# HIV drug resistance with early vs. delayed antiretroviral treatment: HPTN 052

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## BACKGROUND

The HIV Prevention Trials Network (HPTN) 052 was a multi-national, clinical trial that demonstrated reduced HIV transmission and health benefits with early antiretroviral treatment (ART) [1, 2]. The study enrolled 1,763 serodiscordant couples who were followed for up to 10 years (2005-2015). At enrollment, HIV-infected index participants were randomized to the early ART arm (CD4: 350-550 cells/mm$^3$ at ART initiation) or the delayed ART arm (CD4: ≤250 cells/mm$^3$ at ART initiation). All index participants were offered ART at any CD4 cell count after the release of interim study results in May 2011.

In HPTN 052, some index participants experienced virologic failure. A previous study evaluated HIV drug resistance among those who failed ART before May 2011 [3]. This study extends the analysis of HIV drug resistance to include all participants with virologic failure in HPTN 052.

## METHODS

### STUDY COHORT

HPTN 052 enrolled participants from Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand, and USA.

HIV drug resistance was evaluated at baseline (prior to ART initiation) and at virologic failure. Resistance was assessed in participants in the early and delayed ART arms. Resistance was also assessed for participants in the delayed ART arm who initiated ART before vs. after May 2011 (Table 1).

**Table 1. Study groups.**

| | CD4 cell count (cells/mm$^3$) at ART initiation[a] |
|---|---|
| Early ART arm | 350-550 |
| Delayed ART arm with ART initiation before May 2011 | ≤250 |
| Delayed ART arm with ART initiation after May 2011 | any |

[a] ART was also offered to participants with an AIDS-defining illness.

### LABORATORY METHODS

Resistance testing was performed using the ViroSeq HIV-1 Genotyping System v2.8. Resistance was assessed using the Resistance Calculator Program (Frontier Science Foundation) using the Stanford v7.0 algorithm. HV subtype was determined by phylogenetic analysis.

### STATISTICAL METHODS

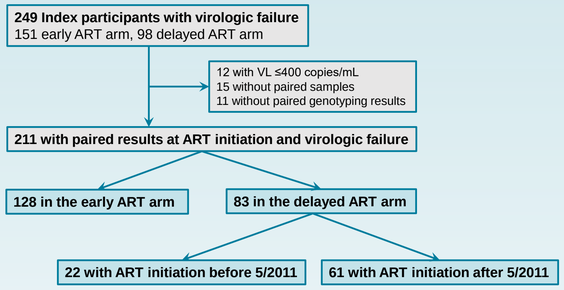
Virologic failure was defined as two consecutive viral loads >1,000 copies/mL >24 weeks after ART initiation. Factors associated with HIV drug resistance were analyzed using Chi-square, anova, t-tests, and logistical regression models, using SAS software.

## RESULTS

### STUDY COHORT

In HPTN 052, 249 participants had virologic failure. Paired baseline/failure resistance results were obtained for 211 participants (128 in the early ART arm; 83 in the delayed ART arm, Figure 1).

**Figure 1. Participants with HIV genotyping results.**



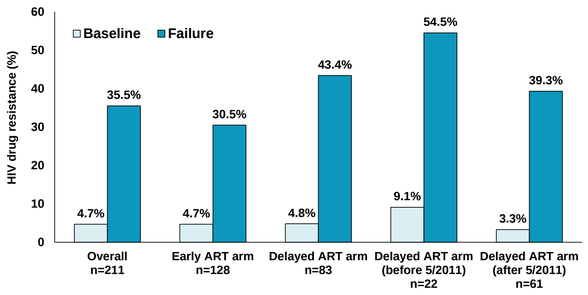

Most participants had HIV subtype C (76.8%) or B (11.8%).

The majority (74.9%) of the participants were on an ART regimen of efavirenz (EFV), lamivudine (3TC), and zidovudine (ZDV). Other participants were on a PI-based regimen or other EFV-based regimens.

### RESISTANCE AT BASELINE AND VIROLOGIC FAILURE

Overall, 4.7% of participants had resistance at baseline and 35.5% had new resistance at failure (Figure 2).

**Figure 2. HIV drug resistance in participants with virologic failure.**




Among those with new resistance at virologic failure, 62.7% had non-nucleoside/nucleotide reverse-transcriptase inhibitor (NNRTI) resistance, 21.3% had nucleoside/nucleotide reverse-transcriptase inhibitor (NRTI) resistance, and 16.0% had multiclass resistance (NNRTI and NRTI). The most common NNRTI and NRTI resistance mutations detected were K103N and M184V (70.1% and 90.3%, respectively).

**Table 2. Factors associated with new resistance at virologic failure.**

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

Footnote: Odds ratios (OR) were calculated using logistic regression. An OR >1 indicates a higher risk of resistance. Variables with a P <0.05 were included in the multivariate regression model.
[a] Per 100 CD4 increment. [b] Per unit $\log_{10}$ viral load increment. [c] South America (Brazil), Asia (India and Thailand), and Africa (Kenya, Malawi, South Africa, and Zimbabwe). [d] Other: protease inhibitor-based regimens (20.9%) and other EFV-based regimens (4.3%). [e] In the 3 months prior to ART initiation.

### FACTORS ASSOCIATED WITH NEW RESISTANCE AT VIROLOGIC FAILURE

New resistance at failure was less frequent in the early ART arm than the delayed ART arm (30.5% vs. 43.4%, p=0.06), and was less frequent in the delayed ART arm in those who started ART before vs. after May 2011 (54.5% vs. 39.3% p=0.032, Table 2).

New resistance at failure was less frequent among participants with higher baseline CD4 cell counts (p=0.047) and lower baseline viral loads (p=0.0001), and was higher among those receiving EFV/3TC/ZDV compared to those on other ART regimens (p=0.0074).

In a multivariate model, new resistance at failure was associated with baseline viral load (p=0.0008) and drug regimen (p=0.024).

## CONCLUSIONS

- New drug resistance at virologic failure was less frequent among participants with early ART initiation, but this difference was not statistically significant.
- New drug resistance at virologic failure was more frequent among those receiving EFV/3TC/ZDV than among those receiving other ART regimens.
- Lower baseline (pre-ART) viral load was the main factor associated with acquisition of HIV drug resistance.

## ACKNOWLEDGEMENTS

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