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HIV drug resistance in adults failing early antiretroviral treatment: results from the HIV Prevention Trials Network 052 trial

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Abstract

Early initiation of antiretroviral therapy (ART) reduces HIV transmission and has health benefits. HIV drug resistance can limit treatment options and compromise use of ART for HIV prevention. We evaluated drug resistance in 85 participants in the HPTN 052 trial who started ART at CD4 counts of 350–550 cells/mm^3 and failed ART by May 2011; 8.2% had baseline resistance and 35.3% had resistance at ART failure. High baseline viral load and less education were associated with emergence of resistance at ART failure. Resistance at ART failure was observed in 7/8 (87.5%) participants who started ART at lower CD4 cell counts.

Keywords

HIV; HPTN 052; early ART; ART failure; resistance

INTRODUCTION

The multi-national HIV Prevention Trials Network (HPTN 052) trial showed that early initiation of antiretroviral treatment (ART) significantly reduces sexual HIV transmission in serodiscordant couples.[1,2] Early ART initiation has also been shown to have health benefits for the HIV-infected individual receiving treatment, including lower rates of severe illness[3–5] and increased survival.[6] In the United States (US), ART has been recommended for all HIV-infected individuals regardless of CD4 cell count since 2012.[7,8] The World Health

Organization guidelines were recently changed to recommend ART for all HIV-infected individuals, regardless of CD4 cell count.[9]

Use of ART for HIV treatment and prevention can be compromised by HIV drug resistance, especially in resource-limited settings where resistance testing is not routinely performed as part of clinical management. There is relatively little information available about emergence of HIV drug resistance in individuals who initiate ART at higher CD4 cell counts. Observational studies in the United Kingdom and North America have reported a lower prevalence of treatment emergent HIV drug resistance among patients who start ART early.[10–12] However, little is known about factors associated with drug resistance in HIV-infected individuals who initiate ART at higher CD4 cell counts, or in settings where ART is used for HIV prevention. In this study, we analyzed HIV drug resistance among HIV-infected individuals who failed ART in the HPTN 052 trial before the interim study report was released.

METHODS

Study cohort

HPTN 052 (NCT00074581) was a Phase 3, randomized, controlled clinical trial that enrolled HIV serodiscordant couples in Africa, Asia, and the Americas.[1–3] HIV-infected (index) participants had CD4 cell counts of 350–550 cells/mm^3 at enrollment. In the early ART arm, index participants initiated ART immediately after enrollment. In the delayed ART arm, index participants initiated ART when their CD4 cell count was <250 cells/mm^3 on two consecutive study visits, or when they developed an AIDS-defining illness.[1] Viral load was measured quarterly.

Enrollment criteria for index participants included no prior antiretroviral (ARV) drug use, except for short-term regimens for prevention of mother-to-child transmission. Participants who had a viral load 400 copies/mL at enrollment were excluded from the analyses; some of those participants were found to be on ART at the time of enrollment, but did not disclose this to study staff.[13] The most common ART regimen used was a combination of efavirenz, lamivudine, and zidovudine.[1] This report includes analysis of data from the start of the trial (June 2007) through May 2011 (interim report of the primary study outcome).

Laboratory methods

HIV viral load and CD4 cell count were determined at study sites.[1] HIV genotyping was performed retrospectively using the ViroSeq HIV-1 Genotyping System, v2.8 (Celera Diagnostics, Alameda, CA). This testing was performed at four study sites (Pune and Chennai, India; Johannesburg, South Africa; Rio de Janeiro, Brazil) and at the HPTN Laboratory Center (Baltimore, MD, USA). Resistance results were calculated using the Resistance Calculator program at Frontier Science Foundation using the Stanford v6.3 algorithm.[14] Sequences were submitted to GenBank (accession numbers: KT833391-KT833560, KU562071-KU562085). HIV subtyping was performed by phylogenetic analysis. Laboratories that performed HIV genotyping participated in the US Division of

AIDS Virology Quality Assurance program.[15] Laboratories that performed CD4 cell count testing participated in the UK NEQAS external quality assurance program.[16]

Statistical analysis

Viral suppression was defined as the first of two consecutive viral load measurements 400 copies/mL after ART initiation. ART failure was defined as the first of two consecutive viral load measurements >1,000 copies/mL after 24 weeks on ART. HIV drug resistance was assessed by testing samples collected at ART initiation (baseline) and ART failure. Demographic and clinical factors were analyzed for association using logistic regression. The association of baseline resistance with time to viral suppression after ART initiation was analyzed using Cox proportional hazards model. Analyses were performed using SAS software, v9.4 (SAS Institute, Cary, NC, USA).

