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Global challenges in human immunodeficiency virus and syphilis co-infection among men who have sex with men

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Abstract

Introduction—Syphilis and human immunodeficiency virus (HIV) co-infection disproportionately affects men who have sex with men (MSM), and the rate of co-infection has been increasing over the last decade. HIV and syphilis co-infection is particularly challenging because the infections interact synergistically thereby increasing the risk of acquisition and transmission as well as accelerating disease progression.

Areas Covered—This paper reviews and summarizes the epidemiology, pathogenesis, diagnosis, clinical management and prevention of HIV and syphilis co-infection among MSM.

Expert Commentary—Research does not support a different syphilis treatment for co-infected individuals; however, co-infection may warrant a recommendation for antiretroviral therapy. In order to reverse the epidemic of syphilis and HIV co-infection, there needs to be greater awareness, improved cultural sensitivity among health care providers, improved access to preventative services and increased screening for syphilis and HIV.

Keywords

Human immunodeficiency virus (HIV); Syphilis; Co-infection; MSM; Prevention

1. Introduction

Despite the promising decline of syphilis infections in the late 1990s in many developed countries, syphilis reemerged in 2000 and continues to be a public health challenge [1]. In developed countries, syphilis disproportionately affects men who have sex with men (MSM), many of whom are co-infected with Human Immunodeficiency Virus (HIV) [2, 3]. From 2000 to 2013, the proportion of syphilis diagnoses reported among MSM versus non-MSM

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Declaration of interest

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in high income countries increased from 26.8% to 55%, with all 18 countries reporting an increase of syphilis prevalence among MSM [2]*. In 2014, over 60% of the 19,999 reported cases of primary and secondary syphilis in the United States were diagnosed in MSM [3]. Of the 26 states that included HIV status and sexual behavior, 51.2% syphilis cases in MSM also had HIV infection [3]. In a study of HIV-infected MSM in Ontario, rates of syphilis diagnosis and reinfection steadily increased from 1.8 to 4.3 per 100 person years in 2006–2010 [4]. Although surveillance of MSM is limited in low and middle income countries, high rates of HIV and syphilis co-infection have been found among MSM in Peru, Panama, India, Malawi and Uganda [5–9], indicating that HIV and syphilis co-infection is in fact a global challenge. Similar reports from China demonstrate increasing HIV and syphilis co-infection among MSM [10–12], with a 2.6% estimated prevalence of co-infection [10, 13]. All available evidence supports that the epidemic of HIV and syphilis co-infection is worsening and primarily concentrated among MSM.

The increase in HIV and syphilis co-infection among MSM may be attributed to behavioral changes in MSM, the successful treatment of HIV and the expansion of communication technology. Among HIV-uninfected MSM, treatment optimism and pre-exposure prophylaxis (PrEP) use may increase sexual risk behavior, including decreased condom use [14–17]. A recent survey of MSM in the United States found decreased condom use regardless of HIV treatment status and serosorting [18]. Serosorting and seropositioning may decrease the probability of HIV transmission, but these practices do not protect against syphilis transmission [1]. Similarly, oral sex is very low risk for HIV transmission, but it efficiently transmits syphilis [19]. HIV-infected patients that are being effectively treated with antiretroviral therapy are likely to feel healthier and to engage in more sexual activity [20, 21]. Geosocial networking applications, such as Grindr™, Jack'd™ and Scruff™, facilitate partner meeting and may increase transmission of sexually transmitted diseases, including HIV and syphilis [22]. A recent case-controlled study of a syphilis outbreak among MSM in Oregon found significantly more syphilis-infected men met their partners online and 55% were co-infected with HIV [23]. Additionally, MSM may face greater challenges to testing and treatment for sexually transmitted diseases (STDs) due to stigma or fear [24].

The rising epidemic of HIV and syphilis co-infection among MSM is complicated by the synergistic interaction between the two infections. Prompt diagnosis and treatment are necessary components to the global response to HIV and syphilis co-infection; however, the guidelines can be conflicting and implementation of testing can be difficult. A multifaceted approach to the prevention of both syphilis and HIV transmission will be required to achieve epidemic control.

