Programmatic Implications of Acute and Early HIV Infection

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Human immunodeficiency virus (HIV) infection includes acute, early, chronic, and late stages. Acute HIV infection lasts approximately 3 weeks and early HIV infection, which includes acute HIV infection, lasts approximately 7 weeks. Many testing and blood screening algorithms detect HIV antibodies about 3 weeks after HIV infection. Incidence estimates are based on results of modeling, cohort studies, surveillance, and/or assays. Viral load is the key modifiable risk factor for HIV transmission and peaks during acute and early HIV infection. Empirical evidence characterizing the impact of acute and early HIV infection on the spread of the HIV epidemic are limited. Time trends of HIV prevalence collected from concentrated and generalized epidemics suggest that acute and early HIV infection may have a limited role in population HIV transmission. Collectively, these data suggest that acute and early HIV infection is relatively short and does not currently require fundamentally different programmatic approaches to manage the HIV/AIDS epidemic in most settings. Research and surveillance will inform which epidemic contexts and phases may require tailored strategies for these stages of HIV infection.

Keywords. acute HIV infection; early HIV infection; recent HIV infection; HIV testing; blood safety; HIV incidence; national strategic plan.

The natural history of human immunodeficiency virus (HIV) infection spans acute, early, chronic, and late stages (Table 1). The clinical [8], modeling [9], and therapeutic [10] implications of acute and early HIV infection have been reviewed previously; however, acute and early HIV infection may also have important implications on access to safe blood, testing algorithms, and incidence estimation. There is also concern that acute and early HIV infection may compromise national HIV control strategies [11]. Therefore, we reviewed (1) the appearance and use of diagnostic markers during acute and early infection, (2) viral dynamics after HIV infection, (3) determinants of HIV risk, (4) estimates of HIV transmission by stage of infection, and (5) relationships between acute and early HIV infection transmission and population surveillance data.

APPEARANCE AND USE OF DIAGNOSTIC MARKERS

Acute HIV infection is defined as the time from HIV infection to the appearance of HIV-specific antibodies [8]. Acute HIV infection is associated with a number of clinical signs and symptoms, such as fever, myalgia, and rash; however, these lack complete sensitivity and specificity [8]. Fiebig et al [1, 12] found that immunoglobulin M (IgM)–sensitive enzyme immunoassays can detect HIV 23.5 days after HIV infection while Robb et al [2, 12] found that it takes 25.3 days. Cumulatively these data suggest acute HIV infection lasts approximately 24 days (Figure 1). Fiebig et al [1, 12] also found that p24 antigen is detectable from approximately 20.3 to 29.1 days after HIV infection (Figure 1).

Data on acute, early, and recent infection can be used for individual and population decision-making (Table 1). It is important to distinguish these purposes. Some
misclassification may be tolerated for population-level HIV insights. For example, although minimizing false-positive results reduces wastage during blood screening, identification of HIV-infected donated blood is required to eliminate transfusion-associated HIV transmission [13]. Ideally the misclassification rate for incidence algorithms to detect recent infection is 0%, but values of <2% have maintained appropriate mean durations of recency and can be accepted [14]. Moreover, some level of false-recency may not affect the overall validity of analyses evaluating the relationship between an individual’s HIV acquisition risk and the prevalence of recent HIV infection in their community. On the other hand, false-positive results are problematic for individual-level diagnostic and treatment purposes. Studies have indicated that false-positive test results can, for some

Table 1. Definitions of Terms

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Acute infection</td>
<td>Time from human immunodeficiency virus (HIV) infection to the presence of HIV-specific antibodies; characterized by a rapid rise in the viremia</td>
<td>Approximately 24 days [1, 2]</td>
</tr>
<tr>
<td>Early infection</td>
<td>Time from HIV infection to a viremic steady state or set point; characterized by replication of the virus and the development of the immune response during which there is a decline in the CD4+ T-cell counts</td>
<td>Approximately 52 days [1, 2]</td>
</tr>
<tr>
<td>Recent infection</td>
<td>State that begins when the biological process of HIV infection is first initiated; this term is used primarily in the context of measuring HIV incidence</td>
<td>First 2 years of HIV infection [3, 4]</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>For people not receiving antiretroviral therapy: fairly constant viremia, steady declines in CD4+ T-cell counts, and increasing rates of opportunistic infections For people receiving antiretroviral therapy: suppressed viral loads, increases in CD4+ T-cell counts, and reducing rates of opportunistic infections</td>
<td>Approximately 10 years, but with a range of 2 to 20 years, after infection for people not receiving antiretroviral therapy [5] or nearly lifelong for people receiving effective antiretroviral therapy [6]</td>
</tr>
<tr>
<td>Late-stage infection</td>
<td>CD4+ T-cell levels decline to very low levels, rapid rises in viremia, and death if infection is left untreated</td>
<td>Approximately 1 year if untreated [7]</td>
</tr>
</tbody>
</table>

