Associations of HIV and syphilis coinfections in KwaZulu-Natal, South Africa

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Abstract

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South Africa has one of the highest burdens of HIV and syphilis worldwide. Syphilis can interact with HIV and lead to accelerated transmission and clinical progression (i.e. neurosyphilis, opportunistic infections). From 2013 to 2017, we enrolled more than 8,000 adults the iThembalabantu Clinic in Umlazi Township, South Africa undergoing HIV testing, with a final analytical sample of those positive for HIV (n=2,580). Participants provided clinical, demographic, and behavioral data. We conducted Poisson regression to assess prevalence ratios (PR) and associations for syphilis coinfection among people living with HIV (PLHIV). 123 (4.7%) were concurrently positive for T. pallidum. Younger age (PR 0.76 per 10-year increase, $p<0.01$), male circumcision (PR 0.38, $p<0.05$), having an HIV-positive partner (PR 1.93, $p<0.05$), and tobacco use (PR 1.52, $p<0.05$) were associated with syphilis coinfection among PLHIV. These covariates remained significant in multivariable analyses adjusted for sex and/or age. When all these variables were included in a combined model, only having an HIV-positive partner remained statistically significant. Having a partner living with HIV was a significant risk factor for syphilis coinfection, even after adjusting for other variables; sexual partnerships contribute to syphilis transmission dynamics. Addressing interconnected sexual networks through targeted interventions, such as expanding syphilis testing for PLHIV, may reduce associated morbidity and mortality, particularly in high-burden, resource-limited settings.

Introduction

In 2022, an estimated 1.3 million people globally acquired HIV, and 630,000 people died of AIDS-related illnesses (1). Concomitant sexually transmitted infections (STIs) –notably genital ulcerative diseases like syphilis– are significant factors increasing the likelihood of HIV transmission and higher viral load (2,3). Furthermore, immunodeficiency from HIV can also lead to a more aggressive progression of syphilis with permanent ophthalmic and neurological consequences when left untreated (4). Syphilis, caused by *Treponema pallidum*, presents a significant public health concern due to its alternating phases of active clinical symptoms and asymptomatic (latent) periods. Individuals and pregnant people with latent syphilis may unknowingly transmit *T. pallidum* to their sexual partners and fetuses, respectively (5). In 2020, a staggering 7.1 million adults globally acquired syphilis, underscoring the pervasive nature of this infection on a global scale (6).

Building upon these complexities of HIV and syphilis coinfection, numerous social factors may influence and/or become exacerbated by an HIV/syphilis coinfection, including age, education, employment, medication adherence, mental health, discrimination, and social stigma (7–10). For example, the WHO guidelines on HIV, viral hepatitis, and STI focus on the risk factors and inequities for key populations like MSM, sex workers, people in prisons, people who inject drugs, trans and gender-diverse, and pregnant individuals (8). Given these social and systemic interplay, the potential implications of syphilis co-infections extend beyond the individual health of PLHIV and their communities.

The United States Centers for Disease Control and Prevention (CDC) recommends that most young adults, especially those below the age of 25, be screened for syphilis and HIV. For those with a known HIV infection, the CDC increases their surveillance recommendation to an

annual syphilis screening regardless of symptoms (11). To further emphasize their caution, the CDC recommends HIV and STI testing every 3-6 months for men who have sex with men (MSM) with additional risk factors (11,12). Thus, public health experts at the CDC prioritize regular screening for STIs and HIV, and their proactive approach underscores the significance of early intervention and effective disease management.

Despite the known interplay between HIV and syphilis, the guidelines from South Africa's National Department Of Health (DoH) guidelines recommend STI testing primarily for symptomatic individuals or screening for pregnant individuals (13). Since a syphilis infection is oftentimes asymptomatic and can lay dormant for periods of time, lack of screening contributes to undiagnosed STIs, community transmission, congenital complications, and may even dampen HIV prevention efforts (14). The Southern African HIV Clinicians Society advocates for making STI, notably syphilis, screening more accessible for key populations to better address risk factors like age, sexual behavior, and coinfections like HIV, which may indicate a higher risk of syphilis infection and thus need more targeted screening (15).

This study was situated at the iThembalabantu "People's Hope" Clinic in the Umlazi township, one of the first free HIV facilities in South Africa (16). Located in the city of Durban within the KwaZulu-Natal province, Umlazi reflects the historical impact of the Apartheid era, marked by government-enforced removals and resettlements. In the 1960s, numerous Black communities were displaced and consolidated into designated townships like Umlazi. The apartheid policies established housing projects –characterized by overcrowded living conditions and inadequate infrastructure– that were primarily occupied by Black South African laborers who worked at nearby White-owned industries(17). In the face of racial segregation and political suppression, the Umlazi residents actively participated in anti-apartheid activism, leading

protests and advocating for educational desegregation and inclusion in municipal administration (18). This resilience shapes the backdrop for understanding the current healthcare landscape in KwaZulu-Natal.

In 2017, the prevalence of syphilis in South African adults was 0.5%, reflecting a steady decline over the past two decades. This reduction can be attributed to public health measures targeting congenital syphilis and improvements in maternal healthcare (19). However, South Africa continues to grapple with a substantial STI burden, characterized by the absence of any decline in gonorrhea and chlamydia and the persistent prevalence of syphilis (7).

