EDITORIAL COMMENT

Is HIV-1 evolving to a less virulent (pathogenic) virus?

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The short answer to this question could be yes, but is this happening fast enough so we are able to measure it merely 24 years after the identification of HIV-1? The answer is addressed in a study by Ariën *et al*. [1] in this issue of *AIDS*. Their findings are provocative. They compared the *ex vivo* replicative fitness of 24 different HIV-1 isolates (i.e., 12 'historical' viruses obtained from 1986–1989 specimens and 12 more 'recent' isolates from 2002–2003 samples) and concluded that, at least on this reduced number of Belgian patients, HIV-1 isolates from 16 years ago seem to have greater replicative fitness values than contemporary viruses. Thus an overall 'attenuation' in the virulence of HIV-1 is suggested. Although the limited numbers of HIV-1 isolates used in this study may have not been enough to assert such an important conclusion, these results do suggest that it may be time to design studies aimed to understand better the role of viral fitness in the co-evolution of HIV-1 and its human host.

By definition, viral fitness is the replicative adaptation of a virus to its environment [2,3]. Therefore, it is related to the capacity of the virus to replicate in a given setting (replication), its capability to be transmitted to a new host (transmission), and its ability to cause disease (virulence or pathogenicity). In this context, it has been described that drug resistant HIV-1 isolates have impaired replicative fitness [4] but it is still uncertain whether these viruses are transmitted less efficiently and/or are less pathogenic. Recent studies suggest that drug resistant viruses with diminished replicative fitness may result in lower steady-state viral load and improved clinical outcome [5–8]. This finding would suggest that resistant viruses are less pathogenic in terms of inducing immune dysfunction than wild-type viruses. Nevertheless, can we correlate *ex vivo* viral replicative fitness values with *in vivo* HIV-1 pathogenesis? Probably yes. We could expect that viruses with reduced replicative fitness would be less virulent, thus delaying disease progression. A few studies have described this correlation [9–11] which may help us understand the clinical significance of HIV-1 fitness.

The relationship between transmissibility and virulence is complex and unknown for most pathogens [12]. 'Contagiousness' (transmission) has been considered to be as important as replication for certain microbes to persist in their host population [12]. In the case of HIV-1, it is possible that the intrinsic transmissibility of the virus is related to its replicative fitness. For instance, it is still uncertain if there is a correlation between replicative fitness and the ability of drug resistant variants to be transmitted (i.e., the actual transmission event and not the ability of the newly transmitted virus to replicate in the new host). If so, it would mean that drug resistant viruses have lower transmission fitness than wild-type strains, an issue still in debate [13–15].

The idea that HIV-1 is already evolving to a less virulent virus after its estimated original introduction into susceptible human populations some 80 years ago [16] may be easy to understand but perhaps more difficult to demonstrate. It is well known that some SIV have become highly adapted to their non-human primate host species (e.g., Sooty mangabeys) and are able to replicate at a high rate without inducing disease [17, 18]. Interestingly, reduced replicative fitness of subtype C HIV-1 strains may be linked to slower disease

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progression, which could have increased the transmission time and further spread of this particular clade [4,19]. The rapid outspread of subtype C viruses during the last 10 years could be the first indication that HIV-1 may be evolving to a more attenuated virus. Therefore, a compromise between transmission, replication, and pathogenicity in HIV-1 evolution could lead to the co-existence of the virus with their host without inducing disease, similar to what has been observed with other viruses [20,21]. For example, it is possible that viruses with impaired replicative fitness that could be associated with diminished pathogenesis (virulence) would in theory delay disease progression and increase the likelihood of transmission. Conversely, individuals infected with a more pathogenic (high replicative) viral strain will progress faster to HIV-1 disease, decreasing the probability of viral transmission (Fig. 1). Infections with influenza or Ebola viruses, respectively, would represent the extreme examples illustrating this phenomenon.

So, is HIV-1 really evolving to a less pathogenic virus? How long it will take the virus and its human host to reach a similar level of co-existence as the observed in SIV and Sooty mangabeys? We will certainly not be able to see it anytime soon. However, selecting for potentially less virulent viruses with highly impaired replicative fitness (e.g., drug resistant variants with specific combination of mutations) could be the key to establish a chronic but more benign infection in antiretroviral-experienced patients.

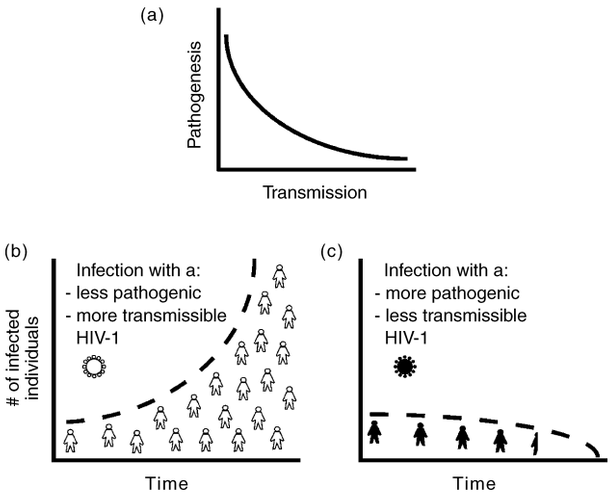

Fig. 1. Schema of the theoretical relationship between transmission and pathogenesis fitness in HIV-1 (a). Two possible scenarios are depicted where a less pathogenic virus is able to infect more susceptible individuals over time (b) while a more pathogenic strain is not able to establish a persistent infection at the population level (c).

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