Figure 1. Appearance of diagnostic and viral markers during acute and early human immunodeficiency virus (HIV) infection. Median HIV loads are up to 100 days after the appearance of HIV RNA in individuals from Kenya, Uganda, Tanzania, and Thailand (top blue curve) [2] and the United States (bottom red curve) [1]. The pairs of lines indicate the range of trends that are consistent with the data as published. It is not possible to define the timing of the fall to a set point with precision by using the US data (follow-up points were approximately 3, 8, 11, 16, 54, and 112 days after infection). The eclipse period, ie, the 11 days from infection to detectable viral load, is not included in this figure [12]. Abbreviation: IgM, immunoglobulin M. This figure is available in black and white in print and in color online.
individuals, result in a false-positive diagnosis and initiation of unnecessary treatment [15].

Rapid tests are an integral component of expanding access to prevention and treatment. Third- and fourth-generation rapid tests can be used to detect IgM antibody and p24 antigen, respectively (Table 2). Although IgM antibody has been shown to be an excellent biomarker for HIV tests, the presence of p24 antigen is often unreliable and brief, leading to limited sensitivity for p24 antigen in fourth-generation rapid tests (Figure 1) [16]. Based on World Health Organization (WHO) guidance, most countries have developed testing algorithms that use third-generation rapid tests in lower-tier health facilities and community-based approaches to diagnose HIV infection [20]. Given the high risk of HIV transmission in some settings, WHO guidelines recommend annual or more-frequent HIV testing for key populations (ie, people who inject drugs [PWID], sex workers, men who have sex with men [MSM], and transgender people) in all epidemic settings and for sexually active people in generalized epidemic settings (ie, people who inject drugs [PWID], sex workers, men who have sex with men [MSM], and transgender people) in all epidemic settings.

Table 2. Performance and Cost of Third-Generation and Fourth-Generation Rapid Human Immunodeficiency Virus (HIV) Tests

