HIV TRANSMISSION DYNAMICS: INFECTIVITY, SEXUAL PARTNERSHIP PATTERNS, 
AND THE ROLE OF EARLY INFECTION

Kimberly Anne Powers

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Approved by:
William C. Miller, MD, PhD
Myron S. Cohen, MD
Azra C. Ghani, PhD
Irving F. Hoffman, PA, MPH
Audrey E. Pettifor, PhD
ABSTRACT

Kimberly Anne Powers

HIV transmission dynamics:
Infectivity, sexual partnership patterns, and the role of early infection
(Under the direction of William C. Miller)

Although remarkable progress has been made in the diagnosis, treatment, and prevention of HIV, a cure is unavailable and many of the most promising prevention interventions have failed. At this critical juncture in the epidemic, there is a necessity for improved understanding of the fundamental drivers of the epidemic, as well as an urgent need for innovative interventions against HIV. This dissertation focuses on two of these fundamental drivers – the heterosexual infectivity of HIV-1 and the details of sexual partnership patterns – as well as the power of interventions initiated during the highly infectious period of early HIV infection (EHI). We conducted a systematic review and meta-analysis of the heterosexual infectivity of HIV-1, defined as the per-contact probability of HIV-1 transmission in a single heterosexual contact between an infected and a susceptible individual. Infectivity estimates were extremely heterogeneous, ranging from zero transmissions after more than 100 penile-vaginal contacts in some sero-discordant couples to one transmission for every 3.1 episodes of heterosexual anal intercourse. Several co-factors were associated with increased infectivity. Infectivity differences (95% confidence intervals), expressed as number of transmissions per 1000 contacts, were 8 (0-16) comparing uncircumcised to circumcised male susceptibles, 6 (3-9) comparing susceptible individuals with and without GUD, 2 (1-3) comparing late-stage to mid-stage index cases, and 3 (0-5) comparing early-stage to mid-stage index cases. We also analyzed recent sexual partnership patterns in a sexually transmitted infections (STI) clinic in Lilongwe, Malawi. We found that multiple
sexual partnerships were uncommon (14%), and partnerships were long on average (mean=858 days). Among those reporting multiple recent partners, patterns ranged from long-term concurrency (mean overlap=246 days) to narrowly spaced consecutive partnerships (mean gap=21 days), presenting a substantial risk for efficient HIV transmission. Finally, we conducted a mathematical modeling study to determine the contribution of EHI to epidemic spread in Lilongwe, Malawi. Our analyses suggest that 38.4% (95% CI: 18.6%-57.5%) of ongoing HIV transmissions in Lilongwe can be attributed to EHI index cases, and that interventions targeting the entire duration of infection will be needed to have a significant, lasting effect on the epidemic.
For Oscar Neal and the siblings that I imagine for him
ACKNOWLEDGEMENTS

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<tbody>
<tr>
<td>AHI</td>
<td>Acute HIV infection</td>
</tr>
<tr>
<td>AIDS</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>ANC</td>
<td>Antenatal clinic</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
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<tr>
<td>ARV</td>
<td>Antiretrovirals</td>
</tr>
<tr>
<td>BV</td>
<td>Bacterial vaginosis</td>
</tr>
<tr>
<td>CHI</td>
<td>Chronic HIV infection</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>EHI</td>
<td>Early HIV infection</td>
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<tr>
<td>GEE</td>
<td>Generalized estimating equations</td>
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<tr>
<td>GUD</td>
<td>Genital ulcer disease</td>
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<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<td>HIV-1</td>
<td>Human immunodeficiency virus, subtype 1</td>
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<tr>
<td>HPTN</td>
<td>HIV Prevention Trials Network</td>
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<tr>
<td>HSV-2</td>
<td>Herpes simplex virus 2</td>
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<tr>
<td>ID</td>
<td>Infectivity difference</td>
</tr>
<tr>
<td>KCH</td>
<td>Kamuzu Central Hospital</td>
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<tr>
<td>MSM</td>
<td>Men who have sex with men</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PLD</td>
<td>Partnership length difference</td>
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<tr>
<td>PLR</td>
<td>Partnership length ratio</td>
</tr>
<tr>
<td>PLWH</td>
<td>People living with HIV</td>
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<td>RNA</td>
<td>Ribonucleic acid</td>
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<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>STI</td>
<td>Sexually transmitted infection</td>
</tr>
<tr>
<td>UNC</td>
<td>University of North Carolina</td>
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<tr>
<td>VCT</td>
<td>Voluntary HIV counseling and testing</td>
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CHAPTER 1: SPECIFIC AIMS

While HIV prevention programs have led to declining HIV incidence in several settings, 2.7 million individuals worldwide became newly HIV-infected in 2008, with the majority of new cases arising in sub-Saharan Africa. Although access to antiretroviral therapy (ART) continues to expand, about 3 million HIV-infected individuals received ART in sub-Saharan Africa during 2008, representing just 44% of those in need. It is clear that prevention must continue to be a dominant strategy for combating the epidemic.

The design of effective prevention interventions requires a detailed understanding of the factors driving HIV transmission. Although much has been learned about HIV transmission in the past several decades, a number of questions remain about its fundamental determinants. In this dissertation, we explored three research areas related to key factors determining HIV spread: the heterosexual infectivity of HIV-1, the various forms that sexual partnerships can take, and the contribution of newly infected index cases to onward HIV transmission.

To study the infectivity of HIV-1, we performed a systematic review and meta-analysis of existing studies conducted worldwide. To examine heterosexual partnership patterns, we analyzed data from a sexually transmitted infections (STI) clinic in Lilongwe, Malawi. To analyze the contribution of early HIV infection (EHI) to epidemic spread, and to predict the potential impact of interventions initiated during this period, we developed a mathematical model of the HIV epidemic in Lilongwe, Malawi. Lilongwe serves as a representative
example of an urban, sub-Saharan African setting where HIV is hyper-endemic, transmission is mainly heterosexual, and access to antiretroviral therapy is limited but growing.

**The heterosexual infectivity of HIV-1 (Aim 1)**

*Specific Aim 1*

Conduct a systematic review and meta-analysis of observational studies estimating the heterosexual infectivity of HIV-1 to: (a) estimate transmission co-factor effects on the heterosexual infectivity of HIV-1, and (b) quantify the extent to which study methods have affected infectivity estimates.

*Rationale for Aim 1*

Although a vast number of HIV transmissions worldwide are attributable to heterosexual contact, the belief that HIV cannot be transmitted efficiently via this route has persisted in biomedical reports, prevention education materials, policy recommendations, and the popular press. This belief has been based on a commonly cited\(^3\) value of ~0.001 for the heterosexual infectivity of HIV-1, defined as the probability of HIV-1 transmission during a single heterosexual contact between an infected and an uninfected individual.

Discrepancies between low infectivity estimates and high HIV prevalence are likely due, in part, to the inherent challenges of infectivity estimation, as well as the use of a single value for “the” heterosexual infectivity of HIV-1. This simplistic approach fails to reflect the effects of potential co-factors, such as direction of transmission (male-to-female vs. female-to-male),\(^8\) type of sexual act,\(^9,10\) viral load,\(^11,12\) male circumcision,\(^13,14\) vaginal flora,\(^15\) age,\(^16\) and STI.\(^17,18\)
While these co-factors have been established at the level of cumulative HIV incidence, their effects at the per-contact level are not well-defined. As infectivity is a fundamental determinant of HIV transmission, more accurate, detailed estimates of this parameter are critical for evaluating potential interventions, understanding the HIV epidemic, and communicating risk.

_Hypotheses for Aim 1_

Methodological features of studies estimating the heterosexual infectivity of HIV-1 have affected the corresponding infectivity estimates. Variables that have been identified as transmission co-factors at the level of cumulative HIV incidence also affect transmission at the per-contact level.

_Overview for Aim 1_

We conducted a systematic review and meta-analysis of heterosexual HIV-1 infectivity estimates published through April 2008. To examine the influence of study features and transmission co-factors, we conducted random-effects meta-analyses and univariable meta-regressions.

_Heterosexual partnership patterns (Aim 2)_

_Specific Aim 2_

Describe partnership patterns and estimate the duration of (a) _partnerships_, (b) _gaps_ between partners, and (c) _overlaps across partners_ among patients attending the Kamuzu Central Hospital (KCH) STI Clinic in Lilongwe, Malawi.

_Rationale for Aim 2_
Sexual partnership dynamics are critical determinants of HIV/STI spread. Measures of partnership patterns include partner change rates, durations of steady partnerships, frequency of sexual contact within steady partnerships, frequency of sexual contact outside of steady partnerships, lengths of gaps between consecutive sexual partnerships, and lengths of overlap across concurrent sexual partnerships. Many of these aspects of sexual contact are not well-defined, particularly in sub-Saharan African settings.

**Hypothesis for Aim 2**

Individuals with STIs engage in multiple partnerships of short duration, resulting in substantial risk for rapid transmission of HIV and STIs.

**Overview for Aim 2**

We conducted a secondary analysis of data collected at the baseline and one-week follow-up visits of a longitudinal study of HIV viral dynamics conducted at KCH STI Clinic in Lilongwe, Malawi. Participants underwent physical exams and HIV tests, and completed questionnaires about demographics, risk behaviors, and sexual partnership characteristics. We used generalized estimating equations to calculate mean partnership lengths, overlaps across concurrent partnerships, and gaps between consecutive partnerships. We used multinomial logistic regression to examine predictors of concurrent and consecutive partnerships.

**The contribution of EHI and its potential as a target for prevention interventions (Aim 3)**

**Specific Aim 3a**
Estimate the proportion of secondary HIV transmissions attributable to index cases with EHI in Lilongwe, Malawi, where HIV is hyper-endemic, spread is mainly heterosexual, and ART uptake is limited.

**Specific Aim 3b**

Predict the reduction in HIV prevalence achievable through detection of EHI cases and implementation of prevention interventions during EHI in Lilongwe, Malawi.

**Rationale for Aim 3**

During the earliest months of HIV infection, concentrations of HIV RNA in blood and genital secretions are sharply elevated, and the probability of secondary HIV transmission is increased. Unfortunately, in the initial portion of this period (the *acute* phase), detectable antibodies to HIV are absent and case identification requires more sophisticated and expensive methods than standard antibody tests. The contribution of EHI to epidemic spread is a complex function of multiple setting-specific factors, including patterns of risk behavior and the stage of the HIV epidemic. If EHI cases are responsible for a substantial number of secondary infections in a particular setting, then identification of EHI cases and implementation of effective prevention interventions during this period could have important public health benefits. In settings where EHI plays only a minor role in perpetuating the HIV epidemic, however, the additional resources required to detect EHI may be difficult to justify. To optimize resource allocation and the beneficial effects of intervention strategies, the role of EHI in epidemic spread must be understood.

Previous modeling studies estimating the contribution of EHI to HIV incidence have used overly simplified model structures, have lacked empirical data from the setting of interest, and/or have focused on men-who-have-sex-with-men (MSM) in western settings. No
previous study has modeled the potential impact of interventions initiated during EHI in sub-Saharan Africa, the region hit hardest by the HIV epidemic. While our model will focus on Lilongwe as a representative of this region, the model can be modified with relative ease in the future to address similar questions in other settings.

_Hypothesis for Aim 3a_

A disproportionate number of secondary HIV transmissions are attributable to index cases with EHI in urban, sub-Saharan African settings.

_Hypothesis for Aim 3b_

EHI case detection and prevention interventions can reduce HIV incidence in urban, sub-Saharan African settings by preventing transmission during the most infectious period.

_Overview for Aim 3_

We developed a deterministic mathematical model to describe heterosexual HIV transmission in Lilongwe, Malawi. The model included steady sexual partnerships, as well as casual, one-off sexual contacts outside of these partnerships. We used the results of Aims 1 and 2 above, along with additional data from our work in Lilongwe, to inform model parameter values. We programmed the model to produce output describing adult HIV prevalence in Lilongwe over time, as well as the proportion of incident cases attributable to contact with EHI index cases. We used the model to explore a range of scenarios with and without interventions targeted to various stages of infection.

_Layout of dissertation chapters_

Specific Aims 1 and 2 are described in Chapters 4 and 5, respectively. Specific Aims 3a and 3b are described in Chapter 6.
CHAPTER 2: BACKGROUND

The HIV/AIDS epidemic in sub-Saharan Africa

More than two-thirds of the world’s 33 million HIV-infected individuals live in sub-Saharan Africa, and approximately the same fraction of AIDS deaths in 2008 occurred in this region.\(^1\)

The burden is especially great in southern and eastern Africa, where more than a third of all people with HIV/AIDS live, and a third of both incident HIV cases and AIDS deaths occur.\(^1\)

The epidemic has exacted a far-reaching toll on nearly all aspects of life in sub-Saharan Africa, compromising not only the well-being of infected individuals, but also the development, security, and stability of the region.\(^28\)

HIV prevalence has stabilized in parts of sub-Saharan Africa, but incidence remains high. Most countries in this region have “generalized” epidemics (prevalence >1% in the general adult population, >5% in high-risk subgroups), driven mainly by heterosexual transmission. In several of these countries, HIV prevalence exceeds 15% in the general population (i.e., HIV is “hyperendemic”) and is as high as 50% in certain subgroups. Although HIV prevalence appears to be reaching a plateau in many countries, nearly 2 million individuals were newly infected in this region during 2008, underscoring the need for intensive prevention efforts among those most at risk of transmitting or acquiring infection.

The need for new HIV prevention interventions

HIV prevention programs have led to declining HIV incidence in several settings; however, 2.7 million individuals worldwide became newly infected in 2008, with most of these new
infections arising in sub-Saharan Africa. Although access to antiretroviral therapy (ART) continues to expand, about 3 million HIV-infected individuals received ART in sub-Saharan Africa during 2008, representing 44% of those in need. Prevention must continue to be a dominant strategy for combating the epidemic.

Clinical trial failures of several prevention interventions underscore the need for new strategies. A number of clinical trials have been conducted to evaluate control of bacterial sexually transmitted infections (STI) as a means of preventing HIV transmission, based on co-factor effects of STIs on HIV susceptibility and infectiousness detected in observational studies. Only one of these trials demonstrated an effect of bacterial STI treatment on HIV incidence. Three recently completed trials – one of diaphragms plus lubricant and condoms, and two of acyclovir for herpes simplex virus type 2 (HSV-2) – also failed to demonstrate a difference in HIV incidence between the intervention and control groups. A number of other interventions, including the Merck Ad5 trivalent vaccine and the microbicides cellulose sulfate and nonoxynol-9, were associated with increased HIV acquisition among patients assigned the intervention. This succession of disappointing results has caused considerable consternation among AIDS researchers, leading to calls for innovative interventions.

**Understanding the determinants of epidemic spread**

Optimal design of interventions requires a thorough understanding of the biological and behavioral factors driving the HIV epidemic. Biological factors include the duration of infection, the inherent infectivity of the virus, changes in infectivity over time, and the presence of co-factors (such as concomitant STIs) that can amplify transmission. Behavioral factors include partner change rates, durations of steady partnerships, frequency of sexual contact within steady partnerships, patterns of temporal overlap across concurrent
partnerships, and durations of gaps between consecutive partnerships. The relative
importance of specific biological and behavioral factors varies across settings, resulting in
different primary risk groups and levels of prevalence around the world.

**The heterosexual infectivity of HIV-1 (Aim 1)**

**The importance of infectivity to HIV spread**

The infectivity of HIV – defined as the per-contact probability of HIV transmission from an
HIV-positive to an HIV-negative individual – is one of the most important parameters
involved in understanding the magnitude of the HIV epidemic, communicating risk to
infected and susceptible individuals, and evaluating the potential impact of control efforts. It
is generally accepted that the majority of HIV infections are attributable to heterosexual
transmission; however, most commonly cited estimates\(^3\)\(^{-7}\) of heterosexual infectivity seem
far too low to explain the vast proportions of the current epidemic. Discrepancies between
low estimates of heterosexual infectivity and the tremendous magnitude of the HIV epidemic
are likely due to the inherent challenges of studying infectivity, as well as under-appreciation
of co-factors that can amplify transmission.

**The challenge of measuring infectivity**

Although the infectivity of HIV via some routes of transmission can be estimated relatively
accurately with observational data, the infectivity of HIV via sexual contact has proven
difficult to measure. In the case of mother-to-child or parenteral transmission of HIV, the
transmission event can be identified with certainty, since exposure to HIV can be verified
and an individual is likely to experience only one such exposure within a given time period.
In the case of sexual transmission of HIV, however, the transmission event typically can only
be narrowed down to the series of all sexual acts occurring in a given time interval. These
acts may involve multiple partners – possibly of unknown HIV status – and be protected or partially protected by condoms. Certainty in identifying the transmission event is decreased further by reliance on self-reported sexual histories.

Infectivity estimation requires an accurate count of the transmission events resulting from a defined number of potentially infectious exposures experienced by a specified population of susceptible individuals. It is difficult to obtain reliable counts of potentially infectious sexual exposures; often, it is only possible to estimate an approximate number of sex acts occurring between one individual who is presumed to be infectious and another who is presumed to be susceptible over some specified time interval. Overestimation of the number of potentially infectious exposures will produce deflated infectivity estimates, and underestimation of the number of exposures will have the opposite effect.

Despite these challenges, more than two dozen studies have produced estimates of the heterosexual infectivity of HIV-1.\textsuperscript{21, 35, 44-67} These studies have differed in many ways, including their methods of exposure and outcome assessment (longitudinal vs. cross-sectional), identification of subjects (as part of a serodiscordant couple or not), HIV testing intervals, analytical models, and treatment of condom use, self-report error, and possible exposures outside of those measured in the study. The extent to which these differences have affected infectivity estimates has not been quantified.

\textit{Modifying effects of transmission co-factors}

Previous studies of cumulative HIV incidence have identified co-factors that may modify the risk of HIV transmission. A substantial amount of evidence suggests that susceptibility to HIV infection is elevated among uncircumcised males\textsuperscript{13, 14} and individuals with sexually transmitted infections.\textsuperscript{17, 18} These factors also may be associated with increased
transmissibility of HIV when present in HIV-infected individuals. Further, HIV transmissibility is thought to vary over the course of infection according to changes in viral concentrations in blood and genital secretions,\textsuperscript{11,12} and perhaps due to other time-varying factors as well.\textsuperscript{22,68} Finally, previous research has suggested that HIV transmission is more efficient from males to females than from females to males,\textsuperscript{8} and by anal rather than vaginal intercourse.\textsuperscript{9,10} While these co-factors have been well-studied at the level of cumulative incidence, efforts to quantify their effects at the per-contact level have been less common, and practical applications of infectivity estimates often fail to take these possible modifiers into account.

\textit{The need for more research}

Neither the influence of particular study methods on infectivity estimates nor the per-contact effects of transmission-modifying co-factors are well-defined. Given the importance of HIV infectivity estimates for understanding the HIV epidemic, communicating risk, and predicting the effects of prevention interventions, there is a need for: 1) clear identification of study methods’ impacts on infectivity estimates, and 2) a detailed understanding of the effects of transmission co-factors at the level of the individual exposure.

\textit{Heterosexual partnership patterns (Aim 2)}

\textit{The importance of partnership dynamics to HIV/STI transmission}

Sexual contact patterns are fundamental determinants of HIV/STI transmission. When sexual partnerships are consecutive (separated by “gaps” in time), an infected index case can pass the infection to only one additional person while a partnership remains intact. Furthermore, earlier partners are protected from infections among later partners. When partnerships are instead concurrent (overlapping in time), neither of these limitations is present, and transmission can be amplified.\textsuperscript{69} Even consecutive partnerships can be
effectively concurrent, however, if an STI is introduced by the earlier partner and the gap between partnerships is shorter than the infecting agent’s infectious period.\textsuperscript{70, 71} Partnership lengths are also important, as longer partnerships may enable more opportunities for transmission. Different combinations of “gap lengths” and partnership durations will have different effects on epidemic spread.\textsuperscript{72}

Given the importance of concurrency, partnership durations, and gap lengths in determining epidemic spread, careful characterization of these parameters is critical for designing prevention interventions and building mathematical models of HIV/STI transmission. In particular, partnership and gap lengths are key input parameters in a specific type of model – referred to as a \textit{pair-formation model} – that explicitly models the formation and dissolution of sexual partnerships.\textsuperscript{73} In these models, the rate of pair formation is the inverse of the gap length, and the rate of pair dissolution is the inverse of the partnership length. Although pair models are capable of representing sexual contact patterns more realistically than are simpler models, their use has been limited by a lack of data on partnership and gap lengths in many settings, particularly among African populations.

\textit{Partnership dynamics in the context of HIV transmission}

In the case of HIV in particular, the infectious period begins at the time of acquisition and spans the remainder of an infected person’s lifetime. This biological fact seems to suggest that gap lengths are less important in determining HIV transmission when compared to other STIs with shorter infectious periods. However, HIV transmissibility varies dramatically over the course of infection, with an extremely high level of infectivity concentrated in the earliest months of infection.\textsuperscript{21, 22} As a result, the transmission dynamics of HIV may be similar to bacterial STIs with short infectious periods, and gap lengths may therefore be important determinants of HIV transmission.
The role of concurrency in HIV transmission has been debated vigorously.\textsuperscript{74-78} While mathematical modeling studies have established the theoretical potential of concurrent sexual partnerships to amplify HIV transmission,\textsuperscript{69, 79-81} an empirical link between concurrency and HIV spread has not been confirmed. Some investigators have hypothesized that the relatively high levels of long-term, concurrent partnerships measured among some sub-Saharan African populations may be to blame for the severe epidemic in that region.\textsuperscript{82, 83} However, this ecological evidence has been mixed, partly due to differing definitions of concurrency across studies. Further, ecological associations are insufficient to definitively establish a link; individual-level data are necessary. Unfortunately, these data are very difficult to collect, as it is a susceptible individual’s partner’s practice of concurrency that results in increased risk to the susceptible individual, rather than an individual’s own practice of concurrency.\textsuperscript{84, 85} Empirically measuring the contribution of concurrency to HIV/STI transmission requires information not only about an individual’s sexual contact patterns, but also the sexual contact patterns of the individual’s partner(s).

To facilitate comparison across settings, the UNAIDS Reference Group on Estimates, Modelling, and Projections recently issued a consensus definition for sexual partner concurrency: “overlapping sexual partnerships in which sexual intercourse with one partner occurs between two acts of intercourse with another.”\textsuperscript{86} While this standardized definition represents an important step forward in the study of concurrency and its effects on HIV transmission, it is unable to capture many important details of sexual partnership patterns. Additional research is needed to improve our understanding of the various forms that sexual partnerships can take, including measurements of partnership lengths, gap lengths, and overlap lengths.
Empirical estimates of gap lengths and the prevalence of concurrency

Gap lengths estimated in previous research have varied widely, and to our knowledge, no prior studies have characterized gap lengths among African populations. Studies conducted in the US have also found substantial proportions of short gaps: a study of women aged 15 to 44 estimated that 47% of gaps between partners in the prior five years were shorter than six months,\textsuperscript{71} and a telephone survey conducted among Seattle adults aged 18 to 39 estimated that 60% of gaps across the last five partners were six months or shorter.\textsuperscript{70} In the Seattle study, the mean gap length was 354 days, and the median was 187 days.\textsuperscript{70} In another study conducted in the US,\textsuperscript{87} the mean gap length was 14.6 days for all partners contacted in the prior seven months by “high-risk” women ages 14-21. By contrast, a recent study among UK heterosexuals ages 16-44 reported that only 9% of gaps between partners contacted in the prior 5 years were shorter than four months.\textsuperscript{72}

Estimated proportions of participants engaging in recent concurrency have varied considerably in African studies. A study conducted among Ugandans ages 15-49 estimated that 2% of women and 14% of men had some degree of overlap across their three most recent partners.\textsuperscript{81} Similarly, a study conducted among South Africans ages 15 to 24 estimated that 2% of women and 11% of the overall population had some degree of concurrency across their two most recent partners contacted in the prior three years; however, the corresponding proportion of men was a much higher 38%.\textsuperscript{88} A study conducted among HIV-positive individuals in Botswana produced higher estimates among men (23%), women (18%), and overall (20%).\textsuperscript{89} A study among Tanzanians ages 15 to 44 also obtained higher estimates overall (26%) and among men (53%), but a lower estimate (4%) among women.\textsuperscript{90} These differences across settings are likely to due to differences in study methods and concurrency definitions, in addition to true differences in concurrency prevalence across populations.
Methodological issues related to measuring sexual partnership patterns

Data collection methods can affect measurement of these parameters in ways that may not be obvious in the study design phase. For example, partnerships may continue beyond the final data collection point; if this possibility is not appropriately addressed in data collection and analysis, partnership lengths may be underestimated (Figure 2.1). Previous studies’ methods for handling partnership censoring have varied, and have not always been explicitly described. In some studies, investigators simply acknowledged the absence of this information as a limitation, or they made assumptions about the likelihood of censoring and then used Kaplan-Meier survival analysis to account for censored observations in estimating partnership lengths. Other investigators asked participants to report whether they expected each partnership to continue, and then used that information with Kaplan-Meier analysis to account for censoring. Although this latter approach likely produces the most valid estimates, its validity depends on the accuracy of participants’ expectations about partnership continuation.

Additionally, studies that have compared several different methods of estimating concurrency have found widely discrepant results across measures. These measures include determining partnership intervals from reported dates of first and last sex, prospective data collection via coital diaries, and direct inquiry about overlap and/or numbers of partnerships at specific times. Further, restriction of partnership recall to a specified “look-back period” can have a constraining effect on gap length measurements. Because the most recent contact with each partner must have occurred within the “look-back period,” each gap between consecutive partners has to be fully contained within that time. Reporting periods in previous gap length studies have ranged from seven months to five years, and one study had an open-ended period. Additionally, the time unit chosen for reporting the start and end of partnerships can affect the resolution of partnership
and gap length measurements, as well as the related classification of partnerships as consecutive or concurrent. Numerous partnership dynamic studies have collected only month and year of first and most recent sexual contacts,\textsuperscript{70-72, 92, 93} necessitating assumptions that could bias measurements of length and could result in misclassification of partnership patterns. Finally, when the number of partners on whom information is assessed is fewer than the total number of partners that an individual has had during the look-back period, an individual's short-term partnerships are less likely to be captured than his or her long-term partnerships.\textsuperscript{91, 97}

\textit{The need for more research}

Several studies have characterized these parameters in various settings, but the implications of data collection methods have not always been thoroughly considered or discussed. There is a need for greater understanding of these methodological issues and for improved accounting for them in future studies. Additionally, there is a particular need for estimates of partnership, gap, and overlap lengths from sub-Saharan Africa, as descriptions of these parameters in this region are sparse.

