A signature for biological heterogeneity in susceptibility to HIV infection?

Nico Nagelkerke [a], Laith J. Abu-Raddad [b, c, *], Susanne F. Awad [b, d],
Vivian Black [e, f], Brian Williams [f, g]

[a] Department of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands
[b] Infectious Disease Epidemiology Group, Weill Cornell Medical College - Qatar, Cornell University, Qatar Foundation - Education City, Doha, Qatar
[c] Department of Healthcare Policy and Research, Weill Cornell Medical College, Cornell University, New York, USA
[d] Population Health Research Institute, St George's, University of London, London, UK
[e] Clinical Microbiology and Infectious Diseases, Faculty of Health Sciences, University of the Witwatersrand, South Africa
[f] Wits Reproductive Health and HIV Institute, University of Witwatersrand, Johannesburg, South Africa
[g] South African Centre for Epidemiological Modeling and Analysis (SACEMA), Stellenbosch, South Africa

ARTICLE INFO

ABSTRACT

Data on female sex workers and sero-discordant couples indicate a pattern of waning of the risk of HIV infection with longer duration of exposure to infected partners. Understanding risk of HIV acquisition and transmission is critical to understanding HIV epidemiology and informing prevention interventions. Informed by empirical data, we aimed to develop a statistical model to explain these observations. In our proposed model, the time to infection for each individual is exponentially distributed, but the marginal (population averaged) distribution of time to infection follows a Weibull distribution with shape parameter of about 0.5, and with the Lévy distribution being the mixing distribution. Simulations based on this model demonstrated how HIV epidemics are destined to emerge rapidly, because of the rapid sero-conversion upon exposure, but also simultaneously destined to saturate and decline rapidly after emergence, just as observed for the HIV epidemics in sub-Saharan Africa. These results imply considerable individual variability in infection risk, probably because of biological heterogeneity in the susceptibility to HIV infection. Factoring this variability in mathematical models, through the methodology provided here, could be critical for valid estimations of impact of HIV interventions and assessments of cost-effectiveness.

---

* Corresponding author. Infectious Disease Epidemiology Group, Weill Cornell Medicine-Qatar, Qatar Foundation - Education City, P.O. Box 24144, Doha, Qatar.
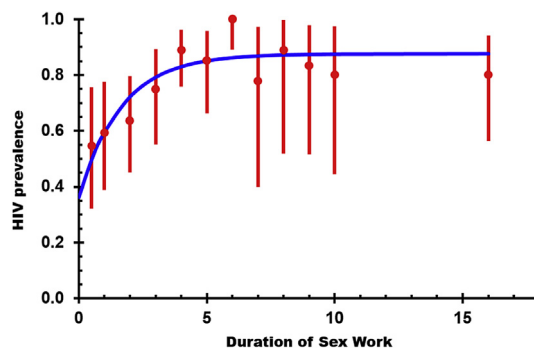E-mail address: lja2002@qatar-med.cornell.edu (L.J. Abu-Raddad).

Fig. 1. HIV prevalence among female sex workers (FSWs) versus duration of sex work in Hillbrow of Johannesburg, South Africa. These data on 268 FSWs illustrates an example of duration of sex work being a (negative) predictor of future HIV infection risk. Infection risk among long-term FSWs appears minimal, despite continuous exposure, and is much lower than that among those who initiated sex work recently.

1. Introduction

Understanding HIV acquisition risk is critical to HIV epidemiology and informing prevention interventions, but there are infection patterns that remain difficult to understand. One of these is the waning of infection risk with duration of exposure to infected partners among female sex workers (FSWs) and sero-discordant couples (SDCs) (Fowke et al., 1996; N.; Nagelkerke et al., 2009; N. J.; Nagelkerke et al., 2014), even after adjustment for the number of unprotected exposures (McKinnon et al., 2015).

Fig. 1 shows an example of this pattern. Since 1998, the Wits Reproductive Health and HIV Institute has provided clinical and outreach sexual and reproductive health services to FSWs in the inner city (Hillbrow) of Johannesburg, South Africa. FSWs (n = 268) attending these services between March and December of 2014 were tested for HIV and various sexually transmitted infections. The data collection was approved by the Human Research Ethics Committee of the University of Witwatersrand.

