

Virus-Host Gene Interactions Define HIV-1 Disease Progression

Daniela C. Monaco, Zachary Ende and Eric Hunter

Abstract In this chapter, we will review recent research on the virology of HIV-1 transmission and the impact of the transmitted virus genotype on subsequent disease progression. In most instances of HIV-1 sexual transmission, a single genetic variant, or a very limited number of variants from the diverse viral quasi-species present in the transmitting partner establishes systemic infection. Transmission involves both stochastic and selective processes, such that in general a minority variant in the donor is transmitted. While there is clear evidence for selection, the biological properties that mediate transmission remain incompletely defined. Nevertheless, the genotype of the transmitted founder virus, which reflects prior exposure to and escape from host immune responses, clearly influences disease progression. Some escape mutations impact replicative capacity, while others effectively cloak the virus from the newly infected host's immune response by preventing recognition. It is the balance between the impact of escape mutations on viral fitness and susceptibility to the host immunogenetics that defines HIV-1 disease progression.

Dedication: This chapter is dedicated to Peter K. Vogt in honor of his 50 years as an editor of *Current Topics in Microbiology and Immunology*, his continued contributions to science and 45 years of mentorship and friendship.

D.C. Monaco · Z. Ende · E. Hunter
Emory Vaccine Center, Yerkes National Primate Research Center,
954 Gatewood Road, Atlanta, GA 30329, USA

E. Hunter (✉)
Department of Pathology and Laboratory Medicine, Emory University,
954 Gatewood Road, Atlanta, GA 30329, USA
e-mail: ehunte4@emory.edu

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1 Introduction

The current HIV/AIDS pandemic reflects a combination of sub-epidemics that vary in routes of transmission, prevalence and incidence rates, different at-risk populations, and viral subtypes. Overall in 2014, an estimated 36.7 million people were living with HIV-1, and 2.1 million new HIV-1 infections occurred globally (UNAIDS 2016). HIV-1, the causative agent of the AIDS pandemic and a member of the *lentivirus* genus of the family *Retroviridae*, continues to contribute to over 1 million deaths globally every year and has been coevolving in its only permissive host, humans, for many decades.

As with all retroviruses, HIV-1 integrates a copy of its genome into the chromosome of the host cell and establishes a chronic infection that is subject to immune control by the host; although, HIV-1 infects a subset of cells, CD4⁺ T cells, that play a key role in orchestrating the immune response. Nevertheless, HIV-1 induces robust humoral and cellular immune responses, the latter of which can limit virus replication to varying degrees (Walker and Yu 2013). Genome-wide association studies have indicated that while genes in the human leukocyte antigen (HLA) locus account for the bulk of host control over virus replication, HLA can only account for approximately one-quarter of the observed variation in setpoint viremia (Fellay et al. 2007; McLaren et al. 2015). In this review, we will discuss recent data that suggest both control of viral replication and disease progression are the result of complex and evolving interplay between the virus that initiates infection and the host immune response.

2 HIV-1 Transmission

Heterosexual transmission of HIV-1 remains the predominant mode of transmission, particularly in sub-Saharan Africa, accounting for nearly 75% of new transmissions worldwide. In contrast, in developed countries of the Western

Hemisphere, men who have sex with men (MSM) continue to represent a majority of those newly acquiring HIV-1. Transmission via direct blood-to-blood contact through intravenous drug use (IDU) or contaminated blood transfusions constitutes a small percentage (<10%) of infections in the U.S., but transmission among IDUs is a significant contributor in parts of Southeast Asia and Eastern Europe. The risk of sexually transmitted infection by HIV-1 is highly dependent on the route of transmission; exposure in MSM via the rectum has an estimated infection probability ranging from 1 in 20–300, whereas for infection via the male genital tract the risk ranges from 1 in 300–7000. Infection in the female genital tract carries a risk of approximately 1 in 200–2000 (Hladik and McElrath 2008). Frequencies of transmission vary based on a number of factors that include the stage of infection and the level of viremia in the transmitting partner, with the risk of infection from patients with acute and early infection being significantly higher than that from those with established infection (Brenner et al. 2007; Miller et al. 2010; Powers et al. 2008; Wawer et al. 2005). This likely reflects the high viral loads (VL) observed in acute infection (Pilcher et al. 2007), lack of neutralizing antibody which may otherwise inactivate a majority of circulating virions in established infection, and essentially clonal amplification of a virus capable of initiating productive infection (see below). Other factors that have been shown to modulate the efficiency of sexual transmission include sexually transmitted diseases, particularly those that result in genital inflammation and ulcers, which can elevate HIV-1 shedding into the genital tract and increase the risk of infection 21-fold (Galvin and Cohen 2004); pregnancy during which a greater than two-fold increase in HIV-1 transmission has been observed (Gray et al. 2005); and circumcision, which in a series of clinical trials was shown to decrease transmission to the male by 60% (Auvert et al. 2005; Bailey et al. 2007; Gray et al. 2007). Transmission may also be biased by the viral subtype present in the population (Kiwanuka et al. 2009; Kamali et al. 2015).

3 Current Concepts of Genital Tract Infection and Systemic Spread

The nonhuman primate model of HIV-1 infection has proven to be a powerful tool for experimentally investigating the transmission event since it is not possible to study the earliest steps of sexual transmission in human subjects. It is well established that HIV-1 has evolved from a simian immunodeficiency virus (SIV_{cpz}) that naturally infects a species of chimpanzee, *Pan troglodytes troglodytes*, while HIV-2 is derived from another that naturally infects sooty mangabeys (*Cercocebus atys*; SIV_{sm}) (Hahn et al. 2000). While relatively benign in its natural host, SIV_{sm} can be adapted to replicate in and induce a rapid immunodeficiency disease in rhesus macaque monkeys similar to that induced by HIV-1 in humans (Paiardini et al. 2009; Klatt et al. 2012). Pathogenic variants isolated from rhesus macaques, referred to as SIV_{mac}, have been particularly informative in defining steps involved

in transmission of and systemic infection by primate lentiviruses when used in intra-vaginal and intra-rectal challenge models (Hatzioannou and Evans 2012; Evans and Silvestri 2013). Studies using high doses of SIV_{mac251} led to a model whereby SIV interaction with the cervicovaginal mucosa induces an innate response, amplified by recruitment of macrophages and plasmacytoid dendritic cells, that signals activated T cells to migrate to the site of infection. This increased availability of CD4⁺ target cells allows amplification of infection from the initially infected cell, a partially activated mucosal CD4⁺ T cell, to a level where virus or virus-infected cells can exit the mucosal tissue and travel to distal sites. These include regional lymph nodes and the gut-associated lymphoid tissue (GALT), where the bulk of early viral replication and T-cell depletion occurs. This model of a localized inflammatory response playing a role in facilitating transmission is supported by experiments demonstrating that vaginal infection could be inhibited by local application of glycerol monolaurate, an inhibitor of inflammation (Li et al. 2009). However, the need for local amplification of infection was recently questioned following a large study, where animals were infected intravaginally with a high dose of SIV_{mac251} and serially necropsied on days 0, 1, 3, 7, and 10. In this study, virus was occasionally detectable in tissues distal from the genital mucosa, such as the gastrointestinal tract, by day 1, and 89% (8 of 9) of animals had detectable levels of viral RNA in at least one distal tissue by day 3, suggesting that viral dissemination can occur rapidly (Barouch et al. 2016). However, the role of these early distal infections in the establishment of systemic infection remains unclear since plasma viremia was not detected until day 10 in a majority of the animals. It is also important to recognize that these high dose infections may not be directly comparable to human sexual transmission, where the inoculum of infectious virus is likely to be much lower.

