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HIV-1 subtypes and differences in heterosexual HIV transmission among HIV-discordant couples in Rakai, Uganda

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Abstract

Objective—To determine whether heterosexual transmission of HIV differs according to HIV-1 subtype

Design—Retrospective observational cohort

Methods—HIV-1 subtype effects on heterosexual HIV-1 transmission were determined among 268 HIV-discordant couples retrospectively identified from a population cohort in Rakai, Uganda. HIV-1 subtype (*gag* & gp41 sequencing and MHA) and viral loads (RT-PCR) were determined. Adjusted incidence rate ratios (Adj.IRR) of HIV transmission by subtype were estimated by multivariable Poisson regression adjusting for characteristics of index HIV positive and negative partners.

Results—Adjusting for index HIV positive partners age, viral load (VL), stage of disease, genital ulcer (GUD), and HIV negative partners GUD and non use of condoms, subtype A viruses were associated with a higher rate of transmission than subtype D (Adj.IRR, 1.98; 95% CI, 1.17-3.34), but no differences in transmission were observed between recombinant viruses and subtype D (adj. RR, 1.53, p=0.25). Index positive partners' age <30 years (Adj.IRR, 3.44; 95% CI, 1.75 - 6.78) and VL (Adj.IRR, 2.37; 95% CI, 1.75-3.21), and index negative partners GUD (Adj.IRR, 1.71; 95% CI, 1.08 - 2.70) and non -use of condoms (Adj.IRR, 1.94, 95% CI, 1.15 - 3.28) were significant determinants of HIV transmission.

Conclusions—In Rakai, Uganda, subtype A viruses have a significantly higher rate of heterosexual transmission than subtype D viruses. Differential subtype transmission efficiency may be important for HIV vaccine evaluation and could contribute to subtype-specific HIV epidemics in sub-Saharan Africa.

Keywords

HIV-1 subtype; discordant couples; HIV transmission; Uganda

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Introduction

The human immunodeficiency virus type 1 (HIV-1) is characterized by a number of subtypes, inter-subtype recombinant forms, and sub-subtypes [1-4]. HIV-1 subtypes differ in pathogenicity, chemokine coreceptor usage, syncytium-forming properties, and viral fitness [5-7]. Despite the increasing evidence of subtype differences in the rate of HIV disease progression [8-11], data on heterosexual HIV-1 transmission by subtype are limited. Information on subtype differences in transmission is important for HIV vaccine development and testing, for understanding the dynamics of HIV-1 epidemics in different geographical regions, and for future projections of the HIV pandemic.

Studies in Thailand found a higher rate of heterosexual transmission for CRF01_AE (formerly subtype E) compared to subtype B [12;13]. A previous Ugandan study found no significant differences in the distribution of subtypes among incident cases during a decade of follow-up [14]. However, that study did not directly address infectivity by HIV subtype. The limited data on heterosexual HIV-1 transmission by infecting subtype may in part reflect the fact that there are few populations with different circulating HIV subtypes transmitted by the same heterosexual route. In this paper, we present findings on subtype differences in HIV-1 transmission among HIV-discordant monogamous couples in Rakai, Uganda, where multiple HIV-1 subtypes and inter-subtype recombinant strains circulate and are transmitted heterosexually.

Methods

Study population

The Rakai community cohort has been under surveillance since 1994. Study procedures have been previously described [15-17] but briefly, individuals aged 15 - 49 years who provided written informed consent were enrolled, interviewed, and followed up in the home at 10 - 12 month intervals. At each survey, information on socio-demographic characteristics and sexual behaviors (including the number of sexual partners, the relationship to each partner, partner-specific coital frequency, and symptoms of sexually transmitted infections (STIs) were collected using a standardized questionnaire. Venous blood was collected for HIV testing. Participants who reported that they were married or in a consensual union (defined as a long-term sexual relationship that was socially and culturally recognized as equivalent to marriage) were asked to provide the name and address of their spouse or consensual partner. This information was used to identify couples through retrospective linkage of partners who were enrolled as individuals as previously described [18;19]. Participants were provided with free treatment for STIs and general medical conditions, and free condoms and health education. Voluntary HIV counseling and testing (VCT) for individuals and for couples was promoted and provided at no cost. Participants were encouraged to share their HIV results with their partners; involuntary disclosure of HIV results to partners is not allowed under the Ugandan Ministry of Health AIDS Control Program policy on HIV testing [20]. Starting June 2004, Cotrimoxazole prophylaxis and antiretroviral therapy (ART) became available to eligible cohort participants funded by the Presidents Emergency Funds for AIDS Relief (PEPFAR). Institutional Review Board approvals were obtained from the Uganda Virus Research Institute's Science and Ethics Committee, Uganda National Council for Science and Technology and from the Institution Review Boards (IRBs) of collaborating US institutions (Walter Reed Army Institute of Research, Columbia University and Johns Hopkins University).

