

REVIEW

Sexually transmitted infections and HIV in the era of antiretroviral treatment and prevention: the biologic basis for epidemiologic synergy

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Abstract

Introduction: HIV is a unique sexually transmitted infection (STI) that is greatly affected by other concomitant “classical” bacterial and viral STIs that cause genital ulcers and/or mucosal inflammation. STIs also serve as a marker for risky sexual behaviours. STIs increase infectiousness of people living with HIV by increasing the viral concentration in the genital tract, and by increasing the potential for HIV acquisition in people at risk for HIV. In addition, some STIs can increase blood HIV concentration and promote progression of disease. This review is designed to investigate the complex relationship between HIV and classical STIs.

Discussion: Treatment of STIs with appropriate antibiotics reduces HIV in blood, semen and female genital secretions. However, community-based trials could not reliably reduce the spread of HIV by mass treatment of STIs. Introduction of antiretroviral agents for the treatment and prevention of HIV has led to renewed interest in the complex relationship between STIs and HIV. Antiretroviral treatment (ART) reduces the infectiousness of HIV and virtually eliminates the transmission of HIV in spite of concomitant or acquired STIs. However, while ART interrupts HIV transmission, it does not stop intermittent shedding of HIV in genital secretions. Such shedding of HIV is increased by STIs, although the viral copies are not likely replication competent or infectious. Pre-exposure prophylaxis (PrEP) of HIV with the combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) prevents HIV acquisition in spite of concomitant STIs.

Conclusions: STIs remain pandemic, and the availability of ART may have led to an increase in STIs, as fear of HIV has diminished. Classical STIs present a huge worldwide health burden that cannot be separated from HIV, and they deserve far more attention than they currently receive.

Keywords: STI; STD; HIV; ART; PrEP; shedding; acquisition; transmission

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1 | INTRODUCTION

HIV is primarily a sexually transmitted infection (STI) [1]. A single sexual encounter between an HIV-positive partner and an HIV-negative partner (a serodifferent/serodiscordant couple) has a low probability of HIV transmission [2-5]. When transmission occurs, a single viral variant (the transmitted founder virus) is detected 80% of the time, and usually only a maximum of two or three viral variants are transmitted [6,7]. The transmission of HIV is generally relatively inefficient, and predicted to require hundreds of exposures in the case of penile-vaginal intercourse [2,3] and dozens of exposures for penile-rectal exposure [4,5].

Such inefficient transmission has made it difficult to understand the magnitude of the HIV pandemic. In part, this can be explained by transmission from HIV-positive people who do

not know their status over many years of asymptomatic infection. HIV transmission reported in stable discordant couples before availability of antiretroviral treatment (ART) was as high as 8.2 to 12.0 per 100 person-years [8,9]. In addition, several factors could amplify HIV transmission [10]. Among the most important amplifying factors are the “classical STIs,” loosely defined bacterial and viral infections that cause genital ulcers and genital mucosal inflammation. Classical STIs are among the most common acute conditions worldwide and have increased in recent years; the World Health Organization (WHO) estimates more than one million incident curable STIs worldwide each day [11]. The purpose of this article is to examine the relationship between the classical STIs and HIV with an emphasis on changes in the nature of this interaction since the availability of antiretroviral agents for the treatment and prevention of infection.

2 | DISCUSSION

2.1 | STIs in people with HIV

The connection between classical STIs (that cause mucosal inflammation or ulcers) and HIV surfaced early in the epidemic [12] and was first referred to as “epidemiologic synergy” by Wasserheit [13]. Subsequent studies have paid considerable attention to biologic mechanisms to explain how STIs promote HIV transmission [12-16]. Such research studies suggested two important roles for STIs: increased infectiousness of the HIV-positive person and increased susceptibility of the HIV-negative person [17]. Increased infectiousness appears to reflect increases in HIV concentration in genital secretions and changes in viral phenotype of HIV variants that favour transmission.

