The risk of HIV transmission within HIV-1 sero-discordant couples appears to vary across sub-Saharan Africa

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ABSTRACT

Background: Representative and precise estimates for the annual risk of HIV transmission (\(\phi\)) from the infected to the uninfected partner in a stable HIV-1 sero-discordant couple (SDC) are not available. Nevertheless, quantifying HIV infectiousness is critical to understanding HIV epidemiology and implementing prevention programs.

Materials and methods: We estimated \(\phi\) and examined its variation across 23 countries in sub-Saharan Africa (SSA) by constructing and analyzing a mathematical model that describes HIV dynamics among SDCs. The model was parameterized using empirical measures such as those of the nationally representative Demographic and Health Surveys. Uncertainty and sensitivity analyses were conducted to assess the robustness of the findings.

Results: We estimated a median \(\phi\) of 11.1 per 100 person-years across SSA. A clustering based on HIV population prevalence was observed with a median \(\phi\) of 7.5 per 100 person-years in low HIV prevalence countries (<5%) compared to 19.5 per 100 person-years in high prevalence countries (>5%). The association with HIV prevalence explained 67% of the variation in \(\phi\), and suggested an increase of 0.95 per 100 person-years in \(\phi\) for every 1% increase in HIV prevalence.

Conclusions: Empirical measures from cohort studies appear to underestimate HIV infectiousness in SSA. The risk of HIV transmission among SDCs appears also to vary across SSA, and this may have contributed to the contrasting HIV epidemic trajectories in this continent.

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Introduction

In a recent landmark randomized clinical trial (RCT), the CAPRISA 004 study assessing the efficacy of vaginal microbicides in reducing HIV acquisition among women in South Africa, very high HIV incidence rates were observed (Abdool Karim et al., 2010). HIV incidence rate was measured at 5.6 and 9.1 per 100 person-years in the intervention and placebo arms, respectively (Abdool Karim et al., 2010). The study participants were 18–40 years old general population women with a reported mean of only five coital acts per month (Abdool Karim et al., 2010). Other studies conducted among general population women in South Africa have also documented high HIV incidence rates (Kharsany et al., 2010a,b). These rates of HIV acquisition among general population women in parts of Africa are striking, as they are comparable or often higher than those observed among high-risk populations such as female sex workers (Braunstein et al., 2011; Ghys et al., 2001), men who have sex with men (Li et al., 2011), or injecting drug users (Des Jarlais et al., 2000; Ghys et al., 2001).

One possible explanation for the elevated infection levels is that these women are predominantly engaged in sexual partnerships with HIV infected men. This explanation is plausible viewing the high HIV prevalence in Southern Africa, and the tendency of women to form partnerships with older men, however, this may not be sufficient to explain such high levels of incidence. An additional potential explanation is that the risk of HIV transmission per partnership is higher, for reasons yet to be well-understood, in some settings in sub-Saharan Africa (SSA) compared to others.

Quantifying HIV infectiousness is key to understanding HIV epidemiology and implementing prevention programs. The risk of HIV transmission in a sexual partnership is measured empirically among cohorts of stable HIV sero-discordant couples (SDCs) such as in the Rakai Study (Wawer et al., 2005), or the Partners in Prevention HSV/HIV Transmission Study (Partners in Prevention) (Celum et al., 2010). An SDC is a spousal or cohabiting heterosexual...
partnership between an HIV sero-positive individual and an HIV sero-negative individual. In these cohorts of SDCs, the HIV sero-negative partners are tested periodically to detect recent HIV acquisition. Sequencing of plasma samples from the index partner and the recently sero-converting partner are then performed and the newly acquired infections are classified as “linked”, that is HIV transmissions occurring within the couple, or “unlinked”, that is HIV infections acquired from sources external to the couple. The risk of HIV transmission among SDCs is then calculated by comparing the number of HIV sero-conversions occurring within couples to the total person-years of follow-up (Celum et al., 2010; Cohen et al., 2011).

