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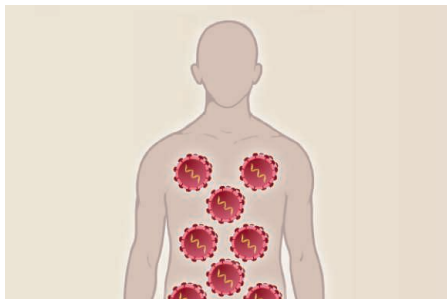
HIV genetics and heritability of virulence likely contribute to disease severity despite intense within-host selection.

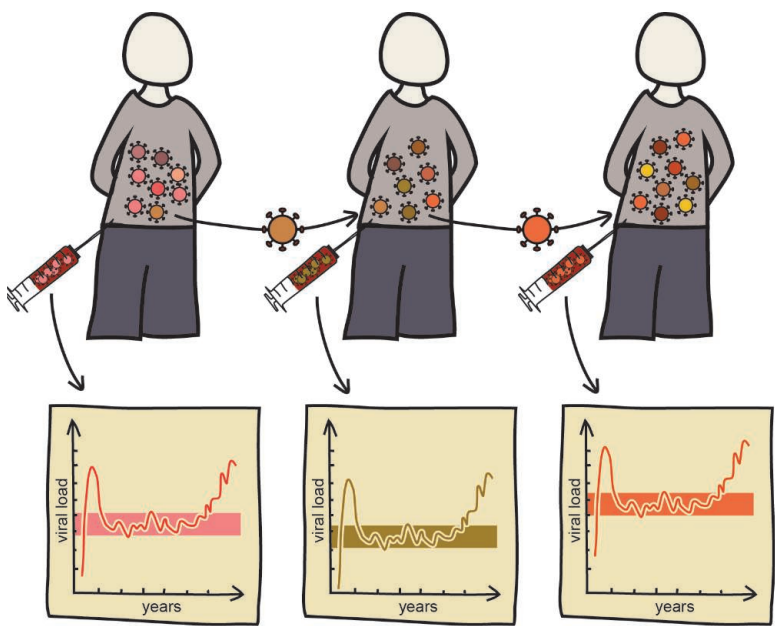


Virulence and Pathogenesis of HIV-1 Infection: An Evolutionary Perspective

Christophe Fraser,* Katrina Lythgoe, Gabriel E. Leventhal, George Shirreff, T. Déirdre Hollingsworth, Samuel Alizon, Sebastian Bonhoeffer

Background: Why some individuals develop AIDS rapidly whereas others remain healthy without treatment for many years remains a central question of HIV research. Of the quantities that predict how quickly an untreated infection progresses, the most widely used is set-point viral load. This measure varies by orders of magnitude between infected individuals and is predictive of infectiousness and time to onset of AIDS. Host factors, predominantly linked to the immune system, are known to influence the set point, but much variation remains unexplained.

Advances: We review recent evidence showing that HIV genotype influences the set point viral load far more than anticipated. Our summary of published estimates suggests that 33% (95% confidence interval, 20 to 46%) of the variation is attributable to the virus. Because set-point viral load is heritable (partially controlled by virus genotype) and is linked to transmissibility, it is likely to have evolved to maintain transmission fitness and may continue to evolve in response to diverse selection pressures. These findings are unexpected and paradoxical because rapid and error-prone viral replication should favor within-host adaptation and rapidly scramble signals of viral genotype as infection progresses, rather than leaving a lasting footprint that is preserved throughout an infection and from one infection to the next in transmission chains.



A transmission chain with heritable virulence. Individuals infected with HIV show differences in clinical progression. Untreated infections are characterized by viral loads (the viral particle density in the blood) that are relatively stable for years, but they can differ by orders of magnitude between individuals. Host factors clearly influence viral load, but viral loads have also recently been found to correlate among individuals in transmission pairs and chains. This indicates a moderate to strong influence of viral genotype on the viral load. Strikingly, this influence persists for years and across transmission events, despite intense within-host viral evolution.

Outlook: We propose that resolving the paradox of heritability of set-point viral load will provide new insights into the mechanisms of HIV pathogenesis. To this end, we provide three parsimonious, testable, and nonexclusive explanatory mechanisms. The first states that HIV evolution in virulence genes is more functionally constrained than previously thought. The second proposes that virulence of HIV is mediated through the virus's capacity to systemically activate target cells in which it can efficiently replicate. The capacity to activate would not be expected to evolve rapidly because it does not provide a specific selective advantage to virus strains that activate more cells; rather, it is an advantage shared by all viruses. The third mechanism implicates the preferential transmission of viruses that are stored in nonreplicating cells or during early infection, and the disproportionate influence on long-term pathogenesis of these early viruses.

In addition to these insights into mechanisms of pathogenesis, we believe that this research highlights a major gap in our knowledge of HIV. The identification of the genetic determinants of HIV virulence, which appear to vary between closely related strains of the virus, should be a major priority. Thus, whole-genome association studies that are focused on the virus genome should be pursued and expanded, as well as more functional and mechanistic studies, which could be guided by hypotheses such as those presented here.

