HHS Public Access

Author manuscript

Genes Immun. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

Genes Immun. 2021 June ; 22(2): 65–74. doi:10.1038/s41435-021-00130-y.

Immunogenetic determinants of heterosexual HIV-1 transmission: Key findings and lessons from two distinct African cohorts

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Abstract

Immunogenetic studies in the past three decades have uncovered a broad range of human genetic factors that seem to influence heterosexual HIV-1 transmission in one way or another. In our own work that jointly evaluated both genetic and non-genetic factors in two African cohorts of cohabiting, HIV-1-discordant couples (donor and recipient pairs) at risk of transmission during quarterly follow-up intervals, relatively consistent findings have been seen with three loci (*IL19*, *HLA-A* and *HLA-B*), although the effect size (i.e., odds ratio or hazards ratio) of each specific variant was quite modest. These studies offered two critical lessons that should benefit future research on sexually transmitted infections. First, in donor partners, immunogenetic factors (e.g., HLA-B*57 and HLA-A*36:01) that operate directly through HIV-1 viral load or indirectly through genital co-infections are equally important. Second, thousands of single nucleotide polymorphisms previously recognized as "causal" factors for human autoimmune disorders did not appear to make much difference, which is somewhat puzzling as these variants are predicted or known to influence the expression of many immune response genes. Replicating these observations in additional cohorts is no longer feasible as the field has shifted its focus to early diagnosis, universal treatment and active management of comorbidities.

Keywords

Africa; epidemiology; genetics; HIV-1 transmission; statistical modeling

Introduction

Sub-Saharan African countries have borne the brunt (60–70%) of the global HIV/AIDS burden for nearly four decades now [1], with heterosexual HIV-1 transmission being a chief driver. Before the implementation of life-long combination antiretroviral therapy (cART) that suppresses viral load, minimizes viral pathogenesis and substantially reduces further spread to at-risk individuals, two study cohorts that began with couple-based voluntary

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Conflict of Interest

The author has no potential conflict of interest to declare.

counseling and testing (CVCT) provided a unique opportunity for studying immunogenetic determinants of heterosexual HIV-1 transmission in countries representing eastern and southern Africa. Based on a longitudinal study design, hundreds of initially HIV-1 discordant couples enrolled in Kigali, Rwanda and Lusaka, Zambia had intra-couple transmission events during quarterly follow-up visits, which were confirmed by phylogenetically related viruses. When these epidemiologically linked couples were compared with non-transmission couples for immunogenetic profiles, including variants at HIV-1 coreceptor genes, human major histocompatibility complex (MHC) and other (genome-wide) loci that mediate immune responses, several consensus findings imply the importance of three loci: *IL19*, *HLA-A* and *HLA-B*. Meanwhile, cohort-specific findings are abundant, which might reflect contrasting genetic backgrounds and different HIV-1 subtypes in these study populations.

To highlight advantages and challenges in these immunogenetic studies, this review will summarize robust evidence and lessons learned since 2004, when cumulative sample sizes were adequate enough to allow meaningful analyses of major factors in individuals or couples (with each donor-recipient pair as a single entity) [2–4]. Consistent observations on three loci uncover both direct and indirect mechanisms related to inflammation and immune control, some of which can be verified experimentally using *in vitro* systems [5–9]. In contrast, thousands of functionally relevant SNPs (single nucleotide polymorphisms), including those known as gene expression quantitative trait loci (eQTLs), have not shown any appreciable impact on heterosexual HIV-1 transmission, suggesting that these eQTLs might not be critical to HIV-1-host interactions at the genital mucosa.

Why do we bother with immunogenetic factors?

Identifying immunogenetic (heritable) correlates of heterosexual HIV-1 transmission is expected to enhance our understanding of host-virus interactions at the genital mucosa and provide much-needed directives for tailoring timely and targeted interventions to suitable subjects or populations. During the course of our cohort studies, the “Fiscal Year 2008 Trans-NIH Plan for HIV-Related Research” [10] made several explicit gestures to encourage the investigation of host factors in HIV/AIDS: (i) “evaluate sexual … transmission and acquisition in relation to...host factors such as sex, age…and host genetic factors,” (ii) “… investigate the contribution of innate host characteristics…and mechanisms for these effects (including host genetic factors…),” (iii) “acquire clinical specimens from populations relevant to HIV vaccine trials…; and (iv) “explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1 and their relationship to class I and class II MHC alleles.” The “Fiscal Year 2012 Trans-NIH Plan”[10] called for strategy that can “delineate the mechanisms by which innate and adaptive immunity, and the effects of genetic or environmental factors on innate and adaptive immunity, influence HIV/SIV replication throughout acute and chronic infection.” By 2019, most of the priorities have shifted to (a) developing next-generation HIV-1 therapies, (b) curing HIV-1 infection and (c) addressing HIV-1-associated comorbidities, coinfections and complications, but reducing the incidence of new HIV-1 infection has remained a critical component [10].

