this study initiated PI- or NNRTI-based HAART.

Eligible participants for this study included HIV-1–seroprevalent WIHS women who reported initiating their 1st ART regimen that included a PI (including ritonavir, indinavir, nelfinavir, or saquinavir) or an NNRTI (including efavirenz, delavirdine, or nevirapine) prior to October 2000. The eligible participants could have reported prior use of combinations of NRTIs (including zidovudine, didanosine, zalcitabine, lamivudine, or stavudine). The women in this analysis were required to have complete HIV-1 RNA and $CD4^+$ cell count measurements at the study visit prior to and immediately following the 1st report of PI or NNRTI use (PI/NNRTI initiation). Furthermore, to allow for genotyping, the HIV-1 RNA level at the visit immediately prior to PI/NNRTI initiation was required to be >1000 cps/mL. Lastly, women with HIV-1 RNA levels >1000 cps/mL after initiation who reported that they had discontinued all antiretroviral therapy since their last study visit were excluded from the analysis. Informed consent was obtained from all participants in this study and followed as per the guidelines of the US Department of Health and Human Services and the authors' institutions.

Laboratory Methods

Plasma HIV-1 RNA levels were measured using the isothermal nucleic acid sequence–based amplification (Nuclisens) method (bioMérieux, Boxtel, NL) in laboratories participating in the National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID) Virology Quality Assurance Laboratory proficiency testing program. The lower limit of quantification was 80 cps/mL using 1.0-mL sample input, although 15 participants with undetectable HIV-1 RNA at limits of 400 or 4000 cps/mL were also excluded from all analyses. Lymphocyte subsets were quantified using standard flow cytometric methods in laboratories participating in the NIH/NIAID Flow Cytometry Quality Assessment Program. The presence of mutations was assessed by population sequencing of codons 1–99 of the protease gene and codons 41–139 and 148–237 of the reverse transcriptase reading frame using the Trugene HIV-1 Genotyping Kit (Bayer Diagnostics, Emeryville, CA) as previously described.[22,23] Clinically significant genotypic resistance was defined by the presence of viral mutations associated with impaired drug susceptibility or virologic response as specified by the International AIDS Society–USA mutations panel, with alterations as noted.[24] Specifically, the presence of at least 1 major mutation among PR D30N, M46I/L, G48V, V82A, V82F/T, I84V, L90M was required for genotypic PI resistance; 1 mutation among RT M41L, E44D, A62V, K65R, D67N; any insertion at T69, K70E/R, L74V, V75I, V75M/S/A/T, F77L, W88G/S, Y115F, F116Y, V118I, Q151M, Q161L, M184I/V, H208Y, L210W, T215Y/F, T215C/D, K219Q was required for genotypic NRTI resistance; and 1 mutation among RT A98G, L100I, K101E, K103N, V106A, V108I, Y181C/I, Y188C/L/H/I, G190A/S, P225H, V179N/E/D, and P236L was required for NNRTI resistance. The RT T215C/D/S/N mutations were included because they indicate previous resistance involving the RT T215Y mutation.[25] Additional minor PR mutations (L10I/R/V, K20M/R, L24I, L24V, V32I, M36I, I47V, I50V, F53L, I54V, I54L, I54M, L63P, I64V, A71T/V, G73S, V77I, N88D, N88S) were also evaluated.

Statistical Analysis

For our analyses, "viral responders" describes women with either an HIV-1 RNA measurement ≤ 80 cps/mL at the visit when PI or NNRTI ART use was first reported, or at the subsequent visit (the latter criteria implemented because study visits may have occurred near to the time of HAART initiation). "Viral failures" included women who did not reach this criterion by the time of the semiannual visit immediately following the visit when PI/NNRTI ART was first reported (thus, 6–12 months from actual PI/NNRTI initiation).