<table>
<thead>
<tr>
<th>Rapid Test (Manufacturer, Country)</th>
<th>Antibody Sensitivity (95% CI)</th>
<th>Antibody Specificity (95% CI)</th>
<th>p24 Sensitivity</th>
<th>Cost, US$ (Year Quoted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Third-generation rapid tests evaluated on whole blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Determine HIV-1/2 Whole Blood (Abbott Laboratories)</td>
<td>100 (95.5–100)</td>
<td>99.4 (96.7–100)</td>
<td>. . .</td>
<td>1.2 (2001)</td>
</tr>
<tr>
<td>First Response HIV-1/HIV-2 Whole Blood (Premier Medical Corporation, India)</td>
<td>100 (95.5–100)</td>
<td>98.8 (95.8–99.9)</td>
<td>. . .</td>
<td>1.15 (2001)</td>
</tr>
<tr>
<td>Uni-Gold HIV (Trinity Biotech, Ireland)</td>
<td>100 (95.5–100)</td>
<td>100 (97.9–100)</td>
<td>. . .</td>
<td>2.34 (2001)</td>
</tr>
<tr>
<td><strong>Third-generation rapid tests evaluated on serum/plasma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alere Determine HIV-1/2 (Alere, Japan)</td>
<td>100 (99.1–100)</td>
<td>98.9 (97.8–99.6)</td>
<td>. . .</td>
<td>0.8–1.25 (2011)</td>
</tr>
<tr>
<td>Colloidal Gold diagnostic Kit for HIV (1 + 2) Antibody (Shanghai Kehua Bioengineering, China)</td>
<td>100 (99.2–100)</td>
<td>98.9 (97.8–99.6)</td>
<td>. . .</td>
<td>0.35–0.65 (2013)</td>
</tr>
<tr>
<td>DoubleCheckGold Ultra HIV 1&amp;2 (Orogenics, Israel)</td>
<td>100 (99.1–100)</td>
<td>99.8 (99.2–100)</td>
<td>. . .</td>
<td>0.9–1.6 (2013)</td>
</tr>
<tr>
<td>First Response HIV 1–2.0 Card Test (Premier Medical Corporation, India)</td>
<td>99.8 (99.2–100)</td>
<td>98.9 (97.8–99.6)</td>
<td>. . .</td>
<td>0.45–1.05 (2013)</td>
</tr>
<tr>
<td>HIV 1/2 STAT-PAK (Chembio Diagnostics Systems, US)</td>
<td>99.5 (98.3–99.9)</td>
<td>100 (99.4–100)</td>
<td>. . .</td>
<td>1.5 (2012)</td>
</tr>
<tr>
<td>HIV 1/2 STAT-PAK DIPSTICK (Chembio Diagnostics Systems, US)</td>
<td>100 (99.1–100)</td>
<td>99.7 (98.9–99.9)</td>
<td>. . .</td>
<td>0.85–0.90 (2011)</td>
</tr>
<tr>
<td>SD Bioline HIV-1/2 3.0 (Standard Diagnostics, Republic of Korea)</td>
<td>99.8 (98.8–100)</td>
<td>99.8 (99.2–100)</td>
<td>. . .</td>
<td>0.8–0.81 (2013)</td>
</tr>
<tr>
<td>Uni-Gold HIV (Trinity Biotech, Ireland)</td>
<td>99.8 (98.7–100)</td>
<td>99.9 (99.2–100)</td>
<td>. . .</td>
<td>1.6–2.8 (2012)</td>
</tr>
<tr>
<td><strong>Fourth-generation rapid tests evaluated on serum/plasma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alere Determine HIV Ag/Ab Combo (Alere, Japan)</td>
<td>100 (99.1–100)</td>
<td>98.8 (97.6–99.5)</td>
<td>16.7 (2/12)</td>
<td>. . .</td>
</tr>
<tr>
<td>SD Bioline HIV Ag/Ab (Standard Diagnostics, Republic of Korea)</td>
<td>100 (99.1–100)</td>
<td>99.1 (98–99.7)</td>
<td>41.7 (5/12)</td>
<td>. . .</td>
</tr>
<tr>
<td>ImmunoComb II HIV 1&amp;2 TriSpot Ag-Ab (Orogenics, Israel)</td>
<td>99.8 (98.7–100)</td>
<td>100 (99.4–100)</td>
<td>25.0 (3/12)</td>
<td>. . .</td>
</tr>
</tbody>
</table>

Data on third-generation tests are from [14], and data on fourth-generation tests are from [16]. Because of the wide number of rapid HIV tests, only third-generation tests that have been procured in quantities of >500,000 and evaluated by the World Health Organization were included [17].

Abbreviation: CI, confidence interval.

* Data are percentage (no. of individuals with reactive test results/no. tested). Measurements were performed in a panel with mixed p24 antigen and HIV type 1 antibody titers.

women in generalized epidemic settings, the acceptability and cost-effectiveness of this approach is unclear for other populations [20].

Blood transfusion is a life-saving intervention that has an essential role in patient management within health systems [13]. WHO recommends routinely screening donated blood for HIV antibodies or both HIV antibodies and p24 antigen to prevent transfusion-related transmission [13]. High-income countries have also demonstrated low rates of transfusion-related HIV transmission by routinely screening donated blood for HIV RNA [13]. Financial, human, and laboratory resource requirements have limited the use of RNA for screening blood in low- and middle-income countries. Affordable and point-of-care technologies may facilitate screening donated blood for HIV RNA and other bloodborne infections such as hepatitis B and hepatitis C. Research should evaluate the potential improvements in blood safety versus costs and logistical requirements in different epidemic and health system contexts.