Before the recent national movement towards National Health Insurance, South Africa's healthcare system operated on a two-tiered structure with a significantly underfunded public sector and a better-resourced private sector(20). In addition, approximately 71% of the population relies on the government-funded public sector, while the remaining 27% can access private care through medical schemes or private health insurance (21). The division results in persistent inequality, burdening the public sector with limited resources as it serves a larger portion of the population. In terms of healthcare access in the past few years, only 9.9% of Black South African households had private medical schemes, while Coloured, Indian, and White South Africans had 17%, 52%, and 73% private coverage respectively (22). This contrast emphasizes the pressing need to address systemic healthcare and racial inequities in South Africa, given the inequitable distribution of resources.

This research contributes to the growing body of knowledge on syphilis co-infections among PLHIV. The potential for transmission during asymptomatic periods underscores the need for increased awareness and preventive measures to curb the spread of syphilis. By proactively

identifying PLHIV individuals with higher susceptibility, healthcare systems can enhance their capacity to disrupt transmission cycles.

While syphilis has been extensively studied globally and in key populations in South Africa, such as MSM, sex workers, people in prisons, people who inject drugs, trans and gender-diverse, and pregnant individuals,(3,9,23) this study expands to additional risk factors beyond these key populations. PLHIV face unique challenges in obtaining healthcare services so identifying coincident risk factors for STI co-infection may inform strategies tailored to prevent the higher morbidity and mortality associated with syphilis and HIV co-infections. Furthermore, this study focuses on a region with limited STI screening services that could greatly benefit from additional resources and guidance for prioritization. South Africa shoulders the largest burden of the HIV pandemic, with an estimated proportion of PLHIV ranging from 11.8% to 29.9% of the global total (1). This underscores the significance of evidence-based research to advocate for expanded syphilis screening and for South Africa's DoH to develop tailored public health strategies for effective prevention, early intervention, and improved healthcare accessibility.

Methods

Setting, Participants, and Study Design

This study presents a retrospective analysis of data collected as part of a larger cohort study conducted at the iThembalabantu People's Hope Clinic in Umlazi Township, Durban, South Africa, between September 2013 and April 2017. The parent study enrolled 2,580 adult participants living with HIV (PLHIV) and followed them for 12 months to measure clinical HIV and STI/associated outcomes, specifically looking for the incidence of cryptococcal infections.

The selection of this study site was based on the strategic choice of the iThembalabantu People's Hope clinic. Founded by AIDS Healthcare Foundation, this clinic was chosen due to its notable provision of free HIV testing services and treatment to an estimated 10,000 individuals each month. Exclusion criteria for this study included individuals who were pregnant at the time of testing and those under 18 years old. Furthermore, in accordance with the parent study's requirements, participants with a recent history of antifungal drug use within the three months leading up to their clinic visit were excluded. Demographic, clinical data, and biological specimens were collected from each participant upon enrollment. Syphilis infection was identified using rapid plasma reagin (RPR) screening, and patients found positive received immediate treatment with the standard of care– oral penicillin.

Statistical Analyses

This cross-sectional study is a secondary analysis of the cryptococcal prospective cohort previously outlined, using data collected at enrollment. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. Categorical variables were presented as counts and percentages, while continuous variables were presented as means and standard deviations. Prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated using robust Poisson regression models (or semiparametric log-linear models) (24). This method was chosen because it provides a more accurate estimation of PRs in cross-sectional studies with binary outcomes (25).

Univariable analyses were conducted to examine the association between risk factors hypothesized *a priori* and HIV/syphilis coinfection. Variables with a p-value < 0.05 in the univariable analyses were then selected for inclusion in two sets of multivariable analyses. First,

individual models for each variable were adjusted for sex and age, unless the nature of the variable required different adjustments (e.g., circumcision status was adjusted only for sex because it reflects present status, not the age at circumcision; age was adjusted only for sex). Second, a combined multivariable model was constructed including all the significant variables and sex. Adjusted prevalence ratios and 95% confidence intervals were reported, with statistical significance set at $p < 0.05$.

Ethical Considerations

This study received ethical approval from the University of Kwazulu-Natal (REF: BF052/13), Partners (Mass General Brigham), and the University of Washington (STUDY00000124) ethics committees, ensuring compliance with established standards. Study data were de-identified before analyses in order to preserve the confidentiality and privacy of study participants. Prior to their involvement in the research, all participants provided written and informed consent, affirming their voluntary participation and comprehension of the study's objectives and procedures.

Furthermore, it is crucial to emphasize the ethical significance of providing appropriate medical care to individuals who tested positive for syphilis during the course of this research. All participants who were found to be positive for syphilis were promptly and ethically treated with the standard of care for this disease, which includes the administration of penicillin. This ethical provision of treatment not only aligns with the principles of beneficence and non-maleficence but also demonstrates the researchers' commitment to the well-being and welfare of the study participants.

Results

Of the 2,580 adults living with HIV, 123 individuals (4.7%) subsequently tested positive for *treponema pallidum* at the time of enrollment.

Of 2580 total participants, the mean age of the participants was 33.3 years (SD = 9.2), with an age distribution of 41.7% between 18-29 years, 37.6% between 30-39 years, 14.3% between 40-49 years, and 6.4% 50 years or older (Table 1). Most participants were female (58.2%). Marital status was predominantly never married (92.6%), with a small percentage being married (6.2%) or widowed/divorced (1.2%).