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Virulence and Pathogenesis of HIV-1 Infection: An Evolutionary Perspective

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Why some individuals develop AIDS rapidly whereas others remain healthy without treatment for many years remains a central question of HIV research. An evolutionary perspective reveals an apparent conflict between two levels of selection on the virus. On the one hand, there is rapid evolution of the virus in the host, and on the other, new observations indicate the existence of virus factors that affect the virulence of infection whose influence persists over years in infected individuals and across transmission events. Here, we review recent evidence that shows that viral genetic factors play a larger role in modulating disease severity than anticipated. We propose conceptual models that reconcile adaptive evolution at both levels of selection. Evolutionary analysis provides new insight into HIV pathogenesis.

The past few years have seen impressive progress in HIV research, particularly in prevention, including the definition and characterization of broadly neutralizing antibodies for vaccine design (*1*), demonstration that antiretroviral treatment almost fully blocks transmission (*2*), and trials of preexposure prophylaxis that have met some success (*3*). Nevertheless, our understanding of pathogenesis—of why some patients progress to AIDS quickly in the absence of treatment, whereas others remain AIDS-free for many years—remains largely unknown (*4*). In this Review, we explore how evolutionary theory grants us a fresh perspective that leads to unexpected insights into HIV biology.

Viral load is the density of virus in someone's blood and by proxy in the rest of their body (*5*) and is relatively stable during asymptomatic infection, fluctuating around a value known as set-point viral load (SPVL) (Fig. 1A). A particularly important task in HIV pathogenesis research is to explain the orders-of-magnitude variation in SPVL. SPVL ranges from as low as <20 virions per milliliter of blood plasma up to 10^6 (Fig. 1B) (*5*–*7*) and correlates with virulence and infectiousness (Fig. 1C). Of the surrogate markers of infection severity, or virulence, SPVL is the most robust and widely used (*5*). Virulence is defined in untreated asymptomatic infection as the speed of progression from infection to AIDS, by which point $CD4^+$ T cells are depleted, immunity is exhausted, and disease becomes apparent.

To date, most research on explaining variation in SPVL has focused on host factors, and particularly on components of the human immune response. Genome-wide association studies (GWASs) have identified more than 300 single-nucleotide polymorphisms (SNPs) in human lymphocyte antigen (HLA)–Class I genes (which implicate the T cell response), and none elsewhere (*8*, *9*), thus confirming earlier findings in the area (*10*). Other non-SNP host-genetic modifiers of SPVL include the Δ-32 deletion in the CCR5 coreceptor (which reduces the ability of CCR5 tropic strains of the virus to infect cells) (*11*) and copy number variation in killer cell immunoglobulin-like receptor genes (which implicate the innate immune response) (*12*). Despite the groundbreaking nature of these studies, the total proportion of variance in SPVL explained by host factors is limited to ~13% (increasing to 22% when adding age and sex as explanatory variables) (*8*).

In parallel to this research, new data and analyses suggest that viral factors are as important as host factors, if not more so, in determining disease severity. Here, we review the evidence for the importance of viral factors, as quantified by heritability of SPVL (defined in Box 1 and below); discuss how an evolutionary perspective may help us identify these factors; and generate new insights into the mechanisms of HIV pathogenesis. We suggest that the influence of viral factors on SPVL, and consequently on disease severity, have frequently been underestimated.

Viral Virulence Factors

Heritability is defined as the proportion of variance in a phenotype that is attributable to the variation in the underlying genotype (*13*). For HIV-1 SPVL, it is defined as the proportion of variance in SPVL that is attributable to viral genetic factors, which we term viral virulence factors because they influence the severity of untreated infection. For an infection trait such as SPVL, heritability is closely related to (but not equivalent to) the relationship between the trait value in the transmitter (donor) host and in the recipient host within a transmission pair. The higher the heritability of SPVL, the more SPVL will be similar between the individuals in the transmission pair.

There is currently a controversy in the field concerning the magnitude of heritability of SPVL (*14*–*21*). At the high end, Alizon *et al*. (*2*) reported heritability estimates exceeding 50%. At the low end, Yue *et al*. (*19*) stated that an "analysis of 195 transmission pairs from Lusaka, Zambia revealed that viral load in the transmitting source partner contributed only 2% of the variance in seroconverter early set-point viral load (P = 0.046 by univariable analysis)." We demonstrate in (*22*) that this variation of an order of magnitude (2 to 50%) between these estimates does not arise from major differences between patient cohorts or any computational issues, but rather because these studies are reporting different quantities that are only indirectly related to heritability. Using a consistent framework, heritability of SPVL in heterosexual couples in sub-Saharan Africa is estimated to be 33% (95% confidence interval, 20 to 46%) and is similar across studies (Box 1). These reinterpreted estimates are also broadly consistent with the results of phylogenetic methods to estimate heritability of SPVL (*14*, *15*), although estimates obtained in this manner have been more dispersed.

Given the potential importance of viral genotype in determining SPVL, we find it surprising that we do not yet have a firm idea of what the virus virulence factors that affect SPVL are, the mechanisms by which they act, nor how they are preserved from one infection to the next despite potentially thousands of rounds of replication and ongoing evolution within the host. However, the two most likely candidates are viral genetic features that modulate the replicative capacity of the virus and those that influence its capacity to induce immune activation.

We consider the replicative capacity (RC) of the virus to be a likely correlate of viral virulence (*23*–*27*). RC is defined as the mean number of cells infected by a typical infected cell (directly or by viral production and infection) with plentiful access to target cells and in the absence of effective immune responses. In practice, although defined in vivo, it is usually measured in in vitro fitness assays in which by definition immune responses are absent. To study the clinical relevance of RC, Kouyos and colleagues predicted RCs from viral sequences based on a

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complex statistical model trained on many in vitro measurements and then demonstrated correlation with SPVL (*24*, *28*).

