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# HIV Drug Resistance in Adults Receiving Early vs. Delayed Antiretroviral Therapy: HPTN 052

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**Introduction:** We evaluated HIV drug resistance in adults who received early vs. delayed antiretroviral therapy (ART) in a multinational trial [HIV Prevention Trials Network (HPTN) 052, enrollment 2005–2010]. In HPTN 052, 1763 index participants were randomized to start ART at a CD4 cell count of 350–550 cells/mm$^3$ (early ART arm) or <250 cells/mm$^3$ (delayed ART arm). In May 2011, interim study results showed benefit of early ART, and all participants were offered ART regardless of CD4 cell count; the study ended in 2015.

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**Methods:** Virologic failure was defined as 2 consecutive viral loads >1000 copies/mL >24 weeks after ART initiation. Drug resistance testing was performed for pretreatment (baseline) and failure samples from participants with virologic failure.

**Results:** HIV genotyping results were obtained for 211/249 participants (128 early ART arm and 83 delayed ART arm) with virologic failure. Drug resistance was detected in 4.7% of participants at baseline; 35.5% had new resistance at failure. In univariate analysis, the frequency of new resistance at failure was lower among participants in the early ART arm (compared with delayed ART arm, $P = 0.06$; compared with delayed ART arm with ART initiation before May 2011, $P = 0.032$). In multivariate analysis, higher baseline viral load ($P = 0.0008$) and ART regimen (efavirenz/lamivudine/zidovudine compared with other regimens, $P = 0.024$) were independently associated with higher risk of new resistance at failure.

**Conclusions:** In HPTN 052, the frequency of new drug resistance at virologic failure was lower in adults with early ART initiation. The main factor associated with reduced drug resistance with early ART was lower baseline viral load.

**Key Words:** HIV, HPTN 052, early ART, virologic failure, resistance

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## INTRODUCTION

Initiation of antiretroviral therapy (ART) at higher CD4 cell counts decreases HIV transmission[1,2] and improves outcomes and quality of life for those on treatment.[3–7] Although there are clear individual and public health benefits to early ART initiation, emergence of HIV drug resistance remains a concern in both HIV prevention and treatment settings. Drug-resistant HIV may emerge during treatment and can be transmitted to others, limiting future treatment options. HIV drug resistance is frequently observed at the time of ART failure.[8–12] Several factors have been associated with drug resistance at failure, including the presence of resistance before treatment, previous exposure to antiretroviral (ARV) drugs, higher baseline viral load, lower baseline CD4 cell count (<50 cells/mm$^3$), low adherence to ART, younger age in women, and having no education/schooling.[13–15] Some studies suggest that individuals who initiate ART at higher CD4 cell counts (>350 cells/mm$^3$) may be less likely to have drug resistance at failure.[13,16,17]

The multinational HIV Prevention Trials Network (HPTN) 052 study evaluated the impact of early ART on HIV transmission in serodiscordant couples.[1,2] HIV-infected index participants were enrolled with CD4 cell counts of 350–550 cells/mm$^3$ (enrollment period 2005–2010). Couples were randomized to 1 of 2 study arms. In the early ART arm, index participants started ART at study enrollment. In the delayed ART arm, index participants started ART once their CD4 cell count dropped below 250 cells/mm$^3$ or they developed an AIDS-defining illness.[1,2] In May 2011, interim study results revealed that early ART initiation prevented 96% of HIV transmissions and offered health benefits to the index participant.[1] After release of the interim study results, all index participants not already on ART were offered ART regardless of CD4 cell count and were informed of the benefits of early ART. The study continued until May 2015. In the delayed ART arm, 96% of the index participants had initiated ART by the end of the study.[2] The overall reduction in HIV transmission in the early ART arm compared with the delayed ART arm was 93%.[2]