2. The synergy of HIV and syphilis co-infection

One challenge of HIV and syphilis co-infection is the bidirectional synergistic effect that facilitates acquisition, transmission and alters disease progression of both infections [25]. Studies demonstrated that a recent syphilis infection can increase the risk of HIV seroconversion by as much as 2.5 times [26, 27]. Primary syphilitic ulcers cause a disruption in genital epithelium, thereby increasing the susceptible surface area for HIV acquisition

[25]. The immune response to syphilis brings additional HIV susceptible inflammatory cells to the infection site, including activated macrophages, CD4 and CD8 T cells, which may facilitate HIV acquisition [1, 25, 28]. In the examination of syphilitic lesions, Salazar et. al found increased expression of CCR5 and DC-SIGN on dendritic cells and increased CCR5 expression on CD4 T cells [28], which are known co-receptors for HIV-1 [29, 30]. The immunological response to syphilis may increase the of risk the HIV acquisition by dendritic presentation to CD4 T cells in regional lymph nodes or by direct infection of CD4 T cells [28]. A recent study by Arnold et. al identified mucosal cytokines that were associated with seroconversion among HIV-uninfected women in Kenya [31]. Similar proinflammatory cytokines, including macrophage inflammatory protein 1B and interferon gamma-induced protein 10, were found to be elevated among syphilis-infected, HIV-uninfected patients in a pilot study of 10 patients in Peru [32]. Increased cytokine expression may further increase local immune activation and be associated with the susceptibility to HIV infection.

In an HIV-infected patient, a new syphilis infection increases HIV viral load, which increases the infectiousness of the patient and risk of HIV transmission [33–35]. Although antiretroviral therapy helps mitigate that response, increased viral load has been reported among patients who had previously undetectable HIV viral loads as well [33–36]. HIV and syphilis co-infection is associated with transient decreases in CD4 T cell counts, which have been attributed to increased viral replication and CD4 T cell turnover [34]. During early and secondary syphilis infection, elevated TNF-alpha and IL-10 are associated with lower CD4 counts and increased HIV viral loads [37]. More research is needed to understand the relationship between syphilis-induced cytokines and the role they may play in seroconversion and HIV expression.

In order to clear the organism responsible for syphilis infection, *Treponema pallidum pallidum (T. pallidum)*, it must be targeted by opsonization for phagocytosis by activated macrophages. A recent study by Marra et. al investigated the serum opsonic activity of HIV-infected compared to HIV-uninfected individuals [38]*. That study found significantly reduced opsonic activity among HIV-infected individuals, which may ultimately result in reduced ability to clear *T. pallidum* from sites of infection and a higher burden of infection [38]. Additional research will be needed to confirm those results and investigate other factors that affect opsonization in HIV-infected individuals.

HIV and syphilis co-infection also alters the presentation and progression of syphilis. Prior to the HIV-era, syphilis was clearly defined as primary, secondary and latent infections that progressed to late neurosyphilis in roughly 7% of untreated cases [1]. In primary syphilis infection, HIV-infected patients are more likely to present with multiple chancres, instead of the characteristic single chancre [39]. Many co-infected patients will present with primary ulcers and secondary lesions simultaneously, blurring the distinction of these stages [40]. Using PCR to evaluate primary syphilic lesions, Tipple et. al found that HIV-infected patients tended to have more *T. pallidum* DNA copies when compared to HIV-uninfected patients, suggesting that co-infected individuals had a higher burden of infection and may be more likely to transmit syphilis as well [41]. HIV-infected patients are more likely to develop early neurosyphilis during early stages of syphilis infection with an estimated incidence of 1.7–2.1% compared to 0.5–0.6% among HIV-uninfected individuals [42, 43].

Even after treatment, a past syphilis infection among HIV-infected patients was associated with poorer cognitive performance, which demonstrates the long-term consequences of co-infection [44]. Although there are non-biological explanations for the increasing incidence of HIV and syphilis co-infection, the immunological interactions between syphilis and HIV infection may also be important contributors to the increased incidence among MSM.