Measuring HIV infection incidence allows HIV/AIDS programs to understand population transmission dynamics and the impact of national strategies to control the epidemic. Identifying people who recently acquired HIV infection is essential.
for understanding the population incidence of HIV infection. One of the challenges is to use widely available biomarkers to accurately identify people with recent, rather than long-standing, HIV infection. For example, several incidence assays use third-generation rapid tests, CD4+ T-cell counts, HIV RNA levels, and/or antiretroviral treatment (ART) status to estimate the incidence of HIV infection in cross-sectional surveys [3, 22]. Recent evaluations indicate that of 5 incidence assays, limiting antigen (LAG) assays had the lowest false-recency rate but still had misclassifications [23]. Studies validating LAG assays against longitudinally measured HIV infection incidence, similar to studies conducted for the BED IgG-Capture Enzyme Immunoassay, are underway and will inform the use of LAG in population-based studies [4, 24]. Although different thresholds have been used to define recent infection, WHO now recommends a threshold of 2 years, owing to lower false-recency rates compared to shorter thresholds [4]. Given the imperfect performance of incidence assays, countries can use the Spectrum software tool to triangulate incidence estimates from mathematical modeling, cohort analyses, surveillance, HIV-related mortality data, and/or incidence assays to develop national estimates [4]. Inclusion of new biomarkers and statistical methods may optimize incidence estimation in the future [4]. For example, cohort studies of recent seroconverters nested within cross-sectional HIV surveys could be a promising approach to improve HIV infection incidence in situations where ART scale-up has affected population mortality rates [25].

**VIRAL DYNAMICS**

Data on viral dynamics during acute and early HIV infection are difficult to obtain because (1) the initial replication of the virus is very fast and transient, (2) people must be enrolled into care before or within days of infection, and (3) they must then be monitored frequently enough to determine the time course of viremia. To our knowledge, 2 studies have followed a cohort of people without HIV infection and monitored them frequently enough after HIV infection to determine the viral dynamics [1, 2] (Figure 1). The earliest study involved people who donated their blood twice weekly in the United States. Fiebig et al analyzed 322 plasma samples from 51 people who became HIV positive [1]. Samples were available for several weeks before and for up to 6 months after HIV antibody seroconversion. In donors developing HIV infection during follow up, viral loads increased rapidly, with a doubling time of 20.5 hours (95% confidence interval [CI], 18.2–23.4 hours) and peaked at a median of 259,000 copies/mL a median of 24 days after HIV infection [1, 12]. Fiebig et al reported data approximately 3, 8, 11, 16, 54, and 112 days after infection, corresponding to what are now referred to as the 6 Fiebig stages, making it possible to define precisely the timing of the initial rise in viral load but not the timing of the subsequent fall to a set point [1]. The second study was conducted in low- and middle-income countries as part of vaccine research efforts. Robb et al collected blood twice weekly from 2000 HIV-negative people at high risk of HIV infection in Thailand, Uganda, Tanzania, and Kenya and were able to monitor the course of infection in 39 people who developed HIV infection [2]. The viral loads peaked at a median 5.0 million copies/mL a median of 23 days after HIV infection [2, 12]. The peak viral load detected by Robb et al was approximately 19-fold higher than that reported by Fiebig et al [1, 2]. This may reflect differences in viral subtype dynamics, clinical characteristics of the study participants, and/or diagnostic methods. Viral loads subsequently decreased to a median set point of 19,952 copies/mL a median 52 days after HIV infection [2, 12]. These 2 studies suggest that the early stage appears to end approximately 52 days after HIV infection (Figure 1).

Given the difficulty and expense of following a cohort of HIV-negative participants prospectively, other studies back-calculated the presumed date of infection among HIV cohorts [26–29]. Peak viral loads in these studies ranged from 235,000 copies/mL [29] to 7.9 million copies/mL [28]. Similar to prospective studies, peak viremia occurred approximately 21 days after HIV infection [30]. However, these studies could suffer from selection bias, as most participants presented because they had symptoms associated with acute HIV infection and such symptoms may not manifest in all people infected with HIV [8].