Another study reported that the main feature distinguishing "elite controllers" (individuals who do not progress to AIDS despite decades without treatment) was that they were infected by very unfit viruses, with low RC (*20*). It appears that the low fitness of the initial infecting viruses was the only factor the elite controllers had in common. Mutations found in some of the low-fitness viruses included drug-resistance mutations as well as escape mutations from HLA-B57 and homologs (HLA-B57 is one of the human genotypes most consistently associated with slow progression to AIDS). Escape mutations with low RC are likely to evolve within a host when the selection pressure exerted by the immune system is stronger than intrinsic selection for increasing RC. However, only 4 out of 20 elite controllers in (*26*) carried HLA-B57 genes or homologs, whereas 6 out of 20 acquired HLA-B57 escape mutations from their infectors. Another study showed that viral escape mutations from protective HLA reduce SPVL, not just in the patient carrying the protective HLA but also in those who are infected by these individuals and who do not harbor that particular HLA type (*29*). Even when these unfit viruses acquired compensatory mutations that increase RC during the course of an infection, an increase in viral load was not always observed (*26*). This latter finding, that later reversion of costly mutations present in early infection does not lead to increased viral load, can be explained if events taking place early in an infection are disproportionately important determinants of SPVL—that is, if it is initial infection with an unfit low RC virus, rather than maintaining this viral genotype during the whole course of infection, that results in a low SPVL.

The second category of viral virulence determinants that might influence viral load are factors inducing $CD4^+$ T cell activation because activation of CD4 cells is a prerequisite for rendering cells permissive to infection (*30*, *31*). Most prominently, *nef* (*32*) but also *vpr* (*33*), *tat* (*34*), and *env* (*35*) have been implicated in modulating T cell activation. Because $CD4^+$ T cell activation correlates with viral load (*36*), these viral genes may have an effect on viral load.

Trade-Offs and Population-Level Evolution of Virulence

Not only is viral load the most widely used prognostic indicator of disease progression, but it is also positively correlated with infectiousness (Fig. 1C) (*7*). This results in an evolutionary trade-off for the virus so that if there is a low SPVL, there will be more time for onward transmission before the host dies, but the probability of transmission per contact will be low. If a higher SPVL establishes, then there will less time for onward transmission, but the probability of transmission per contact will be higher. In the face of such a trade-off, natural selection should favor pathogen strains that maximize the