3. Diagnosis

The diagnosis of syphilis is complicated by the inability to culture or isolate the species responsible for infection, *T. pallidum*. Additionally, the currently available diagnostic tests are relatively insensitive during very early infection [45]. There are multiple types of syphilis antibody tests resulting in a number of algorithms to use in the diagnosis of syphilis. Although there are case reports of high and low titers in syphilis serological tests for HIV infected patients [46–48], these events can occur in absence of HIV infection as well [49]. In general, serological tests are not affected by HIV status and remain the primary diagnostic tool to determine syphilis infection and treatment response [50]. When serological testing does not support syphilis diagnosis, but there remains strong clinical evidence and risk of syphilis infection, treatment should be provided [50]. There is no evidence that syphilis infection affects HIV testing or diagnosis.

In primary syphilis, direct examination of ulcer exudate can identify the characteristic spirochetes with dark-field microscopy, but a 2009 survey of infectious disease specialists in the United States indicated that 81% of respondents did not have access to dark-field microscopy [51]. There has been an effort to develop a PCR assay that can adequately detect syphilis infection. Unfortunately, PCR evaluation of whole blood has low sensitivity and is not used for diagnostic purposes [41, 52]. However, several studies have shown that PCR can detect syphilis infection from primary ulcer exudate earlier than serological tests, which may aid in timely identification of syphilis infection [53–55]. European guidelines encourage the use of PCR for syphilis detection in oral lesions and other lesions that may have commensal treponemes [56]. Yang et. al studied the oral swabs of HIV and syphilis co-infected MSM, and were able to detect treponemal DNA with PCR assays in 68% of patients with oral lesions and 40% of patients without oral lesions [57]*. Oral *T. pallidum* among HIV-infected men without oral ulcers may be a previously unrecognized source of syphilis transmission, especially because many participants reported condomless oral sex [57].

Serologic tests are routinely used for clinical diagnosis; however, these tests cannot detect antibodies within the first weeks of infection [40]. Furthermore, there is some lack of consensus experts or authorities on how best to use the available serologic tests. The traditional diagnostic algorithm uses a non-treponemal test (either rapid plasma reagin [RPR] or venereal disease research laboratory [VDRL]), and if positive, syphilis infection is confirmed with a treponemal test. Non-treponemal tests are less expensive and provide titers that are used clinically to monitor response to treatment. Although the traditional algorithm remains the recommended algorithm of the Centers for Disease Control and Prevention (CDC), it has been called into question due to its lower sensitivity, higher rate of false positive tests among HIV-infected patients and need for manual laboratory operation and subjective evaluation [40, 58].

The United Kingdom (UK) Health Protection Agency and International Union Against Sexually Transmitted Infections encourage the use of the reverse algorithm [59]. The reverse algorithm uses automated treponemal assays, such as multiplex flow immunoassay, chemiluminescence immunoassay or enzyme immunoassay, which may be advantageous in a high volume setting [58]. If the treponemal assay is positive, it is confirmed by a non-treponemal test, such as RPR. If the RPR is negative, clinical management can be unclear and might cause confusion or anxiety among patients and clinicians alike [58]. The CDC recommends using a different treponemal test and the likelihood of syphilis exposure to determine treatment course [50]. Treponemal tests will remain positive for life for most patients, even after treatment. With latent syphilis, non-treponemal response may decrease over time that could result in a negative RPR test; therefore, the reverse algorithm may increase the identification of latent syphilis [60]. Tong et. al confirmed the decreased sensitivity of the traditional algorithm, which failed to diagnose 24% of syphilis-infected patients in their cross-sectional study of 24,124 individuals in China [61]. On the other hand, treponemal tests cannot differentiate between previously treated syphilis and reinfection [62]. Due to high rates of syphilis among MSM, particularly HIV-infected MSM, the reverse algorithm may ultimately require more non-treponemal testing to resolve positive treponemal results, and discordant results could lead to overtreatment.

There are advantages and disadvantages to both the traditional and reverse algorithms for syphilis screening. More research is necessary to determine which method is more appropriate for MSM who have a high prevalence of syphilis, high risk of HIV acquisition and high rates of syphilis reinfection. Although the reverse algorithm may lead to some overtreatment, the higher sensitivity may be required in public health efforts to control the spread of both syphilis and HIV infection.