Although a variety of potential initial targets of infection have been postulated, including resting CD4⁺ T cells, macrophages and dendritic cells, Hope and colleagues recently demonstrated that Th17-lineage CCR6⁺ CD4⁺ T cells are the predominant targets of SIV during vaginal transmission by using a high titer, single-round non-replicating SIV construct that expresses luciferase and m-Cherry, (Stieh et al. 2014, 2016). This cell type plays a key role in maintaining the integrity of the gut mucosa and is rapidly depleted following both SIV and HIV-1 infection (Blaschitz and Raffatellu 2010; Dandekar et al. 2010; Cecchinato and Franchini 2010).

4 HIV-1 Transmission is Linked to a Genetic Bottleneck

The concept that transmission of HIV-1 involves a genetic bottleneck, in which one or a limited number of variants from the diverse population present in the transmitting partner establish productive infection in the uninfected partner, was first established in studies over two decades ago. By analyzing viral sequences from early time points in primary HIV-1 infection, as well as, in some cases, viral

sequences from the donors of a small number of linked heterosexual, homosexual, and mother-to-child transmissions, these studies demonstrated that the virus population in the newly infected individual was much less diverse than that in the transmitting partner or mother (Wolinsky et al. 1992; Wolfs et al. 1992; Zhu et al. 1993; Zhang et al. 1993). Wolfs et al. also observed that in the two heterosexual transmissions described, the transmitted virus appeared to be a minor variant in the blood of the transmitters.

The difficulty of obtaining samples at early time points after infection, and from donors of linked HIV-1 transmission pairs, hindered the investigation of transmitted viral characteristics for over a decade. At this time a more in-depth analysis was performed using samples from heterosexual transmissions in a previously established cohort of serodiscordant couples in Lusaka, Zambia (Derdeyn et al. 2004). Derdeyn et al. sequenced almost 300 cloned HIV-1 Subtype C Envelope gene amplicons derived from eight heterosexual transmission pairs shortly after transmission, and performed genetic and phenotypic studies (Derdeyn et al. 2004). The strength of this study was that the donor and recipient pairs were confirmed to be epidemiologically linked (Trask et al. 2002). A strong genetic bottleneck was observed in each transmission pair, in that the *env* sequences derived from each linked recipient emanated from a single branch on their respective donor *env* sequence phylogenetic tree, arguing that a single transmitted founder (T/F) virus established infection in each case.

More definitive analyses have relied on the use of end-point dilution PCR [termed single genome amplification or SGA (Salazar-Gonzalez et al. 2008)] to amplify sequences from multiple single genomes present in plasma very early after primary infection of individuals followed by direct sequencing of the DNA amplicon. This approach, in contrast to bulk PCR followed by cloning, avoids sequencing errors introduced by the Taq polymerase, in vitro recombination induced by template switching during the PCR reaction, and non-proportional representation of sequences as a result of template resampling. Furthermore, it has been possible to define the number of T/F variants, and the nucleotide sequence of each variant, by applying a mathematical model of early virus evolution to the SGA sequences (Lee et al. 2009). This model assumes that, in the absence of immune selection, replicating genomes accumulate random mutations at a constant rate defined in large part by the error rate of the reverse transcriptase. Using this approach, Keele and colleagues showed that 78 out of 102 subjects with acute subtype B HIV-1 infection had evidence of systemic infection by a single virus, while the remaining 24 had been infected by approximately two to five viruses (Keele et al. 2008). Applying this same method to 20 subtype A and C heterosexual transmission pairs for whom multiple sequences from both partners were derived, Haaland et al. (2009) determined that a single T/F virus established infection in 90% of cases, while an analysis of 69 newly infected subtype C individuals from South Africa by Abrahams et al. (2009) showed that 78% involved single variant transmission. It is clear from such studies, that, in situations where multiple viruses initiate infection, the number of infecting variants does not follow a Poisson distribution, with a majority involving only two or three variants but occasionally

more than five. This is inconsistent with each variant being transmitted independently with low probability (Abrahams et al. 2009). Most likely, in these cases, factors such as sexually transmitted infections and potentially, in young women, the use of hormonal contraceptives, lowered the barrier to transmission (Haaland et al. 2009; Sagar et al. 2004).

Modulation of the genetic bottleneck: Inflammatory responses to both the existing microbiome as well as to sexually transmitted infections clearly increase the frequency of HIV-1 transmission. Recent studies of young women in a South African cohort have shown that in those where the microbiome is deficient in *Lactobacillus* species, and yet diverse with *Prevotella* and *Gardnerella* species, there are increased genital pro-inflammatory cytokine concentrations (Anahtar et al. 2015). This ecologically diverse, *Lactobacillus* deficient microbiome was also associated with a higher risk of HIV-1 acquisition (Gosmann et al. 2017). Moreover, sexually transmitted infections (STIs), including herpes simplex type 2, which induce inflammation and ulcers in an uninfected partner, as well as similar infections in the transmitting partner, are known to increase the risk of transmission (Galvin and Cohen 2004).

Although not necessarily impacting the multiplicity of infection, viral load in the transmitting partner has been shown to modulate the likelihood of transmission. Studies in HIV-1 discordant couples have shown that partners with VL less than 10,000 copies/ml only rarely transmitted to their partners, while those with VL greater than 100,000 copies/ml transmitted much more frequently, with on average a 2.5-fold increase in risk with each $\log_{10}$ increase in VL (Quinn et al. 2000; Fideli et al. 2001). In Zambian discordant couples this increased risk was most evident in female to male (FTM) transmissions (Fideli et al. 2001), which may reflect higher VL in the genital tract of the transmitting partner (Pilcher et al. 2007) and a greater chance of virus reaching the genital mucosa. This is also consistent with NHP studies where both the frequency of infection and the number of transmitted variants increased with the dose of the inoculum (Liu et al. 2010). Moreover, in the macaque model, SIV in the plasma from animals in the acute stage of infection, where potentially neutralizing antibodies are absent, has a specific infectivity almost 100 times greater than that of virus in the plasma from chronically infected animals (Ma et al. 2009).

As highlighted by Joseph et al. (2015) and shown in Fig. 1, virus transmission can fail at multiple steps following inoculation onto a mucosal surface (Joseph et al. 2015). Thus, STIs could abrogate the barrier imposed by an intact mucosa by inducing breaks in the epithelial lining thereby allowing more viral variants to initiate infection in the mucosal tissue; alternatively, inflammation induced by genital infections could increase the availability of activated CD4⁺ cells required to establish a spreading infection, in this way allowing infections that would have failed due to lack of target cells to expand. It is still not defined, under conditions of low multiplicity of infection, where the probability of infection is less than 1% per coital act, how many viruses initiate an abortive infection in the mucosa.