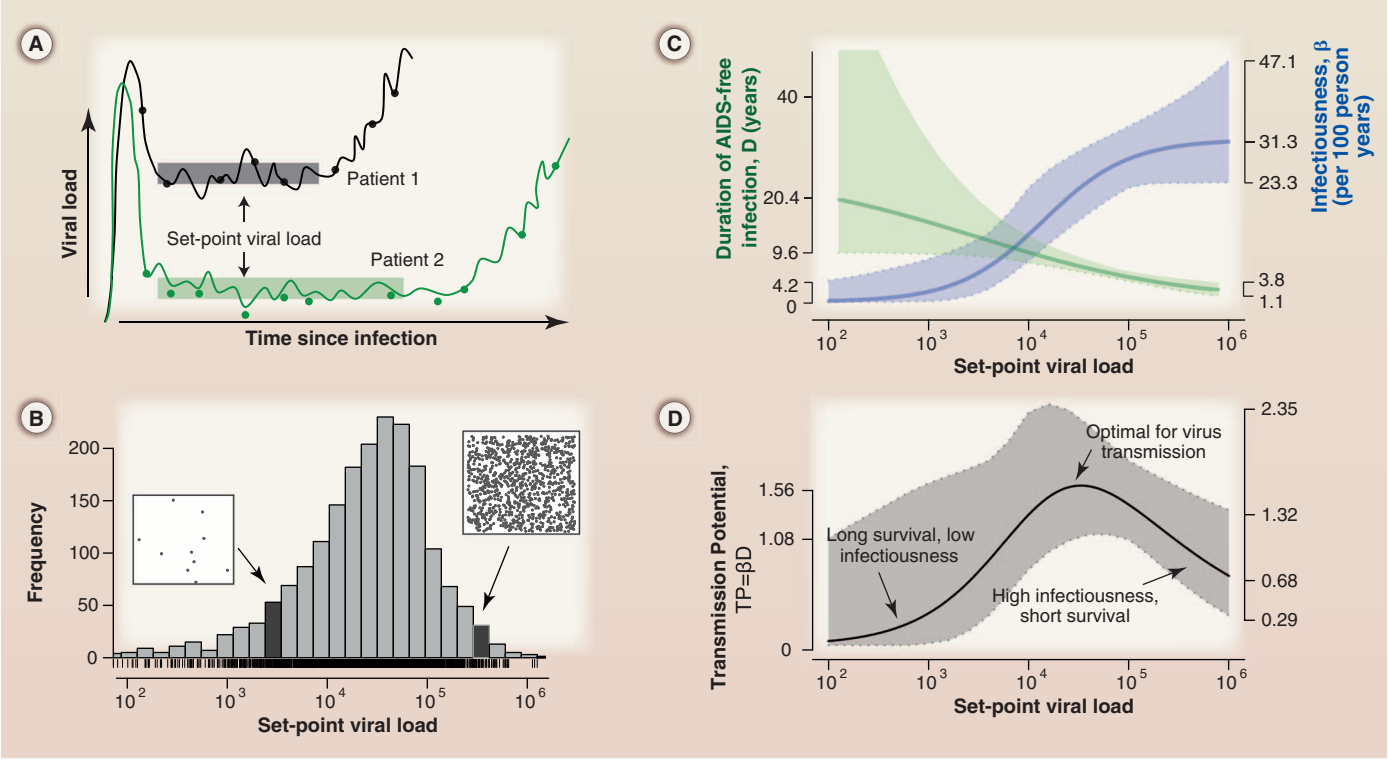

Fig. 1. The evolutionary epidemiology of viral load. (**A**) The typical pattern of viral load in untreated HIV-1 infection, with a very high peak during the first weeks of infection and a gradual increase in the late stages of infection. During asymptomatic infection, viral loads are often relatively steady, fluctuating around the SPVL. (**B**) The distribution of SPVL in a cohort of patients infected with subtype B virus. The distribution is similar across populations and across viral subtypes (*70*). The log-scale is shown on the *x* axis, which demonstrates variability over orders of magnitude. To illustrate the extraordinary extent of this variability, shown in the inset plots are simulated viral density in 5 μL of peripheral blood for two values at either side of the distribution of viral load; thus, viral load is a strong predictor of both infectiousness and rate of progression to disease. The distribution of SPVL was previously described with (*7*), and we have updated this to include SPVL data from 2015 seroconverters in the cohort (with kind permission from de Wolf and Reiss). (**C**) Infectiousness, estimated within heterosexual couples, is shown in blue. The severity of infection, estimated as the mean time from seroconversion to AIDS, is shown in green [from (*7*)]. Lines show best fit, and filled areas show 95% confidence intervals. (**D**) The transmission potential is a summary measure of the epidemiological "success" of an infection with given SPVL: It is the mean number of expected secondary infections over the whole chronic and asymptomatic infectious life span, estimated as the product of infectiousness and duration of asymptomatic infection [from (C)]. The close agreement in between the optimal evolutionary strategy [labeled in (D)] and the distribution of viral loads [plotted in (B)] suggested the hypothesis that the distribution of viral loads is in fact the outcome of viral adaptation to maximize the transmission potential (*7*). None of the calculations account for the effect of treatment. This is reasonable for an evolutionary analysis because treatment has unfortunately only become widely available in recent years.

number of onward transmissions per infection—the basic reproduction number R_0 (*7*, *37*–*39*).

If, as we have argued, HIV virulence factors exist, if these are heritable and are partially transmitted from one infected person to the next, and if in addition these factors affect viral fitness at the between-host level, then a natural corollary is that HIV virulence should be subject to natural selection at the population level. If strains differ in virulence, and this translates to differences in R_0, then evolution will tend to select strains with the highest R_0.

In 2007, Fraser *et al*. (*7*) proposed that HIV-1 SPVL is a life-history trait that has evolved to maximize the number of transmission events. This is quantified by the transmission potential (Fig. 1D), which is the number of people that one infected individual with a given SPVL might infect on average during their asymptomatic lifespan. Crucially, the distribution of SPVLs is clustered around values that maximize the transmission potential (Fig. 1, B and D), suggesting that the virus has evolved to maximize its transmission potential in untreated infection. Repeating the analysis with R_0 rather than transmission potential is more complicated because estimation of R_0 requires assumptions about the distribution of SPVL generated by a strain and the dynamics of the sexual network, and should include transmission during early and late stages of infection in addition to chronic asymptomatic infection. However, such a calculation leads to the same conclusion, that HIV has evolved to maximize the number of onward infections (*7*).

Conceptual Models Reconciling HIV Adaptation at Multiple Levels

Within-host evolution of HIV is a rapid and dominant part of the viral life cycle (Fig. 2A). The virus can complete a full round of replication in an infected host in less than 2 days (*40*, *41*), is under constant immune selection, and can evolve drug resistance in weeks (*41*). In view of ample evidence for high turnover and rapid viral evolution in the host, the finding reviewed in Box 1—that viral influence over SPVL may be partially preserved from one infection