In this paper we describe the NRTI, PI, and NNRTI genotypic resistance profiles of women at the visit (which we term the baseline visit) immediately before the 1st report of PI/NNRTI, and, for women who show viral failure, the profiles at the visit of viral failure (which we term the failure visit), which was the 1st visit after PI/NNRTI initiation with HIV-1 RNA >1000 cps/mL. For the women with genotyping measurements at both the baseline and failure visits who did not show baseline PI or NNRTI resistance mutations, we constructed a linear regression model to analyze the change in $CD4^+$ cell count and $\log_{10}$ HIV-1 RNA concentration between the baseline and failure visit. We standardized the change in markers by the time between baseline and failure visits. In this regression model, the impact of baseline NRTI mutations and mutations (ie, NRTI, PI, and NNRTI) at the failure visit on the change in $CD4^+$ cell count was estimated after controlling for baseline $CD4^+$ cell counts, HIV-1 RNA levels at baseline and failure visits, and PIs or NNRTIs taken after PI/NNRTI initiation and prior to viral failure. A separate model investigated whether the number of major PR mutations predicted $CD4^+$ cell count response. All analyses were run using either SAS (version 8, SAS Institute, Cary, NC) or StatXact (version 5, Cytel Software Corp., Cambridge, MA).

RESULTS

A total of 366 women enrolled in the WIHS fulfilled eligibility criteria for inclusion in this analysis. Of all the HIV-1–seroprevalent women in the WIHS who reported use of a PI or NNRTI (n = 888) prior to October 2000 and had complete HIV-1 RNA and $CD4^+$ data available for the visit immediately prior to PI/NNRTI initiation, 19% (n = 169) were excluded from this analysis because they initiated PI/NNRTI with HIV-1 RNA <1000 cps/mL; 14% (n = 128) were excluded because they did not have marker data at the visit immediately following PI/NNRTI initiation; 14% (n = 123) were excluded because they reported only short-term use of PI/NNRTI between study visits; and 10% (n = 87) were excluded because no ART was reported at the visit when viral failure occurred. Fifteen women were also excluded because their level of HIV-1 RNA measured at PI/NNRTI initiation, or at the visit immediately following PI/NNRTI initiation, was undetectable with a limit of detection of 400 or 4000 cps/mL.

The median (interquartile range [IQR]) date of the visit when PIs or NNRTIs were first reported was June 1997 (January 1997, February 1998). At the baseline visit, the 366 women were a median (IQR) of 38.9 (33.6, 44.0) years old; 42% had previously reported a clinical AIDS-defining illness; and 59% had reported using at least 1 NRTI for >2 study visits. Similar to the entire WIHS cohort, 57% of the women included in this study reported being African American and 26% reported being Latina. The median (IQR) $CD4^+$ cell count and $\log_{10}$ HIV-1 RNA levels at the baseline visit were 269 (143, 409) cells/mm^3 and 4.41 (3.80, 4.95) cps/mL, respectively.

Baseline Resistance Profile

Genotypic resistance measures for the baseline visit were available on 322 women. Genotyping data were missing if repository specimen quantities were unavailable or if genotypic testing failed. Overall, the rate of indeterminate or missing genotype results at the baseline visit was 12% (44/366). Of the 322 women, 123 (38%) were free of NRTI, PI, and NNRTI mutations; 167 (52%) had only NRTI resistance mutations; and 32 (10%) had PI or NNRTI resistance mutations (28 of these 32 women also had NRTI mutations). The prevalence of individual NRTI mutations among the 195 women with NRTI resistance mutations is shown in Figure 1A. The M184I/V mutation occurred in 71% (n = 139) of the 195 women. Figure 1B depicts the use of individual NRTIs at or prior to PI/NNRTI initiation among these 195 women. Prior use of zidovudine and lamivudine was reported by 95% (n = 186) of the women.

The distributions of PI mutations and NNRTI mutations among the 32 women with PI or NNRTI resistance mutations at the baseline visit are shown in Figures 2A and B, respectively. Nine women had PI mutations without NNRTI mutations, 20 had NNRTI mutations without PI mutations, and 3 had both NNRTI and PI mutations. As has been seen by others,[26] a substantial proportion of women (81%) showed the L63P mutation, but none of these women were categorized as resistant to PIs based solely on this criterion. The 15 occurrences of the Y181I mutation occurred concomitantly with the Y188L mutation, although 1 occurrence of the Y188L mutation occurred without Y181I.