In our search for immunogenetic factors, a multidisciplinary approach was necessary as many non-genetic factors are clearly important to heterosexual HIV-1 transmission (Figure 1). To offer "*added values*," our research must first and foremost demonstrate that these gene variants operate independently of other prominent co-factors, especially viral load in the donor partner (Figure 2), genital co-infections in both HIV-1 source partner (SP) and HIV-1-exposed, seronegative partner (HESN), and male medical circumcision in HESNs. Confirmation of these well-known, multifaceted factors can provide further assurance that our study cohorts are valid and can fulfill three main objectives: (i) to advance our understanding of host genetic factors in HIV/AIDS and co-infections; (ii) to identify causal variants of biological importance, through fine-mapping (dense coverage) of target loci and *in vitro* assays; (iii) to gather an integrated dataset for meta-analyses and other population-based studies.

The advantages in studying HIV-1 discordant couples

Since 1995, two large cohorts of HIV-1-discordant couples enrolled in Lusaka, Zambia and Kigali, Rwanda served as an optimal platform on which host and viral factors important to heterosexual HIV-1 transmission and co-infections can be evaluated jointly and systematically to inform translational research. By the time (2012) when treatment as prevention (TasP) [11–15] became a new standard of care that outweighed the benefits of CVCT, these projects had already accumulated 1,355 couples who met all four selection criteria: (i) ages between 18 years at enrollment and 65 years at end of follow-up, (ii) donor/source partner viral load >2,000 RNA copies/mL, (ii) epidemiologically linked transmission events or >12 months of transmission-free follow-up (before therapy, drop-out or end of study), and (iv) at least one known risk factor (e.g., unprotected sex or pregnancy) for transmission during study intervals (Table 1).

By our study design, immunogenetic factors can be evaluated for SPs and their cohabiting HESNs, with further consideration of covariates (e.g., Figure 1). For SPs, the extent of "HIV-1 control" (as measured by plasma viral load) is critical (Figure 2), so is their susceptibility to genital ulcer/inflammation (GUI) that promote viral shedding at genital mucosa. For HESNs, "HIV-1 susceptibility" (acquisition of infection) can be modulated by GUI as well [16]. When each couple is considered jointly as one entity [17–19], "HIV-1 control" for SP immediately becomes a cofactor for "HIV-1 susceptibility" in HESN (two sides of the same coin), which has been largely overlooked in studies with unknown SPs. Moreover, genetic similarity of each SP-HESN pair can be assessed by allele/haplotype sharing [2, 3] as well as genetic distances defined by principal component analysis (PCA), with further enhancements by a "shared environment" for each SP-HESN pair.

Candidate loci

Since the early 1990s, immunogenetic findings have highlighted the importance of a broad range of host genetic factors to HIV-1 transmission, especially those that regulate the expression of HIV-1 co-receptor CCR5 [20–25], as well as prominent candidates highly enriched in the human major histocompatibility complex (MHC) [23–25]. Some of these are "*causal variants*" (e.g., the *CCR5*-Δ32 mutation) with well-defined biological pathways, while others are pure "*association hits*" because of difficulties and uncertainties with fine-

mapping [26, 27]. More recently, “unbiased” approach using genome-wide coverage has gained popularity, but most of the findings from genome-wide association studies (GWAS) simply reiterated the importance of MHC genes as the primary quantitative trait locus (QTL) for HIV-1 viral load [28–30].

To provide a systematic and thorough dissection of immunogenetic factors in heterosexual HIV-1 transmission, including those that can help explain “*elite controllers*” whose persistent viral suppression is the ultimate goal of therapeutic and prophylactic intervention [31–34], our projects followed some of the earlier leads [4, 35, 36], while also considering statistical power within our evolving cohorts (variable sample sizes due to rolling enrollment and continuous updates of clinical findings), with an emphasis on candidate loci (e.g., HLA and cytokine genes) that are (i) amenable to biological interventions (e.g., vaccines and immune adjuvants), (ii) suitable for high-resolution genotyping (to fully resolve alleles and local haplotypes), (iii) related to early events in heterosexual HIV-1 transmission, and (iv) broad implications, especially genital co-infections that facilitate HIV-1 transmission. These efforts further recognized the notion that immunogenetic factors mediate HIV-1 acquisition (by the recipient partners) and immune control of established infection (in the index/source partners) through distinct mechanisms [17, 19, 37], all of which can be altered by inflammation and virus shedding in the genital mucosa.

Genotyping and bioinformatics

In the early phase of our studies, a variety of PCR-based techniques were used to resolve individual SNP genotypes and alleles within each target locus, followed by the evaluation of local and extended haplotypes (resolved by HaploView [38]). The availability of high-throughput assays, including next-generation sequencing and SNP arrays (the ImmunoChip), broadened the search to genome-wide signals or specific gene clusters (e.g., those encoding killer cell immunoglobulin-like receptors/KIRs) that are not adequately covered by other genotyping platforms. In particular, fine-mapping for hundreds of immune response genes was made possible by the ImmunoChip bead arrays (versions 1 and 2) [39–41], although the actual coverage for signal-rich regions (e.g., MHC) remained suboptimal [42, 43]. Occasionally, targeted NGS was able to fill in various gaps through phased allele and haplotype assignments (GenDx, Utrecht, The Netherlands).

