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The contribution of STIs to the sexual transmission of HIV

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Abstract

Purpose of review—We review recent evidence about the link between sexually transmitted infections (STI) and HIV transmission and consider implications for control programmes.

Recent findings—New studies and meta-analyses confirm the association of HIV acquisition and transmission with recent STI, although there is considerable heterogeneity between organisms and populations. Much of the recent evidence relates to HSV-2, where the population attributable risk (PAR) percent for HSV-2 is between 25% and 35% in Africa. Mathematical models show how transmission attributable to STI varies with HIV epidemic phase, and HSV-2 becomes increasingly important as the epidemic matures. HSV-2 suppressive therapy reduces HIV concentrations in plasma and the genital tract in people co-infected with HSV, in part due to direct inhibition of HIV reverse transcriptase. Recent trials of HSV-2 suppressive therapy have not shown an impact on the risk of HIV acquisition, nor in controlling transmission from dually infected people to their sero-discordant heterosexual partners.

Summary—Although there is a plausible link between STI and HIV risk, intervention studies continue to be disappointing. This does not disprove a causal link, but mechanisms of action and the design and implementation of interventions need to be better understood.

Keywords

HIV; STI; HSV-2; preventive interventions

Introduction

There is a strong association between bacterial and viral sexually transmitted infections and both the acquisition and transmission of HIV infection. This was first demonstrated in case series and retrospective studies that showed an association between previous sexually transmitted infections (STI) and human immunodeficiency virus (HIV). [1-2] Prospective studies strengthened this observation by showing a link between STI and incident HIV infection, with the strongest relative risks for genital ulcer disease but potentially large attributable risks from more common inflammatory conditions such as trichomoniasis. [3] Such evidence has continued to accumulate over the decades, but has remained difficult to interpret because of confounding due to shared risk factors, particularly sexual behaviour, and difficulties in determining temporal relationships. [4]

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In addition to the epidemiological evidence, biological findings support the mechanisms for STI increasing HIV acquisition and transmission through direct mucosal disruption, recruitment of HIV target cells to the genital tract, and by increased HIV load in plasma and genital secretions. Further synergies are described whereby HIV can alter the natural history of some STI. [5*]

These observations, together with the fact that HIV itself is a sexually transmitted infection, have underpinned calls for STI management to be an essential part of HIV control programmes. However, results of intervention studies have been disappointing. Several large, well conducted trials of enhanced STI treatment and care have failed to show a consistent impact on HIV incidence. The Mwanza study in Tanzania in the early 1990s showed a reduction in HIV incidence of 38% with enhanced syndromic management of STI, [6]but others have not. [7-9] Interpretation of these results rests on an understanding of different epidemic type and phase, Mwanza was conducted in a period of concentrated epidemic while the others were generalised, and whether the interventions were appropriate for the STI with the largest attributable risk fraction. [10*]

In this article we review evidence about the link between STI and HIV transmission and consider implications for control programmes. We start with a summary of recent epidemiological and modelling studies that cast light on the association of HIV with a number of STI, including those concerning mechanisms and biological plausibility. We then focus on evidence concerning the role of herpes simplex virus type 2 (HSV-2) in sexual transmission of HIV, which has been thought to be key to understanding some of the disparity between earlier observational and interventional studies.

The association between STI and HIV acquisition

New studies and meta-analyses confirm the association of HIV acquisition and transmission with recent STI, although there is considerable heterogeneity between organisms and populations as peviously described. [11]

Evidence of the association comes from ecological, cross sectional, case control and cohort studies. Most of these designs, with the exception of cohort studies, are unable to distinguish between causation, reverse causation and confounding due to a common causal pathway, [4] although some have tried to do this through using innovative designs.

The ecological association between HIV and STI has been reported in the USA, where higher rates of HIV occur in African American than white or Hispanic populations [12], which is thought to be in part due to the disproportionate burden of STI in this group. [13] In Belgium there are also overlapping epidemics in men who have sex with men (MSM) where there are high numbers of HIV diagnoses and of incident STI.[14] Such associations are subject to ecological fallacy, but similar findings are reproduced in individual-based cross sectional studies, including in African American drug using women in the USA and clients of female sex workers in Mexico. [15, 16] Braunstein and colleagues reviewed data around HIV incidence in sub-Saharan Africa; 18 of 22 studies looking at the impact of current or recent STI found an increased HIV risk, the remaining 4 found no association. The highest STI risk was found for HSV-2 seropositivity. [17]

A retrospective study of acute HIV infection in one part of the USA measured the association with having had an STI in the previous month. [18*]MSM were far less likely to have had an STI than heterosexual men or women, and most co-infections were in non-whites suggesting the importance of the overlapping HIV and STI epidemics in the black population in North Carolina.