It has been possible to reproduce the transmission-linked genetic bottleneck in the nonhuman primate model of HIV-1 infection, where rhesus macaque monkeys

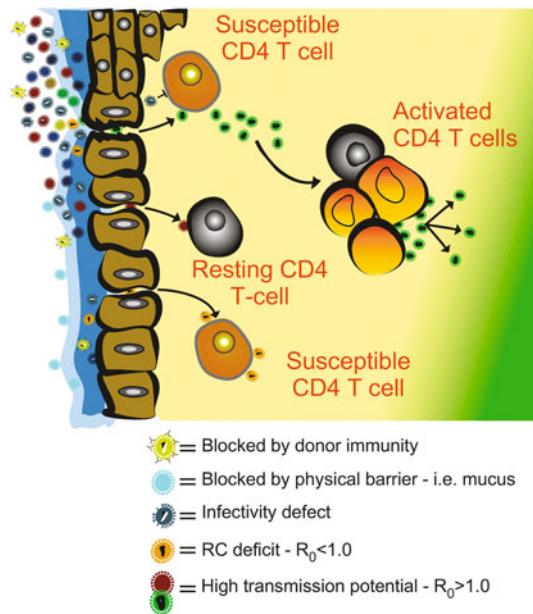


Fig. 1 Potential barriers to HIV transmission across the genital mucosa. During transmission, the virus encounters a number of barriers to infection including mucous and epithelial layers that can block access to target cells. However, viruses can penetrate host defenses through temporary breaks in the epithelium or dendritic cell sampling the mucosal environment. The entering viruses must interact with susceptible CD4+ CCR5+ T cells to propagate since entry into nonpermissive resting CD4+ T cells will result in nonproductive infection. Similarly, if the RC of the virus is unable to sustain a spreading infection ($R_0 < 1.0$), even infection of susceptible cells will not result in dissemination. It is likely that viruses with a replicative advantage will outcompete those that replicate less efficiently. Initial target cells are most likely susceptible CD4+ CCR5+ T cells, a majority of which may be of a Th17 lineage, but infection of macrophages and dendritic cells has also been reported. These cells can replicate virus locally or traffic to local secondary lymphoid structures, though virus could also diffuse there directly. Once virus reaches local lymph nodes and disseminates throughout the body, specifically to the gut mucosa, viral load increases exponentially in the blood. Approximately 70–80% of mucosal infections are established by single variants. Adapted from Ende and Hunter (Ende et al. 2017)

are challenged repeatedly with low doses of SIV intra-vaginally or intra-rectally. Macaques challenged multiple times via the rectal route with a quasi-species of SIV_{mac251} or SIV_{smE660} were found, using the same SGA approach as in infected people, to be infected with a limited number of genetic variants—a majority with a single variant (Keele et al. 2009). The kinetics of virus replication in these animals resembled that observed in acutely infected people (Fiebig et al. 2003). A similar genetic bottleneck, with predominantly single variants establishing infection, was observed when macaques were challenged intra-vaginally or through the penile route, although both were significantly less efficient. Increasing the challenge dose via the intra-rectal route above 10^7 viral RNA copies resulted in infection being

established by multiple (>10) T/F variants, suggesting that in this model system the genetic bottleneck could be overcome by increasing the size of the input inoculum (Liu et al. 2010).

5 Evidence for Both Chance and Selection Influencing Transmission

The question of whether HIV-1 transmission is predominantly a stochastic process, where a single genetic variant establishes infection simply because of the low probability of transmission, has been the focus of much debate over the last several years. Alternatively, certain viral phenotypes, which confer enhanced transmissibility on a viral variant, could be selected for during transmission and systemic spread.

It is very clear that some aspects of the transmission process do involve chance: the genetic variant must be present in the genital fluid of the transmitting partner at the time of intercourse; it must interact with the genital or rectal mucosa; it must cross the epithelial barrier and infect a susceptible CD4⁺ T cell; and it must have a sufficient number of secondary target cells for infection to spread and establish a localized and then a systemic infection [Fig. 1; (Joseph et al. 2015)]. Despite these stochastic aspects of transmission, there is strong evidence that selection pressure is applied and that viruses with specific traits are selected for during the transmission process.

HIV-1 encodes two envelope (Env) glycoproteins gp41 and gp120 that form hetero-trimers on the surface of the virus, where three molecules of the membrane-spanning gp41 anchor an equivalent number of gp120 molecules, through non-covalent associations, in the viral membrane (Hunter 1997). Initially synthesized as a single precursor gp160, which is proteolytically cleaved during transport to the cell surface, these two glycoproteins are critical for viral entry into a target cell. The surface protein, gp120, contains the receptor binding domains, interacting first with CD4 molecules that are expressed primarily on a subset of T cells, CD4⁺ T cells, and macrophages. CD4 binding induces a conformational change in the trimer, leading to interaction with a co-receptor and further conformational changes that allow gp41 to mediate fusion of the viral and target cell membranes (Wilens et al. 2012). Most viruses utilize the chemokine receptor, CCR5 (Deng et al. 1996; Choe et al. 1996; Dragic et al. 1996; Berger et al. 1999; Feng et al. 1996; Alkhatib et al. 1996), as their co-receptor but during chronic infection viruses can evolve to utilize a second chemokine receptor, CXCR4 (Coetzer et al. 2008; Regoes and Bonhoeffer 2005).

Initial evidence for selection came from the finding that the bulk of newly transmitted viruses utilized the CCR5 co-receptor, even if CXCR4 viruses were present in the transmitting partner, providing the first evidence that CXCR4 tropic viruses were selected against, while CCR5 tropic viruses were selected for, in transmission. The discovery that persons at high risk of HIV-1 infection and homozygous for a deletion of 32 amino acids in their CCR5 gene were protected from acquiring HIV-1 by mucosal exposure, provided further evidence that CXCR4

viruses were selected against during HIV-1 transmission and that predominantly CCR5-tropic viruses could infect by this route (Liu et al. 1996; Dean et al. 1996; Zimmerman et al. 1997; Samson et al. 1996; Michael et al. 1997). The propensity for CCR5-tropism remains unexplained (Margolis and Shattock 2006), but could be due to target cell availability at portals of entry (Liu et al. 2014). This would be consistent with the observation that CCR5⁺CXCR4⁺ CD4⁺ T cells are a minor population (<25%) in both the epidermis and dermis of inner and outer foreskin compared to CCR5⁺CXCR4⁻ and CCR5⁺CXCR4⁺ CD4⁺ T cells (Liu et al. 2014), and that CCR5 expression is high on the surface of human vaginal epithelial CD4⁺ T cells (Hladik et al. 2007). It is also consistent with observations in monkey challenge studies, where the number of CCR5⁺ T target cells in the mucosa correlated with susceptibility to infection (Pandrea et al. 2008; Pandrea and Apetrei 2010).

