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Understanding and addressing the HIV and STI syndemics

Guest Editors: Kenneth H Mayer, Henry JC de Vries
Supplement Editor: Marlène Bras

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EDITORIAL

HIV and sexually transmitted infections: reconciling estranged bedfellows in the U = U and PrEP era

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Since the earliest days of the AIDS epidemic, it was clear that HIV and other sexually transmitted infections (STI) had many features in common [1]. Their spread involved the same behaviours, and often affected the same socially marginalized people, including men who have sex with men (MSM), sex workers, substance users and migrants. As the aetiologic agent of AIDS, HIV, was elucidated, it became clearer that there were biological interactions between HIV and STI. Inflammatory and ulcerative STI facilitated HIV transmission and acquisition, and HIV infection led to increased infectiousness of several STI pathogens [2,3]. A more sophisticated understanding of their epidemiology also suggested that individuals who were engaging in behaviours that led to STI acquisition were more likely to be part of sexual networks where HIV transmission or acquisition were more likely. Prior to the advent of antiretrovirals for prevention, common strategies employed to decrease HIV/STI spread, mainly involved the promotion of "ABC": Abstinence, or Behaviour change (decreasing the number of partners), and Condom use.

However, over the past decade, the evidence proving that people living with HIV who had undetectable plasma HIV RNA do not transmit HIV (U = U) [4,5], and the demonstration that pre-exposure prophylaxis (PrEP) using tenofovir-based regimens protects individuals against the sexual acquisition of HIV [6-8] has altered the dynamics of HIV-STI epidemiologic synergy. In the current era, individuals who are adherent to antiretroviral medication, whether for treatment or prevention, can expect to engage in condomless intercourse without either acquiring HIV or transmitting the virus to others, but are still at high risk for acquiring and transmitting STI. Moreover, during this same time period, STI increases have been occurring globally, particularly in key populations.

Historically, HIV researchers, STI specialists and frontline clinicians have had differing perspectives about the relationships between HIV and STI. In the earliest days of the epidemic, HIV research was focused on trying to identify an unknown, highly lethal pathogen, whereas most STI pathogens were well known and well described. HIV clinical care involved treating individuals who were at risk for recurrent opportunistic infections and neoplasms, whereas STI management was able to focus on the development of systems to diagnose and treat infections, with much attention was devoted to identifying people who were HIV-infected and treating their intimate contacts. Because of the dire illnesses that people living with HIV developed, and the rapid growth of the epidemic, a sense of urgency led to funding dedicated siloed programmes, such as the NIH clinical trials networks, the PEPFAR initiative and the Global Fund, with scant consideration of concomitant STI that were frequently co-prevalent. Yet at the same time, STI specialists who worked for decades with high disease burden populations found that support for their work was not expanding, and sometimes shrinking. The separation of HIV and STI support through categorical funding further impeded fruitful collaborations [9,10].

Over the past decade, the situation has been altered dramatically because of the recognition that, although there are now tools to control the HIV epidemic, without addressing STI, their spread will accelerate, leading to widespread morbidity, complicating HIV control efforts [9,10]. Increases in congenital syphilis, expanding antimicrobial resistance in gonococci, and sexually transmitted Hepatitis C are three of many examples of how the global public health community has come to recognize that without addressing STI, the successes in the AIDS epidemic will be compromised. It is with that intent in mind that the International AIDS Society sponsored the STI 2018 pre-conference in Amsterdam in July, 2018.

The two-day meeting featured a variety of presentations that addressed the epidemiological, clinical, behavioural and structural issues that have driven the HIV and STI syndemics. Several key papers have been assembled for this special issue of the *Journal of the International AIDS Society* which summarize the key themes discussed at the conference, in order to inform readers about the current state of the science related to HIV and STI interactions and to discuss challenges ahead

for a more integrated response to these syndemics. Taylor and Wi of the WHO describe the global epidemiology of STI spread, and notably, their paper points out that more than one million treatable STI occur daily across the globe, in addition to even larger numbers of chronic viral infections, like *Herpes simplex* and *Human papillomavirus* [11]. Moreover, many of these infections are prevalent in areas of high HIV incidence, or among populations of greatest HIV risk, underscoring the need for combination approaches to address STI and HIV. Wi and WHO colleagues describe the current status of clinical management of STI globally, noting the issues related to the continued frequent use of empiric, syndromic management [12]. The problems with this approach include mistreating vaginal discharges with inappropriate antibiotics and selecting for antibiotic resistance, and missing the high burden of asymptomatic infections such as chlamydia, especially in women. The paper challenges global public health leaders to strategize about how to provide point-of-care and state-of-the-art nucleic acid amplification testing to make aetiologic diagnoses in resource-constrained, but high disease burden, areas. It is notable that many countries that have active tuberculosis control programmes have platforms that can perform rapid molecular STI screening, but they are not being used for this purpose. More creative thinking about how to integrate these programmes, as well as how to lower the costs of reagents, may lead to wider access to appropriate management of STI.

Although STI are prevalent among the general population in resource constrained populations of the world, higher concentrations are often seen in key populations (KP) such as MSM, transgender women, people who inject drugs, sex workers and migrants. Mayer and Allan-Blitz have summarized many of the factors that increase the KP STI risk, which include biological factors such as the increased susceptibility of anal mucosa to specific STI pathogens, behavioural factors such as depression and substance use leading to lack of self-protective behaviours, structural factors such as punitive legal frameworks and culturally insensitive healthcare workers, resulting in avoidant healthcare behaviour [13].

This special issue also includes several papers focusing on the unique biological interactions of HIV and STIs. Cohen and colleagues summarize what is known about the biological interactions of HIV and STI before and after the advent of highly active antiretroviral therapy [14]. Mwatelah and colleagues summarize the state of knowledge regarding HIV transmission in African women, who may have microbial ecological factors that increase their HIV risk, such as the low prevalence of protective vaginal lactobacilli, as well as socio-epidemiologic factors such as the increased likelihood of choosing older partners who may already be HIV-infected [15]. Chow and colleagues summarize the current state of knowledge regarding extra-genital STI [16]. Their paper discusses some of the questions regarding the role of oro-genital sex in potentiating the spread of gonorrhoea and chlamydia.

The next set of papers focuses on clinical issues that are emerging regarding HIV and STI. de Vries discusses the challenges that clinicians face in addressing STI in the current treatment-as-prevention era [17]. Rojas Castro and colleagues discuss the patterns of STI that have been seen in individuals who use biomedical HIV prevention, that is, PrEP, and address the question of risk compensation versus risk maintenance when individuals who are at high risk for HIV/STI utilize interventions that can protect them against HIV but not STI [18]. The topic of emerging infectious diseases is discussed by Nijmeijer and colleagues, focusing primarily on Hepatitis C but also discussing the potential of other agents that are not often thought of as being sexually transmitted to emerge when behavioural patterns change [19]. Rietmeijer discusses the evolution of STI clinics in recent years, and their continued need to change in order to optimally co-manage HIV and STI [20]. Lastly, Rojas Castro and colleagues discuss the supreme importance of engaging affected communities in order to conduct effective clinical research, to translate science into clinical care, given that stigma is frequently associated with HIV and STI in populations who may have reasons to mistrust the beneficence of researchers and clinicians [21].

The intent of this report is to provide new data to interested readers, to hopefully stimulate further discussion. There remain many questions about optimal strategies to enhance the uptake of, and adherence to, antiretrovirals for treatment and prevention, while at the same time increasing diagnosis, treatment, and partner identification of people who are infected with STI. In the worst case scenario, in a world where antiretrovirals are not easily accessible, and/or the co-factors that affect adherence are not addressed, and STI are not promptly diagnosed and treated, both epidemics could exacerbate each other, leading to a new dark era, which is an emerging reality in many countries in Eastern Europe and Central Asia. Hopefully, this will not be the case, and instead, the ability to offer sexually active people effective means to prevent them from acquiring or transmitting HIV will be incentive for them to come in for frequent STI screening, thereby leading to a mitigation of the spread of STI because of earlier diagnosis and partner notification. In this optimistic scenario, the synergism between the two epidemics could hopefully lead to fewer new STI and HIV infections, but in the short run, there will be substantial need for ongoing research, as well as professional and community education, in order to optimize the promising tools we currently can use.

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AUTHORS' CONTRIBUTIONS

KHM and HdV discussed the content and style of the paper. KHM drafted the paper, and HdV reviewed and edited the draft.

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VIEWPOINT

Transforming and integrating STI surveillance to enhance global advocacy and investment in STI control

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`Sexually transmitted infections (STI) exact an astounding yet preventable toll on the health and lives of men and women worldwide. The World Health Organization (WHO) estimated 376 million new curable STI occurred in 2016, including chlamydia (127 million), gonorrhoea (87 million), syphilis (6.3 million) and trichomoniasis (156 million) [1]. More than 500 million people were estimated to have genital infections with herpes simplex virus (HSV-1 or HSV-2) in 2012 [2]. Approximately 290 million women were estimated to have a human papillomavirus (HPV) infection in 2007 [3]. These infections have predictably serious complications for the men and women infected and their new-born infants. More than 500,000 incident cervical cancer cases, caused by HPV occurred in 2018, with a greater than 50% mortality rate [4]. For 2016, WHO estimated 988,000 pregnant women were infected with syphilis resulting in 660,000 congenital syphilis cases of which 350,000 were adverse birth outcomes including stillbirth and neonatal death [5]. Additional STIs such as viral hepatitis, *Mycoplasma genitalium* infection, and lymphogranuloma venereum add further weight to these estimates [6,7]. Newly emerging viral pathogens Ebola and Zika have gained prominent attention as they are each sexually transmitted. [8,9]

STI have been associated with increased HIV transmission [10,11]. Yet while remarkable progress has been made in reducing HIV transmission and improving lives of patients with anti-retroviral therapy (ART), STI incidence is high and increasing in many regions [1] (Figure 1). Although antiretroviral pre-exposure prophylaxis (PrEP) is associated with reduced HIV transmission, STI incidence tends to be high among PrEP patients, as well among persons living with HIV and other vulnerable populations [12-14]. The biological and behavioural links between HIV and STIs suggest opportunities for improving STI control and surveillance through existing HIV prevention, testing, and treatment services.

In 2016, three linked WHO strategies for HIV, hepatitis and STIs were endorsed by the World Health Assembly [6,7,15]. Each of these strategies called for integration across fields of surveillance and service delivery for these three infection groups.

The WHO strategy on STIs (2016 to 2021) identified four targets for 2030 [7].

- 90% reduction in *Treponema pallidum* incidence globally (based on the 2018 global baseline).
- 90% reduction in *Neisseria gonorrhoeae* incidence globally (based on the 2018 global baseline).
- ≤50 cases of congenital syphilis per 100,000 live births in 80% of countries
- Sustain 90% national coverage and at least 80% in every district (or equivalent administrative unit) in countries with the human papillomavirus vaccine in their national immunization programme.

Robust national-level strategic information systems that incorporate STI case reporting, prevalence surveys, assessment of the aetiology of STI syndromes, and monitoring for

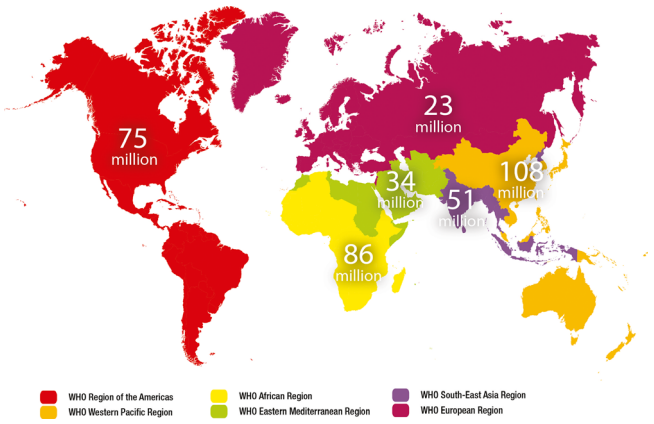

Figure 1. Estimated new cases of curable sexually transmitted infections (gonorrhoea, chlamydia, syphilis and trichomoniasis) by WHO region, 2016 [1].

Box 1. WHO National and Global Sexually Transmitted Infection Surveillance Priorities for Action [7]

Priority actions for countries

- **Strengthen and integrate sexually transmitted infection surveillance into the national health information system** as a part of health system strengthening, using standardized indicators and methodologies *as guided by WHO; ensure that data collection methods yield high-quality information, meet ethical standards, and do not pose risks for communities or the health care workers involved.*
- **Increase the "granularity" of data** including through: enhanced sexually transmitted infection-related disaggregated data collection based on different stratifiers that include age, sex, population and location; *involve affected communities and specific populations to achieve high-quality data and analysis.*
- **Identify specific populations** who are most at risk for sexually transmitted infections and places where most of the transmission is occurring; *establish mechanisms to promote the participation of affected communities;* conduct routine case reporting and periodic prevalence assessments of core sexually transmitted infections to assess the magnitude of the sexually transmitted infection problem in target populations, including by disaggregating the data; *describe the sexually transmitted infection epidemics and measure the impact in terms of sequelae and cost.*
- **Include data on the risk factors and determinants of sexually transmitted infections** in order to understand and address these determinants. *Include a focus on pre-exposure prophylaxis as appropriate. Use both standard and innovative participatory survey methodologies to develop accurate estimates of key population sizes and detailed understandings of subnational epidemics; integrate biological surveillance with other programmes, such as a behavioural surveillance survey in the HIV files – include contact tracing and treatment of partners.*
- **Strengthen national laboratory capacity** through quality assurance and the introduction of point-of-care diagnostics to ensure routine monitoring of sexually transmitted infections and antimicrobial resistance to *Neisseria gonorrhoeae.*

Priority actions for WHO

- **Provide global leadership and assistance to countries** in strengthening sexually transmitted infection surveillance and in using standard methodologies for such surveillance and estimation of the burden and impact; support the development of strategic information systems and sexually transmitted infection epidemics and response mapping, including the analysis of disaggregated data for monitoring inequities; support countries in strengthening case reporting, prevalence assessment, aetiologic assessment and antimicrobial resistance monitoring; strengthen global systems for collecting and sharing national surveillance data on sexually transmitted infections, including disaggregated data and analysis for monitoring equity.
- **Provide guidance on the collection and analysis of disaggregated data** based on different stratifiers and the involvement of affected communities and specific populations, including key populations for HIV, in efforts to obtain high-quality data and achieve high-quality analysis; use internationally endorsed methods for estimating the sizes of key populations for HIV and on setting programme targets for services for key populations for HIV.
- **Ensure linkages** of some components of sexually transmitted infection surveillance to existing mechanisms including HIV and antimicrobial resistance surveillance.

antimicrobial resistance to gonorrhoea are needed to guide programming and clinical service delivery [7,16] (Box 1). As reported in this issue by Wi et al., most countries lack the basic capacity to diagnose and treat STIs let alone implement surveillance [17]. Yet potential stakeholders must first recognize the prevalence and impact of these infections from reliable surveillance data. A vicious cycle of limited STI surveillance and narrow STI program response continues in most resource limited settings. Countries need strong strategic information systems that incorporate STIs to inform and help target prevention and treatment efforts, to rally political commitment, and build a strong national investment case. It is essential for countries to know their STI epidemics and to know the recommended responses in order that up to date, accurate information can guide national programming.

WHO has developed frameworks, targets and priority actions for STI surveillance at national and global levels [7,16,18] (Box 1). Global strategic information systems like the UNAIDS Global AIDS Monitoring system (GAM) [19] have helped to align national-level reporting of key STI indicators related to syphilis and gonorrhoea alongside those of HIV, but reported data are incomplete and many countries are challenged to collect verifiable data. WHO has supported the development of freely available modelling tools such as Spectrum STI [20] and the WHO congenital syphilis estimation tool [21] to allow the use of country-reported data to conduct national-level analysis of incidence and prevalence trends. WHO conducts global surveillance for antimicrobial resistance in gonorrhoea, which captures proportions of resistant organisms from nearly 60 countries [22].

High-income and low-middle income countries with STI surveillance systems frequently rely on case reporting of STI cases or STI syndromes to estimate national incidence [23-26]. Case reporting drastically underestimates the burden of STIs due to the asymptomatic nature of infection, limited access to care for those with symptoms, and limited provider reporting [18]. For these reasons, case reporting alone would not be a reliable measure of national STI burden. National, regional and global incidence and prevalence

can be derived from longitudinal STI prevalence surveys using standard methods [18]. STI prevalence surveys among general and high-risk population groups of men and women can be conducted as part of population-based health surveys such as those done for HIV, or in association with other health surveys or health services such as HIV screening and prevention (PrEP), maternal, reproductive, adolescent and child health services and military, work-related or school-based health screening. As STIs are not equally distributed among sexually active populations and a disproportionally higher burden of the STI/HIV epidemic occurs among certain key population sub-groups, such as men who have sex with men and sex workers, specialized surveillance and culturally tailored programmes to address STIs among these populations are warranted. Routine STI prevalence assessments can identify key populations that can benefit from the implementation of effective STI interventions and further provide evidence of their impact. Global, regional and national estimates of STIs suffer from limited prevalence surveys among general populations, particularly among men [1].

It is evident from recent global and regional estimates of STIs that the necessary stakeholder support, advocacy and investment – both national and international – to support STI programme and surveillance efforts has not been realized. While the burden of prevalent and incident STI cases increases, advocacy for control of these infections has waned. Transforming and strengthening STI surveillance and clinical services can serve as a cornerstone for advocacy and investment in STI prevention and control. Alignment of STI control programmes alongside HIV and hepatitis prevention through linked WHO strategies has offered frameworks for integration yet clinical services and surveillance of STIs continue to lag behind [27].

As part of a transformation process taking place at WHO, set in motion by the Director General in 2018, the global STI surveillance and STI programme support activities will be moved from the WHO Department of Reproductive Health and Research (WHO RHR) to the Department of HIV and Hepatitis, to be duly renamed the WHO Department of HIV, Hepatitis and STIs. STI research will remain with (WHO RHR) ensuring that research continues to inform STI programming. The move of the STI programme will set an example at the global level of the opportunity to integrate these surveillance and country support activities recognizing similar modes of transmission, populations at risk and currently existing health care platforms. This transition is expected to herald a renewed global focus on the importance of STIs as indicators of HIV and hepatitis risk and as opportunities for prevention and control of all STIs while ensuring continued inclusion within the broader framework of sexual and reproductive health and rights [28].

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MT and TW conceived of the paper and provided content and references. MT drafted the paper. MT and TW reviewed and revised drafts prior to submission

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REVIEW

Diagnosing sexually transmitted infections in resource-constrained settings: challenges and ways forward

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Abstract

Introduction: Sexually transmitted infections (STIs) remain prevalent and are increasing in several populations. Appropriate STI diagnosis is crucial to prevent the transmission and sequelae of untreated infection. We reviewed the diagnostic accuracy of syndromic case management and existing point-of-care tests (POCTs), including those in the pipeline, to diagnose STIs in resource-constrained settings.

Methods: We prioritized updating the systematic review and meta-analysis of the diagnostic accuracy of vaginal discharge from 2001 to 2015 to include studies until 2018. We calculated the absolute effects of different vaginal flowcharts and the diagnostic performance of POCTs on important outcomes. We searched the peer-reviewed literature for previously conducted systematic reviews and articles from 1990 to 2018 on the diagnostic accuracy of syndromic management of vaginal and urethral discharge, genital ulcer and anorectal infections. We conducted literature reviews from 2000 to 2018 on the existing POCTs and those in the pipeline.

Results and discussions: The diagnostic accuracy of urethral discharge and genital ulcer disease syndromes is relatively adequate. Asymptomatic *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infections limit the use of vaginal discharge and anorectal syndromes. The pooled diagnostic accuracy of vaginal syndromic case management for CT/NG is low, resulting in high numbers of overtreatment and missed treatment. The absolute effect of POCTs was reduced overtreatment and missed treatment. Findings of the reviews on syndromic case management underscored the need for low-cost and accurate POCTs for the identification, first, of CT/NG, and, second, of *Mycoplasma genitalium* (MG) and *Trichomonas vaginalis* (TV) and NG and MG resistance/susceptibility testing. Near-patient POCT molecular assays for CT/NG/TV are commercially available. The prices of these POCTs remain the barrier for uptake in resource-constrained settings. This is driving the development of lower cost solutions.

Conclusions: The WHO syndromic case management guidelines should be updated to raise the quality of STI management through the integration of laboratory tests. STI screening strategies are needed to address asymptomatic STIs. POCTs that are accurate, rapid, simple and affordable are urgently needed in resource-constrained settings to support the uptake of aetiological diagnosis and treatment.

Keywords: STD/STI; point of care; diagnostics; key and vulnerable populations; treatment

Additional Supporting Information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

Sexually transmitted infections (STIs) remain prevalent and a major burden of morbidity and mortality globally [1], impacting on quality of life, reproductive and child health, and national and individual economies. STIs also facilitate the sexual transmission of human immunodeficiency virus (HIV) [2-4]. WHO reported an estimated 376 million infections of the four most common curable STIs (chlamydia, gonorrhoea, trichomoniasis and syphilis) occurred in 2016 [5].

The global STI strategy, endorsed by the World Health Assembly in 2016 aims to end STIs as a public health threat by 2030 [6].

Thus, appropriate STI diagnosis and treatment is crucial to prevent the transmission and sequelae of untreated infection [6-8]. In resource-constrained settings, aetiological diagnosis of STIs remains difficult due to limited access to laboratory diagnostics to guide appropriate treatment [8]. Where facilities are available, tests results for people with suspected STIs take days or even weeks,

making immediate treatment based on laboratory results unfeasible [8,9].

To overcome limited access to aetiological diagnosis and treatment, syndromic case management was introduced by the World Health Organization (WHO) in 1984 and continues to be used as the standard of care by many countries, especially resource-constrained ones [10]. Syndromic management is based on the identification of consistent groups of symptoms and easily recognized signs (syndromes), and treatment that will deal with most, or the most serious, organisms responsible for producing the syndrome [11].

Syndromic management has been successful in reducing the prevalence of STIs over the years, such as chancroid and the incidence of male urethritis [12-14], but it has now reached its limits for several reasons. Most women with vaginal discharge do not have *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (NG) [15,16]. Additionally, the cause of genital ulcer disease (GUD) syndrome has become less by chancroid or syphilis and more by herpes simplex virus (HSV) [14,17]. With the advent of molecular tests, it has become evident that many more infections exist asymptomatically in both men and women [18,19] and that the diagnostic accuracy of STI syndromes is low [15,16]. In addition, the increasing rates of antimicrobial resistance (AMR) in NG and *Mycoplasma genitalium* (MG) with limited treatment options make it imperative that treatments are based on aetiological diagnosis [20,21].