The risk of HIV transmission among SDCs depends on a biological factor (HIV transmission probability per coital act; p) and a behavioral one (frequency of unprotected coital acts in the partnership; n). Several empirical studies measured the annual risk of HIV transmission (HIV incidence rate) among SDCs in SSA and have yielded variable values ranging from 1.2 to 22.0 per 100 person-years (Allen et al., 1992; Carpenter et al., 1999; Celum et al., 2010; Cohen et al., 2011; Fideli et al., 2001; Glynn et al., 2003; Gray et al., 2000, 2005; Guthrie et al., 2007; Hira et al., 1997; Hugonnet et al., 2002; Kamenga et al., 1991; Roth et al., 2001; Senkoro et al., 2000; Serwadda et al., 1995). It is not clear whether such variability describes genuine heterogeneity in p or n across SSA, or is simply due to differences in study design, systematic biases, or random errors especially considering the wide confidence intervals (CIs) around these estimates.

Against this background, we attempted to answer the following questions: (1) what is the annual risk of HIV transmission from the sero-positive to the sero-negative partner in an SDC (\(\phi\)) across SSA? (2) Does \(\phi\) vary across Africa, and to what extent?

We addressed these two questions using a novel approach that provides a fresh look into an old lingering problem in HIV epidemiology. In this approach, we estimate \(\phi\) by fitting a cohort-type mathematical model to empirical HIV prevalence and discordancy data. Our approach may be limited by several model assumptions, and by the quality and precision of available data to parameterize the model. It also relies on an indirect method, mathematical modeling, and is not a replacement of empirical studies. Nonetheless, the strength of this analysis lies in its independence from specific systematic biases that can affect empirical measures for \(\phi\). Ultimately, our understanding of the risk of HIV transmission among SDCs should be based on a balanced view of all evidence using the different methodologies, and this view should factor the strengths and weaknesses of each approach.

Empirical studies are often constrained by logistical considerations that can affect the generalizability of the results, our estimates for \(\phi\) are based on population-level data, and therefore probably more generalizable. Moreover, empirical studies nearly always rely on recruiting existing SDCs (Celum et al., 2010; Cohen et al., 2011), and therefore could potentially miss the contribution of acute infection to the risk of transmission. Conversely, our model calculates the average \(\phi\) from the onset of HIV infection in the index partner in the SDC until the death of this partner. Accordingly, our approach accounts implicitly for all stages of HIV infection of the sero-positive index partner in the SDC including acute infection. Empirical measures are also often derived from cohort studies where sero-status disclosure and intense counseling are present (Celum et al., 2010; Cohen et al., 2011), thereby biasing possibly the risk of transmission estimates toward lower values. Our approach, based on population-level data, is possibly more representative of the average HIV infectiousness among couples at the national level, yet, regional differences in \(\phi\) could also exist. Lastly, our analysis is not affected by selection bias of more “resistant” couples in the recruitment of SDCs, as could be the case in empirical studies where only “surviving” SDCs, that is couples where the index partner has not yet infected the uninfected partner, are recruited.

Materials and methods

We constructed a cohort-type mathematical model to estimate \(\phi\) for 23 countries in SSA by describing the process of HIV sero-discordancy in a population in the context of an HIV epidemic (Supplementary Data: SuppD). The model was parameterized using nationally representative empirical epidemiological and demographic measures derived from the Demographic and Health Surveys (DHS) (MEASURE DHS, 2012) among other sources (SuppD).

Mathematical model

For each country, we used DHS data to describe a nationally representative cohort of the population in reproductive age. The mathematical model is then used to follow this nationally representative cohort, including SDCs, and the development of epidemiologically relevant events such as the formation and dissolution of partnerships, HIV acquisition and transmission from different sources, and natural and disease mortality (Fig. 1 and Fig. S1 in SuppD). Using the mechanism of competing hazards (events/processes), the model calculates the distribution of key HIV statistics including HIV sero-discordancy measures in this cohort at endemic equilibrium. We then estimate \(\phi\) by fitting the predicted distribution of HIV infection among this cohort to the empirical distribution of HIV infection as observed in the DHS for each country. Further details on the model can be found in SuppD.

Model parameters

Countries were considered for analysis based on the availability of DHS HIV serological biomarker survey. For each country, we used only the most recent DHS survey where HIV data were collected. Consequently, a total of 23 countries in SSA were included in our analysis (SuppD). These surveys were characterized by public acceptability where the response rate to the DHS survey and to HIV testing averaged about 87% across SSA (Table S4 in SuppD). Country-specific couple databases, comprising the HIV sero-status information for both partners in a SC, were formed based on established guidelines for managing DHS data (Rustein and Rojas, 2006).

