Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Antiretroviral Treatment for Prevention of HIV Transmission:
The Final Results of the HIV Prevention Trials Network (HPTN) 052 Trial

Supplementary Appendix

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Determination of the linkage status of partner infections in HPTN 052.

This file presents an overview of the analysis of linkage status of partner infections in HPTN 052. The methods used for this analysis were published in detail in a previous report, which also includes the results of linkage analysis that were available in May 2011, prior to release of interim study findings (Eshleman, et al. Analysis of genetic linkage of HIV from couples enrolled in the HIV Prevention Trials Network 052 trial. J Infect Dis. 2011; 204:1918-1926). The results of the linkage analysis for the entire trial period (through May, 2015) and additional results related to characterization of partner infections were presented in July, 2015 at the 8th IAS Conference on HIV Pathogenesis, Treatment, and Prevention in Vancouver, Canada (Eshleman, et al. Treatment as Prevention: Characterization of partner infections in the HIV Prevention Trials Network 052 trial, Abstract MOAC0106LB).

Methods used to determine the linkage status

Seventy-eight partner infections were observed in the HPTN 052 trial. The three methods were used to assess genetic linkage of HIV from index-partner pairs (see below). The classification "linked" indicates that the index was the likely source of the partner's infection.

(1) Phylogenetic analysis of HIV *pol* region sequences obtained by population (consensus) sequencing

Linkage analysis was performed using plasma samples from partners who acquired HIV infection during the HPTN 052 trial and the corresponding HIV-infected index participants (index-partner pairs). In most cases, two samples collected on different dates were analyzed for each participant; in some cases, results were only obtained for one sample (e.g., in cases where only one HIV-positive sample was collected from the partner after HIV infection; only one sample from a participant had a viral load sufficient for analysis; or one sample failed analysis). Plasma samples were also analyzed from randomly-selected index participants (control samples); 10 control samples were analyzed from each site, with the following exceptions: one set of 10 control samples was included for the three sites in Brazil; control samples were not included for the site in the United States due to low enrollment.

The ViroSeq HIV-1 Genotyping System (Celera, Alameda, CA) was used to generate HIV *pol* sequences. This system provides population (consensus) sequences that encode HIV protease amino acids 1-99 and HIV reverse transcriptase amino acids 1-335. Alternate primers were used for selected samples if the sample failed to amplify using the primers provided with the ViroSeq kit. *Pol* region sequences from index-partner pairs and local controls were aligned using MegAlign v5.07 with the Clustal W method. Sequence distances were calculated using DNADist. Phylogenetic trees and bootstrap values were generated using PHYLIP (Neighbor-Joining and Consense); for partner infections reported in 2011, results from this analysis were compared to those obtained using other phylogenetic methods. MegAlign was used to generate phylogenetic trees for study sites by geographic region; these trees included sequences from index-partner pairs, local control sequences (matched for HIV subtype), and reference sequences. Additional information about the methods used for this part of the linkage analysis and a representative phylogenetic tree are presented in Eshleman et al, 2011, Journal of Infectious Diseases 204:1918-1926. A provisional linkage assignment was based on this analysis; index-partner pairs were provisionally classified as linked if all of the corresponding sequences clustered together on a single monophyletic branch with a high bootstrap value.