**DETERMINANTS OF HIV TRANSMISSION**

Viral load is the key factor in determining HIV-related morbidity, mortality, and transmission. A systematic review and meta-analysis found that rates of HIV transmission increase with increasing plasma viral load [31]. ART-induced viral suppression has been shown to markedly reduce the likelihood of HIV transmission, regardless of sexual orientation. Specifically, there was nearly 0 heterosexual transmission of HIV among people with HIV infection who achieved viral suppression with ART (95% CI, <01 transmission events per 100 person-years) [32]. A similar level of protection was observed with regard to HIV transmission among MSM who achieved viral suppression during ART [33]. Increasing ART coverage among PWID has further decreased the frequency of new HIV infections in PWID networks [34].

The effectiveness of ART in reducing population-level transmission depends on several factors. One factor is how the HIV transmission risk varies during HIV infection. Early analyses fitted a power-law relationship between the risk of transmission and viral load with a power of <1 so that transmission increases as viral load increases but does not reach an asymptote [35]. Based on data from systematic reviews and new data sets of HIV transmission as a function of viral load, transmission appears to increase linearly with viral load up to about 20,000 copies/mL but then converges to an asymptote [36]. These data
suggest that the risk of transmission at the peak of viremia during acute HIV infection would be about thrice the risk at the set point [37]. The data are not sufficient to distinguish between these 2 models, and the power-law assumption tends to imply a higher rate of transmission in the acute phase as compared to the linear increase converging to an asymptote. Since HIV transmission is reduced as ART is initiated closer to HIV infection, the timing of ART initiation is a crucial transmission determinant.

Two systematic reviews of the behavioral and biological determinants of HIV transmission showed that (1) receptive anal intercourse has a greater risk of infection than vaginal sex, (2) genital ulcers in either partner increases the risk of infection, and (3) circumcision reduces susceptibility to HIV in males exclusively practicing insertive sex (Table 3) [18, 19]. One of the reviews also found increased infectivity due to commercial sex exposure relative to noncommercial sex exposure [18]. Increased exposure to bodily fluids in sex or injection partners who are living with HIV increases the cumulative risk of infection. The use of protective barriers such as condoms [38] and chemoprophylaxis [39] also decrease the risk of HIV transmission. Opiate substitution therapy and use of clean needles reduces HIV transmission among PWID [40]. There are also many structural determinants of HIV infection that affect biological and behavioral determinants [41].

Although there is sound evidence for these determinants affecting HIV transmission, there are limited data available on whether the presence of these behavioral and biological determinants varies by stage of HIV infection [42]. Evidence showing that any of these risk factors are more likely to be present in acute and early HIV infection would support the hypothesis that rates of HIV transmission during acute and early HIV infection are elevated beyond what is expected from increased viremia. For example, if MSM do not use condoms during acute and early HIV infection and begin using condoms for the rest of HIV infection, then MSM would have increased acute and early HIV infection transmission not only due to increased viremia but also because of different behavior. It has been suggested that people infected with HIV have a larger number of concurrent sex partners during acute and early HIV infection relative to chronic HIV infection [43]. This would also lead to increased HIV transmission during acute and early HIV infection beyond what is expected from elevated viremia [44]; however, this was not confirmed in a recent systematic review [45]. Data on the presence of behavioral and biological determinants stratified by stage of HIV infection is a research priority.

There are a number of reasons why transmission during the acute and early stages may be elevated outside the context of the biological and behavioral determinants discussed above. For example, it is possible that neutralizing antibodies or other immune modulators are important in determining transmission [46]. Moreover, it is possible that viruses that are able to penetrate the mucosa and establish the infection are more transmissible than other viruses that are unable to penetrate the mucosa [47]. If this is true, viremia during acute and early infection would be dominated by viral strains that are more transmissible than the diversified viral strains present during the chronic and late stages of HIV infection [48]. These topics require further investigation.