In these data, the duration of sex work was found to be a (negative) predictor of future HIV infection risk: after several years of exposure, the prevalence becomes flat. In fact, after five years of sex work, 20 out of 109, and after 10 years of sex work, 6 out of 30, remain HIV uninfected. Infection risk among these long-term FSWs thus appears minimal, despite continuous exposure, and is much lower than that among those who initiated sex work recently. It bears notice that unlike acquired immunity, this apparent decline of risk with exposure is strictly a selection mechanism. Those individual differences existed from the start of exposure and have not changed. Due to the rapid infection of those most susceptible, the average susceptibility of the FSWs as a group declines with "exposure" (that is duration of sex work).

A similarly interesting pattern is found in studies of SDCs (Hughes et al., 2012; Quinn et al., 2000). Consistently, a power-law dependence of HIV transmission probability per coital act on HIV plasma viral load (VL) is identified among these SDCs (Hughes et al., 2012; Quinn et al., 2000) indicating that the risk does not increase linearly with exposure. The manifestation of these patterns, in different contexts and settings, may suggest an underlying biological phenomenon that explains these observations.

Against this background, the objective of the present article is to introduce a population statistical model for HIV risk that is consistent with data and offers an explanation for these patterns. The model was also applied to the Hillbrow FSWs data of Fig. 1. In addition to its epidemiological and theoretical importance, the model has practical applications in assessing the impact of interventions using mathematical modeling, as it provides a technical tool to be used in such mathematical modeling applications (Eaton et al., 2012; Johnson & White, 2011). The model can be incorporated into dynamical population models of HIV epidemics, and can serve as a benchmark for exploring the impact of heterogeneity in susceptibility to HIV infection, on both epidemiological analyses and intervention impact assessments.

2. Methods and results

Let us assume that HIV infection results from clonal expansion of a single virion and that human hosts can mount mechanical and immunological barriers to prevent virions from entering the body and establishing infection. Let p be the probability for an infectious virion to establish infection and let us assume homogeneity of p across individuals. The probability of remaining uninfected after exposure to N virions in one sex act ("dose") is then given by $(1 - p)^N \approx \exp(-pN)$ since p is small; a single virion is responsible for approximately 80% of heterosexual infections (Cohen, Shaw, McMichael, & Haynes, 2011). Infection risk after nt acts, where n is acts frequency and t is time, is then given by $1 - \exp(-pNnt)$ and depends on the cumulative exposure to virions (Nnt) with an exponential survival function (*Uniform Model*; Fig. 2A).