Regarding education, 13.0% of participants had no formal education, 36.9% had primary education, and 50.2% had secondary or higher education. Most participants (85.8%) were employed for 20 hours or less per week. Monthly income distribution showed that 70.2% earned less than 2000 ZAR (11.56 USD).

BMI classifications showed that 5.3% of participants were underweight, 44.8% had a normal BMI, 26.9% were overweight, and 22.9% were obese. Approximately a third of participants had a CD4 count ≤200 cells/mm^3. Among male participants, 68.4% were not circumcised, and 19.7% were circumcised, with 11.8% missing circumcision data. Regarding partner's HIV status, 16.1% of participants had partners negative for HIV, 26.4% had partners positive for HIV, and 56.9% did not know their partner's HIV status.

Alcohol use within the last month was reported by 34.1% of participants, while 22.0% reported cigarette use within the last month. The use of barrier contraception (i.e. condoms) was reported by 4.1% of participants, with the majority (89.9%) reporting use of non-barrier methods or no use of contraceptives.

Participants diagnosed with syphilis (n=123; 4.8%) had a similar age and sex distribution to participants without a syphilis diagnosis, but a smaller proportion of males with syphilis were circumcised and a larger proportion had a partner living with HIV.

In the univariable analyses, lower prevalence of syphilis coinfection was associated with higher age (Table 2): for every 10-year increase in age, the prevalence of syphilis coinfection was 24% lower (prevalence ratio = 0.76, 95% CI: 0.62, 0.92; p = 0.006). Circumcision was also associated with lower prevalence of syphilis, among males (prevalence ratio = 0.38, 95% CI: 0.15, 0.96; p = 0.041). Having an HIV-positive partner and recent cigarette use were both associated with a higher prevalence of syphilis coinfection. Prevalence of syphilis coinfection did not significantly differ by gender, education, income, CD4 count, use of barrier contraception, or recent alcohol or cigarette use (confidence intervals of resulting prevalence ratios include 1.0).

In the multivariable analyses, for every 10-year increase in age, the prevalence of syphilis coinfection was 25% lower, after adjusting for sex (adjusted prevalence ratio = 0.75, 95% CI: 0.61, 0.91; p = 0.004) (Table 3). Circumcision among males was associated with a lower prevalence of syphilis coinfection after adjusting for age (adjusted prevalence ratio = 0.38, 95% CI: 0.15, 0.94; p = 0.03). After adjusting for age and sex, cigarette use within the last month was significantly associated with a higher prevalence of syphilis coinfection after adjusting for age and sex (adjusted prevalence ratio = 1.67, 95% CI: 1.07, 2.59; p = 0.023). Having an HIV-positive partner was also associated with a higher prevalence of syphilis coinfection after adjusting for age and sex(adjusted prevalence ratio = 2.03, 95% CI: 1.09, 3.79; p = 0.026).

Using a combined multivariable model (Table 3) with variables selected based on significance in univariable analyses (age, cigarette use within the last month, circumcision status,

partner's HIV status, and sex), only having an HIV-positive partner remained significantly associated with a higher prevalence of syphilis coinfection ($p = 0.022$).

Discussion

Having an HIV-positive partner is an important risk factor for syphilis coinfection. Younger age, circumcision among males, and frequent cigarette use were also associated with a higher prevalence of syphilis co-infection, though these factors were not significant when included in a combined model. This may indicate collinearity among these variables, given they were significant when included in models adjusted only for age and sex.

The prevalence of syphilis co-infection measured among PLHIV in this study (4.7%) is consistent with other estimates among PLHIV in KwaZulu-Natal, South Africa.(26,27) This is notably higher than the 0.5% estimated prevalence of syphilis in the country overall.(19) The higher risk of PLHIV associated with syphilis coinfection is also seen in the greater Southern African subcontinent region with a 3.1% prevalence, as well as PLHIV all around the world.(28–32) The differences in syphilis prevalence rates between the general population and those living with HIV can be attributed to well-documented factors such that both syphilis and HIV can increase the susceptibility to the other's acquisition due to immunological interactions from a clinical standpoint.(2,33,34) The broader context of STIs in South Africa – where the HIV epidemic affects nearly 8 million individuals— reveals multi-faceted disparities: there is a disproportionate burden of HIV among Black South Africans compared to other racial groups as well as among those with lower socioeconomic status (19,35). Areas with more municipality-level segregation and poverty, like KwaZulu-Natal, have higher HIV prevalence and acquisition

(20,22). Yet this province has relatively lower healthcare access when compared to other areas: less than one healthcare facility per 1000 PLHIV(22).