Aided by bioinformatics tools, allelic variants of classic human leukocyte antigen (HLA) genes in the human MHC could be analyzed for supertypes [44], functional motifs (e.g., HLA-B Bw4/Bw6 and HLA-B signal peptide) [37, 45], as well as individual amino acid residues [27, 46, 47]. Noncoding SNPs resolved by NGS, including those in the 5’ and 3’ untranslated regions, provide further coverage of regulatory variants, and their functional attributes can be readily surveyed in public databases like HaploReg [48], the ENCODE project [49, 50], dbGaP [51, 52], NCBI Global Cross-database, http://www.ncbi.nlm.nih.gov/), eQTL hits [53], and PhenoScanner [54].

Key findings that are consistent between cohorts or withstood the test of time

When comparable datasets from the two study cohorts were analyzed, consensus findings were limited to three loci, i.e., *IL19* (rs12407485-A), *HLA-A* (allele A*68:02) and *HLA-B*

(alleles in the B*57 group and alleles carrying a Met residue at the P2 position of the leader peptide (Table 2). The functional attributes of HLA-A*68:02 and HLA-B*57 in antigen presentation have been well documented (Robinson, 2020 #777), while rs12407485 has been recognized as an expression QTL for four genes (*CD55*, *IL10*, *IL19* and *IL24*). Lack of similar cohorts in other regions has precluded the possibility of further validation (beyond southern and eastern Africa) to fully justify a search for mechanisms underlying these associations.

Robust, cohort-specific associations are also worth noting. For example, data from the Zambian cohort suggest that additional variants at *HLA-A* (allele *A*36:01), *HLA-B* (allele sharing) and *KIR2DS4* (allele *001, corresponding to a functional, full-length receptor) might be informative as well (Table 3). In SPs, A*36:01 promoted HIV-1 transmission in several rounds of data analyses as the number of eligible couples increased over time (Figure 3), and its association with elevated HIV-1 viral load was persistent over time [29]. Epidemiological evidence from an African-American cohort and experimental data supported the association of *HLA-B* allele sharing and *KIR2DS4**001 with unfavorable outcomes in Zambians) [7, 8].

In multivariable models, two unfavorable genetic factors found in the Zambian cohort had similar effect sizes in an expanded dataset (re-analyses of data from two publications [17, 19], including recent updates) (Table 4), before and after stratification by the direction of heterosexual transmission (male-to-female or female-to-male). The difference made by the HLA-A*36:01 allele in donor partners was almost identical to that of viral load (per 1.0 $\log_{10}$ or 10-fold change), but its rarity in the Rwandan cohort precluded a cross-cohort validation.

Genital ulcer/inflammation (GUI) as an important cofactor

HIV/AIDS has a substantial overlap with other infections [55]. As a common manifestation of genital co-infections, GUI appeared to remove a transmission bottleneck such that multiple founder viruses could be transmitted [16, 56]. The importance of GUI to heterosexual HIV-1 transmission was unequivocal in both cohorts, even with a clear additive effect when GUI was observed in both partners (SP + HESN) [17]. In analyses that tested GUI as a secondary outcome (for visits prior to HIV-1 transmission or end of follow-up), KIR2DS4*001 [18] and HLA-A*36:01 (Figure 3) turned out to be unfavorable factors in Zambian SPs, suggesting that both can mediate trans-mucosal infection directly (on viral load) and indirectly (on GUI). Likewise, HLA-A*68:02 as a risk factor for HIV-1 acquisition among Zambian HESNs could be explained in part by high incidence of GUI as well (based on re-analyses of data from two publications [17, 19], including recent updates). Together, these observations revealed two intertwined vicious circles involving distinct immunogenetic pathways. First, unfavorable immunogenetic factors (e.g., KIR2DS4*001 and HLA-A*36:01) in SPs render these subjects susceptible to GUIs, and the spread of genital co-infections (typically more contagious than HIV-1 itself) to HENSs creates a microenvironment that promotes HIV-1 acquisition in HESNs. Conversely, the spread of genital co-infections from HESNs to SPs boosts mucosal HIV-1 shedding and compromises mucosal barriers in SPs, also paving way for HIV-1 transmission. Either way, it was evident

that immunogenetic factors in both donor and recipient partners played a prominent role in GUI.