This model for establishment of infection is reasonable, but is at odds with data. Transmission risk among SDCs demonstrated power-law dependence on HIV VL (V_l): $1 - \exp(-cV_l^\alpha)$ with α in the range of 0.3—0.5 (Hughes et al., 2012;
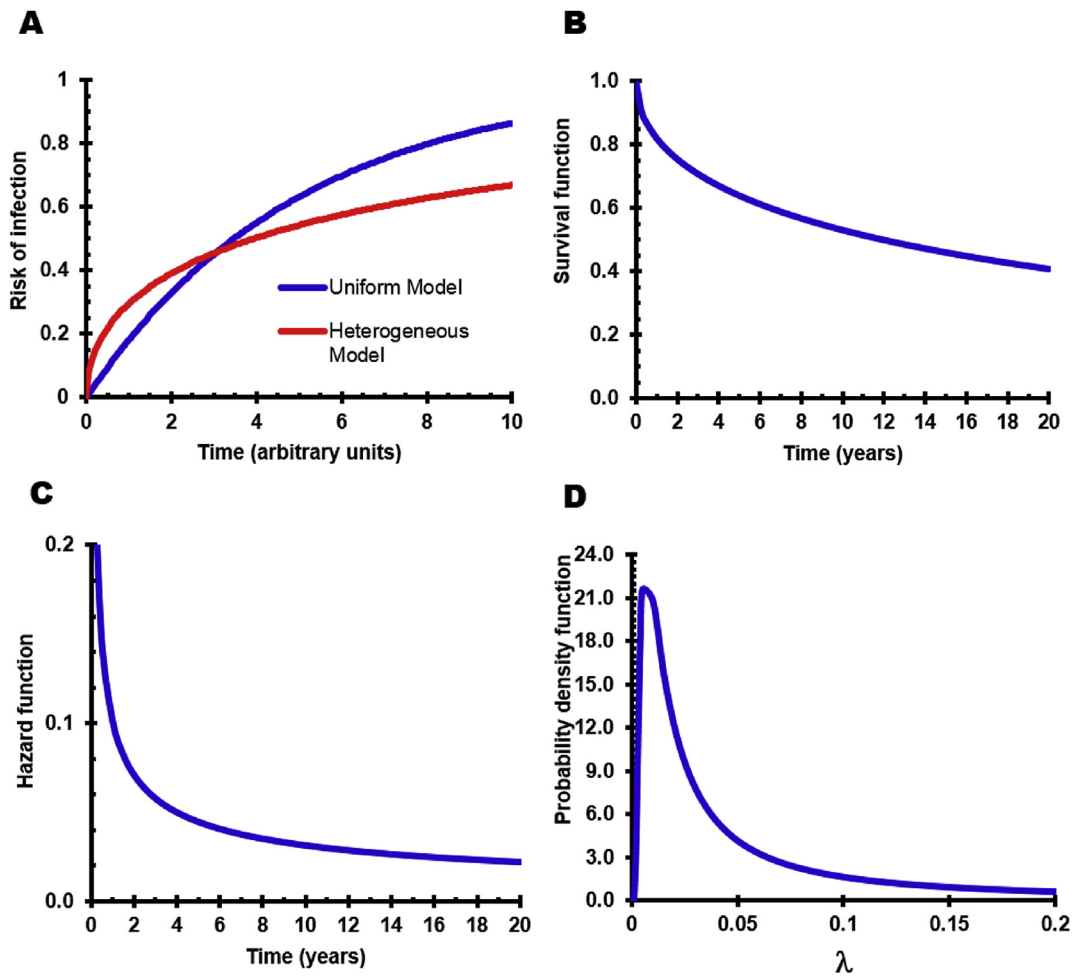
Fig. 2. Risk of HIV infection and related measures. (A) Risk of HIV infection versus time assuming an exponential survival function (Uniform Model) compared to Weibull survival function (Heterogeneous Model). Weibull survival function (B) and hazard function (C) with shape parameter of 0.5 and $\mu = 0.2$. (D) Probability density function of the Lévy mixing distribution with $\mu = 0.2$.

Quinn et al., 2000). Here transmission risk depends approximately on the square root of viral dose, rather than dose itself, with a Weibull survival function and a shape parameter of 0.5.

Similarly, HIV risk for FSWs versus exposure duration (such as in Fig. 1) is consistent with a Weibull survival function $\exp(-p(Nnt)^{\beta})$ with β again close to 0.5 (*Heterogeneous Model*; Fig. 2A). For the data on FSWs in Hillbrow, the estimate of β was 0.212 (95% confidence interval (CI): 0.047–0.377) assuming an HIV prevalence of 15% at the time of initiating sex work, and 0.278 (95% CI: 0.013–0.543) assuming a baseline prevalence of 40%.

Behavioral factors could not explain this pattern for the Hillbrow FSWs. There was no association between self-reported condom use and duration of sex work. There was also no association between self-reported condom use and HIV sero-status. A range of sexually transmitted infections (STIs) were also assessed among these FSWs including chlamydia, gonorrhea, and syphilis. Strikingly, the prevalence levels of these STIs were similar regardless of the duration of sex work, supporting the conclusion that the levels of condom use were also similar among these FSWs. These results suggest that no differential behavioral factors, whether condom use or others, could explain the observed HIV pattern versus the duration of sex work.