\textit{The contribution of EHI and its potential as a target for prevention interventions (Aim 3)}

\textit{The danger of transmission during acute and early infection}

Early HIV infection (EHI) represents a “perfect storm” of conditions for spreading HIV. In particular, acute HIV infection (AHI), which comprises the three- to twelve-week period between HIV acquisition and seroconversion,\textsuperscript{20, 98, 99} is characterized by high concentrations of HIV RNA in blood\textsuperscript{19, 20, 100-104} and genital secretions.\textsuperscript{19, 104} Given the relationship between blood viral load and sexual transmission risk,\textsuperscript{11, 12, 66, 105} transmission is thought to be very
efficient during EHI, particularly during AHI. Furthermore, acutely infected individuals test negative on standard HIV antibody tests, contributing to the likelihood of ongoing, high-risk behavior even if testing is performed. For these reasons, persons with EHI and AHI can transmit the virus to susceptible sexual partners after very few contacts in short periods of time. Phylogenetic and modeling studies have estimated that large proportions of new HIV infections may be attributable to early-stage index cases (Tables 2.1, 2.2).

Recent studies have suggested that the period of increased infectivity is not limited to the time of highest viral loads, and that certain viral factors may result in additional enhancements of transmissibility beyond the elevation due to increased viral loads. An analysis of transmission events among serodiscordant couples in Rakai, Uganda, estimated transmission rates 26 times as high during early HIV infection as during the subsequent asymptomatic period. This transmission rate ratio was more than ten times higher than the ratio the authors calculated based on previously published estimates of the functional relationship between viral load and transmissibility. Further, a mathematical modeling study of the within-host dynamics of simian immunodeficiency virus (SIV) during acute infection concluded that the infectivity of individual virions is likely to decline over the course of the earliest period. While the mechanisms of this effect and the specific form of changes in virion infectivity over time require further elucidation, these observations suggest that additional factors beyond elevated viral loads may enhance the role of EHI in epidemic spread.

**Targeting transmission prevention interventions to EHI**

Prevention interventions during EHI represent an innovative approach to preventing secondary transmission, as most current interventions among HIV-infected persons are
initiated after this period has ended. In settings where EHI is responsible for a large proportion of new cases, interventions initiated during this highly infectious phase could alter the epidemic trajectory. For these reasons, a number of researchers have called upon the public health community to focus intervention efforts on individuals with EHI.\textsuperscript{104, 106, 107, 119-122} Such interventions could include counseling to encourage prevention behaviors during the most infectious period, using a network approach to identify those exposed to acutely infected individuals, treating STIs, and initiating ART.\textsuperscript{104, 106, 107, 119-122}

Interventions during EHI may also have practical advantages over interventions initiated later. Voluntary HIV counseling and testing (VCT) and behavioral interventions can effectively lead to short-term reductions in unprotected sex among people living with HIV (PLWH), STI clinic patients, and HIV-serodiscordant couples;\textsuperscript{123-133} however, many prevention intervention effects decline over time.\textsuperscript{134} In Uganda, a country often lauded as having the most successful national HIV prevention program, HIV incidence recently has begun to rise, due at least in part to fatigue associated with the ABC (abstain, be faithful, use a condom) strategy.\textsuperscript{135} Numerous other interventions among persons with chronic (post-early) HIV infection (CHI), including several of those described above, also have been hampered by poor compliance over the long term.\textsuperscript{136} Intensive, shorter-term interventions that occur only within the brief EHI period are likely to be less susceptible to intervention fatigue and poor compliance than longer-term interventions. Furthermore, compliance with longer-term interventions initiated during EHI (rather than CHI) is likely to remain high at least through the most infectious period, minimizing the detrimental effect of waning compliance over time. Interventions initiated during EHI in sub-Saharan Africa may have an especially strong impact, as high levels of sexual partner concurrency in some parts of this region\textsuperscript{81, 137} may enable rapid and extensive propagation of HIV infection\textsuperscript{69, 79, 138} during the highly infectious early phase.
Identification of cases early in infection

Although identification of infected persons during the narrow AHI window is logistically and financially challenging, AHI screening is feasible – even in resource-limited settings – if pooling of samples and/or targeted screening is performed. In previous cross-sectional studies that we have conducted in a Lilongwe STI clinic, we estimated an AHI prevalence of 1.5% to 2.5%, and we demonstrated that AHI patients can be readily identified via RNA pooling in these types of settings.

To increase the efficiency of AHI screening in this setting, we developed a risk-score algorithm for identifying individuals most likely to be acutely HIV infected, such that HIV RNA or p24 tests could be targeted to those individuals. In the original development of the algorithm and in subsequent validation studies, we estimated that the algorithm could detect 84%-95% of AHI cases and rule out 60%-82% of HIV-negative individuals. In continued use of the algorithm, we have reduced the monthly number of patients receiving HIV RNA tests by 75% and have nearly doubled the number of AHI cases detected each month. Taken together, these results demonstrate that risk score algorithms can enable rapid, reliable AHI detection in resource-limited settings.

Despite the elevated risk of transmission during EHI and the feasibility of AHI detection, the extra effort required to identify AHI cases may be difficult to justify in settings where resources are limited and the actual contribution of EHI is small. The brevity of this period may limit its overall contribution to the epidemic, and the particular sexual behavior patterns and current epidemic phase in a given setting will determine the role of EHI in the local epidemic. If the role of EHI is small, then interventions focusing on the later phases of infection may have the greatest impact on epidemic spread. On the other hand, if the role of EHI is large, then interventions focusing on chronic HIV infection will have a limited effect. It
is therefore important to understand the role of EHI when designing and implementing HIV prevention efforts.

Mathematical Models for Assessing the Role of EHI and the Impact of Interventions

Mathematical models are valuable tools for understanding the mechanisms of disease spread, forecasting the future course of an epidemic, and predicting the effect of interventions. Epidemic models for HIV/AIDS in particular have been used to predict the effects of vaccination, ART, HSV-2 treatment, and behavior change on epidemic spread. Several HIV/AIDS models have explicitly estimated the proportion of new infections due to index cases with early infection (Table 2.2). These estimates have been close to 100% during the epidemic growth phase, and have ranged from <1% to 82% (Table 2.2) at endemic equilibrium.

The extreme heterogeneity of the estimates in Table 2.2 is due to differences in “early HIV” definitions, population-specific parameter values, epidemic phases of interest, and model types. It is difficult to quantify the extent to which different results can be attributed to particular model features, as each model has had a unique and multifaceted set of components, and interactions among parameters and structural features can have non-linear effects. In general, the predicted role of EHI will be higher earlier in the epidemic than later, because the percentage of index cases in EHI declines over time. The predicted contribution of EHI also will increase with its assumed relative duration, and will depend on the model structure used for generating estimates.

Four general model types have been used: linear models and three types of dynamic models. Dynamic models incorporate the non-linear feedback process underlying epidemic systems, in which incidence of new infections depends on infection prevalence in the
population. Linear models ignore this process. While linear models can be useful for short-term planning, dynamic models are more appropriate for providing longer-term insights into epidemic spread and intervention effects. The three types of dynamic models that have been used for estimating the contribution of EHI are: 1) “mixing models” that assume every sexual contact is instantaneous and occurs with a new partner; 2) “pair models” that assume every contact occurs within a monogamous partnership of finite duration; and 3) “hybrid models” that include partnerships of finite duration as well as random, one-off contacts. Mixing models with only one-off contacts predict higher contributions of EHI to the epidemic than do “pair models,” since pair models allow the infection to remain “trapped” within or “excluded” from monogamous partnerships during the most infectious period. Hybrid models that include both types of contact allow these “trapping” and “excluding” effects, but also allow the possibility of HIV “escape” from or “entry” into some partnerships via one-off, casual contacts. Hybrid models are likely to represent sexual contact patterns and HIV transmission dynamics more realistically than pure “mixing” or “pair” models.

The need for more research
No prior study has used a “hybrid” model to examine the contribution of EHI to HIV epidemic spread in Sub-Saharan Africa, the hardest-hit region in the world. Further, no study has examined the potential impact of interventions initiated during EHI in this region, and no prior model has used detailed behavioral and viral load data from the setting of interest to examine the role of EHI and the potential effect of interventions initiated during this time. Given the elevated transmission risk during this period and the corresponding potential for this period to play a large role in perpetuating HIV spread, it is important to gain a better understanding of this period, its effects on HIV transmission, and its power as a target for prevention efforts.
Table 2.1. Proportion of new HIV infections attributable to early index cases in phylogenetic studies

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Population / Setting</th>
<th>Early HIV definition</th>
<th>% new cases due to EHI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yerly (2001) (^{109})</td>
<td>Mixed / Switzerland</td>
<td>First 3-12 months</td>
<td>29%</td>
</tr>
<tr>
<td>Pao (2005) (^{110})</td>
<td>Mostly MSM / UK</td>
<td>First 6 months</td>
<td>34%</td>
</tr>
<tr>
<td>Brenner (2007) (^{111})</td>
<td>Mixed / Quebec</td>
<td>First 6 months</td>
<td>49%</td>
</tr>
<tr>
<td>Lewis (2008) (^{112})</td>
<td>MSM / UK</td>
<td>First 6 months</td>
<td>25%</td>
</tr>
</tbody>
</table>

MSM = Men who have sex with men
## Table 2.2. Proportion of new HIV infections attributable to early index cases in mathematical modeling studies

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Population / Setting</th>
<th>Model type</th>
<th>EHI duration (months)</th>
<th>% new cases due to EHI</th>
<th>Factors varied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacquez (1994)</td>
<td>MSM / USA</td>
<td>Mixing</td>
<td>2</td>
<td>25% - 51%</td>
<td>Number of sexual activity groups; Sexual contact rates; Early transmission probability</td>
</tr>
<tr>
<td>Pinkerton (1996)</td>
<td>MSM / USA</td>
<td>Linear</td>
<td>2</td>
<td>25% - 90%</td>
<td>Early transmission probability; Number of acts per partner</td>
</tr>
<tr>
<td>Koopman (1997)</td>
<td>MSM / USA</td>
<td>Mixing</td>
<td>1.5</td>
<td>20% - 47%</td>
<td>Aging process; Number of sexual activity groups</td>
</tr>
<tr>
<td>Kretzschmar (1998)</td>
<td>MSM / USA</td>
<td>Mixing, Pair</td>
<td>1-2</td>
<td>65% - 82%</td>
<td>Model type (mixing / pair); Pair separation rate</td>
</tr>
<tr>
<td>Coutinho (2001)</td>
<td>Mixed</td>
<td>Linear</td>
<td>1.5</td>
<td>2% - 89%</td>
<td>Aging process; Sexual contact patterns; Relationship: viral load, infectivity</td>
</tr>
<tr>
<td>Xiridou (2004)</td>
<td>MSM / Amsterdam</td>
<td>Hybrid</td>
<td>1 – 5</td>
<td>&lt;1% - 39%</td>
<td>Partnership type (casual / steady); Ratio of partnership to EHI length</td>
</tr>
<tr>
<td>First author (year)</td>
<td>Population / Setting</td>
<td>Model type</td>
<td>EHI duration (months)</td>
<td>% new cases due to EHI</td>
<td>Factors varied</td>
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<tr>
<td>Hayes (2006)(^{115})</td>
<td>Heterosexuals / Uganda</td>
<td>Mixing, Pair</td>
<td>5</td>
<td>23% - 41(^d)</td>
<td>Sexual contact patterns</td>
</tr>
<tr>
<td>Pinkerton (2007)(^{25})</td>
<td>Mixed / USA</td>
<td>Linear</td>
<td>1.5 - 2</td>
<td>3% - 17%</td>
<td>Duration of EHI; Transmission rate ratio (EHI:CHI)</td>
</tr>
<tr>
<td>Abu-Raddad (2008)(^{27})</td>
<td>Heterosexuals / Kenya &amp; Cameroon</td>
<td>Mixing</td>
<td>2.5</td>
<td>7% - 15(^c)</td>
<td>Sexual mixing patterns and risk behaviors</td>
</tr>
<tr>
<td>Salomon (2008)(^{117})</td>
<td>Heterosexuals / Uganda</td>
<td>Linear</td>
<td>5</td>
<td>~20% - 40(^d)</td>
<td>Sexual contact patterns; ART patterns</td>
</tr>
<tr>
<td>Hollingsworth (2008)(^{22})</td>
<td>Heterosexuals / Uganda</td>
<td>Mixing, Pair</td>
<td>2.9</td>
<td>9% - 31%</td>
<td>Model type (mixing vs.pair)</td>
</tr>
<tr>
<td>Prabhu (2009)(^{26})</td>
<td>Mixed / USA</td>
<td>Linear</td>
<td>1.5</td>
<td>11%</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

\(^{a}\) Linear models fail to include the non-linear dependency of HIV incidence on HIV prevalence. Mixing models assume that HIV transmission can only occur during instantaneous contacts between susceptible and infected individuals. Pair models assume that HIV transmission can only occur within serodiscordant couples. Hybrid models combine the transmission routes of mixing and pair models to allow transmission both within and outside of steady partnerships; therefore, hybrid models are likely to capture transmission dynamics more realistically than a pure mixing model or pure pair model.

\(^{b}\) Transmission probabilities were drawn from the population category shown, but the reported estimates result from a range of hypothetical sexual behavior parameters that do not necessarily reflect a specific population.
The range of estimates shown was extracted from the endemic-phase portion of graphs showing the time-course of the proportion due to EHI.

Range of estimates reflects the proportion of all transmissions during an individual’s entire infectious period that occur during EHI. The extent to which this proportion corresponds with the proportion of all transmissions that occur during EHI at the population level will depend on the epidemic phase and the distribution of sexual contact patterns in the population.

Table 2.2 is reprinted from Current Opinion in HIV and AIDS, Volume 5, Issue 4, William Miller, Nora Rosenberg, Sarah Rutstein, and Kimberly Powers, “Role of acute and early HIV infection in the sexual transmission of HIV,” pages 277-282, with permission from Wolters Kluwer Health.
Figure 2.1. Effects of missing censoring information on measuring partnership lengths

Solid and dashed bars represent measured and true partnership lengths, respectively. Partner A is represented in light gray, and Partner B in dark gray. If no information is available to indicate whether a partnership continues beyond the time of interview, it is not possible to determine whether the most recent act is the LAST (partnership-ending) act with a given partner. If a partnership continues beyond the time of interview, as depicted for partner A, then the measured partnership length will be an underestimate of the true partnership length.
CHAPTER 3: RESEARCH DESIGN AND METHODS

For our first specific aim, which was related to the heterosexual infectivity of HIV-1, we conducted a systematic review and meta-analysis of published studies on the topic. For our second specific aim, which was related to describing sexual partnership patterns, we analyzed data from the Kamuzu Central Hospital (KCH) Sexually Transmitted Infections (STI) Clinic in Lilongwe, Malawi. For our third specific aim, which was related to the role of early HIV infection (EHI) in epidemic spread and transmission prevention, we conducted a mathematical modeling study. Our mathematical model was based on findings from the first two aims, as well as additional data from our previous work in Malawi. We provide separate, detailed descriptions of the methods for each aim below.

The heterosexual infectivity of HIV-1 (Aim 1)

Literature search
To identify literature for our review, we searched the PubMed/Medline and Web of Science Databases through April 27, 2008 with the following terms: (HIV OR "human immunodeficiency virus") AND ((transmission AND (probability OR efficiency OR rate)) OR (transmission AND risk AND ((per AND contact) OR (per AND act))) OR infectivity OR infectiousness OR transmissibility) AND (sexual OR heterosexual OR coital).

Study selection
From the articles resulting from the search terms above, we examined the abstracts (if available) to identify articles that met any of the following criteria: 1) articles that mentioned any type of transmission probability estimate, 2) articles that described mathematical models that might have used transmission probability estimates as inputs, or 3) articles that related the frequency of heterosexual contact to HIV transmission in the study population. If the abstract was unavailable, we examined the title to see if it referred generally to heterosexual transmission. To identify articles producing estimates of the heterosexual infectivity of HIV, we then conducted a detailed, manual review of the text and bibliographies of articles meeting any of the criteria described above. We then excluded articles that provided only: 1) graphical displays of continuous infectivity functions (but no point estimates), or 2) upper and lower infectivity limits (but no point estimates) if the same data were used in other articles to generate point estimates.

*Extraction and calculation of infectivity estimates and standard errors*

We extracted two types of estimates (where available) for each study population in each article meeting our inclusion criteria. First, we extracted the most precise overall infectivity estimate; that is, the estimate calculated in the entire study population. Second, we extracted the most precise stratified estimate within each co-factor category available in a given article. The co-factors of interest were genital ulcer disease (GUD), any (non-specific) STI, male circumcision status, female bacterial vaginosis (BV), age, HIV-1 subtype, index disease stage, index viral load, antiretroviral (ARV) use, sexual contact type, geographic region, and transmission direction (male-to-female vs. female-to-male). In articles with all male or all female index cases, the “overall” estimate was the same as the estimate stratified by transmission direction.
As the focus of our analysis was restricted to HIV-1, we included estimates produced specifically for HIV-1, as well as any type-nonspecific estimates derived outside of West Africa, since HIV-1 predominates outside of that region. In cases where an estimate was not reported but could be calculated from the available data, we used Equation 1 in Appendix One to calculate an estimate.

We also recorded the corresponding standard error for each infectivity estimate that we extracted or calculated. If a standard error was not reported, we used the methods described in Appendix One to calculate approximate standard errors.

As multiple articles could share (partially or wholly) a single study population, we included from each study population only the most precise overall estimate and most precise stratified estimate within each co-factor category in order to avoid duplication. We applied a half-integer continuity correction when 0 transmission events were reported.

**Extraction of information about study methodological features**

We extracted information about the following study methods corresponding to each population’s most precise overall estimate: 1) partnership status of susceptible individuals (independent individual versus partner of a person known to be HIV-infected); 2) timing of exposure and outcome assessment (cross-sectional versus longitudinal); 3) method for defining the index case’s infection date (if used to determine the start of HIV exposure); 4) exclusion or inclusion of susceptible individuals reporting sexual contacts outside the defined index case set; 5) exclusion or inclusion of susceptible individuals reporting possible blood exposures to HIV; 6) length of the interval between HIV tests in longitudinal analyses, 7) exclusion or inclusion of condom-protected acts; 8) exclusion or inclusion of adjustment for self-report error; and 9) type of analytical model.
Aim 1 Analyses – Relationship between overall estimates and study methods

To relate the overall infectivity estimates to the study methods of interest, we first calculated a pooled, random-effects estimate of infectivity within each study design or analysis category. We used stratified homogeneity tests to examine the consistency of estimates within categories, based on the stratum-specific p-value for Cochran’s Q. Next, we conducted a series of univariable random-effects meta-regression analyses, each with overall infectivity as the dependent variable. In each meta-regression, a particular study design or analysis feature was the independent variable. To determine whether any infectivity estimates were particularly influential on our results, we conducted a series of repeat meta-regression analyses, excluding one estimate from the analyses in each series.

Aim 1 Analyses – Relationship between co-factors and infectivity

We used a similar approach to examine differences in infectivity according to transmission co-factors. For each co-factor, we performed stratified meta-analyses and univariable meta-regression analyses (this time with stratified estimates), again using a random effects model and the p-value for Cochran’s Q to assess the consistency of estimates within a category. To assess the independent effect of each transmission co-factor (controlling for other factors), we also created one multiple meta-regression model for each combination of co-factors with at least one infectivity estimate available for each stratum. Due to the limited number of stratified estimates, we did not perform influence analyses around transmission co-factor results.

Aim 1 Analyses – Effect Measures

In each meta-regression analysis, the regression coefficient represented the average “infectivity difference” associated with a particular study method or transmission co-factor. In the analysis of study methods, the infectivity difference was the absolute difference in
(weighted) average infectivity comparing studies using one type of method (e.g., longitudinal measurements) with studies at a “reference” level (e.g., cross-sectional measurement). In the co-factor analysis, the infectivity difference compared infectivity for populations at one co-factor level (e.g., 100% GUD) with infectivity for populations at a “reference” level (e.g., 0% GUD).

We used Stata software (StataCorp., College Station, Texas), version 9.2, to conduct all meta-analyses, using restricted maximum-likelihood to estimate the among-population variance in each meta-regression.

Aim 1 Limitations
Due to the ethical and logistical challenges of conducting infectivity studies, current estimates are limited, both in terms of quantity and quality. Therefore, our ability to calculate accurate pooled estimates and to quantify the effects of study methods and transmission co-factors were limited by the available data. As described in greater detail in Chapter 4, the independent effect of a given study method or co-factor of interest could therefore differ considerably from the value we calculated.

Aim 1 Strengths
Our study is the first systematic review and meta-analysis of the heterosexual infectivity of HIV-1, and as such, provides a current and comprehensive summary of this parameter. Our analyses quantify the potential effects of transmission co-factors at the per-contact level, such that future epidemic models can select the most appropriate infectivity estimates for a given setting, and risk communication messages can be appropriately tailored to a particular audience. Additionally, our careful detailing of study methods and their potential effects on infectivity estimates provides a critical framework with which to understand these estimates.
Heterosexual partnership patterns (Aim 2)

Data sources

The data for this aim were collected at the baseline and one-week follow-up visits of a longitudinal study of HIV viral dynamics conducted at KCH STI Clinic.

Study setting

The KCH STI Clinic is a free-standing public clinic that sees approximately 10,000 patients per year. HIV seroprevalence among KCH STI Clinic patients is approximately 40%, and prevalence of acute HIV infection (AHI) is approximately 1.5%. Approximately 14% of KCH STI clinic patients present with genital ulcer disease, 27% of males present with urethral discharge, and 68% of females present with abnormal vaginal discharge or lower abdominal pain.

Study population

The study population comprised adults presenting to the outpatient KCH STI Clinic in Lilongwe, Malawi from February 27, 2003 through October 21, 2004. During this time, trained clinical officers invited all eligible clinic attendees to be screened for enrollment.

Eligibility for screening

In order to be eligible for enrollment, interested participants had to be 18 years of age or older, antiretroviral naïve, presenting with a condition not requiring inpatient care, able and willing to provide informed consent, willing to be HIV tested, and prepared to return for follow up at seven days and periodically for up to four months. Patients living too far from Lilongwe to make regular return visits were discouraged from enrolling.
Recruitment into longitudinal study

As the primary aim of the longitudinal study was to compare HIV viral dynamics in patients with AHI versus chronic HIV infection (CHI), recruitment for the longitudinal study focused on identifying individuals with positive HIV p24 antigen results at baseline. These p24-positive participants were considered “likely acute cases” at enrollment. For each enrolled p24-positive patient, a target of three individuals with negative p24 results were identified, along with one HIV-antibody-positive patient (matched on sex). The secondary analyses in this dissertation include all patients who were recruited into the longitudinal study and returned for the one-week follow-up visit.

Data collection

At the baseline visit, trained HIV counselors provided HIV pre-test counseling and drew blood for HIV testing after written informed consent was obtained. Clinical staff then administered a brief questionnaire with items related to demographics, sexual history, and medical history. Next, a brief physical examination was performed, including a genital examination with speculum in women, and patients were treated for STIs according to the Malawian Syndromic Management Guidelines. All patients were asked to return the next week for follow-up of STI symptoms.

At the one-week follow-up visit, an additional questionnaire sought the following information on a maximum of three sexual partners with whom the participant reported sexual contact in the prior two months: type of partner, number of months since the first sexual contact with the partner, and number of days since the most recent sexual contact with the partner.

HIV testing
HIV antibody testing was performed in accordance with the Malawi AIDS Counseling and Resource Organization scheme. Serum was tested in the STI clinic by with two, parallel, rapid tests: Determine (Abbott Laboratories, Abbott Park, IL) and Unigold (Trinity Biotech, Wicklow, Ireland). Clients with concordant positive rapid tests were counseled as HIV infected, and were referred to the Lighthouse HIV Clinic. Clients with concordant negative rapid tests were counseled as HIV uninfected, but were asked to return to the STI clinic in one week to receive the results of RNA and p24 testing. Patients with discordant rapid test results were informed that their results were indeterminate, and were also asked to return in one week to obtain results from RNA and p24 tests.

PCR testing was performed at the UNC Project Laboratory in Lilongwe, Malawi, which was certified by the NIH-sponsored Virus Quality Assurance Laboratory for Roche Monitor RNA testing. Plasma from all patients with discordant or dual-negative rapid tests were manually pooled using a 50:5:1 scheme. Each master pool of plasma from 50 individuals was tested with the Ultrasensitive Roche Monitor HIV RNA Assay, Version 1.5 (Pleasanton, CA), following the manufacturer’s package insert. If a master pool was found positive for HIV RNA, then its component, intermediate pools were tested with the same assay. All individual specimens in positive intermediate pools were then tested with the standard Roche Monitor assay to identify the infected individual. HIV p24 tests were performed with the Perkin-Elmer p24 antigen assay, and Western Blot was performed using a standard kit (Bio-Rad Laboratories).

**HIV status determination**

We classified subjects with concordant-positive rapid tests as being chronically HIV-infected (CHI). We classified subjects with discordant or dual-negative rapid tests and negative PCR results as HIV-negative. We classified subjects who had detectable HIV RNA and who met
one of the following three criteria as acutely HIV-infected (AHI): 1) dual-negative rapid tests, 2) discordant rapid tests and negative or indeterminate Western Blot, or 3) discordant rapid tests and weakly positive Western Blot with subsequent Western Blot evolution. To confirm that subjects classified as AHI were truly infected, we asked these patients to return for rapid test and Western Blot at weeks 1, 2, 4, 8, 12, and 16 after baseline, in order to establish seroconversion in these patients.

Data management

Data from the questionnaire, physical examination, and HIV tests were collected on paper forms and double-entered into Microsoft Access or Excel (Microsoft Corporation, Redmond, WA). We converted the single-entry databases to SAS System for Windows, Version 9.1 (SAS Institute, Inc., Cary, NC) and checked them against one another. We consulted paper forms to reconcile all discrepancies between the two entries in order to create a validated dataset. We conducted all analyses involving generalized estimating equations (GEE) with Stata 9.2 and all other analyses with SAS 9.1.

Aim 2 Analyses - Probability of Selection

Because study participants were selected based (in part) on their sex and HIV test results, we weighted analyses by participants’ inverse probabilities of selection, calculated as the reciprocal of: the number of enrolled participants of a given sex and HIV status, divided by the total estimated number of patients of that sex and HIV status visiting the STI clinic during the study period. The estimates of the number of patients within a sex and HIV status category visiting the clinic were based on administrative data collected separately from this study.