The concept of selection during transmission has also been supported by phylogenetic analyses of HIV-1 sequences from heterosexual transmission pairs, which suggest that evolution during chronic infection may reduce transmissibility of the virus and favor transmission of earlier less-evolved variants from the transmitting partner. By calculating evolutionary distances of recipient and donor Env sequences to their most recent common ancestor for 10 subtype D and 10 subtype A linked transmission pairs, Sagar et al. provided the initial evidence that newly infecting (recipient) viruses were evolutionarily closer to the most recent common ancestor (MRCA) than transmitting partner (donor) viruses (Sagar et al. 2009). Consistent with the concept of transmission of less-evolved viruses, intra-host diversity was found to be greater than inter-host diversity in two separate cohorts infected with subtypes A or D and B (Redd et al. 2012; Alizon and Fraser 2013). Moreover, a longitudinal analysis of the *env* gene of viruses from donors prior to transmission, also found that the virus that established infection in the recipient more closely resembled earlier viruses in the donor than the viruses circulating at the time of transmission (Redd et al. 2012).

These observations have been supported by a more recent study that included genes outside of *env*. In an analysis of 137 epidemiologically linked clade C heterosexual transmission pairs, Carlson et al. demonstrated a selection bias in favor of cohort consensus amino acid residues and against non-consensus polymorphisms in Gag, Pol and Nef, suggesting a transmission advantage for variants with consensus amino acid residues in proteins outside of Env (Carlson et al. 2014). This was particularly obvious following deep sequencing of the donor quasi-species and the newly infecting viruses from five transmission pairs. As shown in Fig. 2, the transmission efficiency of non-consensus polymorphisms was reduced by approximately 20% compared to consensus amino acids for residues present at both high and low frequencies in the donor virus population. Non-consensus polymorphisms were predicted to reduce the structural stability of viral proteins, consistent with reduced in vivo replicative fitness in their presence. The selection pressure for consensus residues was influenced by gender, with female to male transmission imposing a greater selection bias on the virus than male to female transmission, suggesting that women are infected with less fit viruses than men. Interestingly, selection bias was reduced in men with genital ulcers and inflammation (GUI) and

when the donor partner exhibited high viral load (Carlson et al. 2014). Both factors are known to increase the risk of infection and number of genetic variants transmitted (see above), demonstrating the interplay between factors that influence general susceptibility and stringency of the genetic bottleneck. Preferential transmission of viruses closer to consensus was confirmed over the full genome in the same cohort with six transmission pairs using SGA (Deymier et al. 2015). These findings suggest that diversification and adaptation to immune responses, which occur in the virus population during chronic infection, may hinder its ability to transmit. It is possible, therefore, that if a T/F virus establishes infection and remains in a reservoir that is produced sporadically or has a slow turnover rate, then these viruses over time will be present as minor variants in the host and will also retain the characteristics necessary to transmit again. Recent studies in the Amsterdam cohort, where the phylogenetic relationship of proviruses present in the viral reservoir following suppressive anti-retroviral treatment to viruses from several time points prior to treatment, are consistent with this hypothesis. In several individuals, viral reservoir sequences were PCR amplified that were highly related to viruses observed in acute/early infection, although in each case they were a minority of the population (Brodin et al. 2016).

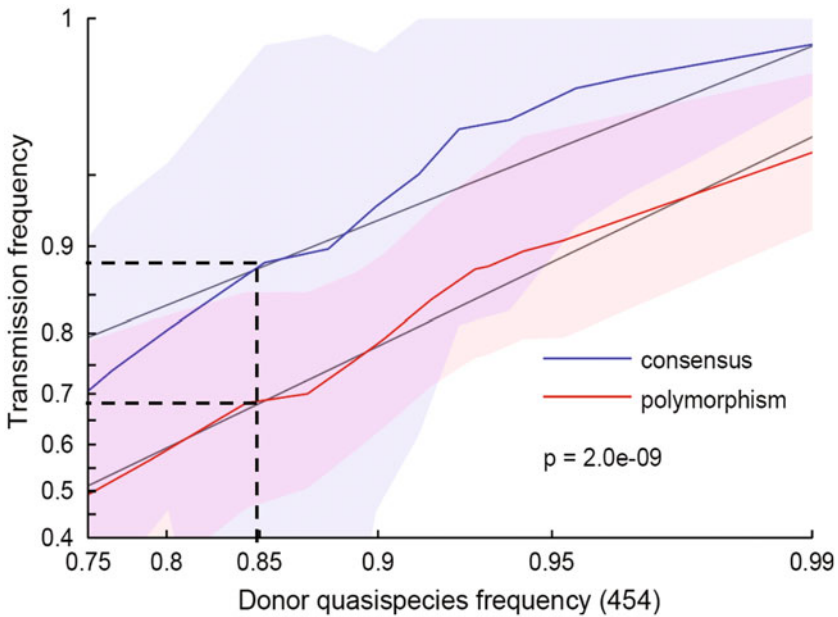


Fig. 2 Selection bias in heterosexual HIV-1 transmission. The odds that the transmitting partner's amino acid will be transmitted to the recipient is a function of the relative frequency of the amino acid in the donor virus quasi-species. The plot shows the empirical transmission probability (odds on a log10 scale) of a variant as a function of the relative in vivo frequency of the variant in the donor quasi-species, with a near 1-to-1 mapping for variants that match cohort consensus. In contrast, polymorphisms are uniformly less likely to be transmitted. Adapted from (Carlson et al. 2014)

Some of the first observations of a genetic bottleneck suggested that transmitted viruses were minor variants of the donor's plasma. In one of the initial studies that compared viral genetic diversity within and between partners in transmission pairs by analyzing virus from plasma, seminal fluid and seminal cells, the transmitted virus could be identified in both cell-free and cell-associated forms in the donor genital tract, and it was generally a minor variant of the genital tract (Zhu et al. 1996). A more recent analysis utilizing SGA of the V1–V4 region of Env from genital tract and plasma samples of eight subtype C infected heterosexual transmission pairs reported very similar results. It showed that, despite significant compartmentalization of viral genotypes with discrete populations within the genital compartment, the virus in the donor that most closely resembled the T/F was a minor variant, either of the genital tract or the plasma (Boeras et al. 2011). While genital tract enriched populations may be transient, and virus populations cannot be sampled precisely at the time of transmission (Anderson et al. 2010; Boeras et al. 2011), both studies do provide additional evidence in favor of HIV-1 selection during transmission.

6 Properties of the Transmitted/Founder Virus

Evidence of the genetic bottleneck and of selection during sexual transmission of HIV-1 has stimulated efforts to define biological characteristics of T/F viruses that could favor their transmission over a majority of the viruses that are circulating in the transmitting partner's quasi-species. To date, other than CCR5 tropism, no single trait has been consistently identified across the different studies and cohorts reported. In some respects, this could reflect the differences in the cohorts under study (e.g., MSM vs. heterosexual), as well as the stringency of the barriers to infection the virus must face (e.g., in the absence or presence of inflammation). Nevertheless, a number of properties have been linked to transmissibility and, while these have been addressed in recent reviews (Joseph et al. 2015; Ende et al. 2017, in press), will be summarized briefly here.