Viral Response After Initiation of PIs/NNRTIs

More women reported initiating PI-regimens than NNRTI regimens during the time of this study: 294 women (80%) reported a PI regimen, 63 women (17%) reported an NNRTI regimen, and 9 women (2%) reported both a PI and NNRTI as part of their initial regimen. Among the 303 women initiating a PI regimen, indinavir was used most often, reported by 45% of the women, followed by saquinavir (25%), nelfinavir (25%), and ritonavir (13%). Most of the 72 women initiating NNRTIs reported use of nevirapine (83%), followed by efavirenz (15%), and 1 woman (1%) reported use of delavirdine.

Of the 366 women fulfilling the enrollment criteria, 40% (n = 148) could be classified as viral responders. The majority

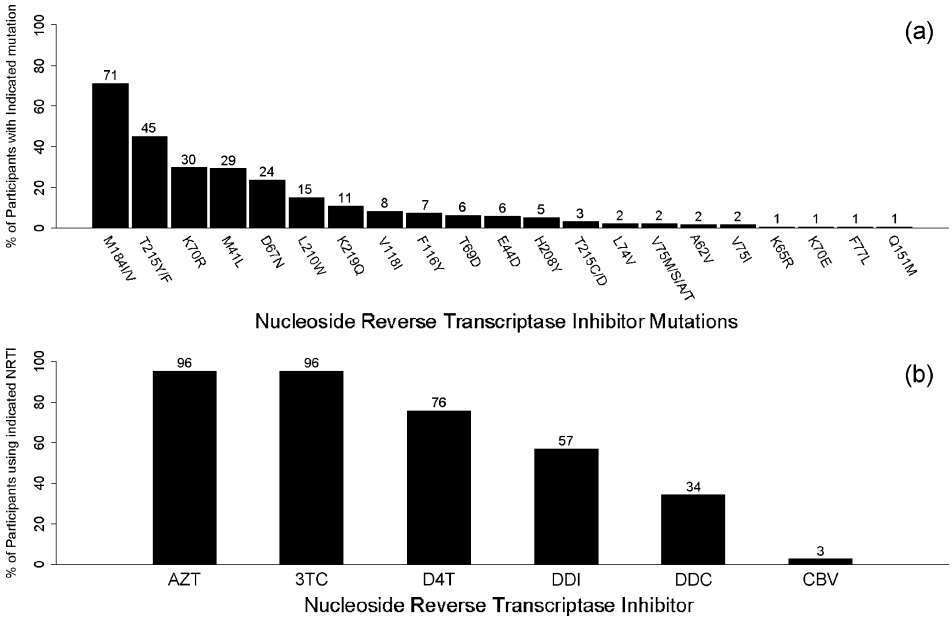

FIGURE 1. a, Distribution of NRTI resistance mutations at the visit immediately prior to PI/NNRTI initiation among the 195 women with NRTI resistance mutations. b, Percentage of women reporting use of zidovudine (AZT), lamivudine (3TC), stavudine (D4T), didanosine (ddI), zalcitabine (DDC), and Combivir (CBV; lamivudine plus zidovudine, GlaxoSmithKline) prior to PI/NNRTI initiation.