Ethical considerations

Written informed consent was obtained from all participants in the HPTN 052 trial. The trial was approved by Institutional Review Boards/Ethics Committees at each participating institution.

RESULTS

Study cohort

In HPTN 052, 886 index participants were randomized to the early ART arm; 95 (10.7%) of those participants failed ART by May 2011. Ten participants were excluded from analysis (two had viral loads 400 copies/mL at enrollment and eight did not have paired genotyping results from baseline and ART failure visits). The remaining 85 participants had a median follow-up of 1.99 years (range: 0.74–5.65) in the period assessed. The median baseline $\log_{10}$ viral load was 4.42 copies/mL (IQR: 3.76–4.86) and the median baseline CD4 cell count was 459.5 cells/mm^3 (IQR: 373–542.5). The majority (39/42=92.9%) of HIV infections at the African sites were subtype C; other infections included varied HIV subtypes with one to eight infections of each subtype (Table). Therefore, HIV subtype was not included in the analyses below. We did not observe an association between region (Africa, the Americas, Asia) and resistance in any of the analyses described below.

In the delayed ART arm, 213 (24.0%) of 887 index participants started ART in this study and nine failed ART by May 2011. Genotyping results were obtained for 7/9 participants at baseline and eight of those participants at ART failure (six had paired baseline/failure results).

HIV drug resistance

In the early ART arm, seven (8.2%) of the 85 participants who failed ART had drug resistance mutations detected at baseline (including four women, one of whom reported prior use of ARV drugs during pregnancy, Figure). Three had non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance only, one had nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) resistance only, and three had NNRTI and NRTI resistance. Thirty (35.3%) of the 85 participants had drug resistance mutations detected at ART failure;

19 had NNRTI resistance only, three had NRTI resistance only, and eight had NNRTI and NRTI resistance (Figure). Twenty-seven (90.0%) of the 30 participants had resistance mutations detected at failure that were not present at baseline. Twenty-three had new NNRTI resistance; all had new resistance to efavirenz, and most had cross-resistance to other NNRTIs. Eight had new NRTI resistance; all had new resistance to lamivudine and emtricitabine; one also had new resistance to abacavir and didanosine. Protease inhibitor resistance was not observed in any samples.

In the delayed ART arm, baseline resistance was detected in two (28.6%) of seven participants with genotyping results. At ART failure, seven (87.5%) of eight participants who had genotyping results had resistance, including all six participants with paired baseline/failure results. Both of the participants who had baseline resistance acquired new resistance at failure. The frequency of resistance at ART failure was significantly higher in the delayed ART arm compared to the early ART arm (7/8 [87.5%] vs. 30/85 [35.2%], P=0.006, Fisher's exact test).

Factors associated with HIV drug resistance

Because only nine participants in the delayed ART failed ART by May 2011 arm, factors associated with HIV drug resistance were assessed in the early ART arm only. None of the clinical or demographic factors analyzed were associated with baseline drug resistance among those who failed ART (Table). Higher baseline viral load was associated with resistance at ART failure and new resistance at ART failure. Having primary or secondary schooling (compared to no education/schooling) was associated with a lower frequency of resistance at ART failure and new resistance at ART failure. Baseline drug resistance was not associated with time to viral suppression after ART initiation among the 85 participants who failed ART; 50 (58.8%) of the 85 participants never achieved viral suppression before meeting the criteria for ART failure. There was no difference (P=0.2, Chi-square test) in the frequency of new resistance at ART failure among those who never achieved viral suppression (15/50=30.0%), those who achieved viral suppression and remained virally suppressed prior to ART failure (10/28=35.7%), and those who achieved viral suppression but had intermittent viremia prior to ART failure (2/7=28.6%).