We propose an explanation for these patterns. Any Weibull distribution with shape parameter <1 can arise as a mixture of exponentials (Jewell, 1982). We propose that p varies among individuals. While time to infection for an individual is exponentially distributed ($S_I(t) = \exp(-\lambda t)$), the marginal (population averaged) distribution of time to infection is Weibull distributed. Informed by the above observed patterns, the shape parameter appears to be around 0.5 leading to the marginal survival function $S(t) = \exp(-\mu t^{0.5})$ (Fig. 1B) with the declining hazard function $h(t) = 0.5\mu t^{-0.5}$ (Fig. 1C). The Weibull survival is then seen as a mixture of exponential survivals, each with parameter λ, with the Lévy distribution (Jewell, 1982) being the mixing distribution with probability density function $f(\lambda) = \mu \exp\left(-\frac{\mu^2}{4\lambda}\right)(4\pi\lambda^3)^{-0.5}$ (Fig. 1D).
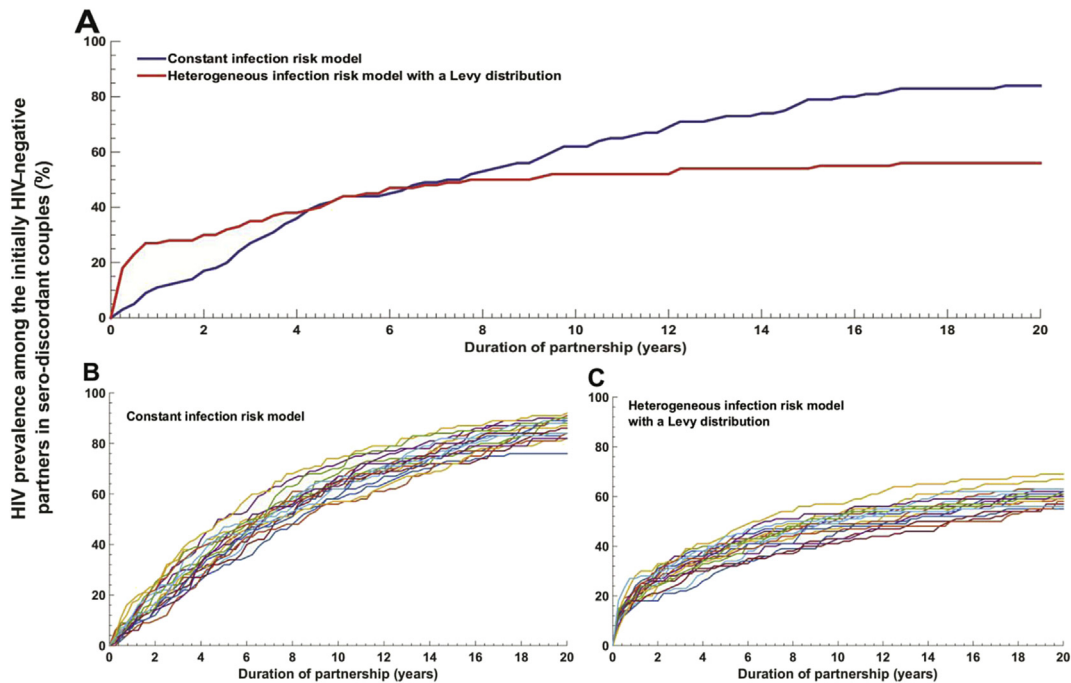
Fig. 3. Demonstration of the consequences of the heterogeneity in infection risk on HIV transmission. Individual-level model stochastic simulations of HIV transmission in a cohort of 100 sero-discordant couples (SDCs) living together for 20 years. (A) One model realization that demonstrates how the heterogeneous infection risk model, compared to the conventional constant infection risk model, leads to rapid sero-conversion for a fraction of the HIV-negative partners in the SDCs. Meanwhile, a large fraction of the HIV-negative partners remain uninfected despite repeated exposures for up to 20 years. (B) 20 realizations of the constant infection risk model. (C) 20 realizations of the heterogeneous infection risk model.