Aim 2 Analyses - Partnership Lengths
To calculate the length of each reported partnership, we first converted the time since first sex into days by multiplying the reported number of months $M$ by 30. We then calculated the partnership length as the number of days between the first and most recent sexual contact with the partner (Figure 5.1A in Chapter 5). Partnerships defined by a single contact were assigned partnership lengths of zero.

We estimated the mean partnership length and corresponding 95% confidence interval across participants, both overall and according to selected predictor variables, using GEE to account for the possibility of multiple partnerships per participant. We used inverse-probability-of-selection weighting and specified an exchangeable working correlation matrix. The predictor variables of interest were sex, age (18-24 years, 25-29 years, 30+ years), marital status (married vs. unmarried), partner type (spouse/live-in partner, non-cohabitating boyfriend/girlfriend, casual acquaintance, transactional partner), partnership pattern in the prior 2 months (<2 partners, concurrency, consecutive – see definitions below), travel in the prior 2 months (any vs. none), transactional sex in the prior 2 months (any vs. none), baseline HIV status (negative, AHI, EHI), baseline genital ulcer disease (GUD) status (GUD vs. no GUD), and baseline urethral discharge (UD) status in males (UD vs. no UD).

Because mean partnership lengths can be heavily influenced by extreme values, we also calculated weighted median partnership lengths in the overall population and in each subgroup, along with the corresponding weighted maxima, minima, and 25th and 75th percentiles. These calculations did not account for multiple partnerships per participant.

To compare partnership lengths across predictor categories, we calculated partnership length differences (PLDs) as the weighted mean partnership length in a comparison group minus the corresponding value in a referent group, and partnership length ratios (PLRs) as
the former divided by the latter. The corresponding 95% confidence intervals were calculated using empirical covariance values from the GEE output.

**Aim 2 Analyses – Gap and overlap lengths**

Among those reporting contact with two or more partners in the two months prior to the STI clinic visit, we also calculated the “gap length” between each set of partners as the number of days since the most recent sexual contact with the less-recently-contacted partner minus the number of days since the first sex with the more-recently-contacted partner (Figure 5.1 in Chapter 5). Positive gap lengths characterized *consecutive partnerships* (no overlap), and zero or negative gap lengths characterized *concurrent partnerships* (overlap).

Among those with negative gap lengths (i.e., concurrency), we calculated the *overlap length* across each set of partners in one of two ways. If one partnership was entirely contained within another, we calculated the overlap length as the time of first sex with the less-recently-contacted partner minus the time of most recent sex with that partner (Figure 5.1B in Chapter 5). If the partnership with the less-recently-contacted partner began prior to the partnership with the more-recently-contacted partner, we calculated the overlap length as the time of first sex with the latter minus the time of most recent sex with the former (Figure 5.1C in Chapter 5). If these two acts occurred on the same day, the overlap length was zero (Figure 5.1D in Chapter 5).

Among those with positive gap lengths (i.e., consecutive partnerships), we calculated the average gap length using negative binomial regression with generalized estimating equations, again with inverse-probability-of-selection weights and an exchangeable working correlation matrix. We used analogous methods to calculate average overlap lengths.
among those with negative gap lengths (i.e. concurrency). There were too few participants reporting multiple partners to compare gap and overlap lengths across predictor categories.

**Aim 2 Analyses – Partnership Patterns**

We calculated the proportion of participants in each of the following categories, based on reported sexual behavior in the two months prior to the STI clinic visit: a) fewer than two partners, b) two or more *consecutive* partnerships (gap length > 0), or c) two or more *concurrent* partners (gap length ≤ 0). We combined those with 0 or 1 partner into a single category (a) to improve estimation efficiency, as these individuals are relatively similar with respect to onward transmission risk (compared with those reporting multiple partners).

To assess the associations of these partnership patterns with the predictor variables of interest, we conducted two rounds of multinomial logistic regression, again using inverse-probability-of-selecting weighting. In the first round, category (a) (< 2 partners) was the referent category; in the second round, category (b) (consecutive partnerships) was the referent.

**Aim 2 Limitations**

The data collection methods utilized in this and similar studies have important implications for measuring partnership, gap, and overlap lengths and for classifying partnership patterns. First, we did not have information about whether partnerships continued beyond the time of the clinic visit. Our method of calculating partnership lengths assumed that the most recent contact was the final (partnership-ending) contact; however, some partnerships are likely to have continued beyond the time of the STI clinic visit. Therefore, the partnership lengths reported in this dissertation reflect the time since participants began having sex with each partner (i.e., the *current* partnership duration), but likely underestimate the *entire* duration of
the partnership from beginning to end (Figure 3.1A; Figure 2.1 in Chapter 2). Only with information about whether partnerships were ongoing, along with Kaplan-Meier survival analysis methods, could we have obtained more accurate partnership length values.

Second, because the most recent contact with each reported partner must have occurred within the “look-back period” of two months, each gap between consecutive partners had to be fully contained within that period. Therefore, the maximum allowable gap length that could be measured in this study was 60 days.

Third, the collection of dates of first sex in terms of months instead of days prior to the clinic visit, along with our method of calculating the number of days as 30 times the number of months, could have biased (in either direction) our partnership and gap length measurements (Figures 3.1B – 3.1E). These methods could also have led to misclassification of both consecutive and concurrent partnerships (Figures 3.1B – 3.1E).

Although the mean and median partnership lengths estimated in each subgroup are likely to be underestimates, given the likelihood of right-censoring of at least some of the partnerships, the PLDs and PLRs that we calculated provide unbiased comparisons between groups if certain conditions hold. Specifically, if partnership lengths were censored by the same absolute amount in each category, then the PLDs will be valid estimates of the absolute differences between groups. If partnership lengths were instead censored by the same relative amounts, then the PLRs will be valid estimates of the relative differences between groups.

In addition to the measurement issues related to data collection that we have discussed, we also note that the necessary reliance on self-reported data may have introduced recall error
and social desirability bias. The former may have biased results in either direction, while the latter is likely to have resulted in deflated estimated proportions of those engaging in multiple partnerships. Additionally, because we collected information only on partners contacted in the two months prior to an STI clinic visit, generalizability to longer-term trends and other types of populations is uncertain. Finally, because the data were cross-sectional and the small sample size precluded multivariable analyses, we were unable to assess causal relationships between predictors and the parameters of interest. However, the main goals of these analyses were descriptive in nature.

**Aim 2 Strengths**

Detailed data on sexual behavior patterns are limited, particularly among sub-Saharan African populations. Our results provide parameter estimates for certain types of mathematical models that have seen limited use previously due to insufficient data; in particular, our Aim 2 results were used in our Aim 3 modeling analyses. The results of our analyses also highlight the need to consider the variety of forms that sexual partnerships can take when describing HIV transmission risk.

We also note that we carefully tailored our analytical approach to the particular features of the primary data that we were analyzing: we used GEE to account for multiple partnerships per participant, we compared mean and median partnership lengths to assess the effects of extreme values, and we calculated PLDs and PLRs to provide valid comparisons of partnership lengths in the presence of censoring.

**The contribution of EHI and its potential as a target for prevention interventions (Aim 3)**

**Study population**
We based our model development and analyses on a single, representative population from an urban, sub-Saharan African setting: the population of Lilongwe, Malawi. As in much of sub-Saharan Africa, the HIV epidemic is mature, hyperendemic, and generalized in Malawi, and heterosexual contact is the primary mode of transmission. The dominant viral subtype is clade C. We chose the population of Lilongwe based on our long-standing research, training, and care collaborations with the Malawi Ministry of Health and the KCH. These collaborative activities have generated large amounts of high-quality data to directly inform our model structure and parameter values.

Data sources

Four general parameter types were important in our modeling: 1) sexual behavior patterns, 2) probabilities of HIV transmission, 3) durations of HIV stages, and 4) demographic rates. We derived values for sexual behavior parameters from the analyses we described above for Aim 2. We based transmission probabilities and HIV stage durations on the results of Aim 1, other published literature, and observed patterns of viral load in our research setting.\(^{12, 19, 22, 145}\) We derived birth and death rates from Malawi census data.\(^{146}\) We describe the use of these data sources for deriving parameter values in greater detail in Chapter 6 and its associated Appendices (Appendices Two – Seven).

Aim 3 Analyses – Model Structure

In real populations, HIV will become “trapped” within a monogamous partnership of two infected individuals, and will be “excluded from” a monogamous partnership of two susceptibles, for the entire duration of the relationship. If sexual contacts occur outside of these partnerships, however (i.e., if a partnership is not mutually monogamous), then HIV can “escape” or “enter” the partnership. To describe HIV transmission dynamics in Lilongwe, we used a modeling approach that explicitly included sexual contacts occurring
within steady partnerships, as well as casual, one-off contacts occurring outside of these partnerships. We describe this type of model as a “hybrid,” as it combines certain features of “mixing models” (which allow only casual, one-off contacts) and “pair models” (which allow contacts only within steady, monogamous partnerships). By combining features from both types of model, the “hybrid” model provides an improved representation of reality over that provided by either type of model alone. Appendix Two contains a diagram of a simplified hybrid model; we show this simple model for ease of illustration, and we describe our modifications to the model below.

To reflect the natural history of HIV, we extended the hybrid model to allow changes in the probability of secondary HIV transmission over the course of infection. To capture the meaningful intervals at which individuals can be detected during early infection, as well as the relationship between viral load and transmission probabilities over time, we divided the early period into five separate intervals (Appendix Three). Additionally, we allowed an increased death rate during AIDS relative to overall (“baseline”) population mortality, and we included two separate risk groups to reflect heterogeneity in risk. These modifications are described in detail in the Chapter 6.

Aim 3 Analyses – Bayesian Melding Procedure

We used a Bayesian Melding approach to account for uncertainty in model input parameters and to express uncertainty about the predicted contribution of EHI to epidemic spread. This approach combines prior information about the model inputs (e.g., sexual behavior, HIV transmission probabilities) with data about one of the primary outputs (HIV prevalence). The sources of prior information on model inputs are described above. For the data on model output, we used HIV prevalence estimates collected at Lilongwe antenatal clinics (ANC) over the period 1987 – 2005. While ANC data must be calibrated to account for biases
toward urban prevalence when applied to model predictions of national HIV prevalence,\textsuperscript{145}.\textsuperscript{147} Our model pertains only to the urban setting of Lilongwe, so we used the Lilongwe ANC data without calibration. We describe the details of our Bayesian Melding analyses in Chapter 6 and Appendix Five.

We used the Berkeley Madonna software package for all modeling analyses. The Berkeley Madonna package allows easy entry of model equations and parameter inputs, and provides both tabular and graphical outputs showing the results of model simulations. We used SAS 9.1 to perform all statistical analyses on model output.

\textit{Aim 3a Analyses – Calculating the Proportion of New Cases Attributable to EHI}

The model outputs included the number of individuals in each model compartment (i.e., the number of individuals who were singles and paired by infection status and stage) at discrete, closely spaced time points over the period modeled. To determine the proportion of new cases attributable to EHI index cases, we included code to calculate the cumulative number of incident infections attributable to index cases in each infection stage, and from those output we then calculated the proportion of new infections attributable to early-stage index cases during each time step.

\textit{Aim 3b Analyses – Estimating Intervention Impact}

We modeled three general intervention scenarios: 1) scenarios where an intervention acted only during EHI, 2) scenarios where an intervention acted only during CHI, and 3) scenarios where an intervention acted during both EHI and CHI. The intervention was assumed to act by reducing the per-contact transmission probability to 0.000033 in those receiving it. This value was calculated based on estimates in the presence of completely suppressed viral loads,\textsuperscript{148} but it can also represent transmission probability from another highly effective
intervention, such as effective condom use. We explored the various intervention scenarios by varying the proportion of infected individuals in EHI or CHI who received the intervention.

We assumed that an intervention acting within a particular infection period began early in that period and remained effective throughout the remainder of the period. All interventions were assumed to begin in 2010. Our primary measure of intervention effect was the predicted reduction in HIV prevalence between 2010 and 2040 (compared to no intervention). We also examined the predicted proportion of new cases averted over a shorter time period (2010-2015). The intervention analyses are described in greater detail in Chapter 6 and its associated Appendices.

Aim 3 Limitations
Mathematical models are simplified representations of complex phenomena, and the accuracy of their results directly depends on how well the model structure and parameters reflect reality. As described above, the hybrid model that we constructed is likely to correspond more closely with reality than simpler “mixing” or “pair” models; however, an important limitation of current HIV transmission models (including our own) is the relative scarcity of valid, reliable estimates for partnership formation and dissolution rates, as well as for per-contact transmission probabilities over the course of HIV infection. Our analyses for Aim 2 provided detailed parameters for our Aim 3 model, allowing us to base partnership dynamics on data from the setting of interest. However, as described in the section corresponding to Aim 2, these analyses had a number of limitations.

Aim 3 Strengths
Most previous models have been limited to simpler structures and/or have had to rely on data from settings other than the population being studied. We used data directly from
Lilongwe for almost all model parameters, allowing us to capture sexual contact patterns and to describe the natural history of HIV with greater realism and resolution than has been possible previously. Additionally, we formally assessed uncertainties in input parameters through our use of a Bayesian Melding approach. This approach allowed us to use HIV prevalence data to “filter” the plausible a priori parameter ranges, producing a set of the most likely parameter values given observed HIV prevalence. This approach also allowed us to express uncertainties in model outputs, producing likely ranges for: 1) the contribution of EHI, and 2) the predicted effects of interventions initiated at various points within the natural history of infection.

Although the scope of the proposed modeling effort was limited to Lilongwe, Malawi, many of the processes and parameter values included in our models are likely to be similar to those in other urban centers in sub-Saharan Africa. Therefore, while the quantitative values produced by our model are directly applicable only to Lilongwe, our qualitative findings are likely to be generalizable to other southern and eastern African settings with mature, heterosexually transmitted epidemics and limited ART access. Furthermore, parameter values in the model can be changed readily in future work to correspond more closely with specific settings outside of Lilongwe.
Figure 3.1 Effects of data collection methods on measuring lengths and classifying patterns

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<td>$F_A$</td>
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Solid and dashed bars represent measured and true partnership lengths, respectively. Bars with upward and downward diagonal hatching represent measured and true overlap lengths, respectively. Figure 3.1A represents the effect of missing censoring information on partnership length measurements. Because no information was available to indicate whether a partnership continued beyond the STI clinic visit, it was not possible to determine whether the most recent act was the LAST (partnership-ending) act with a given partner. If a partnership continued beyond the time of the STI clinic visit, as depicted for partner A, then the measured partnership length will be an underestimate of the true partnership length. Figures 3.1B-3.1E illustrate the effects of collecting the time of first contact $F_{\text{partner}}$ in terms of number of months prior to the clinic visit, assuming that participants reported the number of months correctly within 0.5 month (15 days) and reported without error the number of days since the most recent contact ($MR_{\text{partner}}$). $F_B$ represents the number of days prior to the STI clinic visit that the first contact with partner B occurred, as calculated in our analyses: the reported number of months $M$ prior to the visit, multiplied by 30 days. In Figures 3.1B and 3.1C, $F_B$ represents a date of first contact that was 15 days earlier than $M \times 30$ days and that the participant rounded down to $M$ rather than up to $M + 1$. In this type of situation, $F_B$ will have underestimated by 15 days the number of days prior to the visit, resulting in a measured partnership length 15 days shorter than the true partnership length (Figures 3.1B, 3.1C). If the most recent contact with partner A ($MR_A$) occurred within 15 days of $F_B$ (Figure 3.1C), then we also will have misclassified the pattern as being consecutive, rather than concurrent. In Figures 3.1D and 3.1E, $F_B$ represents a date of first contact that was 15 days later than $M \times 30$ days that the participant rounded up to $M$ rather than down to $M - 1$. In this type of situation, $F_B$ will have overestimated by 15 days the number of days prior to the visit, resulting in a measured partnership length 15 days longer than the true partnership length. In this situation, we either will have overestimated by 15 days the overlap length in a truly concurrent set of partners (if $MR_A < F_B$; Figure 3.1D), or we will have misclassified a set of consecutive partnerships as concurrent (if $MR_A > F_B$; Figure 3.1E). For participants reporting a third partner in the prior two months (partner C), and for actual dates that differed by fewer than 15 days from $M \times 30$, the effects of these data collection methods will have been analogous.
ABSTRACT

**Background:** Studies of cumulative HIV incidence suggest that co-factors such as genital ulcer disease (GUD), HIV disease stage, and circumcision influence HIV transmission; however, the heterosexual infectivity of HIV-1 is commonly cited as a fixed value (~0.001, or 1 transmission per thousand contacts). We sought to estimate transmission co-factor effects on the heterosexual infectivity of HIV-1 and to quantify the extent to which study methods have affected infectivity estimates. **Methods:** We conducted a systematic search (through April 2008) of PubMed, Web of Science, and relevant bibliographies to identify articles estimating the heterosexual infectivity of HIV-1. We used meta-regression and stratified random-effects meta-analysis to assess differences in infectivity by co-factors and study methods. **Findings:** Infectivity estimates were extremely heterogeneous, ranging from zero transmissions after more than 100 penile-vaginal contacts in some sero-discordant couples to one transmission for every 3.1 episodes of heterosexual anal intercourse. Estimates were only weakly associated with methodological features of the studies producing them. Infectivity differences (95% confidence intervals), expressed as number of transmissions per 1000 contacts, were 8 (0-16) comparing uncircumcised to circumcised male susceptibles, 6 (3-9) comparing susceptible individuals with and without GUD, 2 (1-3) comparing late-stage to mid-stage index cases, and 3 (0-5) comparing early-stage to mid-stage index cases. **Interpretation:** Commonly cited values for the heterosexual infectivity of HIV-1 fail to reflect the substantial variation associated with important co-factors. Co-factor effects are
important to include in epidemic models and policy considerations. Prevention messages should emphasize that HIV-1 can be transmitted efficiently through heterosexual contact.

**INTRODUCTION**

Over 33 million people are HIV-infected worldwide, with 2.5 million new infections arising in the past year alone. Every HIV infection results from a transmission event, and one of the fundamental parameters driving the spread of HIV is its *infectivity*, defined as the probability of transmission during a single potentially infectious contact between an infected and an uninfected individual. A commonly cited value of ~0.001 for the heterosexual infectivity of HIV-1 has led to claims in biomedical reports, prevention education materials, policy recommendations, and the popular press that HIV cannot be transmitted efficiently through heterosexual contact. These claims are difficult to reconcile with the large numbers of HIV infections that have been acquired through heterosexual contact since the epidemic began.

Infectivity estimation requires an accurate count of the transmission events resulting from a defined number of potentially infectious exposures experienced by a specified population of susceptible individuals. Reliable counts of potentially infectious sexual exposures are extremely difficult to obtain. Often, it is possible to estimate only an approximate number of unprotected sex acts occurring between one individual who is presumed to be infectious and another who is presumed to be susceptible over some specified interval of time. Overestimation of the number of potentially infectious exposures will deflate infectivity estimates; underestimation will have the opposite effect.

Infectiousness and susceptibility may be influenced by multiple factors, such as direction of transmission (male-to-female vs. female-to-male), type of sexual act, viral load.
circumcision, vaginal flora, age, and sexually transmitted infections (STI). The effects of these transmission co-factors on cumulative HIV incidence have been characterized; however, efforts to quantify their effects at the per-contact level have been rare, and practical applications of infectivity estimates often ignore the possibility of co-factor influence.

Accurate, detailed estimates of the heterosexual infectivity of HIV are essential for understanding the epidemic, evaluating potential interventions, and communicating risk. We undertook a systematic review and meta-analysis of observational studies estimating the heterosexual infectivity of HIV-1 to: 1) summarize existing infectivity estimates, 2) relate these estimates to methodological features of the studies producing them, 3) quantify co-factor effects on infectivity, and 4) identify gaps in understanding.

METHODS

Study Selection

We conducted a literature search in four steps. First, we searched the PubMed/Medline and Web of Science Databases through April 27, 2008 with the following terms: (HIV OR "human immunodeficiency virus") AND ((transmission AND (probability OR efficiency OR rate)) OR (transmission AND risk AND ((per AND contact) OR (per AND act))) OR infectivity OR infectiousness OR transmissibility) AND (sexual OR heterosexual OR coital). Second, we examined the resulting abstracts (or titles if the abstract was unavailable) to identify articles that: 1) mentioned any type of transmission probability estimate, 2) described mathematical models that could have used transmission probability estimates as inputs, 3) related frequency of heterosexual contact to HIV transmission, or 4) referred generally to heterosexual transmission in the title (if the abstract was unavailable). Third, we conducted
a detailed, manual review of the text and bibliographies of articles meeting these criteria to identify articles that produced estimates of the per-heterosexual-contact probability of HIV transmission. Finally, we excluded articles that provided only: 1) per-contact transmission probability estimates that were not conditional on HIV exposure, 2) graphical displays of continuous infectivity functions produced with data that were used in other articles to generate point estimates, or 3) upper and lower infectivity limits (but no point estimates) produced with data that were used in other articles to generate point estimates.

**Data Extraction**

For each study population in each article, we extracted two types of estimates (where available): 1) the most precise overall (whole-sample) infectivity estimate, and 2) the most precise stratified estimate within each co-factor category. The co-factors of interest were genital ulcer disease (GUD), any (non-specific) STI, male circumcision, female bacterial vaginosis (BV), age, HIV-1 subtype, disease stage, viral load, antiretroviral (ARV) use, contact type, geographic region, and transmission direction. In articles with all male or all female index cases, the “overall” estimate and the estimate stratified by transmission direction were one and the same.

We included estimates produced specifically for HIV-1, as well as type-nonspecific estimates derived outside of West Africa, since HIV-1 predominates outside of that region. If an estimate was not reported but could be calculated from the available data, we used Equation 1 (Appendix One) to calculate the estimate. For each infectivity estimate that we extracted or calculated, we also recorded the corresponding standard error. If the standard error was not reported, we calculated an approximate value with the methods described in Appendix One. We applied a half-integer continuity correction when 0 transmission events were reported.
Multiple articles could share (partially or wholly) a single study population. To avoid duplication, we included from each study population only the most precise overall estimate and most precise stratified estimate within each co-factor category. For each population’s most precise overall estimate, we also extracted information about the following methodological features of the corresponding study: 1) partnership status of susceptible individuals (independent individual versus partner of a person known to be HIV-infected); 2) timing of exposure and outcome assessment (cross-sectional versus longitudinal); 3) method for defining the index case’s infection date (if used to determine the start of HIV exposure); 4) exclusion or inclusion of susceptible individuals reporting sexual contacts outside the defined index case set; 5) exclusion or inclusion of susceptible individuals reporting possible blood exposures to HIV; 6) length of the interval between HIV tests in longitudinal analyses, 7) exclusion or inclusion of condom-protected acts; 8) exclusion or inclusion of adjustment for self-report error; and 9) type of analytical model.

Statistical Analyses

Assessing Heterogeneity
To assess the consistency of the overall (whole-sample) estimates, we examined the p-value for Cochran’s Q, a standard homogeneity test statistic.

We conducted two main types of analyses to relate the overall infectivity estimates to the study methods of interest. First, we calculated a pooled, random-effects estimate of infectivity within each study design or analysis category, using stratified homogeneity tests to examine the consistency of estimates within categories. Second, we conducted a series of univariable random-effects meta-regression analyses, each with overall infectivity as the dependent variable and a particular study design or analysis feature as the independent
variable. As a form of influence analysis, we conducted a series of repeat meta-regression analyses, excluding one estimate from the analyses in each series.

We used a similar approach to examine differences in infectivity according to transmission co-factors. For each co-factor, we performed stratified meta-analyses and univariable meta-regression analyses (this time with \textit{stratified} estimates) with the same methods we used for the study design and analysis characteristics. Additionally, to assess the independent effect of each transmission co-factor, we created one multiple meta-regression model for each combination of co-factors with at least one infectivity estimate available for each stratum. Due to the limited number of stratified estimates, we did not perform influence analyses around transmission co-factor results.

We used Stata software (StataCorp., College Station, Texas), version 9.2, to conduct all meta-analyses, using restricted maximum-likelihood to estimate the among-population variance in each meta-regression.

\textit{Effect Measures}

The coefficients produced by the meta-regression analyses represent average “infectivity differences” (ID) associated with study methods or transmission co-factors. In the analysis of study methods, the ID is the \textit{absolute} difference in (weighted) average infectivity contrasting studies using one type of method (e.g., longitudinal measurements) with studies at a “reference” level (e.g., cross-sectional measurement). In the co-factor analysis, the ID compares infectivity for populations at one co-factor level (e.g., 100\% GUD) with infectivity for populations at a “reference” level (e.g., 0\% GUD). For example, a weighted average infectivity of 15 transmission events per thousand contacts among those with a co-factor, compared with a value of 10 transmission events per thousand contacts among those
without the co-factor, corresponds to an infectivity difference of 5 (=15-10) transmission events per thousand contacts. In other words, an average of 5 more transmission events per thousand contacts occurred in the group with the co-factor than in the group without the co-factor.

RESULTS

Literature Search
The literature search produced 5089 articles. Of these, 4652 did not meet the eligibility criteria for detailed review. The abstracts or titles of these ineligible articles addressed various topics – including HIV prevalence, risk behaviors, and risk factors – but did not indicate production or use of per-contact transmission probability estimates. Of the 437 articles that were eligible for detailed review, 31 produced per-heterosexual-contact transmission probability estimates. Two \(^{156, 157}\) estimated transmission probabilities that were not conditional on exposure to HIV, one \(^{158}\) provided only graphical representations of continuous infectivity functions produced with data used in other (included) articles to generate point estimates, and one \(^{159}\) produced only upper and lower infectivity limits from data used in other (included) articles to generate point estimates, so our final set contained 27 articles \(^{21, 35, 44-67, 160}\). The 27 articles reported on a total of 15 unique study populations \(^{44, 57, 58, 62, 64, 65, 161-169}\).

Data Extraction

Overall estimates
We identified 32 overall (whole-sample) estimates (Table 4.1), but included in our analyses only the single most precise overall estimate (highlighted in gray in Table 4.1) from each of the 15 study populations.

Study design and analysis features

Studies based infectivity calculations on two types of events experienced by susceptible individuals: transmission events and heterosexual HIV exposures. The number of transmission events was defined by the number of susceptible individuals found (cross-sectionally or longitudinally) to be HIV-infected. Counts of heterosexual HIV exposures were estimated from the reported number of sexual contacts occurring between susceptible individuals and index cases over a period (retrospective or prospective) when susceptible individuals were assumed or known to be HIV-uninfected and index cases were assumed or known to be HIV-infected. In contexts where index cases were not specifically identifiable (e.g., studies in which the susceptible individuals were commercial sex workers or their clients), infectivity calculations included an additional term for the probability of HIV exposure in a contact, estimated as the HIV prevalence among the population with which susceptible individuals had contact.

