Time-to-ART-Initiation: A Risk Factor Analysis of the HPTN 052 HIV-infected Partners on Delayed Therapy

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BACKGROUND

THE HPTN 052 STUDY

The HIV Prevention Trial Network (HPTN) 052 Study is a Phase III, two-arm, randomized, controlled clinical trial designed to determine whether early antiretroviral therapy (ART) can prevent the sexual transmission of human immunodeficiency virus type 1 (HIV-1).

A total of 1763 sero-discordant couples in which one partner was HIV-1 positive and the other was HIV-1 negative were enrolled in four continents, nine countries and thirteen study sites.

The HIV-1 positive partner was randomly assigned to either of the two arms: immediate therapy with ART initiated upon enrollment plus HIV primary care, or delayed therapy with HIV primary care but ART initiated when the index case would have two consecutive measurements of a CD4+ cell count within or below the range of 200-250 cells/mm^3, or develop an AIDS-defining illness.

An early release of the trial results in May 2011 showed an overwhelming 96% risk reduction for the immediate therapy in the prevention of genetically linked HIV-1 incident transmissions.

Nevertheless, the durability of its long-term effectiveness is yet to be assessed. The HPTN 052 Study is still ongoing, since there may be sufficient contrast in ART-initiation time between the treatment arms. The HPTN 052 Study is will not complete till 2015.

We hence conduct a risk factor analysis to study what factors were associated with the time-to-ART-initiation among those who were on delayed ART therapy

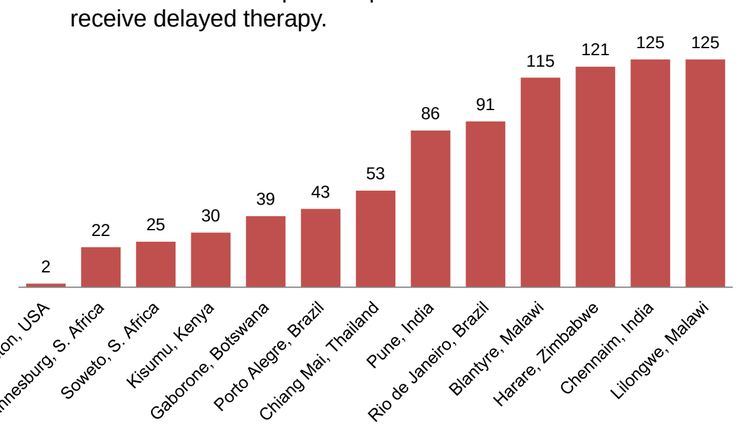
STUDY MATERIALS

STUDY POPULATION

This study was carried out in 9 countries: Gaborone, Botswana; Kisumu, Kenya; Lilongwe and Blantyre, Malawi; Johannesburg and Soweto, South Africa; Harare, Zimbabwe; Rio de Janeiro and Porto Alegre, Brazil; Pune and Chennai, India; Chiang Mai, Thailand; and Boston.

A pilot phase started in April 2005, and enrollment took place from June 2007 through May 2010. Couples were required to have had a stable relationship for at least 3 months, to have reported three or more episodes of vaginal or anal intercourse during this time, and to be willing to disclose their HIV-1 status to their partner. Patients with HIV-1 infection were eligible if their CD4 count was between 350 and 550 cells/mm^3 and they had received no previous antiretroviral therapy except for short-term prevention of mother-to-child transmission of HIV-1.

A total of 877 HIV-1 positive partners were randomized to receive delayed therapy.



METHODS

ANTIRETROVIRAL DRUGS

Study drugs included a combination of lamivudine and zidovudine (Combivir), efavirenz, atazanavir, nevirapine, tenofovir, lamivudine, zidovudine, didanosine, stavudine, a combination of lopinavir and ritonavir (Kaletra and Aluvia), ritonavir, and a combination of emtricitabine and tenofovir (Truvada). A prespecified combination of these drugs was provided to participants at monthly or quarterly visits. Sites could also use locally supplied, FDA-approved drugs if they could be purchased with nonstudy funds. For participants with virologic failure, specified second-line treatment regimens were provided.