### ESTIMATING POPULATION HIV TRANSMISSION USING MATHEMATICAL MODELING

Duration, transmissibility, behavior, coverage of barrier methods, clustering, and epidemic phase are several key parameters that determine the proportion of transmissions that take place during acute and early HIV infection (Table 4). Owing to varying assumptions of these parameters, the estimated proportion of infections that occur in low- and middle-income countries during the acute and early stages ranged from 2% to 89% in mathematical models [37, 44, 49–56]. Most of these models...
were based on 1 set of data from Uganda to calculate the transmission rate during acute HIV infection [57]. This was a retrospective cohort study that relied on survey data collected every 10 months to quantify the rates of HIV transmission according to the stage of HIV infection. The final analysis is based on only 23 concordant HIV-negative couples in which at least 1 partner seroconverted during a mean follow-up time of 17.3 months. The adjusted HIV infection incidence rate ratio for the first and second 10 months was 7.25 (95% CI, 3.05–17.25). However, these estimates are susceptible to several biases. For example, during the 10-month interval in which both partners seroconverted, it was not known whether most transmissions occurred at peak viral loads in the index partner (24 days after HIV infection) or 9 months after HIV infection in the index partner. Moreover, although molecular linkage was done in 64% of couples [57], it was not done for the remaining 36%, making it impossible to exclude that the HIV transmission took place outside of the couple under observation. Finally, since participants were tested and notified of their HIV status every 10 months, the increased transmission rate during the index partners’ first 10 months of infection relative to their second 10 months of infection could have been partially due to people adopting safer sexual behavior after learning their HIV status [58]. These issues significantly decrease our confidence in models that use these data as the basis for estimating the proportion of HIV transmission that occurs during acute and early HIV infection. Indeed, a re-analysis of these data, allowing for the retrospective cohort exclusion criteria and unmeasured heterogeneity in risk, found that acute and early HIV infection play a substantially lower role than previously estimated [59].

The impact of acute and early infection on HIV transmission has also been modeled in high-income countries with concentrated epidemics. These models have also suggested that 2%–89% of HIV transmissions occur during acute and early HIV infection [60–67]. Additional studies from these settings have used phylogenetics to estimate the proportion of transmission among HIV epidemics concentrated in MSM. These studies have estimated that 1%–49% of HIV transmissions occur during acute and early HIV infection [68–73]. Phylogenetics may also be useful for understanding transmission dynamics in generalized epidemic settings [74]. Methodological issues that must be considered when interpreting phylogenetic data include potential selection biases of individuals included in analyses, possible discordance between phylogenetic tree topologies and transmission network structures, and possible reliance on wrong genotypes in individuals in whom multiple viral genotypes were transmitted [59].

### ESTIMATING POPULATION HIV TRANSMISSION USING SURVEILLANCE DATA

It is also possible to use national surveillance data to improve our understanding of the role of acute and early HIV infection on population HIV transmission. One of the few directly observed parameters concerning the epidemiology of HIV is the initial doubling time of HIV prevalence. The doubling time can be used to estimate the case reproduction number, $R_0$, for HIV. $R_0$ gives the number of secondary cases arising if one infected case is introduced into a fully susceptible population and, therefore, the magnitude of the control problem. To eliminate an infectious disease, $R_0$ must be reduced to <1 [75].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Relationship With Overall Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Length of the acute and early stage</td>
<td>Proportion of transmissions during acute and early stages increases with duration</td>
</tr>
<tr>
<td>Transmissibility</td>
<td>Risk of transmitting HIV in the acute and early stage, compared with the chronic stage</td>
<td>Proportion of transmissions during acute and early stages increases with transmissibility</td>
</tr>
<tr>
<td>Frequency</td>
<td>How often people with acute and early HIV infection expose injecting or sex partners</td>
<td>Proportion of transmissions during acute and early stages increases with frequency</td>
</tr>
<tr>
<td>Partners</td>
<td>Number of sex or injecting partners during acute and early stage</td>
<td>Proportion of transmissions during acute and early stages increases with more partners</td>
</tr>
<tr>
<td>Coverage of barrier methods</td>
<td>Use of condoms, chemoprophylaxis, or other barrier methods when partners have acute and early HIV infection</td>
<td>Proportion of transmissions during acute and early stages decreases with higher coverage of barrier methods</td>
</tr>
<tr>
<td>Clustering of partners within the network</td>
<td>Extent that sex or injecting partners are within clusters with a higher acute and early HIV prevalence</td>
<td>Proportion of transmissions during acute and early stages increases with higher clustering within network</td>
</tr>
<tr>
<td>Epidemic phase</td>
<td>Phase of national epidemic (emerging, stable, or declining)</td>
<td>Proportion of transmissions during acute and early stages will be high in the emerging phase (when the majority of people with HIV infection have acute and early HIV infection) - Proportion of transmissions during acute and early stages will also be high in the declining phase in programs with high antiretroviral therapy (ART) coverage (when the majority of people with chronic and late stage HIV are less infectious as a result of ART-induced viral suppression)</td>
</tr>
</tbody>
</table>