The DHS databases (MEASURE DHS, 2012), complemented by population size information from the United Nations Population Division Database (United Nations Department of Economic and Social Affairs, 2010), were used to calculate country-specific demographic statistics such as the size of the population in reproductive age and the population prevalence of SCs (\(P_{\text{couple}}\)). The sexual partnership duration among SCs (\(d\)), at the time of the DHS survey, was estimated using the question: “in what month and year did you start living with your first wife/partner?”.

We also extracted, using the DHS databases, country-specific epidemiological measures such as HIV–1 prevalence in the population (\(P\)), and the distribution of couples based on HIV sero-status (discordant negative, discordant, or discordant positive). We further calculated specific measures of HIV sero-discordancy including the proportion of SDCs among all SCs in the population (\(P_{\text{all}}\)), the proportion of SDCs among all SCs with at least one HIV infected individual in the couple (\(P_{\text{discord}}\)), the proportion of individuals engaged in SDCs among the entire population in the reproductive age (\(I_{\text{all}}\)), and the proportion of couples affected by HIV out of all SCs (\(P_{\text{pos}}\)). The definitions of these measures can be found in Chemaitelly et al. (2012). These sero-discordancy measures were calculated for SCs with complete HIV sero-status information. Missing or incomplete HIV information among SCs ranged from less than 1% in Rwanda to 27% in Zambia, with a mean of 11.6% across countries (Table S4 in SuppD). We applied the sampling weights retrieved from the DHS databases to all of our calculations.
We assumed that the risk of acquiring HIV by a susceptible partner in a couple, from sources external to the couple, can be approximated by HIV population-level incidence rate (Chemaitelly and Abu-Raddad, 2013). Measures of HIV incidence rate were obtained from the Joint United Nations Programme on HIV/AIDS (UNAIDS) SPECTRUM model predictions for each country for the specific year of the DHS survey (UNAIDS, 2010). For 52% of the countries where SPECTRUM model predictions were not available or where the bounds of the 95% CI were not precisely specified (12 out of 23 countries) estimates for the HIV incidence rate were derived using the DHS country-specific HIV prevalence in the population (SuppD). Further details on model parameters can be found in SuppD.

**Model fitting and uncertainty and sensitivity analyses**

The measure of interest ($\phi$) and the stable couple formation rate ($\delta$) were derived by fitting the model to six statistics for each country: $P_c$, $P_{alt}$, $P_{discord}$, $I_{alt}$, and $P_{pos}$. Informative priors were used for all other model parameters. The model was fitted to the data using a nonlinear least-square fitting method. This technique, implemented in MATLAB® (MATLAB®, 2013), minimizes the sum of squares between all data points and the model, using the Nelder–Mead simplex algorithm as described in Lagarias et al. (1998). We applied the 1/4-power transformation method to all six statistics to adjust for the differences in the scales of these statistics, thereby optimizing the fitting for all of them concurrently by harmonizing their scales.

Uncertainty analyses were conducted to generate the distribution of likely values for $\phi$ for each country (SuppD). We implemented 10,000 runs of the model for each country applying at each run Monte Carlo sampling from uniform probability distributions for the CIs or ranges of plausibility of model parameters (Tables S2, S3a, S3b, and S3C in SuppD). Estimates for the mean value of the maximum likelihood estimates for $\phi$ and 95% CI for each country were determined by fitting a log-normal distribution to the country-specific range of estimates (Fig. 2 and Fig. 3 in SuppD).

Several sensitivity analyses were also performed to assess the robustness of our findings. We first assessed the sensitivity of our model predictions for $\phi$ to variations in $P_{discord}$, a key measure for determining $\phi$ (Fig. 4). We also assessed the sensitivity of our estimates for $\phi$ to variations in the average time from onset of HIV infection to disease mortality, a possible effect of the expansion of antiretroviral therapy (ART) coverage in SSA (Fig. 5A). We also assessed the sensitivity of our estimates to variations in the annual probability of acquiring the infection by a susceptible partner in a couple from sources external to the couple (Fig. 5B). Since the DHS derived measure for the partnership duration ($d$) may be biased due to the specificity nature of the survey question, censorship of data, large contribution of young individuals who established

<table>
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A green circle indicates an HIV-sero-negative individual, while a red circle indicates an HIV-sero-positive individual.
their stable partnerships not long ago, and oversampling of longer partnership durations in cross-sectional surveys (Burington et al., 2010; Nelson et al., 2010), two sensitivity analyses were also conducted to assess the sensitivity of our predictions for $\phi$ to this limitation (Fig. 5C and Fig. S4 in SuppD). In the first sensitivity analysis, applied to Tanzania as an example, we assumed $d$ to vary continuously from 20% less of the point estimate to double its value (Fig. 5C). In the second sensitivity analysis (Fig. S4 in SuppD), two model runs were performed for all countries where $d$ was first reduced by 50% (first run) and then doubled (second run).