ASSESSMENT OF TIME-TO-ART-INITIATION

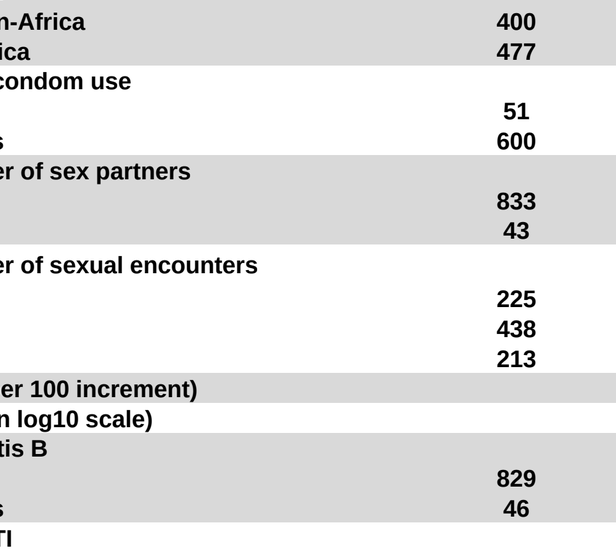
After enrollment, study participants were asked to attend three monthly visits, which were followed by quarterly visits unless they became ill or needed additional antiretroviral medications. therapy was initiated after two consecutive measurements in which the CD4 count was 250 cells per cubic millimeter or less or after the development of an illness related to the acquired immunodeficiency syndrome (AIDS). Those with ART initiated after May 12, 2012 were considered censored.

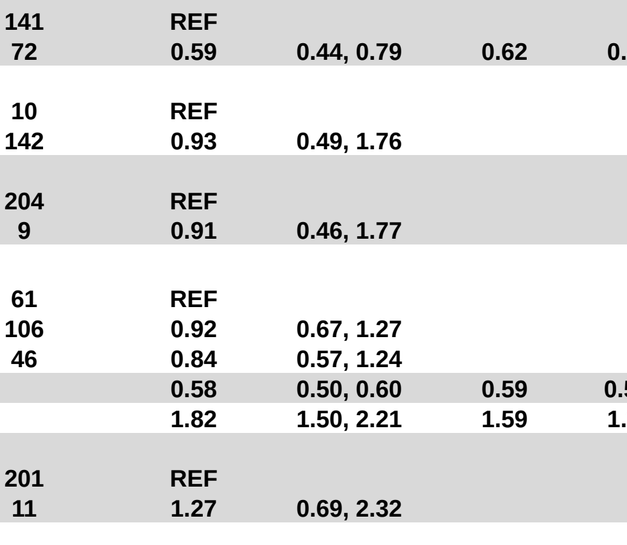
STATISTICAL ANALYSIS

Kaplan–Meier method to calculate event-free probabilities. Univariate and multivariate Cox proportional hazards regression models are used to analyze time-to-ART-initiation in association of selected baseline covariates.

RESULTS

Variables	N at baseline	N of ART initiated	Univariate HR	Univariate 95% CI	Multivariate HR	Multivariate 95% CI
Gender						
Female	441	93	REF			
Male	436	120	1.3	0.99, 1.70		
Age						
18-25	708	161	REF			
>40	169	52	1.47	1.08, 2.02		
Education						
No schooling	69	18	REF			
Primary schooling	347	88	0.94	0.57, 1.57		
Secondary schooling	388	90	0.83	0.50, 1.38		
Post-secondary schooling	72	17	0.95	0.49, 1.85		
Marital Status						
Single/widowed/separated/divorced	44	11	REF			
Married/living with partner	833	202	0.61	0.33, 1.13		
Region						
Non-Africa	400	141	REF			
Africa	477	72	0.59	0.44, 0.79	0.62	0.47, 0.83
100% condom use						
No	51	10	REF			
Yes	600	142	0.93	0.49, 1.76		
Number of sex partners						
0-1	833	204	REF			
>1	43	9	0.91	0.46, 1.77		
Number of sexual encounters						
0	225	61	REF			
1-2	438	106	0.92	0.67, 1.27		
>2	213	46	0.84	0.57, 1.24		
CD4 (per 100 increment)			0.58	0.50, 0.60	0.59	0.51, 0.60
RNA (in log10 scale)			1.82	1.50, 2.21	1.59	1.31, 1.94
Hepatitis B						
No	829	201	REF			
Yes	46	11	1.27	0.69, 2.32		
Any STI						
No	793	192	REF			
Yes	55	13	0.98	0.56, 1.72		
Alcohol use						
No	733	167	REF			
Yes	142	46	1.4	1.01, 1.94		
Substance use						
No	834	199	REF			
Yes	40	13	1.3	0.74, 2.28		





CONCLUSION

- Among the selected baseline covariates, baseline CD4+ counts, and baseline viral loads and geographical region were statistically significantly associated with the timing of ART-initiation
- Higher baseline CD4+ count , lower baseline viral loads and Sub-Saharan Africa Region were associated with later time-to-ART-initiation.

LIMITATIONS

- Additional variable that need to be considered but not collected, such as viral subtype, IL-6, D-Dimer and soluable CD14
- Consideration of laboratory sub-studies that require use of study samples would however be deferred until the end of the trial, to ensure that samples are available to complete all of the testing for primary and secondary study endpoints.

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