Unproductive efforts on genome-wide scans

Consistent with earlier work that targeted recipient partners of discordant couples in African countries [57], our recent genome-wide association scan (GWAS) did not reveal any reproducible association hits for the two study cohorts. This work used a relatively recent GWAS array (the Illumina Multi-Ethnic Genotyping Array) that is considered suitable for African cohorts [58] and covers over 1.5 million SNPs, with extra flexibility for accommodating up to 300,000 custom SNPs. In a more focused screening facilitated by two versions of the Illumina ImmunoChip, which is cost-effective and targets a broad range of SNPs mapped to genes that mediate innate and adaptive immune responses [43], ~195,000 ImmunoChip version 1 SNPs passed various quality control measures and were deemed acceptable for association analyses – a discovery phase (in the larger Zambian cohort) was followed by a validation phase (in the smaller Rwandan cohort). Again, not a single SNP met the typical, minimal level of study-wide statistical significance (P <0.05 in both cohorts, after Bonferroni correction for the number of independent tests). Alternatively, no association signals with a false discovery rate <0.05 could be confirmed in both cohorts, although cohort-specific hits have been observed [59]. The addition of ImmunoChip version 2 data (for more recent samples) did not make any difference (Tang et al., unpublished data), neither did alternative analyses for thousands of SNPs previously known as “causal variants” for more than 30 autoimmune disorders [60].

One main byproduct from the use of ImmunoChip bead arrays was the assessment of overall genetic structures. When SNPs with low pairwise LD (r^2 <0.20) were used for PCA, the first three components captured most of the genetic variability in each cohort (Figure 4), and these quantitative measures could be kept as covariates in all association analyses. Principal components also formed the basis for measuring genetic distance for each donor-recipient pair, but these metrics did not seem to matter to heterosexual HIV-1 transmission in either cohort. Of note, the Kigali, Rwandan cohort showed a greater genetic diversity than the Zambian cohort (Figure 4), coinciding with a rapid influx of migrants into the Rwandan capital after a massive genocide in 1994.

In other applications, genomics data proved useful in determining biological sex, cryptic familial relatedness (kinship) and genetic outliers [43]. In addition, Many SNPs in the extended MHC region helped with the fine-mapping of association signals detected for individual HLA alleles or amino acid residues [9]. Indeed, the vast majority of common HLA variants in each cohort, defined at the 1-field (2-digit) and 2-field (4- or 5-digit) specificity levels, could be imputed by SNP data {Wiener, 2018 #770, 42], which may offer a cost-effective approach (<$60/sample) to HLA-based screening of study participants in future studies.

Challenges and limitations

Heterosexual HIV-1 transmission is a highly inefficient process, so our samples sizes remained modest (still the largest to date) despite efforts spanning nearly two decades. As

the circulating viruses constantly adapt to immune responses, HIV-1 isolates observed at the beginning of our cohort study may well differ from those relevant to the contemporary populations [61–64]. Analyses of transmitted/founder viruses (TFVs), especially their replicative capacity and pre-adaptation to HLA profiles in the recipient partners, can reflect viral fitness or survival advantages [5, 65–67], but not all TFVs can be readily characterized for linked transmission couples with properly stored specimens. Frequent changes (even interruptions) in research priorities under geopolitical, fiscal and cultural pressures are also unpredictable. Accordingly, the scope of work being discussed here needs to be placed in the right context – that our two study cohorts had multiple high bars to clear. As the global HIV/AIDS landscape evolves, some of the original research objectives are no longer attractive even as we have gained strong footholds in pursuing several complex and intertwined research aims that no other cohorts can achieve.

Another main limitation in these studies is the lack of statistical power for examining gene x gene, gene x environment (e.g., sex and age) and host x virus (HIV-1 subtypes A1 and C) interactions. In theory, clinical outcomes may well depend on biological amplifications (or synergies) under certain microenvironments, but heavy penalty for random testing easily becomes an insurmountable hurdle in these efforts. Perhaps leads from other ongoing studies can gradually justify focused analyses of interactive terms [68].

Other implications and future directions

Immunogenetic factors that help shape the natural history of HIV-1 infection, especially during the pivotal, early phases of HIV-1-host interactions, may further impact therapeutic outcomes [69]. As the HIV/AIDS field shifts its focus on immune restoration after cART or eradication of viral reservoirs ("*functional cure*") [70], a "genetic profile" that predicts immunologic deterioration early in the course of infection [71] or atypical response to treatment could alert caregivers to the need for more aggressive versus standard care. The demand for prognostically useful information and its translation into the clinic will accelerate as several phenomena occur in the era of universal cART: (i) options for early and targeted intervention increase, (ii) "genetic profile" or "causal variant" reliably predicts outcome; (iii) pressure intensifies to tailor individual treatment to a predicted disease trajectory (including non-AIDS morbidities) or risk for further transmission (threat to public health); and (iv) barriers (including costs) to routine genetic profiling and counseling diminish.