(2) Bayesian analysis of the genetic distances between *pol* sequences

The probability of linkage was assessed using an algorithm based on Bayes theorem. These methods were used to compare the genetic similarity of HIV *pol* sequences obtained using the ViroSeq system (see above). The genetic similarity between sequence pairs was determined using MegAlign v5.07. Genetic similarity values were compared for the following sequence pairs (all possible combinations): (a) sequences obtained for one individual from samples collected on different dates, (b) sequences obtained for unrelated study participants (other index participants and local control sequences from the same geographic region or study site), and (c) sequences obtained for index-partner pairs. The analysis assumed that paired sequences from unrelated index participants were not linked, and that the genetic similarity of sequences from index-partner pairs was similar to the genetic similarity of two sequences from the same individual. Bayes theorem was used to determine the probability of linkage between sequences from index-partner pairs. Additional information about the methods used for this part of the linkage analysis and plots showing densities of similarities for linked and unlinked events are presented in Eshleman et al, 2011, Journal of Infectious Diseases 204:1918-1926, and in Supplemental File 1 in that publication. Index-partner pairs were provisionally characterized as linked by the Bayesian analysis if they had a linkage probability of $\geq$0.5 for any pair of sequences. Index-partner pairs were provisionally characterized as unlinked by the Bayesian analysis if they had a linkage probability of $\leq$0.5 for all pairs of sequences.