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In an attempt to explore the temporal relationship between STI and HIV, Zetola and colleagues used different study designs to analyse the same population. They studied 36 cases of acute HIV infection in men who have sex with men (MSM), and used a variety of control groups, including one cross over design in which participants acted as their own controls, to better describe time-dependent risk factors and control for confounding. They found that having had an STI in the previous three months was more strongly associated with HIV acquisition that having had STI 12 months before. [19**]

While this innovative study design provides stronger evidence of the possible causal role of STI in incident HIV infection, prospective studies are required to show temporal relationships more definitively. Several important cohort studies have recently been reported and all are consistent in showing an increased risk of HIV in people with STI, but the size of the risk and the importance of the particular pathogens varies by population.

A cohort study of women in two African countries, Zimbabwe and Uganda, followed 4439 women every 3 months for up to two years. [20**]With the exception of syphilis, which was uncommon, all the reproductive tract infections were associated with HIV in at least one statistical model. After controlling for demographic and behavioural factors, the strongest risk was from gonorrhoea, which conferred a 7-fold increase in HIV incidence, but the highest population attributable risk percent (PAR%) was for sero-prevalent HSV-2 (50.4%), with incident HSV-2 contributing 7.9%, gonorrhoea 5.3%, and bacterial vaginosis 17.2%. Calculating PAR% assumes that these associations are causal, and there was some concern that temporal relationships were not always clear, but this important study shows once again how a very common infection such as HSV-2 may play a major role in the transmission of HIV even when the relative risk is not as high as for gonorrhoea.

Two prospective studies of MSM in the USA also showed an important increase in HIV incidence associated with STI. One cohort study found that repeated recent rectal infection with gonorrhoea or Chlamydia increased the risk of HIV more than 8-fold after controlling for known and measured confounders. [21*] Menza and colleagues developed a risk score model for HIV acquisition among MSM based on a longitudinal study, in which a history or current bacterial STI was one of the strongest predictors for HIV acquisition. [22*] A community based cohort of MSM in Australia also found rectal infections to be associated with incident HIV, with both gonorrhoea and anal warts significantly associated after controlling for risky behaviour. [23*]

Two further cohort studies provide evidence for the possible role of human papillomavirus (HPV) in the sexual transmission of HIV. Auvert and colleagues used data from a male circumcision trial in South Africa to look at the association between HPV and HIV incidence. [24**]After controlling for other factors, there was no association between low-risk HPV and HIV, but there was a 4-fold increased risk in men with high-risk HPV, and the incidence increased with the number of high-risk HPV genotypes detected. A similar finding was reported among MSM in the USA, where increasing numbers of anal HPV types increased HIV risk. [25]

Finally, in an extensive systematic review and meta-analysis, Boilly and colleagues summarised data from 25 study populations to estimate the risk of HIV transmission per act in heterosexuals. [26**] They found that current or past genital ulcers in the HIV susceptible partner increased per-act infectivity five-fold compared with no STI.

Taken together these observational studies confirm previous findings of a strong association between STI and increased risk of HIV acquisition, and show that this occurs across a wide range of infections, and that the strength of association and the population attributable risk varies between populations and with epidemic phase.

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Biological plausibility

There are several biological mechanisms thought to account for the synergy between HIV and STI epidemics. Infections that disrupt the epithelial surface of the genital tract may increase acquisition through facilitating the access of HIV-1 to target cells under epithelial surface thus increasing the probability that HIV-1 is able to establish a systemic infection. Ulcers in both partners can facilitate blood to blood contact and thereby transmission, while STI in the HIV infected partner can increased viral shedding in the genital tract.[5*]

A systematic review and meta-analysis of HIV-1 shedding in the presence of an STI adds weight to this biological mechanism. Johnson and Lewis used a fixed effects model to provided pooled estimates for the odds of detection of HIV in the genital tract in the presence of different organisms and syndromes. The largest associations were with urethritis (OR 3.1, 95% CI: 1.1-8.6) and cervicitis (OR 2.7, 95% CI: 1.4-5.2), with significant but smaller effects for gonorrhoea (OR 1.8, 95% CI: 1.2-2.7) chlamydia (OR 1.8, 95% CI: 1.1-3.1) and vulvovaginal candidiasis (OR 1.8, 95% CI: 1.3-2.4). They conclude that conditions that recruit polymorphonuclear leukocytes to the genital tract are associated with an increase in HIV shedding, and suggest that a dose-response relationship may exist. Interestingly, HSV-2 was not found to increase the detection of HIV in the genital tract but to increase the concentration of HIV. [27**].