Point-of-care tests (POCTs) in accordance with the ASSURED criteria (affordable, sensitive, specific, user-friendly, robust/rapid, equipment free and delivered to end users) are essential to address these challenges [22]. While some POCTs exist, implementation barriers at the levels of device, patient, provider and health system make them unavailable in most resource-constrained settings [23].

This paper reviews the diagnostic accuracy of syndromic case management, and the existing POCTs and those in the pipeline to detect STIs that could potentially be used in resource-constrained settings.

2 | METHODS

Because of the challenges in diagnosing STIs in women, we prioritized updating the systematic review of studies from January 2001 to March 2015 and the meta-analysis of the diagnostic accuracy of vaginal discharge by Zemouri et al. [24]. We updated the search from January 2015 to September 2018 in OVID Medline and CENTRAL, and in EMBASE using the two strategies provided in Zemouri (2016). Studies that evaluated the diagnostic accuracy and validation of vaginal discharge flowchart compared to any laboratory diagnostic test were included. The search strategy and results are detailed in Supporting Information. In this review, all flowcharts (the index tests) had the entry point of women complaining of vaginal discharge followed by history taking, including risk assessment and genital inspection to verify the presence of vaginal discharge. Flowcharts were categorized as follows: flowchart 1 = history and risk assessment; flowchart 2 = history, risk assessment and speculum examination; flowchart 3 = history, risk assessment, speculum examination, and vaginal discharge samples for Gram staining and wet-mount microscopy to diagnose the presence of budding yeast or psuedohyphae for *Candida albicans*, motile trichomonads for *Trichomonas vaginalis* (TV) and Amsel criteria for diagnosis of bacterial vaginosis (BV); and flowchart 4 = country-adapted flowcharts with country-specific risk factors or those not defined by the study methods. Four additional studies were added to the meta-analysis [25-28]. We conducted a meta-analysis by pooling of samples from all studies within different types of flowcharts. We calculated the pooled sensitivity and specificity for the different type of the flowcharts using the WINPEPI software (version 11.65, August 2016). If the study had presented the results separately for NG, CT, TV and BV, the study with the higher PPV was included in the meta-analyses so as not to over represent any study.

Based on the diagnostic accuracy for CT/NG of different vaginal discharge flowcharts, we calculated absolute effects on important outcomes – true positive, false positive (resulting in overtreatment), true negative and false negative (resulting in incorrect or missed treatment) in different CT/NG prevalence settings (5%, 15%, 30%). We then calculated the absolute effects on the important outcomes in different CT/NG prevalence settings using rapid diagnostic tests (RDTs) with sensitivities of 60%, 70% and 80%, and specificity of 90%, to represent the ranges of sensitivity and the lowest acceptable specificity of the RDTs detailed in Table 5, and using a molecular assay with a sensitivity of 95% and specificity of 98%, that is, Xpert CT/NG on GeneXpert system [29,30].

We searched the peer-reviewed literature for previous systematic reviews, randomized controlled trials and non-randomized studies from 2000 to 2018 on the diagnostic accuracy of syndromic management for vaginal and urethral discharge, genital ulcer and anorectal infections. We selected studies from searches of the PubMed and Medline databases. We chose articles that appropriately addressed the key issues and we did not apply eligibility criteria to include or exclude articles.

We conducted literature reviews on existing POCTs and those in the pipeline, on patient and healthcare provider (HCP) values and preferences, and on the costs and cost-effectiveness of POCTs for STIs. We searched PubMed and Medline databases from 2000 to 2018. We used the search terms point of care, POC, POCT, rapid test, laboratory tests, laboratory diagnosis, aetiologic diagnosis and sexually transmitted infections/diseases. We searched reviews, editorials and systematic reviews for additional publications.

3 | RESULTS

3.1 | Syndromic case management

Syndromic management for urethral discharge in men had sensitivities ranging from 84% to 95%. Treatment based on this syndrome is simple, inexpensive and cost-effective [31-34]. Apart from CT/NG, aetiologies include MG and TV [35-37].

Genital HSV infection is the predominant cause of GUD that affects the outcome of syndromic management of GUD [14,17,38-40]. In studies evaluating the GUD flowchart, only two in India made a distinction based on the appearance of the ulcer [39,41,42]. Studies revealed the moderate sensitivity and low specificity of clinically differentiating herpetic (sensitivity, 74%; specificity, 33%) and non-herpetic (sensitivity, 51%; specificity, 56%) [39,41,42].

The WHO simplified generic tool includes flowcharts for women with symptoms of vaginal discharge and/or lower abdominal pain. While the flowcharts for abdominal pain are relatively satisfactory [31], those for vaginal discharge have severe limitations. Systematic reviews and meta-analyses of the syndromic approach to diagnose and treat cervical infections (CT/NG) revealed low accuracy, resulting in a high proportion of overtreatment, incorrect treatment and missed treatment [24,31,43,44]. In settings of low STI prevalence, endogenous vaginitis and BV, rather than CT/NG/MG, are the main causes of abnormal vaginal discharge [24,31,43,44]. Attempts to increase the sensitivity and specificity of the vaginal discharge flowchart for the diagnosis of cervical infection using situation-specific risk assessment have not been successful [45,46].

A review by Sloan et al. also revealed that syndromic management had low diagnostic accuracy for screening and case-finding of CT/NG in women [43].

Based on our update of the systematic review and meta-analysis by Zemouri et al. [24], the pooled sensitivity and specificity of the various flowcharts to diagnose vaginal infection (TV and BV) are summarized in Table 1.

The pooled sensitivity and specificity of the various flowcharts to diagnose cervical infection due to CT/NG are summarized in Table 2.

The absolute effect of different prevalence using the pooled sensitivities and specificities of the different vaginal discharge flowcharts reveal that the low diagnostic accuracy of vaginal syndromic case management results in high numbers of false positives (lower specificity), leading to overtreatment, and high numbers of false negatives (lower sensitivity), resulting in incorrect and missed treatment (Table 3). The absolute effects on outcomes in settings with different CT/NG prevalence using RDTs with sensitivities of 60%, 70%, 80% and a specificity of 90%, and with POCT molecular assay (sensitivity of 95% and specificity of 98%), reveal fewer false positives and false negatives and more true positives compared with syndromic case management (Table 4).

The flowchart for syndromic management of anorectal infections intends to treat CT/NG rather than being solely based on symptoms and signs [47,48]. This is similar to treating cervical infection (CT/NG) in the vaginal discharge flowchart. The limitations are thus similar with rectal infections, where the majority are asymptomatic [19,49]. In a small study in Kenya, one in five men with an anorectal CT/NG reported rectal pain [50]; in Côte d'Ivoire, more than half of the men in the study reported anorectal symptoms in the past 12 months [51]; in Germany, 12% of 2247 men who have sex with men (MSM) had anorectal CT/NG, and only 12% of these had local symptoms, and 91% of both rectal and pharyngeal CT/NG would have been missed if only symptomatic men had been tested [52].

Unprotected anal sex is the entry point to the flowchart for anorectal infections. While it is recommended that carefully worded questions can be used to elicit anal sex in sub-Saharan Africa [53], it is unlikely that many MSM will respond appropriately, especially where homosexuality is illegal [54]. A substantial proportion of potential patients is thereby excluded from the flowchart.

3.2 | Aetiological diagnosis of STIs

Nucleic acid amplification tests (NAATs) are the gold standard for the diagnosis of STIs in high-income settings, and most have a sensitivity and specificity ranging from 95% to 99% [6].

Table 1. Pooled sensitivity and specificity of different syndromic flowcharts to diagnose vaginal infections (*Trichomonas vaginalis* and bacterial vaginosis) [24]

Flowchart	Number of studies	Sensitivity, % (95% CI)	Specificity, % (95% CI)
1 (Risk assessment)	9	56.2 (54.5 to 57.9)	71.0 (69.4 to 72.6)
2 (+ speculum examination)	8	74.8 (74.0 to 75.6)	53.2 (52.5 to 54.0)
3 (+ Lab (WM, GS))	2	91.7 (89.2 to 94.2)	100 (99.9 to 100)
4 (Local adaptation)	5	53.1 (50.5 to 55.6)	85.8 (84.7 to 86.9)

Update of the systematic review and meta-analysis by Zemouri et al. [24]. CI, confidence interval; GS, Gram-stained microscopy; WM, wet-mount microscopy.

Table 2. Pooled sensitivity and specificity of different syndromic flowcharts to diagnose *Chlamydia trachomatis* and *Neisseria gonorrhoeae* [24]

Flowchart	Number of studies	Sensitivity, % (95% CI)	Specificity, % (95% CI)
1 (Risk assessment)	7	27.9 (24.7 to 31.1)	57.0 (56.1 to 58.0)
2 (+ speculum examination)	9	44.9 (42.2 to 47.7)	74.2 (73.3 to 75.1)
3 (+ Lab (WM, GS))	3	90.1 (85.8 to 94.4)	35.3 (33.4 to 37.1)
4 (Local adaptation)	7	83.92 (80.9 to 87.0)	45.3 (43.9 to 47.9)

Update of the systematic review and meta-analysis by Zemouri et al. [24]. CI, confidence interval; GS, Gram-stained microscopy; WM, wet-mount microscopy.

Table 3. Absolute effects on outcomes using the diagnostic accuracy of different vaginal syndromic flowcharts to diagnose *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in settings with different prevalence

Cervical infections				Prevalence (per 1000)		
Sensitivity	**Specificity**	**Flowchart**	**Outcomes**	**50**	**150**	**300**
0.28	0.57	Flowchart 1	TP	14	42	84
			FN – missed treatment	36	108	216
			TN	542	485	399
			FP – overtreatment	409	366	301
0.45	0.74	Flowchart 2	TP	22	67	135
			FN – missed treatment	28	83	165
			TN	705	631	519
			FP – overtreatment	245	219	181
0.90	0.35	Flowchart 3	TP	45	135	270
			FN – missed treatment	5	15	30
			TN	335	300	247
			FP – overtreatment	615	550	453
0.84	0.45	Flowchart 4	TP	42	126	252
			FN – missed treatment	8	24	48
			TN	430	385	317
			FP – overtreatment	520	465	383

FP, false positive; FN, false negative; TN, true negative; TP, true positive.

Table 4. Absolute effects on outcomes using the diagnostic accuracy of rapid diagnostic tests and molecular point-of-care tests to diagnose *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in settings with different prevalence

Cervical Infections				Prevalence (per 1000)		
Sensitivity	**Specificity**	**Test**	**Outcome**	**50**	**150**	**300**
0.6	0.9	RDT 1	TP	30	90	180
			FN – missed treatment	20	60	120
			TN	855	765	630
			FP – overtreatment	95	85	70
0.7	0.9	RDT 2	TP	35	105	210
			FN – missed treatment	15	45	90
			TN	855	765	630
			FP – overtreatment	95	85	70
0.8	0.9	RDT 3	TP	40	120	240
			FN – missed treatment	10	30	60
			TN	855	765	630
			FP – over overtreatment	95	85	70
0. 95	0.98	Molecular POCT assay	TP	47	142	285
			FN – missed treatment	3	8	15
			TN	931	833	686
			FP – overtreatment	19	17	14

FP, false positive; FN, false negative; POCT, point-of-care test; RDT, rapid diagnostic test; TN, true negative; TP, true positive.

Several laboratory tests and procedures for specific STIs are elaborated in a WHO manual [55]. Most of the recommended highly sensitive and specific NAATs require resources, training, laboratory infrastructure, longer time for results, and are expensive, thus making them inaccessible for many resource-constrained settings [23].

3.3 | Point-of-care tests for common STIs

3.3.1 | *Syphilis*

Syphilis prevalence is increasing in many countries [56-58]. Untreated syphilis in pregnant women is a major cause of

foetal death and congenital infection [59]. WHO recommends syphilis screening for pregnant women, MSM and sex workers, and RDTs have increased screening uptake [48,60].

There are several syphilis RDTs – rapid POCTs, that is – for screening (e.g. Determine, SD Syphilis 3.0, Syphicheck, Syphilis Rapid Test and Visitect). Most of these tests use whole blood, plasma or serum and can be performed between five and thirty minutes. Based on a meta-analysis by Jafari et al., sensitivity ranges from 75% to 99% and specificity from 92% to 99% compared with *Treponema pallidum* haemagglutination (TPHA) and *Treponema pallidum* particle agglutination tests [61].

The main challenge with most syphilis RDTs, detecting only "specific" treponemal (TP) antibodies, is the inability to differentiate active from previously treated infection. To reduce overtreatment, especially in high-prevalence populations (>5%), an initial RDT is performed and, if positive, this is followed by a rapid plasma reagin (RPR) test, which detects non-TP antibodies, indicating an active infection. If the RPR test is reactive, treatment for syphilis is provided [60,62]. However, the uptake of the sequential RPR test is unknown in many resource-constrained settings. To overcome the challenges with using RPR as a sequential test, a combination RDT screen-and-confirm assay has been developed to detect both TP and non-TP antibodies. A meta-analysis by Marks et al. showed that the sensitivity was higher in patients with higher RPR titre (≥1:16) for both the TP (98.2% vs. 90.1%, $p < 0.0001$) and the non-TP component (98.2% vs. 80.6%, $p < 0.0001$). Overall agreement with TPHA was 85.2% (84.4% to 86.1%). Agreement was highest for high-titre active infection, and lowest for past infection [62].

HIV testing has been scaled up in most countries, while syphilis screening lags behind. Implementing a combination test of HIV and syphilis will increase syphilis screening coverage, contributing to eliminating mother-to-child transmission of HIV and syphilis [59]. A review by Gliddon et al. [63] showed that the diagnostic accuracy of the HIV component of the dual test ranged from 94% to 99% sensitivity and from 92% to 100% specificity. The syphilis diagnostic accuracy ranged from 47% to 96% sensitivity and 90% to 100% specificity. The lowest sensitivity reflected the low diagnostic performance of the test using whole blood. Sensitivity was higher for patients with non-treponemal titres of >1:4, indicating that the syphilis test is more likely to detect active, transmissible infections versus old treated infection. The dual RDT was more cost effective than single RDTs and prevented more adverse outcomes of pregnancy. Qualitative data indicated that dual tests were acceptable in terms of turnaround time, cost and a single finger prick [63].

3.3.2 | Chlamydia trachomatis *and* Neisseria gonorrhoeae

CT infection remains the most prevalent bacterial STI [5] and is often asymptomatic [64,65]. About 10% to 40% of patients are co-infected with NG [37,65-68]. Appropriate laboratory diagnostic tests are essential to screen for asymptomatic CT. Gonorrhoea is the second most prevalent reported bacterial STI [5] and usually asymptomatic in women [16,18]. Because of an increase in NG AMR to the currently recommended treatment for gonorrhoea, laboratory diagnosis is essential [20,21]. If CT/NG infections remain untreated, they can result in infertility, adverse outcomes of pregnancy, newborn infections and increased risk of HIV transmission [6,69].

CT antigen detection POCTs are available. As described in a recent systematic review by Kelly et al. [70], these lateral flow assays (LFA)/immunochromatographic tests (ICT) include ACON chlamydia, aQcare Chlamydia TRF kit, BioRapid Chlamydia Ag test, Chlamydia Rapid Test SAS, Clearview Chlamydia, and QuickVue. The specificity of these rapid POCTs was high across all specimen types (97% to 100%); however, the sensitivities were low (37% for vaginal swabs, 53% for endocervical swabs and 63% for urine). The new aQcare Chlamydia TRF kit, a fluorescent nanoparticle-based LFA, was the best performing POCT, with sensitivities and specificities comparable to POCT NAATs [70].

There have been fewer POCTs developed for gonorrhoea, and many have been validated only by the manufacturer and are not currently commercially available. The diagnostic sensitivities of these tests are generally lower than of the CT LFAs/ICTs (Table 5).

The performance of some NG POCTs was evaluated only against culture, and not the more accurate NAATs (gold-standard test), and only symptomatic patients were included in the evaluation. No gonorrhoea POCT has been evaluated for extragenital sites. Rapid POCTs (LFAs, ICTs and OIAs) take five to seven steps, but have turnaround times of only 25 to 40 minutes, making them suitable for primary care settings [75].

The near-patient Xpert CT/NG (real-time NAAT) on the GeneXpert instruments is approved by the United States Food and Drug Administration (FDA). The diagnostic accuracy from self-collected vaginal swabs, cervical swabs and urine range from 95% to 98%, with specificities ranging from 99.4% to 99.9%. The sensitivity and specificity of this assay for rectal swabs are 86.0% and 99.2% respectively [30,76].

The Xpert CT/NG takes three steps and 90 minutes, and requires equipment (GeneXpert), steady electricity, calibration, a temperature-controlled environment [73]. Several studies have shown that this can be used in settings with basic laboratory infrastructure. The utility of GeneXpert has been evaluated in remote populations such as an aboriginal community in Australia [77]; in routine antenatal care in Papua New Guinea (with STI rates by GeneXpert of CT 20%, NG 11.2% and TV 37.6%) [78]; in HIV-infected pregnant women in South Africa (40.2% with STIs) [79]. Another utility study in South Africa in HIV-negative women presenting for STI care or with symptoms (CT 18.4%, NG 5.2%, TV 3%) resulted in STI testing of symptomatic and asymptomatic women and the same-day treatment, with expedited partner treatment and reduced reinfection after six months [80]. A study in Rwanda has shown that integrating POCTs for BV, TV (OSOM) and CT/NG (GeneXpert) in women with urogenital symptoms and increased risk of STIs has improved diagnostic accuracy, with moderate sensitivity and high specificity for CT/NG/TV compared with using syndromic management, and has remarkably reduced overtreatment [81].

Several platforms and assays are being developed to be more portable, easier to operate, used at the point of care and giving rapid turnaround times for results, with accuracy similar to that of laboratory-based NAATs, such as the GeneXpert Omni, Alere – i platform, RT CPA CT Test, Atlas Genetics

Table 5. Rapid point-of-care tests for diagnosis of *Neisseria gonorrhoeae*

Test Name	Manufacturer	Commercially available	Sensitivity (%)	Specificity (%)	Reference Test	Sample type
ACON CT/NG Duo [71]	ACON	No	12.5	99.8	NAAT (Roche Cobas)	Endocervical swab
ACON NG [71]	ACON	No	Not quantified	97.2	NAAT (Roche Cobas)	Endocervical swab
BioStar Optical ImmunoAssay [72]	Thermo Biostar	No	100[a]	93	NAAT (Hologic Aptima)	Urine (males)
			30 to 60	60 to 90	Culture	Endocervical swab
GC-Check [73]	PATH	No	70	97.2	NAAT (Roche Amplicor)	Endocervical swab
			54.1	98.2	NAAT (Roche Amplicor)	Vaginal swab
OneStep Gonorrhea RapidCard Insta Test [74]	Cortez Diagnostics	No	64 to 94	67 to 97	Culture	Endocervical swab
			61 to 91	67 to 97	Culture	Urethral swab (male)
GC RapidResponse	BTNX	Yes	64 to 94	67 to 97	Culture	Endocervical swab
			61 to 91	67 to 97	Culture	Urethral swab (male)
GC One-step test	Novamed	Yes	68 to 98	68 to 98	Culture	Vaginal swab/Urethral swab (male)

NAAT, nucleic acid amplification test.
[a]Very limited evaluation, including only five *N. gonorrhoeae*-positive clinical specimens from males with symptomatic urethritis.

io Platform [82] and the Truelab Real Time micro PCR system [76,83,84].

POCTs that are inexpensive, rapid and fulfil the ASSURED criteria are under development. These molecular assays include: the microwave-accelerated metal-enhanced fluorescence test, which needs to be simplified and standardized for basic laboratories [84]; a low-cost NAAT called MobiNAAT, which uses a portable device where results are analysed in an automated smartphone diagnostic [83,84]; a POCT paper-fluidic platform to diagnose gonorrhoea that is a highly sensitive molecular assay with visual lateral flow detection and an 80-minute run time [86]; and a rapid multiplex microfluidic CT PCR-based POCT comparable to laboratory-based NAATs [87,88]. A 15-minute run-time recombinase polymerase amplification-based prototype POCT (TwistDx) for CT/NG has been reported to be comparable to laboratory-based NAAT [89]. Improvement of the sensitivity of some LFAs for CT has been described [90].

Some companies are working on antigen- or protein-based detection of AMR in NG (i.e. LFA-type tests). However, this is very early work, and development and commercial pathways are unclear, as are timelines. There are several well-characterized molecular AMR determinants that can be used for effective prediction of AMR in NG, particularly for ciprofloxacin, but less adequate prediction of resistance to azithromycin, cefixime and ceftriaxone [91,92].

3.3.3 | *Trichomonas vaginalis*

TV is the most prevalent curable STI globally and is a major cause of vaginal discharge as well as recurrent urethral discharge in men [5,16,24,36,37]. Wet-mount microscopy is the most common method of diagnosing TV, because it is cheap and rapid but with a sensitivity from 44% to 68% [93]. TV culture (e.g. InPouch TV) has a sensitivity ranging from 44% to 75% for women [93]. Gaydos et al. conducted a systematic review of TV diagnostic tests [94]. Based on this review, the rapid POCT OSOM lateral flow test has a sensitivity ranging from 83% to 86%. The AmpliVue and Solana tests are near-patient NAATs, requiring a small piece of equipment, with a sensitivity of 90.7% for AmpliVue, and 98.6% for Solana test for vaginal swabs and 100% for urine specimens. In addition, the near-patient Xpert TV assay on GeneXpert is now available with around 96% sensitivity for vaginal swabs and 97% sensitivity for urine samples. These new molecular diagnostic assays have a high diagnostic accuracy with rapid turnaround times, and enable the detection of TV in urine in men [94].

3.3.4 | *Healthcare provider perception of point-of-care tests*

Qualitative studies conducted by Hsieh et al. [95] to assess the requirements placed on HCPs by POCTs revealed that an ideal POCT should be like a pregnancy test that can be purchased over the counter for home use. It should be simple to use and interpret and take around 20 minutes to run and release the result. Moreover, the turnaround time should coincide with the time spent for the patient–client interaction. Most HCPs indicate that the accuracy of the test should be the same as that of a laboratory-based NAAT [95].

HCPs have expressed confidence in the POCT NAAT results, and treating patients on this basis [96]. They mentioned that POCTs provide an opportunity for targeted patient treatment, immediate partner notification and reduced follow-up effort [95]. However, the main barriers indicated were the long waiting time, the time consumed in the documentation process, sample collection, inadequate training and the limited availability of POCTs due to a high unit cost per test [95-97].