Thirteen of the 15 overall estimates were generated by one of four basic study designs (Figure 4.1). Four \(^{21, 57, 58, 64}\) were generated by “discordant couples studies,” that is, longitudinal studies of susceptible individuals who were partners of a known HIV-positive index case. Three \(^{63, 65, 160}\) were produced by longitudinal studies of susceptible and presumptively HIV-exposed individuals (e.g. sex workers or their clients) recruited without specific index cases. In each of the longitudinal study types, susceptible individuals were HIV-seronegative at enrollment, and exposures and transmission events were measured prospectively. Five \(^{48, 50, 54, 56}\) estimates (including two from different study populations in \(^{50}\))
were from cross-sectional studies of susceptible individuals who were partners of a known HIV-positive index case. One estimate was produced by a cross-sectional study of susceptible and presumptively HIV-exposed individuals recruited without specific index cases. In each of the cross-sectional study types, HIV exposures were assessed retrospectively and the number of transmission events was assessed as the number of prevalent cases. The two estimates not from basic study designs were from “hybrid” designs: one measured HIV outcomes longitudinally among seronegative individuals reporting (retrospectively) a single sex worker contact just prior to enrollment. The other measured exposures and transmission events both cross-sectionally and longitudinally among partners of known HIV-infected individuals, and provided only an aggregate infectivity estimate across time periods.

Of the six studies that calculated the start of infectious contacts as the index case’s infection date, two (including the estimate using O’Brien data in) were able to determine the index infection date as the date of blood transfusion. The remaining four (including the estimate using California Partner Study data in) used roughly estimated index infection dates based on epidemic curves or incubation periods from previous studies. In longitudinal analyses, the length of the interval between HIV tests ranged from 2 weeks to 10 months. Nine of the 15 estimates were from studies that specified some exclusion criteria based on possible outside exposures to HIV (including two from different populations in), but only eight (including two from different populations in) accounted for condom-protected acts or noted that condom use was rare, and only three overall estimates were adjusted for self-report error. Seven of the estimates were calculated as the number of transmission events divided by the total number of exposures, five were calculated with a Bernoulli model (Appendix One), and three (including two in) were calculated as failure probabilities (Appendix One).
Transmission co-factors

We included six estimates stratified by type of act, nine by susceptibles’ GUD status, three by susceptibles’ (non-specific) STI status, four by male susceptibles’ circumcision status, ten by index disease stage, and 16 by direction of transmission. Eight overall estimates (including two in) were obtained in the US or Europe, six in Africa, and one in Asia. Estimates stratified simultaneously by more than one co-factor ranged from approximately 0 among susceptible males without GUD, most of whom were circumcised, to 0.32 (one transmission event for every 3.1 contacts) for penile-anal sex between late-stage male index cases and susceptible females (half of whom had an STI).

Information was available in fewer than two study populations for susceptible BV and for index STI, GUD, BV, viral load, ARV use, and viral subtype. We were unable to include these co-factors in our analyses, but we included disease stage and geographic region as proxy measures for viral load and subtype, respectively.

Meta-analyses

Overall heterogeneity

As illustrated in Figure 4.1, the overall infectivity estimates were extremely heterogeneous (p<0.0001 on homogeneity test).

Study design features

Our meta-analyses revealed only weak associations between overall infectivity estimates and the design and analysis features of the studies that produced them (Table 4.2). Only one infectivity difference (ID) was larger than one transmission event per thousand contacts: among longitudinal studies, infectivity was inversely associated with the HIV testing interval. Also among longitudinal analyses, studies of independent individuals produced higher
infectivity estimates than did studies of partners of known HIV cases (ID: 1.0 event per thousand contacts; 95% CI: 0.8-1.3) (results not shown in Table 4.2). Influence analyses did not reveal any undue influence of any single study on the meta-regression results.

Transmission co-factors

Numerous transmission co-factors were associated with increased infectivity (Table 4.3, Figure 4.2). In meta-regression analysis, the co-factors most strongly associated with infectivity were GUD in susceptible individuals (ID vs. no GUD: 6.0, 95% CI: 3.3-8.8), lack of circumcision in susceptible males (ID vs. circumcised males: 8.1, 95% CI: 0.4-15.8), early-stage infection in index cases (ID vs. mid-stage: 2.5, 95% CI: 0.2-4.9), and late-stage infection in index cases (ID vs. mid-stage: 1.9, 95% CI: 0.9-2.8). Infectivity was only weakly associated with geographic region (Africa vs. US/Europe), direction of transmission, and mean susceptible age. The limited data available for type of contact, susceptible STI status, and mean index age suggest that infectivity is higher for penile-anal (vs. penile-vaginal) sex, for susceptibles with (vs. without) STI, and for older (vs. younger) index cases; however, there were insufficient data to conduct meta-regression analyses on these co-factors. The single estimate produced in an Asian setting was considerably higher than estimates produced in the US or Europe.

We were able to fit only four multiple meta-regression models, due to missing co-factor information, the limited number of studies, and collinearities among variables. Most associations in the multivariable analyses were in the same direction as in univariable meta-regression, with some attenuation or amplification (results not shown).

DISCUSSION
The use of a single, “one-size-fits-all” value for the heterosexual infectivity of HIV-1 obscures important differences associated with transmission co-factors. Perhaps more importantly, the particular value of 0.001 (i.e., 1 infection per 1,000 contacts between infected and uninfected individuals) that is commonly used appears to represent a lower bound. As such, it dramatically underestimates the infectivity of HIV-1 in many heterosexual contexts. Of the 11 overall estimates near or below 0.001 identified in this study, 9 were produced in analyses of stable couples with low prevalences of high-risk co-factors. In other contexts – particularly if the susceptible partner has an STI or is uncircumcised, if contact is penile-anal, or if the index case is in early- or late-stage infection – heterosexual infectivity can exceed 0.1 (1 transmission per 10 contacts) or even 0.3 (1 transmission per 3 contacts) 44, 48, 51, 55, 65. Claims in both the popular media 170, 171 and the peer-reviewed literature 6, 7 that HIV is extremely difficult to transmit heterosexual are dangerous in any context where the possibility of HIV exposure exists.

Observation of co-factor effects at the level of cumulative incidence has been critical to the development of interventions designed to reduce HIV incidence. Understanding co-factor effects at the per-contact level is also important, as HIV exposure and transmission occur during discrete contacts between infected and uninfected individuals, and many epidemic models rely on parameter inputs at the per-contact level. Our results, which relate to transmission at the per-contact level, are consistent with numerous studies of cumulative HIV incidence showing that STIs, decreased age, and lack of circumcision increase susceptibility; that increased age and both early- and late-stage index infection amplify transmissibility 12-14, 17, 18, 44, 153-155, and that heterosexual transmission is more efficient through penile-anal contact than through penile-vaginal contact 9, 10. Additionally, our finding that penile-anal transmission is more efficient than penile-vaginal is consistent with infectivity studies conducted among men who have sex with men 172, 173. The sharply increased
infectivity reported in an Asian setting may reflect differences by subtype, disease stage, or unmeasured or poorly measured co-factors; the infectivity study \(^{51}\) conducted in Asia took place at the start of the epidemic when a large proportion of index cases were in early stages of infection \(^{51, 52}\). We also note that the study was conducted among commercial sex workers’ clients; therefore, HIV prevalence estimates among the commercial sex worker population were required to estimate the probability of HIV exposure in infectivity calculations. If prevalence were underestimated in these calculations, the infectivity would have been biased upward.

The reduced infectivity observed among circumcised male susceptibles is consistent with results of randomized trials of circumcision for HIV prevention \(^{13, 174, 175}\). The observed increases in infectivity associated with STI are less readily compared to community-randomized trials of STI treatment on HIV incidence. While one such trial achieved a 40% reduction in HIV incidence through syndromic STI management \(^{29}\), other trials of STI treatment interventions have failed to show effects on HIV incidence \(^{31, 168, 176}\). Various explanations have been offered for the lack of intervention effects, including insufficient power \(^{31}\), convergence of treatment intensity between groups \(^{168}\), and high prevalences of HSV-2 in both intervention and control communities \(^{31, 168}\). Because the “STI” group in our analysis was not restricted specifically to those with the same treatable STI targeted in the intervention trials, the results of STI treatment trials are not directly comparable to the STI-related results shown here.

The observed differences in infectivity according to index disease stage deserve particular attention. The estimates produced for “mid-stage” infection were very homogeneous, and the pooled estimate for this stage (0.7 transmissions per 1000 acts) is approximately equal to the commonly cited value of 1 transmission per 1000 acts. The probability of transmission
is likely much higher outside of this period, especially during acute (pre-seroconversion) HIV, when viral loads are sharply elevated, acquired immunity in acutely infected individuals’ partners is absent, and a substantial portion of transmission events occur\textsuperscript{111}. No study has directly measured transmission during the brief acute phase. The “early” infectivity estimate of Leynaert et al\textsuperscript{55} was based on a retrospective exposure period with crudely estimated dates of index infection, and the estimate of Wawer et al\textsuperscript{21} corresponded to the period up through 5 months after seroconversion. As others have noted\textsuperscript{21,177}, couples in whom transmission occurs during the brief acute phase cannot be selected for “discordant couples” studies, which follow susceptible partners only after the index partner has developed HIV antibodies. Our finding that longitudinal couples studies have produced lower estimates than longitudinal analyses of individuals is consistent with this phenomenon.

Most infectivity studies have not explicitly accounted for all important cofactors, producing “population-average” estimates that do not capture variations in infectivity. Additionally, most study designs have been subject to at least one potential bias in determining the number of potentially infectious exposures experienced by susceptible individuals. Estimates from both cross-sectional and longitudinal studies of independent individuals (rather than partners of known HIV-infected index cases) have relied on HIV prevalence estimates to calculate the probability of exposure during a sexual contact. Overestimates of the prevalence will have underestimated infectivity; underestimated prevalence will have had the opposite effect. Cross-sectional analyses have relied on reported sexual contacts that occurred well before the cross-section, and in most of these studies, the start of the exposure period was based on a very crude estimate of the index case’s infection date. In several studies, the earliest possible index infection date was used, likely resulting in the inclusion of sex acts that occurred prior to the true index infection date. Inclusion of these non-exposures in infectivity calculations will have resulted in deflated estimates.
A number of biases common to all study designs also could have affected infectivity estimates. First, unadjusted inclusion of condom-protected acts in the count of potentially infectious exposures could bias estimates downward. Additionally, infectivity estimates could be biased upward if any transmission occurs through "external" (blood or sexual) contacts that are not included in the count of potentially infectious contacts. All but one study assumed (without molecular analysis) that transmission events occurred via exposure to index partners, but molecular analysis in other studies has revealed that 10% or more of apparent transmission events within couples result from exposure to an additional sexual partner. Self-report error in the number of sexual contacts could also bias estimates; this bias could be in either direction. Additionally, no studies included separate counts of oral-genital contacts. Because transmission via oral-genital contact is believed to be extremely inefficient, though, the failure to account for oral-genital contact in estimating penile-anal and penile-vaginal infectivity is unlikely to have resulted in substantial bias. Finally, because all studies have used antibody tests to detect transmission to susceptible individuals, those with acute infections at the time of testing would have been misclassified as uninfected, resulting in underestimated infectivity.

We also note that there were insufficient data to conduct even univariable stratified and meta-regression analyses of several co-factors, such as viral load, viral subtype, and ARV use; however, we have some information for assessing these variables. In the single population for which viral load was analyzed, infectivity increased from 1 transmission per thousand acts to 2.3 transmissions per thousand acts as serum viral load increased from <1700 copies/ml to >38500 copies/ml. In this same population, infectivity was similar across the subtypes (A, D, and V3) analyzed. The increased infectivity values associated with early- and late-stage infection and with the Thai population at the beginning of the epidemic indirectly suggest amplifying effects of high viral load. Higher infectivity among the Thai
population is also consistent with the possibility of increased infectivity associated with subtype E. All studies were conducted prior to the advent or widespread use of ARV, so the estimates reported here correspond to infectivity in the absence of therapy.

In some co-factor and study method strata, the difference between the estimate obtained from stratified meta-analysis and the estimate produced with meta-regression is quite pronounced. Each estimate obtained from stratified meta-analysis made use only of the data in a particular subgroup, whereas each estimate obtained from meta-regression also made use of the data from the other stratum (or strata), and thus involved modeling or smoothing. The stratified estimates are less precise and less model-dependent; the meta-regression estimates are more precise and more model-dependent. The difference between the two methods’ estimates tends to be greater when the data are relatively sparse, which can occur from small sample sizes within studies, from small numbers of studies within strata, or both. The potential for differences is accentuated by the use of random-effects meta-regression, which involves estimation of an among-studies variance. In the meta-regression analyses, this variance is estimated from all studies in either stratum; in the stratified analyses, it is estimated separately within each stratum.

We have focused on one key parameter in HIV transmission dynamics: the conditional probability of HIV transmission given exposure during a single contact. The overall probability of HIV transmission also depends upon the probability of exposure to HIV, which is determined by such factors as HIV prevalence, partner change rate, sexual network position, and contact with partners who are involved in concurrent relationships. These factors, which are outside the scope of this analysis, represent additional, important determinants of HIV transmission.
HIV infectivity studies are extremely difficult to conduct for both logistical and ethical reasons. As a result, information about infectivity is limited, in terms of both the number of existing estimates and the quality of those estimates. Because of the small number of infectivity studies, the shortage of estimates stratified by co-factors, and the methodological issues of existing studies, the true independent effects of co-factors and study features may differ substantially from the estimates that we obtained. Given these limitations of the existing data, we caution against interpreting any quantitative value reported here as “the” infectivity for a particular study design or co-factor stratum, just as we have cautioned against using a value of 0.001 as “the” overall heterosexual infectivity of HIV-1. Caution is especially warranted for estimates associated with particularly sparse co-factor strata (e.g., estimates stratified by STI status), as well as pooled estimates within strata where heterogeneity exists. In cases where heterogeneity within a stratum is substantial, the results of the random-effects meta-regression analyses (which account for across-study variance) should be used to assess infectivity within, and compare infectivity across, strata. In addition to study limitations resulting from shortcomings of the literature, it is possible that we inadvertently excluded some existing infectivity estimates or misclassified some variables, despite a thorough literature search and careful data extraction process. Furthermore, for some infectivity estimates, we were able to obtain only approximate standard errors.

Despite these limitations, our study represents a comprehensive summary and systematic analysis of the current literature on the heterosexual infectivity of HIV-1, a fundamental determinant of the epidemic’s spread. Our findings suggest that in many contexts – particularly in the absence of male circumcision or in the presence of STIs, anal sex, or early or late infection – the heterosexual infectivity of HIV-1 may exceed the commonly cited value of 0.001 by more than an order of magnitude. The vast extent of the current epidemic is
more easily understood in the context of these biological co-factors, which create a more favorable environment for HIV transmission. Our results highlight the need for further infectivity research and reinforce the importance of including co-factor effects in HIV epidemic models, policy considerations, and prevention messages. Future infectivity studies should carefully count infectious exposures and rigorously account for transmission cofactors. Improved infectivity estimates – especially more detailed estimates that quantify the amplifying effects of biological co-factors – will allow us to grasp the magnitude of the HIV epidemic, accurately communicate the level of risk involved in heterosexual sex, and identify the optimal intervention strategies for slowing the epidemic’s spread.
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<th>Number of susceptibles</th>
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</table>

FSW = Female sex worker

The most precise estimate and corresponding standard error within each study population are shaded in grey.

<sup>a</sup> Total included in overall infectivity calculation. Stratified analyses were conducted in subsets containing fewer individuals.

<sup>b</sup> Transmission events per 1000 exposures

<sup>c</sup> Calculated from reported data using Eq. 1 (see Appendix One)
\(^d\) Calculated using method 1 in Appendix One

\(^e\) Calculated from reported confidence limits (see Appendix One)
Table 4.2. Results of stratified meta-analysis and meta-regression based on study design and analysis characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th># ests</th>
<th>Stratified Meta-Analysis Results</th>
<th>Univariable Meta-Regression Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Homogeneity</td>
<td>Infectivity¹,² (95% CI)</td>
</tr>
<tr>
<td>Partnership status</td>
<td>Partner of known HIV+</td>
<td>10</td>
<td>&lt;0.0001</td>
<td>0.73 (0.51-0.96)</td>
</tr>
<tr>
<td></td>
<td>Independent individual</td>
<td>5</td>
<td>&lt;0.0001</td>
<td>0.96 (0.42-1.50)</td>
</tr>
<tr>
<td>Outcome ascertainment</td>
<td>Any cross-sectional</td>
<td>8</td>
<td>&lt;0.0001</td>
<td>0.88 (0.38-1.38)</td>
</tr>
<tr>
<td></td>
<td>All longitudinal</td>
<td>7</td>
<td>&lt;0.0001</td>
<td>0.71 (0.48-0.94)</td>
</tr>
<tr>
<td>Index infection date</td>
<td>Crude estimate</td>
<td>4</td>
<td>0.1</td>
<td>0.61 (0.44-0.79)</td>
</tr>
<tr>
<td></td>
<td>Transfusion date</td>
<td>2</td>
<td>0.8</td>
<td>0.98 (0.50-1.45)</td>
</tr>
<tr>
<td>External sex exposures</td>
<td>Some exclusions</td>
<td>8</td>
<td>0.0001</td>
<td>0.71 (0.49-0.92)</td>
</tr>
<tr>
<td></td>
<td>No exclusions</td>
<td>2</td>
<td>0.002</td>
<td>2.05 (0.00-5.27)</td>
</tr>
<tr>
<td>Blood exposures</td>
<td>Some exclusions</td>
<td>9</td>
<td>&lt;0.0001</td>
<td>0.71 (0.48-0.95)</td>
</tr>
<tr>
<td></td>
<td>No exclusions</td>
<td>6</td>
<td>&lt;0.0001</td>
<td>0.97 (0.52-1.42)</td>
</tr>
<tr>
<td>HIV testing interval</td>
<td>&gt; 3 months</td>
<td>6</td>
<td>0.0001</td>
<td>0.67 (0.50-0.84)</td>
</tr>
<tr>
<td></td>
<td>≤ 3 months</td>
<td>3</td>
<td>0.02</td>
<td>5.36 (0.84-9.89)</td>
</tr>
<tr>
<td>Condom-protected acts</td>
<td>Some protection</td>
<td>5</td>
<td>&lt;0.0001</td>
<td>1.11 (0.35-1.88)</td>
</tr>
<tr>
<td></td>
<td>Protection rare or adjusted for</td>
<td>8</td>
<td>&lt;0.0001</td>
<td>0.70 (0.44-0.97)</td>
</tr>
<tr>
<td>Self-report error</td>
<td>Not corrected or mentioned</td>
<td>12</td>
<td>&lt;0.0001</td>
<td>0.71 (0.47-0.95)</td>
</tr>
<tr>
<td></td>
<td>Corrected</td>
<td>3</td>
<td>&lt;0.0001</td>
<td>1.19 (0.40-1.97)</td>
</tr>
<tr>
<td>Analytical model</td>
<td>Bernoulli model</td>
<td>5</td>
<td>&lt;0.0001</td>
<td>1.13 (0.50-1.77)</td>
</tr>
<tr>
<td></td>
<td>Transmissions / acts</td>
<td>7</td>
<td>&lt;0.0001</td>
<td>0.71 (0.39-1.03)</td>
</tr>
<tr>
<td></td>
<td>Failure probability</td>
<td>3</td>
<td>0.2</td>
<td>0.76 (0.47-1.06)</td>
</tr>
</tbody>
</table>
a Transmissions per 1000 exposures.

b Random-effects estimate pooled within a given stratum of study characteristic.

c From random-effects models with overall infectivity as dependent variable and study feature as independent variable.

d Applies only to studies basing exposure period start on index infection date.

e Applies only to studies of couples.

f Applies only to studies with any longitudinal HIV testing to detect incident cases among susceptibles.

g See Appendix One.
### Table 4.3. Results of stratified meta-analysis and meta-regression based on transmission co-factor characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th># ests</th>
<th>Homogeneity p</th>
<th>Infectivity&lt;sup&gt;a,b&lt;/sup&gt; (95% CI)</th>
<th>Infectivity&lt;sup&gt;a,c&lt;/sup&gt; (95% CI)</th>
<th>Infectivity&lt;sup&gt;a&lt;/sup&gt; difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>USA / Europe</td>
<td>8</td>
<td>0.05</td>
<td>0.59 (0.44-0.75)</td>
<td>0.56 (0.46-0.66)</td>
<td>0.0.</td>
<td></td>
</tr>
<tr>
<td>Africa</td>
<td>6</td>
<td>&lt;0.0001</td>
<td>0.91 (0.59-1.22)</td>
<td>0.64 (0.57-0.71)</td>
<td>0.08 (-0.04-0.20)</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>1</td>
<td>N/A</td>
<td>31.00 (25.00-40.00)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Type of act</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penile-vaginal</td>
<td>5</td>
<td>0.0002</td>
<td>0.84 (0.51-1.17)</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Penile-anal</td>
<td>1</td>
<td>N/A</td>
<td>33.80 (18.51-49.09)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Transmission direction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male-to-Female</td>
<td>10</td>
<td>0.001</td>
<td>0.66 (0.54-0.79)</td>
<td>0.64 (0.57-0.72)</td>
<td>0.</td>
<td></td>
</tr>
<tr>
<td>Female-to-Male</td>
<td>6</td>
<td>&lt;0.0001</td>
<td>2.76 (1.19-4.33)</td>
<td>0.64 (0.45-0.84)</td>
<td>-0.002 (-0.21-0.21)</td>
<td></td>
</tr>
<tr>
<td><strong>Susceptible GUD status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No GUD</td>
<td>4</td>
<td>&lt;0.0001</td>
<td>3.72 (0.70-6.75)</td>
<td>1.46 (0.94-1.97)</td>
<td>0.</td>
<td></td>
</tr>
<tr>
<td>GUD</td>
<td>5</td>
<td>&lt;0.0001</td>
<td>30.55 (11.27-49.84)</td>
<td>7.46 (4.75-10.17)</td>
<td>6.00 (3.25-7.86)</td>
<td></td>
</tr>
<tr>
<td><strong>Susceptible STI status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No STI</td>
<td>1</td>
<td>N/A</td>
<td>12.00 (6.00-25.00)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>STI</td>
<td>2</td>
<td>0.1</td>
<td>55.86 (4.43-107.29)</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Susceptible circum. status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumcised</td>
<td>2</td>
<td>0.4</td>
<td>5.13 (3.37-6.89)</td>
<td>5.13 (3.36-6.89)</td>
<td>0.</td>
<td></td>
</tr>
<tr>
<td>Not circumcised</td>
<td>2</td>
<td>0.02</td>
<td>97.33 (0.00-295.16)</td>
<td>13.21 (5.70-20.72)</td>
<td>8.08 (0.37-15.80)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean susceptible age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 years</td>
<td>6</td>
<td>&lt;0.0001</td>
<td>1.06 (0.56-1.56)</td>
<td>0.94 (0.71-1.16)</td>
<td>0.</td>
<td></td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>2</td>
<td>&lt;0.0001</td>
<td>15.71 (0.00-45.20)</td>
<td>0.99 (0.58-1.40)</td>
<td>0.05 (-0.41-0.52)</td>
<td></td>
</tr>
<tr>
<td><strong>Index disease stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid</td>
<td>4</td>
<td>0.9</td>
<td>0.71 (0.57-0.85)</td>
<td>0.71 (0.57-0.85)</td>
<td>0.</td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>2</td>
<td>0.05</td>
<td>4.67 (0.00-10.46)</td>
<td>3.25 (0.93-5.56)</td>
<td>2.54 (0.22-4.86)</td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>4</td>
<td>0.02</td>
<td>3.18 (0.94-5.42)</td>
<td>2.56 (1.58-3.53)</td>
<td>1.85 (0.86-2.83)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean index age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>1</td>
<td>N/A</td>
<td>0.90 (0.70-1.10)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>≥ 30 years</td>
<td>3</td>
<td>0.02</td>
<td>1.31 (0.66-1.96)</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td>N/A&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>
a Transmissions per 1000 exposures

b Random-effects estimate pooled within a given stratum of transmission co-factor.

c From random-effects models with infectivity as dependent variable and transmission co-factor as independent variable.

d Estimate based on single study only.

e Meta-regression results computed only when the number of estimates exceeded 1 in the comparison group and in the referent stratum.

f Before or during study period
Study-specific infectivity estimates and 95% confidence intervals. For symmetry of confidence intervals on the log axis, the plotted values were calculated from logit-transformed transmission probabilities and their corresponding confidence limits. Untransformed values were used in all meta-analyses. \textsuperscript{a}Ragni data; \textsuperscript{b}O’Brien data; \textsuperscript{c}California Partners Study data.
Study-specific and pooled infectivity estimates and 95% confidence intervals stratified by GUD status, male susceptibles’ circumcision status, index infection stage, and type of sexual contact. For symmetry of confidence intervals on the log axis, the plotted values were calculated from logit-transformed transmission probabilities and their corresponding confidence limits. Untransformed values were used in all meta-analyses.
CHAPTER 5: SEXUAL PARTNERSHIP PATTERNS IN MALAWI: IMPLICATIONS FOR HIV/STI TRANSMISSION

ABSTRACT

Objective: Concurrent sexual partnerships are believed to play an important role in HIV transmission in sub-Saharan Africa, but the contribution of concurrency depends on the details of relationship patterns. To contribute to the understanding of sexual partnership patterns in this region, we estimated partnership lengths, temporal gaps between partners, and periods of overlap across partners at an STI clinic in Lilongwe, Malawi. 

Design: Secondary analysis of data collected at the baseline and one-week follow-up visits in a longitudinal study.

Methods: Participants underwent physical examinations and HIV tests, and responded to questionnaires about demographics and risk behaviors, including detailed questions about a maximum of 3 sexual partners in the previous 2 months. We calculated partnership length as the time between the first and most recent sexual contact with a partner, and gap length as the time between the most recent contact with one partner and the first contact with the next. We defined concurrent and consecutive partnerships as gap length ≤ 0 days and gap length > 0 days, respectively.

Results: The study population (n=183) had a mean partnership length of 858 days (median=176 days). Eighty-six percent reported <2 partners, 5% reported consecutive partnerships, and 9% reported concurrency. Gaps between consecutive partnerships were short (mean=21 days), and overlaps across concurrent partners tended to be long (mean=246 days).

Conclusions: Multiple sexual partnerships were uncommon, and partnerships were long on average. Among those reporting multiple recent partners, patterns ranged from long-term concurrency to narrowly
spaced consecutive partnerships, presenting a substantial risk for efficient transmission of HIV and classical STIs.