The role of HSV-2 in the acquisition, transmission and control of HIV

Much of the recent evidence about the role of STI in the transmission and control of HIV is specifically concerned with HSV-2 as a major driver of some HIV epidemics. Mathematical models have indicated a major role for HSV-2 in HIV transmission in Africa, with PAR% of between 15% and 30%. [28] This is thought to be due to a combination of HSV-1 increasing the risk of HIV-1 acquisition, and then once people are dually infected they become more infectious for HIV thereby fuelling the epidemic.

In an excellent editorial, Glynn and colleagues review the literature as they consider the implications of a study by Tobian. [29**,30] The latter article reports from a large cohort of men assessed for a circumcision trial; after adjusting for sexual behaviour, prevalent HSV-2 increased HIV incidence three-fold, and incident HSV-1 increased it six-fold. In the accompanying editorial, Glynn and colleagues update an earlier meta-analysis of prevalent HSV-2 on incident HIV, and find similar estimates. After adjusting for age and sexual behaviour the relative risk for prevalent HSV-2 and incident HIV is 3.4 in women, 2.8 in men, 1.5 in sex workers and 1.6 in MSM.

These and other findings suggest that prevalent HSV-2 increases the risk of acquisition of HIV, but HSV-2 can also increase the risks of transmission from dually infected people. There are many plausible ways in which HSV-2 can contribute to HIV transmission, through disrupted epithelium, recruitment of HIV target cells and increased HIV viral load. [27] For example, co-infection with HIV-1 and HSV-2 was significantly associated with inflammation of the foreskin in a study using sample from a circumcision trial in Rakai. [31]

The impact of HSV-suppressive therapy on HIV viral load had been assumed to be mediated by the effect on HSV-2, recent in vitro studies suggest a direct inhibitory effect of acyclovir on HIV-1 reverse transciptase. This would suggest that there may be a role for HSV-suppressive therapy in people with HIV-1 who do not have HSV-2. [32]

A number of randomised controlled trials have measured the impact of HSV suppressive therapy on risk of HIV acquisition in people with HSV-2, on viral load and genital shedding

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in people who are dually infected, and on the risk of HIV-1 transmission from people who are dually infected.

Several trials of HSV-2 suppressive therapy have shown a reduction in plasma, seminal and genital HIV-1 RNA in co-infected individuals. [33-34] The impact is dependent upon the drug, the dosage and adherence, with a better response to twice daily doses of acyclovir 800mg or valacyclovir 500mg than acyclovir 400mg. The reduction in HIV viral load is significant, at around 0.3 $\log_{10}$ HIV-1 copies per ml, a scale of difference associated with improved HIV outcomes.[32]

These promising findings have not, unfortunately, been matched by the results of intervention studies. As with the large trials of STI treatment to prevent HIV infection, the results of intervention studies with HSV suppressive therapy have been disappointing. In 2008, Watson-Jones reported on a large RCT of acyclovir in HIV-1 negative, HSV-2 positive women, which showed no impact on HIV acquisition. [35] Later that year a similar trial failed to show a reduction in HIV acquisition, but unlike the previous study did show a 47% reduction in genital ulcers.[36]

More recently results of a major trial of the impact of HSV-2 suppressive therapy on HIV transmission were published. Over 3000 HIV-1 discordant couples were recruited where the HIV-1 infected partner was coinfected with HSV-2. Acyclovir was given to the dually infected partner, and the outcome was transmission to the discordant partner. [37, 38**] Acyclovir reduced genital ulcers by 73% and plasma HIV-1 by 0.25 $\log_{10}$, but it did not reduce transmission.

Interpreting these trials has been challenging, and it is important not to conclude that the intervention is ineffective before questioning whether the intervention could be improved. Similarly, it is worth considering whether the failure to show a reduction in HIV acquisition or transmission due to poor drug adherence, noted in one study [35], although this did not appear to be a factor in the other two trials. Some have suggested that the drug dosage may have been too low, and there is evidence that acyclovir 800mg or valacyclovir 500mg twice daily produce greater viral suppression.[32] However, the reduction in plasma HIV-1 and in genital ulcerations in the transmission study were comparable to other studies and therefore dose and compliance do not appear to be a reason for the lack of impact.[38] It is also important to consider whether the trial design was appropriate. These trials, although very large, may still have been underpowered, particularly if the PAR is relatively small and, as some authors commented,[38] the inclusion of counselling and condoms to both arms of the study meant that the incidence was lower than expected.