Co-receptor utilization: The observation that CCR5-tropic viruses are preferentially transmitted has been reproduced in most studies, including those where discrete T/F virus envelopes and full-length viruses were examined (Baalwa et al. 2013; Isaacman-Beck et al. 2009; Keele et al. 2008; Long et al. 2002; Parrish et al. 2013); however, this is not invariant, and infrequent CXCR4-tropic or dual-tropic transmitted strains have been observed. Although macrophages were once considered potential Trojan horses for carrying HIV-1 across the mucosa, it should be noted that T/F viral Envs mediate inefficient infection of macrophages and show a requirement for high levels of both CD4 and CCR5, with no evidence for preferential use of alternate coreceptors (Keele et al. 2008; Sagar et al. 2009; Salazar-Gonzalez et al. 2009; Isaacman-Beck et al. 2009; Alexander et al. 2010). These studies argue that neither infection of macrophages nor alternate coreceptor usage is advantageous for HIV-1 transmission.

Variable loop size and neutralization sensitivity: A major clue that transmission might select for traits other than co-receptor usage came from a comparison of the viral Env sequences from both partners of seven subtype C and one subtype G HIV-1 transmission pairs. It was found that within each pair, whether male-to-female or female-to-male, the newly transmitted viruses encoded statistically shorter, less glycosylated V1–V4 regions than their chronic counterparts (Derdeyn et al. 2004), raising the possibility that more compact envelope glycoproteins better interacted with critical target cells in the genital mucosa. The observation was confirmed using SGA in an additional 10 subtype C transmission pairs (Haaland et al. 2009). While similar results were obtained in studies of subtype A infected sex-workers in Kenya and subtype D and A transmission pairs from the Rakai district of Uganda (Chohan et al. 2005; Sagar et al. 2009), they have not been seen in most studies of recently transmitted subtype B HIV-1 (Chohan et al. 2005; Frost et al. 2005; Wilen et al. 2011). However, in a study comparing the SGA-derived Env sequences from 135 acutely infected and 140 chronically clade B HIV-infected individuals, statistically fewer N-linked glycosylation (PNLG) sites were found in the gp120s from early infection, with a trend toward fewer PNLG in the V1V2 loops and reduced V4 lengths (Gnanakaran et al. 2011).

An analysis of neutralization of subtype C heterosexually transmitted viruses demonstrated modestly increased sensitivity to antibodies in linked donor plasma taken near the time of transmission (Derdeyn et al. 2004; Deymier et al. 2015), though not to broadly neutralizing antibodies (Parrish et al. 2012) or pooled plasma (Derdeyn et al. 2004). It is possible that bound antibodies could enhance infection through capture by dendritic cell via Fc receptors in the mucosa of the new host, as has been reported for infected volunteers in the VAX004 vaccine trial, but this has not been demonstrated in non-vaccinated populations (Forthal et al. 2012). It is likely that donor antibody sensitivity reflects a surrogate marker of a different phenotype, such as mutational escape away from consensus, which in a recent study inversely correlated with donor antibody sensitivity over six subtype C transmission pairs (Deymier et al. 2015).

Interactions with the integrin $\alpha 4\beta 7$: CD4⁺ T cells expressing $\alpha 4\beta 7$ home to mucosal sites, including the genital and gastrointestinal tract (Hawkins et al. 2000), and are highly susceptible to HIV-1 infection (Cicala et al. 2009). This susceptibility is likely facilitated by HIV-1 gp120 binding to $\alpha 4\beta 7$ via a motif in the second variable region, V2 (Arthos et al. 2008). A comparison of Envs from early in infection to later isolates from the same individual showed early high-affinity binding to $\alpha 4\beta 7$ that was lost over time. This appeared in part to be due to the absence of glycosylation at specific sites in V1 and V2 since mutation of these sites in the chronic envelopes increased $\alpha 4\beta 7$ binding (Nawaz et al. 2011). In addition, an analysis of viruses from the CAPRISA acute infection cohort from South Africa showed that dependence on $\alpha 4\beta 7$ for in vitro replication was high for T/F Env chimeras, particularly those encoding a P/SDI/V tri-peptide binding motif in the V2 region of gp120. This dependence on $\alpha 4\beta 7$ was lost during the first two months of infection, but regained at 39 months post infection for three individuals followed longitudinally (Richardson et al. 2015). An earlier comparison of subtype C T/F

and chronic viruses had not observed differential inhibition of infection by a blocking antibody to $\alpha 4\beta 7$ (Parrish et al. 2012); however, dissecting inhibition from antibody binding activation of cells has complicated the interpretation of this data.

Despite the mixed results of in vitro studies, administering a blocking antibody to $\alpha 4\beta 7$ prior to SIV challenge in rhesus macaques decreased the number of animals infected and increased the number of challenges for infection to occur. Moreover, treated but infected animals showed a significant reduction in $CD4^+$ T cells loss in gut-associated lymphoid tissue (GALT) and evidence for limited trafficking of infection out of the genital mucosa (Byrareddy et al. 2014). Thus viruses with enhanced $\alpha 4\beta 7$ affinity may possess increased transmissibility through the increased efficiency by which virus-infected cells are trafficked to the GALT.

Sensitivity to type I interferons: The innate immune response, in particular the production of type I interferons (IFN), is very important in a number of viral infections including lentiviruses (Doyle et al. 2015). Treatment of rhesus macaques with IFN $\alpha 2$ increased the number of challenges required to establish systemic SIV_{mac} (Sandler et al. 2014) and SHIV infection (Veazey et al. 2016). However, while IFNs are upregulated in the early stages of SIV infection in macaques (Abel et al. 2005), a recent large study of acute infection found that prior to day 10, when plasma viremia was apparent, SIV_{mac239} down-regulated the IFN response in cells it infected and instead stimulated an inflammasome response (Barouch et al. 2016).

Nevertheless, a number of recent papers have presented evidence that T/F variants are relatively resistant to IFN compared to viruses from chronic infection (Parrish et al. 2013; Foster et al. 2016; Iyer et al. 2017), although in a large study comparing T/F and chronic circulating viruses, subtype differences were observed. In this study, where subtype B T/F infectious molecular clones (IMCs) were less susceptible to IFN α , subtype C T/F, and chronic variants exhibited similar sensitivity to interferon (Parrish et al. 2013). In contrast, in a comparison of subtype B and C T/F variants and their matched 6-month post-infection and chronic infection counterparts, the T/F isolates were found to be more resistant to IFN α (Fenton-May et al. 2013). A specific restriction factor associated with co-receptor usage, IFN-induced transmembrane protein 1 (IFITM1), determined the resistance phenotype of the T/F and 6-month virus pairs (Foster et al. 2016), though VPU-tetherin interactions have also been implicated as major determinants of resistance for some of these variants (Kmieć et al. 2016). Both interferon-induced restriction factors IFITM1 and tetherin act at the plasma membrane and interact with the viral Env, which has been associated with IFN resistance in an investigation of SHIVs passaged in rhesus macaque cells in vitro (Boyd et al. 2016). In addition, a recent comparison of viral outgrowth isolates from eight transmission pairs, where the transmitting partner had viral loads exceeding 1×10^5 copies/ml, showed that all of the isolates from acute plasma were more resistant to both IFN α and IFN β than those from the transmitting partner (Iyer et al. 2017).