4 | DISCUSSION

The provision of effective services to symptomatic and ideally also asymptomatic STI patients and their partners should be

among the top priorities of an STI control programme. Symptomatic STI patients may be aware that they are infected and are more likely to seek care. Thus, syndromic management provides an entry point for STI management and control. However, there are clearly limitations to the syndromic approach for the management of STIs, the likely impact on the control of STIs and the link with AMR [4,9,80].

While urethral discharge has relatively adequate diagnostic accuracy, treatment has been limited to CT/NG. It is also critical to address asymptomatic CT/NG and to assess the aetiologies of persistent urethral discharge, including MG and TV, as well as the treatment failures due to AMR in NG and MG.

Previous syndromic management has not considered MG as an important aetiological agent of urethral and vaginal discharge and pelvic inflammatory disease (PID). MG frequently causes non-gonococcal urethritis (NGU) and non-chlamydial-NGU in men and is associated with vaginal discharge and PID in women [98-100]. The high-level of AMR in MG and the lack of effective first-line treatment [21] further complicate the inclusion of MG in syndromic management flowcharts.

Most NG, and especially CT and MG, cervical infections in women are subclinical or asymptomatic so there would be no syndromic presentation [15,18,24,31,43]. The syndromic approach has never been intended as a tool for case finding or for screening asymptomatic patients [43] and, predictably, this misuse of the approach has led to disappointments.

Based on the available evidence, vaginal discharge syndrome has adequate diagnostic accuracy to detect vaginal infections (TV and BV) (Table 1), but has very poor diagnostic accuracy for cervical infection (CT/NG) (Table 2). The absolute effect for diagnosing cervical infections (Table 3) is a high number of false-positive CT/NG cases, resulting in a higher number of individuals being overtreated with extended-spectrum cephalosporins and azithromycin/doxycycline. This can lead to adverse reactions, can facilitate AMR and can create the social and individual effects of falsely being diagnosed with an STI. There is also a high rate of false negatives, resulting in missed treatment, which can facilitate further transmission and severe complications and/or sequelae. On the other hand, RDTs and POCTs (Table 4) can reduce overtreatment and missed treatment by adapting antibiotic prescriptions according to test results, and can facilitate partner notification [80].

Patients with vaginal and urethral discharge syndromes are mostly seen in primary care settings, which do not have accessible diagnostics to confirm either CT/NG/MG/TV. Although one FDA-approved near-patient (POCT) molecular assay (Xpert CT/NG) is available to distinguish between CT and NG, the cost and other limitations [75,101] remain prohibitive for use in primary care.

The severity of symptoms associated with various STI pathogens and the anatomical sites infected greatly influence treatment-seeking behaviour [102,103]. Men with NG are frequently symptomatic [32-34] whereas women with CT, NG and MG are frequently asymptomatic [15,18,24]. Many syphilis cases occur without symptoms [59], as do many anal CT/NG infections [48,49]. Different interventions are thus necessary. Prompt access to effective services for symptomatic infections remains an important approach (syndromic management and integration of POCT), while screening and treatment for syphilis and chlamydial infection, and screening of high-risk populations for CT/NG, are needed.

AMR to the first-line NG treatment regimen of ceftriaxone plus azithromycin, and AMR in MG to azithromycin (first-line) and moxifloxacin (second-line), has now been reported [20,21,99,100]. Because of the low diagnostic accuracy of the syndromic approach to diagnose CT/NG, there is significant overuse of these therapies, which could contribute to AMR emergence. A diagnostic-based antibiotic stewardship strategy is urgently needed. A near-term solution requires a rapid, easy-to-use, low-cost assay to distinguish between CT, NG and MG. Additionally, a rapid, easy-to-use, low-cost assay to determine susceptibility to currently available antibiotics in confirmed NG and possibly MG-positive infections is needed. A longer-term solution will be to incorporate these tests into one assay and to distinguish between multiple STIs as well as detect resistance/susceptibility.

This review highlights the need to integrate currently available laboratory-based diagnostics and POCTs within syndromic case management to decrease overtreatment and missed treatment as well as to contribute to the conservation of NG treatment. A recent study by Verwijs et al. [81] has shown that integrating POCT (CT, NG, TV) in women with urogenital symptoms and for screening resulted in the reduction of NG and CT by half, and of TV by 42% [81].

Laboratory diagnostics will also be essential for implementing STI screening strategies. The unit cost per test can be higher compared with treatment costs, which often remains the major concern of national programmes in investing in laboratory diagnosis. However, the cost savings obtained from the rapid delivery of results, reduction of patient follow-up, facility cost, decreased complications and onward transmission are often overlooked [104]. For example, based on modelling by Vickerman et al., a POCT with a 70% to 80% sensitivity, 95% specificity and a cost of about US$1-2 would be a cost-effective strategy for substantially reducing the impact in HIV transmission and the degree of inappropriate and missed treatment from using syndromic management to diagnose CT/NG in high prevalence settings [105]. The cost-effectiveness of multiplex POCTs (CT, NG, MG, TV) has been demonstrated in a separate modelling study [106].

A cost-effectiveness analysis has shown that a NG NAAT screening of women between 15 and 29 years of age can prevent 1247 cases of PID and save US$177 per patient compared with no screening, while using a potential POCT with about 75% sensitivity can prevent additional PID [107].

Supplementing the laboratory-based NAATs for CT/NG with POCTs NAAT could be cost-saving and patients could benefit from accurate diagnosis, and immediate and appropriate treatment. POCTs can reduce overtreatment and eliminate the need for presumptive treatment [108,109]. A promising CT POCT (with a sensitivity of 92.7%, with 47% of women willing to wait and a test cost of US$33) will likely be cost-effective compared with a traditional NAAT, which could save US$28 in total and avert more PID cases [110].

Modelling the impact of a rapid testing service showed that it could reduce the mean time to treatment notification from eight days to less than a day, and avert more CT/NG transmission. Additionally, there is an annual saving in the number of partner attendances [111].

POCT with AMR detection has shown that there is an additional cost for this POCT, but its use could reduce the cost from follow-up visits and could allow for the use of older and

cheaper drugs, such as ciprofloxacin and, more importantly, conserve the current last-resort options of ceftriaxone and azithromycin [112].

Test cost is a significant factor in the use of available NAATs and the development and utility of POCTs. Although cost-effective, the unit cost per test of a NAATs ranges from US$14 to US$30 per sample, which is often unaffordable in resource-constrained settings [101,113]. There are urgent needs to develop low-cost, simple and rapid POCTs for CT/NG/MG/TV with appropriate performance (accuracy and operational characteristics) to support uptake and widescale use in community settings. An acceptable diagnostic accuracy that will allow the development of more affordable POCTs than are currently available needs to be stipulated. Several compromises may have to be made with the ASSURED criteria [22]. For instance, a cheap assay that has a sensitivity of about 80% and a specificity of at least 90% (Table 4), similar to a syphilis RDT, could be widely used and very valuable if it is affordable and integrated within a vaginal discharge flowchart [114,115]. These potential RDTs/POCTs would be more widely used in primary care and resource-constrained settings and could possibly have a greater public health impact [101,109,114,115].

The potential use of molecular diagnostic assays in resource-constrained settings is driving the development of lower-cost solutions. Several new industry players have entered, or are entering the development space; however, these tests, previously mentioned [76,85-90], are mostly in the early stages of development – and it remains to be seen how these assays perform, and what the global access pricing strategies will be.

The development of POCTs will need to ensure access and uptake at the primary health care level. Self-sampling (e.g. urine, and high vaginal swabs) has shown to increase POCT use and is thus an important consideration in POCT development [116,117]. Self-testing and sampling have increased screening uptake, but innovative treatment services to avoid ineffective and inappropriate treatment should be explored [118-120]. POCT implementation should consider integration within the STI management pathways, including patient flow, immediate treatment, partner management and retesting [121], and the existing health systems [122].

5 | CONCLUSIONS

In the present review, the available evidence on the effectiveness and challenges of syndromic case management further underscores the need to scale up existing STI diagnostics and the development of POCTs for, first, the identification of CT/NG, but ideally also MG and TV, as well as NG and MG AMR in vaginal, urethral and anorectal discharge.

One of the biggest challenges in STI control is that most cases are asymptomatic or have unrecognized symptoms [6-9]. POCTs will increase the uptake of STI screening in vulnerable populations that are at highest risk and will have an impact on detection and treatment. [123-126].

Although near-patient NAAT for CT/NG/TV is commercially available, the cost and other limitations remain prohibitive for use, particularly but not exclusively in resource-constrained settings [9,20,101].

POCTs that are simple and affordable are essential in STI control and are urgently needed in resource-constrained settings. The development and implementation of POCTs will require innovative financing approaches and implementation strategies, and the strengthening of laboratory capacity. Although several POCTs for CT/NG are in the pipeline, the development of affordable POCTs will take several more years. Syndromic management of symptomatic STIs will remain essential in resource-constrained settings. At the interim, guidelines should be updated to improve the standard of care and to explore the utility of available POCTs and near-patient NAATs to improve STI diagnosis and screening. Laboratory and clinical validation studies and cost-effectiveness analyses of integrating POCTs into current syndromic case management, and of screening strategies, are urgently needed to inform guidelines and national policies.

The limitation of the syndromic approach, the availability of molecular assays and the ongoing development of POCTs call for global action to increase the access and affordability of the aetiologically based diagnosis of STIs in resource-constrained settings to improve patient management, and reduce STI transmission and the emergence of drug resistance. Finally, global initiatives are needed to make current near-patient NAATs more affordable through subsidized cost and bulk procurement.

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COMPETING INTERESTS

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

TW drafted the review and all authors contributed. All authors contributed in the final review of the manuscript. NS designed and conducted the search and data extraction for the vaginal discharge syndrome systematic review and meta-analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:
Data S1. Updated systematic review of vaginal discharge.
Figure S1. PRISMA flow diagram

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VIEWPOINT

Similar, but different: drivers of the disproportionate HIV and sexually transmitted infection burden of key populations

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Despite certain sexually transmitted infections (STI), for example, *Chlamydia trachomatis*, being sufficiently prevalent among the general population in some regions that they might be considered endemic, the contribution of "key populations" (KP) to recent increases in STI prevalence and incidence has been increasingly recognized [1]. The definition of who belongs to a KP has varied among normative bodies, but common features include engagement in specific practices that augment risk (e.g. multiple partners, anal sex and/or sharing needles) and social marginalization, which can concentrate the partner pool because of limited opportunities to meet partners outside of risk milieu, while limiting access to needed treatment and prevention. The UNAIDS programme includes men who have sex with men (MSM), transgender people, sex workers, people who inject drugs (PWID) as KP [2] and incarcerated persons [3-7]. Others have considered migrants to also be a KP [8-11], given their disproportionate HIV/STI burden and lack of social protection. Addressing HIV diagnosis, treatment and prevention for KP is important for their individual health, as well as that of the wider community with whom they interact. Understanding the relationship of HIV spread between KP and others is often hindered by insufficient data.

Although members of KP sub-groups may have different patterns of behaviour and social mixing that influence their HIV/STI risks, their vulnerabilities are augmented by common factors (Table 1). Often, KP experience structural barriers and societal discrimination that may increase their HIV/STI vulnerability by encumbering their access to healthcare [12-17]. Moreover, structural factors may not only directly affect susceptibility (e.g. lack of access to testing or treatment), but also shape behaviours and networks (e.g. being socially marginalized limiting partner choice). In settings where behaviours are criminalized [18-20], KP members may be at increased risk for HIV because of lack of access to condoms or sterile syringes, or may engage in avoidant behaviours due to the anticipation that insensitive providers might mistreat them [21], and fear of punitive action if they disclose unapproved sexual practices. KP avoiding healthcare are less likely to benefit from routine screening for HIV/STIs, early HIV/STI therapy (delaying the benefits of treatment as prevention, aka "TasP" for their partners), and/or pre-exposure prophylaxis (PrEP). Internalized stigma and social ostracism have been linked to high rates of KP depression [22-24], anxiety and self-medication with non-prescription substances in order to alleviate distress [25-28], which may further increase risky sexual practices. Their opportunities for gainful employment may be limited because of societal stigma, leading to sex work as their sole means of livelihood [29,30]. Financial incentives to engage in condomless sex, violence and lack of negotiating power exacerbate their vulnerability to HIV/STI.

Although there are common factors affecting HIV/STI vulnerability, some unique issues enhance transmission for some KP. Anal intercourse is extremely important in facilitating HIV/STI spread in MSM and transgender women, given that anal mucosa are particularly susceptible to HIV/STI acquisition and transmission [31,32], and potentiating asymptomatic rectal STIs are common [33,34]. Although oral sex may be seen as an HIV risk reduction practice, it may potentiate the spread of other STIs, for example, *Neisseria gonorrhoeae* [35-38]. Natal males who engage in anal sex with other males have unique role versatility, since they can acquire infection through receptive intercourse, and then transmit as the insertive partner [39]. Similar to enhanced transmission of HIV by sharing unsterile syringes, the risks posed by anal intercourse are addressable through access to condoms and antiretrovirals for prevention.

Social networks play a major role in increasing the efficiency of HIV/STI spread [40,41]. Sex workers and their partners may be at increased risk for HIV/STI [29,30,42]. The presence of sexualized venues such as brothels, bathhouses and sex-seeking social media create specific environments where HIV/STI can be efficiently spread [43,44]. These physical spaces and/or online connections [45-47] may lead to rapid partner turnover,

Table 1. Multilevel drivers of enhanced susceptibility of key populations to HIV and other sexually transmitted infections[a]

Biology	• Enhanced efficiency of anal intercourse • Direct effects of acute STI (e.g. ulceration) • Chronic mucosal inflammation due to multiple partners and sequelae of STI • Microbial dysbiosis • Role versatility (i.e. MSM and transgender women can be incentive or receptive partners)
Individual behaviour[b]	• Depression, and other affective disorders (often due to internalized stigma) • Substance use • Avoidance of healthcare • Condomless sex
Social networks	• Number of partners/time • Assortative mixing in high prevalence pools • Sexualized venues (e.g. brothels, bathhouses, sex-seeking social media)
Structural/institutional factors	• Societal discrimination (e.g. growing up in non-affirming environments) • Health system discrimination (e.g. providers and health care institutions) • Punitive and/or unsupportive laws (e.g. absence of anti-discrimination protection) • Criminalization • Poverty • Violence/victimization

[a]Men who have sex with men (MSM), transgender people, sex workers, people who inject drugs and migrants; Many of these factors are related to, and interact with, other factors depicted here; [b]individual behaviours are often a direct or indirect response to structural factors.

increasing the likelihood of HIV/STI transmission. In socially marginalized populations with high HIV/STI prevalence, the limited choice of new partners leads to increased risk through assortative mixing. This phenomenon has been well-characterized in Black American MSM, who have been shown to not be sexually riskier than demographically matched White MSM [48]. Yet, because they are more likely to have other Black MSM partners, due to decreased social mobility and structural racism, their likelihood of encountering HIV/STI with any new partner is greater than White MSM [49].

Comparing and contrasting the dynamics of HIV/STI spread in different KP sub-groups can help to inform policy, providing insights about general and specific needs. Attention to human rights should be integrated into any intervention focusing on KP, including the promotion of the rights of all individuals to be entitled to access life-saving care, without fear of stigma, criminalization, or punitive practices by authorities, peers or others [50-52]. KP members need to believe that their local healthcare systems are beneficent, and that access to, and affordability of, services are optimized, if they are to be effectively engaged and adherent to key medications. Providers need to be educated to provide culturally competent care [53,54]. An increasing array of resources is available to facilitate this, for example, www.lgbthealtheducation.org. Punitive laws that criminalize specific sexual practices, sex work, injection drug use and other socially marginalized behaviours, need to be removed so that individuals do not avoid seeking healthcare services that may improve their health, and that of their partners and the general community [55]. To effectively address the increasing rise of STIs in the era of TasP and PrEP, sexual health education needs to discuss anal and oral sex among KP in nonstigmatizing ways.

Each KP group has specific issues that should be addressed in order to optimize their sexual health. Community empowerment interventions among sex workers have been associated with increased condom use and a reduction in HIV risk [56–58], while legislation to facilitate gender affirmation may be more beneficial in reducing risk among TP [59,60]. Other interventions may be appropriate for multiple groups. For example, MSM, TP, sex workers and PWID may all benefit from education about the risk of HIV and STI transmission from anal intercourse, contemporary options for safer sex, the benefits of early initiation of antiretroviral therapy for HIV-infected individuals, and PrEP for those at risk. Early initiation of antiretroviral therapy for HIV-infected individuals, and PrEP for those at risk, can decrease HIV spread, but will not mitigate the risk for STIs. Thus, education about the role of condoms in reducing STI transmission remains important, and if condoms are not accepted, then routine STI screening should be promoted. Harm reduction remains a cornerstone of any initiative to decrease HIV/STIs among PWID.

In summary, no single factor is driving increasing STI and HIV rates among KP. Multiple biological, behavioural and structural factors compound one another to potentiate individual and group risk. Most of these factors are socially and legally embedded (e.g. homophobia and transphobia), which may be expressed differently in diverse societies; but the lack of acceptance impeding individual development may lead to reactive depression and/or substance abuse, increasing sexual risk. For such individuals, a multi-pronged approach is necessary if HIV/STI control is to be achieved: first of all: the removal of punitive laws that drive KP away from seeking needed services [62], then complemented by the education of providers and policymakers to develop culturally competent programmes to address clinical issues specific to KP, in addition to individual level interventions. One size will not fit all KP groups or individuals, yet commonalities exist. Understanding the similarities and differences driving risk is needed to effectively address the disproportionate burden of HIV and STI among KP.

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COMPETING INTERESTS

KHM and LA-B have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

KHM conceptualized the paper and wrote the first draft. LA-B provided editorial support, reviewed and revised the manuscript.

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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/serdiscordant 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 eightfold 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 ≥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 alfenamide 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 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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COMMENTARY

Mechanisms of sexually transmitted infection-induced inflammation in women: implications for HIV risk

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Abstract

Introduction: Globally, sexually transmitted infections (STI) affect >300 million people annually, and are a major cause of sexual and reproductive health complications in women. In this commentary, we describe how STIs interact with the immune and non-immune cells, both within and below the cervicovaginal mucosal barrier, to cause inflammation, which in turn has been associated with increased HIV acquisition risk.

Discussion: STIs have a major impact on the female genital mucosa, which is an important biological and physical barrier that forms the first line of defence against invading microorganisms such as HIV. Pattern recognition of STI pathogens, by receptors expressed either on the cell surface or inside the cell, typically triggers inflammation at the mucosal barrier. The types of mucosal responses vary by STI, and can be asymptomatic or culminate in the formation of discharge, ulcers and/or warts. While the aim of this response is to clear the invading microbes, in many cases these responses are either evaded or cause pathology that impairs barrier integrity and increases HIV access to target cells in the sub-mucosa. In addition, innate responses to STIs can result in an increased number of immune cells, including those that are the primary targets of HIV, and may contribute to the association between STIs and increased susceptibility to HIV acquisition. Many of these cells are mediators of adaptive immunity, including tissue-resident cells that may also display innate-like functions. Bacterial vaginosis (BV) is another common cause of inflammation, and evidence for multiple interactions between BV, STIs and HIV suggest that susceptibility to these conditions should be considered in concert.

Conclusions: STIs and other microbes can induce inflammation in the genital tract, perturbing the normal robust function of the mucosal barrier against HIV. While the impact of STIs on the mucosal immune system and HIV acquisition is often underappreciated, understanding their interactions of the infections with the immune responses play an important role in improving treatment and reducing the risk of HIV acquisition. The frequent sub-clinical inflammation associated with STIs underscores the need for better STI diagnostics to reverse the immunological consequences of infection.

Keywords: immunology; inflammation; sexually transmitted infections; women; HIV; bacterial vaginosis; mucosal immune responses; adaptive immune responses

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1 | INTRODUCTION

There are over 50 types of viruses, bacteria and parasites that can be sexually transmitted, eight of which are most widely recognized as sexually transmitted infections (STIs). These include syphilis, gonorrhoea, chlamydia, trichomoniasis, hepatitis B, herpes simplex virus (HSV), human papillomavirus (HPV) and HIV [1]. Most often, STIs are either asymptomatic or mildly symptomatic, and therefore remain undiagnosed and under-recognized by patients and clinicians [2]. Long-term infection by STIs can cause severe reproductive health complications in women, including still birth, preterm delivery, increased risk of HIV acquisition, infertility and cancer, among others [3-5]. In most high-income countries, policies ensure the availability of diagnostic tests, rapid delivery of results and contact tracing for those infected; however, these are not typically available in low- and middle-income countries where STIs are common and managed primarily on the basis of signs and symptoms. While syndromic diagnosis is reasonably sensitive and specific for ulcerative infections, other STIs are often missed due to poor sensitivity and may remain untreated for long periods of time [6].

Another challenge is drug resistance; infections such as *Neisseria gonorrhoeae* are increasingly resistant to standard therapies including macrolides, tetracyclines and cephalosporins [7]. This increase in antibiotic resistance, combined with high prevalence, low rates of treatment, and their association with HIV transmission and reproductive compilations, all

Table 1. Immune evasion strategies employed by common STIs

Strategy	Definition	Examples	References
Internalization	Epithelial cell entry, avoiding extracellular mechanisms of immune surveillance such as antibody responses	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Mycoplasma genitalium*	[26,90,91]
Deregulation of cellular process	Inhibition of important cellular processes in order to dampen the immune response e.g. DNA methylation, maturation of DCs, activation of immunoinhibitory pathways	HPV, HSV2, *C. trachomatis* *Treponema* pallidum	[92-95]
Resistance to antimicrobial peptides	Expression of genes which are highly resistant to antimicrobial peptides	*Haemophilus ducreyi*	[96-99]
Interference with the processes of the complement system	Acquisition of CD59 from different host cells, which inhibits binding of C9 with C5b-C8 that is critical for pore formation. In addition, this pathogen can stimulate iron induced cysteine protease activity.	*Trichomonas vaginalis*	[100,101]
Structure alteration	Pathogen-induced changes to their extracellular structure to avoid detection by the innate immune system.	*M. genitalium*	[37]
Inhibition of Th1 CD4 and CTL responses	Pathogens upregulate specific responses which results to the suppression other immune responses that would result to their clearance. For example, upregulation of Th17 response that results to the downregulation of Th1 response.	*M. genitalium*, *Chlamydia trachomatis* *T. vaginalis*, HSV2, HPV, *Treponema pallidum*, *N. gonorrhoeae*	[95,101-112]
Inhibition of other types of T cell responses (Th2, 17, 22, Treg)	The pathogen downregulates the immune response in specific cells like macrophages, dendritic cells and monocytes.	*T. vaginalis*, HPV, *N. gonorrhoeae*, *T. pallidum*	

underscore the need to better understand the mucosal immune responses to STI-causing organisms.