In terms of risk factors, circumcision has been demonstrated in many different settings to lower the rates of certain sexually transmitted infections, including syphilis.(36–40) Both the CDC and WHO support voluntary male medical circumcision (VMMC) in LMIC regions like Eastern and Southern Africa as a preventative measure against HIV and STIs.(41,42) Others have observed a trend of higher circumcision effectiveness in cohorts with higher HIV incidence, highlighting HIV risk as an important contextual factor for public health interventions.(43) While the result of this study suggests the relationship between circumcision and syphilis/HIV coinfection may be confounded by other factors, other literature suggests it may have a role when integrated into other public health strategies, such as the use of barrier protection and partner HIV testing.(44) Additionally, VMMC programs raise concerns about informed consent and cultural representation, which should be considered to ensure these interventions are ethically and culturally appropriate.(45–48)

Findings from other studies have not identified tobacco smoking as an independent risk factor for HIV/syphilis co-acquisition. The relationship between tobacco use and HIV/syphilis positivity is complex and not immediately clear. One study noted that while a history of tobacco use was independently associated with syphilis positivity, the relationship may be influenced by other lifestyle characteristics that were not controlled for in their analysis. Regardless of its direct association with syphilis co-infection, tobacco use presents significant health risks for PLHIV. Smoking can reduce the life expectancy of PLHIV and significantly increase the risk of death from cardiovascular events and lung cancer. This is particularly pertinent in the South African context, where about 20% of the adult population smoked cigarettes as of a 2017 national survey.

The marketing and increasing use of next-generation tobacco products and e-cigarettes, also affecting South Africa, introduces new public health concerns. Given the high prevalence of smoking and the associated health risks, public health interventions for people living with HIV in South Africa should prioritize smoking cessation and address the broader implications of tobacco use.

With regards to age, there is overwhelming evidence that has identified younger age as a critical risk factor for acquiring both HIV and syphilis, as well as other STIs.(49–51) The importance of addressing the health needs of young people is underscored by South Africa's National Youth Health Policy, which aims to provide integrated sexual and reproductive health and rights services alongside HIV/AIDS prevention and care.(52)

Factors like lack of barrier contraception, less formal education, and alcohol consumption have been identified as risk factors for HIV/syphilis co-infection in various studies.(53–59)However, our study did not find these associations to be significant, which may be attributed to the small sample size of syphilis-positive individuals, limiting statistical power. Additionally, breaking down the cohort into subcategories for certain variables, such as education or contraceptive use, may have resulted in even smaller group sizes, reducing the ability to detect meaningful associations. Lastly, the lack of findings about alcohol consumption could have arisen from how it was categorized in the questionnaire; "drinking within the past month" without defining alcohol consumption as more frequent or heavier, could better reflect binge or overconsumption over a longer period.

As outlined in the results, partner HIV status remained significant after adjusting for age, circumcision, and cigarette use, which emphasizes its unique role in HIV/syphilis coinfection

risk and that there may be overlapping effects or shared pathways influencing syphilis coinfection risk. These findings align with the broader literature, highlighting the importance of partner dynamics in STI transmission.(60,61) Although this study did not specifically assess partner syphilis status, their HIV status likely reflects broader patterns of infection within interconnected sexual networks, serving as a proxy for associated diseases in partners and their networks. (62,63)

This study has several limitations. Partner data was limited to individuals with known HIV status, excluding those whose partner status was unknown. Additionally, the results have limited generalizability beyond the cohort studied; for example, the risk factors for individuals with progressed syphilis –with secondary or tertiary symptoms– remain unknown. Future research should focus on larger cohorts to enhance statistical power and improve generalizability. Longitudinal studies monitoring participants over time could provide valuable insights into symptom progression, as this study was limited to individuals initially asymptomatic for syphilis. Collecting more comprehensive data, such as partner syphilis status and detailed behavioral metrics like pack-year history for tobacco use, would allow for a more nuanced understanding of risk factors and their interplay. Lastly, the potential collinearity of the key associations may have overlapping effects influencing syphilis coinfection risk. This would need further analysis to help disentangle these relationships.

Conclusion

Having a partner with HIV, younger age, and tobacco use were significant risk factors for syphilis coinfection among PLHIV. All of those who screened positive for syphilis were asymptomatic, as in they had no signs of genital lesions or secondary symptoms of syphilis. This

suggests a need for public health interventions that could both address asymptomatic spread and also target risk factors. These findings underscore the importance of improving syphilis screening practices among PLHIV, particularly in areas that deserve more equitable healthcare access like KwaZulu-Natal.

References

1. United Nations Programme on HIV/AIDS. South Africa | UNAIDS [Internet]. 2022 [cited 2024 Jan 15]. Available from: https://www.unaids.org/en/regionscountries/countries/southafrica

2. Jarzebowski W, Caumes E, Dupin N, Farhi D, Lascaux AS, Piketty C, et al. Effect of Early Syphilis Infection on Plasma Viral Load and CD4 Cell Count in Human Immunodeficiency Virus–Infected Men: Results From the FHDH-ANRS CO4 Cohort. Arch Intern Med. 2012 Sep 10;172(16):1237–43.

3. Solomon MM, Mayer KH, Glidden DV, Liu AY, McMahan VM, Guanira JV, et al. Syphilis Predicts HIV Incidence Among Men and Transgender Women Who Have Sex With Men in a Preexposure Prophylaxis Trial. Clin Infect Dis. 2014;59(7):1020–6.

4. Karp G, Schlaeffer F, Jotkowitz A, Riesenberg K. Syphilis and HIV co-infection. Eur J Intern Med. 2009 Jan 1;20(1):9–13.