We previously analyzed virologic outcomes in the HPTN 052 study.[18,19] In the first phase of the study (by May 2011), participants in the delayed ART arm took longer to achieve viral suppression compared with those in the early ART arm.[18] Over the entire trial period, higher pre-ART viral load was associated with a longer time to viral suppression, but was not associated with increased risk of virologic failure.[19] In the first phase of the study, the frequency of HIV drug resistance at the time of virologic failure differed by study arm. That study included resistance data from only 8 participants from the delayed ART arm because most participants in the delayed ART arm did not start ART until after May 2011.[13] A preliminary comparison of drug resistance in the 2 study arms in that study found a higher rate of resistance in the delayed ART arm compared with the early ART arm [7/8 (87.5%) vs. 30/85 (35.3%), $P = 0.006$].[13]

In this report, we extended the analysis of HIV drug resistance in the HPTN 052 trial to include participants who failed ART at any time during the trial (through May 2015). This increased the number of participants analyzed in both study arms, which provided more power for identifying factors associated with emergence of resistance. Inclusion of participants from the entire trial period also allowed us to compare drug resistance among participants in the early ART arm to those in the delayed ART arm who started ART before vs. after release of the interim study results. These 2 groups started ART at different baseline CD4 cell counts and had different knowledge about the benefits of early ART.

## METHODS

### Samples Used for Analysis

HPTN 052 enrolled 1763 HIV serodiscordant couples at 13 sites in 9 countries [Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States of America, and Zimbabwe] (NCT00074581).[1,2] HIV-infected index participants reported being ARV-naive; previous short-term ARV drug use for prevention of mother-to-child transmission (PMTCT) was allowed. This report includes analysis of samples collected before ART initiation (baseline) and at the time of virologic failure. Baseline samples used for genotyping were collected at the enrollment visit in the early ART arm and near the time of ART initiation in the delayed ART arm (range: 1–83 days before ART initiation). After ART initiation, viral load testing was performed at quarterly visits; participants enrolled after November 2006 also had viral load testing 1 month after ART initiation. Virologic failure was defined as having 2 consecutive HIV viral loads >1000 copies/mL more than 24 weeks after ART initiation. Failure samples used for genotyping were collected at 1 of these 2 study visits. Index participants were excluded from analysis if their baseline HIV viral load was ≤400 copies/mL.

In a previous report, we demonstrated that many participants who had HIV viral loads ≤400 copies/mL at enrollment were using ART but did not disclose this to study staff.[20]

## Laboratory Methods

CD4 cell count and HIV viral load were determined at study sites.[1,2] HIV genotyping was performed at 4 study sites (Pune and Chennai, India; Johannesburg, South Africa; and Rio de Janeiro, Brazil) and at the HPTN Laboratory Center (Baltimore, MD, USA) using the ViroSeq HIV-1 Genotyping System, v2.8 (Abbott Molecular, Des Plaines, IL). Drug resistance results were obtained from FASTA files using the Resistance Calculator Program at Frontier Science Foundation using the Stanford v7.0 algorithm. Phylogenetic analysis was performed to determine HIV subtype in the *pol* region (HIV protease and reverse transcriptase). FASTA sequences were aligned using MegAlign v14.0 (Clustal W method); alignments included 139 reference sequences representing different subtypes and circulating recombinant forms from the database of the Los Alamos National Laboratory (https://www.hiv.lanl.gov). PHYLIP v3.695 was used to generate phylogenetic trees and bootstrap values. FASTA files were submitted to a public database (GenBank, accession numbers: KT833391-KT833560, KU562071-KU562073, KU562075, KU562077, KU562079-KU562081, KU562083, KU562085, MF573212-MF573297, and MF594795-MF594950).

## Statistical Methods

Baseline characteristics of groups defined by study arm and study group were analyzed using $\chi^2$, analysis of variance, and *t* tests. Univariate and multivariate associations between baseline factors and HIV drug resistance were analyzed using logistical regression.

## Ethical Considerations

Institutional review boards and ethics committees at each participating institution approved the HPTN 052 study. Written informed consent was obtained from all study participants for participation in the HPTN 052 study.

