

Delayed and Reduced Heterosexual HIV-1 Transmission in Zambians with HLA-B*57

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Abstract

Background. Untreated HIV-1 patients with HLA-B*57 often have low viremia and delayed onset of clinically apparent immunodeficiency. This advantage has been consistently attributed to preferential and effective targeting of HIV Gag epitopes by B*57-restricted cytotoxic T-lymphocytes. The objective of this study was to examine the rate of heterosexual HIV-1 transmission in chronically infected patients with HLA-B*57 and without the B*5701-specific haplotype found in Caucasians.

Methods. HIV-1-discordant (one partner HIV-1 positive and the other negative) Zambian couples were enrolled continuously into longitudinal studies, starting in 1995. HLA class I genotyping was performed for 438 couples who had at least 12 months of follow-up at the end of 2006. Logistic regression and Cox proportional hazard models were used to test the relationship between carriage of HLA-B*57 by the index (seroprevalent) partners and transmission of HIV-1 to their seronegative partners.

Results. B*5703 is the dominant B*57 allele in Zambians, primarily on the A*30-Cw*18-B*57 haplotype (showing strong linkage disequilibrium). Compared with index partners without B*57, those with B*57 ($n = 50$) had lower average viral load ($-0.20 \log_{10}$) and delayed viral transmission to their seronegative partners (relative hazard = 0.60, $p = 0.03$). At the end of the 12-year (1995-2006) study, index partners with B*57 were less likely to be transmitters (odds ratio = 0.50, $p = 0.05$). These relationships were independent of the direction of transmission (male to female or female to male) and could be extended to 43 index partners with the B*57-Cw*18 haplotype (adjusted RH = 0.57, $p = 0.04$).

Conclusion. Reduction in HIV-1 viral load associated with HLA-B*57 in HIV-1 positive individuals can translate to delayed and reduced viral transmission in Zambia, where clade C HIV-1 infection is widespread.

Introduction

- Cytotoxic T-lymphocyte (CTL) responses restricted by human leukocyte antigen (HLA) class I molecules contribute to effective immune control of HIV-1 infection.
- B57 is the most favorable HLA allele in the context of HIV-1 infection, due to its high frequency and effective targeting of conserved HIV-1 epitopes, especially those in the Gag (p24) region (Tang & Kaslow, 2003; Stewart-Jones et al., 2005).
- HLA-B*5701 and B*5703 that encode B5701 and B5703, respectively, are found on different haplotypes involving multiple alleles (e.g. Cw*0602) from neighboring genes like *HLA-C* on the short arm of chromosome 6 (Tang & Kaslow, 2003).
- Exclusive linkage disequilibrium (LD) between B*5701 and a single nucleotide polymorphism (SNP, rs2395029) at the *HCP5* locus has also implied that protection against HIV-1 pathogenesis may be attributable to the *HCP5* SNP in addition to or instead of B*5701 (Fellay et al., 2007).
- Africans who carry B*5703 but not the *HCP5* SNP often have reduced viremia as well (Tang et al., 2002).
- This work examined the influence of HLA-B*57 on HIV-1 transmission and viral load in a cohort native Africans from Lusaka, Zambia.

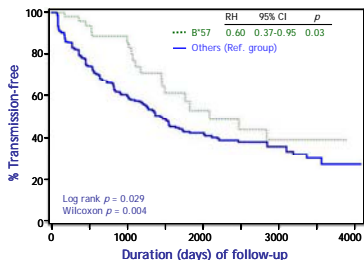


Fig. 2. HIV-1 transmission by index partners with or without HLA-B*57 (mostly B*5703). Delayed HIV-1 transmission was seen in 50 Zambians with B*57 (RH, relative hazards; CI, confidence interval).

Grouping	Number of index partners remaining at various follow-up intervals (days)									
	0	500	1000	1500	2000	2500	3000	3500	4000	4000
B*57+	50	40	29	19	12	9	8	4	0	
Others	379	250	154	92	63	43	32	11	5	
Total	429	290	183	111	75	52	40	15	5	

Subjects and Methods

- Between 1995 and 2006, HIV-1 discordant couples were enrolled continuously for quarterly voluntary counseling and testing (Allen et al., 2003).
- When follow-up was censored on 12/31/2006, 429 out of 566 pairs selected for core studies remained suitable for analyses of within-couple HIV-1 transmission (Figure 1).
- HLA class I genotypes were resolved by a combination of PCR-based techniques, as described previously (Tang et al., 2002).
- Among transmission pairs, viral linkage was established through sequencing of proviral DNA (Trask et al., 2002).
- Several statistical procedures were applied to test associations (Figure 1), with a central hypothesis on HLA-B*57 and its major haplotypes (local and extended).
- Non-genetic risk factors for infection, including genital ulcer/inflammation (in both partners), age, and direction of transmission (male to female versus female to male) were included as covariates in multivariable models.