Conclusion

There is a clear association between bacterial and viral STI and the risk of HIV infection at both individual and population levels. It is highly probable that there is a causal link given the consistency of epidemiological data and the strong biological plausibility and clear mechanisms of effect. Why then have the trials of interventions been so disappointing? For each intervention there are many specific factors, ranging from individual level compliance through to population coverage. The lack of effect of STI treatment trials at a population level may be due to the epidemic phase and specific local conditions.

Further insights are suggested by mathematical modelling studies, although these are of course only as robust as the assumptions and parameter estimates on which they are based. They can be helpful in exploring the potential impact of an effective intervention, and also the factors that may limit the findings of a specific trial. For example, Vickerman and colleages developed a model to explore the impact of presumptive periodic treatment (PPT)

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for STIs on the transmission of STIs and HIV in high-risk groups in a setting of poor STI control. The effectiveness of PPT was analysed in a mathematical model looking at female sex workers in Johannesburg, South Africa. They found that a substantial reduction in HIV incidence (>40%) seemed to be possible through controlling STIs in this population, but found that the decrease in HIV incidence could take several years (2-5 years in the model) and was dependent on a number of factors including the epidemiologic setting [39*]

The lack of impact of HSV-suppression on HIV infection is truly disappointing, and means that other avenues need to be found to tackle these two intersecting epidemics. It may be worth exploring whether suppressive therapy should be given to both partners in HIV-discordant but HSV-concordant couples. HSV-2 vaccination may have greater potential. However, models of the impact of HSV-2 vaccination on HIV transmission show that it would take many years to have any major impact on transmission even with quite high coverage. [40]

There has been some debate about the implications of recent evidence for HIV control programmes. Gray and Wawer have suggested it is time to reassess the importance of STI prevention as part of HIV programmes, arguing that given the lack of evidence of impact, resources should be shifted towards interventions of known efficacy. [41] Given the strength of evidence of the links between HIV and STI, and the major burden of disease represented by STI themselves, it would take a brave person to suggest disinvestment in STI control programmes. From the public health and service provision point of view, whether there is a causal association between concurrent STIs and HIV acquisition does not really matter as the mode of transmission and many of the risk factors are the same. There are many advantages gained from incorporation of STI control into HIV programmes, or rather from providing a more integrated approach to preventive interventions for reproductive and sexually transmitted infections, of which HIV is just one. [42-3]

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References

1. Weber JN, McCreaner A, Berrie E, et al. Factors affecting seropositivity to human T cell lymphotropic virus type III (HTLV-III) or lymphadenopathy associated virus (LAV) and progression of disease in sexual partners of patients with AIDS. Genitourin Med. 1986; 62(3):177–180. [PubMed: 3015772]
2. Piot P, Laga M. Genital ulcers, other sexually transmitted diseases, and the sexual transmission of HIV. BMJ. 1989; 298(6674):623–624. [PubMed: 2496785]
3. Cameron DW, Simonsen JN, D'Costa LJ, et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. Lancet. 1989; ii:403–407. [PubMed: 2569597]
4. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sexually Transmitted Diseases. 2001; 28(10):579–597. [PubMed: 11689757]
5*. Fox J, Fidler S. Sexual transmission of HIV-1. Antiviral Res. Jan; 2010 85(1):276–85. [PubMed: 19874852] A comprehensive recent review of determinants of sexual transmission of HIV.
6. Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. Lancet. 1995; 346:530–536. [PubMed: 7658778]

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7. Wawer MJ, Sewankambo NK, Serwadda D, et al. Rakai Project Study Group. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Lancet. 1999; 353:525–535. [PubMed: 10028980]

8. Kamali A, Quigley M, Nakiyingi J, et al. Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. Lancet. 2003; 361:645–652. [PubMed: 12606175]

9. Kaul R, Kimani J, Nagelkerke NJ, et al. Monthly antibiotic chemoprophylaxis and incidence of sexually transmitted infections and HIV-1 infection in Kenyan sex workers: a randomized controlled trial. JAMA. 2004; 291:2555–2562. [PubMed: 15173146]

10*. Barnabas RV, Wasserheit JN. Riddle of the *Sphinx* revisited: the role of STDs in HIV prevention. Sex Transm Dis. Jun; 2009 36(6):365–7. [PubMed: 19434009] An editorial that provides insight into the interpretation of trial and observational data pointing out the centrality of epidemic phase.