The observed patterns are thus consistent with considerable heterogeneity in individual infection risk, supporting suggestive evidence even dating from the early years of the HIV epidemic (Wiley, Herschkorn, & Padian, 1989). To highlight this variability, let us consider a cohort of SDCs living together for several years. Data suggest a transmission risk of about 0.1% per coital act (Hughes et al., 2012). If couples have been living together for one year with 100 acts per year, then, using $h(t)$, $\mu \approx 0.2$ and $S(1 \text{ year}) \approx 0.8$ (Fig. 2B), consistent with existing modeling estimations (Chemaitelly, Awad, & Abu-Raddad, 2014). Note that while the individual hazards λ are constant over time for each individual, the SDCs (marginal) cohort hazard rate declines over time. At year 1, the hazard rate is declining by 5% annually, but at year 5, the hazard rate is declining by only 0.4% annually (Fig. 2C). Of notice that for highly exposed individuals, such as FSWs, the Weibull parameter μ will be much larger, as the selection of least susceptible individuals may take place much more rapidly.

The Lévy mixing distribution is a highly skewed distribution (Fig. 1D). For $\mu = 0.2$, the median of λ is 0.044 but the third quartile is 0.197 and the 90th percentile is 1.270. That is, 25% of individuals have at least 18% probability of getting infected within a year, and for 10% of individuals, the probability of infection within a year is >70%.

To demonstrate the consequences of this variability in infection risk on HIV transmission and epidemic dynamics, we conducted individual-level stochastic simulations of HIV transmission in a cohort of 100 SDCs living together for 20 years (Fig. 3). Fig. 3A shows one realization of this model and demonstrates how the heterogeneous infection risk model, compared to the conventional constant infection risk model, led to rapid sero-conversion for a fraction of the HIV-negative partners in the SDCs. Meanwhile, a large fraction of these HIV-negative partners remained uninfected despite repeated exposures for up to 20 years. Fig. 3B and C show the same patterns, but this time for 20 realizations of each of the heterogeneous and constant infection risk models, respectively.

These simulations highlight how HIV epidemics, assuming the heterogeneous infection risk model, are destined to emerge rapidly because of the rapid sero-conversion upon exposure, but also simultaneously, destined to saturate and decline rapidly after emergence. This pattern is remarkably one of the hallmarks of the HIV epidemics in sub-Saharan Africa that emerged rapidly in the late 1980s and early 1990s, but have saturated and rapidly declined since mid-1990s (Awad & Abu-Raddad, 2014).

3. Discussion

We proposed a statistical model for infection risk that arises naturally out of the necessity to explain patterns of infection risk. Our results suggest considerable individual variability in acquiring HIV upon exposure. For a minority of individuals,

infection risk is high with the majority acquiring HIV within a year of exposure. For the bulk of individuals, however, infection risk is low and exposure time is a strong (negative) predictor of future infection risk. The dramatic rise and decline of many of the epidemics in sub-Saharan Africa (Awad & Abu-Raddad, 2014) could be a manifestation of this variability. As HIV sweeps through a population, those most susceptible are depleted with rapid infection and the population is "enriched" with "resistant" individuals (N. Nagelkerke et al., 2009).

Existing evidence suggests biological cofactors in HIV transmission such as male circumcision (Weiss et al., 2008), coinfection with other STIs (Korenromp, de Vlas, Nagelkerke, & Habbema, 2001), co-infections increasing HIV VL (Abu-Raddad et al., 2012; Abu-Raddad, Patnaik, & Kublin, 2006), host genetics and immunology (Kaul et al., 2011; Naruse et al., 2016), virus sub-types (Novitsky et al., 2011), hormonal contraception (Heffron et al., 2012), in addition to obvious behavioral factors such as temporal variation in sexual behavior (Awad & Abu-Raddad, 2014), uptake of condom use (Hughes et al., 2012), and differences in coital frequency (Brown, 2000). The infection risk variability may be explained by a combination of these, and possibly other factors. Nevertheless, the context of this variability being observed among cohorts of FSWs and SDCs, who are drawn from specific settings, and given the power-law dependence of HIV transmission probability on HIV VL and the rapid rise and decline of many of Africa's epidemics, suggest a specific explanation. Probably the most simple, coherent, and consistent explanation is a variation in the biological susceptibility to HIV infection due to host genetics and immunology.