However, not all studies have reported results consistent with these most recent observations. In an analysis of six subtype C transmission pairs, where IMCs representing the T/F virus from the newly infected partner and representative viruses from the transmitting partner were generated, replicative capacity (RC) was

found to be positively associated with IFN α inhibition of replication, and a comparison of viruses matched for RC showed no consistent evidence of enhanced interferon resistance for T/F variants (Deymier et al. 2015). Furthermore, in an independent study, T/F isolates from 9 subtype B transmission pairs showed greater rather reduced sensitivity to IFN (Oberle et al. 2016), as did acute Env chimeras derived from 7 acute subtype B IDU infections when compared to chronic controls (Etemad et al. 2014). The conflicting results may stem from differences in the subjects under study, or the approaches taken to isolate infectious virus and assess IFN resistance. Additional studies where viruses from different HIV-1 subtypes and derived from both partners of transmission pairs very near the time of transmission are investigated will be critical to resolving the differences currently observed. Given the known impact of genital inflammation and ulcers in the uninfected partner, and VL in the chronically infected partner, on susceptibility to infection and the genetic bottleneck, it is likely these factors will need to be taken into account when comparing studies.

Infectivity and Replicative Capacity: One of the most compelling hypotheses regarding HIV transmission proposes that T/F variants replicate faster than other variants, granting a competitive advantage during the initial events of viral growth and dissemination (Shaw and Hunter 2012). This would also be compatible with the selection bias for consensus amino acid residues, which are predicted to increase structural stability and presumably function of the Gag and Pol proteins (Carlson et al. 2014). In general, studies have compared both infectivity and replication, in single and multi-round infection assays, respectively. Evidence that transmitted variants have enhanced infectivity is inconsistent and varies between cohorts and studies (Parrish et al. 2013; Selhorst et al. 2017b; Deymier et al. 2014; Oberle et al. 2016; Iyer et al. 2017), but is generally quite subtle (2-3fold) when it has been observed. Interestingly, an analysis of virus isolates and Env pseudoviruses from the CAPRISA 004 tenofovir gel trial showed that variants transmitted to women with genital inflammation were less infectious (Selhorst et al. 2017b). Genital ulceration and inflammation are known to increase the number of transmitting variants (Haaland et al. 2009) and decrease selection pressure (Carlson et al. 2014), consistent with this observation. For subtype B and C Env-pseudotyped (Isaacman-Beck et al. 2009; Oberle et al. 2016) and subtype B and C full-length (Parrish et al. 2013; Deymier et al. 2015; Yue et al. 2015; Ochsenbauer et al. 2012; Salazar-Gonzalez et al. 2009; Oberle et al. 2016) T/F variants, a 50–100-fold range of infectivity was found, similar to that seen in the non-transmitted variants. Chimeric viruses containing Gag from acute and early time points from subtype B (Brockman et al. 2010) and subtype C (Wright et al. 2010; Prince et al. 2012; Claiborne et al. 2015) strains also exhibited a broad range of RCs, which correlated well with those of IMCs derived from the same patients (Claiborne et al. 2015), suggesting that variants with relatively low and high RC in vitro have the potential to transmit. Similarly, most studies have not demonstrated a replicative advantage for transmitted variants measured in multiple round infections in vitro, instead showing transmission of viral variants with a range of RCs (Parrish et al. 2013; Deymier et al. 2015; Yue et al. 2015; Ochsenbauer et al. 2012; Salazar-Gonzalez

et al. 2009; Oberle et al. 2016). Although, a recent study of eight subtype B and C transmission pairs did find that early isolates replicated somewhat (1.4-fold) higher than variants from matched donor partners (Iyer et al. 2017). Nevertheless, current data suggest that, in order to establish infection, the range of infectivity and RC, at least as measured in vitro, can be broad. However, as we will discuss below, the in vitro RC of the T/F virus can have a profound impact on both early pathogenesis and long-term trajectory of disease.

7 A Complex Interplay Between Host Immunity and Transmitted Virus Phenotype Defines Viral Control and Disease Progression

It is clear that traits of the transmitted virus influence the course of the disease. Despite human immunogenetic variability, high viral mutation rates leading to adaptation, and a restrictive genetic bottleneck during transmission, VL set-point in the donor correlates with that in the infected partner, although it is significantly modulated by the sex and immune response genes of the newly infected individual (Hecht et al. 2010; Yue et al. 2013). The heritability of VL suggests that disease progression itself can have a heritable component (Fraser et al. 2014) since VL is a strong predictor of disease progression (Mellors et al. 1995).

As we discuss in more detail below, the cellular immune response of a newly infected individual, programmed by their human leukocyte antigen (HLA) class I alleles, imposes selection pressures on the virus that result in the outgrowth of viruses with mutations in the controlling epitopes. The impact of these mutations on the T/F virus following transmission is complex. If these mutations are in epitopes normally recognized by the newly infected individuals class I alleles, they can reduce the ability of the immune system to control the replication of the virus and, therefore, result in enhanced disease progression (Carlson et al. 2016; Crawford et al. 2009; Monaco et al. 2016). On the other hand, although beneficial for the survival and propagation of the virus in the chronically infected partner, these mutations can negatively impact the replicative fitness of the virus when it is transmitted to an individual that does not share HLA-I alleles that recognize the epitope (Brockman et al. 2010; Chopera et al. 2008; Goepfert et al. 2008). The remainder of this review will discuss this complex interaction between the transmitted virus and its new host.

Host Control of Virus Replication: The cellular immune response plays a central role in controlling HIV-1 viral replication. In humans, the most compelling evidence in favor of this role comes from the consistent observation of a temporal association between the rapid decline in viremia during acute infection and the increase in numbers of HIV-specific cytotoxic T lymphocytes (CTLs) in the blood (Koup et al. 1994; Borrow et al. 1994). Studies in a nonhuman primate model of SIV or SHIV infection have provided the most direct evidence by depleting CD8⁺ T

cells at different stages of infection. During acute infection, transient depletion of CD8⁺ T cells leads to increased plasma and cell-associated virus levels in both the peripheral blood and lymphoid tissues along with prolonged depletion of CD4⁺ T cells and accelerated disease progression (Matano et al. 1998; Schmitz et al. 1999). Similarly, depletion of CD8⁺ T cells during chronic infection results in a rapid increase in viremia that is again suppressed with the reappearance of SIV-specific CD8⁺ T cells (Schmitz et al. 1999; Jin et al. 1999). More recently, the role of CTLs in controlling viremia has also been demonstrated even in the presence of antiretroviral treatment (ART). Depletion of CD8⁺ cells during ART significantly increased plasma VL and reconstitution of these cells was associated with re-establishment of viral control, providing a rationale for the administration of therapeutic vaccines in conjunction with ART (Cartwright et al. 2016).

Selection of CTL escape mutations: The changes in viremia associated with the presence or expansion of HIV-specific CTLs shows that these cells exert immunologic pressure on the virus, though they are still unable to clear or completely control the infection in the majority of infected individuals. A clear manifestation of this immunologic pressure is the appearance of escape mutations. These mutations have been identified both in acute and chronic infection and in all HIV-1 proteins, including accessory proteins, which indicates that the CTLs are constantly and widely targeting the virus during HIV-1 infection (Borrow et al. 1997; Goulder et al. 1997).