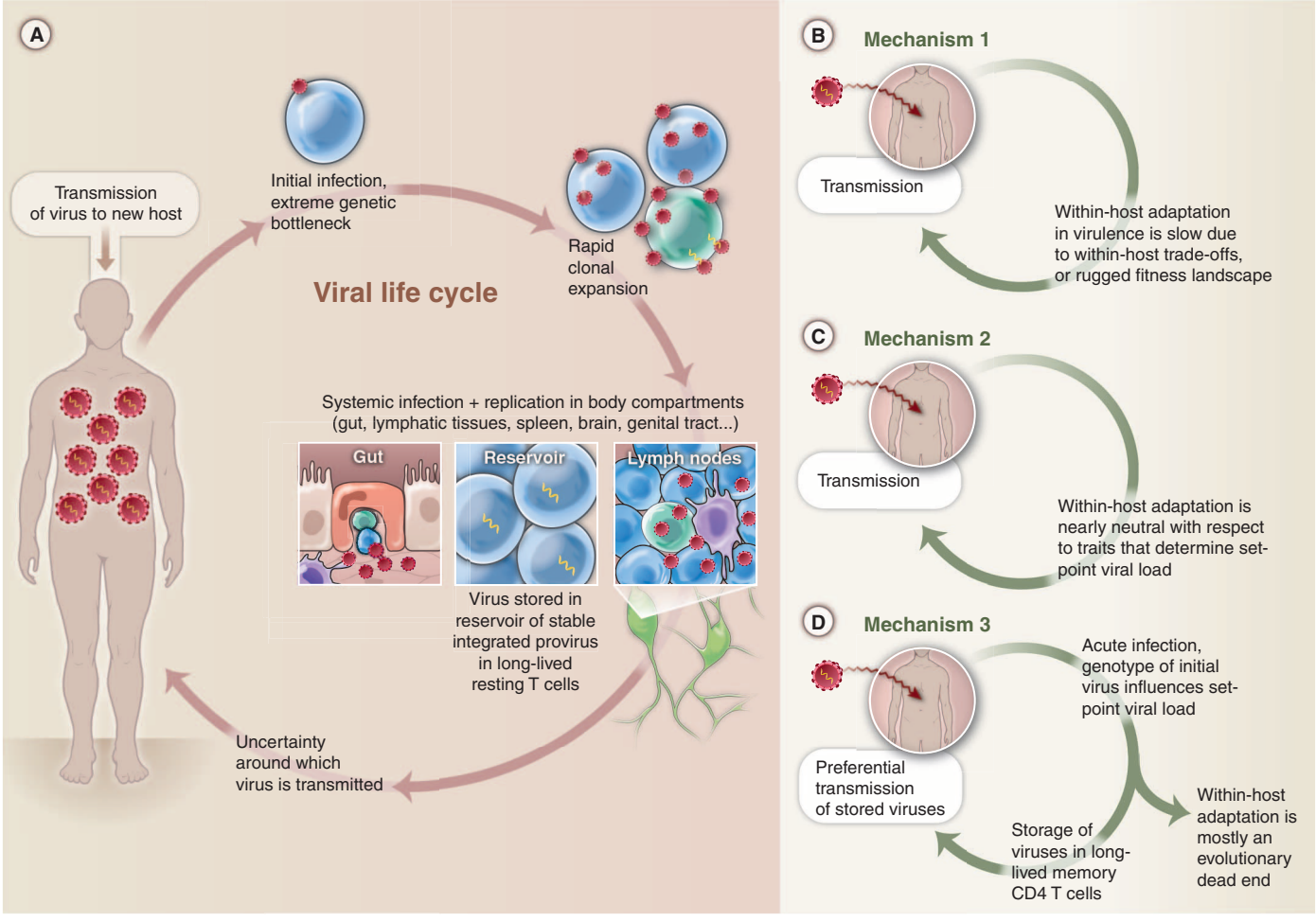

Fig. 2. Mechanisms that could reconcile rapid within-host evolution with heritability of SPVL and adaptation to maximize transmission opportunities. (**A**) Illustration of a full transmission-to-transmission viral replication cycle. During or shortly after transmission, the virus experiences a very strong bottleneck (*71*) and expands clonally, mostly in activated $CD4^+$ T cells. Most viral replication is very fast, with a cellular life cycle of 1 or 2 days (*40*, *41*), but a reservoir of virus in long-lived CD4 cells is quickly established, is continuously replenished, and persists for life (*52*, *53*). Viral replication quickly becomes systemic, assisted by chronic and persistent immune activation, with gut-associated lymphatic tissue and germinal centers in other lymphatic tissues being particularly privileged sites of replication (*53*, *59*). The most uncertainty in the life cycle surrounds which viruses, if any, are preferentially transmitted to found new infections in other hosts. (**B** to **D**) Three mechanisms that could reconcile within-host adaptation with heritability and population-level viral evolution to maximize transmission. These mechanisms are described by schematic representations of the viral life cycle. (B) In mechanism 1, population-level evolution is explained by evolutionary constraints that slow within-host evolution of virulence traits in the host, perhaps owing to virulence genotypes requiring complex combinations of mutations rather than individual noninteracting point mutations. (C) In mechanism 2, population-level evolution is explained by an absence of selection within the host for viral virulence factors. (D) In mechanism 3, population-level evolution is explained by separation of within-host and between-host adaptation caused by preferential transmission of viruses that are stored during early infection, together with disproportionate influence of the founder genotype on SPVL.

Box 1. Heritability quantifies the effect of viral genotype on SPVL.