Unfortunately, both the traditional and reverse algorithm serological testing require patients to return to clinic for their results and treatment. Decreasing the interval between screening and treatment with rapid point of care tests will prevent forward transmission and loss to follow up with immediate intervention. Rapid point of care tests that combine both treponemal and non-treponemal antibody tests are highly sensitive and specific for syphilis diagnosis, but do not provide an actual non-treponemal titer information to help monitor disease progression [60, 63–66]. Some point of care tests also combine HIV, Hepatitis B and/or Hepatitis C antibody detection, which are particularly useful in communities with high rates of those infections. Point of care tests are valuable in resource-poor settings, but are also useful in non-clinical settings that often serve patients that may be unlikely to return for treatment. While single treponemal tests have been validated and approved for use, evaluation of new dual or multiplex point of care tests has been limited to plasma or serum [64, 65]. Additional field research is required to validate their use with whole blood.

HIV and syphilis co-infected patients are at a higher risk of neurosyphilis; however, the diagnosis of neurosyphilis can be particularly difficult in co-infected patients. There is debate among experts regarding when cerebrospinal fluid (CSF) analysis is necessary for HIV and syphilis co-infected patients. There is agreement that CSF analysis should be performed in the presence of neurological symptoms, such as headache, visual or mental status changes [67]. The indications for CSF analysis in the asymptomatic, co-infected

patient have been more difficult to determine. The CDC recommends CSF analysis for patients whose non-treponemal titers do not decrease by four-fold within 12–24 months [50]. Although there have been studies that suggest a reduced CD4 cell count (≤350 cells/mm^3) or an RPR titer of ≥1:32 are correlated with neurosyphilis [68, 69], the CDC does not support these criteria for as an indication for CSF analysis. Ghanem et. al found those criteria to be sensitive in the diagnosis of asymptomatic neurosyphilis, but would ultimately lead to a 20% increase in the number of CSF analyses performed [67]. The benefit of treating asymptomatic neurosyphilis is unknown.

Once a lumbar puncture is performed, there is no gold-standard diagnostic test to exclude neurosyphilis [60]. A diagnosis of neurosyphilis can be determined by CSF serological testing, using CSF-VDRL and/or fluorescent treponemal antibody absorption test (FTA-ABS) [50]. FTA-ABS is often used to rule out neurosyphilis due to its high sensitivity [70]. Abnormal CSF white cell count or protein was previously used as diagnostic criteria for neurosyphilis, but CSF abnormalities are not uncommon among HIV-infected patients, even among those without a syphilis infection [71]. Therefore, there is a need to identify and develop new diagnostic tools for neurosyphilis. In 2015, Mothapo et. al found that CXCL13, a chemokine, was significantly increased in patients with neurosyphilis with a sensitivity of 50% and a specificity of 90%, and the added diagnostic value was higher for HIV-infected patients (70%) compared to HIV-uninfected patients (33%) [52]. More research is necessary to determine if CXCL13 is a useful biomarker for neurosyphilis and whether it could be added to the available diagnostic criteria. PCR has been explored for the diagnosis of neurosyphilis, but is not adequately sensitive [52].

4. Clinical management

The preferred treatment of syphilis is penicillin, with the option of using doxycycline, tetracycline or a cephalosporin for patients with a history of penicillin allergy [50, 60]. Azithromycin should not be used, particularly in groups with high syphilis prevalence such as MSM, due to documented cases of resistance [72, 73]. The course of penicillin treatment differs depending on the stage of syphilis. For early syphilis (primary, secondary and early latent), the standard treatment is a single dose of benzathine penicillin G (BPG) 2.4 million units intramuscularly, whereas late latent syphilis requires three doses of BPG at one-week intervals [50]. In order to ensure CSF penetration, neurosyphilis treatment requires higher blood levels of penicillin. Neurosyphilis can be treated over the course of 10–14 days with aqueous crystalline penicillin G 18–24 million units per day intravenously or procaine penicillin G 2.4 million units per day intramuscularly and probenecid 500 mg orally four times daily [50]. According to the CDC, UK and European guidelines, the treatment of syphilis does not differ for patients with or without HIV infection [50, 56, 74]. Similarly, the treatment of HIV does not change with a diagnosis of syphilis.