HLA genotyping has been well received in clinics where there is a need to promptly identify HLA-B*57:01 patients who are destined to develop life-threatening hypersensitivity reactions to abacavir [72]. Beyond this immediate application, prognostic genetic profiling can benefit clinical trials by improving trial efficiency (pre-treatment stratification) and reducing subgroup heterogeneity (as a covariate in analysis of efficacy) [73], as reflected by data from a promising AIDS vaccine trial in Thailand (RV144) [74, 75] and in certain nonhuman primate models [76]. Various research activities related to the two study cohorts in Rwanda and Zambia are being integrated into the International AIDS Vaccine Initiative [77, 78] and may prove to have far-reaching significance in the African epicenter, although follow-up research will certainly require some strategic adjustments, under the new premises

of the 90:90:90 initiative – to rid the world free of AIDS by substantially reducing the further spread of HIV-1 infection, through concerted efforts for active diagnosis, early treatment and targeted prevention [79, 80]. A new generation of investigators, who have been trained by several research teams involved in these cohort studies, are now armed with well-documented expertise in epidemiology, genetics, immunology, virology and biostatistics. Their contributions to scientific research will undoubtedly go beyond HIV/AIDS.

Acknowledgements

The original data included in this review came primarily from an R01 project (AI071906) funded by the National Institute of Allergy and Infectious Disease, with further funding from R01-AI64060. Unpublished genomics data for African-Americans and European Americans came from a third project (R21-AG051309). I am grateful to Dr. Richard A. Kaslow, Dr. Susan Allen and Dr. Eric Hunter for their leadership during these projects. Members of the Rwanda-Zambia HIV-1 Research Group were essential to patient enrollment and data management. Refinements of earlier findings based on updated datasets were made possible by statistical models prepared by Mr. Xuelin Li, Dr. Heather A. Prentice, and Dr. Howard Wiener.

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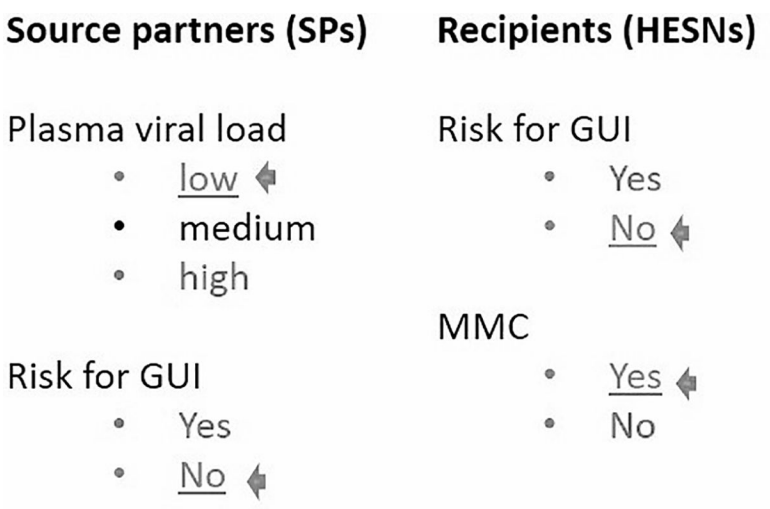
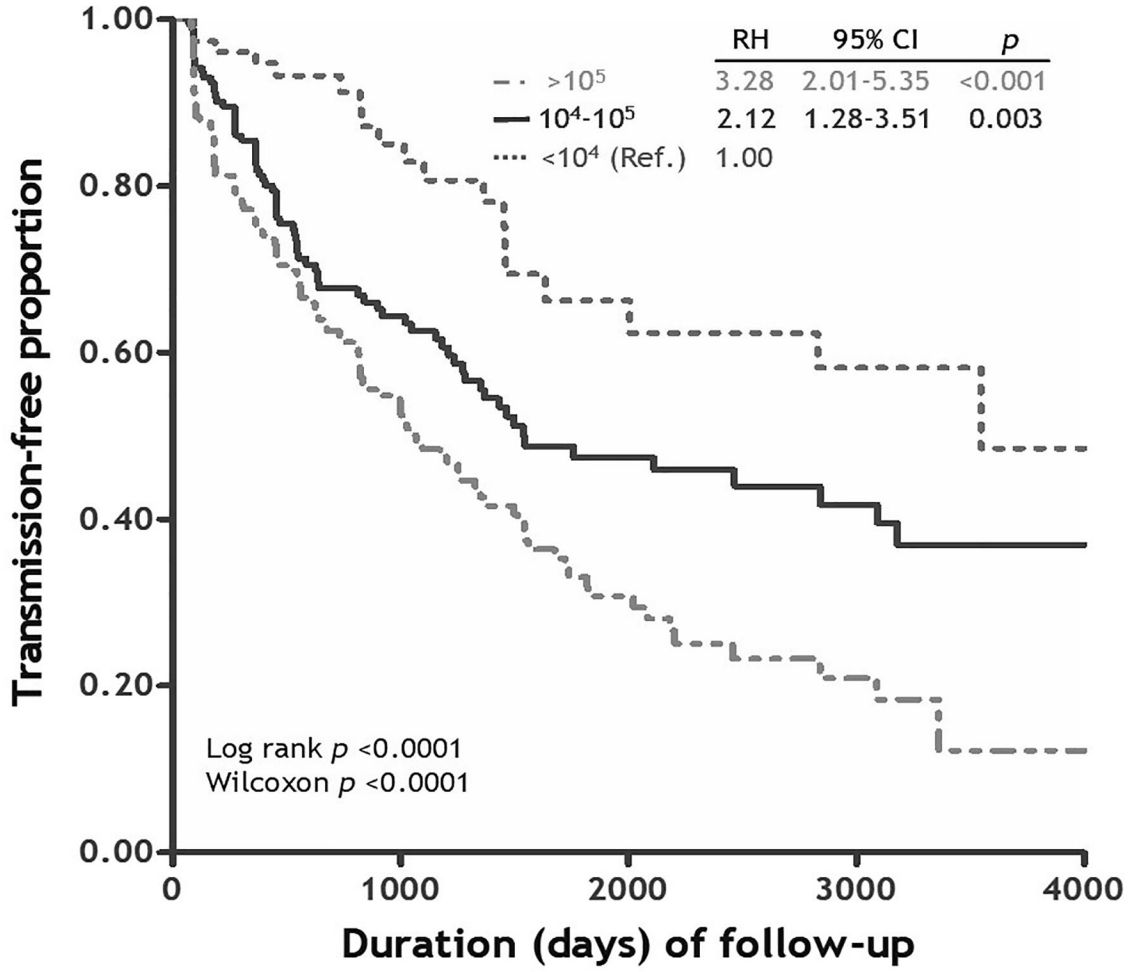