11. Sexton J, Garnett G, Rottingen JA. Metaanalysis and metaregression in interpreting study variability in the impact of sexually transmitted diseases on susceptibility to HIV infection. Sexually Transmitted Diseases. 2005; 32(6):351–7. [PubMed: 15912081]

12. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. Jama. 2008; 300(5):520–9. [PubMed: 18677024]

13. Adimora AA, Schoenbach VJ, Floris-Moore MA. Ending the epidemic of heterosexual HIV transmission among African Americans. American Journal of Preventive Medicine. 2009; 37(5): 468–471. [PubMed: 19840704]

14. Sasse A, Defraye A. HIV infections and STI co-infections in men who have sex with men in Belgium: sustained increase in HIV diagnoses. Euro Surveill. 2009; 14(47)

15. Miller M, Liao Y, Wagner M, Korves C. HIV, the clustering of sexually transmitted infections, and sex risk among African American women who use drugs. Sexually transmitted diseases. Jul; 2008 35(7):696–702. [PubMed: 18418289]

16. Patterson TL, Goldenberg S, Gallardo M, et al. Correlates of HIV, sexually transmitted infections, and associated high-risk behaviors among male clients of female sex workers in Tijuana, Mexico. AIDS. 2009; 23(13):1765–1771. [PubMed: 19584699]

17. Braunstein SL, van de Wijgert JH, Nash D. HIV incidence in sub-Saharan Africa: a review of available data with implications for surveillance and prevention planning. AIDS reviews. Jul-Sep; 2009 11(3):140–156. [PubMed: 19654856]

18*. McCoy SI, Eron JJ, Kuruc JD, et al. Sexually transmitted infections among patients with acute HIV in North Carolina. Sexually transmitted diseases. Jun; 2009 36(6):372–374. [PubMed: 19387421] This analysis shows variation in recent STI infection in people with acute HIV, with the highest levels in heterosexual men and women.

19**. Zetola NM, Bernstein KT, Wong E, et al. Exploring the relationship between sexually transmitted diseases and HIV acquisition by using different study designs. Journal of acquired immune deficiency syndromes. 2009; 50(5):546–551. [PubMed: 19367993] This study of MSM included 3 different control groups to help understand the temporal relationship between STI and incident HIV and proivdes important insights into the asocation and also the importance of using complementary study designs.

20**. van de Wijgert JH, Morrison CS, Brown J, et al. Disentangling contributions of reproductive tract infections to HIV acquisition in African Women. Sexually transmitted diseases. Jun; 2009 36(6):357–364. [PubMed: 19434010] This cohort study provides estimates of the HIV population attributable risk % for different reproductive tract infections in two African countries.

21*. Bernstein KT, Marcus JL, Nieri G, et al. Rectal Gonorrhea and Chlamydia Reinfection Is Associated With Increased Risk of HIV Seroconversion. JAIDS. 2010; 53(4):537–543. [PubMed: 19935075] A retrospective cohort study identifying repeat rectal infections as important predictors of HIV.

22*. Menza TW, Hughes JP, Celum CL, Golden MR. Prediction of HIV acquisition among men who have sex with men. Sexually transmitted diseases. Sep; 2009 36(9):547–555. [PubMed: 19707108] Reports a risk score for HIV acquisition among MSM based on data from men attending an STI clinic more than once and validated in another population.

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23*. Jin F, Prestage GP, Imrie J, et al. Anal sexually transmitted infections and risk of HIV infection in homosexual men. Journal of acquired immune deficiency syndromes. Jan 1; 2010 53(1):144–149. [PubMed: 19734801] Community-based cohort of 1427 HIV-negative homosexual men in Sydney, Australia

24**. Auvert B, Lissouba P, Cutler E, et al. Association of oncogenic and nononcogenic human papillomavirus with HIV incidence. Journal of acquired immune deficiency syndromes. Jan 1; 2010 53(1):111–116. [PubMed: 19779357] Cohort study of HIV incidence and its association with pre-existing HPV I South Africa

25. Chin-Hong PV, Husnik M, Cranston RD, et al. Anal human papillomavirus infection is associated with HIV acquisition in men who have sex with men. AIDS. Jun 1; 2009 23(9):1135–1142. Online. [PubMed: 19390418]

26**. Boily MC, Baggaley RF, Wang L, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. The Lancet infectious diseases. Feb; 2009 9(2):118–129. [PubMed: 19179227] Extensive meta-analysis on the heterosexual risk for HIV-acquisition per sexual act.