2.2 | HIV in genital secretions

Cohen *et al.* studied HIV in semen of men with concomitant gonorrhoea [18] and trichomonas [19] and noted a significant increase in viral concentration relative to a control group without urethritis; the increase in HIV in semen was reduced by appropriate antibiotic treatment, albeit only after several weeks. Shedding of HIV in semen also increases with CMV and perhaps other herpes virus co-infections [20]. Similar increases in the detection of HIV in female genital secretions in the presence of STIs and inflammation have been reported [14,21,22], although such findings have not always been consistent [23]. Cohen *et al.* reported increased HIV in female genital secretions with bacterial vaginosis, with significantly increased risk of HIV transmission to sexual partners [24].

Indeed, higher concentrations of HIV in blood [9] and genital secretions [25] increase the probability of HIV transmission. The increases in concentration of HIV detected in genital secretions with STIs could reflect increased replication of the virus, an influx in the number of HIV-infected cells into the genital mucosa, and/or increased exudation of contaminated blood and fluids in ulcerated or denuded mucosal epithelium [17].

2.3 | HIV-1 compartmentalization in the genital tract

Over the course of untreated infection, a diverse quasispecies emerges within an individual [26]. The emergence of multiple viral variants can be attributed in part to the error-prone replication of HIV-1 [26,27], as well as selective pressure from the host's immune system [28,29]. However, as noted above, most new HIV-1 infections are initiated with a single, or at most a few, viral variants [6,7] emphasizing the idea that there is a “bottleneck” or “sieve” at the point and time of mucosal transmission [27].

Regional (compartmental) differences in viral diversity can be observed when virus that has been sequestered in an anatomic region undergoes replication independently from virus circulating in the blood. Over time, this independent replication can result in the formation of genetically distinct, compartmentalized viral populations. This phenomenon has been extensively studied in the central nervous system [30,31] and the male [32-34] and female [35-37] genital tracts.

For example, early on Ping and colleagues [34] utilized a heteroduplex tracking assay to analyze the HIV-1 variants present in the blood plasma and seminal plasma of men from Malawi with and without symptomatic urethritis. The authors hypothesized that in the presence of an inflammatory STI, T-cell trafficking to the male genital tract would be increased, thus bringing potentially infected cells from the blood into the genital tract and causing the viral populations from the two compartments to mix. In the absence of inflammation, there is less exchange of cells between the male genital tract and the periphery, which would support the formation of genetically distinct compartmentalized viral populations. Overall, the latter study noted discordant viral populations between the blood and semen in 40% of individuals studied, regardless of whether or not they were co-infected with another STI [34].

We have recently reexamined the relationship between HIV and STIs using single genome amplification followed by Sanger sequencing [32], as well as Primer ID [38,39] and deep sequencing [40]. Co-infection with another STI did not appear to strongly influence the establishment of compartmentalized populations in this cohort, but individuals with urethritis tended to have more dynamic viral populations in the semen, than did men without urethritis [40].

Studies examining HIV-1 diversity in the female genital tract during early infection have observed multiple variants not detected in the blood plasma [41]. Multiple variants appear to be able to establish local foci of infection in the female genital tract, although perhaps only one or two are capable of initiating a disseminated infection. Subsequently, variable compartmentalization of HIV-1 between the female genital tract and the blood has been observed. For example, Kemal *et al.* noted genotypically and phenotypically different HIV-1 envelopes from viruses recovered from the female genital tract as compared with the blood [37]. Phenotypic differences included the use of CXCR4 as a coreceptor and an increased number of N-linked glycosylation sites. This observation, coupled with the fact that compartmentalized lineages were most often found in individuals with low CD4 counts, led to the hypothesis that local immune pressures in the female genital tract were driving viral evolution.

However, as PCR techniques and sequencing methods that limit recombination and resampling were developed, a different picture of compartmentalization in the female genital tract has emerged [35,36]. Although genetically distinct lineages are often found in the genital tract, they are most often monophyletic, indicative of short bursts of replication. Furthermore, when women were followed longitudinally for five years, no tissue-specific phenotype persisted [36]. While more work is needed, it appears that compartmentalization in the female genital tract may be a transient phenomenon. Longitudinal studies of compartmentalization in the male genital tract in the presence and absence of STIs are currently in progress, but a similar pattern of transient compartmentalization was observed in a small number of men who were followed for 180 days during acute and early infection [33].