CTL escape mutations are thus able to release the pressure exerted by HIV-specific CTLs, and function at three different stages during the process of antigen presentation. First, these mutations can prevent the processing of the protein via the proteasome, abrogating the generation of the epitope before being loaded onto the HLA Class I molecule. Second, CTL escape mutations can compromise the loading of the HLA Class I molecule, which occurs in the endoplasmic reticulum before the loaded complex travels to the cell surface, by reducing its binding affinity for the epitope (Yokomaku et al. 2004). Finally, these mutations can reduce or prevent the interaction of the T Cell Receptor (TCR) with the HLA Class I-epitope complex (Iglesias et al. 2011).

While initial studies focused on mutations identified by subsequent increases in viremia in individuals harboring a particular HLA-I allele, CTL escape mutations have been identified more recently in population analyses using statistical methods. This approach is able to identify HIV-1 polymorphisms that are significantly more prevalent in individuals harboring a particular HLA-I allele, while at the same time correcting for covarying sites, linkage disequilibrium among HLA-I alleles, and mutations that could have arisen during the evolutionary history of the virus instead of in response to HLA-mediated immune pressure (Bhattacharya et al. 2007; Carlson et al. 2008).

Impact of CTL escape mutations on chronic and acute HIV-1 infection: CTL escape mutations are rapidly selected after the cytotoxic immune response is mounted (Fischer et al. 2010; Henn et al. 2012), and the time in which these mutations arise has been shown to be much faster in response to protective HLA alleles such as HLA B*57 or HLA B*27 (Roberts et al. 2015). Although these

mutations confer a fitness advantage to the virus by preventing CTLs from targeting infected cells, they usually carry a significant replicative fitness cost (Martinez-Picado et al. 2006). However, because HIV-1 is a chronic disease, with continued virus replication, secondary or compensatory mutations frequently arise that reduce the impact of CTL escape mutations on replication, and allows for their maintenance (Brockman et al. 2007; Schneidewind et al. 2007).

Direct evidence for an impact on HIV-1 disease following transmission of CTL escape mutations has come from mother-to-child transmission (Goulder et al. 2001) as well as from serodiscordant couples (Goepfert et al. 2008; Crawford et al. 2009; Monaco et al. 2016; Carlson et al. 2016). In both cases, the viral quasi-species present in the donor at the time of transmission can be studied in order to distinguish transmitted mutations from those that arise early in the newly infected individual. Even though HLA B*27 and HLA B*57 are generally associated with protection against disease progression in HIV-infected individuals (Kaslow et al. 1996; Fellay et al. 2007; Kiepiela et al. 2007; Schneidewind et al. 2007), these earlier studies showed that transmitted CTL escape mutations, and the pre-adapted epitopes associated with these alleles, are linked to rapid loss of control of viral replication and accelerated disease progression in HLA-matched individuals (Goulder et al. 2001; Crawford et al. 2009). These findings highlighted the fact that, when transmitted to HLA-matched individuals, CTL escape mutations abrogate protection against disease progression.

Population studies of the prevalence of CTL escape mutations indicate that these mutations are accumulating both over time (Cotton et al. 2014; Dilemnia et al. 2008) and in relation to HLA allele prevalence (Kawashima et al. 2009). This phenomenon can lead to the circulation of viruses that are potentially already adapted to the HLA alleles in the HIV-1 negative population. While a study of the North American epidemic did not observe significant adaptation over time in circulating viruses over 20 years, this could have been related to the high HLA diversity and low genetic frequency of each allele in this population (Cotton et al. 2014). Since transmission of pre-adapted viruses compromises the ability of the CTL immune response to target these viruses in the newly infected individual, this raises the possibility that pre-adaptation of the T/F virus could have a significant impact on both viral control and disease progression.

This question was answered in recent studies of epidemiologically linked HIV-1 transmission pairs from a Zambian acute infection cohort, where the degree of preadaptation of the transmitted viruses was accurately estimated by focusing on polymorphisms present both in the donor and in the recipient. These polymorphisms were located both in positions statistically linked to the HLA alleles of the recipient and also in epitopes with a higher predicted HLA-I binding affinity. This analysis showed that approximately one-third of possible HLA-linked target sites were already adapted in T/F viruses and that this pre-adaptation compromised early immune recognition of the transmitted virus. Evaluation of CTL responses against adapted (meaning harboring HLA-linked mutations) and nonadapted epitopes across the entire Gag protein according to each individual's HLA alleles showed that adapted epitopes were significantly less recognized than nonadapted epitopes

and, in the cases where an IFN- γ response was detected, it was of a lower magnitude. Moreover, in individuals that were infected with viruses where 50% of the HLA-linked target sites were pre-adapted, significantly fewer and less potent IFN- γ responses were elicited (Monaco et al. 2016). A parallel study, in which Carlson and colleagues used a mathematical model to estimate autologous adaptation of the transmitted virus, showed that CTLs targeting adapted epitopes had reduced antigen sensitivity and killing capacity when compared to those targeting nonadapted epitopes in both structural and accessory proteins (Carlson et al. 2016).

The degree of pre-adaptation in the Gag protein of a transmitted virus was also associated with higher viral loads and faster decline of CD4⁺ T cells (Monaco et al. 2016), and this association was also true when the analysis was extended to Gag, Pol and Nef proteins (Carlson et al. 2016). However, this association with VL was stronger after accounting for polymorphisms that were not linked to the HLA molecules of the newly infected individual (nonassociated polymorphisms), which conversely associated with lower VL and slower decline of CD4⁺ T cells. These results illustrate how HIV-1 disease progression is ultimately dictated by the balance between the two opposing forces of transmitted pre-adaptation, which determines the number and quality of epitopes effectively targeted—both initially and subsequently during the course of infection—and nonassociated polymorphisms, which likely lead to reduced viral replicative fitness (Monaco et al. 2016) (Fig. 3).

Importantly, the role of pre-adaptation and transmitted nonassociated polymorphisms on viral control and disease progression remained significant in the context of other factors known to influence clinical outcomes. In the case of disease

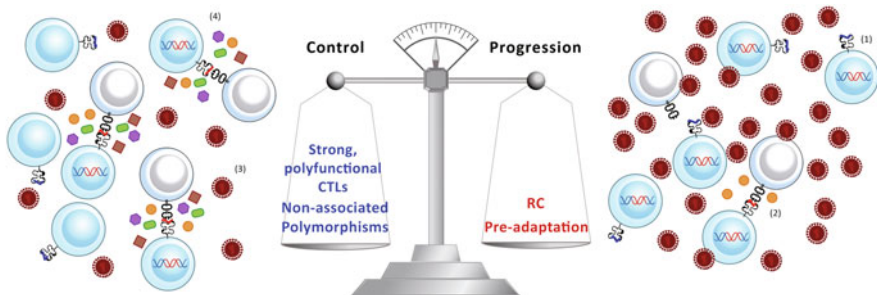


Fig. 3 The balance between transmitted viral characteristics and early CTL immune responses determines disease progression. High pre-adaptation and RC of the transmitted virus will tip the scale in favor of rapid disease progression. Pre-adaptation leads to impaired cytotoxic immune responses since the transmitted escape mutations prevent HLA molecules from presenting HIV epitopes (1) or lead to the presentation of epitopes that are poorly recognized by the TCR on the CTLs (2). High replication contributes with larger viral loads and proportions of infected cells, including the subsets associated with latency. On the other hand, large numbers of nonassociated polymorphisms and strong, poly-functional cytotoxic immune responses tip the scale in favor of slow disease progression or control. These polymorphisms impair virus replication (3) but may as well negatively impact innate immune responses while the activity of strong, poly-functional CTLs contributes to reducing viral load (4)

progression, a ratio between pre-adaptation and transmitted nonassociated polymorphisms was the strongest predictor of decline of CD4⁺ T cells, followed by set-point VL and RC. The impact of pre-adaptation may reflect the reduced capacity of the immune system to target the virus both early in infection as well as late in infection, as the virus continues to adapt.