(3) Phylogenetic analysis of HIV *env* region sequences obtained by next generation sequencing (NGS, selected samples)

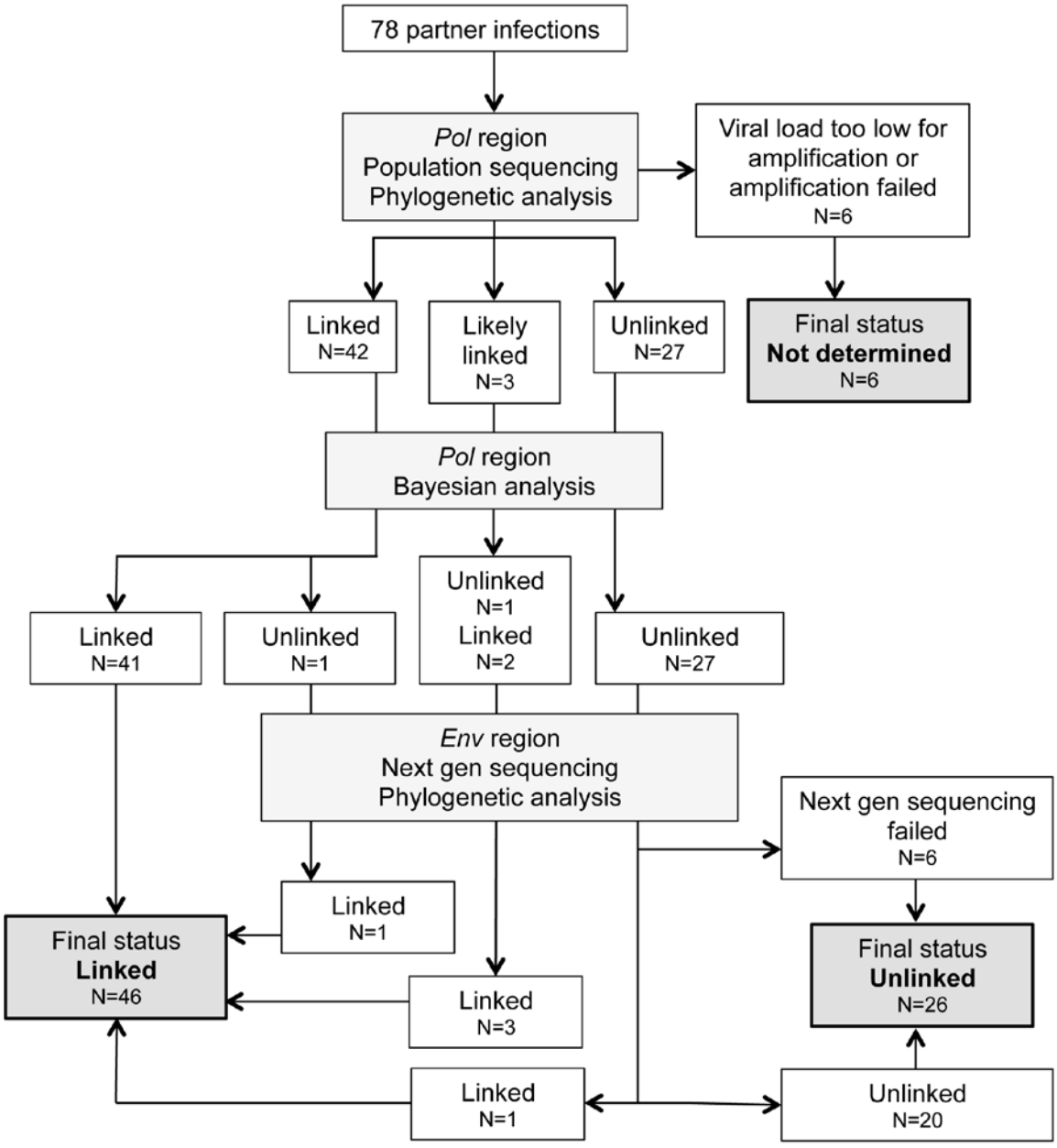
Index-partner pairs that were provisionally characterized as linked by both phylogenetic and Bayesian analysis of *pol* region sequences were classified as linked and were not analyzed further. Additional analysis using NGS was performed for the remaining index-partner pairs. NGS was performed for a region of gp41. The gp41 region was amplified using a combined reverse transcription / nested polymerase chain reaction (PCR). This was followed by a nested PCR that included using primers with DNA barcodes that identified each sample. Amplified DNA was analyzed by gel electrophoresis and was purified using the Amplicon Library Preparation Method (Roche, Branford, CT). Library pools of bar-coded template DNA were prepared, which were used to generate templated beads for NGS. NGS was performed using a Roche 454 instrument (Roche, Branford, CT). The GS Amplicon Variant Analyzer version 2.5 (Roche) was used to generate consensus sequences; quality control procedures were used to determine which sequence reads were included in the analysis. Sequences from samples were aligned with reference sequences using Clustal W. Phylogenetic trees were generated using Neighbor-Joining. Bootstrap values were obtained based on 500 replicate analyses. Additional information about the methods used for this part of the linkage analysis and representative phylogenetic trees are presented in Eshleman et al, 2011, Journal of Infectious Diseases 204:1918-1926. Index-partner pairs were classified as linked if multiple consensus sequences obtained for the index and the partner clustered together on a branch with a high bootstrap value.