DISCUSSION

HIV drug resistance may compromise use of ART for HIV treatment and prevention. ART is now recommended for all HIV-infected individuals, regardless of CD4 cell count.[7–9,17,18] However, few studies have evaluated HIV drug resistance when ART is initiated at higher CD4 cell counts. Among participants who failed ART in the early ART arm of HPTN 052 (data through May 2011), 8.2% had resistance at the time of ART initiation. This is similar to the frequency of baseline resistance among participants who failed ART in the ACTG 5175 study (PEARLS), which enrolled participants at many of the same study sites as HPTN 052. In PEARLS, ART was initiated at lower CD4 cell counts (<300 cells/mm^3); the frequency of baseline resistance in PEARLS was 9.4% among those who failed ART, and 4.3% among those in a case control group of those who did not fail ART.[19]

In HPTN 052, the frequency of resistance at ART failure was significantly lower in the early ART arm than in the delayed ART arm (35.3% vs. 87.5%, P=0.006). It is important to note, however, that very few participants in the delayed ART arm failed ART by May 2011. In other studies where ART was initiated at lower CD4 cell counts, the frequency of resistance at ART failure was also higher than that observed in the early ART arm of HPTN 052 (70–84% in two clinical cohort studies in sub-Sarahan Africa;[20,21] 50% in a in a randomized-controlled clinical trial in the United States[22]). Many factors may have contributed to the lower rate of HIV drug resistance observed in the early ART arm of HPTN 052. In HPTN 052, participants in both study arms received adherence counseling and had quarterly viral load monitoring. Participants in the early ART arm may have been more likely to adhere to ART, since they were taking ART primarily as an intervention to prevent partner infection, rather than for their own health.

Among participants in the early ART arm who failed ART, there was a strong association between higher baseline viral load and emergence of resistance at ART failure. This is consistent with results from an observational cohort study in Canada that reported an association of high baseline viral load and resistance at ART failure when ART was initiated at lower CD4 cell counts (median 280 cells/mm^3).[23] Persons with higher baseline viral loads may have more diverse viral populations with a higher frequency of low-level drug resistant variants, or may have higher viral replication rates; these factors could favor emergence of resistant variants at ART failure. Of note, relatively few of the participants analyzed in this study had baseline resistance; therefore, further studies are needed to evaluate the clinical relevance of this association. We also found an association between educational level and resistance at ART failure. Further studies are needed to determine whether this reflects an association between educational level and ART adherence.

More than half of the participants who failed ART in this study never achieved viral suppression. There was no difference in resistance at ART failure among those who never achieved viral suppression, those who achieved viral suppression and remained suppressed until ART failure, and those who achieved viral suppression but had intermittent viremia prior to ART failure. Therefore, emergence of resistance at ART failure in this study does not appear to be driven by selection of resistant variants after ART initiation, before viral suppression was established. This study reports resistance results in participants who failed ART by May 2011, when the interim study report was released (before participants were informed of the benefits of early ART for both the index and partner). Studies are underway to compare drug resistance in the early vs. delayed arms of the trial over the entire trial period and to assess the association of time to viral suppression, ART adherence (assessed through self-report, pill counts, and retrospective ARV drug testing), and drug resistance.

Emergence of HIV drug resistance in the setting of ART is concerning. On-going adherence counseling, frequent viral load monitoring, and prompt cessation of ART at ART failure (with a switch to a new regimen where feasible and appropriate) are likely to maximize the success of ART and reduce the risk of HIV drug resistance in both treatment and prevention settings.