5. Centers for Disease Control and Prevention. Syphilis (Treponema pallidum) 2018 Case Definition | Centers for Disease Control and Prevention [Internet]. 2022 [cited 2024 Jan 16]. Available from: https://ndc.services.cdc.gov/case-definitions/syphilis-2018/

6. World Health Organization. Fact sheet on Syphilis [Internet]. [cited 2024 Jan 17]. Available from: https://www.who.int/news-room/fact-sheets/detail/syphilis

7. Semwogerere M, Dear N, Tunnage J, Reed D, Kibuuka H, Kiweewa F, et al. Factors associated with sexually transmitted infections among care-seeking adults in the African Cohort Study. BMC Public Health. 2021 Apr 16;21(1):738.

8. WHO Global HIV, Hepatitis and STIs Programmes. Policy brief: Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations [Internet]. [cited 2024 Jan 24]. Available from: https://www.who.int/publications-detail-redirect/9789240053274

9. Hoque M, Hoque ME, Hal G van, Buckus S. Prevalence, incidence and seroconversion of HIV and Syphilis infections among pregnant women of South Africa. South Afr J Infect Dis. 2021 Nov 24;36(1):8.

10. WHO Global HIV, Hepatitis and STIs Programmes, Guidelines Review Committee, Sexual and Reproductive Health and Research. WHO guideline on syphilis screening and treatment for pregnant women [Internet]. [cited 2024 Jan 25]. Available from: https://www.who.int/publications-detail-redirect/9789241550093

11. Centers for Disease Control and Prevention. STI Screening Recommendations [Internet]. 2022 [cited 2024 Jan 15]. Available from: https://www.cdc.gov/std/treatment-guidelines/screening-recommendations.htm

12. DiNenno EA, Prejean J, Irwin K, Delaney KP, Bowles K, Martin T, et al. Recommendations for HIV Screening of Gay, Bisexual, and Other Men Who Have Sex with Men — United

States, 2017. Morb Mortal Wkly Rep. 2017 Aug 8;66(31):830.

13. South Africa National Department Of Health. Sexually Transmitted Infections Management Guidelines 2018 [Internet]. [cited 2024 Jan 15]. Available from: https://www.health.gov.za/wp-content/uploads/2020/11/sti-guidelines-27-08-19.pdf

14. Kaida A, Dietrich JJ, Laher F, Beksinska M, Jaggernath M, Bardsley M, et al. A high burden of asymptomatic genital tract infections undermines the syndromic management approach among adolescents and young adults in South Africa: implications for HIV prevention efforts. BMC Infect Dis. 2018 Oct 3;18(1):499.

15. Peters RPH, Garrett N, Chandiwana N, Kularatne R, Brink AJ, Cohen K, et al. Southern African HIV Clinicians Society 2022 guideline for the management of sexually transmitted infections: Moving towards best practice. South Afr J HIV Med. 2022 Sep 27;23(1):1450.

16. Medicus Mundi Switzerland. The People's Hope — aidsfocus.ch [Internet]. [cited 2024 Jan 18]. Available from: https://www.aidsfocus.ch/en/news/the-peoples-hope/index.html

17. Maharaj B. The Historical Development of the Apartheid Local State in South Africa: The Case of Durban*. Int J Urban Reg Res. 1996 Dec;20(4):587–600.

18. Gwala Z. Rebellion in the last outpost: the Natal riots. Indic South Afr. 1985 Jan;3(2):6–11.

19. Kularatne RS, Niit R, Rowley J, Kufa-Chakezha T, Peters RPH, Taylor MM, et al. Adult gonorrhea, chlamydia and syphilis prevalence, incidence, treatment and syndromic case reporting in South Africa: Estimates using the Spectrum-STI model, 1990-2017. PLoS ONE. 2018 Oct 15;13(10):e0205863.

20. de Villiers K. Bridging the health inequality gap: an examination of South Africa's social innovation in health landscape. Infect Dis Poverty. 2021 Mar 1;10(1):19.

21. Statistics South Africa. General Household Survey [Internet]. Statistics SA; 2018 [cited 2024 Jan 23]. Available from: https://www.statssa.gov.za/publications/P0318/P03182018.pdf#page=37

22. Mhlanga D, Garidzirai R. The Influence of Racial Differences in the Demand for Healthcare in South Africa: A Case of Public Healthcare. Int J Environ Res Public Health. 2020 Jul;17(14):5043.

23. Ribeiro A, Trevizol A, Oluwoye O, McPherson S, McDonell MG, Briese V, et al. HIV and syphilis infections and associated factors among patients in treatment at a Specialist Alcohol, Tobacco, and Drugs Center in São Paulo's "Cracolândia." Trends Psychiatry Psychother. 2020;42(1):1–6.

24. Talbot D, Mésidor M, Chiu Y, Simard M, Sirois C. An Alternative Perspective on the Robust Poisson Method for Estimating Risk or Prevalence Ratios. Epidemiology. 2023 Jan;34(1):1.

25. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol. 2003 Oct 20;3(1):21.

26. Kharsany ABM, McKinnon LR, Lewis L, Cawood C, Khanyile D, Maseko DV, et al. Population prevalence of sexually transmitted infections in a high HIV burden district in KwaZulu-Natal, South Africa: Implications for HIV epidemic control. Int J Infect Dis. 2020 Sep;98:130–7.