The purpose of this commentary was to describe how STIs interact with the vaginal mucosal barrier, and the commensal microbes that line its luminal surface, to cause inflammation. While this commentary focuses on STIs in women, some similar mechanisms have been suggested for male genital immunology [8-10]. Many of the pathological effects of STIs correspond to biological mechanisms that may favour HIV acquisition in women.

2 | DISCUSSION

2.1 | Types of mucosal immune responses to STIs

There are several ways to classify STIs, the most obvious being by the type of causative organism, that is, bacterial, viral or parasitic. A second important way is by clinical presentation; although STIs are frequently asymptomatic, they can also cause (a) ulcers in genital, anal, oral and perianal tissues (e.g. *Treponema pallidum*, HSV), (b) urethral and vaginal discharge (e.g. *Chlamydia trachomatis*, *N. gonorrhoeae* and *Mycoplasma genitalium*), or (c) genital warts (e.g. HPV) [11].

Yet another way to classify STIs is by the different mechanisms through which they cause infections and evade immunity. STIs result in a large inflammatory response that can lead to pathology throughout the genital tract, including pelvic inflammatory disease, ectopic pregnancy and infertility, and degradation of the epithelium. As part of this inflammatory response, an influx of immune cells including neutrophils has been associated with discharge and lesions in the genital tract, resulting in further damage to the epithelial barrier [12]. We and others have shown that this epithelial damage may be due to increased protease expression, which functions to degrade epithelial integrity [13,14].

Although the mechanisms differ, the ability of all STI-causing pathogens to induce an inflammatory response, damage the epithelial barrier, and impair natural innate defences is believed to increase the risk of HIV acquisition, by providing the virus better access to HIV target cells in the sub-mucosa and beyond. Inflammation may simultaneously increase the number of and location of these cells relative to the lumen or induce phenotypic changes that increase their cellular susceptibility to virus infection [15]. The inflammatory responses induced by STIs is intended to (and in some cases may) play an important role in protecting the host, but in many other cases this response favours the pathogen. This could be due to evasion of the effector mechanisms that are aimed at pathogen clearance (see Table 1), but also by causing collateral damage to host tissues [16-18]. For example, in *C. trachomatis* infection, neutrophils are among the first immune cells to be recruited to the site of infection. Delayed apoptosis is a strategy used by *C. trachomatis* to avoid a complete immune response whereby it reduces the neutrophil sensitivity towards the stimuli from apoptosis, hence contributing towards pathogen persistence [19].

2.2 | STIs and genital inflammation

Genital inflammation, defined by elevated cytokines, has been a strong predictor of HIV acquisition risk and decreased TFV gel efficacy [20,21]. Elevated levels of inflammatory cytokines have been highly correlated to increased protease activity, which may decrease the integrity of the epithelial barrier [13,14]. South African women with laboratory-confirmed STI infections had increased the levels of inflammatory cytokines in the genital tract, including IL-1α, IL-4, fractalkine, TNF-β, macrophage-derived chemokine, IL-1β and interferon-γ [20,22]. STIs have been associated with increased genital inflammation signatures specifically among those with *C. trachomatis* infections [23-26]. Many studies have established that mucosal cytokine production occurs after STI acquisition, forming a central feature of the ensuing immune response. Therefore, consideration of the broader immune pathways that drive these cytokine responses could provide important insight into how STIs change the mucosal milieu [27,28].

2.3 | Intracellular and extracellular recognition of STIs by pattern recognition receptors

Mucosal epithelial cells are the first barrier against infection, forming an early line of defence against pathogen invasion. Epithelial cells are equipped with receptors that are crucial for pathogen detection, and these cells function to initiate and modulate the inflammatory cascade aimed at inducing pathogen clearance [29,30]. Inflammation leads to a series of reactions which induce adaptive immunity, including effector mechanisms that can clear infection. However, tight regulation of inflammation is required in order to avoid self-damage [30,31]. In the case of STIs, a combination of immune evasion, potent induction of inflammation and poor natural immunity represents scenarios in which HIV entry may be increased (Figure 1).

Toll-like receptors (TLRs) play an important role in detecting pathogens including STIs, and initiating appropriate innate and adaptive immune responses. TLRs bind to their cognate ligands, resulting in a signalling cascade that culminates in the

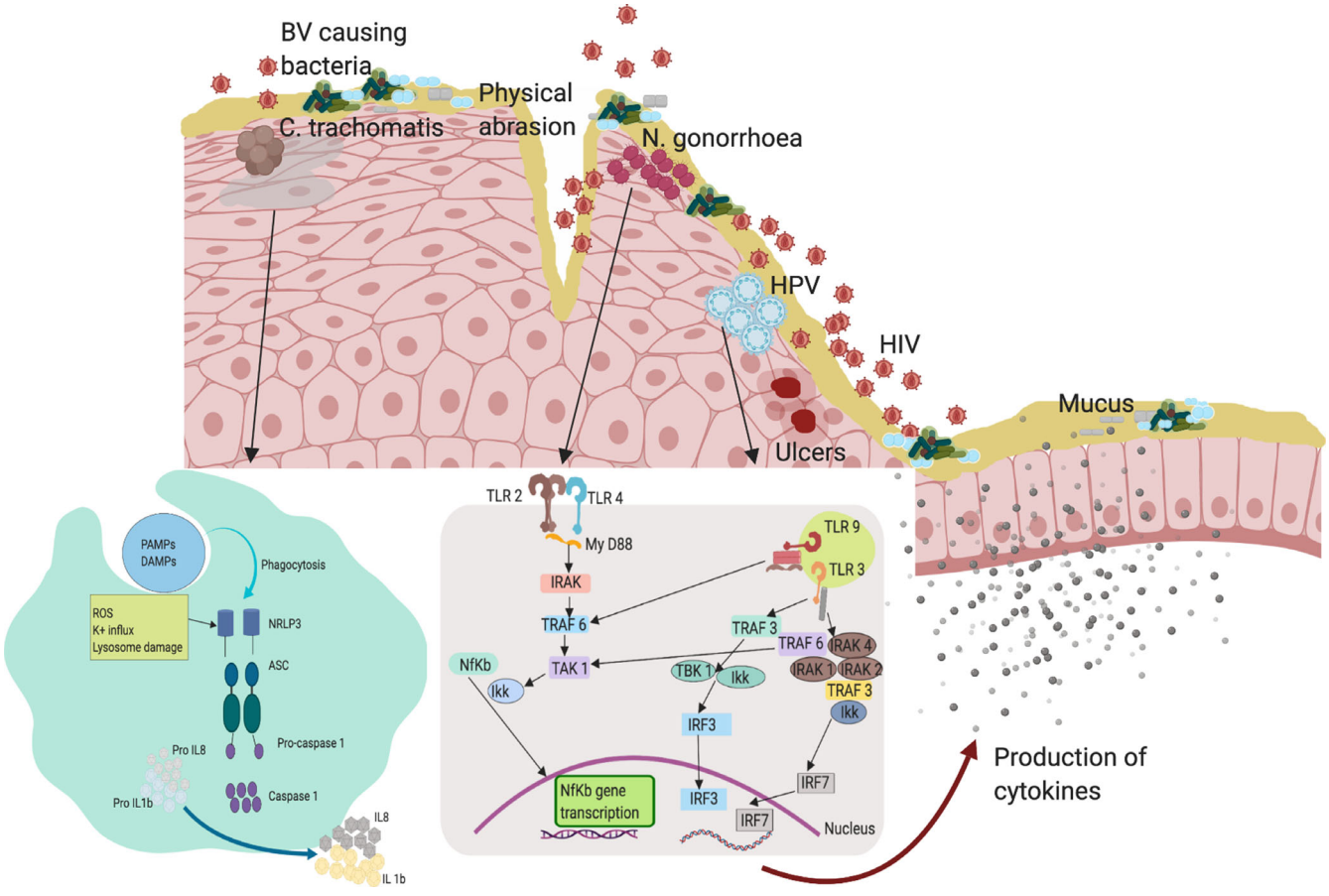

Figure 1. Mucosal innate immune responses to STIs in the female genital tract that could potentiate HIV transmission risk.
Depicted are several of the modes through which STIs might increase the risk of HIV acquisition. Infection with STIs results to physical abrasion, ulcer formation and increase of pro-inflammatory cytokines resulting in inflammation. Inflammation increases the availability of HIV target cells in the sub-mucosa. During *N. gonorrhoeae* infection, TLR2 and 4 detect lipooligosaccharide and induce a NF-KB driven immune response resulting to production of cytokines. Infection with *C. trachomatis* results in death of some cells which in turn produce elementary bodies. *C. trachomatis* infection is detected by inflammasomes resulting to production of IL-1b and IL-8 through the NLR3 pathway. TLR9 detects the CpG island in Genomic material of the HPV virus inducing an immune response through the MYD88 pathway. TLR3 detects the viral nucleic acid to induce an immune response through the IRF and IR7 pathways.

expression of pro-inflammatory cytokines. TLRs can be classified as both intracellular (TLR3,7,8,9,11,12 and 13) and extracellular (TLR1,2,4,5,6 and 10), on the basis of their expression and where ligand recognition typically occurs [32,33]. TLRs recognize pathogen-associated molecular patterns (PAMPs), including bacterial DNA, viral nucleic acid and viral proteins, with the eventual goal of inducing specific T-cell and antibody responses. For example, TLR9 detects the unmethylated CpG sequences in bacterial DNA molecules. Many TLRs signal via MyD88, an important intracellular protein adaptor molecule. MyD88 is responsible for induction of the IL-1 family, a group of 11 mainly inflammatory cytokines that regulate innate immune cell function. IL-1R-associated kinase is recruited via MyD88 activation, further activating the NF-kB pathway culminating in transcription of pro-inflammatory cytokine genes [34,35].

Several bacterial STIs induce innate inflammatory responses by interacting with extracellular TLRs. A recent study that utilized a 3D model of endocervical cells showed that *M. genitalium* was recognized by TLR2, 4 and 6, a pattern of TLR usage that initiates the NF-KB pathway and is unique to this bacterium [36,37]. In microorganisms such as *Neisseria*, protein elements are detected both intracellularly and extracellularly, both of which can induce an NF-KB driven inflammatory response. TLR 2 and 4 detect LPS, outer membrane vesicles, porins and other proteins, while additional pattern recognition molecules called NOD 1 and 2 detect additional STI biochemical structures such as gamma glutamyl diaminopimelic acid and muramyl dipeptide, which also results in induction of NF-KB-driven inflammation [38,39].

Intracellular TLRs mainly detect viral infections. In contrast to many extracellular TLRs, which tend to recognize protein structures, intracellular expression of TLR3, TLR7, TLR8 and TLR9 mediates viral nucleic acid sensing. In a recent study that evaluated TLR gene expression by qPCR in endocervical cells of women, increased levels of TLR and IFN-α2 were observed among those who had cleared HPV-16 infection, suggesting that TLR responses may be associated with viral clearance. Moreover, HPV-16 may interfere with these responses, thus enhancing their persistence [40]. In this study, TLR9 expression was upregulated during high-risk HPV infection and was higher in HPV-positive compared to HPV-negative individuals, confirming that TLR9 plays an important role in the detection of CpG islands in the DNA motifs during HPV infection *in vivo* [41].

STIs similarly induce immune responses through inflammasomes (multi-protein intracellular structures located in the cytosol). The inflammasome is activated by the signalling of PAMPs, DAMPs (damage associated molecular proteins), changes in the ion concentrations of cytosol and by extracellular adenosine triphosphate (ATP). Once activated, this molecular complex leads to expression of pro-inflammatory cytokines and can also initiate an inflammatory form of cell death called pyroptosis [42-44]. Activation of the inflammasome often occurs through NOD-like receptors (NLRs, especially NLR3), which interacts with apoptosis-associated speck-like protein containing a CARD (ASC). This protein is located in the nucleus of macrophages and monocytes and is responsible for activating caspase-1, which in turn cleaves and activates IL-1β and IL-8 [44]. *C. trachomatis*, co-cultured with epithelial cells, were found to activate inflammasomes resulting in IL-1β and IL-8 production and activation of pyroptosis. An inactivated form of *C. trachomatis* was tested in the same model and was still found to lead to priming of the inflammasome, but without the resulting inflammatory response, implying that pathogen replication may be critical for cytokine induction [45]. This inflammatory pathway also applies to other STIs; for example, the LPS of *N. gonorrhoeae* has been shown to harbour hexa-acylated lipid A, which can activate the NRLP3 inflammasome [46]. *H. ducreyi* elicits IL-1β responses that are dependent on activation of caspase-1, -5 and NLRP3 in both M1 and 2 macrophages [47]. In viral STIs such as HPV, cytosolic viral DNA is detected by AIM2 inflammasome and IFI16, an intracellular DNA sensor, resulting in the production of IL-1β and IFN-β respectively. Blocking of AIM2 resulted in increased production of IFN-β thus it has the ability to block the production of IFN-β an important mediator of antiviral response [48].

2.4 | Co-infection with STIs, bacterial vaginosis and HIV

In addition to the mucosal barrier, the composition of the vaginal microbiome can play an important role in providing immune defence at the genital mucosa. In particular, women with certain *Lactobacillus*-dominant communities are able to produce lactic acid and maintain a low mucosal pH, which inhibits the growth of pathogenic bacteria including STIs. In the absence of *Lactobacillus* spp., with the exception of *Lactobacillus iners*, a more diverse microbiome population is typical, which is often associated with bacterial vaginosis (BV). BV, defined either by Nugent scoring or using molecular methods [49], has been associated with an increased risk of both STI and HIV acquisition [50-57]. Both STIs and BV are associated with increased levels of inflammatory cytokines like IFN-α2, IL-1α, IL-1β, TNF-α, IFN-γ and IL-8 [51,58]. Epithelial cells of the genital mucosa produce glycogen, an energy source that allows *Lactobacillus* spp. to flourish [59,60], which has been suggested provide protection against *Chlamydia* infection [61].

Synergism between BV and STIs is in part through the production of metabolites by the BV causing bacteria, which are utilized by STIs as growth factors. An example is seen between BV and *C. trachomatis* infections. Bacterial species that produce tryptophan have been associated with the increased risk of *C. trachomatis* infection among women whereas Indoleamine-2,3-dehydrogenase 1 (IDO1) producing species have been associated with decreased risk. IDOL1 inhibits the availability of tryptophan. This shows that BV may play an important role in both first time and recurrent *C. trachomatis* infections [62,63]. Ziklo *et al.* found that chlamydia infection was associated with reduced IFN-γ response. IL-17 was also reduced among infected individuals, and this cytokine is important in boosting host defence and maintaining mucosal barrier. Therefore, the increased levels of kynurenine, the byproduct of tryptophan breakdown, is associated with increased risk of HIV acquisition [63-65]. Studies have suggested that ethnicity and not metabolic mechanisms may also underlie the association between chlamydia and HIV [28,66,67]. Increased risk of *Trichomonas vaginalis* acquisition has been associated with BV in both HIV-positive and -negative women [68].

Durable and effective treatment of BV has been a major challenge for the field. Oral or topical metronidazole is effective in the short term, yet recurrence occurs among more that

50% of women within three to twelve months [50,69,70]. However, periodic presumptive treatment has proven to be an effective method in reducing STI incidence [71,72]. This strengthens the case for a causal relationship between BV and STIs, and also suggests that reducing BV may help to reduce STI incidence.

STI co-infection in HIV-positive women, particularly by *N. gonorrhoeae* or HSV-2, increases inflammatory responses and mucosal HIV shedding [22,73-75]. In addition to mucosal inflammatory response, STIs such as *N. gonorrhoeae* have been found to increase plasma viral load and reduce CD4 T-cell counts, indicating that both STI and HIV act synergistically resulting in detrimental effects to the host. While studies have suggested that STI treatment could reduce HIV shedding and transmission [73], this may be a moot point in the era of effective antiretroviral therapy, which, if taken correctly, reduces HIV transmission almost completely [76].

2.5 | Role of adaptive immune response in STIs

Mechanisms of immunity to STIs are poorly understood, forming an obvious barrier to vaccine development. Epidemiological evidence for immunity to Chlamydia has been shown in the context to treatment [77]. While the mechanism for the immunity is unclear, *C. trachomatis* infection has been associated with the formation of follicles [78]; the presence of IFN-γ+ CD4+ T cells in these follicles has been thought to provide an immune response in the case of a secondary infection [79]. In some STI infections, re-infection occurs long after the primary infection [80-82], as the adaptive immune response following primary infection plays a major role in immune surveillance and forms the first line of immune response in secondary infection.

Memory T-cells were initially divided into central and effector memory T-cells, which preferentially home to non-lymphoid and secondary lymphoid organs respectively. Since that time, it is clear that there is an additional population of tissue-resident memory lymphocytes that either do not re-circulate, or re-circulate very slowly, and provide rapid responses to re-infection [83,84]. The role of these cells in the STI response is only beginning to be explored, with some data emerging for HSV-2. In HSV-2, a persistent infection occurs at the dermal epidermal joint (DEJ) of the mucosal lining with CD8+ T cells being the most predominant immune cells at this site. An assessment of CD8+ T-cells at the DEJ in biopsies of HSV-2 infected individuals revealed a high proportion of CD8 TCRαβ T-cells. A comparison of the prevalence of CD8β or CD8α subsets at the DEJ showed that there was a higher population of CD8α mRNA, which were specifically CD8αα homodimers, an indication that they are responsible for containing HSV-2 infection. The CD8α T-cells formed clusters around epithelial cells that were HSV-2 specific [85].

Additional cells including mucosal associated invariant T (MAIT) cells, invariant natural killer T (iNKT) cells, γδ T-cells, innate lymphoid cells and IELs form part of the connection between the innate and adaptive response, and play a major role in guarding the integrity of the tissue and generation of local immune responses. Some studies support the presence of these cells in the vagina [86-89], however, their responses to STIs have not been extensively explored.

3 | CONCLUSIONS

In summary, STIs induce inflammatory responses through interactions with the epithelial barrier and immune cells at the site of infection. There are several molecular pathways involved in the inflammatory response to a diverse range of STIs, all of which likely function to cause pathology by weakening the mucosal barrier. At the same time, STIs use a variety of immune evasion strategies to dampen the immune response and enhance their persistence. STIs and BV likely both increase the risk of HIV acquisition by damaging the mucosal barrier and increasing pro-inflammatory cytokines, increasing the availability of HIV target cells. The impact of STIs on mucosal immune responses and HIV acquisition is often under-appreciated, but improved control of these infections through better diagnosis, treatment and prevention could make an important contribution to reducing HIV risk and improving reproductive health outcomes.

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COMPETING INTERESTS

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

RM wrote the first draft of the paper. LRM, CB, SSAK and QAK provided critical review of the paper.

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REVIEW

The role of saliva in gonorrhoea and chlamydia transmission to extragenital sites among men who have sex with men: new insights into transmission

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Abstract

Introduction: Gonorrhoea and chlamydia cases have been rising among gay, bisexual and other men who have sex with men (MSM) over the last decade. The majority of cases are extragenital and occur at the oropharynx and anorectum. The aim of this narrative review was to review the risk factors and mode of transmission for gonorrhoea and chlamydia at the oropharynx and anorectum among MSM.

Results and discussion: New evidence suggests that oropharyngeal gonorrhoea can be transmitted by kissing in addition to through the established route of condomless oral sex; and anorectal gonorrhoea can be acquired when saliva is used as a lubricant for anal sex and rimming in addition to the established route of condomless penile-anal sex in MSM. In contrast, condomless penile-anal sex remains the major route for chlamydia transmission.

Conclusions: Substantial transmission of gonorrhoea may occur with practices other than the established routes of condomless oral and/or anal sex and hence condoms may not be effective in preventing gonorrhoea transmission to extragenital sites. In contrast, condoms are effective for chlamydia control because it is mainly transmitted through condomless penile-anal sex. Novel interventions for gonorrhoea that reduce the risk of transmission at extragenital site are required.

Keywords: *Neisseria gonorrhoeae*; *Chlamydia trachomatis*; transmission; men who have sex with men; control; sexual behaviours; sexual practices; saliva; kissing; throat; anal; sexually transmitted infections; sexually transmitted diseases

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1 | INTRODUCTION

Sexually transmitted infections (STIs), are increasing globally, particularly in gay, bisexual and other men who have sex with men (MSM) [1-5]. To address these rises, there have been many novel campaigns and interventions for STIs but these interventions have not been associated with effective STI control in MSM [6-11]. The failure of these campaigns and interventions to reduce STIs could be due to several reasons including that they are not reaching the core group, or because they are based on an incomplete understating of how infections are transmitted. The control of STIs may be more difficult with the introduction of treatment as prevention (TasP) and HIV pre-exposure prophylaxis (PrEP) which has successfully reduced new incident HIV in MSM but has been associated with changes in sexual practices that increase STI risk [12-14]. In this context, it is time to revisit our understanding of how infections are transmitted with the aim of designing new effective interventions to improve STI control.

Both gonorrhoea and chlamydia until recently were thought to be mainly transmitted through condomless penetrative intercourse such as penile-vaginal, penile-anal and oral sex [15-23]. However, in the context of rising STI rates and ineffective interventions, it is important to review the transmission of both infections particularly at extragenital sites in MSM which are largely asymptomatic [24-27]. Other anal sexual activities such as fingering, fisting and rimming are commonly practiced among MSM and may play an important role in transmission [28-30]. Several epidemiological studies have found these activities are associated with the acquisition of any STIs (that is, gonorrhoea, chlamydia or syphilis) in MSM; [28,31,32] however, there are limited studies examining the role of these practices in the transmission of gonorrhoea and chlamydia independently. The aim of this narrative review was to revisit the transmission of gonorrhoea and chlamydia to the oropharynx and anorectum in MSM. Several reviews have already described the prevalence and epidemiology of gonorrhoea and chlamydia, behavioural and social risk factors, and possible interventions; [1,4,17,33-35] and thus these areas will not be covered in this review.

2 | RESULTS AND DISCUSSION

2.1 | Prevalence of extragenital gonorrhoea and chlamydia in MSM

Many epidemiological studies have reported on the point prevalence of extragenital gonorrhoea and chlamydia in MSM. Chan and colleagues published a review in 2016 summarising the prevalence of extragenital gonorrhoea and chlamydia from 53 studies (Table 1); [17] however, these estimates vary substantially across geographical regions and study settings. Overall, the authors reported that the median prevalence of gonorrhoea at the oropharynx (4.6%) was similar to the anorectum (5.9%). In contrast, the median prevalence of chlamydia in the anorectum (8.9%) was much higher than in the oropharynx (1.7%).