2.4 | STIs and susceptibility to HIV

Transmission of classical STIs is generally more efficient than HIV, and therefore may set the stage for increased risk of HIV acquisition [17]. Inflammation and ulcers can be expected to

lower the barrier(s) to infection [15,42,43]. Recent studies have tried to more precisely define the conditions that lead to HIV acquisition in women, with a focus on unique cytokine profiles [15,44] and disturbance of vaginal microbiome [45] with resultant “dysbiosis” (non-optimal vaginal flora) [46]. STIs can evoke an influx of receptive cells with expression of a greater number of CCR5 and CD4 receptors per cell [17]. The risk of HIV acquisition for a woman with mucosal inflammation or a genital ulcer is greatly increased [17]. *Trichomonas* infection in women, a common pathogen, also increases HIV acquisition [22]. It should be noted that people with an STI appear to be susceptible to an HIV viral variant with reduced fitness [42].

The foreskin is a critical point of acquisition of HIV by men. It has been argued that low-grade inflammation in this tissue, perhaps critical to decrease commensal bacterial colonization and to resist STIs, increases the risk of HIV acquisition [47,48]. Circumcision greatly decreases the risk of HIV infection [49]. Circumcision also appears to reduce the risk of genital ulcer disease in men [47].

Rectal mucosa is a vulnerable tissue and unprotected anal intercourse has the greatest risk for HIV acquisition [3-5,50]. Rectal mucosa is thin and friable and heavily defended against infection, thereby enriched with cells receptive to HIV. Bernstein *et al.* reported that in men who have sex with men (MSM) with a history of syphilis and two rectal gonorrhoea or chlamydia infections in the past two years, there was an eight-fold risk of HIV acquisition [51].

2.5 | STIs and prevention trials

The role of STIs in the spread of HIV led to a series of randomized clinical trials designed to reduce the incidence of HIV infection in communities [52-57], in individuals [58,59] and in serodifferent couples [60,61,62]. Of the nine clinical trials, successful prevention of HIV through treatment of STIs was only noted in Mwanza, Tanzania [52]. The differing results of these trials have been extensively reviewed [16,17,61,62]. Failure to see population level prevention of HIV acquisition by more aggressive or mass treatment of STIs is best ascribed to the difficulty of providing effective drugs to the right people at the right time, and the difficulty of assuring that the trial participants are able to adhere to the antimicrobial regimens selected.

An alternative approach has been to focus on HSV-2 treatment to prevent individual HIV acquisition [58,59] or transmission [60]. HSV-2 was chosen as a key target because it is such a common infection and so strongly associated with HIV transmission [61,63]. Acyclovir was used to suppress HSV-2 replication. No prevention benefit was observed whether the agent was used to treat HIV positive or negative people (the latter representing HSV-2 PrEP). It seems likely that subclinical inflammation in spite of treatment reduced the anticipated benefit(s) of acyclovir [64]. Mugwanya *et al.* [65] has reported that high-dose valacyclovir (1.5 grams twice daily) might reduce HIV-1 infectiousness more than acyclovir treatment used in earlier clinical trials.

2.6 | STI biology in the era of ART

Several studies have shown that ART prevents secondary HIV transmission independent of STI coinfections [66-71]. In the

HPTN 052 multinational randomized controlled trial, HIV transmission was virtually eliminated in HIV discordant heterosexual couples when viral replication was successfully suppressed [66,69]; STIs were commonly detected in study subjects over more than 10,000 person-years of follow-up. The latter results were confirmed by more recent observational cohort studies of both heterosexual and MSM couples [67,68,70,71]. The PARTNER study [67] followed HIV-serodifferent couples reporting condomless sex and where the HIV-infected partner was taking ART, during 1238 person-years in 888 partnerships, no genetically linked HIV transmissions were detected when the HIV-positive partner was virally suppressed, despite frequent incident STIs in the HIV-positive partner (18% among MSM and 6% among heterosexual men and women) or negative partner (17% among MSM and 6% among heterosexual men and women). More recently, Rodger *et al.* reported that in a continuation of the Partner study, 779 MSM couples reported 76,088 episodes of condomless anal intercourse with no linked HIV transmission events [70,71]. In this study, 24% of HIV positive men and 27% of their HIV negative sexual partners acquired an STI. In the Opposites Attract study of serodifferent MSM couples [68], 1/3 of HIV-positive participants and 1/4 of HIV-negative participants acquired STIs during follow-up, with an incidence rate of 22.8 STIs per 100 person-years and 15.1 STIs per 100 person-years respectively. However, no genetically linked HIV transmission events were documented during the 588.4 couple-years of follow-up [68].