# RESULTS

## Study Cohort

In HPTN 052, 249 of 1671 participants who initiated ART during the study met the criteria for virologic failure; 38 (15%) of the 249 participants were excluded from analysis (12 had viral loads ≤400 copies/mL at ART initiation, 15 did not have paired baseline/failure samples available for resistance testing, and 11 did not have paired resistance results because of genotyping failure). Resistance results were obtained from paired baseline/failure samples for 211 participants with virologic failure, including 128 participants in the early ART arm and 83 participants in the delayed ART arm. The 83 participants in the delayed ART arm included 22 who started ART before May 2011 and 61 who started ART after May 2011 (Table 1).

Table 1 shows characteristics of participants included in this report. By design, the median [interquartile range (IQR)] baseline CD4 cell count was significantly higher in the early ART arm compared with the delayed ART arm [454 (373–535) cells/mm$^3$ vs. 311 (236–415) cells/mm$^3$, $P < 0.001$]. Baseline CD4 cell count was also higher in the delayed ART arm among those who initiated ART after May 2011 (when ART was offered to all index participants regardless of CD4 cell count) than among those who initiated ART before May 2011. Median (IQR) baseline HIV viral load was significantly lower in the early ART arm compared with the delayed ART arm [4.5 (3.8–5.0) $\log_{10}$ copies/mL vs. 4.9 (4.4–5.3) $\log_{10}$ copies/mL, $P < 0.001$]; median (IQR) baseline viral load was also significantly lower in the early ART arm compared with the subgroup in the delayed arm who started ART before May 2011 [4.5 (3.8–5.0) $\log_{10}$ copies/mL vs. 5.2 (4.3–5.5) $\log_{10}$ copies/mL, $P = 0.006$].

HIV subtype was determined for all 211 participants. The most common HIV subtype was subtype C (n = 162, 76.8%), followed by subtype B (n = 25, 11.8%). The HIV subtypes of the other 24 participants were: A1 (n = 7), A2 (n = 1), D (n = 1), F1 (n = 6), CRF01_AE (n = 4), and other recombinants (n = 5). Among the 211 participants, 158 (74.9%) were taking a regimen of efavirenz (EFV), lamivudine (3TC), and zidovudine (ZDV); 44 (20.9%) were taking protease inhibitor (PI)–based regimens (28 were taking atazanavir-based ART; 16 were taking lopinavir/ritonavir-based ART), and 9 (4.3%) were taking other EFV-based regimens. There were no significant differences in enrollment region (America, Africa, and Asia), ART regimen type (EFV/3TC/ZDV vs. other), educational level, marital status, or number of sex partners among participant groups (Table 1).

## HIV Drug Resistance at Baseline

Among the 211 participants with virologic failure, 10 (4.7%) had drug resistance at baseline (Fig. 1). Five had nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance and 5 had dual-class resistance (NNRTI resistance and nucleoside reverse transcriptase inhibitor [NRTI] resistance). PI resistance was not detected. The most common NNRTI resistance detected at baseline was K103N (40.0%), which causes high-level resistance to EFV and nevirapine. Other baseline NNRTI resistance mutations were Y181C and K101E, which also cause resistance to etravirine and rilpivirine. The only baseline NRTI resistance mutation detected was M184V, which causes high-level resistance to 3TC and emtricitabine, with low-level resistance to abacavir and didanosine; this mutation also increases susceptibility to tenofovir and other NRTI drugs. Of the 10 participants with baseline resistance, 9 failed an EFV-based ART regimen and 1 failed a PI-based ART regimen.