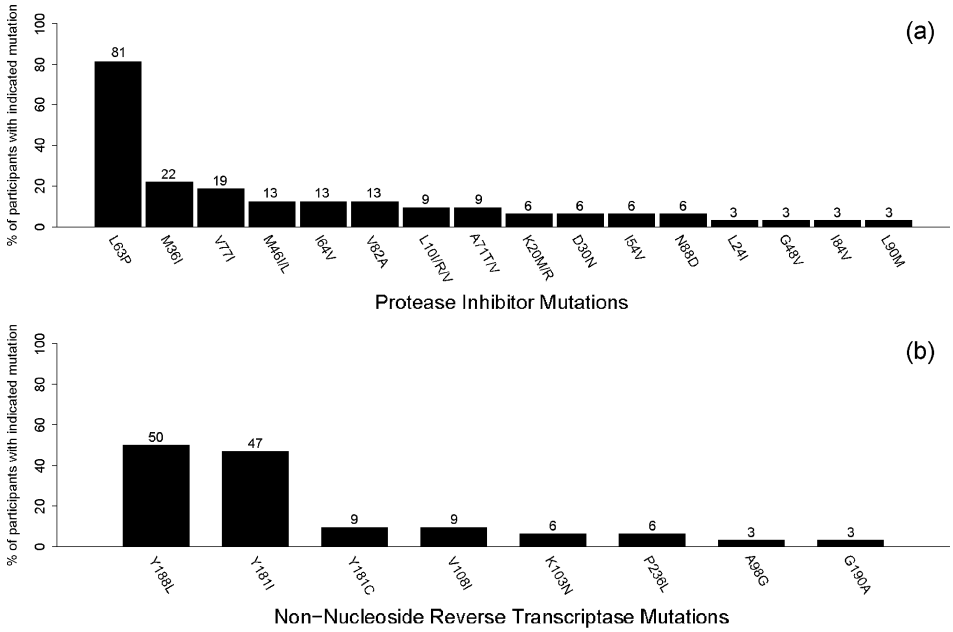

FIGURE 2. Distribution of (a) PI and (b) NNRTI mutations at the visit immediately prior to PI/NNRTI initiation among the 32 women with either PI or NNRTI resistance mutations.

(72%) of these responders had HIV-1 RNA 1 ≤80 cps/mL concurrent with the 1st reported use of a PI/NNRTI; the remaining 28% reached this level at the semiannual visit immediately following the 1st report of PI or NNRTI. Of the viral failures who maintained detectable HIV-1 RNA at the visit of PI/NNRTI initiation, 16% (34/218) showed a partial response with HIV-1 RNA between 81–1000 cps/mL at the visit immediately following PI/NNRTI initiation.

Resistance Profile at Failure Visit

Excluding the women without baseline genotyping data, those without genotyping data at failure visit, and those with PI or NNRTI resistance at baseline provided 258 women for analysis. Figure 3 displays the follow-up for these women stratified by whether they had NRTI-resistant mutations present at baseline. Overall, 75 women developed PI or NNRTI resistance after 1 year, representing 54% of the women with viral failure. The women with baseline WT genotypes were more likely to have a viral response (51%) than those with NRTI resistance (43%) but the difference was not statistically significant ($P = 0.208$).

The women who showed short-term viral failure during the timeframe of this study with baseline NRTI resistance were much more likely to have viral failure with PI or NNRTI resistance mutations than women with WT genotypes at baseline (66% vs. 36%, $P < 0.001$). Additionally, all but 6 women who had PI or NNRTI mutations at the visit of viral failure also had NRTI mutations. Figure 4 displays the distribution of PI (Fig. 4A) resistance mutations among the 55 women with PI resistance and NNRTI (Fig. 4B) resistance mutations among the 75 participants with viral failure and PI or NNRTI resistance mutations. All 55 women with PI mutations reported use of PIs prior to viral failure, but 7 of the 27 women who had NNRTI mutations reported use of PIs and did not report use of NNRTIs. Four of these women had Y181I/Y188L mutations, and the other 3 had V108I, K103N/Y181C, and Y181C mutations. Of the 55 women with PI mutations, 40 (73%) had 1 major mutation, 10 (18%) had 2 major mutations, and 5 (9%) had 3 or 4 major mutations.

Changes in CD4$^+$ Cell Counts and HIV-1 RNA Concentration

The median (IQR) time between baseline and failure visits was 1.00 (0.98, 1.08) years. The overall mean change in CD4$^+$ cell count among these women showing viral failure of therapy was +42 cells/mm^3. The mean change in CD4$^+$ cell counts for women with complete viral suppression was +95 cells/mm^3. Table 1 shows the results of the multivariable linear regression model evaluating the impact of HIV-1 resistance genotypes on CD4$^+$ cell count changes between the baseline and failure visit, with the difference in CD4$^+$ cell