2.7 | Do STIs influence HIV-1 shedding in spite of antiretroviral therapy?

However, while HIV treatment reliably prevents HIV transmission, it does not prevent shedding of the virus in the genital secretions of men [72] or women [73].

2.8 | STIs and HIV in the female genital tract

There are a large series of reports of detection of HIV virus in the female genital tract with a wide variety of STIs [74-76]. Graham and colleagues sought to understand how genital ulceration impacted cervical and vaginal shedding of HIV-1 in women receiving ART in Kenya [77]. Among 145 women who initiated ART, 36 developed a genital ulcer after at least two months of ART; ten women (28%) had detectable HIV-1 RNA in their genital secretions. King and colleagues [78] followed 1114 women initiating ART to determine factors that influence viral shedding. During 5.8% of patient visits (among 76 women with 83 visits), HIV-1 RNA was detected in genital secretions but not blood plasma. The median concentration of HIV-1 RNA in genital secretions was between 1000 and 5000 copies/mL. As time on ART increased, the proportion of women with detectable genital HIV-1 RNA decreased. Correlates of detectable HIV-1 RNA in the genital tract in women with undetectable HIV in blood included more advanced WHO stage of disease, the presence of an ulcerative STI, cervical tenderness and the antiretroviral combination employed. The latter observation emphasizes differences in the pharmacology of ART in the male and female genital tract that can influence the suppression of replication of HIV [27,79-81].

2.9 | STIs and HIV in the male genital tract

Kalichman *et al.* studied the relationship between blood and seminal plasma, and shedding of HIV in semen in spite of ART [82]. He reviewed studies demonstrating 100s and sometime 1,000s of copies of HIV-1 RNA in semen when less than 50 copies of HIV were detected in blood. Anderson *et al.* reviewed the association between seminal cells and HIV transmission, and the possibility that ART may not eliminate cells that remain infectious [83]. HIV virus can be detected in semen in 5-30% samples obtained from men on ART [82,84]. It should be noted that different antiretroviral regimens may reduce HIV viral concentration in genital secretions with different speed and efficiency [80,81]; integrase inhibitors appear particularly effective in reducing HIV in semen [85].

Only a few studies of the effects of STIs on semen shedding in men receiving ART have been reported. Sadiq *et al.* studied the blood and seminal fluid of 24 men receiving ART who acquired urethritis [86]. They reported two men (17%) with urethritis who had low blood viral loads at study screening with increased HIV viral loads in semen (5928 and 1512 copies HIV RNA/mL). The seminal viral loads reverted to <1000 copies HIV RNA/mL after STI treatment.

To further investigate the issue, we have enrolled HIV-infected men with acute urethritis into an ongoing prospective observational cohort [87]. Among 56 men enrolled in the study with at least 12 weeks of ART (<1000 copies/mL blood at baseline), nine subjects (16%) had HIV \geq 1000 copies/mL detected in semen within the first two weeks of enrolment. HIV in semen was <1000 copies/mL within eight weeks of treatment for urethritis, consistent with an earlier study [18].

In men with acute urethritis who were not on ART at enrolment but initiated treatment within one week, HIV copy number in both blood and semen were comparable (baseline median viral loads of 4.7 and 4.1 \log_{10} copies/mL respectively) [88]. However, while both compartments showed decreasing viral loads after ART initiation, (week eight median viral loads of 2.0 and 0.0 \log_{10} copies/mL in the blood and semen respectively); semen viral loads showed higher variability over time.

There is also little information to date about the effects of STIs on HIV viral shedding in the rectum. Kelley *et al.* examined the associations between rectal chlamydia and gonorrhoea, HSV-2 seropositivity and HIV viral shedding, and found that STIs had little effect [89]. Although these results were underpowered to stratify by ART use, 74% of the participants in the study were prescribed ART, and the results showed no effect of STI coinfection at low blood plasma viral loads of <1000 copies/mL. Davies *et al.* also assessed differences in rectal viral loads among MSM on ART with and without STIs [90]. Among their 18 participants, they found no significant difference in rectal viral loads between those with and without STIs; all rectal viral loads from both STI groups were below the limit of detection [90].

