Virologic outcomes when antiretroviral therapy is used for HIV prevention: HPTN 052

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ABSTRACT

In May 2011, an interim analysis of the HPTN 052 trial showed that early initiation of antiretroviral therapy (ART) prevented 96% of linked HIV infections in serodiscordant couples [1]. ART was then offered to all index participants and they were counseled on the benefits of early ART. The trial continued until May 2015 [2].

In HPTN 052, some linked infections were diagnosed after the HIV-infected index participant initiated ART, either near ART initiation or after virologic failure [3]. In this study, we evaluated factors associated with time to viral suppression and virologic failure among index participants who initiated ART in HPTN 052.

METHODS

SAMPLES USED FOR ANALYSIS

Virologic outcomes were evaluated in three study groups:

(1) early ART arm (ART initiation at enrollment, CD4 350-550 cells/mm^3)

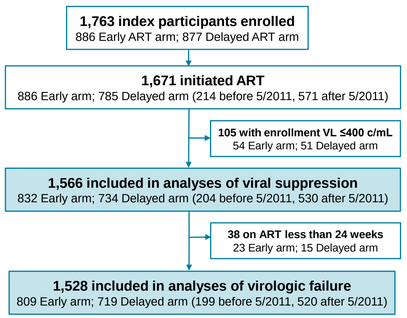
(2) delayed ART arm with ART initiation before May 2011 (ART initiation at CD4 <250 cells/mm^3 or with an AIDS-defining illness)

(3) delayed ART arm with ART initiation after May 2011 (ART initiation at any CD4 cell count)

Viral suppression was defined as two consecutive viral loads ≤400 copies/mL. Virologic failure was defined as two consecutive viral loads >1,000 copies/mL >24 weeks after ART initiation.

Participants included in these analyses are shown in Figure 1.

Figure 1. Study cohort



RESULTS

ANALYSIS OF VIRAL SUPPRESSION AFTER ART INITIATION

Viral suppression was achieved by 93% of the participants 12 months after ART initiation. There was no significant difference in time to viral suppression in the three study groups (early ART arm; delayed ART arm before May 2011; delayed ART arm after May 2011, Figure 2A). Table 1 shows that longer time to viral suppression was independently associated with higher viral load at ART initiation (baseline), younger age, and region.

Table 1. Factors associated with time to viral suppression*

	Total, N	Virally suppr., N (%)	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Study arm				0.06		
Early ART arm	832	748 (89.9)	Ref			
Delayed ART arm	734	680 (92.6)	0.91 (0.82, 1.01)			
Study group				0.095		
Early ART arm	832	748 (89.9)	Ref			
Delayed ART arm (bf 5/2011)	204	194 (95.1)	0.85 (0.72, 0.99)	**0.038**		
Delayed ART arm (af 5/2011)	530	486 (91.7)	0.93 (0.83, 1.05)	0.23		
Age at ART initiation				**0.0026**		**0.0007**
<25 years	147	120 (81.6)	Ref		Ref	
25-39 years	992	905 (91.2)	1.39 (1.15, 1.69)	**0.0006**	1.40 (1.16, 1.70)	**0.0006**
≥40 years	427	403 (94.4)	1.38 (1.13, 1.69)	**0.0020**	1.49 (1.21, 1.83)	**0.0002**
Gender				0.44		
Male	806	747 (92.7)	Ref			
Female	760	681 (89.6)	0.96 (0.87, 1.06)			
CD4 at ART initiation[a]	1560	1422 (91.2)	1.07 (1.03, 1.11)	**0.0007**		
VL at ART initiation[b]	1563	1425 (91.2)	0.73 (0.68, 0.78)	**<0.0001**	0.71 (0.66, 0.76)	**<0.0001**
Time to ART initiation (yr)	1566	1428 (91.2)	0.98 (0.95, 1.02)	0.38		
Region				0.07		**0.015**
Africa	824	749 (90.9)	Ref		Ref	
Asia	487	444 (91.2)	1.14 (1.02, 1.28)	**0.027**	1.19 (1.05, 1.34)	**0.0046**
Americas	255	235 (92.2)	1.00 (0.86, 1.15)	0.96	1.02 (0.88, 1.19)	0.74
Regimen				**0.015**		
Other	474	442 (93.2)	Ref			
EFV/3TC/ZDV	1092	986 (90.3)	0.87 (0.78, 0.97)			
Education				0.20		
None	150	129 (86.0)	Ref			
Primary/secondary school	1273	1162 (91.3)	1.10 (0.92, 1.32)	0.29		
Post-secondary school	143	137 (95.8)	1.24 (0.98, 1.58)	0.08		
Marital status				0.16		
Married	1478	1344 (90.9)	Ref			
Not married	88	84 (95.5)	1.17 (0.94, 1.46)			
Number of sex partners				0.08		
0-1	1498	1363 (91.0)	Ref			
>1	66	63 (95.5)	1.25 (0.97, 1.61)			

* In Table 1 and 2, hazard ratios (HR) were calculated using Cox regression models. In Table 1, a HR>1 indicates higher risk of viral suppression at any time (shorter time to viral suppression). In Table 2, a HR>1 indicates higher risk of virologic failure. The multivariate models were created using backward model selection methods. Note, the analyses were updated from the time the abstract was submitted to include study arm (Table 1 and 2) and only use one covariate for time to suppression (3 months, Table 2).