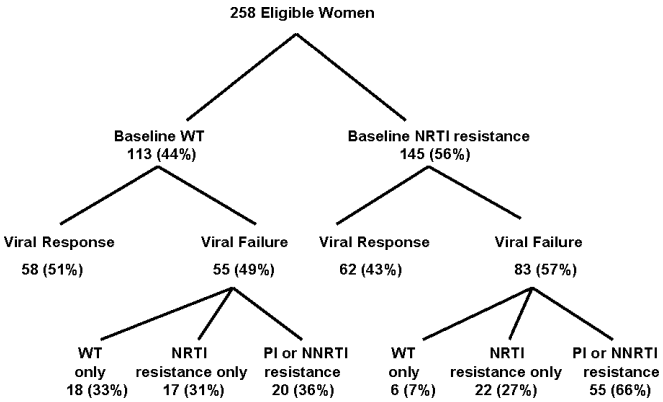

FIGURE 3. Characterization of 258 women enrolled in the WIHS Viral Resistance Study. Eligibility for this analysis included women who had either had viral response and baseline genotype data or had viral failure and both baseline (ie, visit prior to PI/NNRTI initiation) and failure visit genotype data, stratified by baseline genotype. Thirty-two women with PI or NNRTI resistance at the baseline visit were excluded.

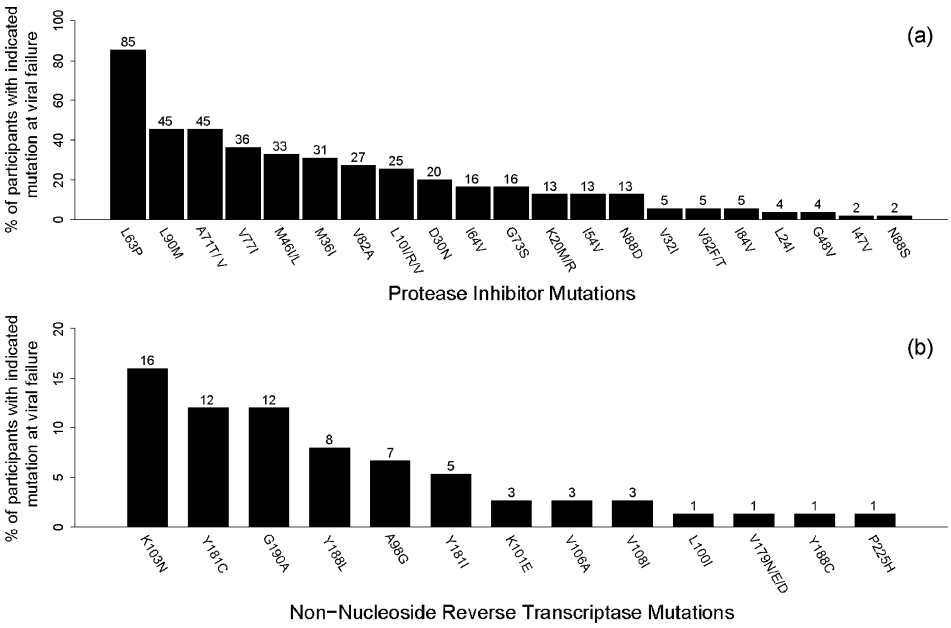

FIGURE 4. a, Distribution of PI mutations at the failure visit among the 48 women reporting use of PIs with PI mutations. b, Distribution of NNRTI mutations at the failure visit among 75 women having PI or NNRTI resistance mutations.