Several studies have compared the prevalence of extragenital gonorrhoea and chlamydia in MSM by HIV status. A US study reported that HIV-positive MSM had a higher prevalence of anorectal gonorrhoea (8.2% vs. 3.3%) and anorectal chlamydia (9.0% vs. 6.6%) than HIV-negative MSM; however, the prevalence was similar in both groups for oropharyngeal infection (that is oropharyngeal gonorrhoea: 5.2% in HIV-positive vs. 4.3% in HIV-negative; oropharyngeal chlamydia: 1.6% in HIV-positive vs. 1.3% in HIV-negative) [15]. These findings are consistent with another study conducted in Melbourne, Australia, showing that the prevalence of anorectal gonorrhoea was higher in HIV-positive MSM (15.4%) than in HIV-negative MSM (7.3%) but the prevalence of oropharyngeal gonorrhoea was similar in both in HIV-positive MSM (9.9%) and HIV-negative MSM (8.1%) [36].

2.2 | Oropharyngeal gonorrhoea

Oropharyngeal gonorrhoea is relatively short lived and commonly asymptomatic [7,25,37-39]. A natural history study of 18 individuals (12 men and six women) with untreated oropharyngeal gonorrhoea has suggested that the majority of oropharyngeal gonorrhoea infections clear by six weeks and all by 12 weeks [39]. Another natural history study of 60 untreated individuals with positive oropharyngeal gonorrhoea culture has shown that more than half (55%) of oropharyngeal gonorrhoea infections clear within seven days [40]. Other epidemiological studies also support the short duration of oropharyngeal gonorrhoea [24,38,41]. However, length time bias may have occurred due to the detection of prevalent infection in these studies.

Oropharyngeal gonorrhoea had been thought to be primarily acquired from oro-genital contact such as condomless fellatio (Table 2) [24,42]. Fellatio is commonly practiced among MSM (that is, 72.7% of MSM had fellatio with their last male partner) and condoms are rarely used for fellatio in MSM [43,44].

Studies of symptoms associated with urethral gonorrhoea have been contradictory. In the 1970s, two studies have reported that about 40% of heterosexual men reporting contact with their female partners with gonorrhoea had asymptomatic urethral gonorrhoea [45,46]. However, other studies report that at least 90% of men with urethral gonorrhoea are symptomatic [26,27,47], and develop dysuria and urethral discharge within two to five days of exposure [47,48].

In countries with good access to healthcare, men with symptomatic urethral gonorrhoea usually receive treatment within a few days of the onset of symptoms [49]. In this context, the point prevalence of urethral gonorrhoea is estimated to be relatively low in the MSM population (approximately 0.2% [50]) compared to the extragenital sites; and hence, this has led some investigators to question whether urethral infection alone could be responsible for the high incidence of oropharyngeal gonorrhoea (26 per 100 person-years) [50]. This is consistent with the observation by Passaro (2018) who reported the prevalence of oropharyngeal gonorrhoea did not differ between MSM who had receptive oral-penile sex (10.3%) and those who did not (9.8%) [20]. Indeed some investigators have hypothesized that the oropharynx may be a more important anatomical site for gonorrhoea transmission in MSM than the urethra [50,51].

These same investigators have undertaken a series of studies related to their hypothesis. They undertook a study of 33 MSM with untreated culture positive oropharyngeal gonorrhoea and obtained saliva samples from these men up to 14 days after screening [52]. The study found that all men (100%) tested positive for *Neisseria gonorrhoeae* in saliva by nucleic acid amplification test (NAAT) and almost half (43%) of men where their saliva samples were detected by culture [52,53]. In addition, two past studies in the 1970s and 1980s have also found that gonorrhoea can be cultured from saliva but the estimates ranged between 8% [54] and 67% [40]. Furthermore, these findings raise the question of whether oropharyngeal gonorrhoea could potentially be transmitted between the oropharynges through kissing, and also between the oropharynx and the anorectum through rimming (Table 2) [21,22,41,50].

Several case reports purposed kissing could be a risk factor for oropharyngeal gonorrhoea in the 1970s [37,54,55]. In

Table 1. Prevalence of extragenital gonorrhoea and chlamydia in MSM

	Prevalence (%)	
STI	**Median**	**Range**
Oropharyngeal gonorrhoea	4.6%	0.5% to 16.5%
Oropharyngeal chlamydia	1.7%	0% to 3.6%
Anorectal gonorrhoea	5.9%	0.2% to 24.0%
Anorectal chlamydia	8.9%	2.1% to 23.0%

Note. Data were obtained from a review of 53 studies published by Chan *et al.* (2016) [17].

Table 2. Summary of studies examining the route of gonorrhoea and chlamydia transmission to the oropharynx in MSM

Possible route of transmission	Oropharyngeal gonorrhoea	Oropharyngeal chlamydia
Kissing	[21,41,56,57]	[63]
Insertive rimming (oral-anal)	[21,41,56]	[63]
Fellatio (oral-penile)	[41,56]	[63]

these early studies, cases were diagnosed using culture, which has poor sensitivity and specificity for *Neisseria gonorrhoeae* in the oropharynx. Rather surprisingly, there have been only three epidemiological studies conducted since using NAAT, which is a more sensitive test than culture.

The Australian Health In Men (HIM) study by Templeton *et al.* was the first longitudinal study examining the association between oropharyngeal gonorrhoea and kissing [41]. The HIM study recruited 1427 HIV-negative MSM in Sydney between 2001 and 2007 and they found that both dry and wet kissing with casual partners in the last six months were associated with the incident oropharyngeal gonorrhoea. However, this association disappeared after adjusting other sexual practices including receptive condomless fellatio and insertive oro-anal contact (that is rimming). In the multivariable analysis, men who often engaged in insertive rimming were 1.6 (95% CI: 1.1 to 2.5) times more likely to have oropharyngeal gonorrhoea than men who never engaged in insertive rimming in the last six months.

The second study by Cornelisse *et al.* was an age-matched 1:2 case–control study conducted among 531 MSM in Melbourne in 2015 [56]. Similarly, the study found that men who kissed their casual partners in the last three months were 2.2 (95% CI: 1.3 to 3.6) times more likely to have oropharyngeal gonorrhoea than those who did not kiss their casual partners in the univariable analysis. However, the authors were not able to perform multivariable analysis due to high collinearity with other sexual practices. Consistent with Templeton *et al.*'s study, Cornelisse *et al.*'s study also identified that both insertive rimming and receptive fellatio are risk factors for oropharyngeal gonorrhoea in MSM in the univariable analysis [41].

Both Templeton *et al.*'s [41] and Cornelisse *et al.*'s study [56] measured kissing as part of sexual practices and did not investigate kissing without sex as a risk factor. The third study by Chow *et al.* addressed this concern [57]. It was a cross-sectional study conducted among 3677 MSM in Melbourne in 2016-2017 that measured male partners in three different categories: (1) kissing-only partners where men only kissed their partners but did not have sex with them; (2) sex-only partners where men only had sex with their partners but did not kiss them; and (3) kissing-with-sex partners where men kissed and had sex with their partners. Chow *et al.*'s study defined sex as any oral or anal sexual contacts and the finding showed that both kissing-only and kissing-with-sex partners in the last three months were strongly associated with oropharyngeal gonorrhoea in the adjusted analysis. In addition, the risk of oropharyngeal gonorrhoea increased with an increasing number of kissing-only and kissing-with-sex partners. However, the number of sex-only partners in the last three months was not associated with oropharyngeal gonorrhoea. This was the first study identified to show kissing in the absence of sex may be an important and neglected risk factor for oropharyngeal gonorrhoea; however, this study did not measure oral sex as a separate sexual act and so could not adjust for it separately.

Although studies have shown that kissing may be a risk factor for oropharyngeal gonorrhoea in MSM, the role of saliva in gonorrhoea transmission is still poorly understood. If saliva can carry infectious gonorrhoea, it is hypothesized that men could acquire oropharyngeal gonorrhoea through kissing by contacting infectious saliva, but it is unclear how much saliva is adequate for gonorrhoea transmission. Moreover, the salivary flow and its production vary between individuals. It is estimated that the salivary flow rate is about 0.3-0.4 ml per min while unstimulated [58], and the salivary flow rate increases up to 4-5 ml per min while stimulated such as chewing and eating but no studies have assessed saliva flow rates during kissing or sex [59,60].

2.3 | Oropharyngeal chlamydia

The majority of the oropharyngeal chlamydia infections are asymptomatic in men and therefore their diagnosis primarily depends on asymptomatic screening [61,62]. Unlike oropharyngeal gonorrhoea, age does not seem to be a significant predictor for oropharyngeal chlamydia [62,63]. The HIM Study was a longitudinal study examining the risk factors for oropharyngeal chlamydia transmission in MSM. [63] The HIM study found that men who often engaged in receptive oral-penile sex with ejaculation were 5.3 (95% CI: 1.7 to 16.7) times more likely to have oropharyngeal chlamydia compared to men who never had receptive penile-oral sex with ejaculation with their casual partners in the last six months (Table 2) [63]. Other activities (for example kissing (both dry and wet kissing), receptive oral-penile sex without ejaculation and insertive rimming) have found to be not associated with oropharyngeal chlamydia among MSM (Table 2) [63]. Similarly, a study conducted in Lima, Peru has shown that there was no significant difference in the prevalence of oropharyngeal chlamydia between MSM who had receptive oral-penile sex (4.1%) and those who did not (3.4%) [20]. However, a strong association between oropharyngeal chlamydia acquisition and history of receptive oral-penile sex was observed among women [64].

A number of laboratory studies have been undertaken to examine the role of saliva in oropharyngeal chlamydia transmission. Two studies in the 1990s found that saliva has an inhibitory effect against *Chlamydia trachomatis* [65,66]. Further studies with better technology and a more sensitive diagnostic test are important to validate whether saliva can carry chlamydia to provide a better understanding of transmission.

2.4 | Anorectal gonorrhoea

Most men infected with gonorrhoea in the anorectum are asymptomatic; [27] however, among those with symptoms, anal discharge, pain and itching are common. Similar to oropharyngeal gonorrhoea, younger MSM are at higher risk of acquiring anorectal gonorrhoea than older MSM [67,68]. Condomless anal sex is a clear risk factor for anorectal gonorrhoea [67,69,70]. But other modes of transmission may also occur. For example, an epidemiological study has found that there was no difference in the prevalence of anorectal gonorrhoea between MSM who had receptive penile-anal sex (8.8%) and those who did not (6.6%) [20]. This suggests that other non-receptive anal sexual intercourses (for example, receptive fingering, receptive fisting (insertion of the hand into the rectum), receptive rimming and dildo insertion) may also be associated with anorectal gonorrhoea (Table 3) [67].

Given that saliva can carry infectious gonorrhoea, it is hypothesised anal sex that involves in saliva (for example use of saliva as a lubricant for anal sex or saliva on a penis before insertion) may be associated with anorectal gonorrhoea (Table 3). A cross-sectional study of 283 young MSM conducted in San Francisco has shown that about 87% of MSM

Table 3. Summary of studies examining the route of gonorrhoea and chlamydia transmission to the anorectum in MSM

Possible route of transmission	Anorectal gonorrhoea	Anorectal chlamydia
Oral infection passing through the gastrointestinal tract to the rectum	Nil	[73,75,76]
Receptive rimming (oral-anal)	[30,67]	[67,72]
Receptive fisting	[67]	[67]
Receptive fingering	[30, 67]	[67,72]
Receptive of dildos	[67]	[67]
Saliva use as a lubricate for anal sex	[30]	[72]

used saliva as a lubricant for anal sex during their lifetime but only 31% of MSM used it in the last six months [71]. Another study conducted among 1312 MSM in Melbourne in 2014-2015 found that 69% of MSM used saliva as a lubricant for anal sex in the last three months [30]. The authors also identified that men who used saliva as a lubricant for anal sex were 2.2 (95% CI: 1.0 to 4.7) times more likely to have anorectal gonorrhoea by culture than those who did not use saliva as a lubricant for anal sex after adjusting for other confounding factors including condom use.

2.5 | Anorectal chlamydia

Anorectal chlamydia is primarily transmitted through condomless penile-anal sex in MSM [22,67]. The HIM study found that receptive fingering, receptive fisting and receptive rimming were risk factors for incident anorectal chlamydia in the univaraible analysis; however, only receptive fingering was an independent risk factor after adjusting for other confounding factors (Table 3) [67]. The authors concluded the men who often had receptive fingering were 4.6 (95% CI: 2.3 to 9.3) times more likely to have anorectal chlamydia than those who never had receptive fingering in the last six months. Unlike anorectal gonorrhoea, a Melbourne study by Cornelisse *et al.* showed that the use of saliva as a lubricant for anal sex is not a risk factor for anorectal chlamydia in MSM [72].

A meta-analysis published in 2019 has concluded that anal intercourse is associated with anorectal gonorrhoea but not with anorectal chlamydia among women [16]. This suggests that the mode of transmission for gonorrhoea and chlamydia is likely to be different and hence it leads to several new hypotheses of anorectal chlamydia acquisition. Animal studies have shown that chlamydia can survive in the gastrointestinal tract suggesting that this may also apply to human [73,74]. New paradigm has been proposed that it is possible oropharyngeal chlamydial infection can pass through the gastrointestinal tract to the anorectum [73,75,76]. However, further studies are certainly required to confirm this hypothesis.

3 | CONCLUSIONS

MSM can acquire gonorrhoea and/or chlamydia at the oropharynx and anorectum although the epidemiological evidence suggests the modes of transmission differ. For gonorrhoea, infections at extragenital sites are transmitted through non-genital contacts such as kissing, rimming and use of saliva in addition to condomless oral or anal sex. For chlamydia, condomless anal sex is the main risk factor. However, the uncertainty about the hypotheses of the route of transmission for gonorrhoea and chlamydia via saliva among MSM should be acknowledged [77]. This uncertainty arises in part because infection at multiple sites is common in MSM and multiple sexual practices usually occur during one single sex act [20,43], making it difficult to clearly delineate which specific sexual practice was responsible for the transmission between anatomical sites [77]. Furthermore, existing data regarding chlamydia transmission to extragenital sites are insufficient to draw meaningful conclusions and thus more research is required. Condoms may not necessarily be effective in preventing some extragenital infections [78]. Other interventions that target the extragenital site related to its mode of transmission are required [1,35,79,80].

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AUTHORS' CONTRIBUTIONS

EPFC wrote the first draft of the manuscript. All authors contributed to the concept, literature search, writing and revisions of the manuscript. All authors critically revised it for important intellectual content and approved the final version of the manuscript.

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VIEWPOINT

Current challenges in the clinical management of sexually transmitted infections

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With the emergence of HIV in the 1980s, the first people diagnosed with AIDS were treated by a variety of medical specialists. For some, like internal medicine specialists, dealing with a sexually transmitted infection (STI) was a new aspect in their patient contact. For others, like genitourinary medicine specialists and dermatologists, the many HIV-related internal medicine-related morbidities posed a challenge. Frequent interdisciplinary consultation made clinical care for people living with HIV/AIDS a multidisciplinary endeavour right from the start.

AIDS was first diagnosed in men who have sex with men (MSM) who had had multiple previous STIs [1]. MSM were considered a key population both for HIV and STIs early on. Yet the HIV epidemic had a dramatic effect on adherence to safe sex measures and, as a result, the incidence of bacterial STIs declined rapidly.

With the availability of effective antiretroviral therapy (ART) since 1996, HIV was no longer a deadly infection for those with access to medication. People with HIV on ART could live healthy lives, including having sex. This phenomenon, coined "treatment optimism," resulted in a rise in bacterial STIs, especially among HIV-positive MSM [2].

The intertwining of the HIV and bacterial STI epidemics highlights that, to be truly effective, the response to HIV and other STIs should not be echeloned. People living with HIV (PLHIV) are affected disproportionally by STIs, and individuals with STIs are more susceptible to HIV acquisition. This applies especially to MSM, transgender persons and (female) sex workers. In this viewpoint, five current issues of concern in the clinical management and prevention of STI and HIV are discussed. Although the main focus here is on MSM, this does not imply that the STI burden in heterosexual men and women is not substantial.

BIOMEDICAL INTERVENTIONS FOR HIV AND RISK COMPENSATION

Concerns have been raised that the treatment as prevention (TasP) paradigm for HIV-positive people and pre-exposure prophylaxis (PrEP) for HIV-negative people will induce more risky sexual behaviour, thus increasing the incidence of other STIs [3]. This phenomenon is sometimes called risk compensation, where one perceives that antiretrovirals are protective against HIV transmission. However, increases in sexual risk have antedated the implementation of TasP and availability of PrEP [3]. The increasing practice of condomless sex and the transmission of STIs and HIV among MSM began after effective antiretrovirals became widely available in 1996, when HIV was no longer considered a deadly disease [4].

Preliminary indications of risk compensation in PrEP demonstration projects and observational studies are conflicting [5-9]. This discrepancy might arise from decreased onward transmission of STIs due to more frequent STI screening, whereas ascertainment bias may increase STI detection. Since the maximum follow-up time in the published studies was less than two years, it might be too short to observe risk compensation at this time. All in all, HIV clinicians should be prepared for increasing numbers of patients with STI co-infections. In some regions (such as continental Europe), STI and HIV care are fragmented and offered at different sites; managing co-infections in PLHIV can be especially challenging in these regions, and integrating care should be considered.

EMERGING STIs

Around the turn of the century, unusual outbreaks of STIs were encountered in PLHIV. Lymphogranuloma venereum (LGV) [10] and hepatitis C (HCV) [11] were emerging STIs

that were, by far, mostly diagnosed in HIV-positive MSM living in metropolitan areas, and engaging in risky behaviour such as fisting.

LGV is caused by an invasive variant of *C. trachomatis* and causes a severe and destructive infection in the anogenital region. The true magnitude of the LGV epidemic is underestimated because of a scarcity of routine screening and surveillance efforts, as well as the considerable proportion of presentations that are asymptomatic [10]. Moreover, preventive measures to reduce transmission are hindered, and they will be, as long as the mode of transmission is not fully understood. The overrepresentation of anorectal versus genital LGV infections (15:1) suggests that other modes of transmission occur apart from anal sex.

Among the first people diagnosed with LGV, alarming numbers of HCV co-infections were also diagnosed [12]. Sexual transmission of HCV was subsequently identified among HIV-positive MSM. Until then, it had been considered to be a blood-borne disease [11]. Most recently, transmission of HCV from HIV-positive MSM to HIV-negative MSM who use and intend to use PrEP has been observed [13]. Suggested causes are "sero-mixing" (sex between serodiscordant partners) and risk compensation. As with LGV, the sexual transmission of HCV is not fully elucidated, which hinders preventive measures.

Many HIV-positive MSM form core STI transmitters and often take a central position in sexual networks. These networks expand globally, as demonstrated for HCV [14] and LGV [15]. For HIV care specialists, this stresses the importance of close ties with public health institutions, continued global surveillance and early warning measures.

MULTIPLEX DIAGNOSTIC NUCLEIC ACID AMPLIFICATION TESTS

Nucleic acid amplification tests (NAATs) have revolutionized the diagnostic process for STIs. Traditionally, STI screening relied on direct light microscopic visualization, cultivation of pathogens and serology. Although these tests modalities are characterized by high specificity, sensitivity was often low. The amplification of pathogenic DNA or RNA proved extremely useful for the development of highly sensitive and specific tests [16]. Although still way too expensive for most low- and middle-income countries, the ease of use in sample collection for NAATs has led to wide implementation in high-income countries.

NAATs allow the integration of STI screening outside the traditional STI outpatient clinic setting, for example, in the context of routine HIV care. Moreover, NAATs offer options of (patient) self and home collection, thus substantially simplifying STI screening. Commercial parties increasingly launch NAATs that can diagnose multiple pathogens in a single specimen. This can have cost benefits in the elucidation of the causative organism of an STI-related syndrome, such as urethritis, vaginal discharge or genito-ulcerative disease.

Yet there is a downside that can induce over-treatment of organisms considered to be non-harmful or clinically irrelevant. *Mycoplasma genitalium* is one such organism, whose clinical relevance, especially in asymptomatic people, is debated [17-19]. *M. genitalium* has been associated with urethritis in men, and most guidelines recommend testing only in symptomatic people. Moreover, the treatment of *M genitalium* is increasingly complicated by antimicrobial resistance. The advent of commercial multiplex NAATs containing *M. genitalium* as the target puts clinicians and microbiological laboratories in a treatment dilemma. When positive results are found in asymptomatic individuals, over-consumption of antibiotics will only increase antimicrobial resistance, which is another emerging threat in the management of STIs.

ANTIMICROBIAL-RESISTANT GONORRHOEA

With 78 million new cases of gonorrhoea globally, gonorrhoea is the second most prevalent bacterial sexually transmitted infection worldwide [20]. Persistent infections may cause severe genital and reproductive tract inflammation and damage, like pelvic inflammatory disease, ectopic pregnancy, epididymitis and infertility; gonorrhoea also increases the transmission of HIV [21]. The World Health Organization's (WHO's) first general global report on antimicrobial resistance, published in 2014, revealed that antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world. This is even more worrisome since no major new types of antibiotics have been developed over the past 30 years [22]. Moreover, this report specifically mentions treatment failures due to resistance to extended spectrum cephalosporins (the last-resort treatments for gonorrhoea) in 10 countries, and decreased susceptibility in 36 countries. Thus, gonorrhoea may soon become untreatable. There are some promising antibiotics in the pipeline, such as zoliflodacin [23] and gemifloxacin, which have not reached market yet [24].

SHORTAGES OF OUT-OF-PATENT ANTIBIOTICS

In 2017, a global shortage of benzathine penicillin G (BPG), the first-line treatment option for syphilis, was reported. The largest indication for BPG is rheumatic heart disease; syphilis accounts for only 1% of BPG prescriptions. BPG is the only option considered safe for pregnant women in the prevention of congenital syphilis [25]. Since the profit margins of BPG are small and the production costs are high, the active pharmaceutical ingredient was produced in only three factories, all based in China. This has dramatically increased the stock-out risk. Recently, two of the manufacturers terminated their production due to governmental regulatory and environmental issues.

WHO has recognized BPG as an essential medicine at high risk for stock-out [26]. It has invited manufacturers to apply for WHO pre-qualification to ensure acceptable quality, safety and efficacy standards of BPG supplied by international agencies (for example, the Global Fund to Fight AIDS, Tuberculosis and Malaria).

From a demand perspective, national-level BPG forecasting and procurement systems should be strengthened and appropriate treatment of syphilis should be prioritized. Since the first-line treatment options for chlamydia, gonorrhoea and trichomoniasis are also off-patent antibiotics, future shortages can be envisioned here as well.

CONCLUDING REMARKS

Since key populations often overlap each other, it is necessary to de-silo STI and HIV care. In the UK and most former Commonwealth countries, HIV and STI care are fully integrated in sexual health clinics. From a quality of care perspective, this seems to be most ideal: a "one-stop shop" setting where patients are holistically managed. From a public health perspective, integrated care offers the opportunity to address contact tracing and preventive interventions for both HIV and STI key populations.