After treatment, patients should be followed with non-treponemal serological testing to determine successful response, defined as a four-fold decrease in non-treponemal titers from the baseline titer collected on day of treatment [50]. In comparison to HIV-uninfected patients, RPR titers of HIV-infected patients are slower to normalize [75, 76]; therefore, extended follow-up of 3, 6, 9, 12 and 24 months is recommended [50]. Serological failure is

associated with higher HIV viral loads, lower CD4 counts and lack of antiretroviral treatment, emphasizing the benefits of HIV therapy while treating syphilis in a co-infected individual [77]. Marra et. al demonstrated that the normalization of RPR titers can also predict the resolution of infection in neurosyphilis patients, which could help avoid follow-up CSF analysis [78]; however, that recommendation has yet to be included in standard guidelines for neurosyphilis.

Despite the fact that treatment guidelines unanimously state that clinical management of HIV-infected patients does not differ, some providers use three dose BPG in HIV-infected patients for several reasons: 1) a higher risk of asymptomatic neurosyphilis, 2) reduced immune clearance of infection, and 3) higher serological failure compared to HIV-uninfected patients [60, 79]. In fact, a 2009 study found that 62% of American infectious disease clinicians would prescribe three doses of BPG to treat an HIV-infected patient with secondary syphilis, even though the recommendation only requires one dose [51]. Therefore, it appears some clinicians might not follow treatment guidelines in practice, thereby leading to inconsistent patient care. Although enhanced treatment can be rationalized, the evidence is lacking [80]. Experts have acknowledged that the available research on syphilis treatment among HIV-infected patients has been limited and primarily focused on serological outcomes [79, 81, 82]. Even though non-treponemal titers have been used to monitor syphilis response for decades, Tuddenham and Ghanem argue that serological titers may not correlate to clinical outcomes, especially for HIV-infected patients who can have persistently elevated non-treponemal levels unrelated to syphilis activity [83]. The frequency of true treatment failure among HIV-infected patients is rare [82]. More robust research on the treatment for HIV and syphilis co-infected patients with an emphasis on clinical outcomes might be necessary to strengthen the evidence for current guidelines.

5. Prevention

A concerted response to prevent HIV and syphilis co-infection is necessary to reverse the rising epidemic among MSM. There are many interventions available that focus on behavioral change to reduce STI risk among MSM, with a range of goals including increased condom use, reduced number of sexual partners and increased testing frequency. However, most of these studies use endpoints that rely on self-reported behavior, opposed to reduced STI incidence, and ultimately demonstrate little efficacy to reduce STI transmission [84, 85]. In one of the few studies of behavioral intervention for MSM in the United States with an endpoint of HIV incidence, the study failed to demonstrate a reduction in HIV incidence between the two groups [86, 87]. A review of behavioral interventions in China found participants reported a reduction in risky behaviors, but there was no change in HIV or syphilis incidence [88]. Although education and counseling to reduce STI risk remains important, it needs to be combined with other biomedical prevention measures to have an impact on HIV and syphilis co-infection, such as PrEP administration, STI screening and condom use [84, 85]. Condom use should still be promoted because it is an effective method to prevent both HIV and syphilis transmission; however, condom use has been declining among MSM over the past decade [18].

Screening is always a keystone of STD prevention; however, with limited resources, it must be determined how best to implement screening for a given population. Through modeling, Gray et. al compared the effect of increasing the coverage of screening, the frequency of screening of current testers and contact tracing. They found that increasing the frequency of syphilis screening of high-risk MSM to every three months was the most effective strategy to reduce the incidence of syphilis at the population level [89]. Similarly, Tuite et. al replicated that finding in a model with the syphilis epidemic driven by a core group of MSM, as characteristic of many urban sexual networks [90]. In response to those findings, the international guidelines recommend syphilis screening in MSM every three months, regardless of HIV status [91, 92].