Our findings suggest that mathematical models that use uniform risk assumption may not provide reliable estimates and predictions, particularly if the exposure risk is high in comparison to the population turnover. Yet, these models are widely used (Eaton et al., 2012; Johnson & White, 2011). For example, in a review of 12 mathematical models used to predict the impact of treatment as prevention, 10 of the models made this assumption, and none explicitly considered heterogeneity in susceptibility (Eaton et al., 2012).

Moreover, the risk variability can have large influences on the predicted impact of interventions and assessments of cost-effectiveness. The statistical model introduced here offers a solution for a realistic parameterization of infection risk. Not capturing this variability in models may lead to erroneous conclusions and less than optimal high-stakes policy decisions. Yet, this variability can easily be incorporated in individual-based models, as they are flexible and can easily be modified to accommodate heterogeneity in susceptibility. Admittedly, for population-based compartmental models, incorporation of this variability is more challenging, as model complexity can grow rapidly with more population stratification.

Our study aimed to introduce a novel statistical model to explain observed HIV acquisition patterns. While the proposed model provided a coherent and consistent explanation, it is conceivable that other models may be able to explain these patterns based on alternative assumptions.

In conclusion, observed infection patterns suggest a signature for considerable variability in the biological susceptibility to HIV infection. Elucidating the biology behind this variability may provide breakthroughs in understanding establishment of infection and potential cure. Factoring this variability in mathematical models, through the methodology provided here, could be critical for valid estimations.

References

Abu-Raddad, L. J., Barnabas, R. V., Janes, H., Weiss, H. A., Kublin, J. G., Longini, I. M., Jr., et al. (2012). Have the explosive HIV epidemics in sub-Saharan Africa been driven by higher community viral load? *AIDS*. https://doi.org/10.1097/QAD.0b013e32835cb927.

Abu-Raddad, L. J., Patnaik, P., & Kublin, J. G. (2006). Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. *Science, 314*(5805), 1603–1606. https://doi.org/10.1126/science.1132338.

Awad, S. F., & Abu-Raddad, L. J. (2014). Could there have been substantial declines in sexual risk behavior across sub-Saharan Africa in the mid-1990s? *Epidemics, 8*, 9–17. https://doi.org/10.1016/j.epidem.2014.06.001.

Brown, M. S. (2000). Coitus, the proximate determinant of conception: Inter-country variance in sub-Saharan Africa. *Journal of Biosocial Science, 32*(2), 145–159.

Chemaitelly, H., Awad, S. F., & Abu-Raddad, L. J. (2014). The risk of HIV transmission within HIV-1 sero-discordant couples appears to vary across sub-Saharan Africa. *Epidemics, 6*, 1–9. https://doi.org/10.1016/j.epidem.2013.11.001.

Cohen, M. S., Shaw, G. M., McMichael, A. J., & Haynes, B. F. (2011). Acute HIV-1 infection. *The New England Journal of Medicine, 364*(20), 1943–1954. https://doi.org/10.1056/NEJMra1011874.

Eaton, J. W., Johnson, L. F., Salomon, J. A., Barnighausen, T., Bendavid, E., Bershteyn, A., et al. (2012). HIV treatment as prevention: Systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Medicine, 9*(7), e1001245. https://doi.org/10.1371/journal.pmed.1001245.

Fowke, K. R., Nagelkerke, N. J., Kimani, J., Simonsen, J. N., Anzala, A. O., Bwayo, J. J., et al. (1996). Resistance to HIV-1 infection among persistently sero-negative prostitutes in Nairobi, Kenya. *Lancet, 348*(9038), 1347–1351. https://doi.org/10.1016/S0140-6736(95)12269-2.