**INTRODUCTION**

Transmission of sexually transmitted infections (STIs), including HIV, depends on behavioral and biological factors. When sexual partnerships are completely separated by “gaps” in time, an infected index case can transmit infection to only one person while a partnership remains intact. Furthermore, an individual’s earlier partners are at no risk of acquiring infections introduced by an individual’s subsequent partners. When partnerships are concurrent (overlapping in time), neither of these limitations is present, and HIV/STI transmission can be amplified. However, the details of these partnership patterns matter greatly, because the transmission event is constrained by biological rules unique to each pathogen. For example, consecutive partnerships may have similar transmission risk as concurrent partnerships if an earlier partner introduces an STI and the gap between partnerships is shorter than the infectious period for that pathogen.\(^{70, 71}\) Partnership lengths are also important, as longer partnerships generally present a greater number of transmission opportunities. The combination of “gap length” and partnership duration helps to determine the rate of epidemic spread.\(^{72}\)

The role of sexual partner concurrency in explaining the severe HIV epidemic in sub-Saharan Africa has been debated vigorously.\(^ {74-78}\) Mathematical models have suggested the potential for concurrency to magnify transmission,\(^ {69, 79-81}\) and some investigators have reported that concurrency is common in sub-Saharan Africa.\(^ {82, 83}\) However, studies estimating the empirical association between concurrency and HIV have had mixed results,\(^ {179-181}\) partly due to the considerable variation in operational definitions of concurrency.\(^ {76, 78}\) To address some of these issues, the UNAIDS Reference Group on
Estimates, Modelling, and Projections recently issued a consensus definition for concurrent sexual partnerships, an action that will facilitate comparison of concurrency across settings. While this standard measure is immensely useful, concurrency takes many different forms, and a detailed understanding of the predominant partnership patterns in a particular setting is critical for designing interventions to prevent HIV and other STIs.

In this study, we examined sexual partnership patterns in an STI clinic population in Lilongwe, Malawi. We analyzed partnership durations, gaps between consecutive partners, and overlaps across concurrent partners, and we examined predictors of consecutive partnerships and concurrency. Our findings identify ways in which specific contact patterns may have contributed to the efficient spread of HIV and other STIs in sub-Saharan Africa.

**METHODS**

*Study Design, Setting, and Population*

We performed a secondary analysis of data collected at the baseline and one-week follow-up visits in a longitudinal study of HIV viral dynamics conducted at Kamuzu Central Hospital STI Clinic in Lilongwe, Malawi (2003-2004). As described previously, study screening began with two parallel rapid HIV antibody tests, followed by HIV p24 and batched HIV RNA testing in all individuals with negative or discordant antibody results. Individuals with positive p24 results were invited to enroll in the longitudinal study. For each enrolled p24-positive patient, three p24-negative controls were screened for enrollment, along with one HIV-antibody-positive patient (matched by sex).

*Data Collection*
Participants completed a verbally-administered questionnaire and underwent a physical examination (including genital examination) at baseline. The questionnaire included items about demographics and recent risk behaviors. One week later, a follow-up questionnaire sought the following information on up to 3 sexual partners contacted in the prior two months: partner type (spouse or co-habiting boyfriend/girlfriend; non-cohabiting boyfriend/girlfriend; transactional partner; or casual acquaintance), number of months since the first sexual contact, and number of days since the most recent sexual contact.

Data were recorded on paper forms and double-entered into electronic databases. We consulted the original paper forms to reconcile discrepancies between electronic entries.

**Data Analysis**

We used Stata 9.2 (StataCorp, College Station, Texas, USA) for analyses with generalized estimating equations (GEE), and SAS 9.1 (SAS Institute, Cary, North Carolina, USA) for all other analyses.

**HIV Status Determination**

Patients with negative or discordant antibody results and detectable HIV RNA were considered to have acute HIV infection (AHI). Patients with negative or discordant antibody tests and undetectable HIV RNA were classified as HIV-negative. Participants with positive antibody results were classified as having chronic (post-acute) HIV infection (CHI).

**Probability of Selection into the Study**

Because participants were not sampled at random, it was necessary to account for the participant selection process before drawing inferences about the entire clinic population.
To account for selection based on sex and HIV test results (described under “Study Design, Setting, and Population” above), we calculated participants’ inverse probabilities of selection as the reciprocal of: the number of enrolled participants of a given sex and HIV status, divided by the estimated number of patients of that sex and HIV status visiting the clinic during the study period. For example, thirty-seven HIV-negative women were enrolled in our study, and an estimated 2171 HIV-negative women attended the clinic in the twenty months during which the study took place. The corresponding probability of selection for an HIV-negative woman was $37/2171 = 0.017$ and the corresponding inverse probability of selection was $1/0.017 = 58.8$. The estimated numbers of patients attending the clinic during the study period (2171 in this example) were based on administrative data collected separately from the study protocol.

**Partnership Lengths**

To calculate the length of each reported partnership, we converted the time since first sex into days by multiplying the reported number of months ($M$) prior to the visit by 30. We calculated the partnership length as the number of days between the first and most recent sexual contact with the partner (Figure 5.1A). Partnerships defined by a single contact were assigned a length of zero days.

We estimated mean partnership lengths and corresponding 95% confidence intervals with negative binomial regression, using GEE to account for the possibility of multiple partnerships per participant. We used inverse-probability-of-selection weighting and an exchangeable working correlation matrix. Predictor variables related to participant characteristics included sex, age (18-24, 25-29, 30+ years), marital status (unmarried vs. married), partnership pattern in the prior 2 months (<2 partners, multiple concurrent partnerships, multiple consecutive partnerships – defined below), travel in the prior 2 months
(any vs. none), transactional sex in the prior 2 months (any vs. none), and baseline HIV status (negative, AHI, CHI), genital ulcer disease (GUD) status (GUD vs. no GUD), and urethral discharge status (discharge vs. no discharge, males only). We also examined participants’ classifications of partner type (spouse/live-in partner, non-cohabiting boy/girlfriend, casual acquaintance, or transactional partner) as a predictor variable.

Because extreme values can influence mean partnership lengths, we calculated weighted median partnership lengths and weighted maxima, minima, and 25th and 75th percentiles as complementary measures of partnership length distributions. These calculations did not account for multiple partnerships per participant.

To compare partnership lengths across predictors, we calculated partnership length differences (PLDs) as the weighted mean partnership length in a comparison group minus the corresponding value in a referent group, and partnership length ratios (PLRs) as the former divided by the latter.

**Gap and overlap lengths**
Among those reporting contact with ≥2 partners in the prior two months, we calculated the “gap length” between each set of partners as the number of days since the most recent sexual contact with the less-recently-contacted partner minus the number of days since the first sex with the more-recently-contacted partner (Figure 5.1). Positive gap lengths characterized consecutive partnerships (Figure 5.1A). Zero or negative gap lengths characterized concurrency (Figures 5.1B-5.1D). Any partnership pattern (<2 partners, multiple consecutive partners, multiple concurrent partners) could include partners of any of the following participant-reported types: spouse or cohabiting boyfriend/girlfriend, non-cohabiting boyfriend/girlfriend, transactional partner, or casual acquaintance. We described
partnerships with positive gaps as “consecutive” rather than “serially monogamous” to avoid any connotation that partnerships meeting this definition were necessarily stable and long-term.

Among those with negative gap lengths (concurrency), we calculated the overlap length across each set of partners in one of two ways (Figures 5.1B and 5.1C), depending on whether one partnership entirely contained another. If one partnership ended and another began on the same day, the overlap length was zero (Figure 5.1D).

Among those with positive gap lengths (consecutive partnerships), we calculated the mean gap length using the same GEE approach used for mean partnership lengths. We used analogous methods to calculate mean overlap lengths among those with non-positive gap lengths (concurrency). There were too few participants reporting multiple partners to compare gap and overlap lengths across predictors.

**Partnership Patterns**

We calculated the proportion of participants in each of the following categories, based on reported behavior in the prior two months: <2 partners, ≥2 consecutive partners, or ≥2 concurrent partners. To assess associations of partnership patterns with predictors, we conducted two rounds of weighted multinomial logistic regression: one with <2 partners as the referent, and one with consecutive partners as the referent.

**RESULTS**

*Population demographics and HIV status*
A total of 183 participants were eligible for these analyses. All results reported below take selection weights into account to adjust for the non-random sampling of participants (see Methods). The population was predominantly female, and evenly split according to marital status (Table 5.1). The mean age (95% CI) was 27.0 (25.9, 28.1) years and the median age (interquartile range) was 25 (22-30) years.

**Partnership Lengths**

Overall, the mean partnership length was 858 days and the median was 176 days (Table 5.2). Partnership lengths were greater among those who were female, older, married, or free of urethral discharge (males); or who reported just one partner, no travel, or no transactional sex in the prior two months (Table 5.2). Partnerships that participants classified as being with spouses/cohabiting partners were longer (mean partnership length = 1424 days) than partnerships reported to be with non-cohabiting girlfriends/boyfriends (216 days), transactional partners (38 days), and casual acquaintances (14 days). Partnerships were longer, on average, among those who were HIV-negative or free of GUD, but these estimates were imprecise.

As described in the Methods section, a small number of extremely long partnerships can elevate the mean partnership length above the median, and both measures are useful in understanding partnership length distributions. For every predictor variable that we examined, the order of mean partnership lengths across sub-groups was the same as the order of medians (Table 5.2), with two exceptions. While the mean partnership length increased directly with age, the median was considerably higher in the middle age group (25-29 years) than in the other groups. Additionally, while the mean partnership length was greatest for HIV-negative participants (935 days) and intermediate for CHI patients (753 days), the corresponding medians were reversed (152 days and 556 days, respectively).
These results reflect the relatively greater presence of extremely long partnerships among older and HIV-negative patients, elevating the mean to a greater extent in these groups.

**Partnership patterns, gap lengths, and overlap lengths**

Overall, 86% of the population reported <2 partners in the previous two months: 77% reported one partner and 9% reported zero partners. Five percent reported $\geq 2$ consecutive partnerships; and 9% reported $\geq 2$ concurrent partnerships (Table 5.3). Many of the consecutive partnerships were short (Figure 5.2A), with 27% comprising only a single contact. Gap lengths among participants reporting consecutive partnerships were also short, with a mean (95% CI) of 21 (13, 29) days and a maximum of 50 days. By contrast, partnership lengths among those with concurrency were long (Figure 5.2B), with long periods of overlap on average (mean = 246 days). Among those reporting consecutive or concurrent partnerships, we observed four basic patterns: consecutive partnerships comprising one-off contacts only (Figure 5.2A rows A1-A9), consecutive partnerships with at least one partnership of duration $>1$ week (Figure 5.2A rows A10-A16), sporadic concurrency only (Figure 5.2B rows B1-B6), and longer-term concurrency with or without additional sporadic concurrency (Figure 5.2B rows B7-B19).

Consecutive partnerships (vs. <2 partners) were associated with male sex, being unmarried, reporting travel or transactional sex in the prior two months, having GUD, and having urethral discharge (males) (Table 5.3). Participants aged 25-29 years were also more likely to report consecutive partnerships (vs. <2 partners) than younger or older participants.

Most factors associated with consecutive partnerships were also associated with an increased odds of concurrency (vs. <2 partners) (Table 5.3); however, the strength of the positive association was somewhat weaker for male sex, being unmarried, reporting travel in
the prior 2 months, reporting transactional sex in the prior 2 months, and having GUD. In other words, participants in each of these categories were less likely to report concurrent than consecutive partnerships. The association between age 25-29 years and concurrency was in the opposite direction than the corresponding association with consecutive partnerships.

Detailed comparisons of partnership patterns by HIV status were hindered by small numbers, but those with AHI or CHI were more likely to report concurrency than <2 partners. Those with AHI were also more likely to report consecutive partnerships (vs. <2 partners), but the measure was imprecise. In general, AHI was associated with multiple recent partnerships (odds ratio with “concurrent” and “consecutive” categories collapsed: 2.5, 95% CI = 1.0 – 6.3; result not shown in Table 5.3).

**DISCUSSION**

We have presented an analysis of sexual partnership patterns – including durations of partnerships, gaps, and overlaps – among STI clinic patients in Lilongwe, Malawi. We found that most partnerships were long and monogamous, that concurrent partnerships were infrequent but tended to have long periods of overlap, and that consecutive partnerships had short intervening gaps that could facilitate rapid HIV/STI spread. These results highlight the variability of sexual partnership patterns, and provide new information about determinants of HIV/STI transmission in a semi-urban, sub-Saharan African population.

Most participants in the “high-risk” STI clinic population that we studied reported <2 partners in the two months prior to their clinic visits. This result underscores the fact that the number of recent partners is not the only determinant of STI/HIV acquisition (as nearly all
participants presented with STIs), and highlights the importance of partner characteristics (such as partners’ patterns of contact with others) in determining an individual’s STI risk. The idea that HIV/STI acquisition risk depends not only on one’s own behavior, but on the behavior of one’s partners (and one’s partners’ partners), has been recognized as an important transmission prevention message in some sub-Saharan African settings. Our results indicate the importance of including this message in Malawian prevention campaigns.

Recent partnerships in our study were long on average, and partnership lengths differed predictably across subgroups. The mean partnership lengths fall within the range of values obtained in other African settings, where estimates have varied from 3.2 months for Tanzanian males’ non-marital partners to 239 months for Ugandan spouses. Notably, the mean overlap in concurrent partnerships was also long, as has been observed elsewhere in sub-Saharan Africa. We note that none of the concurrent partnerships reported in this population was polygynous, consistent with the relatively low levels of polygyny reported in population-based surveys from Malawi. Polygyny is one type of long-term concurrency that may have a relatively benign effect on HIV/STI spread, as it can trap infection in small, isolated network components.

The patterns of consecutive partnerships observed in this study could lead to transmission amplification similar to that expected with some types of concurrency, as the mean gap (21 days) among those reporting consecutive partnerships was shorter than the infectious period of many STIs. Although gap lengths among African populations have not been previously characterized, short gaps between consecutive partnerships have been observed in the US. In our study, all gaps were \( \leq 50 \) days, a result that is related to constraints in our measurement methods: because the most recent contact with each partner must...
have occurred within the “look-back period” of two months, each gap had to be fully contained within that time frame. Despite this limitation in estimating mean gap lengths, the occurrence of numerous consecutive relationships in rapid succession suggests considerable transmission potential.

Those who were male or unmarried, or who had traveled or had transactional sex recently, were more likely to report multiple consecutive or (to a lesser extent) concurrent partnerships (vs. having <2 partners). Our finding that individuals in the middle age group (25-29 years) were more likely than those in the adjacent age groups to report consecutive partnerships – but less likely to report concurrency – may be explained by a greater likelihood of those in the middle group to be unmarried (result not shown), and hence more likely to engage in consecutive partnerships than concurrency. Elsewhere in sub-Saharan Africa, elevated levels of concurrency among many of these same subgroups have been observed, although definitions of concurrency have varied. In fact, some definitions have simply required the existence of multiple partnerships in a given interval, without directly assessing whether there was any overlap. Many of the partnerships that we considered to be “consecutive” would have been classified as “concurrent” using this less precise definition.

Although this study was conducted in an STI clinic population and therefore focused on individuals whose recent behavior resulted in STI acquisition, this study was not designed to determine which specific behaviors led to infection in these participants. Essentially all participants had some STI symptoms, leaving no “STI-free” group to serve as a referent for evaluating various behaviors as risk factors for participants’ STI acquisition. Additionally, these data are cross-sectional, so causality between participants’ behaviors and HIV/STI acquisition cannot be confirmed. Instead, the associations among partnership patterns
(consecutive, concurrent) and HIV, GUD, or urethral discharge are best interpreted with respect to the risk of onward transmission from these infected individuals.\textsuperscript{84, 85} In our population, the greater odds of having multiple recent partners among those with GUD or urethral discharge suggests considerable potential for onward transmission, whether by concurrency or back-to-back consecutive partnerships. These results suggest that prevention messages should address both concurrency and rapid partner change in this setting.

HIV transmission deserves special consideration. Because the infectious period for HIV is lifelong after infection acquisition, short gaps between partnerships would seem to be of only minor importance to HIV transmission. However, the transmissibility of HIV is most highly concentrated during the first weeks or months of infection, as well as during an STI co-infection.\textsuperscript{21, 22, 104} Therefore, the short gaps observed in this study would certainly create great risk for onward transmission of HIV. The increased likelihood of concurrency among those with CHI, and of multiple recent partnerships in general among those with AHI, suggests substantial HIV transmission risk from these individuals.

As with all sexual behavior studies, the necessary reliance on self-reported data may have introduced recall error, which could bias results in either direction, and social desirability bias, which would likely deflate the estimated proportions engaging in multiple partnerships, especially among women. Additionally, we did not have information about whether partnerships continued beyond the time of interview, a common problem in studies of partnership dynamics\textsuperscript{71, 72, 87} that can result in underestimated partnership lengths. Despite this possibility of bias in our estimated means and medians, the PLDs and PLRs reported in Table 5.2 provide unbiased comparisons between groups if certain conditions hold. Specifically, if partnership lengths were censored by the same \textit{absolute} amount in each
category, then the PLD is a valid estimate of the *absolute* difference between groups. If partnership lengths were instead censored by the same relative amount, then the PLR is a valid estimate of the *relative* difference between groups. Finally, we note that although our results are based on a relatively small number of participants, these findings contribute to our limited understanding of partnership patterns in sub-Saharan Africa.

A lack of empirical data linking specific sexual partnership patterns to HIV transmission lies at the heart of the debate about the role of concurrency in spreading HIV. To address this issue, the UNAIDS Reference Group on Estimates, Modelling, and Projections recently issued a consensus definition of concurrency: “overlapping sexual partnerships in which sexual intercourse with one partner occurs between two acts of intercourse with another.” While this suggestion will facilitate comparisons of this particular measure across settings, this limited definition is unlikely to capture the rich and variable characteristics of sexual partnerships. We have described additional features of sexual partnerships, including relationship durations, gap lengths, and overlap lengths, in an STI clinic population in Lilongwe, Malawi. Additional descriptions of these characteristics are essential, as a detailed understanding of sexual behaviors in a given context is necessary for the optimal design of prevention interventions. Without improved descriptions of the predominant sexual partnership patterns in various settings, we will be limited in our understanding of HIV/STI transmission dynamics throughout the world.
We calculated the **partnership length** for each reported partnership as the time between the first sexual contact (\(F_{\text{partner}}\)) and the most recent sexual contact (\(MR_{\text{partner}}\)) with that partner (Figure 5.1A). For participants reporting two partners in the prior two months, we calculated the **gap length** between partners A and B as \(MR_A - F_B\). Because times of first and most recent sex were reported as (or converted to) the number of days before the clinic visit, earlier events have larger values. Therefore, positive gap lengths correspond to situations...
of consecutive partnerships (Figure 5.1A). Figures 5.1B and 5.1C illustrate situations of concurrency in which the most recent contact with partner A ($MR_A$) occurred after the first contact with partner B ($F_B$). In these situations, $F_B > MR_A$ and the gap length $< 0$. In Figure 5.1B, one partnership is entirely contained within another, and the overlap length (diagonally hatched bar) is equal to the partnership length of the subsumed partnership. In Figure 5.1C, overlap is only partial; the overlap length is equal to $F_B - MR_A$. Figure 5.1D illustrates a situation of concurrency in which the most recent contact with partner A ($MR_A$) occurred on the same day as the first contact with partner B ($F_B$). In these situations, $F_B = MR_A$; therefore, the gap length $= 0 =$ the overlap length. For participants reporting a third partner in the prior two months (partner C), the gap lengths between – and overlap lengths across – partners B and C were calculated analogously.
Figure 5.2. Patterns of consecutive and concurrent partnerships among those reporting multiple partners.
Partnership patterns are shown for each of the 35 participants whose patterns in the two months prior to the STI clinic visit could be categorized as either exclusively consecutive (Figure 5.2A) or having one or more sets of concurrent partners (Figure 5.2B). For ease of presentation, the time axis is left-truncated at 100 days prior to the STI clinic visit. The horizontal white, black, and dark gray bars represent the partners contacted most recently, second-most-recently, and third-most-recently, respectively. The four participants who reported 2 or more partners but could not be classified as having consecutive vs. concurrent partnerships (due to missing data) are excluded.
Table 5.1. Characteristics of Kamuzu Central Hospital STI Clinic population

<table>
<thead>
<tr>
<th></th>
<th>N (weighted %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>183 (100.0)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>50 (56.9)</td>
</tr>
<tr>
<td>Male</td>
<td>133 (43.1)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>18-24 years</td>
<td>86 (44.4)</td>
</tr>
<tr>
<td>25-29 years</td>
<td>54 (29.4)</td>
</tr>
<tr>
<td>30+ years</td>
<td>43 (26.2)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>76 (49.7)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>107 (50.3)</td>
</tr>
<tr>
<td><strong>Travel in last 2 months</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>125 (74.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>57 (25.3)</td>
</tr>
<tr>
<td><strong>Transactional sex in last 2 months</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>117 (72.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>65 (27.8)</td>
</tr>
<tr>
<td><strong>HIV status</strong></td>
<td></td>
</tr>
<tr>
<td>HIV-negative</td>
<td>130 (58.0)</td>
</tr>
<tr>
<td>CHI</td>
<td>37 (41.7)</td>
</tr>
<tr>
<td>Acute HIV</td>
<td>16 (0.3)</td>
</tr>
<tr>
<td><strong>Current GUD status</strong></td>
<td></td>
</tr>
<tr>
<td>No GUD</td>
<td>123 (76.0)</td>
</tr>
<tr>
<td>GUD</td>
<td>60 (24.0)</td>
</tr>
<tr>
<td><strong>Current discharge status (males)</strong></td>
<td></td>
</tr>
<tr>
<td>No urethral discharge</td>
<td>72 (52.7)</td>
</tr>
<tr>
<td>Urethral discharge</td>
<td>61 (47.3)</td>
</tr>
</tbody>
</table>

GUD = genital ulcer disease; CHI = chronic (post-acute) HIV infection; AHI = acute HIV infection
Table 5.2. Partnership lengths among those with ≥1 partner in the overall population and by predictor variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients N</th>
<th>Partnerships N</th>
<th>Weighted median PL in days (IQR)</th>
<th>Weighted mean PL in days (95% CI)</th>
<th>PLD in days (95% CI)</th>
<th>PLR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>161</td>
<td>204</td>
<td>176 (30, 898)</td>
<td>858 (630, 1169)</td>
<td>---</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>42</td>
<td>46</td>
<td>646 (147, 1780)</td>
<td>1126 (748, 1696)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>Male</td>
<td>119</td>
<td>158</td>
<td>48 (0, 357)</td>
<td>557 (374, 827)</td>
<td>-569 (-1081, -59)</td>
<td>0.5 (0.3, 0.9)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24 years</td>
<td>75</td>
<td>94</td>
<td>152 (35, 657)</td>
<td>405 (280, 584)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>25-29 years</td>
<td>47</td>
<td>57</td>
<td>771 (16, 1780)</td>
<td>1029 (706, 1500)</td>
<td>624 (209, 1040)</td>
<td>2.5 (1.5, 4.3)</td>
</tr>
<tr>
<td>30+ years</td>
<td>39</td>
<td>53</td>
<td>173 (30, 2369)</td>
<td>1525 (877, 2651)</td>
<td>1120 (264, 1976)</td>
<td>3.8 (1.9, 7.3)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>69</td>
<td>84</td>
<td>771 (130, 2309)</td>
<td>1414 (1013, 1973)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>Unmarried</td>
<td>92</td>
<td>120</td>
<td>106 (16, 272)</td>
<td>314 (173, 569)</td>
<td>-1100 (-1607, -593)</td>
<td>0.2 (0.1, 0.4)</td>
</tr>
<tr>
<td>Partner type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spouse / live-in partner</td>
<td>80</td>
<td>81</td>
<td>777 (353, 1799)</td>
<td>1424 (1043, 1945)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>Non-cohabiting girl/boyfriend</td>
<td>73</td>
<td>88</td>
<td>40 (21, 174)</td>
<td>216 (108, 431)</td>
<td>-1208 (-1686, -731)</td>
<td>0.2 (0.1, 0.3)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Patients N</td>
<td>Partnerships N</td>
<td>Weighted median PL in days (IQR)</td>
<td>Weighted mean PL in days (95% CI)</td>
<td>PLD in days (95% CI)</td>
<td>PLR (95% CI)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>------------</td>
<td>----------------</td>
<td>----------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Transactional partner</td>
<td>6</td>
<td>7</td>
<td>0 (0, 0)</td>
<td>38 (6, 262)</td>
<td>-1386 (-1837, -936)</td>
<td>0.03 (0.004, 0.2)</td>
</tr>
<tr>
<td>Casual acquaintance</td>
<td>23</td>
<td>26</td>
<td>0 (0, 10)</td>
<td>14 (4, 49)</td>
<td>-1410 (-1855, -965)</td>
<td>0.01 (0.003, 0.04)</td>
</tr>
<tr>
<td>Partnership pattern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 partner</td>
<td>122</td>
<td>122</td>
<td>358 (113, 1673)</td>
<td>1006 (720, 1407)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>Consecutive multiple</td>
<td>16</td>
<td>34</td>
<td>0 (0, 9)</td>
<td>140 (54, 362)</td>
<td>-866 (-1229, -504)</td>
<td>0.1 (0.05, 0.4)</td>
</tr>
<tr>
<td>Concurrent multiple</td>
<td>19</td>
<td>44</td>
<td>159 (30, 556)</td>
<td>635 (312, 1291)</td>
<td>-371 (-935, 191)</td>
<td>0.6 (0.3, 1.4)</td>
</tr>
<tr>
<td>Travel in last 2 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>106</td>
<td>133</td>
<td>419 (80, 1128)</td>
<td>1033 (735, 1452)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>Yes</td>
<td>54</td>
<td>69</td>
<td>69 (11, 616)</td>
<td>428 (295, 732)</td>
<td>-605 (-1025, -185)</td>
<td>0.4 (0.2, 0.8)</td>
</tr>
<tr>
<td>Transactional sex in last 2 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>98</td>
<td>114</td>
<td>625 (60, 1431)</td>
<td>1105 (790, 1548)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>Yes</td>
<td>62</td>
<td>89</td>
<td>106 (8, 186)</td>
<td>398 (198, 802)</td>
<td>-707 (-1172, -242)</td>
<td>0.4 (0.2, 0.8)</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: PL = progression index; PLD = progression index difference; PLR = progression index ratio; IQR = interquartile range; CI = confidence interval.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients N</th>
<th>Partnerships N</th>
<th>Weighted median PL in days (IQR)</th>
<th>Weighted mean PL in days (95% CI)</th>
<th>PLD in days (95% CI)</th>
<th>PLR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-negative</td>
<td>112</td>
<td>142</td>
<td>152 (21, 1012)</td>
<td>935 (615, 1424)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>CHI</td>
<td>34</td>
<td>39</td>
<td>556 (120, 777)</td>
<td>753 (490, 1158)</td>
<td>-182 (-692, 327)</td>
<td>0.8 (0.4, 1.5)</td>
</tr>
<tr>
<td>AHI</td>
<td>15</td>
<td>23</td>
<td>15 (0, 346)</td>
<td>436 (202, 942)</td>
<td>-499 (-1016, 18)</td>
<td>0.5 (0.2, 1.1)</td>
</tr>
<tr>
<td>Current GUD status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No GUD</td>
<td>107</td>
<td>128</td>
<td>346 (39, 898)</td>
<td>882 (614, 1267)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>GUD</td>
<td>54</td>
<td>76</td>
<td>130 (0, 712)</td>
<td>786 (437, 1413)</td>
<td>-96 (-657, 465)</td>
<td>0.9 (0.4, 1.8)</td>
</tr>
<tr>
<td>Current discharge status (males)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No urethral discharge</td>
<td>61</td>
<td>84</td>
<td>117 (0, 1128)</td>
<td>868 (565, 1334)</td>
<td>0.</td>
<td>1.</td>
</tr>
<tr>
<td>Urethral Discharge</td>
<td>58</td>
<td>74</td>
<td>30 (0, 138)</td>
<td>252 (111, 574)</td>
<td>-616 (-1043, -189)</td>
<td>0.3 (0.1, 0.7)</td>
</tr>
</tbody>
</table>

* Numbers sum to more than 161 because participants could have more than one type of partner.