Acknowledgments

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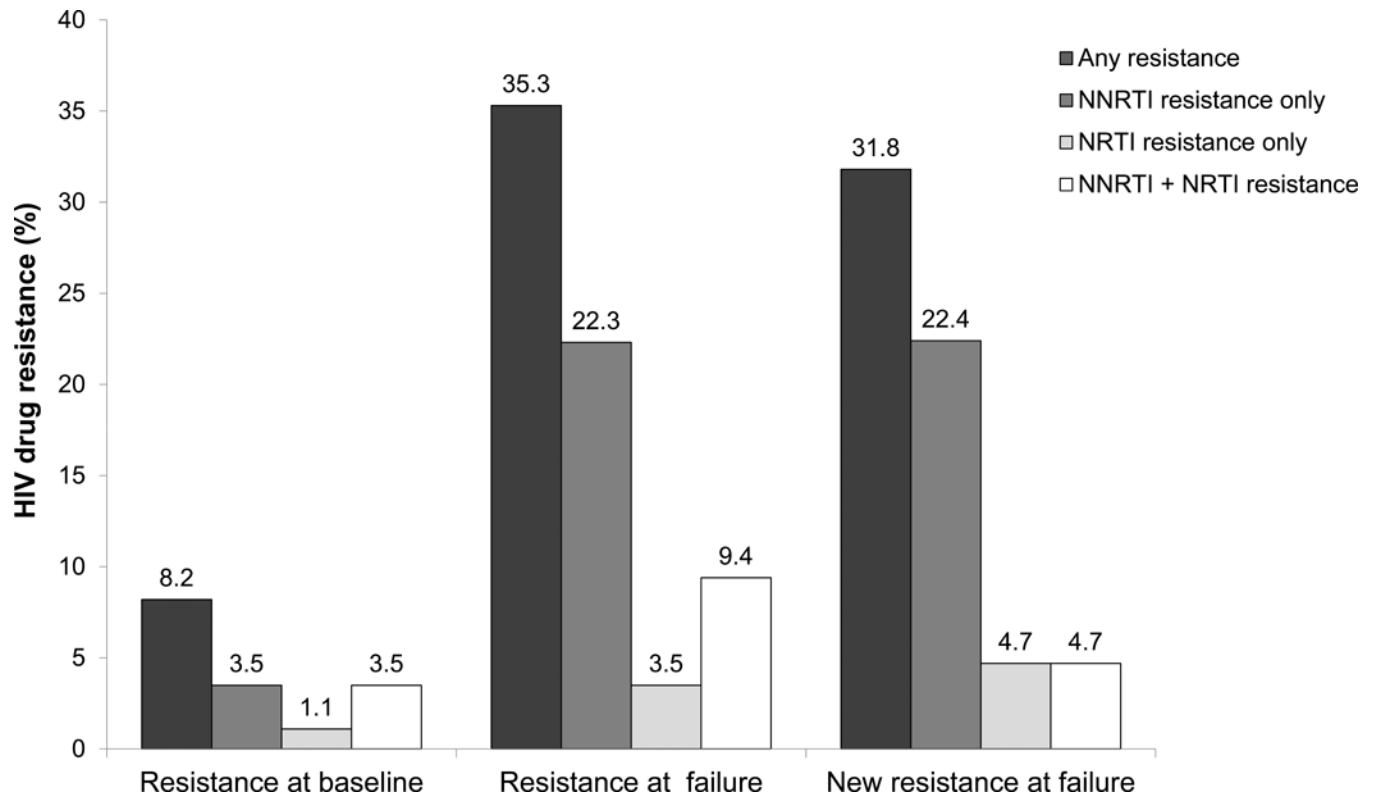
Figure. Proportion of participants with HIV drug resistance at baseline and at treatment failure
The figure shows the frequency of HIV drug resistance among participants in the early ART arm of HPTN 052 who failed ART (N=85 with paired baseline/failure results). Seven (8.2%) participants had resistance at baseline. The most common NNRTI and NRTI mutations were Y181C and M184V, which were each detected in three of the seven cases. All of the mutations detected at baseline, with the exception of one Y181C mutation, were also present in the corresponding failure samples. Thirty (35.3%) had resistance at ART failure. The most common NNRTI mutation was K103N, which was detected in 20 (66.7%) of the 30 cases. The most common NRTI mutation was M184V, which was detected in 11 (36.7%) of the 30 cases. Twenty-seven (90.0%) of those 30 participants had one or more resistance mutations detected at failure that was not present at the time of ART initiation (K103N [n=18], M184V [n=8], V106M [n=4], V108I [n=2], K238T [n=2], G190A [n=1], and K101E [n=1]). Twenty-three (85.2%) had new resistance to efavirenz, and most had cross-resistance to other NNRTIs (nevirapine [N=21], rilpivirine [N=2], and etravirine [N=1]). Eight (29.6%) had new NRTI resistance; all had new resistance to lamivudine and emtricitabine; one also had new resistance to abacavir and didanosine, due to the acquisition of M184V in addition to the baseline mutations M41L and T215E. Protease inhibitor resistance was not observed in any samples. Among the 78 (91.8%) participants who did not have baseline resistance, 23 (27.1%) had resistance at failure (not shown).
Abbreviations: NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside/nucleotide reverse transcriptase inhibitor.