Figure 1. Several scenarios in the setting of heterosexual HIV-1 transmission among discordant couples.

When two main factors in the HIV-1-infected source partners (SPs) are assessed along with two well-documented factors in the recipient partners (also known as HIV-1-exposed, seronegative individuals or HESNs), couples can be divided into various composite risk groups. The group with extremely low risk (having all factors indicated by arrows) is expected to obscure the search for immunogenetic determinants, especially when duration of follow-up is short. GUI, genital ulcer/inflammation (clinical manifestations of genital co-infections); MMC, male medical circumcision (rates of uptake <5% in our cohorts).



VL Groups	Events	Number of index partners remaining at various follow-up intervals (days)								
		0	500	1000	1500	2000	2500	3000	3500	4000
$>10^5$	106 (62%)	171	114	68	40	24	13	9	2	1
10^4-10^5	77 (45%)	172	113	73	45	32	23	19	7	2
$<10^4$	19 (25%)	77	59	40	24	17	16	12	6	1
Total	202 (48%)	420	286	181	109	73	52	40	15	4

Figure 2. Kaplan-Meier curves showing the impact of HIV-1 viral load (VL) in donor/index partners on heterosexual HIV-1 transmission among 420 HIV-1 discordant Zambian couples with longitudinal follow-up.

The three VL categories followed earlier strategies [83], and subjects with low VL ($<10^{-4}$ RNA copies/ml of plasma) were treated as the reference (ref.) group. The estimates of relative hazards (RH) and 95% confidence interval (CI) were based on a Cox proportional hazards model. Graph is redrawn from data published in 2008 [17]. Couples that remained eligible for further assessment at various follow-up intervals are indicated below the curves.