CHI = chronic (post-acute) HIV infection; AHI = acute HIV infection; GUD = genital ulcer disease; PL = partnership length; PLD = partnership length difference; PLR = partnership length ratio
Table 5.3. Association of partnership patterns with demographic and risk predictors

<table>
<thead>
<tr>
<th>N (weighted %)ᵃ</th>
<th>Weighted odds ratios</th>
<th>Consecutive multiple vs. &lt;2 partners</th>
<th>Concurrent multiple vs. &lt;2 partners</th>
<th>Concurrent vs. consecutive multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consecutive multiple</td>
<td>Concurrent multiple</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall 144 (86.5) 16 (4.6) 19 (8.9) N/A N/A N/A</td>
<td>1.</td>
<td>1.</td>
<td>0.4 (0.3, 0.5)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female 46 (92.5) 1 (1.5) 2 (6.0)</td>
<td>1.</td>
<td>1.</td>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>Male 98 (78.5) 15 (8.8) 17 (12.7)</td>
<td>6.8 (5.1, 9.0)</td>
<td>2.5 (2.1, 3.0)</td>
<td>0.4 (0.3, 0.5)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24 years 70 (85.1) 7 (3.3) 8 (11.6)</td>
<td>1.</td>
<td>1.</td>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>25-29 years 44 (90.2) 6 (7.8) 3 (2.0)</td>
<td>2.2 (1.7, 2.9)</td>
<td>0.2 (0.1, 0.3)</td>
<td>0.07 (0.05, 0.1)</td>
<td></td>
</tr>
<tr>
<td>30+ years 30 (84.4) 3 (3.4) 8 (12.2)</td>
<td>1.1 (0.8, 1.5)</td>
<td>1.1 (0.9, 1.3)</td>
<td>1.0 (0.7, 1.5)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
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</tr>
<tr>
<td>Married 62 (92.0) 4 (2.3) 8 (5.7)</td>
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<td>1.</td>
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<tr>
<td>Unmarried 82 (81.1) 12 (6.9) 11 (12.0)</td>
<td>3.3 (2.6, 4.3)</td>
<td>2.4 (2.0, 2.9)</td>
<td>0.7 (0.5, 1.0)</td>
<td></td>
</tr>
<tr>
<td>Travel in last 2 months</td>
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</tr>
<tr>
<td>No 99 (88.1) 8 (3.6) 14 (8.3)</td>
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<tr>
<td>Yes 45 (82.7) 7 (6.8) 5 (10.5)</td>
<td>2.0 (1.6, 2.6)</td>
<td>1.4 (1.1, 1.6)</td>
<td>0.7 (0.5, 0.9)</td>
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<td>Transactional sex in last 2 months</td>
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<tr>
<td>No 101 (89.2) 7 (3.3) 7 (7.5)</td>
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</tr>
<tr>
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<td>0.7 (0.5, 0.9)</td>
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<tr>
<td>HIV status</td>
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<tr>
<td>HIV-negative 102 (85.5) 14 (8.0) 11 (6.5)</td>
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<tr>
<td>CHI 31 (87.9) 0 (0.0) 5 (12.1)</td>
<td>N/Aᵇ</td>
<td>1.8 (1.5, 2.2)</td>
<td>N/Aᵇ</td>
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</tr>
<tr>
<td>Acute HIV 11 (70.7) 2 (11.7) 3 (17.6)</td>
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<td>3.3 (1.0, 10.3)</td>
<td>1.9 (0.4, 9.3)</td>
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<td>Current GUD status</td>
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<tr>
<td>No GUD 104 (89.1) 9 (3.4) 9 (7.5)</td>
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<tr>
<td>GUD 40 (77.9) 7 (8.8) 10 (13.3)</td>
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<td>2.0 (1.7, 2.4)</td>
<td>0.7 (0.5, 0.9)</td>
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<tr>
<td>Current discharge status (males)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No urethral discharge 53 (80.1) 8 (7.8) 9 (12.1)</td>
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<tr>
<td>Urethral discharge 45 (76.6) 7 (10.0) 8 (13.4)</td>
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<td>1.2 (0.9, 1.5)</td>
<td>0.9 (0.6, 1.2)</td>
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</tbody>
</table>
Row percents

Estimates accounting for zero cells from weighted multinomial logistic regression are unavailable.

Note: Omitted from this table are 4 participants reporting ≥2 partners who did not have sufficient information to categorize their patterns as consecutive or concurrent.

CHI = chronic HIV infection, AHI = acute HIV infection, GUD = genital ulcer disease
ABSTRACT

Background: HIV transmission risk during acute and early HIV infection (EHI) is sharply elevated, but the contribution of EHI to epidemic spread is not well-defined. In settings where EHI is responsible for a large proportion of secondary transmissions, EHI is an important target for prevention efforts. We estimated the contribution of EHI to HIV incidence in Lilongwe, Malawi, and we predicted the future impact of a hypothetical intervention affecting EHI only, chronic HIV infection (CHI) only, or both stages. Methods: We developed a deterministic mathematical model describing heterosexual HIV transmission, using detailed behavioral and viral load data from our work in Lilongwe. We included sexual contact within and outside of steady pairs, and we divided the infectious period into multiple intervals to allow for changes in transmissibility by infection stage. We used a Bayesian Melding approach to fit the model to longitudinal HIV prevalence data from Lilongwe antenatal clinics. We assumed that the intervention reduced the per-contact transmission probability to 0.00003 in those receiving it, and we varied the proportion of individuals receiving the intervention in each stage. Results: Our analyses suggest that 38.4% (95% CI: 18.6%-57.5%) of ongoing HIV transmissions in Lilongwe can be attributed to EHI index cases. Interventions acting only during EHI substantially reduced HIV prevalence, but did not lead to elimination, even with 100% coverage. Interventions acting only during CHI essentially eliminated HIV within 20 years, but only with 100% coverage. In scenarios with <100% CHI coverage, additional interventions reaching 25%-75% of EHI...
cases led to sizable further reductions in prevalence.  **Conclusions:** EHI plays an important role in HIV transmission in this semi-urban, sub-Saharan African setting with a mature epidemic. Without 100% coverage, interventions during CHI will have incomplete effectiveness unless complemented by strategies targeting the heightened transmission risk of EHI.

**INTRODUCTION**

The earliest weeks of HIV infection represent a potentially important target for transmission prevention, as viral factors and greatly elevated viral loads result in an exceptionally high risk of onward transmission during this period. However, because detectable antibodies are absent during the initial (acute) portion of this period, identifying cases of early HIV infection (EHI) for potential interventions is challenging. Additionally, the population-level effect of interventions initiated during this period will vary across settings, depending on the contribution of EHI index cases to epidemic spread. Estimates of this contribution have varied widely, as the role of EHI is a complex function of multiple site-specific factors, including patterns of risk behavior and the current stage of the local HIV epidemic. Allocation of limited resources toward the more complex and expensive RNA or p24 antigen tests required to detect acute HIV infection (AHI) may be difficult to justify in settings where EHI plays only a minor role.

While HIV prevention programs have led to declining HIV incidence in some settings, 2.7 million individuals worldwide became newly infected in 2008. Recently, universal “Test-and-Treat” strategies have received considerable attention as potentially effective measures for turning the tide on HIV. The effectiveness of these strategies will depend to some extent on the role of EHI in epidemic spread. If EHI plays a major role, the effectiveness of
Test-and-Treat strategies will be limited. Therefore, the contribution of EHI must be elucidated when considering such interventions.

In this study, we estimate the contribution of EHI to HIV incidence in Lilongwe, Malawi, where HIV is hyper-endemic and transmission is mainly through heterosexual contact. We also assess the population-level impact of interventions affecting only EHI, only chronic (post-“early”) HIV infection (CHI), or both EHI and CHI. To address these aims, we developed a mathematical model describing heterosexual HIV transmission, using detailed data from our work in Lilongwe.\textsuperscript{19, 193} We conducted our model analyses within a Bayesian Melding framework\textsuperscript{145, 147} to fit our model to empirical HIV prevalence data and to reflect uncertainty surrounding model inputs and predictions.

METHODS

Basic model structure
We constructed a compartmental, deterministic mathematical model that explicitly describes the formation and dissolution of heterosexual partnerships (Appendix Two). Following the modifications of Xiridou et al\textsuperscript{114} on the classic pair-formation model,\textsuperscript{73} sexual contact was assumed to occur in three separate contexts: 1) at a constant frequency within steady partnerships, 2) as casual, one-off contacts by paired individuals outside of their steady partnerships, and 3) as casual, one-off contacts by singles. We chose this structure to capture phenomena that are especially important in the context of HIV, given its time-varying infectivity. More specifically, HIV is “trapped” within a pair as long as each infected member is monogamous, but HIV can “escape” if the partnership dissolves or the infected member(s) has sexual contact outside of the pair. Additionally, pairs of uninfected
individuals are “sheltered” from HIV as long as each partner is monogamous, but HIV can “enter” through outside contacts.

To achieve greater resolution in the variation of HIV transmission probabilities over time, we extended earlier models by dividing HIV into four periods: EHI, asymptomatic HIV, pre-AIDS, and AIDS. We defined EHI as the initial one- to six-month period of sharply elevated infectivity, based on the best available estimates of transmission rates by stage of infection, calculated among HIV-serodiscordant couples in Rakai, Uganda (Appendix Three). To allow changes in transmission probabilities related to evolving viral loads within this period, we further divided EHI into five intervals (intervals 1-5) (Appendix Three). The first four intervals (intervals 1-4) had durations of one week each to capture the most rapid changes in viral load. We sampled the fifth interval from a uniform distribution of 1.4 week to 5 months, corresponding to the total assumed EHI duration of ~1 to ~6 months (Appendix Three). We note that under this approach, the duration of EHI is based on the period of elevated infectivity from studies of transmission, rather than the estimated period of greatest viral loads.

Following others, we represented the subsequent asymptomatic period as a series of three equal intervals (intervals 6-8) of 1.8 to 3.3 years each to approximate observed survival time distributions. We based the durations of the final two stages, “pre-AIDS” (interval 9) and “AIDS” (interval 10), on the analyses of Rakai data.

As an additional extension, we stratified our model population into two groups to accommodate heterogeneity in sexual behavior. Steady partnerships were assumed to be of longer duration in the “lower-risk” group than in the “higher-risk” group, and singles in the “lower-risk” group were assumed to have lower rates of sexual contact than singles in the
“higher-risk” group (Appendix Four). The model did not include movement between groups or formation of steady pairs across groups; however, one-off contacts with casual partners were chosen at random (without restriction to a single group). The model also allowed for increased transmission probabilities in the higher-risk group, corresponding to an assumed greater likelihood of transmission-amplifying cofactors, such as ulcerative STIs or anal intercourse. Sexual contact rates for a given group did not vary by HIV status or infection interval.

Individuals entered the model population as singles, and exited after an average sexual lifespan of 35 years, with additional mortality due to AIDS among those in the final stage of infection.

Statistical analyses

We used a Bayesian Melding approach$^{145,147}$ to fit the model to empirical HIV prevalence data, to account for uncertainty in model input parameters, and to express uncertainty about model outputs. This approach combines prior information about the model inputs (e.g., sexual behavior, HIV transmission probabilities) with data about one of the primary outputs (HIV prevalence). The sources of prior information on model inputs are described in the next section. For data on model output, we used HIV prevalence estimates collected at Lilongwe antenatal clinics (ANC) over the period 1987 – 2005$^{194}$. While ANC data must be calibrated to account for biases toward urban prevalence when applied to model predictions of national HIV prevalence$^{145,147}$, our model pertains only to the urban setting of Lilongwe, so we used uncalibrated data. We implemented a sample-importance-resample algorithm to identify the sets of input parameters that produced epidemic curves most closely matching the observed ANC data, a procedure that we detail in Appendix Five. Briefly, we ran
100,000 model simulations, sampling randomly from the prior distributions of the input parameters in each simulation. Next, we weighted each simulation according to its likelihood-based compatibility with ANC data, and then we resampled (with replacement) from the simulations, with probability of selection proportional to the assigned weight. Under this approach, the simulation resampled most frequently (i.e., the simulation most compatible with empirical HIV prevalence data) represents the estimated mode for the output parameters of interest. The 2.5th and 97.5th percentiles correspond to 95% credible limits.

We used the Runge-Kutta 4 algorithm in Berkeley Madonna 8.0.1 (Berkeley, California, USA) to solve the model numerically in each run. We calculated sampling weights, performed the resampling procedure, and conducted all statistical analyses with SAS version 9.1 (Cary, North Carolina, USA).

**Parameter values**

We based the initial size of the adult (ages 15-49) population on Malawi census data\(^{146}\) (Table 6.1), and specified a range of 1960-1985 for the time of the very first HIV case in Lilongwe, reflecting the substantial uncertainty around this time.

We based the constant per-contact transmission probability for the asymptomatic period, along with the presumed effects of transmission amplifying co-factors, on meta-analysis estimates\(^{189,190}\) (Appendix Three). To calculate an average per-contact transmission probability for EHI, we multiplied the asymptomatic-period estimate by the transmission rate ratio comparing EHI to asymptomatic infection from the Rakai data (Table 6.1, Appendix Three).\(^{22}\) We then used longitudinal viral load data from AHI cases in Lilongwe,\(^{19}\) along with relative transmission rates according to blood viral load,\(^{12}\) to estimate separate transmission
probabilities within each EHI interval, subject to the constraint that the weighted average transmission probability across intervals equaled the overall EHI-period average. We also calculated the transmission probability for pre-AIDS from relative transmission rates according to disease stage (Appendix Three). The transmission probability for AIDS was assumed to be 0, reflecting an assumption of no sexual activity due to illness during this stage.

We estimated sexual behavior parameter values from data we collected at Kamuzu Central Hospital STI Clinic in Lilongwe (Appendix Four). These data included detailed information about sexual partnership durations and sexual contact frequency by both marital status and partner type, allowing us to carefully characterize the various sexual behavior parameters in the setting of interest.

**Estimating the proportion of new HIV infections due to contact with EHI index**

We calculated the annual numbers of new infections by index infection period, along with the corresponding proportions attributable to EHI transmitters, from model equations tracking cumulative numbers of incident infections according to index infection period.

**Predicting the effect of prevention interventions according to time of initiation**

We explored the potential effects of a generic HIV prevention intervention, such as condom use or antiretroviral therapy, designed to reduce per-contact transmission probabilities. We considered three general scenarios: an intervention acting during EHI only, an intervention acting during chronic (post-“early”) HIV infection (CHI) only, or an intervention acting during both EHI and CHI. We explored these scenarios by varying the proportion of individuals in whom transmission probabilities were reduced in each period (0%, 25%, 50%, 75%, or 100%). Among those receiving any intervention, the per-contact transmission probability
was assumed to be 0.000033. This value is the midpoint of male-to-female and female-to-male transmission probabilities calculated under the assumption of complete viral suppression, but can also approximate very effective condom use or other highly effective interventions.

To compare the maximum possible benefits of interventions acting in each period, we assumed that interventions began early in a given period. More specifically, interventions during EHI were assumed to start in week 3 (interval 3) and to continue through the end of EHI. This assumption, which is based on our experience with detection of AHI cases in Lilongwe (Irving Hoffman, personal communication), allows for a blood draw in the second week of infection and an additional week to return a positive HIV RNA or p24 result to the patient. Interventions acting in CHI were assumed to start at the beginning of the earliest CHI interval (interval 6) and to continue through AIDS. While this assumption likely reflects diagnosis and treatment earlier than the stage at which many cases are currently treated, it approximates a hypothetical Test-and-Treat program with annual HIV tests. All interventions were assumed to begin in 2010 (at a mature epidemic phase), and were added to the model equations through the insertion of intervention terms (Appendix Two). Our primary measure of intervention effect (versus no intervention) was the predicted reduction in HIV prevalence over the years 2010-2040. As a complementary analysis, we predicted the percentage of new infections averted between 2010 and 2015.

For “base case” analyses, we used the input parameters from the modal simulation (see Statistical Analyses above). To explore the likely range of intervention effects in situations with a greater or lesser importance of EHI, we used input parameters from the runs that most closely matched the upper and lower 95% credible limits of the estimated proportion of new cases attributable to EHI in 2010.
RESULTS

Our Bayesian Melding procedure produced a posterior distribution of 380 unique epidemic curves that were in good agreement with empirical ANC data on HIV prevalence (Figure 6.1). From the modal simulation (see Methods), we estimated that HIV prevalence in the general adult population of Lilongwe peaked at 24.7% in 1996, and that current prevalence is 14.3%. For comparison, ANC prevalence estimates peaked at 27.0% (95% CI: 22.7%, 31.6%) in 1996 and declined to 18.6% (16.0%, 21.3%) in 2005, the time of the most recent survey.

Our results suggest that 38.4% (18.6%, 57.5%) of ongoing incident HIV infections are attributable to contact with an EHI index, and that this proportion is approaching a steady state (Figure 6.2). The best-fitting EHI duration corresponding to these estimates was 4.9 months (calculated with Appendix Three equations using posterior mode estimates in Table 6.1), and the best-fitting per-contact transmission probabilities ranged from 0.003 to 0.04 across the EHI period in the low-risk group (see Methods for risk group definitions). Transmission probabilities were estimated to be five times as great in the higher-risk group as in the lower-risk group, corresponding to a greater presence of transmission co-factors in the former group.

**Intervention effects on HIV prevalence**

Figure 6.3 displays the results of intervention analyses, with the colored lines representing changes in prevalence due to different levels of coverage during EHI only (1st column), CHI only (2nd column), or both periods (3rd column). In base-case analyses where 38.4% of incident HIV infections were attributable to contact with an EHI index (top row of Figure 6.3), intervention strategies acting only during EHI (with no residual effect during CHI) substantially reduced HIV prevalence in Lilongwe, but did not lead to HIV elimination, even
with 100% coverage (solid green line in Figure 6.3A). For example, the predicted prevalence after 30 years was 12.3% with no intervention, 8.9% with 75% EHI coverage, and 6.3% with 100% EHI coverage. By contrast, CHI-only interventions initiated approximately 6 months after infection and lasting through the remainder of CHI were predicted to essentially eliminate HIV within 20 years, but only if 100% of CHI cases were reached (dashed green line in Figure 6.3B). In scenarios with less than 100% coverage during CHI (e.g., dashed blue line in Figure 6.3C), the addition of interventions during EHI (dotted lines in Figure 6.3C) provided the extra reduction in prevalence needed to bring the epidemic toward elimination.

We observed the same general patterns in sensitivity analyses where EHI was assumed to contribute just 18.6% (our lower 95% credible limit) of ongoing transmissions (middle row of Figure 6.3). In these scenarios, interventions acting only during EHI had little effect on prevalence (Figure 6.3D), and interventions reaching 100% of CHI cases again led to HIV elimination (figure 6.3E). However, interventions acting in EHI were still necessary to bring the epidemic toward elimination if 100% coverage during CHI was not achieved (Figure 6.3F).

The impact of interventions during EHI was especially important in sensitivity analyses where EHI was assumed to contribute 57.5% of new infections (our upper 95% credible limit) (bottom row of Figure 6.3). In this context, interventions acting only during EHI (Figure 6.3G) were more effective than those acting at the same level of coverage only during CHI (Figure 6.3H). Interventions acting only during CHI could not achieve elimination, even with 100% coverage (Figure 6.3H), and interventions during EHI were critical to sustaining reductions in HIV prevalence (Figure 6.3I).
**Intervention effects on HIV incidence**

In a complementary analysis examining the effects of interventions on HIV incidence, we estimated that the reduction in incident cases resulting from an intervention reaching 100% of *only* EHI cases (black triangle in Figure 6.4) was approximately equal to the assumed proportion of new infections due to EHI index cases (38.4%, our mode value). By contrast, although CHI index cases were responsible for 61.6% (=100% - 38.4%) of new infections, the predicted reduction in incidence resulting from an intervention reaching 100% of CHI cases was much greater than 61.6% (black star in Figure 6.4). In this latter case, the basic reproductive number $R_0$ (defined as the number of secondary infections resulting from one index infection in an entirely susceptible population) was driven below 1. Below this threshold value, an epidemic cannot be sustained (dashed green line in Figure 6.3B).

Some combinations of interventions reaching both periods were predicted to be more effective than interventions reaching a higher level of coverage within a single period only. For example, an intervention reaching 25% of CHI cases and 75% of EHI cases was predicted to avert 43% of new infections (black dot in Figure 6.4), while a CHI-only intervention at 50% coverage was predicted to avert 38% of new infections (black square in Figure 6.4), and an EHI-only intervention at 100% coverage was predicted to avert 37% of new infections (black triangle in Figure 6.4). We found similar relationships in sensitivity analyses using input parameters from the runs that most closely matched the upper and lower 95% credible limits of the estimated proportion of cases attributable to EHI in 2010 (Appendix Six).

**DISCUSSION**

Using detailed behavioral and viral load data from our work in Lilongwe, we have developed an extended pair-formation model to examine the contribution of EHI to epidemic spread in
this setting. Our analyses suggest that EHI continues to play an important role in this
generalized HIV epidemic, several decades after its start. As a result, prevention
approaches acting across HIV disease stages are likely to have the greatest, most durable
effect on the HIV epidemic in this setting.

Our estimates of the current proportion of new HIV infections resulting from EHI cases in
Lilongwe ranged from approximately 20% to 60%, with a mode estimate of 38.4%. These
estimates are consistent with the wide range of results from other mathematical models\cite{22-27,73,113,114} (Appendix Seven), which have differed considerably in terms of their structures,
populations, epidemic phases, and analysis methods. Endemic-phase estimates from sub-
Saharan Africa in particular have ranged from 7% to 31%\cite{22,27}. Differences in two important
parameters are likely to be at least partially responsible for the higher estimates in our study:
the longer duration of EHI (~5 versus ~3 months) and the higher relative transmissibility
during this period (~30 versus ~26). Although the ranges that we specified for these
parameters were consistent with the previous studies from this region, the estimated modes
that we obtained from our fit to observed HIV prevalence data were slightly larger. We also
note that the estimated five-month period of elevated infectivity is considerably longer than
the 10-week period of elevated viral loads that we have observed in Lilongwe\cite{19}. This
finding is consistent with virologic and modeling studies suggesting that viral load is not the
only determinant of increased infectivity during this period\cite{22,68}. As future research specifies
the mechanisms and temporal profiles of these additional factors, our model can readily
accommodate alternative patterns of infectivity, allowing us to adapt our predictions to our
evolving understanding of early HIV.

Our model is unique in several regards. First, it explicitly incorporates both steady pairs and
casual, one-off contacts, allowing us to model specific contact patterns relevant to HIV
transmission dynamics. More specifically, the inclusion of steady pairs allows uninfected couples to be “sheltered” from HIV and enables HIV to be “trapped” within discordant couples while the partnerships are intact and monogamous. The inclusion of casual, one-off contacts enables HIV transmission by unpaired individuals, as well as by paired individuals who have sexual contact outside of a steady partnership. Second, our model is based directly on sexual behavior data from Lilongwe, allowing us to define contact patterns specific to the setting of interest. Additionally, we have used detailed viral load data from AHI patients in Lilongwe, allowing a high level of resolution in the time-course of transmission probabilities during the most infectious period. Finally, we have used a Bayesian Melding approach to fit our model to empirical HIV prevalence data and to account for the substantial uncertainty around input parameters and model results. To our knowledge, our study is the first to include all of these features in addressing the contribution of EHI to epidemic spread, and we believe the results accurately reflect the contribution of EHI in this setting.

Taken together, our results reinforce the idea that EHI should not be ignored, and support calls for interventions across HIV disease stages. Our results suggest that even if the true contribution of EHI to epidemic spread is as low as ~20% (our lower credible limit), interventions acting only during CHI will not eliminate the epidemic unless 100% coverage throughout the entire CHI period is achieved. When EHI plays a larger role in perpetuating the spread of HIV, the addition of interventions reaching even a small percentage of EHI cases can lead to a dramatic improvement over CHI-only interventions. In general, we found that strategies reaching approximately 75% of CHI and EHI cases provide the greatest chance for durable, significant reductions in HIV prevalence.
In our model, we assumed that interventions acting during CHI (reliable condom use or suppressive antiretroviral therapy) were virtually completely effective in blocking transmission from the very beginning of CHI (~5 months after infection acquisition) through the remainder of the infectious period among those receiving the intervention. Therefore, the “CHI-only” strategy approximates a “Test-and-Treat” program that encourages annual HIV antibody tests, as annual testing will detect cases an average of six months (the testing interval midpoint) after infection. This scenario represents a hypothetical ideal, as current HIV testing behaviors likely result in diagnoses much later in the time-course of infection. Therefore, the additional benefits of EHI detection and intervention under current conditions are likely to be greater than the benefits that we predicted by adding EHI interventions to the idealized CHI intervention schemes in the model.