Table

Factors associated with HIV drug resistance at initiation of antiretroviral treatment (baseline) and at the time of treatment failure.[*]

Variables		Total		Resistance at baseline		Resistance at ART failure			New resistance at ART failure		
		N	N (%)	OR (95% CI)	P	N (%)	OR (95% CI)	P	N (%)	OR (95% CI)	P
Age	<25 years	12	2 (17)	ref		6 (50)	ref		5 (42)	ref	
	25–39 years	57	5 (9)			20 (35)	0.54 (0.15–1.90)	0.34	18 (32)	0.65 (0.18–2.32)	0.50
	40 years	16	0 (0)			4 (25)	0.33 (0.07–1.65)	0.18	4 (25)	0.47 (0.09–2.34)	0.35
Gender	Male	47	3 (6)	ref		17 (36)	ref		17 (36)	ref	
	Female	38	4 (11)	1.73 (0.36–8.23)	0.49	13 (34)	0.92 (0.37–2.25)	0.85	10 (26)	0.63 (0.25–1.61)	0.33
Baseline CD4 cell count[a]		84	7 (8)	0.92 (0.47–1.80)	0.80	30 (35)	0.70 (0.46–1.05)	0.09	26 (31)	0.75 (0.49–1.13)	0.17
Baseline $\log_{10}$ viral load[b]		85	7 (8)	0.65 (0.21–1.99)	0.45	30 (35)	2.36 (1.17–4.78)	**0.017**	27 (32)	3.02 (1.41–6.49)	**0.0046**
Region[c]	Americas	14	2 (14)	ref		5 (36)	ref		5 (36)	ref	
	Asia	29	2 (7)	0.44 (0.06–3.54)	0.44	10 (34)	0.95 (0.25–3.60)	0.94	10 (34)	0.95 (0.25–3.60)	0.94
	Africa	42	3 (7)	0.46 (0.07–3.09)	0.43	15 (36)	1.00 (0.28–3.53)	1.00	12 (29)	0.72 (0.20–2.59)	0.62
Regimen[d]	EFV/3TC/ZDV	66	6 (9)	1.80 (0.20–15.9)	0.60	26 (39)	2.44 (0.73–8.16)	0.15	24 (36)	3.05 (0.81–11.5)	0.10
	Other	19	1 (5)	ref		4 (21)	ref		3 (16)	ref	
Education	None	16	2 (13)	ref		10 (63)	ref		9 (56)	ref	
	Primary or secondary schooling	65	5 (8)			19 (29)	0.25 (0.08–0.78)	**0.017**	17 (26)	0.28 (0.09–0.85)	**0.026**
	Post-secondary schooling	4	0 (0)			1 (25)	0.20 (0.02–2.39)	0.20	1 (25)	0.26 (0.02–3.06)	0.28
Marital status	Married	81	6 (7)	ref		28 (35)	ref		25 (31)	ref	
	Not married	4	1 (25)	4.17 (0.37–46.4)	0.25	2 (50)	1.89 (0.25–14.2)	0.53	2 (50)	2.24 (0.30–16.8)	0.43
Number sex partners	0–1	82	7 (9)	ref		29 (35)	ref		26 (32)	ref	
	>1	3	0 (0)			1 (33)	0.91 (0.08–10.5)	0.94	1 (33)	1.08 (0.09–12.4)	0.95
Baseline resistance	Yes	7				7 (100)	–		4 (57)	3.19 (0.66–15.4)	0.15
	No	78				23 (29)	–		23 (29)	ref	

*
The analyses included the 85 HIV-infected index participants in the early ART arm of HPTN who failed ART (see text).

Abbreviations: ART: antiretroviral therapy; N: number; OR: odds ratio; CI: confidence interval; P: P-value; ref: reference group; EFV: efavirenz; 3TC: lamivudine; ZDV: zidovudine; VS: viral suppression; mo: months.

P-values <0.05 are bolded. Regression models could not be generated if any cell was 0 for the categorical variable.

a
Assessed as increments of 100 CD4-positive cells/mm^3.

b
Assessed as increments of log10 viral load.

c
The 85 participants had the following HIV subtypes: 69 (81.2%) subtype C (Malawi [N=29], India [N=28], Zimbabwe [N=7], South Africa [N=3], and Brazil [N=2]), eight subtype B (Brazil), three subtype F1 (Brazil), one subtype A2 (Kenya), two A1 (Kenya), one CRF1_AE (Thailand), and one CRF12_BF (Brazil).

d
The majority of participants who started ART on the EFV/3TC/ZDV regimen (with the exception of pregnant women) received a fixed-dose formulation of these drugs.