counts adjusted for the time between the 2 time points. Positive coefficients indicate an improved $CD4^+$ cell count response after PI/NNRTI initiation. After adjusting for baseline $CD4^+$ cell count, baseline and failure visit HIV-1 RNA levels, and type of antiretroviral therapy used between PI/NNRTI initiation and the failure visit, women with NRTI resistance at baseline had worse but statistically nonsignificant response (mean decrease of 31.0 cells/mm^3) compared with women with no NRTI resistance at baseline. NRTI resistance mutations at the failure visit did not affect $CD4^+$ cell count response (P = 0.611) although Figure 3 shows only 17 women developed de novo NRTI mutations without PI or NNRTI mutations. In contrast, women with PI or NNRTI resistance mutations at the failure visit showed better $CD4^+$ cell count responses relative to women with no resistance mutations at baseline. Specifically, women with PI mutations showed an average improvement of 64.4 cells/mm^3 (95% CI: 14.7, 114.2) in $CD4^+$ cell count change relative to women with no PI mutations. We found a significant interaction between the occurrence of NNRTI mutations at viral failure and whether the women possessed any baseline NRTI mutations, whereby in women with no baseline NRTI mutations, there was no association of NNRTI mutations with $CD4^+$ cell count changes (P = 0.976). However, among women who had NRTI mutations at baseline, those with NNRTI mutations showed a significantly better average response of 118.3 cells/mm^3 (95% CI: 38.3 to 198.4)

TABLE 1. Results From Multivariable Regression Models Predicting CD4 Change and Log_{10} HIV RNA Concentration From Baseline to Failure Visit Among 138 Women With Viral Failure

	Estimated Impact on Mean Change (95% CI)	*P* Value*
Change in $CD4^+$ cell count (cells/mm^3)		
NRTI resistance at baseline visit	−31.0 (−82.1, 20.1)	0.233
NRTI resistance at failure visit	−14.7 (−71.6, 42.3)	0.611
PI resistance at failure visit	64.4 (14.7, 114.2)	0.012
NNRTI resistance at failure visit		
No baseline NRTI resistance	1.5 (−95.3, 98.2)	0.976
Baseline NRTI resistance	118.3 (38.3, 198.4)	0.004
Log_{10} HIV-1 RNA at failure visit	−72.7 (−105.0, −40.4)	<0.001
Change in log_{10} HIV RNA (copies/mL)		
NRTI resistance at baseline visit	0.196 (−0.039, 0.432)	0.102
NRTI resistance at failure visit	−0.297 (−0.586, −0.008)	0.044
PI resistance at failure visit	−0.038 (−0.297, 0.222)	0.774
NNRTI resistance at failure visit	−0.013 (−0.346, 0.320)	0.938

*Multivariable model simultaneously adjusting for all listed variables, $CD4^+$ cell count and HIV RNA level prior to PI/NNRTI initiation, and type of PI and NNRTI therapies.
Changes were standardized by duration between baseline and failure visit.

relative to women with no NNRTI mutations. We were unable to reliably assess interactions between PI and NRTI and PI and NNRTI mutations at the visit of viral failure because only 7 women with both PI and NNRTI mutations were observed in this study. A regression model using the number of major PI mutations as a predictor instead of PI resistance was also statistically significant and provided similar results (data not shown).

The bottom half of Table 1 displays similar results when using the change in $\log_{10}$ HIV-1 RNA concentration as the outcome. The overall mean change in $\log_{10}$ HIV-1 RNA among these women showing viral failure of therapy was -0.335 $\log_{10}$ cps/mL. Here, the only significant factor influencing HIV-1 RNA change was NRTI resistance at failure visit, in which women with NRTI resistance mutations showed a larger average decrease in HIV-1 RNA (-0.297 cps/mL) than other women.

DISCUSSION

In this cohort of HIV-infected women initiating PIs or NNRTIs, we have found that viral failure with genotypic resistance in 1 year is relatively common, and we have described the genotypic resistance profiles at baseline and at the time of viral failure. Our rate of approximately 40% viral suppression after 1 year is lower than that reported in other population-based settings.[7,8] This study is one of the largest studies of genotypic resistance and viral failure among HIV-1–infected, primarily minority women, a group for whom the HIV/AIDS epidemic represents an increasing and persistent health threat.