Overview of linkage analysis for index-partner pairs in HPTN 052

Seventy-eight partner infections were observed in the HPTN 052 trial (see Figure). *Pol* region sequencing was successful for index and partner samples in 72 cases; linkage status could not be determined for the remaining six cases (two in the early ART arm; four in the delayed ART arm). Forty-two cases were provisionally classified as linked by phylogenetic analysis of *pol* region sequences. The remaining cases were provisionally classified as likely linked (N=3) or unlinked (N=27) by phylogenetic analysis of *pol* region sequences. *Pol* region sequences from all 72 cases were also analyzed using Bayesian methods (see above). In 41 cases, samples were classified as linked by both phylogenetic and Bayesian analysis of *pol* sequences; these cases were classified as linked (no further analysis was performed). Next generation sequencing (NGS, *env* region) was performed for the remaining 31 cases; *env* sequences obtained by NGS were analyzed using

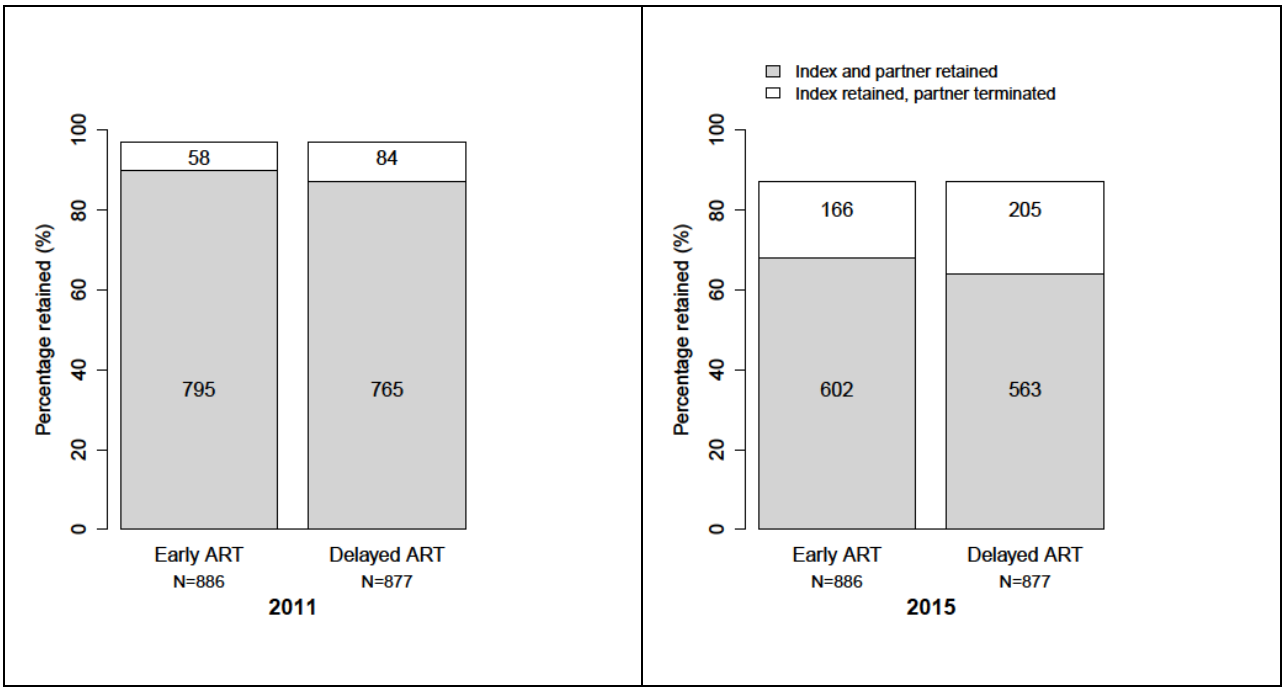
phylogenetic methods (see above). In five cases, partner infections were classified as linked based on NGS. In 20 cases, partner infections were characterized as unlinked based on NGS. NGS failed in six cases (three in the early ART arm; three in the delayed ART arm). All six cases of these cases were clearly unlinked by both phylogenetic and Bayesian analysis of *pol* region sequences; those cases were classified as unlinked based on the *pol* region results. The probability that NGS would have shown linkage in these cases is low. There were 21 cases that were clearly unlinked by *pol* region phylogenetic and Bayesian analysis where NGS results were obtained; only one case was linked by NGS (probability <5%). In that case, the couple was in the delayed ART arm and the index participant had not started ART.

Supplement Figure S1. Linkage analysis of HIV from index-partner pairs.