Table 4. Key Parameters Influencing Estimates of Acute and Early Human Immunodeficiency Virus (HIV) Transmission in Mathematical Models
Time trends in the prevalence of HIV measured in annual antenatal care clinics surveys in South Africa give an initial doubling time of 1.25 years [76], from which we can estimate $R_0$, using various assumptions about the risk of transmission in the acute and early stages relative to the chronic and late stages and the duration of the acute and early stages (Supplementary Materials). If most of the transmission occurs during the acute phase, then a doubling time of 1.25 years would imply an $R_0$ very close to 1; if most of the transmission occurs during the chronic phase, then a doubling time of 1.25 years implies a value of $R_0$ of about 6 (Figure 2). Paradoxically, therefore, the greater the contribution of acute and early HIV infection to overall transmission, the lower the value of $R_0$ and the easier it would be to control HIV through conventional prevention methods [9, 79].

In Can Tho Province, Vietnam trends in the prevalence of HIV suggest an initial doubling time of 6.2 months in PWID [77]. If most of the transmission occurs during the acute phase, then a doubling time of 6.2 months would imply an $R_0$ close to 11; if most of the transmission occurs during the chronic phase, then a doubling time of 6.2 months implies an $R_0$ of about 16 (Figure 2). Therefore, as in the generalized epidemic setting, $R_0$ appears to be lower when acute and early HIV infection transmission is more important. Since the provincial surveillance data in Vietnam suggest a larger $R_0$, it is unlikely that acute and early HIV infections are the primary drivers of this epidemic.

Our review of the surveillance data may help policy makers understand where to focus prevention efforts; however, there are some methodological issues that should be considered. These simple models assume random mixing, which cannot be strictly true. Even in generalized epidemics, nonrandom assortment can lead to mini-outbreaks in certain geographic settings with higher values of $R_0$ in certain groups that drive the epidemic in the initial stages but eventually form a small part of all those at risk [80]. Nonetheless, independent mathematical modeling from South Africa on this issue drew the same conclusion [81]. In concentrated epidemics, the dynamics are different, including spatially and socially focused transmission often with small networks in which there is very high-risk behavior. Our analyses were drawn from available surveillance data and could be biased by limited geographic representativeness, inefficient testing algorithms in surveillance efforts, and selection bias. Furthermore, the surveillance data were collected during the emerging and stable phases of the HIV/AIDS epidemic; as population transmission is reduced and countries enter the declining phase of the epidemic, it is possible that stemming transmission from outbreaks of individuals with acute and early HIV infection will play a more critical role (Figure 3).

**CONCLUSIONS**

This review confirms the limited nature of the data characterizing acute and early HIV infection and helps inform a number of research priorities (Table 5). The available data suggest that acute HIV infection lasts for approximately 3 weeks, that early HIV infection lasts for approximately 7 weeks, and that in most settings substantial HIV transmission occurs outside of this short period. Although they do not detect infection during the brief acute HIV infection, detecting HIV antibodies are a fundamental component of blood screening and testing algorithms. National incidence can be estimated through triangulation of available data. Viral load, sexual behavior, sexual frequency, and the preventive measures used to limit transmission are key determinants of HIV transmission. Mathematical models have projected different proportions of transmission during acute and early infection, owing to heterogeneity in parameter estimates. Moreover, these models have relied on a single data set [57], for which the original analysis was shown to be biased [59]. Surveillance data collected from the onset of a concentrated and generalized epidemic suggest that acute and early HIV infection may have a limited role in overall transmission. Combination prevention approaches, including universal access
to testing and treatment, are unlikely to be affected by acute and early HIV infection transmission; however, it remains possible that specific epidemic contexts and phases may require strategies tailored to reduce transmission during these stages of infection. As more-robust data are generated, programs could consider that current global and national strategies can control the HIV/AIDS epidemic.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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