There was no significant difference in frequency of baseline drug resistance by study arm (4.7% early ART arm vs. 4.8% delayed ART arm, $P = 0.96$; Supplemental Digital Content 1, http://links.lww.com/QAI/B105). The frequency of baseline drug resistance was highest (9.1%) among the 22 participants in the delayed ART arm who started ART before May 2011. None of the other factors analyzed were associated with baseline drug resistance (Supplemental Digital Content 1,

**TABLE 1.** Baseline Characteristics of HIV-Infected Index Participants With Virologic Failure in HPTN 052

| Variables | Early ART, N = 128 | Delayed ART, N = 83 | *P* | Delayed ART (Before 5/11), N = 22 | Delayed ART (After 5/11), N = 61 | *P* |
|---|---|---|---|---|---|---|
| Median age (IQR) | 31 (26–36) | 33 (27–39) | 0.08 | 33 (25–40) | 33 (27–37) | 0.87 |
| Sex | | | 0.06 | | | 0.69 |
| Male | 65 (50.8%) | 31 (37.3%) | | 9 (40.9%) | 22 (36.1%) | |
| Female | 63 (49.2%) | 52 (62.7%) | | 13 (59.1%) | 39 (63.9%) | |
| Median CD4 cell count (IQR) | 454 (373–535) | 311 (236–415) | **<0.001** | 226 (196–249) | 361 (301–440) | **<0.001** |
| Median $\log_{10}$ viral load (IQR) | 4.5 (3.8–5.0) | 4.9 (4.4–5.3) | **<0.001** | 5.2 (4.3–5.5) | 4.9 (4.4–5.2) | 0.58 |
| Median time to ART initiation (IQR) | 0 (0–0) | 2.4 (1.7–3.2) | **<0.001** | 1.8 (0.81–2.5) | 2.5 (2.0–3.2) | **0.001** |
| Region | | | 0.75 | | | 0.07 |
| America | 24 (18.8%) | 18 (21.7%) | | 7 (31.8%) | 11 (18.0%) | |
| Asia | 38 (29.7%) | 21 (25.3%) | | 8 (36.4%) | 13 (21.3%) | |
| Africa | 66 (51.6%) | 44 (53.0%) | | 7 (31.8%) | 37 (60.7%) | |
| Regimen* | | | 0.78 | | | 0.68 |
| EFV/3TC/ZDV | 95 (74.2%) | 63 (75.9%) | | 16 (72.7%) | 47 (77.0%) | |
| Other | 33 (25.8%) | 20 (24.1%) | | 6 (27.3%) | 14 (23.0%) | |
| Education | | | 0.39 | | | 0.29 |
| None | 22 (17.2%) | 10 (12.0%) | | 1 (4.5%) | 9 (14.8%) | |
| Primary or secondary schooling | 100 (78.1%) | 71 (85.5%) | | 21 (95.5%) | 50 (82.0%) | |
| Postsecondary schooling | 6 (4.7%) | 2 (2.4%) | | 0 (0.0%) | 2 (3.3%) | |
| Marital status | | | 0.17 | | | 0.55 |
| Married | 122 (95.3%) | 82 (98.8%) | | 22 (100.0%) | 60 (98.4%) | |
| Not married | 6 (4.7%) | 1 (1.2%) | | 0 (0.0%) | 1 (1.6%) | |
| No. of sex partners† | | | 0.55 | | | 0.45 |
| 0–1 | 123 (96.1%) | 81 (97.6%) | | 21 (95.5%) | 60 (98.4%) | |
| >1 | 5 (3.9%) | 2 (2.4%) | | 1 (4.5%) | 1 (1.6%) | |

*P*-values <0.05 are bolded. The $\chi^2$ test was used for categorical variables. For continuous variables, *t* tests were used for 2-group comparisons, allowing for unequal variance; analysis of variance was used for 3-group comparisons.

*Among the 211 participants who failed ART, 158 (74.9%) were taking EFV/3TC/ZDV, 44 (20.9%) were taking PI-based regimens (26 were taking atazanavir-based ART and 2 were taking atazanavir/ritonavir-based ART), and 9 (4.3%) were taking a different EFV-based regimen.

†Number of sex partners in the 3 months before ART initiation.

http://links.lww.com/QAI/B105). The failure to see associations of baseline resistance and other factors may have reflected the low frequency of baseline resistance in this cohort.