Laboratory methods

HIV-1 serology was determined by two HIV-1 enzyme immuno-assays (EIAs) namely Vironostika HIV-1, Organon Teknika, Charlotte, NC and Cambridge Biotech, Worcester, MA. EIA discordant and all concordant positive results were confirmed by Western blot (HIV-1 Western Blot, Bio-Merieux-Vitek, St. Louis, MO). HIV-1 plasma viral load was determined by a reverse-transcriptase polymerase chain reaction (RT-PCR) assay (AMPLICOR HIV-1 MONITOR version 1.5 Roche Molecular Systems, Branchburg, N.J.); the standard assay with a lower detection limit of 400 copies/ml. HIV-1 subtype data were determined by genomic sequencing of PCR products from portions of gag (HXB2 nt 1249 to 1704) and gp41 (HBX2 nt 7858 to 8260) [21-24] and by the Multi-region Hybridization Assay (MHA) [25;26]. Subtype assignments of sequence fragments was performed using the NCBI genotyping database. Subjects for whom both gag and gp41 sequences, or MHA probe based data that were uniformly subtype A, C, or D were considered infected with that subtype. If the subtype assignments were discordant between loci within a given individual, that individual was considered to be infected with a recombinant strain of HIV. All sequences were submitted to Genbank (accession numbers pending). All tests were performed following manufacturers protocols.

Statistical analysis

Between 1997 and 2002, we identified 340 HIV-1 discordant couples in whom the index HIV-negative partners were monogamous by self-report (i.e., reported sexual intercourse only with the HIV-positive linked sex partner throughout the at-risk period of observation). HIV-1 subtype and viral load data were available for 268 couples and these constituted the study population.

The study endpoint was HIV seroconversion among the initially seronegative partners in whom infection was estimated to occur at the midpoint between the last negative and first positive serologic tests. Chi-square and Fisher's exact tests were used to compare participant characteristics by HIV-1 subtype. Condom use was coded as “consistent” if reported in all at-risk follow up intervals, “inconsistent” if the participant reported use of condoms in at least one at-risk interval but reported no condom use in other risk intervals; and condom use was coded as “none” if no condom use was reported in any follow up intervals.

Multivariable Poisson regression was used to estimate the adjusted incidence rate ratios (Adj.IRRs) of HIV transmission and 95% confidence intervals (CI) based on robust standard errors [27]. The natural logarithm of the index HIV negative partner's person-time at risk was used as the offset term. Covariates that were significant at $p < 0.10$ in univariate analysis were included in multivariable analyses. Type of discordance (M+F- and M-F+), index negative partners coital frequency and male circumcision were dropped from multivariable models because these covariates were not significant in univariate analyses. There were 38 couples (14%) in whom the male partners were circumcised and analyses in this paper were restricted to the period prior to the Rakai circumcision trials and the introduction of ART in the study population. The final model included seroconversion in the initially HIV negative partners as the outcome and HIV-1 subtype as the main predictor, with adjustment for potential confounders including age of the index HIV positive partner, stage of HIV disease in the positive partner (defined as early disease ≤12 months from seroconversion, latent disease > 12 from seroconversion but prior to the development of AIDS, and late stage disease from the onset of AIDS to death or study closure). The model also included adjustment for $\log_{10}$ HIV viral load, genital ulcer disease (GUD) in the HIV positive partners, and GUD and condom use reported by the HIV-negative partners. Statistical analyses were performed using Stata™ Release 10 (Stata Corporation, 4905 Lakeway Drive, College Station, Texas 77845 USA).

Results

Of the 340 HIV-1 discordant self-report monogamous couples, 268 (78.8%) had HIV-1 subtype and viral load data and these constituted the study population. Those with no subtype data did not differ significantly from those with subtype information with regard to age of index positive (p=0.85), condom use (p=0.38), GUD among index HIV-infected partners (p=0.76), and GUD among index uninfected partners (p=0.36) [data not shown]. Of the 268 HIV-1 discordant couples, 199 (74.3%) had males as the index HIV positive partners (M+F-) while in 69 (25.7%) females were index positives (M-F+). HIV-1 subtype distribution among these couples was 73.9% (198) subtype D, 11.6% (31) subtype A, and 14.5% (39) recombinant viruses. HIV transmission occurred in 34.3% (92/268) of the couples and there were no differences between male-to-female and female-to-male transmission (p=0.82) (data not shown). The mean (SD) and median (IQR) duration of follow up were 3.93 (2.89) and 2.95 (1.66 - 5.48) person years. As shown in Table 1, age of the index positive partner (p=0.49), HIV viral load (p=0.71), GUD in the negative partners (p=0.24), GUD in positive partners (p=0.18), and coital frequency (p=0.57) did not differ between HIV-1 subtypes. However, the proportion of M-F+ couples was lower among persons infected with recombinant viruses (10.3%) compared to subtypes A and D (29.0% and 28.3% respectively, p=0.04), and non-use of condoms was higher among subtype D infected persons (74.8%), compared to the other subtypes (p=0.02).