In quantitative genetics, the heritability of a trait is the proportion of the variance in the phenotypic value observed in a population that is attributable to genotype (*13*). This measure indicates the importance of genetic variation in shaping phenotypic variation. Recently, this concept has been applied to infectious diseases: For HIV, the heritability of a phenotypic trait (such as virus load) is the proportion of variance in this trait that is attributable to viral genetic factors. Because SPVL is a feature of the natural history as a whole, heritability of SPVL is defined with respect to the ensemble of genotypes of viruses that infect and evolve within the host. The simplest study design to measure heritability in SPVL is to look at the similarity in trait values between individuals in couples in which transmission is strongly suspected to have occurred (*16*–*21*). If SPVL is indeed heritable from one infection to the next, there should be similarity between a "recipient" and "donor" viral load. More technically, broad-sense heritability (conventionally denoted h^2) is estimated by the slope of the regression line (r) of the recipient viral load on the donor viral load (supplementary materials). Estimates of r obtained by independent studies have been quite consistent, despite differences in their presentation due to differences of focus: Few studies have presented h^2 as the key summary statistic. Estimates of h^2, adjusted for many confounders, are shown for several studies in Table 1. An alternative design for estimating heritability, inspired by the phylogenetic comparative method, is to use virus sequence data from each host to reconstruct a phylogeny of infections and estimate the relationship between virus genetic relatedness and SPVL (Fig. 3). On the basis of this approach, Alizon *et al.* (*15*) found that up to 59% of variance could be explained by viral genotype. Variation among heritability estimates obtained in different studies should not necessarily be taken as an expression of the uncertainty of the individual estimates because heritability is a measure that also depends on the population in which it is estimated (*13*). For example, a very low-diversity epidemic resulting from an explosive burst of transmissions would exhibit lower heritability than would a high-diversity mature epidemic because of low background diversity in genotypes against which to make comparisons.

N couples	Heritability	Study (reference)	Country, subtype(s)	Adjustments
97	36% (6 to 66%)	Hollingsworth *et al.* (*17*)	Uganda, mostly A, D, and recombinants	Age, sex, subtype, symptomatic genital ulcer disease (GUD)
141	44% (19 to 69%)	Lingappa *et al.* (*18*)	Partners in Prevention (14 sites in East and Southern Africa), diverse subtypes	Age, sex, subtype, sexually transmitted infection, GUD, circumcision, hormonal contraceptive use, source partner characteristics
195	26% (8 to 44%)	Yue *et al.* (*19*)	Zambia, mostly C	Age, sex, HLA, HLA sharing between partners
433	33% (20 to 46%)	Overall summary estimate (weighted by standard error)		

Table 1. Summary of estimates of heritability of SPVL from transmission couples in sub-Saharan Africa, and overall aggregate summary estimate. Studies reviewed here were selected as studies of transmission among heterosexual couples in sub-Saharan Africa.

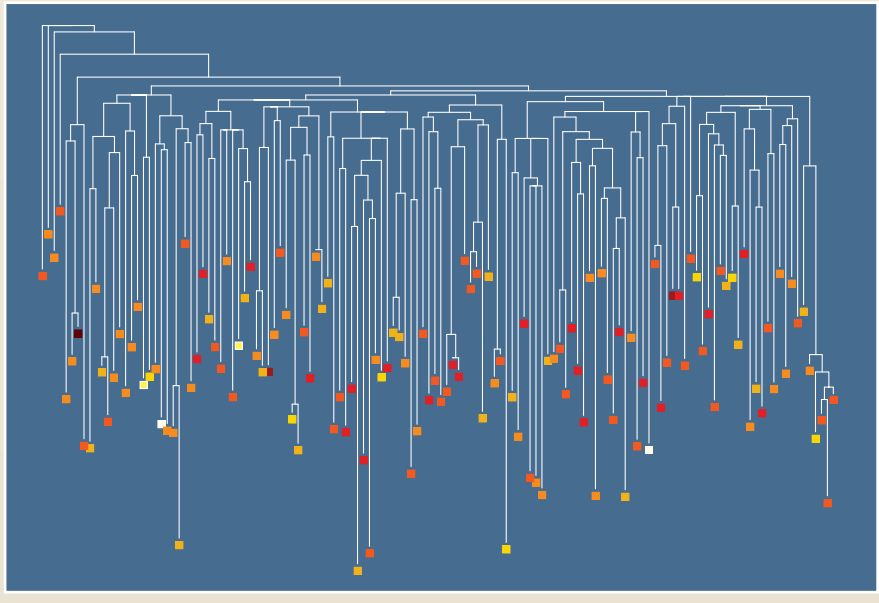

Fig. 3. Phylogenetic proximity yields similar values for heritable traits. Shown is the phylogeny of HIV isolated from 134 Swiss men who have sex with men with well-defined SPVL (indicated by the color of tips). Heritability is estimated by comparing phylogenetic proximity to similarity in SPVL (*15*).

to the next—is unexpected. Evolution to maximize population-level transmission potential is even more surprising. From an evolutionary perspective, we would naively expect evolution to induce adaptation at the level most proximal to viral replication: within the host, a process sometimes termed "short-sighted" evolution (*42*, *43*). We might expect most adaptation to be targeted at optimal replication in local tissues, with no correlation of viral loads between transmitting individuals, rather than the adaptation to maximize the transmission potential of the virus suggested in Fig. 1. Nonetheless, there is now sufficient empirical evidence that HIV heritability needs to be explained, and therefore that mechanisms of HIV pathogenesis need to be compatible with multilevel selection, allowing the virus to adapt to both proximal within-host and distant between-host selection pressures. This compatibility requirement is a strong constraint. We propose three possible (and not mutually exclusive) mechanisms which meet this constraint in Fig. 2, B to D.