Yet in many regions, STI and HIV care are still offered by separate medical specialties in separate settings. As a result, at the least, resources are wasted. More often though, fragmentation of care leads to delays, non-adherence, loss to follow up and, onward propagation of infections. It is important that these settings work towards desegregation of care and adopt the format of integrated sexual health clinics where screening, treatment, follow up and preventive interventions are offered to patients and to key populations.

PrEP has proved to be a highly effective tool against ongoing transmission of HIV. Yet, PrEP also offers opportunities to assess new STI prevention strategies. The currently developed NAATs promise faster availability of results and will become true point-of-care tests that can be integrated into routine HIV care. This will enable infection management (including counselling, treatment and contact tracing) while the person waits during a single consultation, further limiting ongoing transmission. Treatment of STIs will remain a point of concern in the coming years, either due to emerging antimicrobial resistance or drug shortages.

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COMPETING INTERESTS

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DEBATE

Give PrEP a chance: moving on from the "risk compensation" concept

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Abstract

Introduction: While bio-behavioural interventions (BIs) for sexually transmitted infections (STIs) and HIV prevention have shown their effectiveness (e.g. treatment for syphilis, HPV vaccination or pre-exposure prophylaxis [PrEP]), they have also aroused major concerns regarding behavioural changes that could counteract their benefit. Risk compensation (RC) fears concerning BIs in the HIV/STIs prevention field are intimately linked to representations, judgements and social control on sexual behaviour. With an increasing number of PrEP studies describing a rise in STIs due to RC, this paper argues for a shift away from the focus on RC and proposes a more constructive approach to respond to the needs of people living with HIV and populations most at risk.

Discussion: The concept of RC, stemming from road safety and derived from economic theory, relies on rational theoretical models of human behaviour. Although widely applied in several contexts its use has been reasonably questioned. Major methodological issues regarding RC have been raised within HIV/AIDS literature. Although behavioural changes (e.g. condomless sex and number of sexual partners) are often erroneously assimilated with RC, there is no evidence that behavioural changes have undermined the effectiveness of previous and current BIs. Still, PrEP has not escaped RC concerns. Increases in condomless sex within the context of growing uptake of PrEP signals a continued need for integrated and innovative HIV and STI prevention strategies and a comprehensive sexual health approach. Routine HIV/STI testing, peer-led counselling, and identification of sexual health needs within the PrEP model of care could become a gold standard in the sexual health field for all populations.

Conclusions: RC remains a frequent argument against the availability and provision of prevention methods for vulnerable populations. Individuals should be able to benefit from the full panel of BIs options available, to find and adapt methods according to their needs. Current, past and future PrEP users, with other stakeholders, may provide valuable insight into innovative solutions and programmes to control HIV and other STIs.

Keywords: bio-behavioural prevention; PrEP; risk compensation; sexual behaviour; sexually transmitted infections; HIV

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1 | INTRODUCTION

In 2015, in spite of strong evidence of the efficacy of pre-exposure prophylaxis (PrEP) to prevent HIV infection [1-4] and WHO recommendations [5], a rebuttal to the Lancet HIV editorial "PrEP: why are we waiting?" stated that decision-makers lacked information regarding the "normative aspects" of PrEP use [6]. More precisely, they explained that the main reason for not implementing this bio-behavioural intervention (BI) was lack of information regarding "people's own responsibility to use a condom, the relevance of being free of fear of HIV infection when having sex, and the relative importance of preventing HIV versus a possible rise in other sexually transmitted diseases because of reduced condom use" [6]. This quote makes explicit important points that have overshadowed PrEP and other BI: moral judgements on sex and HIV prevention as a means of controlling sex [7-9].

What the PrEP example shows is nothing new. In the last decades, other prevention tools were all met with caution as they could possibly induce behavioural changes leading to an increased risk and consequently counteract the benefit of the prevention tool in question: the oral contraceptive pill in the 1950s [10,11], treatment for syphilis in the 1960s [12] and 1970s [13,14], needle exchange programmes for injecting drug users [15-17], the morning-after pill [18], and more recently HPV vaccination [19-21]. Although different BI for HIV prevention have shown their effectiveness (e.g. condoms, male circumcision, highly-active antiretroviral treatment (HAART), post-exposure prophylaxis (PEP), treatment as prevention (TasP) and pre-exposure prophylaxis (PrEP)), each and every one has aroused concerns regarding "risk compensation" (RC) [22-25]. The HIV/AIDS field has scarcely challenged the use of the RC concept [26] at the expense of focusing on other positive aspects of BI such as increased quality of

(sexual) life, empowerment to discuss safer sex and to disclose HIV status, reduced fear of transmitting or getting HIV, or the possibility to re-engage in sexual activity after an HIV diagnosis, to name a few [27-29].

At the start of the epidemic, sexually transmitted infections (STIs) were already present and a health concern [30]. Most likely due to its fatal nature and lack of treatment, demanding specific medical interventions and innovations, HIV/AIDS was treated separately from other STIs. Evidence that STIs facilitate HIV transmission led to recognition of an "epidemiological synergy" between HIV and other STIs, thus leading to calls for prevention programmes and strategies that addressed both HIV and other STIs [31,32]. Whereas some prevention methods such as condoms provide protection against HIV and other STIs, other "no barrier" HIV prevention strategies such as TasP and PrEP have changed the scene.

In the context of an increasing number of PrEP studies describing a rise in STIs due to "RC," this paper provides a critical view of the origin, use and consequences of this concept in the HIV prevention field and argues for a shift away from the focus on RC. In a time when more effort is needed to reduce the number of new infections among key populations (KP) and their sexual partners [33], and STIs are a health concern, we propose a more constructive approach that responds to the needs of people living with HIV (PLHIV) and most-at-risk populations.

2 | DISCUSSION

2.1 | Is RC a pertinent and valid framework?

Although RC has been used interchangeably with "disinhibition" in scientific literature, these are in fact two different concepts [14]. *Disinhibition* refers to the lowering or absence of self-restraint to avoid risk [14,34]; for example when an inebriated person is aggressive or engages in sexual risk behaviour (SRB) because he/she no longer cares about the risk [35]. *Risk compensation* is related to the "risk equilibrium" which is defined as "a system in which individuals accept a certain level of subjectively estimated (or perceived) risk to their health in exchange for benefits they expect to receive from (an) activity" [36].

Since most of the literature regarding BI refers to RC, it is worth focusing on the origins of this widely used concept. The National Highway Traffic Safety Administration (USA), with the goal of preventing road injuries, issued in 1968 29 Federal Motor Vehicle Safety Standards (FMVSS) regarding features such as seat belts. In 1975, economist Sam Peltzman, evaluated FMVSS with the perspective that since safety is an exchangeable "good," individuals would exchange safety for "driving intensity" if the car is safer than expected [37]. His results, since proven to be erroneous [38], led to the conclusion that security standards had no effect on overall traffic fatalities and increased pedestrian deaths. Decades of debates on these results, but also on others such as those showing seat belt laws were not effective [39-41], introduced RC as a plausible framework to understand road safety despite experiments unable to provide useful evidence and evaluation contaminated by poor data and uncontrolled factors [42].

There exist well-established psychosocial theories and models to approach the behavioural change in relation to health, such as, amongst others, the theory of reasoned action/planned behaviour [43-46], the transtheoretical model of behaviour change [47] or the information-motivation-skills model [48-50]. However, the road safety field has focused on so-called "risk models," such as the "Threat-avoidance model" [51], the "Model of drivers' decision making and behaviour" [52] or the "Risk Homeostasis Model" [53], in which the risk concept plays a major role. The concept of risk homeostasis or RC described in 1982 claims that human behaviour falls under the same mechanism as a thermostat [54]. Thus, interventions to prevent car accidents, or the use of helmets by bicycle riders [55], would not be useful since individuals would change their behaviour so that their level of risk stays constant [56,57]. The RC concept relies on rational theoretical models of human behaviour, derived from economic theory, that have been widely criticised [58-60], nevertheless it has attracted great attention [61]. Otherwise, literature has shown that seat belts and helmets do not lead to behavioural changes leading to a risk increase and are, undoubtedly, effective [60,62,63].

Methodological issues regarding RC have been also raised within HIV/AIDS literature [64]. To accurately claim that a BI leads to an increased risk for HIV, a randomized control trial would have to compare a group believing that the intervention would reduce risk with another group believing that the intervention would not reduce risk [22]. Because of ethical issues, this design is not a viable option [64]. Other methodological considerations have been drawn [23]: (1) studies are mostly focused on behavioural measures, failing to account for the possibility that changes in attitudes or risk perceptions (essential to the RC theory) may occur before behaviour change; (2) timing in the change of attitudes and behaviour is important but not always clear; condomless sex (CLS) can precede "optimistic attitudes" regarding HIV exposure; (3) some studies did not find that change in behaviour led to risk increase [2,65-69]; (4) even if changes in behaviour or risk perception are observed they will likely not undermine the high effectiveness of the prevention strategy [23]; (5) interventions are not considered from a community level, therefore are limited to an individual approach [23].

2.2 | Evidence of changes in sexual behaviour or evidence of "risk compensation"?

Despite the emergence of various forms of BI, strategies such as male circumcision [25] and condom promotion were suspected of engendering RC [70]. However, these strategies did not induce enough behavioural changes to have an impact on their effectiveness [71,72]. The advent of HAART in 1996 led to obvious beneficial clinical effects. HIV was no longer perceived as a life-threatening disease [73-75], generating fears of unintended effects on sexual behaviour [76,77] and on the incidence of STIs [78]. Increasing public information on how an undetectable viral load reduces the level of infectiousness of HIV-positive individuals [65], which was then confirmed in the "Swiss Statement" [79], also followed the same path. Whereas evidence of RC should be shown in the decreased effectiveness of a given BI to prevent HIV transmission, most of the literature aiming to find and evaluate evidence of RC, primarily concern behavioural changes. A meta-analysis [80] was undertaken aiming to determine if ART use was associated with changes in "unprotected" sex and STI diagnoses.

Among 56 studies, condomless sex was found to be lower in participants receiving ART compared to those who were not (OR: 0.73 (95% CI: 0.64 to 0.83); $p < 0.001$). Among 11 studies, STI diagnoses were found to be lower among participants receiving ART compared to those who were not (OR: 0.58 (95% CI: 0.33 to 1.01); $p = 0.053$).

As a BI, PrEP has shown to be a viable method for those that do not systematically use condoms, ineffectively use other risk reduction strategies (RRS), or wish to have an extra layer of protection [81,82]. The demonstrated efficacy and effectiveness of PrEP among other KP, which led to expanding WHO PrEP recommendations, has been followed by numerous studies aiming to evaluate "RC" among PrEP users, some of which have been analysed in systematic reviews and meta-analyses. STIs have been a major focus of these studies. While STIs are an obvious health concern and prevention strategies must be fully implemented in order to reduce their incidence, opportunities can be missed for those most at risk for HIV and other STIs if reflection on STI is restricted to the BI framework. First, because BI do not aim to reduce STI but HIV incidence. Second, because even if a same behaviour, CLS, leads to HIV and other STIs, the underlying psycho-social mechanisms to prevent the former and the latter are different [27]. STIs do not represent for individuals the same health concern as HIV, and the information, motivation and skills required to mobilise to prevent STIs are therefore different.

In a systematic review and meta-analysis of the effectiveness of oral PrEP among at-risk populations, sexual behaviour (defined as condom use and number of sexual partners, and used to identify the presence of RC) was studied as an outcome in addition to HIV infection, adverse events, and antiretroviral drug resistance [83]. This analysis found that PrEP effectively protected against HIV infection across all populations. Although the authors found no evidence of RC with PrEP, and no evidence of RC in open-label extension (OLE) studies which are more likely to show "real-world use," they caution that study participants benefited from behaviour counselling and were previously trial participants [83].

A systematic analysis of OLE and demonstration studies investigated the effect of PrEP use on SRB [84]. While the authors rightly excluded studies that measured beliefs about PrEP use and/or predicted future behaviour, increase in "risky sexual behaviours" and "risk compensation" are used synonymously. "RC" was measured by using several outcomes, however, due to inconsistency across the studies in the measures of CLS and number of condomless partners, meta-analysis was limited to STI diagnosis. Although there is evidence to suggest that an increase in number of CLS partners and general decline in condom use, this may be restricted to the proportion of MSM who already reported these behaviours [84].

The impact of PrEP use on SRB and RRS has also been examined in qualitative studies. Among 41 participants of the PROUD PrEP study [81], only half of them declared an increase in "risk taking behaviour." The participants reported using various RRS before using PrEP (e.g. strategic positioning, sero-sorting, PEP use), however, all reported (some) CLS. Overall, given inconsistent condom use and situations and contexts that may lead to increased risk taking, participants declared that PrEP filled a prevention gap or added another layer of protection for participants already at high risk [81].

A qualitative sub-study conducted with iPrEx OLE participants [27] found that, in opposition to feelings of worry and concern regarding HIV infection that pervaded respondents' lives, PrEP enabled to replace them with feelings of safety. For participants not using condoms prior to PrEP, thinking of a "PrEP-as-condom-replacement theory" had no sense. For those using condoms and willing to use PrEP to engage in CLS, did not actually engage in CLS. More interestingly, respondents reporting sexual behavioural changes (going "crazy") declared that the possible emergence of a STI was a reminder of PrEP's limits [27]. Changes were therefore more emotional than behavioural.

Recently, Holt and Murphy [23] have introduced the concept of community-level RC in the context of PrEP in which "changes in risk perceptions and behaviour (could occur) as a result of increased optimism about avoiding HIV among people not directly protected by PrEP." However, due to increased PrEP uptake and consistent PrEP use among PrEP users, protection at the community-level actually increased (reduction of HIV incidence). They propose monitoring changes in sexual behaviour in addition to attitudes to PrEP and perceived HIV risk. This could measure HIV "prevention optimism" defined as "the belief that it is easier to avoid HIV infection or transmission because of PrEP and that it is more acceptable and safer to engage in condomless sex because the risk of HIV is perceived to be reduced" [23]. Further research is needed to explore the impact of "optimism," particularly among non-PrEP users.

2.3 | PrEP: a concern or an opportunity for STI control?

PrEP is a significant step forward in the fight against HIV, not only for its impact on HIV transmission, but also its opportunity to increase the frequency of HIV and other STIs testing, to promote early diagnosis and treatment of HIV and other STIs. According to one modelling study, high PrEP coverage among MSM could lead to an important decline in STI incidence, largely attributed to routine testing which allows early detection and treatment of asymptomatic STIs [85]. PrEP also has the potential to alleviate fears of HIV, to allow for a more fulfilling sex life [26,27], and to empower individuals to protect themselves and others [86]. Adapted and quality counselling around PrEP, sometimes community-based, may be a favourable environment to have a discussion on sexual behaviour, drug use and other sexual health needs [28,87,88].

Several studies, however, have shown barriers on the part of medical providers to have such discussions [87,89], and on the part of patients [90,91] to share information regarding their sexual behaviour. Behavioural changes associated with BI need to be studied, however, there is still a major health issue: reaching, informing, testing, treating and empowering individuals, in order to integrate them into a preventive health path, not only for HIV but also for other STI.

Peer-led counselling, offered in the ANRS-Ipergay [4] and currently offered in the ANRS-Prevenir study [92] by the French community-based organisation AIDES, moves away from a "curative health system" perspective in which health consultations are driven by symptoms, towards a health path for HIV-negative individuals that addresses overall sexual health based on the individual needs at a given point in life

[88]. From the perspective of PrEP users, peer counsellors use both their personal and community experience to inform and discuss the spectrum of prevention methods and how they may fit with individual needs. Building individual capacity to evaluate personal risk, and thus, empower PrEP users to find prevention strategies that meet their needs for a satisfying sexual life, can potentially have lasting effects, regardless of the duration of PrEP use. Although limited, longitudinal data on PrEP use has shown important decreases in retention over time [93,94]. Changes in sexual behaviours, perceived HIV risk, financial cost, adverse effects and problems related to adherence have been identified as reasons for PrEP discontinuation [93,95]. It is therefore increasingly important to address the fact that PrEP users may not be lifetime users and to put individuals on a preventive health path that is sustainable after PrEP discontinuation. Current PrEP studies should explore this issue to find potential solutions to minimize HIV and STI risk when individuals choose to no longer use PrEP.

Global rates of STI, which were rising before PrEP [30], remain a concern. While rising STI rates among PrEP users may be partially explained by increased testing in multiple anatomic sites within the context of PrEP follow-up, other bio-behavioural interventions, in addition to information, counselling and notification, must be explored. Over time, it is possible that repeat STI testing may result in a change of behaviour, particularly among those with high-risk behaviours who may come to realise the limits of PrEP (e.g. repeat STIs) [27] and therefore may implement or return to other prevention methods.

New interventions should systematically be accompanied by measures to better inform on STIs, to reinforce individual perception of STI risk and to promote behavioural changes adapted to individual needs. These behavioural changes could result in condom use for some individuals, however, there are other interesting alternatives such as partner notification or BI for STIs. Recent studies on the prophylactic use of doxycycline for bacterial STIs have shown promising results post-exposure [96] and used daily [97], but remain to be confirmed in studies with longer follow-up [98]. Use of doxycycline may be particularly pertinent among PrEP users who experience recurrent STIs; a recent analysis has shown that among MSM PrEP users, 25% participants accounted for a little more than three-quarters of all STIs [99].

Such an integrated sexual health approach has a lot to learn from the PrEP model, which could become a gold standard in handling prevention. The PrEP model needs to be developed and expanded not only for those at risk for HIV, and among them, mostly for MSM, but also for all the populations, which could also prevent STIs. Women, migrants, transgender individuals, drug users could take benefit of a comprehensive health offer (as with PrEP).

If we want this to become a reality several conditions are needed. First, work with health-care providers is needed. In order not to limit prevention options of patients, non-judgmental discussion on sexual behaviour, and drug use, has to be ensured. Improving the patient-provider relationship can be key to moving away from RC focus to a positive and integrated sexual health approach.

Second, medical practice and HIV prevention research will benefit from knowledge from other disciplines and methods. For example, qualitative studies can provide new and complementary information to already existing data. Additionally, a more critical approach to the theories or concepts exported from other fields would allow for a more efficient response to eliminate the epidemic and respond to the health needs of KP.

Finally, effective STI control will not be possible without political will, corresponding funding and implication of all stakeholders to test interventions such as partner notification, integration of sex education programmes in schools, or legislative changes regarding antibiotic treatment among others [30].

3 | CONCLUSIONS

Effective BI for HIV and STIs have been plagued by debates of RC for centuries. The concept of RC, stemming from the field of road safety, has been the subject of theoretical controversy and its use has been reasonably questioned. And yet, RC remains a frequent argument to justify moral judgements against the availability and provision of prevention methods for vulnerable populations who already experience stigma and discrimination [100]. Unsurprisingly, PrEP and its possible large-scale implementation has also been discussed within the framework of RC potentially undermining its efficacy. Would the availability of an effective HIV vaccination prompt the same debates?

Gaps to improve and guarantee access to testing, treatment and to reach an undetectable viral load for KP are a harsh reality, which means that the end of the HIV epidemic will not happen anytime soon. Lack of access to HIV/STI treatment and prevention is deeply linked to the shame associated with them and to the stigma and discrimination that those with the disease have to face from some health providers. For these reasons, the full range of existing prevention options has to be made available. With the information and support provided by healthcare providers, and by community stakeholders, individuals must have the opportunity to choose the prevention method(s) that best respond to their health needs at a given point of their (sexual) life and thus protect themselves. From a human rights perspective, BI access should not be barred based on the presence (absence) of STIs or changes in sexual behaviour [28]. Finally, the role of community-based stakeholders cannot be overlooked in increasing knowledge regarding sexual health and the empowerment of populations deemed "at risk" to identify and adapt prevention strategies that best fit their needs.

HIV and STIs cannot be thought and addressed in a social vacuum [26,101]. Interdisciplinarity, community perspectives and long-term evidence from PrEP cohorts are needed to disentangle the effects of the combination of different BI that coexist with societal changes that have an impact on individual and community behaviours and social representations of sex, sexual orientation and experience of STIs, including HIV. Despite proven efficacy and effectiveness of PrEP, scientific literature seems to have been more concerned on how PrEP could "increase risk" instead of on how it reduces it or on how PrEP could lead to the empowerment of individuals regarding sexual health [27,28]. Science, working hand-in-hand with communities, can dramatically improve the response not only to HIV but also to other STIs by implementing and

assessing adapted interventions that are based on individual health needs.

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COMPETING INTERESTS

DRC and RMD declare no conflicts of interest. JMM is on the advisory boards for Gilead Sciences, Merck and ViiV.

AUTHORS' CONTRIBUTIONS

DRC, RMD and JMM, discussed key ideas and concepts forming the basis of this debate article. RMD and DRC wrote the manuscript. All authors reviewed and approved the final version.

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REVIEW

Sexually transmitted hepatitis C virus infections: current trends, and recent advances in understanding the spread in men who have sex with men

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Abstract

Introduction: Hepatitis C virus (HCV) is a major public health threat. Although the recent availability of highly effective directly acting antivirals created optimism towards HCV elimination, there is ongoing transmission of HCV in men who have sex with men (MSM). We here report current epidemiological trends and synthesise evidence on behavioural, network, cellular and molecular host factors associated with sexual transmission of HCV, in particular the role of HIV-1 co-infection. We discuss prevention opportunities focusing on the potential of HCV treatment.

Methods: We searched MEDLINE, fact sheets from health professional bodies and conference abstracts using appropriate keywords to identify and select relevant reports.

Results and discussion: Recent studies strongly suggest that HCV is transmitted via sexual contact in HIV-positive MSM and more recently in HIV-negative MSM eligible for or on pre-exposure prophylaxis. The reinfection risk following clearance is about 10 times the risk of primary infection. International connectedness of MSM transmission networks might contribute to ongoing reinfection. Some of these networks might overlap with networks of people who inject drugs. Although, the precise mechanisms facilitating sexual transmission remain unclear, damage to the mucosal barrier in the rectum could increase susceptibility. Mucosal dendritic cell subsets could increase HCV susceptibility by retaining HCV and transmitting the virus to other cells, allowing egress into blood and liver. Early identification of new HCV infections is important to prevent onward transmission, but early diagnosis of acute HCV infection and prompt treatment is hampered by the slow rate of HCV antibody seroconversion, which in rare cases may take more than a year. Novel tests such as testing for HCV core antigen might facilitate early diagnosis.