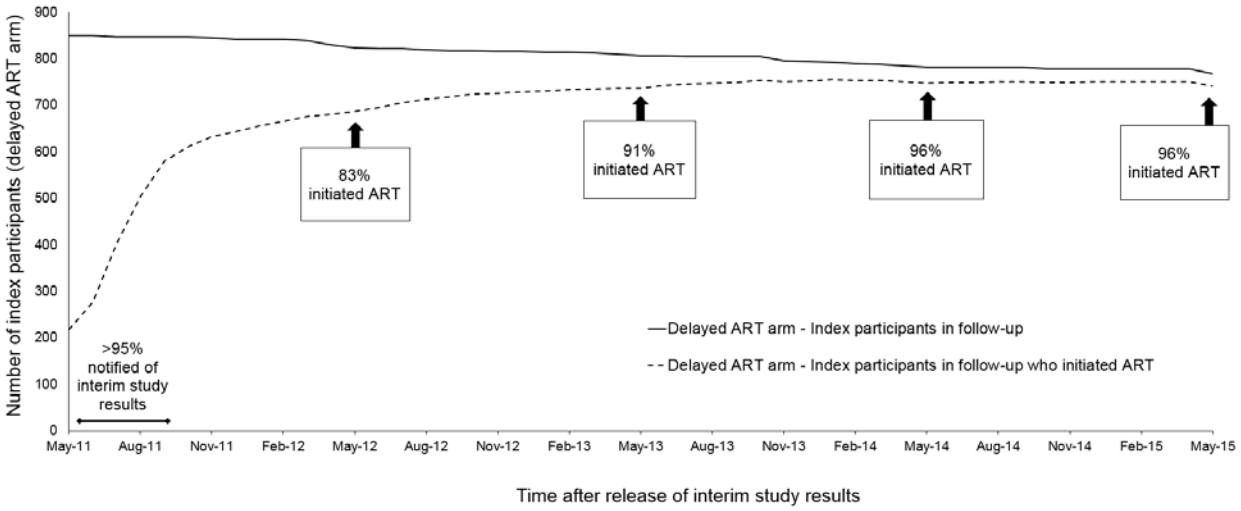
Supplement Figure S2. Retention of study participants.

The graphs show the number and percentage of couples (index and partner participants) retained (shaded) and the number and percentage of index participants retained in cases where the partner was terminated or lost to follow-up (not shaded). Data obtained through May 2011 (prior to release of the interim report) are shown in the left panel; data obtained from May 2011 through May 2015 (after release of the interim study report when all index participants were offered ART) are shown in the right panel.



Supplement Figure S3. Initiation of ART in the delayed ART arm of the study.

The graph shows the number of HIV-infected index participants in the delayed ART arm who were still in follow-up after the release of interim study results (solid line), and the portion of those participants who had initiated ART (dashed line). At the time that the interim results were released (May 2011), 218 (26%) of the index participants in the delayed ART arm had initiated ART, consistent with study guidelines (i.e., due to a fall in CD4 cell count, development of an AIDS-defining illness, or pregnancy). By September 2011, the majority (>95%) of study participants in the delayed ART arm had been notified of the interim study results and offered ART. Most participants chose to start ART as soon as they learned of the interim results, or at their next scheduled study visit; however, others declined for a variety of reasons. Eighty-three percent of index participants in the delayed ART arm who were still in follow-up started ART by May 2012. By the end of the study (May 2015), 96% of index participants who were still in follow-up had started ART.



Supplement Table S1. Cumulative incidence of sexually transmitted infections*.

	Index		Partner	
	Early ART Arm	Delayed ART Arm	Early ART Arm	Delayed ART Arm
Total	886	876	903	889
Person-years	5011.4	5019.9	4324.5	4184.7
HBV[a]	47 (0.94)	47 (0.94)		
Syphilis	78 (1.56)	66 (1.31)	53 (1.23)	50 (1.19)
Gonorrhea	49 (0.98)	53 (1.06)	40 (0.92)	34 (0.81)
C. trachomatis	65 (1.30)	64 (1.27)	49 (1.13)	58 (1.39)
Women	432	441	445	418
Person-years	2435.8	2538.0	2230.7	2115.3
Bact. Vaginosis	190 (7.80)	216 (8.51)	135 (6.05)	121 (5.72)
Trichomonas	74 (3.04)	78 (3.07)	46 (2.06)	41 (1.94)
Yeast	195 (8.01)	204 (8.04)	161 (7.22)	167 (7.89)

* Incidence rates were calculated as number of infections per 100 person-years. Data are shown for men and women combined (Total) and for women only. Person-years of follow-up are shown from the time of study enrollment.

[a] Hepatitis B virus (HBV) testing was required only for index participants and was performed only at study enrollment.

Abbreviations: HBV: hepatitis B virus; C. trachomatis: chlamydia trachomatis; Bact: bacterial.

Supplement Table S2. Year-specific incidence rates and rate ratios.