[a] Per 100 CD4 increment. [b] Per unit $\log_{10}$ viral load (VL) increment.

ANALYSIS OF VIROLOGIC FAILURE

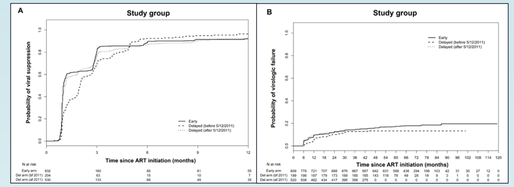
The annual incidence of virologic failure was 3.6% (95% CI: 3.1%-4.1%). There was no significant difference in virologic failure among participants in the three study groups (Figure 2B). Table 2 shows that a higher risk of virologic failure was strongly associated with younger age, lower education level, and lack of viral suppression by 3 months. Lower baseline viral load and higher baseline CD4 cell count were also associated with virologic failure.

Table 2. Factors associated with virologic failure*

	Total, N	Virologic failure, N (%)	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Study arm				0.18		
Early ART arm	809	144 (17.8)	Ref			
Delayed ART arm	719	94 (13.1)	0.83 (0.64, 1.09)			
Study group				0.31		
Early ART arm	809	144 (17.8)	Ref			
Delayed ART arm (bf 5/2011)	199	26 (13.1)	0.75 (0.49, 1.13)	0.17		
Delayed ART arm (af 5/2011)	520	68 (13.1)	0.87 (0.65, 1.17)	0.37		
Age at ART initiation				**<0.0001**		**0.0018**
<25 years	141	40 (28.4)	Ref		Ref	
25-39 years	969	157 (16.2)	0.55 (0.39, 0.78)	**0.0007**	0.78 (0.55, 1.11)	0.17
≥40 years	418	41 (9.8)	0.32 (0.21, 0.50)	**<0.0001**	0.46 (0.29, 0.72)	**0.0007**
Gender				**0.025**		
Male	784	106 (13.5)	Ref			
Female	744	132 (17.7)	1.34 (1.04, 1.73)			
CD4 at ART initiation[a]	1522	237 (15.6)	1.10 (1.00, 1.20)	**0.047**	1.11 (1.00, 1.22)	**0.044**
VL at ART initiation[b]	1525	237 (15.5)	1.05 (0.89, 1.25)	0.56	0.81 (0.67, 0.98)	**0.026**
Time to ART initiation (yr)	1528	238 (15.6)	0.97 (0.88, 1.07)	0.51		
Region				0.16		
Africa	803	123 (15.3)	Ref			
Asia	472	65 (13.8)	0.88 (0.65, 1.19)	0.41		
Americas	253	50 (19.8)	1.26 (0.91, 1.75)	0.17		
Regimen				0.33		
Other	464	65 (14.0)	Ref			
EFV/3TC/ZDV	1064	173 (16.3)	1.15 (0.87, 1.53)			
Education				**0.0019**		**0.0007**
None	145	33 (22.8)	Ref		Ref	
Primary or secondary school	1244	195 (15.7)	0.66 (0.46, 0.96)	**0.029**	0.62 (0.43, 0.89)	**0.018**
Post-secondary school	139	10 (7.2)	0.29 (0.14, 0.58)	**0.0005**	0.27 (0.15, 0.54)	**0.0004**
Marital status				**0.049**		
Married	1440	231 (16.0)	Ref			
Not married	88	7 (8.0)	0.47 (0.22, 1.00)			
Number of sex partners				0.62		
0-1	1462	228 (15.6)	Ref			
>1	64	9 (14.1)	0.85 (0.43, 1.65)			
Lack of VS by 3 months				**<0.0001**		**<0.0001**
No	1182	107 (9.1)	Ref			
Yes	346	131 (37.9)	5.53 (4.28, 7.14)		6.65 (5.04, 8.76)	

To explore whether the findings were affected by late failure events, the virologic failure analyses were repeated using data that was censored to 4 years after ART initiation. In the multivariate analysis, the same variables were significantly associated with virologic failure after censoring with the exception of CD4 cell count.

Figure 2. Kaplan-Meier estimates for virologic outcomes after ART initiation by study group



Kaplan-Meier plots show the relationship of study group with time to viral suppression (Panel A) and virologic failure (Panel B) after ART initiation. The numbers below each graph show the number of participants who were at risk of viral suppression or virologic failure at each time point.

CONCLUSIONS

- Longer time to viral suppression was strongly associated with higher baseline viral load, younger age, and region.
- Virologic failure was strongly associated with younger age, lower education, and lack of viral suppression by 3 months; lower baseline viral load and higher CD4 cell count were also associated with virologic failure.
- Virologic outcomes did not differ by study arm. In addition, awareness of the interim findings of the trial (personal health benefits and lower risk of HIV transmission with early ART initiation) did not improve virologic outcomes in those who initiated ART at higher CD4 cell counts.
- Recognition of factors associated with virologic outcomes may help optimize ART for HIV treatment and prevention.

ACKNOWLEDGEMENTS

The authors thank the HPTN 052 study team and participants for providing the samples and data used in this study. We also thank the laboratory staff who helped with sample management and testing.

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The HIV Prevention Trials Network is sponsored by the U.S. National Institute of Allergy and Infectious Diseases, the U.S. National Institute of Mental Health, and the U.S. National Institute on Drug Abuse, all components of the U.S. National Institutes of Health.

Poster Number: 1002
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