Table 2 shows incidence rates and rate ratios of HIV-1 transmission in these couples. Controlling for index HIV positive partners' age, stage of disease, HIV viral load and GUD, as well as index HIV negative partners' GUD and condom use, subtype A viruses were associated with a significantly higher rate of transmission than subtype D (adj. IRR=1.95, 95% CI, 1.16-3.29). Inter-subtype A/D recombinants had a higher transmission rate than subtype D, but the differences were not statistically significant (adj. IRR = 1.53, 95% CI, 0.74-3.16). Regardless of infecting HIV-1 subtype, younger age of the index positive partner <30 years (adj.IRR = 3.44, 95%CI, 1.75-6.78), GUD in negative partners (adj.IRR = 1.71, 95%CI, 1.08-2.70), $\log_{10}$ HIV viral load (adj.IRR= 2.37, 95%CI, 1.75-3.21), and non-use of condoms (adj.IRR = 1.94, 95% CI, 1.15-3.28) were significantly associated with increased risk of HIV transmission. We have not yet completed viral genomic characterization to determine whether the transmitted virus in the index HIV-positive partner was homologous with the virus acquired by the initially uninfected partners. However, in all cases of transmission, the subtype in the HIV-infected partner was identical to the subtype acquired by the initially uninfected partner.

We examined HIV transmission rates among couples with GUD reported by one partner or both partners compared with couples in which neither partner reported GUD. Compared to couples with no GUD, the adj.IRR of HIV transmission was 1.76 (95% CI, 1.09-2.83) for couples in whom only one partner reported GUD, and 3.70 (95% CI, 1.98-6.89) for couples in which both partners reported GUD (p<0.001).

Discussion

Among HIV-discordant couples in whom the initially HIV negative partners were monogamous, we found a statistically significant higher rate of HIV transmission for subtype A viruses relative to subtype D (adj. IRR, 1.95, p=0.01). We also found a higher rate of HIV transmission for recombinant viruses relative to subtype D, but the difference was not statistically significant (adj. IRR, 1.53, p=0.25). This suggests that subtype D viruses may be less infectious during heterosexual intercourse than non-D viruses.

It is not yet clear why heterosexual HIV-1 transmission differs by infecting viral subtype, although this may reflect differences in subtype-specific chemokine co-receptor tropism. CCR5 (R5) binds macrophage-tropic (M-tropic) strains of HIV-1 and CXCR4 (×4) binds T-cell-tropic (T-tropic) HIV strains. It is thought that primary HIV infection is established mainly through R5 usage (30). Subtype D viruses more frequently are ×4 tropic than subtype A and recombinants [6;7;29]. Thus, the higher frequency of ×4 tropism in subtype D viruses may partly explain their reduced transmissibility relative to subtype A. More studies on HIV-1 subtype and co-receptor tropism are needed.

We previously found that subtype D was associated with a faster rate of disease progression than subtype A [11] while in this study we found a lower rate of transmission for subtype D relative to subtype A. Taken together, these findings suggest that that over time, the proportion of infections due to subtype A viruses should increase while the proportion due to subtype D infections should decrease. This hypothesis is supported by a recent study of population-level changes in HIV-1 subtype distribution over an eight year interval in Rakai. We found a significant decrease in the proportion of subtype D viruses from 71% to 63% and an increase in subtype A viruses from 15% to 20% ($p = 0.015$) [31].

We found that HIV viral load, younger age of the index positive partners (< 30 years), GUD, and non-use of condoms were significant determinants of HIV transmission – observations that are consistent with previous studies [19;28]. There were no couples who used condoms consistently in all the at-risk intervals of observation. However, none use of condoms was associated with a statistically significant increased risk of HIV transmission compared to inconsistent condom use (Table 2). Unlike a previous Ugandan study that found higher HIV viral load among persons infected with subtype D compared to those with subtype A [32], we found no differences in plasma HIV viral load by infecting HIV-1 subtype (p=0.71).