**Results**

Our mathematical model fitted well the epidemiological and demographic variables for nearly all measures in all countries (Fig. S2 in SuppD and Table S1 in SuppD). The mean of the country-specific $\phi$ clustered between 4 and 20 per 100 person-years with few notable exceptions of higher values (Fig. 2). The median $\phi$ was 11.1 per 100 person-years across countries. A clustering based on HIV prevalence was observed with a median of 7.5 per 100 person-years in low HIV prevalence countries (<5%) compared to 19.5 per 100 person-years in high prevalence countries (>5%).
Our model predicted exceptionally high values for $\phi$ of 30 per 100 person-years or more in Burundi, Rwanda, and Swaziland, which were treated as outliers (Fig. 2). A regression analysis on the model predictions indicated that HIV prevalence in the population explained 67% of the variation in the predicted $\phi$ across SSA (Fig. 3). With every 1% increase in HIV prevalence, $\phi$ increased by 0.95 person-years (95% CI: 0.62–1.28). The uncertainty analyses suggested some skewness toward lower values in the country-specific likelihood distributions for $\phi$ (Fig. S3 in SuppD), particularly for low HIV prevalence countries.

The sensitivity analysis with respect to $P_{\text{discord}}$, that is the fraction of couples that are HIV discordant as opposed to being HIV concordant positive, revealed, as expected, a strong functional dependence of $\phi$ on this measure (Fig. 4). The lower is $P_{\text{discord}}$, the higher is $\phi$. The dependence of $P_{\text{discord}}$ on $\phi$ was linear when $P_{\text{discord}}$ was large, but was non-linear and sensitive to small changes in $P_{\text{discord}}$ as $P_{\text{discord}}$ approached 50%.

Our estimates for $\phi$ were also sensitive to variations in the time from onset of HIV infection to disease mortality (Fig. 5A). Conversely, variations in the annual probability of acquiring the infection by a susceptible partner in a couple from sources external to the couple had minimal impact on our predictions for $\phi$ (Fig. 5B). The sensitivity analyses with respect to variations in the sexual partnership duration demonstrated generally rather small sensitivity of the $\phi$ predictions to potential systematic biases in the values of $d$ (Fig. S5C and Fig. S4 in SuppD). Overestimation of $d$, possibly because of bias in oversampling longer partnership durations in the DHS, would lead generally to overestimation of $\phi$. Meanwhile, underestimation of $d$, possibly because of bias in censorship of DHS data, would lead to overestimation of $\phi$, particularly in high HIV prevalence countries (Fig. S4 in SuppD).

**Discussion**

Our model predictions for the annual risk of HIV transmission from the sero-positive to the sero-negative partner in an SDC ($\phi$) hovered around 10 per 100 person-years for the majority of countries in SSA. The median of our estimates (11.1 per 100 person-years) is roughly at the mid-range of the measures reported in observational studies which varied between 1.2 and 22 per 100 person-years (Allen et al., 1992; Carpenter et al., 1999; Celum et al., 2010; Cohen et al., 2011; Fideli et al., 2001; Glynn et al., 2003; Gray et al., 2000, 2005; Guthrie et al., 2007; Hira et al., 1997; Hugonnet et al., 2002; Kamenga et al., 1991; Roth et al., 2001; Senkoro et al., 2000; Serwadda et al., 1995). Nevertheless, overall the predicted values are larger than those of empirical data. Our predicted median value, though higher, is comparable to one of the most representative empirical measures for $\phi$, that of the Rakai Study at 8.4 per 100 person-years (among a cohort including only chronically infected index persons) (Wawer et al., 2005).