27**. Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis. Sexually Transmitted Diseases. 2008; 35(11):946–959. [PubMed: 18685546] Analysis of the impact of STI on shedding of HIV in the genital tract.

28. Abu-Raddad LJ, Magaret AS, Celum C, et al. Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV prevalence in Africa. PLoS ONE. 2008; 3(5):e2230. Arte Number. ate of Pubaton: 21 May 2008. [PubMed: 18493617]

29**. Glynn JR, Biraro S, Weiss HA. Herpes simplex virus type 2: a key role in HIV incidence. AIDS. 2009; 23:1595–1598. [PubMed: 19512858] Excellent summary with updated meta-analysis

30. Tobian A, Ssempijja V, Kigozi G, et al. Incident HIV and herpes simplex virus tupe 2 infection among men in Rakai, Uganda. AIDS. 2009; 23:1589–1594. [PubMed: 19474649]

31. Johnson KE, Sherman ME, Ssempiija V, et al. Foreskin inflammation is associated with HIV and herpes simplex virus type-2 infections in Rakai, Uganda. AIDS. Sep 10; 2009 23(14):1807–1815. [PubMed: 19584700]

32. Vanpouille C, Lisco A, Margolis L. Acyclovir: a new use for an old drug. Current Opinion in Infectious Diseases. 2009; 22(6):583–587. [PubMed: 19726982]

33. Zuckerman RA, Lucchetti A, Whittington WL, et al. HSV suppression reduces seminal HIV-1 levels in HIV-1/HSV-2 co-infected men who have sex with men. AIDS. Feb 20; 2009 23(4):479–483. [PubMed: 19169140]

34. Baeten JM, Strick LB, Lucchetti A, et al. Herpes simplex virus (HSV)-suppressive therapy decreases plasma and genital HIV-1 levels in HSV-2/HIV-1 coinfected women: a randomized, placebo-controlled, cross-over trial. The Journal of infectious diseases. Dec 15; 2008 198(12): 1804–1808. [PubMed: 18928378]

35. Watson-Jones D, Weiss HA, Rusizoka M, et al. Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. N Engl J Med. 2008; 358:1560–1571. [PubMed: 18337596]

36. Celum C, Wald A, Hughes J, et al. Effect of acyclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet. 2008; 371:2109–2119. [PubMed: 18572080]

37. Lingappa JR, Kahle E, Mugo N, Mujugira A, Magaret A, Baeten J, et al. Characteristics of HIV-1 discordant couples enrolled in a trial of HSV-2 suppression to reduce HIV-1 transmission: the partners study. PloS one. 2009; 4(4):e5272. [PubMed: 19404392]

38**. Celum C, Wald A, Lingappa JR, et al. Acyclovir and Transmission of HIV-1 from Persons Infected with HIV-1 and HSV-2. N Engl J Med. 2010; 362:427–39. [PubMed: 20089951] Major randomized controlled clinical trial that failed to show an effect of HSV-2 suppression on transmission of HIV.

39*. Vickerman PT, Ndowa F, O'Farrell N, et al. Using mathematical modelling to estimate the impact of periodic presumptive treatment on the transmission of STIs and HIV amongst female sex workers. Sexually transmitted infections. Oct 22.2009 Doi: 10.1136/sti.2008.034678. Interesting model exploring factors affecting the impact of a preventive intervention

40. Freeman EE, White RG, Bakker R, et al. Population-level effect of potential HSV2 prophylatic vaccines on HIV incidence in sub-Saharan Africa. Vaccine. 2009; 27:940–946. [PubMed: 19071187]
41. Gray RH, Wawer MJ. Reassessing the hypothesis on STI control for HIV prevention. The Lancet. 2008; 6/21(371(9630)):2064–2065.
42. Steen R, Wi TE, Kamali A, Ndowa F. Control of sexually transmitted infections and prevention of HIV transmission: Mending a fractured paradigm. Bulletin of the World Health Organization. Nov; 2009 87(11):858–865. [PubMed: 20072772]
43. Chersich MF, Rees HV. Vulnerability of women in southern Africa to infection with HIV: Biological determinants and priority health sector interventions. AIDS. Dec; 2008 22(SUPPL. 4):S27–S40. [PubMed: 19033753]

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