Mechanism 1: Slow Evolution of Replicative Capacity

We know that viral turnover and mutation rate are both high, but this does not necessarily imply that all viral phenotypes, such as virulence traits, should evolve rapidly (Fig. 2B). First, the within-host fitness landscape may be highly complex and rugged (*28*, *44*), which might slow within-host evolution and adaptation. Second, viral strains with a high in vitro replicative capacity might not reach sustained high frequencies within an individual if they are intrinsically more immunogenic, or because they are preferentially targeted by acquired immunity as a result of their dominance during early infection. For example, one common consequence of immune selection is the emergence of mutations that allow the virus to escape cytotoxic T-lymphocyte (CTL) responses. Many CTL escape mutations reduce the in vitro replicative capacity of the virus but are nonetheless under intense positive selection during the course of infection because they help the virus evade the host immune response (*45*). Compensatory mutations can restore fitness after escape, but evolution through a process of continuous immune escape and compensatory evolution may slow the overall pace of evolution of net replicative fitness and would shift the balance of selection toward population-level selection.

Mechanism 2: Little Within-Host Selection for Viral Load

It is conceivable that there are viral factors that strongly affect viral load but are neutral with respect to within-host fitness and thus do not evolve rapidly within a host (Fig. 2C) (*46*). Owing to the absence of strong within-host selection, such factors would result in the heritability of virulence and the evolution of viral loads that maximize the between-host transmission potential. Using a generic model of HIV replication, Bonhoeffer *et al*. (*6*) proposed that differences in the rate of activation of target cells may be a major source of variation in virus load. Although it can replicate in many cell types, HIV replicates most efficiently in activated $CD4^+$ T cells (*31*). If the virus activates target cells systemically, then any viral strain that activates cells provides a replication benefit that is not exclusive to just this strain but rather to all competing strains in the body, to the extent that all are provided with additional target cells. Thus, virus-induced activation of target cells can be regarded as contributing toward a "public good" (*46*), and there would be no selective advantage for a viral strain that increases the production of target cells. Which viral factor fulfills the required criteria for virus-induced and systemic target cell activation remains unclear. However, *nef* is clearly an interesting candidate. First, one of the *nef*-linked pathways of T cell activation may indeed be systemic because it is mediated through the release of soluble factors secreted by *nef*-expressing macrophages (*32*, *47*). Second, patients with *nef*-deficient virus have low viral load (*48*, *49*).

Mechanism 3: Influence and Transmission of Founder Viral Strains

Another explanation for heritability of SPVL and evolution of HIV to maximize transmission could be preferential transmission of viruses that have not undergone many rounds of replication in the host, either because transmission occurs during early infection (*50*) and/or because of the transmission of viruses that have been sequestered in long-lived cells [a process referred to as "store and retrieve" (*51*)]. This process, coupled with the disproportionate influence of the genotype of viruses from early infection on SPVL, would essentially make any within-host adaptation an evolutionary dead end for the virus (Fig. 2D). The viral response to multilevel selection would thus be akin to differentiation made between the germ line and soma, that could itself be an adaptive strategy of the virus to maintain transmissibility. During the course of HIV infection, a small fraction of infected $CD4^+$ T cells transition into long-lived memory $CD4^+$ cells containing an integrated copy of the viral genome, thus creating a long-lived reservoir of stored virus (*52*). Because much of this sequestration occurs during the early stages of infection (*53*) when viral loads are greatest, the reservoir acts as an archive of early viral sequences similar to the ancestral sequence (or sequences) that initiated the infection. Occasionally, sequestered virus is retrieved from the archive by the reactivation of a latently infected cell (*52*). If retrieved virus is preferentially transmitted, then the virus that an individual transmits will be similar to the virus that initiated the infection (Fig. 2D). There is evidence that viruses present during acute and early infection have a transmission advantage associated with distinct genotype (*54*) and phenotype (*55*), lending support to this hypothesis. This mechanism also explains the long-standing phylogenetic puzzle of why HIV evolves faster within hosts than it does at the epidemiological level (*51*, *56*, *57*) and is partially supported by data from deep sequencing of viruses in transmission events (*58*). On the other hand, that both immune-escape and drug-resistance mutations are on occasion transmitted (*26*) demonstrates that on at least some occasions, it is extant and not stored viruses that are transmitted. The quantification of the preferential transmission of stored viruses requires further study.

To explain evolution to maximize transmission, it is not enough that a founder virus is preferentially transmitted. Its genotype also needs to influence viral loads throughout the course of infection more than variants that arise later. An example of such influence is that individuals infected with viruses with low RC tend to develop low SPVL even though the virus may increase its RC during the course of infection (*26*, *29*), as previously discussed. One mechanism that could generate such an association would be if the RC of the virus affects the severity of acute infection and in particular the extent of damage to the gut. Gut damage would exacerbate the long-term level of microbial translocation, hence promote immune activation and increase the supply of target $CD4^+$ T cells, and thus enhance the SPVL (*59*). Whatever the mechanistic basis, there is some empirical evidence that acute infection severity correlates with SPVL (*60*, *61*).

Distinguishing Between the Mechanisms

Each of these mechanisms is sufficient to generate heritability of SPVL and allow population-level evolution to take place, but they are not mutually exclusive. Distinguishing which of these mechanisms are at work would require a better understanding of which aspects of viral biology influence SPVL. Large-scale HIV viral whole-genome association studies that search for correlations between viral polymorphisms and SPVL may enable us to detect which parts of the viral genome are correlated with disease severity, provided that the relevant mutations or genomic motifs are common and have sufficiently strong effect. Follow-up experimental work may elucidate their mechanism of action. In addition to recapitulating well-known findings on the association between human HLA and viral genotype and SPVL, Bartha *et al*. (*62*) reported a viral whole-genome association study on SPVL that did not find any statistically significant association between virus proteome and SPVL. The study, with $n = 698$ individuals, was however only powered to detect individual amino acid variants that explained at least 4% of variation of SPVL.