Despite that recommendation, there is evidence that MSM may not be offered quarterly screening as recommended [93]. A 2009 study in Ontario found that only 55% of HIV infected MSM received annual syphilis screening [94]. That is particularly concerning because Tuite and Fisman's model of elevated, but suboptimal screening actually lead to a higher equilibrium incidence of syphilis [90, 95]. Although it may be seem contradicting that increased screening may lead to more syphilis infections, Tuite and Fisman claimed that increased screening would identify patients with latent infections, who are no longer infectious nor susceptible [95]*. With treatment, those patients are susceptible to reinfection and if infected, could contribute to forward transmission. Therefore, it is necessary that screening for both HIV and syphilis achieve recommended frequency. Unfortunately, the CDC guidelines for STD testing frequency among PrEP users only recommends testing every six months [96], although syphilis screening is recommended quarterly for MSM by other US guidelines [91]. The contradicting guidelines may lead clinicians to provide inadequate screening to a population most at-risk for syphilis and could possibly reduce the effectiveness of PrEP due to increased probability of HIV acquisition with syphilis infection [26]. PrEP guidelines should be updated to include quarterly syphilis screening for MSM to clarify the STD screening frequency for clinicians.

Several studies have examined how to best help clinicians and patients meet the recommended screening frequency. A study in Northern California found that syphilis screening among HIV-infected patients significantly improved after provider training and the implementation of an STD-risk assessment [97]. In order to reach the goals of sufficient screening, additional clinician training appears to be necessary. A 2013 Australian study compared syphilis screening frequency among clinics that used opt-in, opt-out and risk assessment policies for HIV-infected MSM [98]*. The opt-in and opt-out screening policies achieved significantly greater screening frequencies of 39% and 48% participants completing more than three syphilis tests per year respectively, compared to 8% of participants at clinics that used risk assessment [98]. Although opt-out strategies will result in more testing for lower-risk MSM, this policy may be necessary to improve screening frequency. Screening may also be improved when providers and patients receive electronic reminders. An Australian study showed that syphilis screening increased from 77% to 89% for high-risk MSM when providers were prompted by the electronic medical record [99]. Similarly, 67% of patients that received e-mailed or texted reminders for their 3-month syphilis screening completed the visit, compared to 39% in the control group [100]. In an effort to increase screening awareness and testing services to MSM, several studies have

found advertising STD services on geosocial networking applications to be feasible and could become part of STD outreach soon [101–103].

PrEP is an exciting pharmacological advance that could help substantially reduce HIV risk. Truvada®, a daily dose combination of emtricitabine and tenofovir disoproxil fumarate, was approved in 2012 by the U.S. Food and Drug Administration as an effective HIV chemoprophylaxis for high-risk individuals, including MSM [104, 105]. Unfortunately, the roll-out of PrEP has not been universally executed; only the United States, France, South Africa, Kenya, Israel and Canada have currently implemented PrEP as part of the national HIV prevention policy [106]. The European Centre for Disease Control endorsed the use of PrEP in 2015, but access widely varies in each country [107]. Despite the successful PrEP results and evidence of its cost-effectiveness from the PROUD trial in the UK [107, 108], the National Health Services has decided not to support PrEP administration in the UK, which has sparked considerable controversy [109]. That decision may lead other countries, clinicians or patients to question the efficacy of a clearly advantageous HIV prevention option. Increasing acceptability and access to PrEP remains a focus of HIV prevention efforts [107].

PrEP has demonstrated that chemoprophylaxis is an acceptable and successful strategy to prevent HIV infection. Therefore, in order to further study chemoprophylaxis, Bolan et. al conducted an innovative pilot study to determine the feasibility of daily 100 mg doxycycline to prevent STDs among 30 HIV-infected MSM [110]*. The 48-week study found that daily doxycycline was well tolerated, and resulted in decreased incidence of *Nisseria gonorrhoaea*, *Chlamydia trachomatis* and syphilis [110]. A larger, randomized controlled trial is necessary to confirm the effectiveness and safety of STD chemoprophylaxis. If confirmed, STD chemoprophylaxis could significantly improve the prevention of syphilis and other STDs.