The detection of HIV RNA and the DNA in the genital secretions evoked by an STI suggests escape of the virus (or some part of the virus) from the cell, or release of latent virus, or viral replication. However, failure of HIV-positive people to infect their sexual partners [66-70] strongly suggests that viral copies detected are defective (and not replication competent) and/or that ART in the genital tract also contributes to HIV prevention. The majority of HIV viruses recovered from the

latent pool in blood are defective and not replication competent [91], similar detailed studies have not yet been conducted with viral copies recovered from the genital tract.

2.10 | STIs and blood HIV burden

A related question is the effects of STIs on blood viral burden. As noted above, genital ulcers significantly increase the amount of viral RNA shed in both the male [92] and female genital tracts [14]. Buchaz *et al.* reported increased HIV in blood in people with primary and secondary syphilis [93]. Dyer *et al.* [92] found an increase in blood viral burden in men with genital ulcers and urethritis. Celum *et al.* [60] found a modest reduction of HIV in blood from treatment of HSV-2 with acyclovir. Lingappa *et al.* [94] reported that acyclovir could reduce progression of HIV disease in people dually infected with HIV and HSV-2. These results suggest a systemic effect of HSV-2 infection.

Antiretroviral therapy is highly effective at suppressing HIV-1 replication in the blood, including in people with STIs. In a meta-analysis of 14 studies looking at the effects of STI infection on HIV-1 blood viral load, Champredon and colleagues concluded that co-infection with an STI correlates with a 0.11 \log_{10} increase in HIV-1 viral load suggesting that when an individual is suppressed on ART, STIs have little effect on blood viral load [95].

2.11 | STIs and pre-exposure prophylaxis in MSM

A series of clinical trials demonstrated that TDF/FTC can prevent HIV acquisition in MSM [96-98] and women [reviewed in 99].

TDF/FTC prophylaxis was approved by the US CDC in 2012 and guidelines are available [100]. However, one major concern has been the effects of pre-exposure prophylaxis (PrEP) on sexual behaviours that might lead to an STI. In a systematic review of 17 open label PrEP studies with meta-analysis of eight studies that included measurement of STIs, Traeger *et al.* noted a modest increase (odds ratio 1.24, 95% CI: 0.99-1.54) in STI risk associated with TDF/FTC PrEP, especially in more recent studies [101]. However, another meta-analysis estimated that among MSM taking TDF/FTC PrEP, the incidence rates for gonorrhoea, chlamydia and syphilis were 25.3, 11.2 and 44.6 times the incidence rates among MSM not taking PrEP [102]. Although both results suggest increased risk of STIs among men taking TDF/FTC PrEP, the relative strengths of the associations reported were quite dissimilar. As noted in the respective studies and further commentary [103], selection of high-risk participants into PrEP studies and decreased STI detection among non-PrEP users may have biased some results upwards.

Most recently, Traeger *et al.* [104] prospectively evaluated incidence of chlamydia, gonorrhoea and syphilis in 2891 MSM and bisexual men enrolled in a PrEP trial in Victoria, Australia. The authors noted significant increases in STIs over 1.1 years of follow-up. However, 76% of STIs were noted in only 736 of the study participants. In addition, increases in STIs were not associated with decreased condom usage, although condom usage was not always consistent, and condoms were probably not used during oral-penile sex when some pathogens could be transmitted [105]. The investigators suggested that

changes in sexual networks or sexual behaviours in some PrEP users might lead to increases in STIs. They found risk factors predicting an incident STI in men receiving TDF/FTC PrEP to include younger age, greater partner number and group sex. The results support the frequent measurement and treatment of STIs in PrEP users [100].