Our findings of comparable but higher estimates for $\phi$ suggest that existing empirical measures of HIV infectiousness in SSA could be underestimating the actual risk of HIV transmission among SDCs in the population at large. This could be explained by selection biases affecting the empirical measures including the recruitment of “resistant” SDCs, not accounting for acute infection, and the presence of sero-status disclosure and counseling (Celum et al., 2010; Cohen et al., 2011; Guthrie et al., 2007). These biases can under-estimate the actual population-based values of $\phi$. An example to this end are the estimates of the Partners in Prevention (Celum et al., 2010) and HPTN052 (Cohen et al., 2011) studies (about 2–3 per 100 person-years) which are much lower than ours. This highlights how the incidence rates reported in these trial settings, with HIV sero-disclosure and intensive counseling and prevention, may not be representative of the risk of HIV transmission among SDCs in the wider population.

Our findings suggest variability in $\phi$ across SSA. There is a trend for $\phi$ to be substantially higher in higher HIV prevalence countries (Figs. 2 and 3). Indeed, under our generic model (SuppD), HIV population prevalence explained 67% of the variation in HIV infectiousness across SSA (Fig. 3). This may explain in part the high HIV incidence rates found even among general population women, despite relatively low coital frequency, in parts of SSA such as in South Africa (Abdool Karim et al., 2010; Kharsany et al., 2010a,b).

A key variable determining the predicted values for $\phi$ is the proportion of SDCs among all SCS with at least one HIV infected individual in the couple ($P_{\text{discord}}$, Fig. 4). In fact, the strong association between $\phi$ and HIV prevalence (Fig. 3) is only a reflection of the strong association between HIV prevalence and $P_{\text{discord}}$ documented...
Fig. 5. Sensitivity analysis assessing the sensitivity of the annual risk of HIV transmission from the infected to the uninfected partner in a stable HIV sero-discordant couple ($\phi$) to variations in (A) the time from onset of HIV infection to disease mortality; (B) the annual probability of acquiring HIV infection by a susceptible partner in a couple from sources external to the couple; and (C) sexual partnership duration among stable couples. The three panels describe how $\phi$ would vary at different levels of these parameters, and are generated based on the demographic and epidemiological data for Tanzania. The model prediction for $\phi$ for Tanzania is also included in this figure (red marker). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article).

earlier (Chemaitelly et al., 2012). Higher levels of $P_{discord}$ are generally observed in low compared to high HIV prevalence countries (means of 75% versus 58%, respectively) (Chemaitelly et al., 2012). Assuming a stable HIV epidemic at endemic equilibrium, a high $P_{discord}$ may indicate that a small proportion of SDCs are becoming concordant positive among SCs affected by HIV, and hence implicitly, a lower risk of HIV transmission from the infected to the uninfected partner in an SDC. Conversely, a low $P_{discord}$ suggests a higher HIV transmission rate from the infected to the uninfected partner in an SDC.

The strong functional dependence of $\phi$ on $P_{discord}$ can be seen in Fig. 4. It suggests that countries in SSA cluster into two overall patterns. In low HIV prevalence countries, $P_{discord}$ is high and $\phi$ is low with values in the neighborhood of 10 per 100 person-years. In high HIV prevalence countries, where $P_{discord}$ approaches values around 50%, $\phi$ is two- to three-fold higher and the predicted values of $\phi$ are sensitive to even small changes in $P_{discord}$. The dependence of $\phi$ on $P_{discord}$ may explain the outlier predictions for Burundi, Rwanda, and Swaziland. In these three countries, the empirical values for $P_{discord}$ were exceptionally smaller than those in the other countries ($P_{discord} \leq 50\%$). It is not clear why these countries have such low levels of sero-discordancy, or whether these sero-discordancy estimates, based on DHS data, may not be representative of sero-discordancy in the SC population at large.

We performed multiple uncertainty and sensitivity analyses to assess the robustness of our model predictions for $\phi$. The skewness in the distribution of likely values for $\phi$ seen in our uncertainty analyses (Fig. S3 in SuppD), and the sensitivity analysis with respect
to the censorship of DHS data for the partnership duration (Fig. 5C and Fig. S4 in SuppD), suggest that our estimates may be biased toward slightly higher values for φ particularly in countries with low \( p_{\text{disc}} \) (high HIV prevalence).

In absence of country-specific empirical data on the annual probability of acquiring HIV infection by a susceptible partner in a couple from sources external to the couple (\( \lambda \)), we assumed \( \lambda \) to be equal to HIV population-level incidence rate. To assess the impact of this assumption on our model predictions for φ, we conducted a sensitivity analysis with respect to \( \lambda \) using Tanzania as an example (Fig. 5B). The analysis revealed minimal sensitivity with respect to \( \lambda \) suggesting that sexual risk behaviors external to the SDC have a rather limited impact on our predictions for the risk of HIV transmission from within the SDC. This result is consistent with the fact that external infections contribute minimally to HIV incidence among SDCs in SSA—that is \( \lambda \) is much smaller than φ (Chemaityelli et al. and Abu-Raddad, 2013).