Although modeling has shown partner notification is not the most effective method of STD prevention as compared to increased screening frequency and coverage [89], it still plays an important role to identify and treat recently exposed individuals thereby interrupting the cycle of forward transmission. Contact tracing and partner notification can be time-intensive and costly, and has been complicated by the anonymous nature of sexual contact via the Internet and mobile partner seeking services often used by MSM. Online partner notification applications, such as inSPOT (www.inspot.org) and Let Them Know (www.letthemknow.org.au), can facilitate partner notification and linkage to care with anonymous e-mails or text messages [111, 112]. However, those services require cases to know the e-mail addresses or phone numbers of their recent partners. A study in North Carolina increased partner notification by contacting individuals directly through partner seeking online sites, which are often the only contact information available [113]. Training partner services providers in the routine use of websites and mobile applications that are frequently used by MSM could increase partner notification and may help patients feel more connected with their providers [114, 115]. In particularly high volume settings, individualized provider contact tracing can be cumbersome with inadequate follow-up. The North Carolina study found that partner notification was increased by centralizing online contact tracing to one designated person in the department [113]. Future research on

streamlining and integrating partner notification systems with online applications may reveal additional strategies to improve contact and successful follow-up.

6. Expert commentary

In order to better understand the global syphilis and HIV co-infection epidemic, more research focusing on MSM in low and middle income countries is necessary because different approaches may be required for each community. In regions that have documented high rates of HIV and syphilis co-infection among MSM, clinicians and providers have to receive the appropriate support so they are prepared to care for this population. First, we must increase the awareness among clinicians and providers to improve the screening frequency, treatment and follow-up for MSM [116]. Additionally, cultural sensitivity needs to be improved among clinicians to help reduce stigma and increase the number of MSM seeking testing and treatment, particularly in countries with less acceptance of same-sex sexual practices. Although there can be hesitation to ask patients sensitive questions, clinicians should be advised to take better and more complete sexual histories for improved identification of high-risk patients [116, 117]. The sexual history should include questions regarding the patient's sexual identity, sexual activities and condom use [117]. By increasing the clinician's understanding of the sexual health risks facing MSM and providing a more inclusive environment for MSM, it is likely more MSM will be offered necessary screening, PrEP and treatment.

A new syphilis diagnosis requires an HIV test to rule out co-infection. In the event of a negative HIV test, it is recommended to have a follow-up HIV test in three months [50]. However, because syphilis infection is associated with incident HIV, an nucleic acid amplification test would be the best test to rule out acute or very early infection [118]. Acute HIV-infected individuals are known to have higher levels of viremia and infectivity [118]. Additionally, one study in San Diego found that sexually risky behaviors were associated with acute HIV infection among MSM, thereby increasing the probability of HIV transmission [119]. MSM with new syphilis infections represent a high-risk population that could benefit from HIV nucleic acid amplification testing to appropriately diagnosis acute HIV infections, despite the increased cost.

There is no clear evidence that supports an enhanced syphilis treatment course for HIV and syphilis co-infected individuals. However, there is significant evidence that co-infected individuals benefit from antiretroviral treatment: 1) reduction or lack of viral load increase that typically accompanies early syphilis [33–36], 2) reduction in serological failure [77, 120], and 3) reduction in early neurosyphilis risk [121]. Due to the potential benefits for HIV and syphilis co-infected patients, antiretroviral treatment should be added to the international syphilis treatment guidelines. That recommendation is similar to guidelines for tuberculosis and pregnancy, which have added indications for initiation of antiretroviral therapy regardless of CD4 count for HIV-infected patients. Additionally, the START and TEMPRANO studies investigated the effect of immediate antiretroviral treatment for HIV-infected patients with a CD4 count greater than or equal to 500, and found a 50% reduction of morbidity and mortality for patients that started antiretroviral treatment immediately [122, 123]. Therefore, antiretroviral treatment is currently recommended for all HIV-infected

individuals. The addition of antiretroviral treatment to syphilis treatment guidelines for HIV and syphilis co-infected patients would emphasize the importance of antiretroviral treatment for these patients and may help ensure proper initiation or management of antiretroviral therapy.

7. Five-year view

Since 2000, syphilis diagnoses have continued to rise globally, disproportionately affecting MSM and often accompanied by HIV co-infection. Over the next five years, that trend seems unlikely to change unless there is a concerted effort to improve prevention and screening of both syphilis and HIV infection. While condom use helps prevent the transmission of STDs including HIV and syphilis, its use has been declining for the past decade [18], and that trend may continue in the future. There appears to be little value for public health efforts to promote condom use. Prevention efforts should focus on other methods with higher acceptance among MSM. For HIV prevention, PrEP access and use should be expanded and available for all MSM, despite the concerns of risk compensation. For syphilis and other STD prevention, additional research should investigate the feasibility, efficacy and safety of chemoprophylaxis.