27. Kufa T, Woldesenbet S, Cheyip M, Ayalew K, Kularatne R, Manda S, et al. Syphilis screening coverage and positivity by HIV treatment status among South African pregnant women enrolled in the 2019 antenatal HIV sentinel survey. Sci Rep. 2023 Apr 1;13(1):5322.

28. Mussa A, Jarolimova J, Ryan R, Wynn A, Ashour D, Bassett IV, et al. Syphilis Prevalence Among People Living With and Without HIV in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. Sex Transm Dis. 2024 Mar;51(3):e1.

29. Torrone EA, Morrison CS, Chen PL, Kwok C, Francis SC, Hayes RJ, et al. Prevalence of sexually transmitted infections and bacterial vaginosis among women in sub-Saharan Africa: An individual participant data meta-analysis of 18 HIV prevention studies. PLOS Med. 2018 Feb 27;15(2):e1002511.

30. Tsuboi M, Evans J, Davies EP, Rowley J, Korenromp EL, Clayton T, et al. Prevalence of syphilis among men who have sex with men: a global systematic review and meta-analysis from 2000-20. Lancet Glob Health. 2021 Aug;9(8):e1110–8.

31. Varshney K, Ikanovic A, Ghosh P, Shet P, Di Sipio M, Khatri C, et al. A Global Scoping Review of the Factors Associated with HIV and Syphilis Co-Infection: Findings from 40 Countries. Venereology. 2022 Jun;1(1):98–113.

32. Wu Y, Zhu W, Sun C, Yue X, Zheng M, Fu G, et al. Prevalence of syphilis among people living with HIV and its implication for enhanced coinfection monitoring and management in China: A meta-analysis. Front Public Health. 2022 Oct 17;10:1002342.

33. LaFond RE, Lukehart SA. Biological Basis for Syphilis. Clin Microbiol Rev. 2006 Jan;19(1):29–49.

34. Wu MY, Gong HZ, Hu KR, Zheng H yi, Wan X, Li J. Effect of syphilis infection on HIV acquisition: a systematic review and meta-analysis. Sex Transm Infect. 2021 Nov 1;97(7):525–33.

35. Mabaso M, Makola L, Naidoo I, Mlangeni LL, Jooste S, Simbayi L. HIV prevalence in South Africa through gender and racial lenses: results from the 2012 population-based national household survey. Int J Equity Health. 2019 Oct 30;18(1):167.

36. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. PLoS Med. 2005 Nov;2(11):e298.

37. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. The Lancet. 2007 Feb 24;369(9562):643–56.

38. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. The Lancet. 2007 Feb 24;369(9562):657–66.

39. Weiss HA, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. Sex Transm Infect. 2006 Apr;82(2):101–9; discussion 110.

40. Peck ME, Bronson M, Djomand G, Basile I, Collins K, Kankindi I, et al. HIV, syphilis, and hepatitis B virus infection and male circumcision in five Sub-Saharan African countries: Findings from the Population-based HIV Impact Assessment surveys, 2015–2019. PLOS Glob Public Health. 2023 Sep 18;3(9):e0002326.

41. Peck ME. Voluntary Medical Male Circumcisions for HIV Prevention — 13 Countries in Eastern and Southern Africa, 2017–2021. MMWR Morb Mortal Wkly Rep [Internet]. 2023 [cited 2024 Jul 4];72. Available from: https://www.cdc.gov/mmwr/volumes/72/wr/mm7210a2.htm

42. World Health Organization [WHO],. Preventing HIV through safe voluntary medical male circumcision for adolescent boys and men in generalized HIV epidemics: recommendations and key considerations [Internet]. 2020 [cited 2024 Jul 4]. Available from: https://www.who.int/publications/i/item/978-92-4-000854-0

43. Farley TM, Samuelson J, Grabowski MK, Ameyan W, Gray RH, Baggaley R. Impact of male circumcision on risk of HIV infection in men in a changing epidemic context – systematic review and meta-analysis. J Int AIDS Soc. 2020 Jun 18;23(6):e25490.

44. World Health Organization, UNAIDS. Male circumcision: global trends and determinants of prevalence, safety and acceptability. 2008;(UNAIDS/07.29E/JC1320E):35.

45. Fish M, Shahvisi A, Gwaambuka T, Tangwa GB, Ncayiyana D, Earp BD. A new Tuskegee? Unethical human experimentation and Western neocolonialism in the mass circumcision of African men. Dev World Bioeth. 2021;21(4):211–26.

46. Luseno WK, Rennie S, Gilbertson A. A review of public health, social and ethical implications of voluntary medical male circumcision programs for HIV prevention in sub-Saharan Africa. Int J Impot Res. 2023 May;35(3):269–78.

47. Lawal TA, Olapade-Olaopa EO. Circumcision and its effects in Africa. Transl Androl Urol. 2017 Apr;6(2):149–57.

48. Gwandure C. The ethical concerns of using medical male circumcision in HIV prevention in sub-Saharan Africa. South Afr J Bioeth Law. 2011;4(2):89–94.

49. Martin K, Dauya E, Simms V, Bandason T, Azizi S, Machiha A, et al. Risk factors for curable sexually transmitted infections among youth: findings from the STICH population survey in Zimbabwe. Sex Transm Infect. 2024 Dec 1;100(8):484–91.