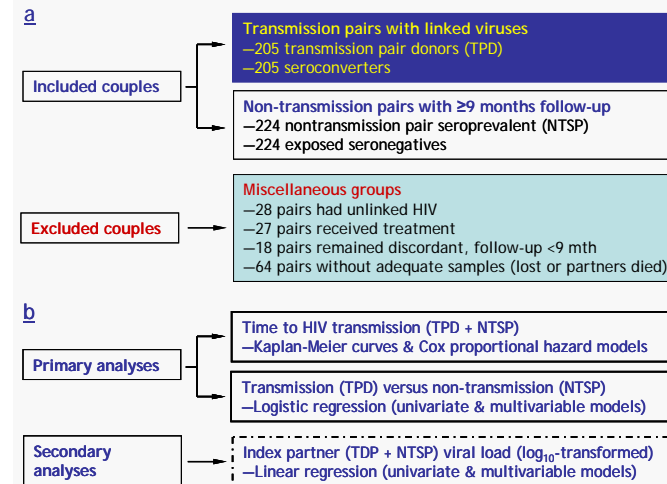


Fig. 1. Selection of 429 (205 + 224) couples for primary and secondary analyses. We excluded both non-transmission couples with inadequate (<9 months) follow-up and transmission couples with unlinked or ambiguous viruses (Panel a). Analyses focused primarily on HIV-1 transmission (Panel b) and secondarily on viral load (earliest measure after enrollment).

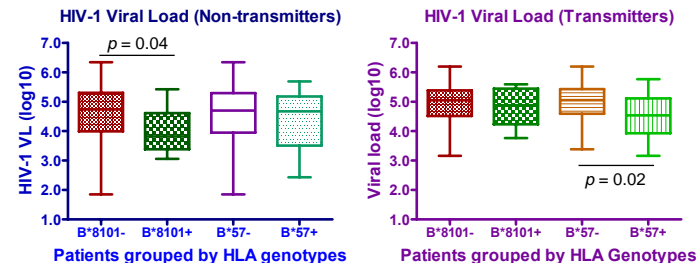


Fig. 3. HIV-1 viral load (RNA copies/ml of plasma) in index partners with or without two favorable HLA markers (B*57 and B*8101). For each group, median and interquartile ranges (boxes) are shown, along with the full range of measures. Transmitters are those whose seronegative partners became infected during follow-up.

Results

- Index partners ($n = 50$) with HLA-B*57 (mostly B*5703) showed a delayed HIV-1 transmission to their seronegative partners within the follow-up period (Figure 2).
- B*57 was also negatively associated with HIV-1 transmission status (OR = 0.50, $p = 0.05$), although it was not a major factor when tested in multivariable models (Table 1).
- Index partners with B*57 had lower average viral load ($-0.20 \log_{10}$), especially among the transmitting partners ($-0.36 \log_{10}$, $p = 0.02$) (Figure 3).
- HLA-B*8101 was another favorable factor associated with lower viral load (Figure 3) but did not appear to protect against HIV-1 transmission.
- Statistical adjustment for non-genetic factors did not alter the relationships of B*57 to HIV-1 transmission or viral load in index partner.
- As a result of tight linkage disequilibrium, the B*57-Cw*18 haplotype found in 43 patients could contribute to the effects ascribed to B*57, with adjusted RH = 0.57 (95% CI = 0.34-0.97, $p = 0.04$).
- The effect of the haplotype extended to the *HLA-A* allele (A*30-Cw*18-B*57) was much weaker ($p > 0.10$, data not shown).

Table 1. Multivariable logistic regression models for HIV-1 transmission.

Host and viral factors in index partners	Model 1			Model 2		
	Odds ratio	95% CI	p	Odds ratio	95% CI	p
HLA-B*57	0.64	0.35-1.17	0.146	0.74	0.38-1.44	0.371
Age (per year) ^a	0.96	0.92-0.99	0.045	0.95	0.91-0.99	0.030
Male to female ^b	1.46	0.99-2.15	0.057	1.19	0.76-1.85	0.443
Genital ulcer/inflammation (each pair)	NA	-	-	3.23	2.06-5.06	<0.001
High viral load (>10 ⁵ copies/ml) ^{b,c}	NA	-	-	3.97	2.07-7.64	<0.001
Medium viral load (10 ⁴ -10 ⁵ copies/ml) ^{b,c}	NA	-	-	2.11	1.11-4.02	0.023

^a Age difference within each couple. CI, confidence intervals. ^b Viral load is $-0.30 \log_{10}$ higher in males than in females (Tang et al., 2002). ^c Patients with low viral load (<10⁴) as the reference group.

Discussion & Conclusions

- Favorable HLA factors like B*57 (or the B*57-Cw*18 haplotype) in Zambians have a dual impact on viral load (HIV-1 pathogenesis) and heterosexual transmission.
- A modest (<0.30 \log_{10}) average reduction in viral load was sufficient to at least delay subsequent viral transmission.
- Among transmitting B*57+ index partners, the lack of association between that allele and lower viral load may reflect viral immune escape in later stages of infection.
- The impact of other HLA factors (e.g. B*8101) on HIV-1 transmission and viral load can also be examined in the Zambian population.

References

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