Heffron, R., Donnell, D., Rees, H., Celum, C., Mugo, N., Were, E., et al. (2012). Use of hormonal contraceptives and risk of HIV-1 transmission: A prospective cohort study. *The Lancet Infectious Diseases, 12*(1), 19–26. https://doi.org/10.1016/S1473-3099(11)70247-X.

Hughes, J. P., Baeten, J. M., Lingappa, J. R., Magaret, A. S., Wald, A., de Bruyn, G., et al. (2012). Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. *The Journal of Infectious Diseases, 205*(3), 358–365. https://doi.org/10.1093/infdis/jir747.

Jewell, N. P. (1982). Mixtures of exponential distributions. *The Annals of Statistics,* 479–484.

Johnson, L. F., & White, P. J. (2011). A review of mathematical models of HIV/AIDS interventions and their implications for policy. *Sexually Transmitted Infections, 87*(7), 629–634. https://doi.org/10.1136/sti.2010.045500.

Kaul, R., Cohen, C. R., Chege, D., Yi, T. J., Tharao, W., McKinnon, L. R., et al. (2011). Biological factors that may contribute to regional and racial disparities in HIV prevalence. *American Journal of Reproductive Immunology, 65*(3), 317–324. https://doi.org/10.1111/j.1600-0897.2010.00962.x.

Korenromp, E. L., de Vlas, S. J., Nagelkerke, N. J., & Habbema, J. D. (2001). Estimating the magnitude of STD cofactor effects on HIV transmission: How well can it be done? *Sexually Transmitted Diseases, 28*(11), 613–621.

McKinnon, L. R., Izulla, P., Nagelkerke, N., Munyao, J., Wanjiru, T., Shaw, S. Y., et al. (2015). Risk factors for HIV acquisition in a prospective Nairobi-based female sex worker cohort. *AIDS and Behavior, 19*(12), 2204–2213. https://doi.org/10.1007/s10461-015-1118-7.

Nagelkerke, N. J., Arora, P., Jha, P., Williams, B., McKinnon, L., & de Vlas, S. J. (2014). The rise and fall of HIV in high-prevalence countries: A challenge for mathematical modeling. *PLoS Computational Biology, 10*(3), e1003459. https://doi.org/10.1371/journal.pcbi.1003459.

Nagelkerke, N., de Vlas, S. J., Jha, P., Luo, M., Plummer, F. A., & Kaul, R. (2009). Heterogeneity in host HIV susceptibility as a potential contributor to recent HIV prevalence declines in Africa. *AIDS, 23*(1), 125–130. https://doi.org/10.1097/QAD.0b013e3283177f20.

Naruse, T. K., Sakurai, D., Ohtani, H., Sharma, G., Sharma, S. K., Vajpayee, M., et al. (2016). APOBEC3H polymorphisms and susceptibility to HIV-1 infection in an Indian population. *Journal of Human Genetics, 61*(3), 263–265. https://doi.org/10.1038/jhg.2015.136.

Novitsky, V., Ndung'u, T., Wang, R., Bussmann, H., Chonco, F., Makhema, J., et al. (2011). Extended high viremics: A substantial fraction of individuals maintain high plasma viral RNA levels after acute HIV-1 subtype C infection. *AIDS, 25*(12), 1515–1522. https://doi.org/10.1097/QAD.0b013e3283471eb2.

Quinn, T. C., Wawer, M. J., Sewankambo, N., Serwadda, D., Li, C., Wabwire-Mangen, F., et al. (2000). Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai project study group. *The New England Journal of Medicine, 342*(13), 921–929. https://doi.org/10.1056/NEJM200003303421303.

Weiss, H. A., Halperin, D., Bailey, R. C., Hayes, R. J., Schmid, G., & Hankins, C. A. (2008). Male circumcision for HIV prevention: From evidence to action? *AIDS, 22*(5), 567–574.

Wiley, J. A., Herschkorn, S. J., & Padian, N. S. (1989). Heterogeneity in the probability of HIV transmission per sexual contact: The case of male-to-female transmission in penile-vaginal intercourse. *Statistics in Medicine, 8*(1), 93–102.