Conclusions: High-risk sexual behaviour, network characteristics, co-infection with sexually transmitted infections like HIV-1 and other concomitant bacterial and viral sexually transmitted infections are important factors that lead to HCV spread. Targeted and combined prevention efforts including effective behavioural interventions and scale-up of HCV testing and treatment are required to halt HCV transmission in MSM.

Keywords: hepatitis C virus; sexual transmission; men who have sex with men; epidemiology; dendritic cells; prevention

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1 | INTRODUCTION

In 2015, viral hepatitis was responsible for an estimated 1.3 million deaths from acute infection and hepatitis-related liver cancer and cirrhosis – a toll comparable to that of HIV and tuberculosis [1]. Hepatitis C virus (HCV) infections account for almost 30% of these deaths. Worldwide most HCV infections have been acquired by exposure to infected blood or blood products. After the first commercial test became available in 1991 and HCV transmission through blood product was effectively halted, sharing of injecting equipment among people who inject drugs (PWID) became the major route of transmission in high-income countries [2]. In contrast to hepatitis B, the risk of sexual transmission of HCV has always been considered low [3,4]. This low risk was confirmed by a recent study among 500 anti-HCV-positive, HIV-negative persons and their long-term HCV-negative heterosexual partners, reporting a maximum incidence rate of HCV transmission by sex of 0.07% per year or one infection per 190,000 sexual contact, and a lack of association with specific sexual practices [5]. However, in the mid-2000s, HCV infection emerged in men who have sex with men (MSM) [6],

likely due to sexual contact [7]. Although there was skepticism among some investigators, who assumed the cause was under-reporting of injecting drugs, further evidence from Europe, the United States and Australia that MSM who denied injecting drug acquired HCV [8,9], reopened the discussion on the importance of sexual transmission of HCV [7]. The high reinfection rates among MSM who cleared HCV spontaneously or who were successfully treated [10-12], further underscored the importance of sexual behaviour in HCV transmission. As new HCV infections were typically found in HIV-positive MSM, it was initially suggested that HIV-1 status could be an important factor for sexually acquired HCV [10,13-15]. However, recent studies suggest that sexual transmission of HCV also occurs in HIV-1-negative MSM eligible for or using pre-exposure prophylaxis (PrEP), indicating that HIV-1 infection status is not the only factor affecting susceptibility [16-18]. The frequency of exposure to HCV within specific sexual networks is also important as recent studies show that HIV-negative MSM are infected with HCV-strains already circulating among HIV-positive MSM [19-21]. Although directly acting antiviral (DAA) treatment is very effective in clearing HCV [22], and its availability created optimism towards HCV elimination, the high HCV (re)infection rates, likely via sexual contact, highlight the need for a better understanding of the mechanisms involved in sexual transmission of HCV.

We reviewed the current knowledge regarding HCV infection in MSM to summarize epidemiological trends and synthesise evidence on behavioural, network and host factors associated with sexual transmission of HCV. We also discuss prevention opportunities focusing on the potential of HCV infection treatment programmes on the spread of sexually acquired HCV.

2 | METHODS

We have systemically searched MEDLINE, fact sheets from health professional bodies including the World Health Organization, Center for disease Control and Prevention, the American Association for the Study of Liver Diseases and recent conference abstracts, published in English before January 2019. We have searched these databases using the following keywords: HCV, acute HCV, sexual transmission, MSM, HIV-1 coinfection, DAA, PrEP, reinfection, molecular epidemiology, HCV diagnosis, HCV treatment guidelines, phylogenetics and phylogeography to identify and select relevant reports.

2.1 | Epidemiology of sexually transmitted HCV

2.1.1 | Trends in HCV infections in HIV-positive and -negative MSM

Outbreaks of sexually transmitted HCV have been reported globally among HIV-positive MSM since 2000 [7,23]. Using data from the international CASCADE collaboration, it was found that HCV incidence among HIV-positive MSM significantly increased from 0.07/100 person-years in 1990 to 1.8 per 100 person years in 2014 [24]. These findings are in line with the incidence rates and the time trend observed in a meta-analysis pooling incidence data from 17 individual studies [10]. Trends differed per European region: while HCV incidence has stabilized in western Europe, likely due to increased awareness, testing and uptake of therapy, it continues to increase in northern Europe [24]. Furthermore, time from HIV to HCV infection has shortened in recent years [24]. The risk of reinfection is more than 10 times higher than primary infections, which is of great concern [10]. The European NEAT study, including data from eight centres in Austria, France, Germany and the UK, reported an overall reinfection incidence of 7.3/100 person-years in HIV-positive MSM who spontaneously cleared their HCV infection, which occurs in approximately 15% of acute HCV infections in HIV-positive MSM [25], or responded to treatment [12]. These findings are in line with studies from Australia and elsewhere in Europe, showing that up to one-third acquired a reinfection within two years [11,26-28]. Temporal trends in the incidence of HCV reinfection have not been investigated, with exception of one recent study from Canada showing that reinfection rates did not diminish over time [29]. Reinfection rates in this study were about half the rates observed in studies from Europe and Australia, indicating that infection rates might be regional specific [29].

In contrast to HIV-positive MSM, HIV-negative MSM are generally not in routine clinical care. Hence, data on HCV incidence are more difficult to obtain. Meta-analyses estimated a 4-to-19-fold times lower HCV incidence in HIV-negative MSM compared to their HIV-positive counterparts and a pooled incidence rate of 0.04-0.15/100 person-years in HIV-negative MSM [30-32]. This is comparable to the incidence observed among HIV-positive MSM in the early 1990s [10,24]. The HCV prevalence among HIV-negative MSM ranged between 0.3% and 1.5% in studies published from 2012 to 2018 [33-40]. These data suggest that HV-negative men remain largely unaffected by the outbreak of HCV among HIV-positive MSM. A higher prevalence (3-4%) was found in studies from Canada and the U.S., but HCV infections were strongly associated with lifetime injecting drug use [41,42]. Data on a rise in HCV incidence among HIV-negative MSM are limited and inconsistent [7]. A serial cross-sectional study among HIV-negative MSM attending a large clinic treating sexually transmitted infections (STI) in the Netherlands showed a stable HCV prevalence (about 1% each year) over the period 2007-2017 [39], suggesting HCV incidence is not increasing in this group. Recently, an unexpectedly relatively high anti-HCV prevalence (4.8%) was found at PrEP initiation among MSM enrolled in a PrEP demonstration project in the Netherlands [19]. An additional concern is that during follow-up in PrEP studies in France and the Netherlands, HCV incidence rates of about 1/100 person-years for primary HCV infection [20,43] and 25/100 person-years for reinfection were found [43], comparable to incidence rates for HIV-positive MSM. Acute HCV infections in MSM using PrEP have also been reported in the United States and United Kingdom [17,18].

2.1.2 | Molecular epidemiology

Molecular epidemiology is increasingly used to identify clusters and transmission pathways in rapidly evolving pathogens such as HIV and HCV. The main aim of these molecular approaches was to aid the public health response by identifying factors of the epidemic, such as hotspots or emerging clusters, otherwise missed.

Molecular epidemiology has revealed several important aspects of the complexity of HCV transmission networks since the first reports on sexually transmitted HCV infections were published in the mid-2000s. Phylogenetic analyses of HCV sequences derived from HIV-positive MSM in England, the Netherlands, Germany, France [23,44], Australia [45] and the USA [46] between 2002 and 2009 revealed the international connectedness of transmission networks. Molecular approaches also demonstrate the overlap of MSM and PWID clusters in Australia, suggesting the existence of social networks in which both injection drug use and sexual risk behaviours are present [47]. The opposite has also been observed: no overlap of MSM and PWID was observed in the Netherlands when comparing genotype 4 infections [48]. Hence, geographically distinct clustering patterns exist. Transmission clusters of genotypes 1a, 1b, 3a and 4d in MSM have been described globally and represent the major circulating variants, although regional differences exist. In Australia, genotype 1 and 3 are overrepresented among MSM, whereas in the United States subtypes 1a and 1b are more prevalent [40]. Subtypes 1a and 4d cause the majority of infections among MSM in western Europe [12,23], whereas in Asia, subtype 1b and 3a are more prevalent [23,49,50]. Moreover, subtype distribution may even vary by country.

Molecular sequence analyses have demonstrated that HIV-negative MSM on PrEP or eligible for PrEP in the Netherlands and France are infected with HCV strains circulating among HIV-positive MSM [19,43]. Transmission from HIV-positive to HIV-negative MSM seems to occur [19,21]. It is difficult to determine precisely to what extent this transmission occurs via injecting drug use, sexual transmission, or other risk factors, but it seems unlikely that injecting drug use is responsible for a majority of the transmission events in HIV-negative MSM; of the HCV-positive MSM using PrEP in the Amsterdam PrEP cohort, only 23.5% (4/18) reported injecting drug use [19], but in France this was 83% (5/6) [21]. However, numbers in both studies were small. Furthermore, declaring injecting drug use does not equate to sharing injection equipment. Viral sequences collected in Australia and New Zealand suggest that HCV transmission occurs through discrete networks, particularly among HIV and HCV co-infected individuals [51]. In this study, three distinct risk profiles based on the molecular analysis were described: PWID, HIV-positive MSM with low probability of injecting drug use, and MSM with both injecting drug use and sexual risk behaviour. Some clusters with low-probability of injecting drug use contained both HIV-positive and HIV-negative MSM.

These findings suggest that sexual networks of HIV-positive and HIV-negative overlap and that HCV transmission occurs between the two groups. Molecular analyses of already collected HCV strains provide insight in the network complexities of sexual HCV transmission. However, they do not easily translate into actionable public health interventions. Real-time molecular surveillance of these networks may be necessary to eliminate HCV from local MSM communities, especially since high HCV treatment uptake may not be sufficient to lower the HCV incidence in this population, as shown in France [52]. Monitoring of cluster emergence, cluster growth, and cluster characteristics provides a way to identify an outbreak early and the drivers thereof. For HIV, efforts to develop such a system led to HIV-TRACE, a real-time molecular surveillance tool that produces data that can be translated into action [53,54]. Real-time molecular surveillance could aid public health professionals in focusing prevention efforts; an epidemic with new infections that primarily cluster with other locally circulating variants requires a different prevention approach than an epidemic with mostly externally introduced variants. In order to facilitate characterization of external introductions, good regional or global reference sequences are necessary, and testing in combination with active data sharing of HCV sequences is needed. Lastly, network variables that may correlate with cluster emergence/growth (e.g. venue of meeting sexual partners, belonging to specific subcultures) [55,56] should be collected prospectively to target specific prevention measures.

2.1.3 | *Risk factors for acquiring sexually transmitted HCV*

Evidence on risk factors for acute HCV infection is largely based on studies among HIV-positive MSM evaluating determinants of primary HCV infection. Although study design, statistical approach and data collection on potential risk factors differ across studies, these studies have consistently shown that in multivariable analyses incident or acute HCV infection is associated with high risk sexual behaviour, including receptive condomless anal intercourse, unprotected fisting, sharing of toys, chemsex and group sex [10,31,57-60]. Also, the association with recent STIs supports a sexual route of HCV transmission [13,58,60-64]. In addition, a recent study from Canada concluded that all but one HCV reinfection in MSM appeared to have been sexually transmitted [29] and the few studies that restricted behavioural risk factor analysis to MSM who denied injecting drug use, demonstrated risks of sexual transmission of HCV [8,65]. However, there is also evidence for blood-to-blood routes of HCV transmission: injecting drug use, which is reported by a minority of HCV-positive MSM in several studies, sharing snorting drug equipment (straws) and rectal bleeding are associated with an increased risk of incident HCV infection [57,58,60,66-68]. Furthermore, younger MSM, peaking at around age 35, are at increased risk of incident HCV infection [24,62].

Finally, studies consistently show that biological factors might play a role: confection with STI, HIV-1 infection in itself, a lower CD4 cell count and higher HIV RNA levels are associated with an increased risk of incident HCV infection [24,58,66,68]. These factors might affect the mucosal microenvironment and activate specific immune cells within mucosal tissues, which would allow HCV entry and retention.

2.2 | Dendritic cells in sexual transmission of HCV

HCV coinfections with other STIs such as HIV-1, Herpes Simplex Virus type 2 (HSV-2), Chlamydia, Human Papillomavirus (HPV), gonorrhoea and syphilis are common [69-71], suggesting that STIs might directly affect the increased susceptibility to HCV upon sexual contact. Dendritic cell (DC) subsets play an important role in sexual transmission of viruses such as HIV-1 and HCV across mucosal tissues [72,73]. DCs patrol the mucosal tissues to capture invading pathogens for antigen presentation to T cells in the lymph nodes [74]. Anal intercourse is the primary route for HIV-1 infection among MSM

individuals [75], underscoring the importance of the anal mucosa as entry site for sexually transmitted viruses. Langerhans cells (LCs), a mucosal DC subset, have been identified in human sigmoid colon, rectal mucosal tissues [76] and anal tissue of MSM [73,77-79]. Also, HCV is shed into the rectum of MSM with HCV infection [80]. Therefore, LCs could be among the first cells that encounter HCV upon sexual contact. Recently, it has been shown that immature LCs do not transmit HCV but activation of LCs changes this protective behaviour and allows for HCV dissemination to hepatocytes (Figure 1) [73]. HIV-1 infection or activation alters the ability of LCs to efficiently capture and retain infectious HCV either for transmission or to receptive cells for HCV viral egress into the bloodstream (Figure 1) [73]. Also, plasmacytoid DCs (pDCs) are able to sense HCV to receptive cells resulting in antiviral type I interferon (IFN) production by pDCs [81], therefore inhibiting viral spread without becoming infected themselves [82]. Both LCs and submucosal DCs migrate to lymph nodes. The migration of DCs to the lymph nodes might allow transmission of HCV to T cells, as HCV RNA has been detected in peripheral blood mononuclear cells [83-86].

Various receptors have been identified on different DC subsets that are efficient in virus capture, infection and transmission [87,88]. The C-type lectin receptors (CLRs) DC-SIGN and L-SIGN recognize high-mannose N-glycans expressed by different viruses and viral glycoproteins to promote capture of the virus through their carbohydrate recognition domain [89,90]. Both DC-SIGN and L-SIGN interact with HCV glycoproteins expressed by pseudotyped HCV particles or HCV present in sera of infected individuals [88,91]. Co-culture of HCV-treated cells with human liver cells leads to virus transmission to the susceptible liver cells *in vitro* [92,93]. Thus, DC-SIGN and L-SIGN mediate HCV transmission and moreover, capture by these CLRs protects the virus from degradation [94], which could further enhance HCV dissemination. L-SIGN is expressed by liver sinusoidal endothelial cells and could therefore facilitate egress from blood into the liver [88]. DC-SIGN is expressed by submucosal DCs and could be involved in sexual transmission of HCV. Notably, single nucleotide polymorphisms in DC-SIGN that reduce DC-SIGN expression were shown to be associated with a reduced risk of acquiring HCV sexually within a MSM cohort [95]. Upon activation, LCs might upregulate other attachment receptors that facilitate capture and transmission. Cell membrane HSPG, called Syndecans have shown to be important in HCV infection of hepatocytes [96]. The interplay of attachment receptors might be important in allowing HCV entry into mucosal tissues and further dissemination of HCV to the liver. Thus, HCV might hijack DC subsets for transmission and important determinants are HIV-1 exposure and/or immune activation by other STIs. Novel therapies targeting HCV interaction with DC subsets and abrogation of DC activation by HIV-1 or other STIs might prevent HCV transmission.

2.3 | Prevention and the treatment potential

Currently, there is no vaccine to prevent HCV infection. However, the recent availability of DAA for the treatment of chronic HCV with cures rates over 95% [97] has created optimism towards HCV elimination. In many countries treatment is now available for all individuals with a chronic HCV infection, irrespective of fibrosis stage [98]. Modelling studies were the first to demonstrate that rapid scale-up of DAA might limit onward transmission and chronic HCV prevalence and incidence among MSM could decline [99-101]. However, for substantial reductions a decline in risk behaviour is needed as the scale-up of DAA is counterbalanced by ongoing risk behaviour, resulting in initial and reinfections [99-101]. In addition, early treatment, including treatment of acute infection, might further reduce HCV incidence [101,102]. As treatment is costly and treatment uptake varies considerably across countries [103], effective behavioural interventions for MSM at risk of (re-)infection are urgently needed. Qualitative research among HIV-positive MSM with a cured HCV infection in the pre-DAA era showed that the strongest motive to implement risk reduction strategies was the reward of avoiding HCV retreatment and its side effects [104], but this may have changed with the less burdensome DAA treatment. Also sexual risk norms within the MSM population, HCV stigma and non-disclosure of HCV status forms barriers to safer sex, and drug use directly impedes the self-efficacy of MSM to take risk reduction measures [104].

Recently, several studies evaluating the effect of behavioural and/or testing interventions with prompt treatment, on HCV incidence among HIV-positive MSM have been initiated [104]. "Real-life" settings in the Netherlands and Switzerland showed that high uptake of DAA among HIV-HCV co-infected MSM in clinical care, in Switzerland combined with intensive HCV-RNA screening and behavioural intervention, was followed by a reduction in HCV incidence [64,105]. In Switzerland, intensive HCV-RNA screening combined with behavioural intervention was followed by a reduction in HCV incidence [64,105]. However, in France, despite a comparable DAA uptake and cure rate, incidence of primary HCV infection continued to increase and reinfection incidence did not significantly change [52]. More data from "real-life" settings are needed to clarify the impact of DAA uptake on the epidemic. As HCV is also circulating among HIV-negative MSM with high risk behaviour [19,20,52,106] effective interventions, behavioural counselling and routine HCV testing as part of comprehensive sexual health care are needed, to curb the HCV epidemic, in particular for MSM eligible for or using PrEP. For the larger population of HIV-negative MSM routine screening is not recommended but periodic monitoring of HCV prevalence remains important [107]. Finally, efforts to identify and motivate the relatively small proportion of MSM unaware of their positive HIV-1 status to test should be continued as this group might harbor undiagnosed HCV infections.

2.4 | Diagnosis and testing

A large proportion of acute new HIV infections among MSM is caused by MSM who were themselves recently infected by HIV [108]. However, for sexually transmitted HCV there are no studies yet formally quantifying sources of recent infections. The continuing transmission of HCV among MSM in areas with high treatment uptake [52,64,105] suggests that apart from undiagnosed HCV infections in MSM, recently HCV-infected MSM might disproportionally contribute to onward transmission. For treatment as prevention to succeed, early diagnosis and prompt treatment of any new infection is

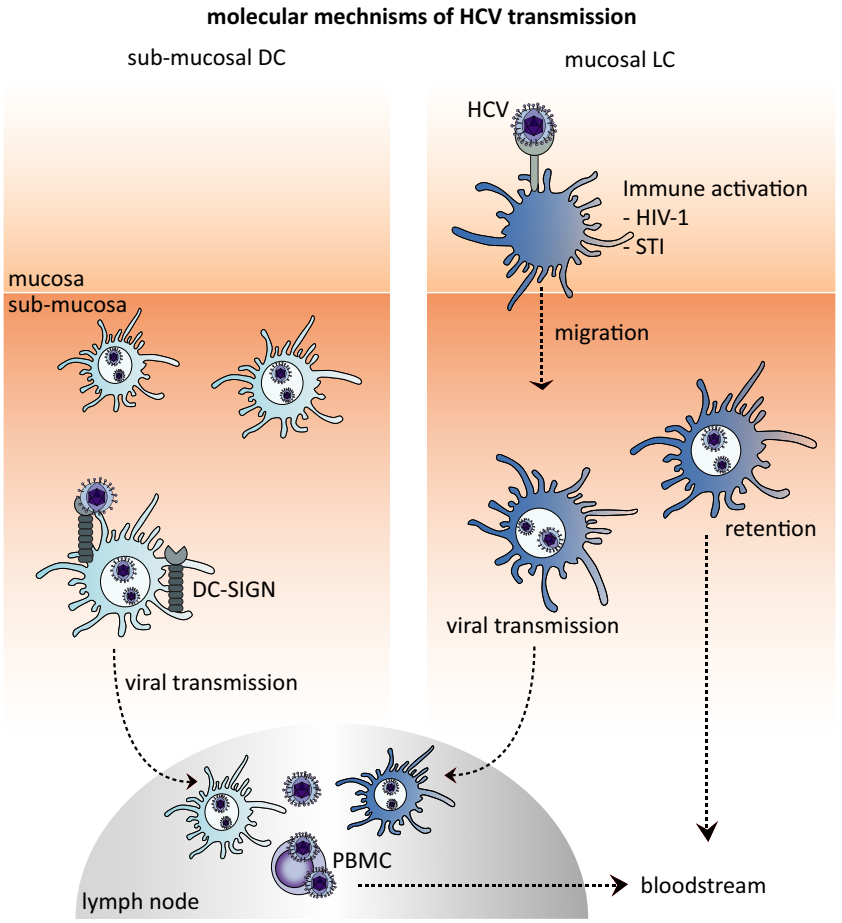

Figure 1. Molecular mechanisms of HCV transmission.
(**A**) Sub-mucosal DCs capture HCV and migrate into the lymphoid tissues to transmit HCV to PBMCs which might lead to further dissemination HCV to the liver. (**B**) Mucosal LCs capture HCV after immune activation by STIs and either retain HCV in the tissue which could increase the chance of virus to egress into the bloodstream and disseminate to the liver or migrate into the lymphoid tissues thereby allowing HCV dissemination to the liver. DC-SIGN, dendritic cell-specific ICAM-grabbing non-integrin; HCV, Hepatitis C virus; HIV-1, Human immunodeficiency virus type 1; PBMC, peripheral blood mononuclear cells; STI, Sexual transmitted infections.

paramount and testing frequency is an important factor in determining success of treatment as prevention [109,110]. Diagnosis of chronic HCV infection includes detection of anti-HCV antibodies, followed by an HCV-RNA test, to distinguish between past and ongoing infection. Diagnosis of acute HCV infection is more challenging as clinical signs and symptoms pointing to acute hepatitis are often absent or aspecific [111]. In addition, HCV-specific antibodies may take a long time to appear: the median time from infection to seroconversion for HCV antibodies is 74 to 91 days in HIV-positive MSM [112,113]. In addition, a minority of patients (less than 5%) remain anti-HCV negative for more than a year [113,114]. Delayed or even absence of seroconversion appears to be caused by HIV-related immunosuppression, as a CD4 + count below 200 cells\μL was associated with seronegative HCV infection [115]. Finally, for diagnosis of acute HCV reinfection, antibody tests cannot be used as after clearance of a primary infection, antibodies may remain present for a long time [112]. Clearly, for diagnosing acute infection early, regular screening, also in asymptomatic patients with a test that directly detects viral RNA or antigen rather than antibodies would be the optimal testing strategy for identifying new cases.