Our results suggest that the observed variability in the empirical measures for φ (Allen et al., 1992; Carpenter et al., 1999; Celum et al., 2010; Cohen et al., 2011; Fideli et al., 2001; Glynn et al., 2003; Gray et al., 2000, 2005; Guthrie et al., 2007; Hira et al., 1997; Hugonnet et al., 2002; Kamenga et al., 1991; Roth et al., 2001; Senkoro et al., 2000; Serwadda et al., 1995) may reflect genuine heterogeneity in transmission risk across SSA, beyond the effects of study design and systematic and random errors. This finding poses a question about the drivers of this variability in HIV infectiousness, and whether this heterogeneity may contribute to explaining the stark differences in HIV epidemic trajectories within SSA.

The variability in φ may reflect both biological (HIV transmission probability per coital act; \( p \)) and behavioral (frequency of unprotected coital acts in the partnership; \( n \)) cofactors that vary across SSA. Male circumcision is one evident biological cofactor as it affects \( p \) and varies in coverage across the African continent (Auvert et al., 2005; Bailey et al., 2007; Gray et al., 2007; Weiss et al., 2008). Our descriptive analysis of the DHS suggests that male circumcision coverage varies between 8.2% in Swaziland and universal coverage in other countries such as Congo-Brazzaville, Niger, Guinea, and Liberia (Chemaityelli et al., 2013). Variability in ART coverage across countries can induce differences in HIV infectiousness per coital act and the average time from onset of infection to disease mortality, and hence can impact our estimates for φ and induce variability in φ across countries (see for example Fig. 5A). However, ART mass scale-up is relatively a recent initiative, and ART coverage may not have been substantial at the time the DHS data were collected (most DHS data used in this work are few years old). Different circulating virus sub-types are another potential biological cofactor. HIV-1 subtype C is found predominantly in areas of high HIV prevalence in SSA and appears to be linked to extended high viremia (Kaul et al., 2011; Novitsky et al., 2011). Other potential biological cofactors include STIs such as herpes simplex virus type 2 (Abu-Raddad et al., 2008; Korenromp et al., 2001), tropical co-infections increasing HIV viral load (Abu-Raddad et al., 2006, 2013), hormonal contraception (Heffron et al., 2012), and host genetics and immunology (Kaul et al., 2011).

Behavioral co-factors may also contribute to explaining the variability in transmission risk, but this is true only for within couple sexual behavior since our estimates were found largely insensitive to the risk of external HIV acquisition (Fig. 5B). The main behavioral factors that may contribute to explaining this variability are coital frequency and condom use. For example, differences in sero-status disclosure and voluntary counseling can lead to variability in coital frequency and condom use across countries (Hughes et al., 2012). Nevertheless, the frequency of coital acts in SCS is not well documented in SSA and appears to vary (Brown, 2000; Wawer et al., 2005). In absence of country-specific data on coital frequency, we are unable to assess whether differences in coital frequency could explain the variability in φ.

The uptake of condom use in couples appears also to vary across SSA (Hughes et al., 2012; Weller and Davis, 2001). Our descriptive analysis of the DHS data revealed very low levels of condom use among SCs that rarely exceeded 10%, with a mean reported condom use of 5.3% across SSA. The only exceptions are Swaziland and Lesotho where the reported condom use reached up to 24% at the time of these surveys. These higher rates of condom use nonetheless are probably a recent phenomenon in these two countries. Accordingly, it does not appear that condom use differences can explain the variability in φ.

Our analysis is limited by the quality and precision of the available data. Although DHS data are among the best available nationally representative data, DHS data have a number of inherent limitations that are not amenable for adjustment in our analysis. These include the recentness of the analyzed surveys, the small sample sizes and wide CIs around some of the country-specific data such as those for Senegal, the country with the lowest number of couples affected by HIV (only 27 couples), and the incomplete HIV testing information among couples that might have led to databases that are not representative of the couple population (MEASURE DHS, 2012). Our analysis is also limited by the definitions of some of the DHS questions such as those related to sexual partnership duration, and potentially by the cross-sectional nature of the surveys leading to data censoring or oversampling of SCs with longer partnership duration (Althaus et al., 2012; Burington et al., 2010; Foxman et al., 2006; Nelson et al., 2010). Our reliance on multiple data sources that use different methodologies could also potentially lead to inconsistencies that may have affected our model fits and our predictions.