Interventions initiated during EHI may have additional benefits and challenges that are not explicitly captured in our model. Compliance with interventions initiated during EHI is likely to remain high at least through the most infectious period, minimizing the detrimental effect of waning compliance over time that has been observed with interventions that must be sustained for life. Additionally, early initiation of treatment may result in improved individual-level prognoses. While standard antibody tests may detect some EHI cases toward the end of the early period, a “Test-and-Treat” approach to EHI detection will miss many of these cases unless the testing interval is brief (~3-6 months). As large-scale programs of quarterly or semi-annual HIV testing would be extremely difficult to implement and sustain, intervention strategies intended for EHI will require more targeted recruitment approaches, such as contact tracing or partner notification. Campaigns aimed at encouraging HIV testing among individuals with recent risky behavior, sexually transmitted infections, and acute retroviral symptoms should also be considered. These case-finding strategies, in combination with pooling of blood samples and/or targeted HIV RNA
screening,\textsuperscript{141} could detect large numbers of EHI cases, even in resource-limited settings. The feasibility of this approach would be enhanced further with the availability of point-of-care rapid tests for EHI detection in the field.

Although we based our model structure and parameters on the best available data from the setting of interest, all models are necessarily oversimplified. In our model, individuals and pairs were restricted to a given risk group, and only a very simple form of concurrency – one-off encounters outside of pairs – was captured. Nevertheless, our division of EHI into numerous intervals, our inclusion of more than one risk group, and our incorporation of both steady and casual contacts may reflect transmission dynamics more accurately than previous models. Additionally, most of the data informing our input parameters were collected in a “high-risk” population of STI clinic attendees; however, none of the parameter estimates was particularly extreme. In general, our input parameters had considerable uncertainty, due to the inherent difficulties of collecting sexual behavior data and estimating transmission probabilities. To account for these uncertainties, we used a Bayesian Melding approach to specify plausible ranges and then identify the sets of parameters most compatible with empirical HIV data. Future HIV modeling efforts would benefit from more detailed, reliable estimates of HIV transmission probabilities and sexual behavior parameters. Finally, we note that the purpose of our simple analysis was to identify the relative levels of coverage required to substantially reduce HIV prevalence in this setting. Prior to implementation of a specific intervention package, a number of considerations, such as drug resistance, side effects, behavioral disinhibition, and cost, must be addressed.

Our results suggest that EHI plays an important role in sustaining the mature, generalized HIV epidemic of Lilongwe, Malawi. Interventions that fail to address the substantial risk of onward transmission during the earliest period of infection are therefore unlikely to achieve
the desired result – elimination of HIV transmission. Transmission prevention strategies should not be confined to a single infection stage, but should instead marry interventions that act in chronic HIV infection with those acting in the earliest period of infection, when the danger of onward transmission is greatest.
Table 6.1. Model input parameter definitions, prior distributions, and posterior distributions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Input value / Prior distribution</th>
<th>Posterior distribution</th>
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<tr>
<td></td>
<td></td>
<td>Input value / Prior distribution</td>
<td>Mode (95% CI)</td>
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<td><strong>Demographic parameters</strong></td>
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<tr>
<td>( \mu )</td>
<td>Rate of leaving sexually active population</td>
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<tr>
<td>( n )</td>
<td>Initial size of entire Lilongwe population</td>
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<tr>
<td>( \theta )</td>
<td>Proportion of initial population in 15-49-year age group</td>
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<td><strong>Sexual behavior parameters</strong></td>
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</tr>
<tr>
<td>( \pi_0 )</td>
<td>Proportion of initial population in low-risk group</td>
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<td>0.6 (0.5, 0.8)</td>
</tr>
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<td>( Q_0 )</td>
<td>Proportion of low-risk individuals in a steady partnership</td>
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<td>0.6 (0.6, 0.9)</td>
</tr>
<tr>
<td>( \sigma_0 )</td>
<td>Rate of steady pair separation in low-risk group (separations per year)</td>
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</tr>
<tr>
<td>( \varphi_0 )</td>
<td>Unprotected contact frequency in low-risk pairs (contacts/year)</td>
<td>Normal (65.1, 18.6)</td>
<td>33.1 (24, 96)</td>
</tr>
<tr>
<td>( s_0 )</td>
<td>Rate of low-risk singles having one-off, casual contacts (casual partners/year)</td>
<td>Uniform (0.6)</td>
<td>3.0 (0.2, 5.7)</td>
</tr>
<tr>
<td>( \chi_0 )</td>
<td>Rate of low-risk paired individuals having one-off, casual contacts (casual partners/year)</td>
<td>Normal (2.1, 0.97)</td>
<td>2.4 (0.2, 3.6)</td>
</tr>
<tr>
<td>( Q_1 )</td>
<td>Proportion of high-risk individuals in a steady partnership</td>
<td>Uniform (0.1, 0.9)</td>
<td>0.8 (0.3, 0.9)</td>
</tr>
<tr>
<td>( \sigma_1 )</td>
<td>Rate of steady pair separation in high-risk group (separations per year)</td>
<td>Uniform (0.2, 26.1)</td>
<td>9.0 (1.6, 25.8)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Definition</td>
<td>Input value / Prior distribution$^a$</td>
<td>Posterior distribution Mode (95% CI)</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>$\phi_1$</td>
<td>Unprotected contact frequency in high-risk pairs (contacts/year)</td>
<td>Uniform (16,45)</td>
<td>33.5 (17, 44)</td>
</tr>
<tr>
<td>$s_1$</td>
<td>Rate of high-risk singles having one-off, casual contacts (casual partners/year)</td>
<td>Uniform (0,24)</td>
<td>0.8 (0.7, 24)</td>
</tr>
<tr>
<td>$\chi_1$</td>
<td>Rate of high-risk paired individuals having one-off, casual contacts (casual partners/year)</td>
<td>Uniform (0,24)</td>
<td>2.1 (0.8, 24)</td>
</tr>
<tr>
<td><strong>Parameters related to per-contact HIV transmission probabilities</strong>$^c$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$VL_1$</td>
<td>Log$_{10}$ viral load in early HIV, interval 1</td>
<td>Normal (1.709, 0.5)</td>
<td>1.7 (0.8, 2.7)</td>
</tr>
<tr>
<td>$VL_2$</td>
<td>Log$_{10}$ viral load in early HIV, interval 2</td>
<td>Normal (5.273, 0.5)</td>
<td>5.5 (4.2, 6.2)</td>
</tr>
<tr>
<td>$VL_3$</td>
<td>Log$_{10}$ viral load in early HIV, interval 3</td>
<td>Normal (6.769, 0.5)</td>
<td>6.7 (5.8, 7.8)</td>
</tr>
<tr>
<td>$VL_4$</td>
<td>Log$_{10}$ viral load in early HIV, interval 4</td>
<td>Normal (6.157, 0.5)</td>
<td>6.2 (5.2, 7.0)</td>
</tr>
<tr>
<td>$VL_5$</td>
<td>Log$_{10}$ viral load in early HIV, interval 5</td>
<td>Normal (5.219, 0.3)</td>
<td>4.5 (4.7, 5.7)</td>
</tr>
<tr>
<td>$h_{6,0}$</td>
<td>Low-risk per-contact transmission probability in Asymptomatic HIV (intervals 6-8)</td>
<td>Normal (0.0007, 0.00007)</td>
<td>0.0007 (0.0006, 0.0009)</td>
</tr>
<tr>
<td>$h_{7,0}$</td>
<td>Low-risk per-contact transmission probability in Asymptomatic HIV (intervals 6-8)</td>
<td>Normal (0.0007, 0.00007)</td>
<td>0.0007 (0.0006, 0.0009)</td>
</tr>
<tr>
<td>$h_{8,0}$</td>
<td>Low-risk per-contact transmission probability in Asymptomatic HIV (intervals 6-8)</td>
<td>Normal (0.0007, 0.00007)</td>
<td>0.0007 (0.0006, 0.0009)</td>
</tr>
<tr>
<td>$h_{10}$</td>
<td>Per-contact transmission probability in AIDS (interval 10)</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>$\ln(r_E)$</td>
<td>Natural log of relative transmission rate: early vs. asymptomatic HIV</td>
<td>Normal (3.26, 0.37)</td>
<td>3.4 (2.8, 4.1)</td>
</tr>
<tr>
<td>$\ln(r_L)$</td>
<td>Natural log of relative transmission rate: pre-AIDS vs. asymptomatic HIV</td>
<td>Normal (1.97, 0.32)</td>
<td>2.0 (1.3, 2.7)</td>
</tr>
<tr>
<td>$\ln(r_v)$</td>
<td>Natural log of relative transmission rate per log$_{10}$ increase in viral load</td>
<td>Normal (0.896, 0.145)</td>
<td>0.9 (0.6, 1.2)</td>
</tr>
</tbody>
</table>

$^a$ Uniform and Normal distributions are defined as $\mu \pm \sigma$.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Input value / Prior distribution</th>
<th>Posterior distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td>Relative change in transmission probabilities in high-risk group</td>
<td>Uniform (1,6)</td>
<td>5.4 (2.5, 6.0)</td>
</tr>
<tr>
<td>HIV infection interval durations&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$1/\gamma_1$, $1/\gamma_2$, $1/\gamma_3$, $1/\gamma_4$</td>
<td>Duration of each of first 4 intervals of early HIV (intervals 1-4)</td>
<td>1 week each</td>
<td>N/A</td>
</tr>
<tr>
<td>$1/\gamma_5$</td>
<td>Duration of early HIV, interval 5 (years)</td>
<td>Uniform (0.026, 0.42)</td>
<td>0.33 (0.06, 0.41)</td>
</tr>
<tr>
<td>$1/\gamma_6$, $1/\gamma_7$, $1/\gamma_8$</td>
<td>Duration of each interval of asymptomatic HIV (intervals 6-8) (years)</td>
<td>Uniform (1.83, 3.17)</td>
<td>1.9 (1.9, 3.1)</td>
</tr>
<tr>
<td>$1/\gamma_9$</td>
<td>Duration of pre-AIDS (interval 9) (years)</td>
<td>Normal (0.75, 0.2)</td>
<td>0.9 (0.3, 1.1)</td>
</tr>
<tr>
<td>$1/\gamma_{10}$</td>
<td>Duration of AIDS (interval 10) (years)</td>
<td>Normal (0.83, 0.12)</td>
<td>1.1 (0.6, 1.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> For parameter values that varied across model runs, distributions are given as: Uniform(lower limit, upper limit), Normal(mean, standard deviation). Parameters not specified in this format were held constant at the listed value across runs.

<sup>b</sup> These parameters are described in detail in Appendix Four.

<sup>c</sup> These parameter are described in detail in Appendix Three.
HIV prevalence data from the sentinel surveillance site in a Lilongwe antenatal clinic are shown as points, with the corresponding 95% credible intervals as bracketed vertical lines. HIV prevalence output generated from the mode (i.e., most frequently resampled) set of input parameters is shown as the solid curve. The dashed curves were generated from the 2.5\textsuperscript{th} and 97.5\textsuperscript{th} percentile values from the entire posterior set of model-produced prevalence predictions at each time point.
Figure 6.2. Estimated proportion of incident HIV infections attributable to contact with EHI index case

The solid curve represents the annual proportion of incident HIV infections attributable to contact with an EHI index case predicted by the mode set of input parameters. The dashed curves were generated from the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentile values from the entire set of model-produced predictions at each time point.
Figure 6.3. Predicted effects of interventions during EHI only, CHI only, or both periods
HIV prevalence in Lilongwe is shown for scenarios with no intervention (solid black curve) and for interventions initiated in 2010 with various levels of coverage in early HIV infection (EHI) and/or chronic HIV infection (CHI). The figures in the top row (6.3A-6.3C) correspond to input parameters from the modal simulation. The figures in the second and third rows result from simulations corresponding most closely to the lower (6.3D – 6.3F) and upper (6.3G – 6.3I) 95% credible intervals of the predicted proportion of new infections due to contact with EHI index cases, respectively. Figures 6.3A, 6.3D, and 6.3G compare the “no-intervention” scenario with “EHI-only” interventions reaching 25%, 50%, 75%, and 100% of those with EHI. Figures 6.3B, 6.3E, and 6.3H compare the “no-intervention” scenario with “CHI-only” interventions reaching 25%, 50%, 75%, and 100% of those with CHI. Figures 6.3C, 6.3F, and 6.3I compare the “no-intervention” scenario with four different strategies in which 75% of CHI cases are reached: one that reaches only CHI cases, one that also reaches 25% of EHI cases, one that also reaches 50% of EHI cases, and one that also reaches 75% of EHI cases.
Figure 6.4. Predicted effects of interventions by coverage level and time of initiation within the natural history of HIV infection

Shaded contours represent the range of model-predicted proportions of new HIV infections averted in the years 2010 (start of intervention) to 2015 with the input parameters from the modal simulation (see Methods). The horizontal and vertical axes give the proportion of CHI and EHI cases, respectively, in whom per-contact transmission probabilities are reduced to 0.000033 (a value approximating transmission probabilities under complete viral suppression or condom use). The points where contour lines meet the horizontal axis represent the proportion of new HIV infections averted if CHI-only interventions (i.e., coverage in EHI=0%) are used. For example, the black square represents 50% CHI coverage and 0% EHI coverage, and the black star represents 100% CHI coverage and 0% EHI coverage. The points where contour lines meet the vertical axis represent that proportion if EHI-only interventions (i.e., coverage in CHI=0%) are used. For example, the black triangle represents 100% EHI coverage and 0% CHI coverage. All other points on the graph represent interventions that cover intermediate proportions of each period. For example, an intervention achieving 25% CHI coverage and 75% EHI coverage averts 43% of new infections; the corresponding black dot lies in the band representing the values 0.4 to 0.5.
CHAPTER 7: DISCUSSION

HIV has reached pandemic proportions, leading to widespread devastation in many parts of the world.\textsuperscript{1, 28} Although the international scientific, medical, and public health communities have made tremendous progress in the detection, treatment, and prevention of this disease, a cure for HIV eludes us and new cases continue to outpace the numbers of infected individuals receiving treatment.\textsuperscript{2} Again and again, trials of seemingly promising prevention methods have had disappointing results.\textsuperscript{30-32, 36-41} At this critical juncture in the epidemic, there is a necessity for improved understanding of the fundamental drivers of the epidemic, as well as an urgent need for innovative interventions against HIV. This dissertation has focused on two of these fundamental drivers – the heterosexual infectivity of HIV-1 and the details of sexual partnership patterns – as well as the power of interventions initiated during early HIV infection (EHI).

The heterosexual infectivity of HIV-1 (Aim 1)

Summary of findings

In our systematic review and meta-analysis, we found that current estimates of the heterosexual infectivity of HIV-1 are extremely heterogeneous. Estimates ranged from nearly zero in some studies of HIV-serodiscordant couples to almost one transmission for every three acts of anal intercourse. While infectivity estimates were only weakly associated with methodological features of the studies producing them, we found strong associations between infectivity and certain transmission-modifying cofactors. For example, infectivity
differences (expressed as transmission events per thousand unprotected sexual contacts) were 8.1 (95% CI: 0.4-15.8) comparing uncircumcised to circumcised susceptible men; 6.0 (3.3-8.8) comparing susceptibles with and without genital ulcer disease; 1.9 (0.9-2.8) comparing late-stage index cases to mid-stage index cases; and 2.5 (0.2 – 4.9) comparing early-stage index cases to mid-stage index cases. Infectivity estimates stratified by co-factors were relatively sparse, and most studies were hampered by a number of biases, likely due to the ethical and logistical challenges of conducting infectivity studies.

Interpretation
Existing infectivity estimates should be interpreted with care, given the study biases that we identified and the transmission co-factor effects that we observed. While the heterosexual infectivity of HIV-1 may be as low as one transmission event per thousand contacts in some exposures, the presence of certain co-factors can amplify this probability by more than an order of magnitude. Continued use of a single, small, “one-size-fits-all” estimate for the heterosexual infectivity of HIV-1 will perpetuate the dangerous misconception that HIV cannot be transmitted efficiently via heterosexual contact.

Public health significance
Our systematic review and meta-analysis represents one of the most comprehensive, detailed, and up-to-date analyses of the heterosexual infectivity of HIV-1. Estimates of this parameter have numerous public health applications. Perhaps most importantly, these estimates are used to communicate the level of risk involved in heterosexual exposure to HIV, and can therefore affect the types and levels of risky behavior in which susceptible and infected individuals engage. Additionally, infectivity estimates are critical inputs in mathematical models of the HIV epidemic. Because these mathematical models can inform policy decisions and resource allocation, accurate and detailed infectivity estimates are
essential to maximizing the public health benefits of these decisions. Finally, estimates that account for transmission-modifying co-factors allow us to better understand how heterosexual contact could have fueled the HIV epidemic to its current magnitude.

**Future research directions**

The ethical and logistical challenges of conducting infectivity studies will continue to limit the number of studies estimating this parameter; however, the ongoing HIV Prevention Trials Network 052 Study (HPTN 052) is one study that is expected to make a substantial contribution to our understanding of this quantity. HPTN 052 is a Phase III, randomized, controlled trial designed to determine the effectiveness of antiretroviral therapy in preventing HIV transmission within serodiscordant couples. The study aims to enroll 1750 couples on four continents, each followed for five years. The results of this study are anticipated to provide the most valid and reliable estimates of the heterosexual infectivity of HIV-1 to date.

**Heterosexual partnership patterns (Aim 2)**

**Summary of findings**

In our analysis of partnership patterns and partnership, gap, and overlap lengths among STI clinic attendees Lilongwe, Malawi, we found that most participants (86%) did not engage in multiple recent partnerships. Additionally, we found that partnerships were long on average (mean=858 days), and that overlaps among those reporting concurrency were also long (mean=246 days). Among those reporting recent serial monogamy, the mean gap between consecutive partnerships was short (21 days).

**Interpretation**
Our findings highlight the fact that risk of HIV/STI acquisition is not only a function of one’s own behavior, but also the behavior of one’s partner(s) and beyond. Most of the individuals presenting to our STI clinic had not engaged recently in sexual behaviors that are typically considered “high-risk.” However, among the minority of participants who did report multiple recent partnerships, the patterns of concurrency and narrowly spaced serial monogamy that we observed suggest a substantial risk of onward HIV/STI transmission.

**Public health significance**

Sexual behavior patterns are one of the fundamental determinants of HIV/STI spread, and as such, these parameters are critical inputs in mathematical models describing epidemic dynamics and predicting the impact of potential interventions. Unfortunately, the types of models that can be used in a given setting are limited by the level of detail in the available data. Detailed estimates of partnership lengths, gaps, and overlaps enable the use of more sophisticated models that can capture transmission dynamics more realistically than simper models. Of particular note, without the estimates that we obtained in Aim 2, we would have been limited to a much simpler (and less realistic) model for the analyses in Aim 3.

The role of concurrency in the spread of HIV has been a topic of recent debate. While mathematical models have established that concurrency could accelerate HIV transmission, empirical evidence of an association between concurrency and HIV has been limited. Some ecological studies have suggested that HIV prevalence tends to be higher in areas with greater levels of sexual partner concurrency, but results of these studies have been mixed. Only with a more detailed understanding of sexual partnership patterns in various settings will we be able to understand HIV/STI transmission dynamics throughout the world. Detailed data of this type from sub-Saharan Africa – the region hit hardest by HIV/AIDS – are relatively sparse. Our study has contributed new information
about sexual partnership patterns, durations of partnerships, gaps between partnerships, and overlaps across partnerships in this region.

**Future research directions**

To improve our understanding of HIV/STI transmission dynamics in a variety of contexts, additional estimates of partnership lengths, gaps, and overlaps from other settings are required. As described in the Background and Methods chapters of this dissertation, partnership dynamics studies have suffered from some common limitations. For improved estimates of these parameters, future studies should: 1) carefully ascertain whether partnerships are likely to continue; 2) account for censoring in estimating partnership lengths; 3) consider the effects of the “look-back” period, the number of partners on whom information is assessed, and the time unit chosen for reporting of contact dates; 4) compare concurrency estimates across multiple measures; and 5) carefully assess condom use in different types of contacts.

**The contribution of EHI and its potential as a target for prevention interventions (Aim 3)**

**Summary of findings**

In our mathematical modeling study of the HIV epidemic in Lilongwe, Malawi, we estimated that 38.4% (95% CI: 18.6%-57.5%) of ongoing incident HIV infections in this setting are due to contact with an EHI index case. Additionally, we found that an intervention suppressing transmission only during EHI could not eliminate HIV, even if 100% of EHI cases were successfully reached by the intervention. By contrast, an intervention suppressing transmission in 100% of CHI cases could lead to HIV elimination, but lower levels of CHI coverage did not result in elimination. The addition of EHI interventions to programs of sub-
optimal CHI coverage provided the additional reduction in prevalence needed to bring the epidemic toward elimination.

**Interpretation**

Interventions acting across all stages of HIV infection will be needed to produce substantial, durable reductions in HIV incidence and prevalence.

**Public health significance**

Although the probability of onward transmission is greatest during the earliest weeks of infection, most interventions designed to prevent HIV transmission from HIV-positive individuals have focused on individuals in the chronic phase of infection. One such intervention, a universal “Test-and-Treat” strategy, has received much recent attention as potentially powerful approach to eliminating the HIV epidemic. Our analyses suggest that unless transmission can be suppressed in 100% of chronically infected individuals for the entire duration of the chronic period, this strategy will fail to have its desired effect. As it is extremely unlikely that these conditions can be met, our study indicates that interventions targeting the entire infectious period of HIV – from the earliest weeks of infection onward – are needed to achieve lasting, powerful reductions in HIV incidence and prevalence.

**Future research directions**

We are actively engaged in additional studies of acute and early HIV infection in Lilongwe. We are currently developing a program to identify and inform persons with acute HIV infection (AHI) in a number of clinical sites. As part of this program, we will evaluate a short-term, combined behavioral and antiretroviral therapy (ART) intervention to prevent HIV transmission among persons with AHI. Additionally, we are planning further mathematical modeling studies to determine the potential individual and combined impact of each
component of the intervention. We will use the mathematical model that we have constructed for these dissertation analyses to conduct some of these future analyses, and we will use this model as the foundation for additional, more complex models designed to address further research questions related to early and acute HIV.
APPENDIX ONE: CALCULATING INFECTIVITY AND CORRESPONDING STANDARD ERRORS

Calculating infectivity

Studies estimated the infectivity ($\beta$) in one of five ways: by dividing the total number of susceptibles who became infected by the total number of unprotected sex acts occurring in the study population during the risk period (Eq. 1); by estimating the transmission rate per unit time during the risk period and then converting the rate into a failure probability (Eq. 2); by fitting the “Bernoulli model” (Eq. 3a) to individual-level sexual contact data with maximum-likelihood methods to estimate $\beta$; by substituting population-average sexual contact data into the Bernoulli model (Eq. 3b) and solving for $\beta$; or by fitting population-level incidence and sexual contact data to compartmental, dynamic models containing $\beta$ as a free parameter.

$$\hat{\beta} = \frac{\sum_{i=1}^{n} x_i}{\sum_{i=1}^{n} s_i}$$

(Equation 1)

$$\hat{\beta} = 1 - e^{-\lambda(\tau(t))}$$

(Equation 2)

$$\frac{\sum_{i=1}^{n} x_i}{N} = 1 - (1 - \phi \beta)^{x_i}$$

(Equation 3a)

$$\frac{\sum_{i=1}^{n} x_i}{N} = 1 - (1 - \phi \beta)^{x_i}$$

(Equation 3b)

In these equations, the variable $x$ represents susceptible individuals and the variable $s$ represents unprotected sex acts. If susceptible individual $i$ becomes HIV-infected during the risk period, then $x_i = 1$, and if susceptible individual $i$ remains uninfected during the risk
period, then $x_i = 0$; therefore, $\sum_{i=1}^{n} x_i$ represents the total number of transmission events observed among the $N$ susceptible individuals in a population. The parameter $s_i$ is the number of unprotected sex acts for a given susceptible individual during the risk period, $\lambda(t)$ is the transmission rate per unit time, $\bar{x}(t)$ is the average number of sex acts per unit time during the risk period, $\bar{x}$ is the average number of sex acts occurring during the entire risk period, and $\varphi$ is the probability that a susceptible individual’s partner is HIV-infected. When a susceptible individual is the partner of someone known to be HIV-positive, $\varphi = 1$; when the index case is not specifically identifiable, $\varphi$ is estimated as the population prevalence of HIV-1.

**Calculating standard errors**

When 95% confidence limits were reported for an infectivity estimate, we calculated the corresponding standard error as (upper confidence limit – lower confidence limit) / 3.92.

When 95% confidence limits were not reported for an infectivity estimate, we calculated an approximate standard error as follows:

1) If the Eq. 1 (Appendix 1) denominator $\sum_{i=1}^{n} s_i$ (the total number of unprotected contacts)

and numerator $\sum_{i=1}^{n} x_i$ (the total number of transmission events) were provided, or if the numerator was provided and the denominator could be calculated as $\sum_{i=1}^{n} s_i = \frac{\sum_{i=1}^{n} x_i}{\beta}$, we used $\sum_{i=1}^{n} x_i$ and $\sum_{i=1}^{n} s_i$ with Stata’s cii command, which calculates Wald confidence intervals and corresponding standard errors.
2) If values $\sum_{i=1}^{n} s_{i,j=1}$, $\sum_{i=1}^{n} s_{i,j=2}$, $\sum_{i=1}^{n} x_{i,j=1}$, and $\sum_{i=1}^{n} x_{i,j=2}$ were unavailable for stratified estimates with two categories ($j=1$, $j=2$), we first obtained the unstratified values $\sum_{i=1}^{n} s_{i}$ and $\sum_{i=1}^{n} x_{i}$. If $\sum_{i=1}^{n} s_{i}$ was not reported, we either used method 1 to calculate $\sum_{i=1}^{n} s_{i}$, or we estimated $\sum_{i=1}^{n} s_{i}$ as $N\bar{s}$, where $N$ = the number of susceptibles at risk and $\bar{s}$ = the average number of unprotected sexual HIV exposures occurring during the risk period.