50. Mofolorunsho K, Mabaso N, Nundlall N, Nightingale A, Nyirenda M, Abbai N. African

Journal of Reproductive Health. [cited 2024 Nov 29]. Prevalence and associated risk factors of chlamydia and gonorrhoea infections among men who have sex with men in Durban, South Africa. Available from: https://journals.co.za/doi/10.29063/ajrh2024/v28i4.10

51. Mugay GB, Kimwise A, Lukwago I. DETERMINANTS OF CONSISTENT CONDOM USE AMONG STUDENTS IN KAMPALA: A CROSS-SECTIONAL CASE STUDY OF CAVENDISH UNIVERSITY UGANDA. Cavendish Int J Sci Technol. 2024 Aug 4;1(1):11–11.

52. Hodes R, Cluver L, Barron P, Dlamini NR, Madisha L, Mazibuko N, et al. National Adolescent and Youth Health Policy 2017 [Internet]. Department of Health South Africa; 2017 Jul [cited 2024 Jul 18]. Available from: https://www.health.gov.za/wp-content/uploads/2022/06/National-Adolescent-and-Youth-Health-Policy-2017.pdf

53. Ahmed S, Lutalo T, Wawer M, Serwadda D, Sewankambo NK, Nalugoda F, et al. HIV incidence and sexually transmitted disease prevalence associated with condom use: a population study in Rakai, Uganda. AIDS Lond Engl. 2001 Nov 9;15(16):2171–9.

54. Shilaih M, Marzel A, Braun DL, Scherrer AU, Kovari H, Young J, et al. Factors associated with syphilis incidence in the HIV-infected in the era of highly active antiretrovirals. Medicine (Baltimore). 2017 Jan;96(2):e5849.

55. Gilbert L, Dear N, Esber A, Iroezindu M, Bahemana E, Kibuuka H, et al. Prevalence and risk factors associated with HIV and syphilis co-infection in the African Cohort Study: a cross-sectional study. BMC Infect Dis. 2021 Oct 30;21(1):1123.

56. Shimelis T, Lemma K, Ambachew H, Tadesse E. Syphilis among people with HIV infection in southern Ethiopia: sero-prevalence and risk factors. BMC Infect Dis. 2015 Apr 17;15:189.

57. Mutagoma M, Nyirazinyoye L, Sebuhoro D, Riedel DJ, Ntaganira J. Syphilis and HIV prevalence and associated factors to their co-infection, hepatitis B and hepatitis C viruses prevalence among female sex workers in Rwanda. BMC Infect Dis. 2017 Jul 28;17(1):525.

58. Napierala S, Bair EF, Omollo OD, Egbe TI, Wesonga JO, Rajaratnam A, et al. High prevalence of STIs among men engaged in transactional sex and alcohol use in western Kenya: important implications for STI prevention interventions. Sex Transm Infect [Internet]. 2024 Nov 7 [cited 2024 Nov 29]; Available from: https://sti.bmj.com/content/early/2024/11/07/sextrans-2024-056266

59. Simões LA, Mendes JC, Silveira MR, da Costa AMG, Lula MD, Ceccato M das GB. Factors associated with HIV/syphilis co-infection initiating of antiretroviral therapy. Rev Saúde Pública. 2022 Jun 20;56:59.

60. Choi KH, Ning Z, Gregorich SE, Pan Q chao. The Influence of Social and Sexual Networks in the Spread of HIV and Syphilis Among Men Who Have Sex With Men in Shanghai, China. JAIDS J Acquir Immune Defic Syndr. 2007 May 1;45(1):77.

61. Allen S, Meinzen-Derr J, Kautzman M, Zulu I, Trask S, Fideli U, et al. Sexual behavior of HIV discordant couples after HIV counseling and testing. AIDS. 2003 Mar 28;17(5):733.

62. Grewal R, Allen VG, Gardner S, Moravan V, Tan DHS, Raboud J, et al. Serosorting and recreational drug use are risk factors for diagnosis of genital infection with chlamydia and gonorrhoea among HIV-positive men who have sex with men: results from a clinical cohort in Ontario, Canada. Sex Transm Infect. 2017 Feb;93(1):71–5.

63. Khosropour CM, Dombrowski JC, Kerani RP, Katz DA, Barbee LA, Golden MR. Changes in Condomless Sex and Serosorting Among Men Who Have Sex With Men After HIV Diagnosis. J Acquir Immune Defic Syndr 1999. 2016 Dec 1;73(4):475–81.

Tables

Table 1. Cohort characteristics among PLHIV with and without syphilis co-infection

