Over the past 10 years, the world has witnessed one of the most significant chronic disease interventions ever seen—that of highly active antiretroviral therapy (HAART) for HIV infection. Morbidity and mortality have plummeted in those areas of the world with unrestricted access to these drugs [1], and HIV/AIDS has been transformed from an almost certain death sentence to, for those receiving treatment, a long-term, manageable disease, with a potentially normal life expectancy. By contrast, this success has not been matched by reductions in HIV transmissions over the same period. Indeed, current surveillance data suggest that transmissions are increasing in resource-rich communities—particularly among men who have sex with men (MSM) [2], in addition to the large epidemics ongoing within the resource-poor world. Such increases represent a public health failure. The inevitable outcome of widespread HAART use in the midst of increasing HIV transmission—namely, transmission of drug-resistant viruses—has now become a worldwide reality [3–5].

The suboptimal impact of safe sex messages over the past 20 years suggests that more innovative and effective preventive strategies are required. More research is necessary to uncover the dynamics and drivers of transmission within different communities and risk groups, to inform an evidence base for such interventions.

Phylogenetic approaches have long been used for illustrating the evolutionary relationships among HIV strains, leading to fundamental insights into cross-species transmissions, spread of specific viral lineages, and recombination [6]. These methodologies have also been used to study specific transmission events. However, until recently, the paucity of large sequence data sets and the expense in generating such data have limited studies to the investigation of individual transmission events and/or outbreaks [7, 8]. With the increasingly widespread implementation of HIV resistance testing, involving the generation of large volumes of sequences from the pol gene (~10% of the complete genome), these limitations have been overcome. Epidemiological and cohort approaches to HIV transmission dynamics can now be complemented by phylogenetic data. We estimate that there may be many hundreds of thousands of HIV-1 sequences potentially available for analysis from resistance-testing laboratories worldwide. The original hesitation with using pol sequences for evolutionary studies—they are relatively conserved compared with gag and env genes and may also be subject to bias (apparent convergent evolution) due to drug-resistance mutations—has been generally overcome [9, 10], and a number of recent studies have taken advantage of the ever-growing sequence repositories. Although the identification of specific transmission events with high statistical confidence through phylogenetics will always be subject to significant caveats (e.g., cannot exclude a common, unknown source of 2 similar infections, cannot identify direction of transmission, and ignores the potential of superinfection), as well as ethical concerns (consent for use to identify potential sources of infection), the potential to provide insights into transmission dynamics within communities is now being realized. Indeed, as guidelines on undertaking resistance testing at first diagnosis [11, 12] become implemented, we will move toward a complete set of viral sequences for all diagnosed individuals within defined geographical areas. This will represent a resource of huge potential for the detailed study of HIV transmission dynamics and will be a model for the study of other human pathogens. Laboratories holding data as a product of resistance testing must
be encouraged to share sequences to facilitate such studies.

In this issue of the Journal, Brenner et al. [13] have used phylogenetic analyses on such a local sequence data set to explore the likely source of new infections in the mainly MSM Quebec cohort. They use well-established methods of HIV-1 pol gene analysis, incorporating very high bootstrap values and low genetic distance criteria, to demonstrate the high transmission rate from those with primary HIV infection (PHI) and show that nearly 50% of acute infections within their cohort as a whole are linked to other primary infections. As discussed above, phylogenetic analyses on their own cannot provide definitive evidence for transmission events; however, the consistency between this and other studies using such phylogenetic techniques in individuals with PHI [14, 15] suggests that their conclusion—that primary infection is a critical period for onward transmission of HIV—is valid.

This assertion is biologically plausible because PHI represents a period of extremely high viral load levels. Indeed, prospective longitudinal studies among heterosexual HIV-1 serodiscordant couples in the developing world have clearly demonstrated that viral load and early stage of infection are predictors of transmission [16, 17], alongside the presence of sexually transmitted infections [18] and circumcision status [19]. Large prospective studies continue to investigate the impact of empirically or syndromically treating sexually transmitted infections or suppressing herpes simplex infection, as well as the use of male circumcision, on reductions in transmission.

However, these strategies may be of limited effectiveness if individuals at or near to PHI represent a major source of onward transmission, because many such interventions depend on an initial positive diagnosis. It is well recognized that the symptoms associated with PHI are nonspecific, and this entity frequently remains undiagnosed by health care providers. Indeed, it is estimated that only a small proportion of infected individuals are diagnosed in early infection [20]. By contrast, active ascertainment and high levels of testing can improve the diagnosis of recent infection, to the extent that up to 50% of recent infections can be identified [21]. Normalization of HIV testing within health care settings, such as the policy recently announced by the Centers for Disease Control and Prevention, is clearly a major advance [22]. However, it must be recognized that selection of testing strategies must also be appropriate for optimizing the detection of early infection, such as combined antibody-antigen tests [23] or pooled HIV-RNA testing [24].

What are the advantages of early HIV diagnosis with regard to prevention of transmission? First, it is recognized that an HIV diagnosis per se results in subsequent risk reduction [25]. However, more contentious is the potential role of antiretroviral therapy in reducing transmission. Although reductions in plasma viremia are mirrored by reductions in the transmissible virus in the genital tract [26], there has been little discussion of the prevention role of HAART outside of mother-to-child transmission and, more recently, preexposure prophylaxis scenarios [27]. Current guidelines for initiating HAART are based on the risk-benefit for the infected individual, and treatment is rarely recommended with a CD4 cell count >350 cells/µL [11]. As clinical management of HIV infection improves and HAART suppression of viremia is maintained for longer periods of time, the source of further transmissions will shift more toward untreated (including undiagnosed) individuals. We should therefore consider the role of extending treatment to those with higher CD4 cell counts, for benefit of individual and community. Such an extension can now be contemplated in light of recent improvements in drug formulations (thus enhancing adherence) and reductions in HAART toxicities [28]. Indeed, one study of HAART use at high CD4 cell counts to prevent transmission in discordant couples is underway [29]. A possible implication of such a policy could be the risk of emergence of drug resistance and subsequent transmission. Against this must be cited the low risk of resistance emerging for those starting on current HAART triple therapies [30]. Indeed, as treatment efficacy continues to improve, an increasing proportion of transmitted resistance is likely to originate from untreated individuals [31], who are themselves infected with resistant strains and in whom high levels of viremia persist without reversion of virus to wild type [32]. This, therefore, identifies a further reason for extending treatment.

Changing the paradigm of treatment rationale is even more pertinent for primary infection. Trials of short-term HAART in the setting of PHI are currently under way [33]. Such trials are largely constructed around the potential immunological and virological benefits for the treated individual. In view of the recognition of primary infection as a major driver of transmission, we argue that the reduction of transmission risk, by reducing viral load, should also be considered as a measurable benefit of early interventions.

HAART is no replacement for enhanced behavioral approaches to reduce transmission. It is expensive, and relatively toxic, and many regions of the world still have not implemented therapy to many of their infected populations. However, we argue that the current focus on increasing HIV diagnoses through more widespread testing requires a parallel strategy for minimizing ongoing transmission. Through cohort and molecular epidemiological studies, the importance of early infection in maintaining these transmissions will be better understood. It is now time to evaluate application of the most potent intervention to treat this disease—namely, antiretroviral therapy—to its prevention. Furthermore, strategies to improve recognition of recent infection, in addition to identifying undiagnosed chronic infection, are crucial for effective implementation of prevention strategies.
References