## HIV Drug Resistance at Failure

Overall, 83 (39.3%) of the 211 participants had drug resistance detected at failure. The 83 participants included all 10 participants who had drug resistance at baseline. Newly acquired resistance was detected in 75 (35.5%) of the 211 participants (Fig. 1). Of those with new resistance, 47 acquired NNRTI resistance only, 16 acquired NRTI resistance only, and 12 acquired dual-class resistance (NNRTI + NRTI resistance). PI resistance was not detected. Among the 75 participants with new resistance at failure, 2 had baseline NNRTI resistance and acquired NRTI resistance during

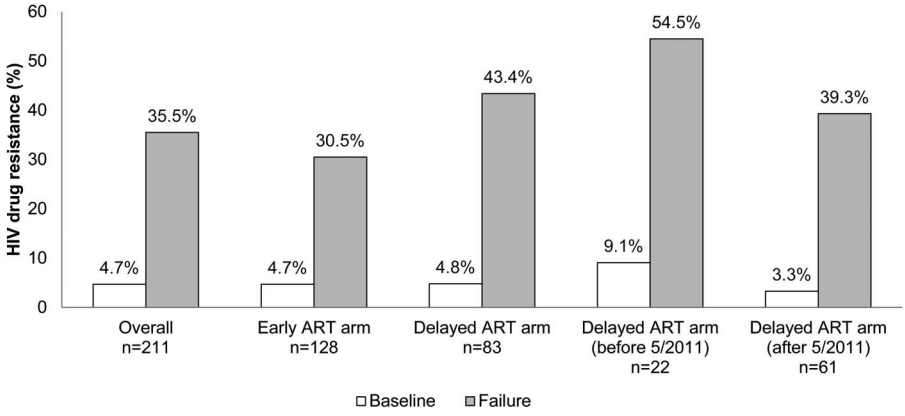


**FIGURE 1.** The figure shows the frequency of HIV drug resistance at baseline and new resistance at failure among participants with virologic failure in HPTN 052. Paired baseline and failure HIV genotyping results were obtained for 211 participants. ART was initiated at a CD4 cell count of 350–550 cells/mm$^3$ (early ART arm) or <250 cells/mm$^3$ (delayed ART arm, before release of the interim study report in May 2011). After May 2011, all HIV-infected index participants in the delayed ART arm were offered ART regardless of CD4 cell count.

treatment. The resistance mutations detected in 71 (94.7%) of the 75 participants were consistent with the ARV drugs in their ART regimens. In the other 4 cases, participants with new NNRTI resistance were taking a PI-based ART regimen (none had baseline resistance). None of the 4 participants switched ART regimens before failing treatment; 1 reported having received a single dose of nevirapine for PMTCT before enrollment.

The most common NNRTI resistance mutation acquired during treatment was K103N [detected in 47 (79.7%) of the 59 cases with new NNRTI resistance]. The most common NRTI resistance mutation acquired during treatment was M184V (detected in all 28 cases with new NRTI resistance). In 2 cases, participants acquired thymidine analog mutations in addition to M184V (1 acquired D67N and 1 acquired K219R). The NRTI resistance mutation, K65R, was not detected. This mutation reduces susceptibility to several NRTI drugs, including tenofovir and emtricitabine, which are used for HIV treatment and prevention. There were no significant differences in the types of mutations detected in participants in the 2 study arms, or in participants infected with subtype C HIV vs. other subtypes.

The frequency of new drug resistance at failure was lower among the 128 participants in the early ART arm than among the 83 participants in the delayed ART arm, but the difference was not statistically significant (30.5% vs. 43.4%, $P = 0.06$, Table 2 and Fig. 1). The $\log_{10}$ viral load at the time of virologic failure was similar in the 2 study arms ($P = 0.19$, data not shown); therefore, the failure to observe a difference in the frequency of drug resistance in the 2 arms was not due to low viral load (sampling error during HIV genotyping). The frequency of new resistance was significantly lower among participants in the early ART arm than among participants in the delayed ART arm who started ART before May 2011 (30.5% vs. 54.5%, $P = 0.032$, univariate analysis, Table 2 and Fig. 1). Other factors associated with new drug resistance at virologic failure in univariate analyses included: ART regimen (EFV/3TC/ZDV compared with other ART regimens, $P = 0.0074$), higher baseline viral load ($P < 0.0001$), and lower baseline CD4 cell count ($P = 0.047$, Table 2). In a multivariate model, 2 factors remained significantly associated with new drug resistance at failure: ART regimen (EFV/3TC/ZDV, $P = 0.024$) and higher baseline viral load ($P = 0.0008$, Table 2).