Taken together, these recent studies have significant implications for vaccine development. Immunogens harboring escape mutations may not be able to effectively prime an immune response. On the other hand, efficiently primed responses targeting epitopes where CTL escape mutations are frequently transmitted in a population may be less able to control those pre-adapted viruses. In this context, the use of immunogens that focus on inducing CTLs against conserved regions of the HIV-1 proteome where selection and transmission of CTL escape mutations are less frequent could help overcome these challenges.

Impact of immune selection on replicative capacity and subsequent disease progression: In contrast to the disease-enhancing effects of CTL escape mutations that represent preadaptation in the new host, CTL escape mutations transmitted to HLA mismatched individuals show the opposite effect by providing an advantage for the newly infected individual that is associated with a loss of replicative fitness. The fact that these detrimental mutations usually revert or are compensated for shortly after transmission is consistent with their impact on virus replication since natural selection favors viruses with higher replicative fitness (Crawford et al. 2007; Leslie et al. 2004; Schneidewind et al. 2009).

Since the most protective HLA alleles, HLA B*57 and B*27, target epitopes in the p24 capsid protein of HIV-1, initial studies focused on the impact of escape mutations in this region of the viral proteome on virus replication. Brockman et al. demonstrated that an escape mutation located in the B*57 TW10 epitope in Gag, T₂₄₂N, reduced replicative capacity of NL4-3 but this defect could be partially compensated by mutations at a second site in p24 (Brockman et al. 2007). Similarly, Crawford et al. demonstrated that the A₁₆₃G escape mutation in the B*5703 KF11 epitope in Gag impaired replication but could be effectively compensated by an accompanying S₁₆₅N mutation. In each case, individuals with mutations that compensated for the replication defect exhibited higher viral loads than those harboring just the escape mutation itself, correlating in vitro replication to in vivo levels of virus. Consistent with this, the in vitro RC of chimeric NL4-3 viruses encoding the *gag* gene (and a small region of protease) of viruses derived from individuals exhibiting elite control of VL was significantly lower than that of viruses derived from chronic progressors (Miura et al. 2009; Miura et al. 2010). In a large study of over 800 subtype B chronically infected individuals for whom Gag-Pro chimeras were constructed, a modest positive correlation was observed between RC and VL, while a negative correlation was observed between RC and CD4⁺ T cell count, consistent with RC influencing CD4⁺ T cell decline (Brockman et al. 2010). Similar results were observed in a South African subtype C cohort (Wright et al. 2010).

In two studies of subtype C acutely infected individuals, higher numbers of transmitted CTL escape mutations in Gag, but not in Nef, were associated with

lower VLs and higher CD4⁺ T cell counts in the newly infected HLA-mismatched recipient (Goepfert et al. 2008; Chopera et al. 2008). These data suggested that transmission of CTL escape mutations in the *gag* gene of the T/F virus might impact both viral control and disease progression through reduced RC. In an initial study of over 100 acutely infected Zambians, the RC conferred by transmitted subtype C *gag* sequences was moderately correlated with set-point VL. Moreover, individuals harboring low RC viruses exhibited significantly slower CD4⁺ T cell decline during the first three years after transmission compared to those harboring high RC viruses (Prince et al. 2012). Studies with similarly constructed Gag-Pro chimeric viruses derived from recently infected individuals in South Africa also showed a trend toward more rapid CD4⁺ T cell decline for high RC viruses (Wright et al. 2011).

A follow-up study also in acutely infected Zambians showed that RC of the transmitted variants predicted CD4 decline independently of other risk factors, such as VL and protective HLA alleles (Claiborne et al. 2015), a finding also confirmed in samples from the CAPRISA 004 trial (Selhorst et al. 2017a). The RCs of the Gag-Pro chimeric viruses studied correlated well with those of IMCs derived from the same patients (Claiborne et al. 2015). Infection with a high RC virus was associated with profound changes in immune function compared to infection with a low RC virus. For high RC viruses, high levels of inflammatory cytokines and markers of bacterial translocation were observed very early (~45 days after the estimated date of HIV-1 infection), as were activation/proliferation markers (CD38, HLA-DR, Ki-67) and markers of T-cell dysfunction (PD-1) in both CD4⁺ and CD8⁺ T cell populations. In addition, elevated levels of HIV-1 proviral DNA were observed in naïve and central memory CD4⁺ T cells. All of these features appeared to contribute to more rapid disease progression (Claiborne et al. 2015), indicating that the replication phenotype of the T/F virus can have a profound impact on the earliest virus-host interactions that then define the trajectory of disease.

8 Conclusions

The past several years have seen significant progress in understanding the virology of both HIV-1 transmission and subsequent disease progression. It is established that in most instances of HIV-1 sexual transmission, a single T/F variant, or a limited number of variants, from the diverse quasi-species present in the transmitting partner, establishes systemic infection. What is less clear, in the context of the level of virus exposure common during sexual activity, is how many variants initiate localized replication, and how many of those may fail to propagate to more distal sites. Nor is it clear, given the different selection pressures in the presence and absence of mucosal infections and inflammation, for example, whether any one property, such as in vivo RC or reduced sensitivity to IFN, will set apart T/F viruses from their non-transmitted counterparts. Clearly, based on the spectrum of in vitro RC observed for T/F viruses, it seems likely that the bar for transmission can be

quite low. It will be interesting to observe whether in vivo models such as the humanized mouse or in vitro mucosal tissue explant models will shed additional light on viral properties that facilitate transmission.

While selective bias does result in the partial loss of non-consensus polymorphisms (mutations) during transmission, a majority (many of which represent immune response escape mutations) are present in the T/F variant. Those that impact virus replication in a negative fashion, and result in viruses with low RC, can be highly protective to the newly infected host in terms of disease progression, by inducing lower levels of inflammation and immune dysfunction. They also result in lower levels of proviral DNA in naïve and memory CD4⁺ T cells early in infection, which may mean smaller viral reservoirs post-ART and a greater opportunity for studies aimed at long-term remission (or cure). In contrast, mutations in epitopes that are normally targets for the immune response genes of the newly infected individual can have an opposite effect on disease progression by reducing immune recognition, target cell killing, and virus control. It is the balance of this complex interplay between the phenotype defined by viral genetics and host immunogenetics that ultimately defines the trajectory of HIV-1 disease in a newly infected individual, with the virus genotype playing a much greater role than previously envisaged.

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