Models and early research have demonstrated the importance of quarterly syphilis screening for MSM [89, 90, 95, 98]. Both providers and MSM will need to be educated regarding the optimal frequency of testing. As quarterly syphilis screening is added to more international guidelines, additional research will need to be conducted to determine the impact of increased screening across different populations, the best strategies for reaching this goal and whether screening targets are being met.

Point of care diagnostics will continue to be refined and may become even more inexpensive and available in the next five years, which will benefit resource-limited or non-clinical settings. With an emphasis on cultural competence and community engagement, non-clinical STD services will continue to serve an important role in screening and linkage to care. Some studies have shown the feasibility and success of HIV self-test distribution through kiosks in emergency rooms [124], advertising on Grindr™ [125] and in bathhouses [126]. Point of care diagnostics will expand the possible venues for STD screening. Because MSM face significant challenges seeking sexual health care, point of care diagnostics should also be considered for at-home testing. Point of care diagnostics will continue to incorporate more testing information on a single unit. Combined treponemal and RPR point of care diagnostics will expedite syphilis screening, and multiplex testing of HIV, syphilis and hepatitis will address the concern of co-infection.

If we succeed to increase screening rates, there is an even greater need for partner notification services to improve contact tracing. As electronic notification becomes more widespread for testing results, electronic partner notification services should be integrated in follow-up instructions. Public health efforts should utilize partner seeking online applications to increase the options available for contact tracing. New technological advances in the next five years may help improve patient and partner notification that we have not yet considered, but telehealth will undoubtedly play a role.

In an effort to better understand interaction between syphilis and HIV, more research in the next five years should focus on immunological changes during syphilis and HIV monoinfection that produce susceptibility to co-infection. In particular, elevated cytokines may serve as biomarkers in the future, particularly for neurosyphilis diagnosis. As we improve our understanding of this interaction, we may be able to improve our approach to prevention, diagnostics and clinical management for HIV and syphilis co-infection.

Although HIV and syphilis co-infection among MSM presents a significant public health challenge, we currently have many tools available to address it. It will require increased awareness among the health care professionals, successful implementation of recommended screening frequencies, upscaling PrEP use, vigilant contact tracing, political will and community mobilization.

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Key Issues

- Men who have sex with men (MSM) are disproportionately co-infected with syphilis and Human Immunodeficiency Virus (HIV).
- The immunological changes that accompany syphilis and HIV monoinfections results in greater susceptibility to the other infection.
- The higher sensitivity of the reverse algorithm (treponemal screening followed by non-treponemal confirmation) may be required in public health efforts to control the spread of both syphilis and HIV infection.
- There is no evidence that supports a different syphilis treatment course for HIV-infected patients versus non-HIV infected patients. Additional research focusing on clinical outcomes should be performed to determine if enhanced treatment is necessary for co-infected patients.
- Due to the increased serological response for HIV and syphilis co-infected patients on antiretroviral therapy, antiretroviral treatment initiation and/or management should be added to syphilis treatment guidelines.
- The recommended syphilis screening frequency for MSM is quarterly. Opt-out screening appears to be more a successful for strategy for meeting screening recommendations compared to opt-in or risk-assessment strategies.
- Pre-exposure prophylaxis (PrEP) is a safe and successful method to prevent HIV acquisition for high-risk individuals, such as MSM; however, PrEP is not universally accepted as standard of care and/or may not accessible. We must improve acceptance and access to PrEP to prevent new HIV infections.
- Awareness and cultural sensitivity needs to be improved among clinicians to help reduce stigma and increase the frequency of MSM seeking testing and treatment, particularly in countries with less acceptance of same-sex sexual practices.

Call Out Box

Immunological changes during syphilis infection that increase HIV susceptibility

- Syphilis ulcers create epithelial disruption
- Inflammatory response brings additional HIV susceptible immune cells to infection site
- Increased expression of co-receptors for HIV-1: CCR5 and DC-SIGN on dendritic cells and CCR5 on CD4 T cells
- Elevated cytokines may increase likelihood of seroconversion