The median (IQR) baseline viral load was 4.98 (4.42–5.39) $\log_{10}$ copies/mL among those with new resistance at failure and 4.48 (3.92–4.94) $\log_{10}$ copies/mL among those without new resistance ($P < 0.0001$). We also analyzed the association of ART regimen and new resistance at failure when all participants on EFV-based ART were grouped together; when participants on EFV-based ART were compared with those on PI-based ART, the association between ART regimen and new resistance at failure was only significant in the univariate model (Table 2, footnote).

One factor that may have affected the results was that the follow-up period between ART initiation and virologic failure was different in the 2 study arms (early ART arm: 177 person-years and delayed ART arm: 83 person-years). To address this, additional statistical analyses were performed in which follow-up time in the early ART arm was censored at 2.7 years (the maximum length of follow-up in the delayed ART arm) (Supplemental Digital Content 2, http://links.lww.com/QAI/B105). The additional analysis indicated that the different length of ART follow-up in the 2 study arms did not significantly affect the study findings.

The proportion of participants with new resistance at virologic failure was similar among those who did or did not achieve viral suppression before virologic failure [45/114 (39%) vs. 30/97 (31%), $P = 0.20$] and was similar among those who did or did not achieve viral suppression in the first 3 months after ART initiation [34/91 (37%) vs. 41/120 (34%), $P = 0.63$]. Among the 75 participants with new resistance at failure, only 18 (24%) were virally suppressed for 12 months or longer before failing ART.

## DISCUSSION

This report extends our previous analysis of HIV drug resistance in HPTN 052 by including virologic failure events that occurred throughout the HPTN 052 study (through May 2015). This increased the number of participants included in the analysis for both study arms (from 85 to 128 in the early ART arm and from 8 to 83 in the delayed ART arm), and allowed us to assess resistance among participants in the delayed ART arm who started ART before vs. after release of the interim study report. This report includes analysis of 211 participants with virologic failure. The frequency of baseline (pretreatment) resistance in this group was 4.7% and was similar in the 2 study arms. Other studies have detected pretreatment resistance in ~5% of participants in ART-naive cohorts,[8,21–25] with higher frequencies (>9%) among those who later failed ART.[8,23] In HPTN 052, none of the clinical or demographic factors evaluated were associated with baseline drug resistance.

At virologic failure, 36% of the participants in HPTN 052 had new resistance to at least one drug. Higher rates of resistance have been reported in other studies in which ART was initiated at lower CD4 cell counts (50%–95%).[8–12,17] The risk of resistance increases if individuals continue to receive an ART regimen after virologic failure.[26–29] The lower frequency of resistance observed in HPTN 052 compared with previous studies may reflect frequent viral load monitoring, which may have limited exposure to ART in participants who were not virally suppressed.[1] In this study, 4 participants (3 women and 1 man) were on a PI-based regimen and had new NNRTI resistance at failure; in these cases, the NNRTI-resistant variants may have been selected during previous exposure to NNRTIs in PMTCT regimens or undisclosed ARV drug use or may have been acquired by superinfection with an NNRTI-resistant HIV strain.