Follow-up period*		Early ART arm			Delayed ART arm			
		Events	PY	Rate (95% CI)	Events	PY	Rate (95% CI)	**Rate ratio (95% CI)**[a]
		no.		%	*no.*		%	
All partner infections								
0-1 yr	Before 5/2011	2	834.2	0.2 (0.0-0.9)	19	827.7	2.3 (1.4-3.6)	0.10 (0.01-0.43)
	Total	2	847.6	0.2 (0.0-0.9)	19	839.0	2.3 (1.4-3.5)	0.10 (0.01-0.43)
1-2 yr	Before 5/2011	1	566.5	0.2 (0.0-1.0)	14	563.3	2.5 (1.4-4.2)	0.07 (0.00-0.47)
	Total	2	779.7	0.3 (0.0-0.9)	17	760.1	2.2 (1.3-3.6)	0.11 (0.01-0.48)
2-3 yr	Before 5/2011	1	247.9	0.4 (0.0-2.2)	5	245.3	2.0 (0.7-4.8)	0.20 (0.00-1.77)
	Total	3	721.2	0.4 (0.1-1.2)	8	691.7	1.2 (0.5-2.3)	0.36 (0.06-1.50)
3-4 yr	Before 5/2011	0	60.1	0.0 (0.0-6.1)	4	57.1	7.0 (1.9-17.9)	0.00 (0.00-1.44)
	Total	4	673.6	0.6 (0.2-1.5)	7	638.0	1.1 (0.4-2.3)	0.54 (0.12-2.13)
4-5 yr	Before 5/2011	0	29.8	0.0 (0.0-12.4)	0	24.8	0.0 (0.0-14.8)	-
	Total	4	616.5	0.6 (0.2-1.7)	2	586.7	0.3 (0.0-1.2)	1.90 (0.27- 1.04)
5+ yr	Before 5/2011	0	12.8	0.0 (0.0-28.8)	0	12.8	0.0 (0.0-28.9)	-
	Total	4	686.0	0.6 (0.2-1.5)	6	669.2	0.9 (0.3-2.0)	0.65 (0.13-2.74)
Linked partner infections								
0-1 yr	Before 5/2011	1	834.2	0.1 (0.0-0.7)	17	827.7	2.1 (1.2-3.3)	0.06 (0.00-0.37)
	Total	1	847.6	0.1 (0.0-0.7)	17	839.0	2.0 (1.2-3.2)	0.06 (0.00-0.37)
1-2 yr	Before 5/2011	0	566.5	0.0 (0.0-0.7)	12	563.3	2.1 (1.1-3.7)	0.00 (0.00-0.36)
	Total	0	779.7	0.0 (0.0-0.5)	15	760.1	2.0 (1.1-3.3)	0.00 (0.00-0.27)
2-3 yr	Before 5/2011	0	247.9	0.0 (0.0-1.5)	4	245.3	1.6 (0.4-4.2)	0.00 (0.00-1.50)
	Total	0	721.2	0.0 (0.0-0.5)	6	691.7	0.9 (0.3-1.9)	0.00 (0.00-0.81)
3-4 yr	Before 5/2011	0	60.1	0.0 (0.0-6.1)	3	57.1	5.3 (1.1-15.3)	0.00 (0.00-2.30)
	Total	0	673.6	0.0 (0.0-0.5)	3	638.0	0.5 (0.1-1.4)	0.00 (0.00-2.29)
4-5 yr	Before 5/2011	0	29.8	0.0 (0.0-12.4)	0	24.8	0.0 (0.0-14.8)	-
	Total	1	616.5	0.2 (0.0-0.9)	1	586.7	0.2 (0.0-0.9)	0.96 (0.01-74.7)
5+ yr	Before 5/2011	0	12.8	0.0 (0.0-28.8)	0	12.8	0.0 (0.0-28.9)	-
	Total	1	686.0	0.1 (0.0-0.8)	1	669.2	0.1 (0.0-0.8)	-