From a public health perspective, it is particularly important to assess changes in HIV-1–related clinical parameters in populations of HIV-1–infected individuals who are demographically and behaviorally representative of the majority of infected individuals in the United States. The efficacy of PIs and NNRTIs has been demonstrated in numerous clinical trials, but clinical trial participants are often not representative of patient populations[27] and significantly underrepresent women[27,28] and racial minorities. Observational studies such as the WIHS are generally larger, of longer duration, and enroll participants who are more representative of the population at large. Although therapies in WIHS are not randomized, are based on self-report, and depend on a variety of demographic and health-related factors,[29–31] they reflect current treatment patterns in the community of individuals most influenced by HIV and AIDS. Some possible misclassification in therapy use may have occurred despite our best efforts at data collection, which may explain some of the baseline PI/NNRTI mutations and discordance of mutations with reported therapy. However, trends in individual therapies[30] and therapy response[9,32] provide a measure of assurance of the validity of these methods. In seeking to predict and understand the effects of therapeutic interventions, information from both clinical trials and observational studies is needed.

We have shown that women with viral failure with PI and NNRTI resistance mutations (among those with baseline NRTI mutations) that occurred 1 year after PI/NNRTI initiation demonstrated better $CD4^+$ cell count responses than women with viral failure and no PI or NNRTI resistance mutations. What might account for these associations? First, we might hypothesize a difference in the duration of PI/NNRTI therapy use. By nature of our design, however, we limited our analysis to looking at the $CD4^+$ cell count changes from the visit immediately preceding 1st PI/NNRTI report to the visit of HIV-1 RNA failure. We gain some assurance that differences in duration did not confound our results because we adjusted for duration of therapy use in the calculation of change in CD4 and HIV-1 RNA. However, because we did not have precise data for identifying when drugs were initiated during the time of this study, we cannot completely eliminate the possibility of continued residual confounding of duration of therapy.

Second, we are limited by the absence of adherence data during the time of this study. Given existing literature on the association of resistance and adherence, we can assume that women who showed viral failure with WT mutations had lower drug exposure than women with PI/NNRTI resistance mutations, due to either poor adherence or pharmacokinetic bioavailability because we excluded women discontinuing therapies altogether. If drug utilization were to completely explain the effects of PI or NNRTI mutations, however, we would expect there to be an association of these mutations with changes in viral load, and we would expect that adjustment for the change in viral load between baseline and failure visits would attenuate the association with $CD4^+$ cell count changes in our multivariate model. Interestingly, after adjustment for HIV-1 RNA concentration, we found no such effect, and evaluating $\log_{10}$ HIV-1 RNA concentration as an outcome also failed to show any effect of PI or NNRTI mutations. Thus, although women with PI and NNRTI mutations are showing better $CD4^+$ cell count response, the lack of association with HIV-1 RNA changes suggests that PI and NNRTI resistance was not mediated simply through HIV-1 RNA levels.

Lastly, our results are consistent with prior research that has demonstrated continued $CD4^+$ cell count benefits while viremic,[15–20] although few studies have conducted as extensive genotypic resistance testing outside of a clinical trial setting. Previous reports have indicated that PI-resistant viruses may be associated with continued $CD4^+$ benefits and impaired virulence or fitness,[13] but there have been few data regarding individuals with NNRTI resistance.[33–36] A recent study by Piketty et al[37] showed that interrupting NNRTI only, when it was part of a failing regimen, did not result in a further loss of $CD4^+$ cells, indirectly implying that NNRTI mutations are not associated with a loss of virulence. The interaction between baseline NRTI mutations and NNRTI mutations at the failure visit is also notable. It is possible that the improvements seen in this group reflect increased hypersensitivity among those taking NNRTI therapy with NRTI mutations.[38,39] Our results suggest that continued evaluations of the immunologic consequences of infection with either PI- or NNRTI-resistant viruses are warranted.

In summary, we have characterized the virologic changes in a prospective cohort of women initiating a PI or NNRTI, demonstrating favorable $CD4^+$ changes in the 1st year among individuals who showed PI or NNRTI viral resistance. Although efforts to promote adherence to therapies are necessary and need continued research, our results emphasize the short-term benefits of these therapies even during viral failure. Whereas complete viral response should remain a goal of the use of antiviral therapy, these data mitigate some concerns about the clinical

consequences of virologic failure. This may be an important consideration for considering the introduction of antiviral therapies in high-risk patient populations and in developing countries, although long-term evaluation is needed.

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