A second critical question is the efficacy of TDF/FTC PrEP when an STI is acquired. This question was addressed in an observational report from Kaiser Permanente California [106]. Among 687 men who initiated TDF/FTC PrEP, 187 acquired STIs; however, no incident cases of HIV acquisition were noted. In recent prospective clinical trials in MSM—IPERGAY, and Proud—TDF/FTC PrEP prevented 86% and 96% respectively, of HIV infections regardless of high incidence of STI infections during the trials [97,98]. In the IPERGAY trial [98], 43% of MSM randomized to the PrEP arm acquired one or more STIs. In the Proud study [97], 57% of study subjects receiving PrEP had an STI and 36% had rectal gonorrhoea or chlamydia. These results convincingly demonstrate that incident STIs do not compromise the prevention benefit of TDF/FTC PrEP in MSM. However, as new PrEP drugs are developed (see below) each agent must independently demonstrate the ability to withstand the inflammatory changes evoked by an STI.

2.12 | STIs and PrEP in women

PrEP effectiveness in either partner in serodifferent heterosexual couples [107], and in HIV-negative women [107-113], has also been examined but with mixed results. The Partners PrEP and TDF2 studies both found significant reductions in HIV acquisition among men and women using oral TDF [107] or TDF/FTC [107,111] in Sub-Saharan Africa. The CAPRISA study found modest reduction in HIV acquisition among women in Sub-Saharan Africa with 1% vaginal gel formulation of a tenofovir topical microbicide [108], as did trials using a dapivirine vaginal ring microbicide [109,114].

The VOICE trial [110], which evaluated oral TDF, oral TDF/FTC and 1% tenofovir vaginal gel, and the FEM-PrEP trial [112], which evaluated oral TDF/FTC failed to find significant reductions in HIV-acquisition among women in Sub-Saharan Africa. For the most part, these differences have been ascribed to limited adherence to PrEP products, including topical microbicides. However, it is possible that one or more concomitant STIs compromise the efficacy of oral or topical PrEP in women [113]. Indeed, McKinnon *et al.* [48] reported that genital inflammation reduced the efficacy of tenofovir gel.

2.13 | New PrEP drugs and STIs

Most recently the results of a clinical trial that directly compared TDF/FTC with tenofovir alafenamide TAF and FTC demonstrated the equivalency of the latter combination, although very few incident infections were detected [115]. As an alternative to oral PrEP the integrase strand inhibitor cabotegravir has potential for long acting PrEP [116]. Landovitz *et al.* identified a dose and dosage schedule for cabotegravir as PrEP [116]. This agent is now being compared directly to TDF/FTC daily and TDF/FTC every eight weeks injection in more than 5000 high risk men and women (NCT02720094; NCT03164564). An important consideration

is the HIV prevention efficacy of cabotegravir in the presence of an STI, and this is being explored. There is considerable interest in other means of delivering long acting HIV prevention in vaginal rings [109,114], or implants [117] or microneedle patches [118]. These devices could potentially combine HIV and STI prevention, and contraception into a “multipurpose intervention.”

2.14 | Mathematical modelling

Mathematical modelling has been used to understand the spread of HIV and compare prevention strategies [119-121]. Such combination interventions generally include voluntary male circumcision, behaviour change (which generally includes emphasis on detection and treatment of STIs), and ART used as “treatment as prevention” (TaSP) or PrEP. Chesson and coworkers have argued that gonorrhoea, chlamydia and syphilis contribute to the HIV epidemic, and that their treatment may be a cost effective way to reduce the spread of HIV [122,123]. However, as indicated above, mass treatment of STIs did not have the benefits anticipated in these models. These results demonstrate the difficulty of treating bacterial and viral STIs, and the concern that STIs may reflect risk behaviours and exposure to HIV rather than (or at least as much as) serving to amplify HIV transmission.

Jenness *et al.* [123] have suggested a unique benefit of PrEP for MSM in the United States and perhaps other high-income settings. In their model they propose that adherence to CDC PrEP guidelines [100] would increase STI screening so much that 42% of gonorrhoeal infections, and 40% of chlamydial infections could be prevented over the next decade [123].

2.15 | PrEP for STIs

As already noted, HIV PrEP trials have found high incidence of classical STIs [96-98,104]. Bolan *et al.* [124] and Molina *et al.* [125] have reported the successful use of doxycycline prophylaxis to reduce the incidence of syphilis and chlamydia in high risk MSM. Doxycycline was not effective for prevention of gonorrhoea. These results further emphasize the importance of consideration of STIs in the treatment and prevention of HIV infection.