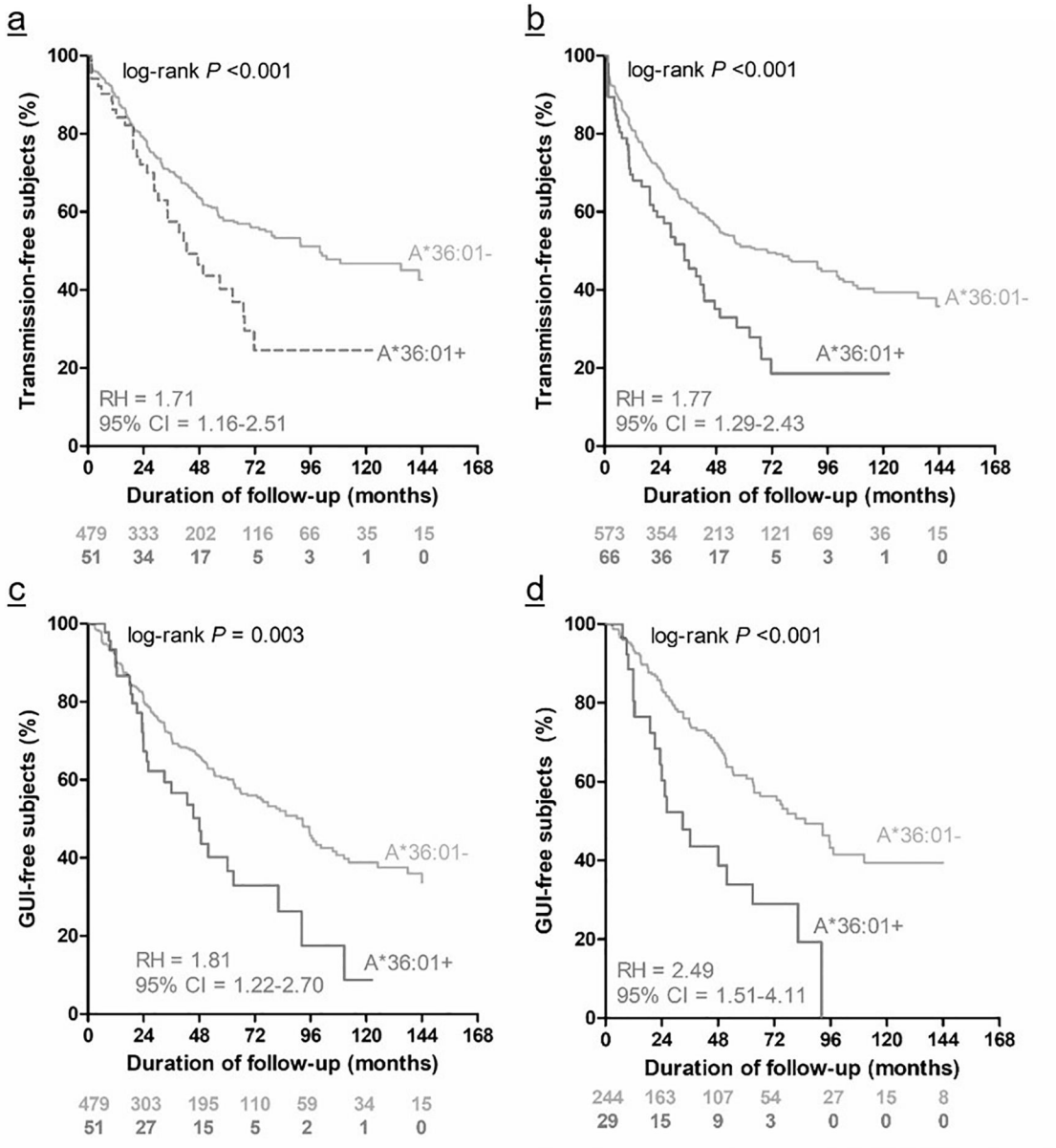


Figure 3. Kaplan-Meier curves showing the impact of HLA-A*36:01 in donor/index partners on heterosexual HIV-1 transmission and genital ulcer/inflammation (GUI) during longitudinal follow-up.

Prompted by our original report on 429 HIV-1 discordant Zambian couples [17], several analyses of expanded datasets (530 couples in panel a versus 639 couples in panel b) confirmed that HLA-A*36:01 in donor/index partners was persistently an unfavorable factor for HIV-1 transmission. This association was partially explained by elevated HIV-1 viral load setpoint in donor partners, as well as presence of GUI over time (panel c, 530 couples), the association with GUI was mostly seen in female-to-male transmission (panel d, with 273 couples) (combined data from two publications [17, 19], including recent updates). The estimates of relative hazards (RH) and 95% confidence interval (CI) were based on Cox proportional hazards models.

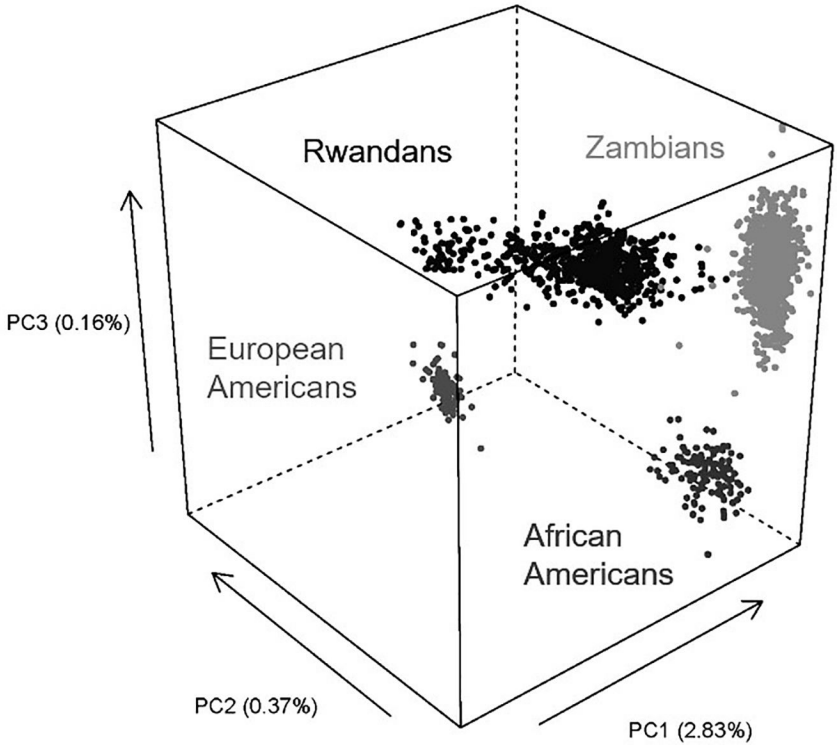


Figure 4. A 3D graph showing the clustering of subjects from three countries.