Our previous report, which included only 8 participants in the delayed ART arm, found a significant difference in the frequency of new resistance in the early vs. delayed ART arms.[13] This association was not observed in the extended analysis in this report, which included 83 delayed ART arm participants. We did find that participants in the early ART arm were less likely to acquire resistance during treatment than the subset of participants in the delayed ART arm who initiated ART at lower CD4 cell counts, before release of the

**TABLE 2.** Factors Associated With New HIV Drug Resistance at the Time of Virologic Failure in HPTN 052

| | | New Resistance at Failure | | | |
|---|---|---|---|---|---|
| | | Univariate | | Multivariate | |
| | n/N (%) | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Study arm | | | 0.06 | | |
| Early ART arm | 39/128 (30.5) | Ref | | | |
| Delayed ART arm | 36/83 (43.4) | 1.73 (0.98 to 3.10) | | | |
| Study group* | | | 0.08 | | 0.43 |
| Early ART arm | 39/128 (30.5) | Ref | | Ref | |
| Delayed ART arm (before 5/2011) | 12/22 (54.5) | 2.74 (1.09 to 6.87) | **0.032** | 2.11 (0.68 to 6.57) | 0.20 |
| Delayed ART arm (after 5/2011) | 24/61 (39.3) | 1.48 (0.78 to 2.80) | 0.23 | 1.12 (0.55 to 2.30) | 0.75 |
| Age at ART initiation | | | 0.94 | | |
| <25 yrs | 14/37 (37.8) | Ref | | | |
| 25–39 yrs | 48/136 (35.3) | 0.90 (0.42 to 1.90) | 0.77 | | |
| ≥40 yrs | 13/38 (34.2) | 0.85 (0.33 to 2.20) | 0.74 | | |
| Sex | | | 0.26 | | |
| Male | 38/96 (39.6) | Ref | | | |
| Female | 37/115 (32.2) | 0.72 (0.41 to 1.28) | | | |
| CD4 at ART initiation† | | 0.81 (0.65 to 1.00) | **0.047** | 1.00 (0.77 to 1.31) | 0.98 |
| VL at ART initiation‡ | | 2.54 (1.63 to 3.98) | **<0.0001** | 2.29 (1.41 to 3.72) | **0.0008** |
| Time to ART initiation§ | | 1.09 (0.89 to 1.33) | 0.40 | | |
| HIV subtype | | | 0.63 | | |
| C | 59/162 (36.4) | Ref | | | |
| Non-C | 16/49 (32.7) | 0.85 (0.43 to 1.67) | | | |
| Region | | | 0.92 | | |
| America | 16/42 (38.1) | Ref | | | |
| Asia | 21/59 (35.6) | 0.90 (0.40 to 2.04) | 0.80 | | |
| Africa | 38/110 (34.5) | 0.86 (0.41 to −1.79) | 0.68 | | |
| Regimen‖ | | | **0.0074** | | |
| EFV/3TC/ZDV | 64/158 (40.5) | 2.60 (1.25 to 5.43) | | 2.51 (1.13 to 5.58) | **0.024** |
| Other | 11/53 (20.8) | Ref | | | |
| Education | | | 0.31 | | |
| None | 15/32 (46.9) | Ref | | | |
| Primary or secondary schooling | 58/171 (33.9) | 0.58 (0.27 to 1.25) | 0.16 | | |
| Postsecondary schooling | 2/8 (25.0) | 0.38 (0.07 to 2.16) | 0.27 | | |
| Marital status | | | 0.68 | | |
| Married | 72/204 (35.3) | Ref | | | |
| Not married | 3/7 (42.9) | 1.37 (0.30 to 6.31) | | | |
| No. of sex partners¶ | | | 0.24 | | |
| 0–1 | 71/204 (34.8) | Ref | | | |
| >1 | 4/7 (57.1) | 2.50 (0.54 to 11.47) | | | |
| Baseline resistance | | | 0.27 | | |
| Yes | 2/10 (20.0) | 0.44 (0.09 to 2.12) | | | |
| No | 73/201 (36.3) | Ref | | | |
| Previous PMTCT# | | | 0.46 | | |
| Yes | 5/18 (27.8) | Ref | | | |
| No | 70/193 (36.3) | 1.47 (0.51 to 4.32) | | | |

*P*-values <0.05 are bolded. Odds ratios (OR) were calculated using logistic regression. An OR >1 indicates a higher risk of resistance. The OR could not be estimated if any cell was 0 for the categorical variable. Variables with a $P < 0.05$ were included in the multivariate regression model.