Mathematical models are by design a simplification of reality and some model assumptions may not hold thereby potentially affecting our predictions. Our conceptual approach, based on competing hazards, assumes implicitly a largely stable HIV epidemic, but this may not apply across countries. Multiple countries across SSA have been witnessing declines in HIV prevalence over the last decade and, in some countries intensive HIV prevention programs, including HIV testing and counseling among couples, have been put into action (UNAIDS et al., 2011). For countries that are experiencing rapidly declining HIV epidemics, existing SDCs may become concordant positive at a faster rate than new partnerships become discordant. This would lead to higher sero-positive concordancy among couples affected by HIV (low \( p_{\text{disc}} \)), and hence, possibly superfluously higher estimates of φ in our model than is reality. This scenario may apply to the three countries with outlier predictions for φ (Burundi, Rwanda, and Swaziland), as well as to some extent, Lesotho, Malawi, Zambia, and Zimbabwe where the empirical values for \( p_{\text{disc}} \) were low. However, we examined an extension of this model that incorporated temporal dynamics, and the preliminary results suggested no substantial impact of temporal dynamics on our predictions.

Our model was constructed to provide an overall average for φ among the actual cohort of persons engaged in stable partnerships in each country, rather than to examine differences in this measure by age or sex. Accordingly, we did not stratify the population by age or sex. Yet, in light of the equal distribution of HIV index partners among males and females in SDCs (Chemaityelli et al., 2012; Eyawo et al., 2010), and in light of the large proportion of the sexually active population that are engaged in SCs even at a young age (Table S1 in SuppD and not-shown analysis of the distribution of couples by age), the estimated φ is probably not a biased estimate of the actual average φ across the population of each country though regional differences may still exist.

Despite these limitations, our model fitted well the measured epidemiological indicators across the countries (Fig. S2 in SuppD
and Table S1 in SuppD) and predicted values for \( \phi \) that chime nicely with empirical values from observational studies such as the Rakai cohort (Allen et al., 1992; Carpenter et al., 1999; Fideli et al., 2001; Glynn et al., 2003; Gray et al., 2000, 2005; Guthrie et al., 2007; Hira et al., 1997; Hugonnet et al., 2002; Kamenga et al., 1991; Roth et al., 2001; Senkoro et al., 2000; Serwadda et al., 1995; Wawer et al., 2005), though substantially higher than those found in RCTs involving sero-status disclosure and counseling (Culum et al., 2010; Cohen et al., 2011). This was achieved despite building a terse parsimonious model where all model parameters are constrained by direct empirical measures. Of note that we explored variations and extensions to the model structure where we incorporated additional effects and complexities such as heterogeneity in risk behavior, transmission dynamics, and epidemic temporal evolution among others. The results were invariable. This suggests the inherent consistency of our model structure and its ability to capture the essence of HIV dynamics among SCs. Our uncertainty (Fig. 2 and Fig. S3 in SuppD) and sensitivity (Figs. 4 and 5, and S4 in SuppD) analyses also affirmed our findings and inferences. Yet, it remains to be seen whether other variations to the model structure would impact our findings.

In conclusion, we presented a novel approach based on mathematical modeling to estimate the annual risk of HIV transmission from the infected to the uninfected partner in an SDC (\( \phi \)). Our findings suggest that \( \phi \) is about 10 per 100 person-years in most countries in SSA, and is higher in high compared to low HIV prevalence countries. Existing empirical measures from cohort studies could be somewhat underestimating HIV infectiousness in the population at large. The heterogeneity in the risk of HIV transmission across SSA may have contributed to the contrasting HIV epidemic trajectories across this continent. HIV prevention efforts should factor this variability in transmission risk whenever prevention programs among SDCs are considered.

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HC managed the DHS databases, conducted the bulk of the statistical and mathematical modeling analyses, and wrote the first draft of the paper. SFA programmed and conducted the model simulations for the uncertainty and sensitivity analyses. IJA-R conceived, led the design of the study, mathematical modeling analyses, and drafting of the article. All authors contributed to the conduct of the study, interpretation of the results, and the writing of the article.

Conflict of interest

There are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.epidem.2013.11.001.

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