If $\sum_{i=1}^{n} x_{i}$ was not reported, we used Eq. 1 to estimate $\sum_{i=1}^{n} x_{i} = \hat{\beta} \sum_{i=1}^{n} s_{i}$. After obtaining $\sum_{i=1}^{n} s_{i}$ and $\sum_{i=1}^{n} x_{i}$, we solved the following system of equations for $\sum_{i=1}^{n} s_{i,j=1}$, $\sum_{i=1}^{n} s_{i,j=2}$, $\sum_{i=1}^{n} x_{i,j=1}$, and $\sum_{i=1}^{n} x_{i,j=2}$:

$$
\sum_{i=1}^{n} s_{i} = \sum_{i=1}^{n} s_{i,j=1} + \sum_{i=1}^{n} s_{i,j=2}
$$

$$
\sum_{i=1}^{n} x_{i} = \sum_{i=1}^{n} x_{i,j=1} + \sum_{i=1}^{n} x_{i,j=2}
$$

$$
\hat{\beta}_{j=1} = \frac{\sum_{i=1}^{n} x_{i,j=1}}{\sum_{i=1}^{n} s_{i,j=1}}
$$

$$
\hat{\beta}_{j=2} = \frac{\sum_{i=1}^{n} x_{i,j=2}}{\sum_{i=1}^{n} s_{i,j=2}}
$$

After solving the system of equations, we used the cii command in Stata with the stratum-specific numerators and denominators to estimate the stratum-specific standard error.
APPENDIX TWO: MODEL DESCRIPTION

Figure A2.1  Simplified diagram of model structure

Unshaded boxes represent single (unpaired) individuals; shaded boxes represent steady partnerships. As detailed by the accompanying labels, arrows represent flows from one compartment to another via demographic processes (entering & exiting the population), partnership formation and dissolution, or HIV transmission. For ease of illustration, the diagram does not illustrate the two separate risk groups, and it represents HIV infection with a single compartment. In the model, twenty separate equations represent singles in the ten assumed intervals of infection in the two risk groups, and 132 separate equations represent the 66 possible HIV infection interval/status combinations within steady pairs in the two risk groups.
**Basic Model Equations**

Let $X_k^0$ be the number of HIV-uninfected singles in risk group $k$ ($k=0$ for low-risk group, $k=1$ for high-risk group), and $X_k^i$ be the number of HIV-infected singles in risk group $k$ and infection interval $i$ ($i=1$ to 10). Let $P_k^{i,j}$ be the number of pairs of individuals where one partner is in infection interval $i=0..10$ and the other in infection stage $j=0..10$ (with $i=0=j$ representing HIV-uninfected status). For notational convenience we assume symmetry of pairs, i.e., that $P_k^{i,j} = P_k^{j,i}$.

Following Kretzschmar & Dietz\textsuperscript{73} and Xiridou et al,\textsuperscript{114} the model is described by the following differential equations:

\[
\frac{dX_k^0}{dt} = \nu_k + (\sigma_k + \mu)(2P_k^{0,0} + \sum_{j=1}^{10} P_k^{0,j}) + \gamma_{10} P_k^{0,10} - (\mu + \rho_k + \lambda_k)X_k^0
\]

\[
\frac{dX_k^1}{dt} = (\sigma_k + \mu)(2P_k^{1,1} + \sum_{j \neq 1} P_k^{1,j}) + \gamma_{10} P_k^{1,10} - (\mu + \rho_k + \gamma_1)X_k^1 + \lambda_k X_k^0
\]

\[
\frac{dX_k^i}{dt} = (\sigma_k + \mu)(2P_k^{i,i} + \sum_{j \neq i} P_k^{i,j}) + \gamma_{10} P_k^{i,i} + \gamma_{i-1} X_k^{i-1} - (\mu + \rho_k + \gamma_i)X_k^i \quad \text{for } i = 2..9.
\]

\[
\frac{dX_k^{10}}{dt} = (\sigma_k + \mu)(2P_k^{10,10} + \sum_{j \neq 10} P_k^{10,j}) + 2\gamma_{10} P_k^{10,10} + \gamma_9 X_k^9 - (\mu + \rho_k + \gamma_{10})X_k^{10}
\]

\[
\frac{dP_k^{0,0}}{dt} = \frac{1}{2} \rho_k \frac{(X_k^0)^2}{X_k} - (\sigma_k + 2\mu + 2\omega_k)P_k^{0,0}
\]

\[
\frac{dP_k^{0,1}}{dt} = \rho_k (1-h_{1,k}) \frac{X_k^0 X_k^1}{X_k} - (\sigma_k + \phi_k h_{1,k} + 2\mu + \gamma_1 + \omega_k)P_k^{0,1} + 2\omega_k P_k^{0,0}
\]
\[
\frac{dP_{k}^{i,j}}{dt} = \rho_{k} (1 - h_{j,k}) \frac{X_{k}^{i} X_{k}^{j}}{X_{k}} + \gamma_{j-1} P_{k}^{i,j-1} - (\sigma_{k} + \phi_{k} h_{j,k} + 2 \mu + \gamma_{j} + \omega_{k}) P_{k}^{i,j} \quad \text{for } j = 2..10.
\]

\[
\frac{dP_{k}^{1,i}}{dt} = \frac{1}{2} \rho_{k} \frac{(X_{k}^{i})^{2}}{X_{k}} + \rho_{k} h_{1,k} \frac{X_{k}^{0} X_{k}^{1}}{X_{k}} + \phi_{k} h_{1,k} P_{k}^{0,1} - (\sigma_{k} + 2 \mu + 2 \gamma_{1}) P_{k}^{1,i} + \omega_{k} P_{k}^{0,1}
\]

\[
\frac{dP_{k}^{2,i}}{dt} = \rho_{k} \frac{X_{k}^{1} X_{k}^{2}}{X_{k}} + \rho_{k} h_{2,k} \frac{X_{k}^{0} X_{k}^{2}}{X_{k}} + \phi_{k} h_{2,k} P_{k}^{0,2} + 2 \gamma_{1} P_{k}^{1,1} - (\sigma_{k} + 2 \mu + \gamma_{1} + \gamma_{2}) P_{k}^{1,2} + \omega_{k} P_{k}^{0,2}
\]

\[
\frac{dP_{k}^{i,j}}{dt} = \rho_{k} \frac{X_{k}^{i} X_{k}^{j}}{X_{k}} + \rho_{k} h_{j,k} \frac{X_{k}^{i-1} X_{k}^{j}}{X_{k}} + \phi_{k} h_{j,k} P_{k}^{i-1,j} + \gamma_{j-1} P_{k}^{i-1,j-1} - (\sigma_{k} + 2 \mu + \gamma_{i} + \gamma_{j}) P_{k}^{i,j} + \omega_{k} P_{k}^{i-1,j}
\]

for \(i = 1, j = 3..10\)

\[
\frac{dP_{k}^{i,j}}{dt} = \frac{1}{2} \rho_{k} \frac{X_{k}^{i} X_{k}^{j}}{X_{k}} + \gamma_{j-1} P_{k}^{i-1,j} - (\sigma_{k} + 2 \mu + \gamma_{i} + \gamma_{j}) P_{k}^{i,j} \quad \text{for } i \geq 2, i = j
\]

\[
\frac{dP_{k}^{i,j}}{dt} = \rho_{k} \frac{X_{k}^{i} X_{k}^{j}}{X_{k}} + \gamma_{i-1} P_{k}^{i-1,j} + 2 \gamma_{i} P_{k}^{i,j-1} - (\sigma_{k} + 2 \mu + \gamma_{i} + \gamma_{j}) P_{k}^{i,j} \quad \text{for } i \geq 2, j = i + 1
\]

\[
\frac{dP_{k}^{i,j}}{dt} = \rho_{k} \frac{X_{k}^{i} X_{k}^{j}}{X_{k}} + \gamma_{i-1} P_{k}^{i-1,j} + \gamma_{j-1} P_{k}^{i,j-1} - (\sigma_{k} + 2 \mu + \gamma_{i} + \gamma_{j}) P_{k}^{i,j} \quad \text{for } i \geq 2, j > i + 1
\]

Here

\(X_{k} = \sum_{i=0}^{10} X_{k}^{i}\) is the total number of singles in group \(k\);

\(\nu_{0} = \mu m \theta \pi_{0}\) and \(\nu_{1} = \mu m \theta (1 - \pi_{0})\) are the population recruitment rates, which assume constant population size in the absence of HIV;

\(h_{j,k}\) is the per-contact transmission probability from an index in infection interval \(j\) and group \(k\);

\(\rho_{k}\) is the rate of pair formation in group \(k\);
\( \phi_k \) is the rate of unprotected sexual contact within steady pairs in group \( k \);

\[ \sigma_k = \chi_k \times h' \] is the force of infection from a casual, one-off contact on a paired individual in risk group \( k \);

\[ \lambda_k = s_k \times h' \] is the force of infection from a casual, one-off contact on a single in risk group \( k \);

\( \chi_k \) is the rate at which paired individuals in group \( k \) have casual, one-off contacts;

\( s_k \) is the rate at which singles in risk group \( k \) have casual, one-off contacts; and

\( h' \) is the weighted average per-contact transmission probability across HIV intervals and risk groups:

\[ h' = \sum_{k=0}^1 \sum_j h_{j,k} \alpha_{j,k} \]

where

\[ \alpha_{j,k} = \frac{\eta_{j,k}}{\eta'} \] is the probability of selecting a casual contact who is in risk group \( k \) and interval \( j \) of HIV infection;

\[ \eta_{j,k} = s_k X_k^j + \chi_k (2P_k^{i,j} + \sum_{j \neq i} P_k^{i,j}) \] is the number of casual contacts on offer by those in group \( k \) and interval \( i \) of HIV infection;

\[ \eta' = \sum_{k=0}^1 (s_k X_k^j + \chi_k 2P_k) \] is the total number of casual contacts on offer in the population (including by susceptibles); and

\[ P_k = \sum_{j \neq i} P_k^{i,j} \] is the total number of pairs in subgroup \( k \).

**Interventions**

To model the impact of a generic intervention targeted at individuals at different stages of infection, we simply reduce the per-contact transmission probability in interval \( j \) and group \( k \) among those receiving an intervention to:

\[ h_{j,k} = 3.3 \times 10^{-5} \]
The intervention is given to a proportion \( \varepsilon_i \) of individuals in a given interval \( i \) of HIV infection who receive an intervention. In the intervention scenarios, \( \varepsilon_i = 0 \) until the time of intervention start (calendar year 2010), and \( \varepsilon_i = (0, 0.25, 0.5, 0.75, 1) \) thereafter, depending on the intervention scenario.

For scenarios with interventions in EHI only, the reduction in transmission probabilities occurs in infection intervals 3 to 5, while for scenarios with interventions in CHI only, the reduction in transmission probabilities applies to infection intervals 6 to 10.
APPENDIX THREE: DERIVING TRANSMISSION PROBABILITIES

To describe changes in transmission probabilities across stages of infection, we:

1. Identified four broad periods of infection: “early” HIV, “asymptomatic HIV,” “pre-AIDS,” and “AIDS;”
2. Identified a mean per-contact transmission probability for low-risk index cases in the asymptomatic period;
3. Generated an expression for the mean per-contact transmission probability during “early” HIV in the low-risk group, using published relationships between early-period and asymptomatic-period transmission rates;
4. Generated an expression for the mean per-contact transmission probability during “pre-AIDS” in the low-risk group, using a similar method as that described in step 3 for early HIV;
5. Divided the “early” period into five intervals;
6. Calculated the mean $\log_{10}$ viral load among EHI patients in Malawi during each early interval;
7. Related viral loads to transmission probabilities using a published functional relationship between changes in viral load and transmission probabilities;
8. Combined these sources of information to calculate per-contact transmission probabilities for each interval of early HIV; and
9. Identified estimates for the amplifying effect of a putative co-factor in the high-risk group.

We describe steps 2-9 in more detail below.
**Step 2: Identifying a mean per-contact transmission probability for asymptomatic HIV in low-risk group**

We represented the asymptomatic period as a set of three intervals \( i = 6,7,8 \) to approximate observed survival time distributions. Each interval was assumed to have the same duration and transmission probability. We identified a mean per-contact transmission probability of \( h_{6,0} = h_{7,0} = h_{8,0} = 0.0007 \) (SD = 0.00007) for this period in the low-risk group, based on meta-analysis estimates.\(^{189,190}\) The range of durations for the asymptomatic period given in Table 6.1 was based on Hallett et al.\(^{145}\)

**Step 3: Generating an expression for the mean per-contact transmission probability during early HIV**

We related the mean per-contact transmission probability across the entire EHI period in the low-risk group \( h_{\text{early},0} \) to the mean transmission probability in the low-risk group during asymptomatic infection \( h_{6,0} \), using the transmission rate ratio \( r_E \) comparing EHI to asymptomatic infection in Hollingsworth et al.:\(^{22}\)

\[
h_{\text{early},0} = r_E \times h_{6,0}, \quad \text{(Equation A3.1)}
\]

As indicated in Table 6.1, we specified prior distributions around both \( h_{6,0} \) and \( \ln(r_E) \) in the model, and sampled from those distributions in model simulations. The mean and standard deviation for \( h_{6,0} \) are described in Step 2 above; the mean and standard error for \( \ln(r_E) \) were taken from Hollingsworth et al.\(^{22}\)

**Step 4: Generating an expression for the mean per-contact transmission probability during pre-AIDS**

We generated a similar expression for the per-contact transmission probability during pre-AIDS in the low-risk group \( h_{9,0} \):

\[
h_{9,0} = r_L \times h_{6,0}, \quad \text{(Equation A3.2)}
\]
where \( r_L \) = the transmission rate ratio comparing pre-AIDS to asymptomatic infection in Hollingsworth et al.\(^{22}\). We specified a normal distribution around \( \ln(r_L) \), based on the mean and standard deviation in Hollingsworth et al.\(^{22}\). We also note that the mean and standard deviation for the duration of this interval, as well as the duration of AIDS, were based on estimates from Hollingsworth et al.\(^{22}\).

**Step 5: Dividing the early period into intervals**

We divided the early period into five intervals (\( i = 1 \) to 5), roughly based on the times at which different types of tests are capable of detecting infection (Table A3.1):

<table>
<thead>
<tr>
<th>Interval</th>
<th>Duration</th>
<th>Available tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 week</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>1 week</td>
<td>HIV RNA only</td>
</tr>
<tr>
<td>3</td>
<td>1 week</td>
<td>RNA or p24 antigen</td>
</tr>
<tr>
<td>4</td>
<td>1 week</td>
<td>RNA or p24 antigen</td>
</tr>
<tr>
<td>5</td>
<td>Duration of “highly infectious period” estimated in Hollingsworth et al, less the first 4 weeks</td>
<td>RNA or HIV antibody</td>
</tr>
</tbody>
</table>

We specified a prior distribution on the duration of interval 5 based on the mean and standard error calculated by Hollingsworth et al.\(^{22}\) minus the first four weeks contained by intervals 1 through 4.
We define the relative duration $rd_i$ of each early interval $i$ as:

$$rd_i = \frac{d_i}{D}$$

where $D =$ the duration of the entire EHI period. \hfill (Equation A3.3)

We note that the mean per-contact transmission probability $h_{\text{early},0}$ calculated in Step 3 can be expressed as the sum of the individual interval transmission probabilities ($h_{i,0}$), each weighted by their relative durations:

$$h_{\text{early},0} = r_E \times h_{6,0} = \sum_{i=1}^{5} (rd_i) \times h_{i,0}$$

\hfill (Equation A3.4)

**Step 6: Calculating the mean blood viral load during each early interval**

We used a function describing longitudinal measurements of blood viral load in Lilongwe EHI patients\textsuperscript{19} to calculate the area under the curve (AUC) for each early-period interval. Then we calculated the constant log\textsubscript{10} viral load (VL\textsubscript{i}) having the same AUC in each interval $i$ (Figure A3.1). We specified each VL\textsubscript{i} as normally distributed in the model, with means specified at the constant values just described, and standard errors matching those reported in Pilcher et al.\textsuperscript{19}

Figure A3.1. Blood viral load curve for early HIV patients and corresponding constant viral loads
Step 7: Relating viral loads to transmission probabilities

Next, we used the constant viral loads in Figure A3.1, along with the relationship $\left( r_v \right)$ between viral load and transmission probability published in Quinn et al\textsuperscript{12} to obtain the following equations:

\begin{align*}
h_{2,0} &= r_v \times \text{logdiff}_2 \times h_{1,0} \\
h_{3,0} &= r_v \times \text{logdiff}_3 \times h_{1,0} \\
h_{4,0} &= r_v \times \text{logdiff}_4 \times h_{1,0} \\
h_{5,0} &= r_v \times \text{logdiff}_5 \times h_{1,0}
\end{align*}

Equations A3.5
where \( \text{logdiff}_i \) is the \( \log_{10} \) difference in viral loads comparing interval \( i \) to interval 1. We specified \( \ln(r_V) \) as normally distributed in the model, using the mean and standard error published in Quinn et al.\(^{12}\).

**Step 8: Combining information**

Finally, substituting the right-hand terms from this last set of equations A3.5 for \( h_{2,0} \) through \( h_{5,0} \) in Equation A3.4 and collecting terms, we obtain the following expression for \( h_{1,0} \):

\[
h_{1,0} = \frac{r_E \times h_{6,0}}{r_{d1} + r_{c} \times \sum_{i=2}^{5} (r_d_i \times \text{logdiff}_i)}.
\]

Equation A3.6

All of the terms on the right-hand side of A3.6 were either sampled directly in a given run, or could be calculated directly from sampled parameters, allowing us to solve for \( h_{1,0} \). The value of \( h_{1,0} \) can then be entered into equations A3.5, along with the sampled logdiff; and \( r_V \) values to calculate the transmission probabilities for the other intervals of early HIV.

**Step 9: Identifying range for co-factor effects**

To incorporate a possible increase in transmission risk due to transmission-amplifying co-factors (such as concomitant STIs or anal intercourse), we incorporated a multiplicative term \( c \) corresponding to every sexual contact with a “high-risk” individual (as we assumed a greater presence of these co-factors in this group). The effect was assumed to be fixed across the entire infectious period (i.e., for each interval \( i \)):

\[
h_{i,1} = c \times h_{i,0}.
\]

In identifying the range of values for the prior uniform distribution on this parameter, we specified a lower limit of 1, corresponding to no change in transmission probabilities across groups. We specified an upper limit of 6, corresponding to meta-analysis values between 5
and 6 comparing the per-contact heterosexual HIV transmission risk among groups with genital ulcer disease to groups without genital ulcer disease.\textsuperscript{189, 190}
APPENDIX FOUR: DERIVING SEXUAL BEHAVIOR PARAMETERS

We defined two separate risk groups, indexed by \( k \) in the model: 1) a “lower-risk” group (\( k=0 \)) in which casual, one-off contacts by singles were assumed to occur (on average) less frequently and “steady pairs” were longer, and 2) a “higher-risk” group (\( k=1 \)) in which casual, one-off contacts by singles occurred (on average) more frequently and steady pairs were shorter. Parameter values for steady pairs in the “lower-risk” group were based on analyses of marital/cohabiting partnerships, and parameter values for steady pairs in the “higher-risk” group were based on analyses of non-spousal, non-cohabiting partnerships. With no information with which to determine the proportion of the initial population in the low-risk group (\( \pi_0 \)), we specified a very wide range (0.1, 0.9). We calculated the five sexual behavior parameters in each risk group as follows, with all calculations based on data from our previous work at KCH STI Clinic.\(^{193}\)

**The rate of steady pair dissolution (\( \sigma_k \))**

The mean rate of steady pair dissolution is equal to the inverse of the mean steady pair duration. In the “lower-risk” group, then, we defined \( \sigma_0 \) based on the length of marital / cohabiting partnerships calculated among KCH STI clinic patients. Given the likelihood that our partnership length estimates were biased downward due to unmeasured censoring (see Powers et al\(^{193}\)), we assumed that the estimated median partnership length for marital/cohabiting pairs (2.13 years) represented a lower bound. Therefore, we used the inverse of this value (0.47 per year) as the upper limit of the prior distribution for \( \sigma_0 \). With very little data to inform the upper bound on partnership lengths, we selected a high value (20 years) to reflect the considerable uncertainty in this parameter. The corresponding lower bound on \( \sigma_0 \) was 0.05 per year (= 1/20 years).
In the “higher-risk” group, we assumed a lower bound of 2 weeks for the mean partnership length (under the assumption that anything shorter would be more similar to a one-off contact than a true, steady partnership); the corresponding upper bound on $\sigma_1$ in this group was 26.1 per year. We placed an upper limit of 5 years on partnership lengths in this group, roughly based on the measured non-marital / non-cohabiting partnership length of 3.33 years in our data (with some additional time added to account for censoring). The corresponding lower bound for $\sigma_1$ was 0.2 per year.

**The rate of steady pair formation ($\rho_k$)**

Since we did not have any direct data on the rate of steady pair formation, we specified $\rho_k$ with the following equation:

$$\rho_k = Q_k(\sigma_k + 2\mu) / (1 - Q_k),$$  \hspace{1cm} \text{Equation A4.1}

where $\sigma_k$ = the rate of steady pair dissolution (described above), $Q_k$ = the proportion of group $k$ currently in a steady pair, and $\mu$ = the underlying rate of population exit (defined in Table 6.1 of the main text as 0.029 / year = the inverse of the assumed sexual lifespan).

In the lower-risk group, $Q_0$ = the proportion of group 0 that is in a marital / cohabiting pair. Malawi Demographic and Health Survey estimates of the proportion of the entire population currently in a married or cohabiting pair range from ~60% to ~70%.\textsuperscript{185} We hypothesized that the corresponding proportion in our “low-risk” group, which corresponds to the group that gives rise to marital/co-habiting pairs, would be higher than the proportion in the whole population. Therefore, we placed a range of 0.6 to 0.9 on $Q_0$.

In the higher-risk group, $Q_1$ = the proportion of group 1 that is in a non-marital / non-cohabiting pair. With no data on which to base this value, we specified a very broad range of 0.1 to 0.9.
The frequency of unprotected sexual contact within steady pairs ($\phi_k$)

For $\phi_0$, we first calculated the mean number of unprotected contacts in a 4-week period in each marital/cohabiting pairs, based on the reported number of unprotected contacts in such pairs in the two four-week periods immediately prior to interview. We multiplied this mean by 13 to estimate the number of unprotected contacts within each marital/cohabiting pair per year. We then calculated the overall mean and standard error (reported in Table 6.1).

We used a similar method to calculate $\phi_1$, using numbers of unprotected contacts reported by unmarried/non-cohabiting participants within steady, non-marital and non-cohabiting partnerships.

The annual number of casual partners for each single individual ($s_k$)

To calculate the annual number of casual partners for each single individual, we obtained the reported number of new partners in the prior two months for each individual who reported being unmarried and non-cohabiting at the time of interview, and we multiplied that value by six. Based on the assumption that singles who ultimately form longer-term pairs (i.e., “low-risk” singles) tend to exhibit lower-risk behavior between partners, we specified the range for the low-risk group as the lower limit of these reported values (0 per year) to the median (6 per year). We specified the range for the high risk group as the entire range reported among study participants (0 to 24 partners per year).

The annual number of casual, one-off contacts among individuals in steady pairs ($\chi_k$)

For $\chi_0$, we calculated the mean and standard deviation for the number of partners in the previous year reported by marital/cohabiting individuals (minus their spouse or co-habiting
partner). For $\chi_1$, we used the same range that we used for $s_1$, since we did not have more specific data with which to define this value.
Following others,\textsuperscript{145,147} we denote the simulation model described in Appendix Two as $M$, the input parameters (described in the main text) as $\theta$, and the model-predicted prevalence output as $\rho = M(\theta)$. We denote the prior distribution for each model parameter as $q(\theta)$. We denote the data on model output (that is, the ANC prevalence data) as $W$, and the associated likelihood on the model outputs as $L(\rho) = p(W|\rho)$. The posterior distribution of inputs, then, can be expressed as: $p(\theta) \propto q(\theta) L(\rho)$.

We implemented a sample-importance-resample algorithm (Rubin 1988) to approximate the posterior distribution, as the model is not invertible and an analytic solution with which to calculate the posterior distribution is not possible. First, we generated a set of input parameters $\theta^{(i)}$ by randomly sampling from their respective prior distributions, and then we evaluated the model using that set of parameters: $\rho^{(i)} = M(\theta^{(i)})$. Next, we calculated the sampling weight for the model run as $L(\rho^{(i)})$, and then repeated the entire process 100,000 times. From the resulting discrete distribution of epidemic simulations, we resampled (with replacement) 11,000 times, with probability of selection proportional to the sampling weights. The resulting set of model runs approximates the posterior distribution for the inputs, which translates to an induced posterior on model outputs. Under this approach, output from the simulation resampled most frequently (i.e., the simulation most compatible with empirical HIV prevalence data) represents the estimated mode for the output parameters of interest. The 2.5\textsuperscript{th} and 97.5\textsuperscript{th} percentiles correspond to 95% credible limits.
APPENDIX SIX: SENSITIVITY ANALYSES OF INTERVENTION EFFECTS ON HIV INCIDENCE

We repeated the analysis of intervention effects on new infections from 2010 to 2015 using the input parameters corresponding most closely to the 2.5th and 97.5th percentile values of the predicted contribution of EHI in 2010. We found that the relative impact of interventions initiated during EHI increased with the assumed contribution of EHI to ongoing transmission. When EHI was assumed to contribute 18.6% of new transmissions (Figure A6.1), these proportions ranged from 0% to 98% for CHI-only interventions and from 0% to 16% for EHI-only interventions. In scenarios where EHI was assumed to contribute 57.5% of new transmissions (Figure A6.2), these proportions ranged from 0% to 86% for CHI-only interventions and from 0% to 60% for EHI-only interventions.

Figure A6.1. Predicted effects of interventions over period 2010-2015 by coverage level and time of initiation within the natural history of HIV infection using 2.5th percentile of EHI contribution.
Shaded contours represent the range of model-predicted proportions of new HIV infections averted in the years 2010 (start of intervention) to 2015 with the input parameters from the simulation most closely matching the 2.5th percentile of the predicted contribution of incident infections due to EHI in 2010 (see Methods). The horizontal and vertical axes give the proportion of CHI and EHI cases, respectively, in whom per-contact transmission probabilities are reduced to 0.000033 (a value approximating transmission probabilities under complete viral suppression or condom use). The points where contour lines meet the horizontal axis represent the proportion of new HIV infections averted if CHI-only interventions (i.e., coverage in EHI=0%) are used. The points where contour lines meet the vertical axis represent that proportion if EHI-only interventions (i.e., coverage in CHI=0%) are used. All other points on the graph represent interventions that cover intermediate proportions of each period.

Figure A6.2 Predicted effects of interventions over period 2010-2015 by coverage level and time of initiation within the natural history of HIV infection using 97.5th percentile of EHI contribution
APPENDIX SEVEN: SUMMARY OF EXISTING MODELING RESULTS

* Range of estimates reflects the proportion of all transmissions during an individual’s entire infectious period that occur during EHI. The extent to which this proportion corresponds with the proportion of all transmissions that occur during EHI at the population level will depend on the epidemic phase and the distribution of sexual contact patterns in the population.

** Transmission probabilities were drawn from the population category shown, but the reported estimates result from a range of hypothetical sexual behavior parameters that do not necessarily reflect a specific population.
† The range of estimates shown was extracted from the endemic-phase portion of graphs showing the time-course of the proportion due to EHI.
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