3 | CONCLUSIONS

The early history of the HIV pandemic was marked by realization that HIV infection led to a new, fatal sexually transmitted disease with risk to both sexually active men and women, and that several classical STIs amplified both infectiousness and acquisition of HIV [10,13,17]. While all STIs can and do occur concomitantly, the influence of classical STIs on HIV transmission is unique. Emphasis on this relationship led to attempts to reduce HIV incidence through more STI testing and treatment. But failure of mass treatment to reduce HIV infection in most clinical trials [61] reduced the interest of the HIV research community in STIs, and perhaps reduced funding for detection and treatment of STIs. Sadly, a wide variety of factors have accelerated spread of STIs, especially among MSM at high risk for HIV acquisition [11]. Particularly severe

problems with syphilis infections and increasing resistance of gonorrhoea to antibiotics have been emphasized [11].

Where do we go from here? We have no choice but to rethink STI research goals and intervention funding, and the relationship between STIs and HIV; and new questions have arisen. We do not understand the biology of shedding of HIV in the genital tract that persists despite clearance in the blood with ART. This problem is highly relevant to thinking about the cure of HIV. Several strategies are now being pursued to permit remission (no drugs required) or sterilising cure of HIV. Among the most popular is the “kick and kill” strategy with reactivation of latent HIV virus and concomitant elimination of HIV infected cells [126,127]. The increased shedding of HIV in the genital tract evoked by some STI infections demonstrates the well documented compartmentalization of HIV. In this case, STIs are acting as a “kick.” So lessons learned about the effects of shedding of HIV in the genital tract are highly relevant and perhaps critical to the ultimate cure of the infection. This situation also draws attention to the need for better understanding of the pharmacology of antiretroviral agents in the genital tract [80,81]. However, viral copies detected in the genital tract under these conditions do not lead to HIV transmission.

Finally, there is the complex and evolving relationship between PrEP, STIs and HIV acquisition. Currently, the only agent approved in the US as pre-exposure prophylaxis (PrEP) is the fixed dose combination of tenofovir disoproxil fumarate and emtricitabine (TDF/FTC). The use of TDF/FTC has been accompanied by recognition of high incidence of STIs in PrEP users [96-98,104,106]. Sexual risk behaviours that preceded availability of PrEP and increased post PrEP risk behaviours (from reduced fear of HIV because of excellent treatment of HIV and PrEP or other social forces) have been convincingly demonstrated [11]. But fortunately, STIs do not increase HIV acquisition in people using TDF/FTC PrEP; importantly, the prevention benefit of TDF/FTC is not overwhelmed by ulcers or inflammation. However, for each new PrEP agent, such as with tenofovir alafenamide (TAF) (Discover, NCT02842086) [115], or cabotegravir LA (an injectable long acting integrase inhibitor, HPTN 083, NCT02720094, HPTN 084, NCT03164564) or one or more broad neutralizing antibodies [128], we must prove that the prevention benefit persists in the presence of one or more STIs.

STIs are a harbinger of HIV acquisition, depending on the prevalence of HIV in the community, the number of people on treatment, and the degree of difficulty in detection and treatment of STIs and HIV. STIs serve as a critical surrogate for the need for PrEP [100,129], and they represent a critical problem by themselves, a fact that is sometimes overlooked in public health funding decisions. STIs have critical consequences for sexual and reproductive health of men and women [11]. The important and rapidly evolving STI pandemic will affect the spread and control of HIV. The relationship between STIs and HIV has been demonstrated over and over again during the past 30 years and this “synergy” [13] will not just go away; STIs must be urgently addressed with new ideas and increase in resources.

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COMPETING INTERESTS

MSC is on the Advisory Board for Merck and Gilead. ODC and JSC have no potential conflicts.

AUTHORS' CONTRIBUTIONS

MSC provided conception and design, as well as analysis and interpretation of data; drafted manuscript, provided critical revisions and gave final approval of submission. ODC participated in drafting the article and critically revising for intellectual content. JSC participated in drafting the article and critically revising for intellectual content.

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