*Study groups included: early ART arm (ART initiated at enrollment), delayed ART arm with ART initiation before May 2011, and delayed ART arm with ART initiation after May 2011.

†Per CD4 cell count increment of 100 cells/mm$^3$.

‡Per viral load increment of 1 $\log_{10}$ HIV RNA copies/mL.

§Per 1 year increment.

‖Among the 211 participants who failed ART, 158 (74.9%) were taking EFV/3TC/ZDV, 44 (20.9%) were taking PI-based regimens, and 9 (4.3%) were taking a different EFV-based regimen. One participant switched ART regimens before virologic failure, and one received ARV drugs for PMTCT before enrolling in the HPTN 052 trial. The association of ART regimen with new resistance at virologic failure was also analyzed for the 167 participants taking EFV-based ART compared with the 44 participants taking PI-based ART. In this alternate model, the association between ART regimen and resistance was statically significant in univariate analysis (OR: 2.17, 95% CI: 1.00 to 4.68; $P = 0.04$), but not in multivariate analysis (OR: 1.95, 95% CI: 0.85 to 4.50, $P = 0.12$).

¶Number of sex partners in the 3 months before ART initiation.

#Previous PMTCT indicates those who received a regimen for PMTCT while enrolled in the study, before they started their primary ART regimen.

CI, confidence interval; N, number; OR, odds ratio; Ref, reference group; VL, viral load.

interim study report in May 2011. After May 2011, all participants in the delayed ART arm were offered ART regardless of CD4 cell count. In an observational cohort study in the United States, the frequency of resistance at failure was 22% among those who started ART with CD4 cell counts >350 cells/mm$^3$ compared with 50% among those who started ART with CD4 cell counts <350 cells/mm$^3$; however, the difference was not statistically significant ($P = 0.06$).[17] In HPTN 052, emergence of resistance at failure was significantly associated with baseline CD4 cell count in univariate analysis ($P = 0.047$), but not in a multivariate model ($P = 0.98$).

In multivariate analysis, 2 factors were independently associated with new resistance at failure: higher baseline viral load and ART regimen (EFV/3TC/ZDV vs. other regimens). An association between higher baseline viral load and resistance at failure was reported in an observational cohort in Canada[30] and a clinical trial in Africa and Asia.[31] In theory, the risk of acquiring resistance among those who start ART with higher viral loads could reflect a longer time between ART initiation and viral suppression; delayed viral suppression could provide more time for resistant variants to emerge. However, as in our previous report,[13] we found no association of viral suppression or time to viral suppression with the emergence of new resistance at failure, and only 1/4 of the participants with new resistance were virally suppressed for at least 12 months before failing ART. An alternate explanation for the association observed in this study is that higher baseline viral loads may reflect higher viral replication rates, which could favor selection of resistant variants.

In this study, 75% of the participants who failed ART received a drug regimen containing EFV, 3TC, and ZDV.[19] Participants receiving this regimen were more likely to acquire resistance during treatment than those on other regimens (40.5% vs. 20.8%, Table 2). Among those taking other regimens, 83% were on PI-based regimens and others were on alternate EFV-based regimens. No PI resistance was observed in this cohort. This may reflect the higher genetic barrier for PI resistance than NRTI and NNRTI resistance.[32]

A limitation of this study is that only baseline factors were used to analyze factors associated with new resistance at failure. We did not evaluate the association of ART adherence and resistance at failure. In a previous report, adherence to ART in HPTN 052, measured by self-report and pill count, was found to be relatively high overall (>80%) and was associated with viral suppression.[33] However, those measures may be unreliable.[34–36] A multidrug assay[37] could be used to provide a direct, biomedical assessment of ART adherence in HPTN 052 participants.

In summary, 36% of the participants with virologic failure in HPTN 052 had new resistance at the time of virologic failure. In multivariate models, new resistance at failure was associated with higher baseline viral load, but was not associated with baseline CD4 cell count.

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