HIV-1 Transmission Linkage Among Seroconverting Partners in HIV-Discordant Relationships in Kenya

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BACKGROUND

- A large proportion of HIV-1 transmissions occur in context of stable HIV sero-discordant relationships and understanding the distribution of infections originating from within current partnership (linked) versus from an outside sexual relation (unlinked) is relevant to prevention interventions
- Linkage of HIV-1 transmissions in previous studies have shown unlinked transmissions ranging from 13% to 26%

Study	Population	Intervention used	Transmission rates per 100py	Unlinked Transmissions
*Zambia-UAB Research	Zambia	None	8.5	13.0%
$Partners in Prevention (PIPS) study	Kenya, Uganda, S.Africa	Acyclovir, placebo	~ 2.0	26.5%
#HPTN052 Study	Africa, Asia, America	Early initiation of ART	1.2	18.4%
★PARTNERS PrEP study	Kenya, Uganda	Tenofovir, Truvada, placebo	0.5 – 2.0	22.5%

*Trask SA, et al; 2002. *J.Virol*, $Campbell M, et al; 2001. *PLoS One,* #Cohen MS, et al; 2011. *NEJM*,
★Baeten J; 2014. Personal Communication

- We obtained viral sequences from couple at seroconversion to determine linkage of viral transmissions

COHORT DESCRIPTION & SAMPLE COLLECTION

- HIV-1 serodiscordant couples recruited from VCT centers in Nairobi (2007-2009), and followed for 2 years with quarterly study visits.
- Eligible participants reported sex ≥ 3 times in 3 months prior to screening and maintained relationship for at least 2 years; and ineligible if woman was pregnant, or if HIV-1 infected partner on ART or had a history of clinical AIDS (WHO stage IV) at enrolment
- Blood samples collected from couples at baseline, at quarterly clinic visits from uninfected partners, and every 6 months from infected partners
- Participants who seroconverted had additional specimens collected at time of seroconversion and at 3 and 6 months after seroconversion

LABORATORY AND STATISTICAL METHODS

LABORATORY METHODS AND PHYLOGENETIC ANALYSIS

- DNA extracted from PBMCs collected at seroconversion and HIV-1 *envelope* V1–V5 sequences obtained using single genome amplification
- Phylogenetic trees constructed and genetic pairwise distances calculated for all sequences within each seroconvertor pair
- Linkage based on clustering of HIV-1 *env* sequences with distributions of genetic distances estimated from phylogenetic analysis

STATISTICAL METHODS

- Demographic and behavioral factors compared between unlinked and linked HIV-1 transmission. Cox proportional hazards regression to assess factors associated with risk of seroconversion; Chi-square tests with Fisher's exact p-values to assess dichotomous factors; student's t-tests used to compare continuous factors

RESULTS

- 12 incident HIV-1 infections occurred in 458 HIV-1 serodiscordant couples (1.5/100 person-years)
- Phylogenetic analysis identified 8 (67%) incident infections as link transmissions and 4 (33%) as unlinked [Table 1, Figure 1]
- Viruses from the linked transmission pairs were closely related wi genetic distance 3.4%; and unlinked transmission pairs distantly re with mean genetic distance 13.7% [Table 2].
- All unlinked HIV transmissions were in males, compared to only 2 of 8 linked transmissions (p=0.061) [Table 1]
- Unlinked transmission subjects:
  - reported more lifetime sexual partners (p=0.008), and sex with ou partners (p=0.018);
  - had partners with a higher CD4 count (p=0.027) than those with a transmission [Table 1]

TABLE 1: Characteristics of HIV-1 seroconverters and their part for couples with linked and unlinked transmission events

Characteristics	Linked (N=8)	Unlinked (N=4)	
	N (%)		*p*
Male	2 (25.0)	4 (100)	0.061
Any unprotected sex	3 (37.5)	0 (0)	0.491
Male circumcision (men only)	2 (100)	3 (75.0)	0.999
Pregnancy during follow-up (couple)	1 (12.5)	2 (50.0)	0.236
HSV-2 seropositive	7 (87.5)	1 (25.0)	0.067
Couple separated during study	0 (0)	1 (25.0)	0.333
Sex with outside partner	**0 (0)**	**3 (75)**	**0.018**
Male	2 (25.0)	4 (100)	0.061
	Mean (SD)		
Age	31.6 (7.9)	29.0 (5.3)	0.719
Lifetime sexual partners	**2.8 (1.3)**	**10.8 (7.0)**	**0.008**
Sex acts in the past month	8 (4.6)	5.5 (3.7)	0.373
Time until seroconversion (years)	0.7 (0.5)	1.3 (0.8)	0.139
Partner's HIV viral load (log_{10} c/ml)	5.4 (0.3)	3.8 (2.3)	0.072
Partner's CD4 count (cells/µl)	**290.9**	**479.3**	**0.027**