In principal component analyses using genome-wide SNPs with low linkage disequilibrium (pairwise r^2 <0.20), the first three dimensions (PC1-PC3) captured most of the genetic variations for subjects enrolled from Kigali (Rwanda), Lusaka (Zambia) and Birmingham (United States). The Birmingham cohort consists of African Americans and European Americans. Variance explained by each component is shown in parentheses (Tang et al., unpublished data).

Table 1.

Assembly of two study cohorts for immunogenetic studies.[a]

Overall characteristics	Lusaka, Zambia	Kigali, Rwanda
Participants	HIV-1 discordant couples	HIV-1 discordant couples
Enrollment dates	1995–2011	2002–2011
Intervention	CVCT & cART	CVCT & cART
Follow-up visits	Quarterly	Quarterly
Genital co-infections[b]	GUI	GUI
Total enrollment	4,759 couples	1,748 couples
Subset for immunogenetic studies[c]	994 pairs (21%)	361 pairs (21%)

[a]Whenever applicable, data from other studies pertinent to HIV-1 transmission in African countries are also discussed in the text.

[b]Genital ulcer/inflammation (GUI) was frequent enough for ancillary studies. Other abbreviations: CVCT, couple-based voluntary counseling and testing; cART, combination antiretroviral therapy.

[c]Selection criteria: (i) ages between 18 at enrollment and 65 at end of follow-up, (ii) >12 months of follow-up before therapy or drop-out (while transmission-free), (iii) donor/source partner viral load >2,000 RNA copies/mL, and (iv) at least one known risk factor (e.g., unprotected sex or pregnancy) for transmission during study intervals.

Table 2.

Summary of consensus immunogenetic findings from two study cohorts.

Locus	Variant (allele or aa residue)	Setting	Association	Reference(s)
IL19	rs12407485-A[a]	HESNs	Resistance to HIV-1 acquisition	[43]
HLA-A	A*68:02[b]	HESNs	Susceptibility to HIV-1 acquisition	[19]
HLA-B	B*57[b]	SPs	HIV-1 transmission	[17, 78]
HLA-B	Alleles carrying P2-Met[c]	HESNs	Susceptibility to HIV-1 acquisition	[6]

[a]Within a predicted enhancer region. According to a recent (March 2021) search in PhenoScanner (version 2), rs12407485 is a well-recognized eQTL, being associated with the expression of four genes (*CD55*, *IL10*, *IL19* and *IL24*).

[b]Confirmative results from the Rwandan cohort have not been published.

[c]Mostly B*57:03 and often reflected by its persistent impact on viral load

[d]Methionine at position 2 of a leader peptide that binds to HLA-E; also supported by in vitro assays [6].

Table 3.

Cohort-specific immunogenetic findings with various supporting evidence.

Locus	Variant (allele or aa residue)	Setting	Association	Reference(s)
HLA-A	A*36:01[a]	Zambian SPs	Promoting HIV-1 transmission	Ref. [17]
HLA-B	Alleles sharing[b]	Both partners	Promoting HIV-1 transmission	Ref. [2]
KIR2DS4	Full-length allele *001[c]	Zambian SPs	Promoting HIV-1 transmission	Ref. [18]

[a]Observation was confirmed multiple times in expanded cohorts (e.g., Figure 2), with clear impact on viral load in the SP partners.

[b]Supported by experimental evidence [8].

[c]The only allele encoding a functional, full-length receptor, with implications for inflammation mediated through natural killer cells [7].

Table 4.

Multivariable models that jointly assess the relative impact of three risk factors (host and viral) on heterosexual HIV-1 transmission among Zambian couples.

Factors in model[a]	All subjects (638 couples)				MTF subset (312 couples)				FTM subset (316 pairs)			
	n	RH	95% CI	*p*	*n*	RH	95% CI	*p*	*n*	RH	95% CI	*p*
Donor VL[c]	634	1.8	1.6–2.2	<0.0001	312	1.67	1.3–2.2	<0.0001	316	1.9	1.5–2.5	<0.0001
A*36:01 (donor)	63	1.6	1.2–2.2	0.004	28	1.44	0.9–2.3	0.130	35	1.8	1.2–2.9	0.009
A*68:02 (recipient)[b]	99	1.5	1.1–2.0	0.006	58	1.51	1.0–2.2	0.029	41	1.5	0.9–2.4	0.099

[a]Data from an expanded Zambian cohort (638 couples) (combined data from two publications [17, 19], including recent updates). Results were consistent with earlier findings based on analyses of paired recipient and index/donor partners (each couple was counted as one unit) [17], even when the cohort was split by the direction of transmission (male-to-female/MTF versus female-to-male/FTM).

[b]HIV-1 viral load (VL) was treated as a continuous variable after $\log_{10}$-transformation. The summary statistics, including relative hazards (RH) and 95% confidence interval (CI), are based on Cox proportional hazards models (adjusted for factors in each model).

[c]Data missing in several subjects. Of note, two earlier reports have portrayed the A2 supertype, including A*68:02, as protective against HIV-1 acquisition in cohorts from Kenya [81, 82].