In all transmitting cases, the viral subtype of the index positive partner was the same as that acquired by the initially HIV-negative partner. However, a limitation of this study is that we do not as yet have data to fully characterize the transmitted viruses in order to determine whether there was viral homology between the index positive and newly infected partners. Self-reported monogamy of the initially uninfected partners was used as a surrogate measure. In a prior Rakai study of 46 transmitting couples, homologous viruses were detected in 92% of initially HIV negative individuals who self-reported monogamy [18]. Thus, it is likely that self-reported monogamy provides a reasonable surrogate measure.

In conclusion, among HIV-1 discordant couples in Rakai, Uganda, subtype A viruses appear to have a significantly higher rate of heterosexual transmission than subtype D viruses. Differential subtype transmission efficiency may be important for HIV vaccine evaluation and could contribute to subtype-specific HIV epidemics in sub-Saharan Africa.

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Table 1

Characteristics of monogamous HIV-discordant couples by HIV-1 Subtype (n=268)

Characteristic	HIV-1 Subtype				
		A *(n=31)*	D *(n=198)*	R *(n=39)*	P-value
	All	N (%)			
Gender of HIV+ partner					
M+F-	199 (74.3)	22 (71.0)	142 (71.7)	35 (89.7)	
M-F+	69 (25.7)	9 (29.0)	56 (28.3)	4 (10.3)	0.04
Age of HIV+ partner (years)					
(Index positive)					
<30	97 (36.2)	13 (41.9)	70 (35.5)	14 (35.9)	
30 – 39	121 (45.1)	11 (35.5)	95 (48.0)	15 (38.5)	
40+	50 (18.7)	7 (22.6)	33 (16.7)	10 (25.6)	0.49
Genital ulcer disease					
Index positive partners					
Yes	29 (10.9)	3 (9.7)	25 (12.6)	1 (2.6)	
No	239 (89.1)	28 (90.3)	173 (87.4)	38 (97.4)	0.18
Index negative partners					
Yes	82 (30.6)	12 (38.7)	62 (31.3)	8 (20.5)	
No	186 (69.4)	19 (61.3)	136 (68.7)	31 (79.5)	0.24
Sexual frequency					
(coital times/year)					
<100	151 (56.3)	14 (45.2)	89 (44.9)	14 (35.9)	
100+	117 (43.7)	17 (54.8)	109 (55.1)	25 (64.1)	0.57
Condom use					
Inconsistent	79 (29.5)	15 (48.4)	50 (25.2)	14 (35.9)	
None	189 (70.5)	16 (51.6)	148 (74.8)	25 (64.1)	0.02
HIV viral load (index positive)					
(median log VL and IQRs)	4.47 (3.94 - 4.99)	4.46 (4.04 - 4.97)	4.48 (3.96 - 4.97)	4.44 (3.87 - 5.23)	0.71

Table 2

Incidence Rate Ratios (IRRs) of HIV transmission among discordant couples with known HIV-1 subtypes

Characteristic	N	Transmissions/py	IR per 100py	Incidence Rate Ratio (95% CI)		
				Unadjusted	Adjusted	P-value
Age of index positive partner (years)						
<30	97	49/227.8	21.5	2.67 (1.39 – 5.13)	3.44 (1.75 – 6.78)	<0.001
30 – 39	121	32/447.3	7.1	0.89 (0.45 – 1.76)	1.31 (0.62 – 2.76)	0.48
40+	50	11/136.8	8.0	1*	1*	
Stage of HIV disease						
Early/Acute	33	13/110.9	11.7	3.92 (1.43-10.74)	2.87 (0.95-8.69)	0.062
Latent	191	73 /500.4	14.6	4.87 (2.05-11.58)	5.21 (2.09-13.0)	<0.001
Late/AIDS	44	6/200.5	3.0	1*	1*	
Genital ulcer disease						
Index negative partners						
Yes	82	41/251.9	16.3	1.79 (1.14 – 2.80)	1.71 (1.08 – 2.70)	0.02
No	186	51 /559.9	9.1	1*	1*	
Index positive partners						
Yes	29	16 / 75.7	12.1	2.05 (1.15 – 3.65)	1.43 (0.85 – 2.42)	0.17
No	239	76/736.1	10.3	1*	1	
Condom use (Index negative partners)						
None	189	62/515.3	12.0	1.19 (0.74 – 1.90)	1.94 (1.15 – 3.28)	0.012
Inconsistent	79	30/296.5	10.1	1*	1*	
HIV viral load ($\log_{10}$)				2.05 (1.56 – 2.70)	2.37 (1.75 – 3.21)	<0.001
HIV-1 subtype						
A	31	16/103.2	15.5	1.47 (0.81 – 2.68)	1.95 (1.16 – 3.29)	0.01
Recombinants	39	13/109.1	11.9	1.13 (0.58 – 2.22)	1.53 (0.74 – 3.16)	0.25
D	198	63/599.5	10.5	1*	1*	

PY --- person years of observation,

*Reference category