Characteristic, N(%)	Participants N (%)		
	Syphilis negative (N=2457)	Syphilis (N=123)	Total (N = 2580)
Age, mean (SD)	33.4 (9.3)	31.2 (7.6)	33.3 (9.2)
Age groups			
18-29	1013 (41.2)	63 (51.2)	1076 (41.7)
30-39	926 (37.7)	44 (35.8)	970 (37.6)
40-49	357 (14.5)	13 (10.6)	370 (14.3)
50+	161 (6.6)	3 (2.4)	164 (6.4)
Gender			
Female	1370 (55.8)	69 (56.1)	1439 (58.2)
Male	1087 (44.2)	54 (43.9)	1033 (41.8)
Employment			
≤20 hours	2107 (85.7)	107 (87.0)	2214 (85.8)
>20 hours	350 (14.3)	16 (13.0)	366 (14.2)
Marital Status			
Never married	2273 (92.5)	117 (95.1)	2390 (92.6)
Married	154 (6.3)	6 (4.9)	160 (6.2)
Widowed/divorced	30 (1.2)	0 (0.0)	30 (1.2)
BMI			
Underweight (<18.5)	130 (5.3)	8 (6.5)	138 (5.3)
Normal (18.5-24.9)	1088 (44.8)	68 (55.28)	1156 (44.8)
Overweight (25-29.9)	667 (26.9)	27 (21.95)	694 (26.9)
Obese (30+)	571 (22.9)	20 (16.26)	591 (22.9)
Missing	1 (0.0)	0 (0.0)	1 (0.0)
CD4 count (cells/mm^3), mean (SD)	328 (228.8)	310.8 (195.6)	327.2 (227.4)
CD4 count (cells/mm^3)			
≤200	777 (31.6)	40 (32.5)	817 (31.7)
>200	1659 (687.5)	79 (64.2)	1738 (67.4)
Missing	21 (0.9)	4 (3.3)	25 (1.0)
If male, history of circumcision			
not circumcised	736 (67.7)	45 (83.3)	781 (68.4)
circumcised	220 (20.2)	5 (9.3)	225 (19.7)
Missing	131 (12.1)	4 (7.4)	135 (11.8)
Alcohol use within the last month			
None to used within the last year	1618 (65.9)	76 (61.8)	1694 (65.7)

Used within the last month	832 (33.9)	47 (38.2)	879 (34.1)
Missing	7 (0.3)	0 (0.0)	7 (0.3)
Cigarette use (Used within month)			
None to used within the last year	1923 (78.3)	86 (69.9)	2009 (77.8)
Used within the last month	530 (21.6)	37 (30.1)	567 (22.0)
Missing	4 (0.2)	0 (0.0)	4 (0.2)
Partner's HIV status			
negative for HIV	404 (16.4)	12 (9.8)	416 (16.1)
positive for HIV	643 (26.2)	38 (30.9)	681 (26.4)
Not tested or unknown status	1394 (56.7)	73 (59.3)	1467 (56.9)
Missing	16 (0.7)	0 (0.0)	16 (0.6)
Education completion			
None	318 (12.9)	17 (13.8)	335 (13.0)
Primary	901 (36.7)	50 (40.7)	951 (36.9)
Secondary or above	1238 (50.4)	56 (45.5)	1294 (50.2)
Monthly income			
<2000 ZAR (11.56 USD)	1725 (70.2)	87 (70.7)	1812 (70.2)
≥ 2000 ZAR (11.56 USD)	710 (28.9)	36 (29.3)	746 (28.9)
Missing	22 (0.9)	0 (0.0)	22 (0.9)
Current use of barrier contraception			
No birth control or non-barrier**	2212 (90.0)	107 87.0)	2319 (89.9)
Condoms or another barrier	101 (4.1)	6 (4.9)	113 (4.1)
Missing	144 (5.9)	10 (8.1)	154 (6.0)

*fever, cough, hemoptysis, night sweats, fatigue, weight loss

**Non-barrier: oral contraceptive pill, hormonal injections, or intrauterine device

Table 2. Associations between syphilis coinfection and characteristics, Univariable

Characteristic (Reference)	Prevalence Ratio	95% CI	p-value
Age (10 years)	0.76	(0.62, 0.92)	0.006
Gender (Female)			
Male	0.99	(0.69, 1.39)	0.941
Education completion (None)			
Primary	1.04	(0.61, 1.77)	0.897
Secondary or above	0.85	(0.50, 1.45)	0.556
Income (< 2000 ZAR (11.56 USD)/mo)			
≥ 2000 ZAR (11.56 USD)/mo	0.96	(0.68, 1.35)	0.836

Initial CD4 count (≤200 cells/mm3)			
>200	0.93	(0.64, 1.37)	0.695
History of circumsion (Not circumcised)			
Circumcised	0.38	(0.15, 0.96)	0.041
Use of barrier contraception (None)			
Condoms or another barrier	1.22	(0.54, 2.70)	0.633
Partner's HIV status (HIV negative)			
HIV positive	1.93	(1.02, 3.66)	0.042
Alcohol use within the last month (No)			
Yes	1.19	(0.83, 1.69)	0.332
Cigarette use within the last month (No)			
Yes	1.52	(1.05, 2.22)	0.027

Table 3. Associations between syphilis coinfection and characteristics, Multivariable

Characteristic	Individual Model			Combined Model		
	Adjusted Prevalence Ratio	95% CI	p-value	Adjusted Prevalence Ratio	95% CI	p-value
Age (10 years)*	0.75	(0.61, 0.91)	0.004	0.71	(0.44, 1.13)	0.146
Cigarette use **	1.67	(1.07, 2.59)	0.023	1.13	(0.51, 2.49)	0.759
Circumcision***	0.38	(0.15, 0.94)	0.037	0.43	(0.13, 1.40)	0.161
Partner's HIV status**	2.03	(1.09, 3.79)	0.026	3.98	(1.22, 12.92)	0.022

*adjusted for sex

**adjusted for age, sex

***adjusted for age

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