Future viral whole-genome association studies will require greater sample sizes and should include viral genetic polymorphisms and motifs in analyses. Identification of viral factors and of their mode of action will enable us to better

understand pathogenesis and to distinguish between viral replication as the primary factor influencing virulence, viral-induced immune activation, or other as yet unknown factors. Further testing to show whether ancestral sequences are indeed preferentially transmitted should also be an important goal of future research. This would require not only deep sequencing of viruses from donor and recipient patients close to the time of transmission, but sequencing from the donor sampled at multiple times before transmission. For ethical reasons, such studies would need to be retrospective and could also be expanded to consider transmission chains. Without these data, there is no way of determining whether a transmitted virus is an early variant that previously has been sequestered in long-lived cells. Studying viruses sampled from different body compartments in such transmission pairs would also be valuable because the blood compartment may be less relevant to sexual transmission than are the genital mucosa or semen, for example.

Beyond the Theory

Most recent research on HIV pathogenesis has focused on the host and its immune response, with more recent developments than can be summarized here [an up-to-date collection of reviews is available in (*63*), also from http://perspectivesinmedicine.cshlp.org/cgi/collection/hiv]. The aim of this Review has been to suggest the debate on HIV pathogenesis should include greater emphasis on the virus and its genotype, how viral variation interacts with the host response, and how certain heritable viral characteristics influence the course of disease. It is now difficult to ignore the mounting evidence that heritable viral virulence factors exist and that they have an important role in HIV pathogenesis. But what they are, how they are maintained during the course of infection and from one infection to the next—despite extensive viral replication between transmission events—and how they interact with now well-studied host factors are gaping holes in our knowledge. We have presented a framework to reconcile the potentially conflicting observations and key questions regarding HIV pathogenesis in the context of a synthesis based on evolutionary models.

In interpreting our findings, it is tempting to compare our estimate of HIV SPVL heritability (33%) with the lower estimate of 13% attributed to host genotype by GWASs, but these numbers are unfortunately not strictly comparable. GWASs tend to be conservative because of the problem of massive multihypothesis testing. In addition, they typically focus on "narrow-sense" heritability, which is the sum of individual contributions to SPVL directly attributable to single SNPs in human genomes (*64*). In contrast, the estimate of 33% for viral effects is "broad-sense" heritability and accounts for the total effect of viral genotype on SPVL, including possible complex interactions between viral SNPs and other genotypic motifs. As a result, broad-sense heritability is always larger than narrow-sense heritability. Furthermore, if some of the variance is caused by interactions between host and virus genotype, there could be double counting in these measures. The relative role of host, virus, and interactions in explaining SPVL is still not defined, but we have argued that viral virulence factors that influence SPVL have often been underestimated.

Understanding viral virulence factors will help us to predict how the virus may evolve in response to different mass public health interventions. The widespread deployment of antiretroviral treatment, one of the great public health success stories of our time, alters the transmission trade-off and could plausibly select strains of increased virulence. SPVLs appear to have been increasing in some highly treated populations (*65*), although observations remain inconsistent (*66*). In predicting future changes, a further trade-off between increased virulence and drug resistance also needs to be considered because, as discussed above, drug resistance appears at least in some cases to attenuate the virus (*26*). If changing virulence is a concern, sentinel surveillance of viral load among treatment-naïve individuals could be straightforwardly combined with drug-resistance testing and would provide sufficient data. Furthermore, increasing virulence is expected to be slow and limited and does not challenge the current priorities of HIV treatment and prevention programs because it only reinforces the need for prompt diagnosis and treatment. Thinking further afield, an understanding of virulence factors could inform therapeutic strategies aimed at attenuation of infection in-host because at least in some cases of naturally attenuated infection, rapid reversion of virus back to higher levels does not seem to occur (*26*, *29*, *49*).

Our focus here has been predominantly on mechanistic evolutionary models of HIV virulence as assessed in individuals infected with closely related viruses. Future work could expand this approach to explain the documented difference between subtypes of HIV in which both disease and infectiousness may vary (*67*, *68*), to explain virulence in the ancestral SIV viruses infecting a wide range of Old World monkeys and primates with very variable outcomes of infection (*69*), and to study virulence and multilevel selection in other RNA viruses causing chronic infection, such as human T lymphotropic virus and hepatitis C virus. Perhaps most importantly, an evolutionary perspective provides new insight into the basic mechanisms of HIV pathogenesis.

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Supplementary Materials

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Science

Virulence and Pathogenesis of HIV-1 Infection: An Evolutionary Perspective

Christophe Fraser, Katrina Lythgoe, Gabriel E. Leventhal, George Shirreff, T. Déirdre Hollingsworth, Samuel Alizon and Sebastian Bonhoeffer

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HIV Virulence

A major focus of research on HIV is on host responses to infection—understandably, because the virus targets the immune system and because of the interest in vaccine development. In reviewing what little research has been done on viral virulence determinants, **Fraser *et al.*** (10.1126/science.1243727) present evolutionary explanations for some of the poorly understood phenomena that mark HIV infection, including long-term survivorship, latency, rapid within-host evolution, and inheritability of between-host virulence.

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