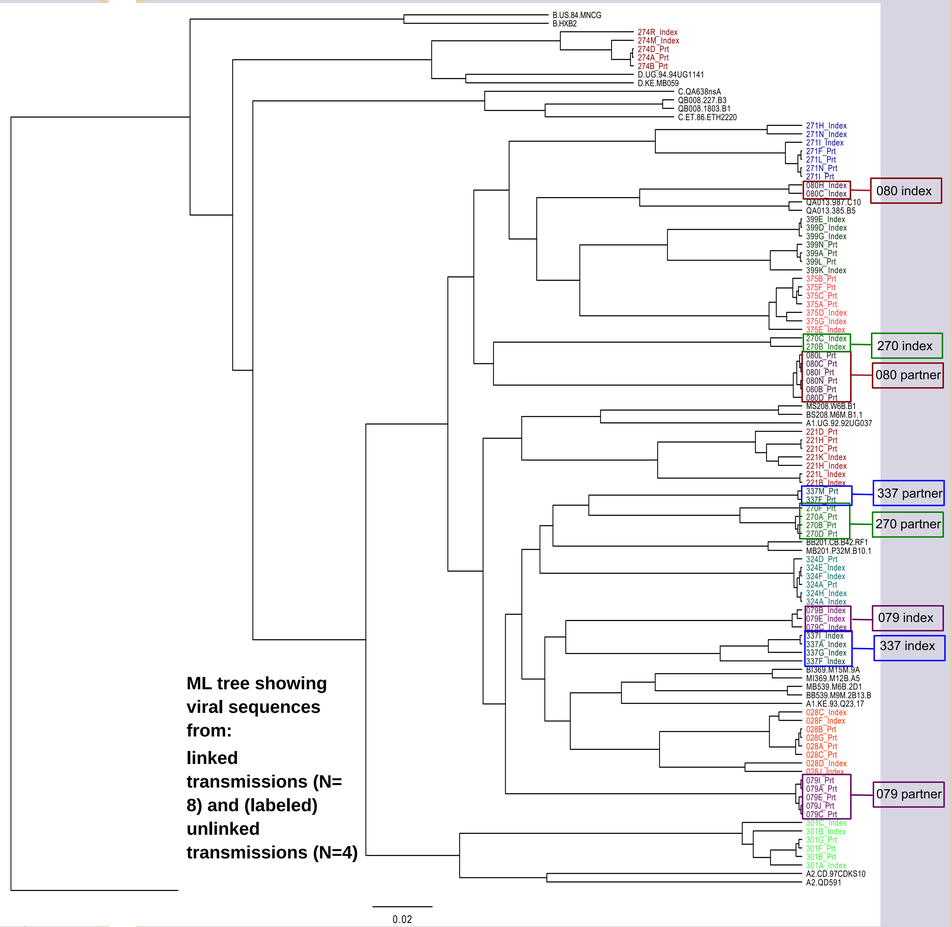
TABLE 2: *Pairwise Genetic Distances of HIV-1 *env* sequences between transmission pairs

Transmission linkage	Mean Genetic Distance %	Range Genetic Distance %
Linked N=8	3.4	0.12 – 6.23
Unlinked N=4	13.7	9.22 - 17.51

*Pairwise genetic distances calculated for sequences within each seroconvertor pair under TN93 model using APE, reporting the maximum distance between each pair

PHYLOGENETIC TREE

FIGURE 1: Maximum Likelihood Tree of HIV-1 *env* V1-V5 sequences



ML tree showing viral sequences from:
linked transmissions (N= 8) and (labeled) unlinked transmissions (N=4)

Phylogenetic trees constructed using GTR Substitution Model and Gamma Site Heterogeneity Model with a Strict molecular clock in BEAST

CONCLUSIONS AND IMPLICATIONS

- A third of HIV-1 incident infections in this treatment-naïve serodiscordant couple cohort were unlinked transmissions with a high frequency occurring in males consistent with other studies in sub-Saharan Africa
- Interventions, e.g. PrEP or condom use, to prevent HIV transmission in discordant couples should address the risk of infection from an outside sexual partner. This may be particularly important when the uninfected partner is male

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