As this comes with a considerable cost, measuring liver enzymes as Alanine Aminotransferase (ALT) level is frequently used as a first step in a diagnostic testing algorithm and has been shown to be more sensitive than testing for anti-HCV antibodies for diagnosing acute HCV infection [113,116]. Although using ALT levels as a first screening step greatly reduces cost as compared to directly detecting HCV RNA, this may result in early acute cases remaining undiagnosed [112,116].

Recently, HCV core antigen has been shown to be a reliable marker for diagnosing HCV infection in chronically infected patients [117]. Regular screening for HCV core antigen may therefore present an attractive strategy for frequent screening of MSM at risk for sexually transmitted HCV. However, reported sensitivity of the core antigen test in a large study with chronically infected patients was 94% when compared with HCV RNA as a gold standard [117]. The reduced sensitivity compared to HCV RNA testing, could result in acute cases remaining undiagnosed, as these

sometimes present with low HCV RNA levels. The few small studies validating the core antigen test for the detection of acute HCV report a sensitivity of 89% to 100% [68,118,119]. Larger studies which include acute HCV cases with a well-documented narrow window of infection are needed before antigen testing can be recommended as a reliable screening strategy for acute HCV infection in routine care.

The cost-effectiveness of HCV screening in MSM could also be increased by focussing on MSM with behaviour facilitating HCV acquisition. Indeed, according to guidelines of the American Association for the Study of Liver Diseases, men with reported high risk behaviour should be offered more frequent HCV testing than the minimal recommended annual testing frequency [109,110]. Risk behaviour can be quantified by using a risk score that is based on risk factors associated with HCV infection. A risk score for identifying acute HCV cases based on six self-reported behavioural risk factors has been developed using data from the MOSAIC study in the Netherlands and appeared to be useful in identifying MSM at high-risk for acute HCV-infection [39]. This risk score was validated using data from three different sources and in these validation studies from Belgium, the UK and the Netherlands, sensitivity ranged from 73% to 100% [39,107]. A risk score could therefore be used as a tool to direct testing resources.

Finally, home-based testing represents an interesting strategy to increase test uptake among high-risk MSM, for example, MSM with a cleared HCV infection, who are at high risk for reinfection. However, currently, only anti-HCV antibody self-tests are available for home-testing, which – as explained above – are not suitable for detecting early acute primary infections or reinfections [120]. Dried blood spots (DBS) collected at home which are sent to a laboratory for HCV RNA testing could be an alternative strategy to facilitate HCV RNA testing. Technically, HCV RNA can be detected on DBS with sufficient sensitivity [121]. The use of home-collected DBS for this purpose remains to be formally validated in terms of technical performance and acceptance by key-populations including key-populations including MSM and PWID. Core-antigen testing on DBS has lower sensitivity and is therefore less suitable for diagnosing acute HCV infection [122].

3 | DISCUSSION

There is growing evidence that HCV is transmitted sexually. In the past decades this epidemic was mostly confined to HIV-positive MSM. However, recent data show that PrEP-using MSM are also at risk for HCV infection, presumably because there is a shared HCV transmission network of HIV-negative and HIV-positive MSM. The association with specific sexual practices strongly suggests that behaviour plays an important role in the ongoing epidemic among MSM. The use of drugs in a sexual context, especially injecting drugs and snorting drugs, is also a major risk factor. The implementation of biomedical HIV-1 prevention strategies, i.e. PrEP and "U=U" (undetectable is untransmittable), might have reduced condom use, and changed sexual networks. This might result in an expanding HCV epidemic in HIV-negative MSM as HCV is more common in HIV-positive MSM. Hence, routine HCV testing and behavioural counselling should be part of PrEP programmes and the epidemic in the larger population of HIV-negative MSM should be closely monitored. And even though DAAs are very effective, the high rate of reinfections further highlights the need for frequent HCV-RNA testing and providing HCV-risk-reduction counselling to MSM with a history of HCV in clinical care. In addition, research into effective interventions aimed at reducing risk behaviour and preventing reinfection should be prioritized as there is a lack of evidence-based interventions and prevention messages might not be sufficient to reduce risk behaviour. Finally, prompt HCV treatment might also contribute to a decrease in HCV prevalence and incidence, especially when combined with additional interventions as part of comprehensive sexual health services.

Factors such as receptive condomless anal intercourse, immune activation by STIs and high-risk sexual practices (e.g. fisting) might increase susceptibility to HCV and could potentially damage the mucosal tissue and cause rectal bleeding, which would facilitate HCV infection [57,60,123,124]. Besides mucosal damage, the activation of mucosal LCs might also allow HCV to enter mucosal tissues and dissemination. HIV-1 infection is a major risk factor in HCV susceptibility, partly because lower CD4 counts but also low HIV-1 replication and immune activation might increase susceptibility. Identification of the molecular mechanisms such as the receptors involved in virus attachment might lead to therapies that prevent sexual transmission of HCV.

Early identification of any recent HCV infections and thus frequent testing of MSM reporting risk behaviour is paramount as these might feed onward transmission. Real-time sequence collection combined with molecular phylogenetics and data collection on network characteristics could identify transmission hotspots, characterize transmission clusters, and determine the relative roles of sustained local transmission versus external introductions, all directing public health efforts to restrain the HCV epidemic among MSM.

3.1 | Study limitations

Studies have consistently shown that the incident of acute HCV infections are associated with high risk sexual behaviour. The role of hygienic procedures (e.g. cleaning sex toys) has not been assessed in these studies but would add to our understanding. Also, no direct comparison of testing strategies, that is, comparing ALT, anti-HCV, HCV RNA and core-antigen longitudinally, for diagnosing acute HCV infection in patients with documented seroconversion exists. As a result, recommendations about testing strategies tend to be somewhat imprecise. Moreover, data on HCV incidence in the wider population of HIV-negative MSM are generally scarce as these men are not in routine clinical care in contrast to HIV-1 infected MSM and MSM using PrEP. In addition, risk factors for incident infection in HIV-negative MSM and for reinfection in HIV positive MSM have not been studied extensively. The lack of such data limits our knowledge on the biological factors that are involved in sexual transmission of HCV. Epidemiological studies show that biological factors also play a role in increased risk of HCV infection. Coinfection with

STIs might affect the mucosal microenvironment and immune activation might change the function of mucosal DC subsets. However, in vivo studies are urgently needed to understand the relevance of the immune cells in HCV transmission and to decipher the route from mucosa to liver.

As HCV (re)infection rates might be regional-specific, more data from other parts of the world than Western Europe, North America, and Australia are needed to obtain a more detailed view of the HCV epidemic among MSM. DAAs are highly effective in curing HCV, but more data from "real-life" settings are needed to clarify the impact of DAA uptake on the epidemic.

4 | CONCLUSIONS

It has been established that HCV can be transmitted via sexual contact. The spread of HCV among HIV-positive MSM in the past two decades and the recent finding of HCV infections in HIV-negative MSM eligible or on PrEP, as well as the association with specific sexual practices, strongly suggest that behaviour plays an important role in the ongoing epidemic among MSM.

Drug use in a sexual context and biological factors as coinfection with STI and HIV-1 also seem to play a role in facilitating HCV spread. At mucosal sites, DC subsets might play a role in HCV dissemination. Targeted and combined prevention efforts including effective behavioural interventions and scale-up of HCV testing and treatment are required to halt HCV transmission in MSM. In addition, real-time molecular surveillance could guide and evaluate prevention strategies.

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COMPETING INTERESTS

All authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

BMN wrote the manuscript, assembled and edited the manuscript. JK wrote the manuscript. JS wrote and edited the manuscript. MP wrote, edited and reviewed the manuscript. TBHG wrote, edited and reviewed the manuscript.

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COMMENTARY

Improving care for sexually transmitted infections

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Abstract

Introduction: Rising rates of reported sexually transmitted infections (STIs) in the US and Europe are a public health priority and require a public health response. The diagnosis and treatment of STIs have been the cornerstone of STI control and prevention for many decades and, historically, publicly funded STI clinics have played a central role in the provision of STI care. Innovations in non-invasive diagnostic techniques, especially nucleic acid amplification tests in the mid-1990s, have facilitated the expansion of STI testing and treatment outside traditional STI clinics, including primary care, family planning, school-based health, outreach, corrections, emergency departments and HIV prevention and care settings. As a result, the continued need for categorical STI clinics has been debated. In this Commentary, we discuss how practice can be improved at each level of STI care.

Discussion: STI practice improvement plans should be tailored to the strengths of each care setting. Thus, in primary care, the focus should be on improving STI screening rates, the provision of hepatitis B and human papillomavirus vaccines and, in jurisdictions where this is legal, expedited partner therapy for gonorrhoea and chlamydia. Extragenital (pharyngeal and rectal) testing for gonorrhoea and chlamydia should be available in settings serving populations more vulnerable to STI acquisition at these anatomical sites, including men who have sex with men. In family planning settings with a mostly female patient population, there are opportunities to serve male partners with both contraceptive and STI services. STI screening rates can also be improved in other settings serving populations at increased risk for STIs, including school-based clinics, emergency departments, correctional health facilities and providers of HIV care and prevention. These improvements are predominantly logistical in nature and not dependent on extensive STI clinical expertise. While some providers in these settings may have the clinical knowledge and skills to evaluate symptomatic patients, many do not, and STI speciality clinics must be available for consultation and referral and evolve from "safety net" providers of last resort to STI centres of excellence.

Conclusions: A tailored practice improvement plan can be envisioned to achieve an optimally functioning STI care continuum.

Keywords: STI; medical care; prevention; differentiated care; HIV prevention; health systems

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1 | INTRODUCTION

The consistent rise in the number of reported sexually transmitted infections (STIs) in the US [1] and Europe [2] presents a public health priority requiring an urgent public health response.

The reasons for rising STI rates are not fully understood. Men who have sex with men (MSM) are most vulnerable to STI acquisition and have experienced disproportional increases in gonorrhoea and syphilis rates [1]. Evidence suggests that changing perspectives on HIV transmission risks brought about by effective HIV treatment and pre-exposure prophylaxis (PrEP) have led to changes in attitudes towards condom use and other prevention strategies with the unfortunate result that HIV risk reduction may be accompanied by increasing the risks for other STIs [3-5]. However, rising STI rates are not limited to MSM. The resurgence of syphilis in the US now also involves heterosexual men and women, and the increasing congenital syphilis rates are alarming [1]. Other reasons may contribute to rising STI rates. Substance use ("chemsex") is associated with increased sexual risk behaviours [6,7] and the recruitment of sex partners is facilitated by online dating sites and apps [8]. Increased case finding also plays a role, for example, the implementation and adherence to annual chlamydia screening for sexually active women [9]. In addition, it has been appreciated for some 15 years that asymptomatic extragenital (pharyngeal and rectal) gonorrhoea and chlamydia infections are very common among MSM and that failure to screen these anatomical sites may lead to underestimating the infection burden by more than 50% [10]. Current STI screening guidelines stress the importance of extragenital testing among MSM [9], and thus lead to enhanced case finding. Finally, a fraying public health infrastructure is blamed for the syphilis resurgence among heterosexual populations and the associated rise in congenital syphilis [1].

While the underlying causes of the rising STI trends will continue to be elucidated, this should not delay an urgently needed public health response.

Historically, the diagnosis and treatment of STIs have played a key role in public health STI control efforts. However, while

the concept of "treatment as prevention" has only recently entered the lexicon of HIV prevention [11], it has been the guiding principle for STI control and prevention for many decades, enabled by the introduction of penicillin and other antibiotics after the second world war when syphilis and gonorrhoea were at epidemic highs. Given the public health importance of STI treatment and the stigma associated with these diseases, publicly funded "categorical" STI clinics became a critical component in the fight against STIs. Frequented by patients with symptomatic STIs who did not have other sources of medical care or who chose these clinics for confidentiality reasons even if they had access to other care providers, these clinics became a "safety net" for stigmatized populations at high risk for STIs, including MSM, sex workers and people who inject drugs.

An important limitation of relying on the care of symptomatic patients to control STI was the increasing recognition of the asymptomatic nature of many STIs and a growing awareness that STI control could not be accomplished by just focusing on patients with symptomatic infections: the proverbial tip of the iceberg. However, the alternative – the establishment of screening programmes for asymptomatic (high-risk) persons – was stymied by insensitive and cumbersome tests requiring invasive (urethral, cervical) sampling techniques that were not widely available and not particularly attractive to the public.

The development of highly sensitive nucleic acid amplification tests (NAATs) using non-invasive, self-sampled specimens (urine, vaginal or anal swabs) have dramatically changed the STI prevention landscape since the mid-1990s [12]. Such tests, including combined chlamydia/gonorrhoea NAATs, could now be done easily in a variety of non-STI clinic settings, including primary care, family planning, HIV prevention and care and even outreach [13] as well as home-based testing programmes facilitated by the growing popularity of the Internet [14]. Public health screening recommendations, for example, routine annual chlamydia screening for young sexually active women [9], became feasible. As a result, increasing numbers of STIs, especially chlamydia infections, are now reported from non-STI clinic settings, including primary care (both private and public) and family planning clinics [1].

With the widening array of STI care providers and with increasing access to these providers, for example, through the implementation of the Affordable Care Act in the US, the role of publicly funded STI clinics as safety net providers has become increasingly scrutinized and a number of clinics have closed their doors or have curtailed their services [15]. Unfortunately, at the same time, STI rates have been increasing in the US and elsewhere, and it is tempting to speculate that the dismantling of the public health STI care infrastructure may be causally related to these trends [15].

2 | DISCUSSION: IMPROVING STI SERVICES

The increasing importance of multiple sources in the overall provision of STI care should be recognized. Rather than fearing a fragmented system, a practice improvement plan should be designed that builds on this diversity and tailors recommendations to the STI services that are provided at each level.

2.1 | Primary care

Screening for chlamydia and gonorrhoea using non-invasive NAATs has become a standard of practice in many primary care settings, including private providers and publicly funded health centres. Indeed, a large number of infections are reported from these providers already [1]. But there is room for improvement. It is estimated that only 40% to 50% of sexually active women under the age of 25 are screened for chlamydia annually in primary care settings in the US [16]. With advances in electronic medical records, allowing for automated prompts, as well as test reimbursement schemes, there is no reason why screening rates should not be higher.

Likewise, coverage for HBV and HPV vaccinations can be improved by including it in standard immunization schemes recommended for primary care settings [17]. Also, in jurisdictions where this is legal, primary care providers should be encouraged to implement expedited partner treatment (EPT) for patients diagnosed with gonorrhoea or chlamydia [9].

However, while some primary care physicians serve populations at high risk for STIs and are quite comfortable with the differential diagnosis and treatment of STI, most encounter symptomatic STIs infrequently, and their expertise may vary when evaluating and treating patients presenting with relatively rare STI, including primary and secondary syphilis and lymphogranuloma venereum. Developing such skills would not be practical in settings with an already overburdened medical staff. It is important, however, that they should have easy access to consultation with STI experts in their region or through online resources [18].

2.2 | Family planning

Priorities in family planning facilities are focused on the provision of contraception, but with growing expertise, these clinics have become important providers of STI care, especially for women. Screening for chlamydia and other STIs has become common practice in this setting, especially since the widespread adoption of chlamydia/gonorrhoea NAAT assays. Family planning clinics are also increasingly encouraged to expand their services to men. However, even though average male attendance is growing, it is still low in many clinics, for example, less than 10% in publicly funded family planning clinics in the US [19]. As a more holistic sexual health paradigm is gaining ground [20], further STI service and skills development in family planning clinics and appeal to other populations would be a welcomed expansion of the STI care infrastructure.

2.3 | HIV prevention and care settings

The resurgence of STIs among MSM [3] has profoundly affected traditional HIV prevention and care settings. HIV testing sites, whether clinic- or outreach-based, are increasingly providing chlamydia/gonorrhoea NAATs and syphilis serologic testing. Many sites now offer chlamydia/gonorrhoea testing for all exposed anatomical sites (including urine, anal and pharyngeal sampling) and, with most

laboratories validated for testing of extragenital samples, this should be the standard of care at these settings. However, many HIV testing sites are staffed by non-medical (outreach) providers, and clinical expertise is often not available for further evaluation and treatment. Strong collaborations with local STI or HIV care clinics are necessary for consultation, treatment and follow up of clients presenting with (symptomatic) STIs [21].

Persons living with HIV, especially MSM, are at disproportionate risk for STIs, including syphilis, gonorrhoea and chlamydia [1]. Regular screening for these infections, including extragenital gonorrhoea/chlamydia testing, should thus be the standard of care in HIV care practice. Most guidelines recommend screening at six-month intervals, but the frequency should be determined by sexual risk assessment [9]. Since HIV care providers (in contrast to STI clinics) see their patients regularly, they have a unique opportunity to identify and treat incident STIs in this key population.

Models for the provision of HIV PrEP are developing, ranging from active referral mechanisms to on site provision of antiretrovirals in a variety of settings, such as HIV care, STI clinics and primary care. There is much debate about whether PrEP is related to increases in sexual risk behaviours. But there is no doubt that persons on PrEP have a high risk for STIs [22] and regular (three to six months) screening for STIs should thus be part of the standard of PrEP care [23].

2.4 | Other settings

Given the highest rates of chlamydia and gonorrhoea among women aged 15 to 20 years and men aged 20 to 25 [1], there is a strong rationale for offering basic STI services, including chlamydia and gonorrhoea screening and condom distribution to sexually active adolescents and young adults in school- and college-based health centres. At least one recent US study suggests that there is considerable public support for offering these services in these settings [24]. Other settings serving populations at high risk for STIs where basic STI screening is feasible but not yet fully scaled up include correctional facilities [25,26] and emergency departments [27].

2.5 | The future of the STI clinic

Within the landscape of multiple STI care providers, evidence supports the continued importance of categorical STI clinics. In numerous countries where health insurance is near universal and where primary healthcare providers offer basic STI testing, STI clinics are nonetheless thriving. For example, the STI clinic in Amsterdam is on course to see almost twice the number of patients in 2018 (50,000 visits) than it saw in 2000. This is despite universal healthcare access in the Netherlands and a clinic policy that defers low-risk and asymptomatic patients to their primary care physicians.

This growth in patient population is in large part but not exclusively due to increasing numbers of MSM visiting the clinic, reflective of higher rates of STI in this population over the past two decades [28]. Similar shifts towards higher proportions of MSM visiting STI clinics has been observed elsewhere, including the US [29,30]. Reasons for continued use of STI clinics include client perceptions of clinic expertise, confidentiality, easy access, same-day services and low or no cost [31]. Even patients with newly acquired health insurance will continue to use the STI clinic as they may be reluctant to use their insurance due to confidentiality [31].

In this emerging landscape of STI care, what should the future role of publicly funded STI clinics be? Foremost, it should be recognized that categorical STI clinics, unlike other STI service providers, have STI treatment and prevention as their primary public health mission. They should thus function as a central hub in their local and/or regional STI provider network and be an essential partner in the overall STI public health response in the region. Rather than "safety net clinics" that are doomed to become obsolete once access to (primary) health services is assured, these clinics should be centres of excellence that provide the delivery of expert STI clinical care, state-of-the-art diagnostic capabilities and on-site treatment and follow up, (including EPT). They should be available for low-threshold referral and consultation. They should also be a resource for sentinel surveillance research, including gonococcal resistance [29,32], and for research in the development of new STI diagnostics and treatment, as well as for clinical training and workforce development [33,34].

From a morbidity/mortality and cost perspective, HIV is still the most important STI. STI clinics disproportionally serve populations at high risk for HIV, diagnose persons with HIV and link them to care, and are becoming an increasingly important gateway for PrEP care [35]. HIV prevention services are thus a central component of the STI clinic mission. In fact, some clinics, where patients find it difficult to follow through on HIV care or PrEP referral, have started to provide HIV and PrEP care on site, essentially making the concept of "safety net provider" come full circle [36].

With typically constrained resources, STI clinics must provide their services in the most cost-efficient manner. Non-invasive NAATs for the diagnosis of gonorrhoea and chlamydia allow the triage of patients into those that need full examination versus those who need only screening: so-called "express visits," which has significantly increased efficiency and lowered costs for STI clinics [37-39]. The "express visit" model has now been widely adopted and has even led to the emergence of stand-alone express clinics, for example, Dean Street Express in London [40]. While such stand-alone clinics are promising for asymptomatic populations that require frequent STI testing (such as persons receiving HIV PrEP), they may not be staffed to serve patients with symptomatic STI and should thus have a mechanism to refer those patients to STI speciality care [41].

Finally, in an era of dwindling public spending, publicly funded STI clinics should be proactive in finding ways to diversify their funding. Given overlaps between STI and pregnancy risk among (young) women, the provision of family planning services in STI clinics makes sense from a sexual health perspective, and many clinics have integrated these services and broadened their funding base [42].

Billing patients for services may seem to be anathema to the public health mission of STI clinics as it could raise barriers to access. However, carefully designed schemes that encourage patients to use their insurance, while readily allowing them access if they choose not to use insurance and have no other means of paying, could still result in a

sizeable source of revenue [43]. In the US, nurse practitioners, but not regular nurses, can independently bill for services. This has been an additional impetus for certain clinics to provide a billable service that can be provided by these practitioners, including PrEP and the placement of intrauterine birth control devices and other long-acting, reversible contraceptives.

Given their patient/client base, STI clinics are also in a good position to apply for (sentinel) surveillance and research projects, including studies on gonococcal antimicrobial resistance and rapid, point-of-care diagnostics. Currently, few STI clinics are positioned to profit from these opportunities. However, there are many more clinics that, with additional effort, could rise to a level that would benefit not only their patients but also their bottom line.

3 | CONCLUSIONS

The future of STI control and prevention is daunting, but it is also promising. There is now a large and potentially growing array of STI service providers, both in public and private sectors, that can have significant impact on STI control when forged together in a single vision. The diversity of STI care providers has in large part been made possible by the advent of non-invasive testing technologies. Further advancement in technology, specifically the development of rapid, sensitive and specific point-of-care testing, which is already on the horizon, will provide additional tools for STI diagnosis and control. What is needed above all is a continued passion and advocacy for STI and HIV prevention.

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COMPETING INTERESTS

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VIEWPOINT

Community engagement in the provision of culturally competent HIV and STI prevention services: lessons from the French experience in the era of PrEP

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Communities have been a driving force in the response to the HIV epidemic, advocating for research, the access to treatment and healthcare, and human rights for key populations (KP) and people living with HIV (PLHIV). The importance of community engagement (CE) in the development and implementation of pertinent programmes throughout the HIV care continuum has been widely recognized [1-3]. In the context of increasing pre-exposure prophylaxis (PrEP) research, interest and access (though still limited), there is an opportunity to have a fresh look at CE regarding HIV/STI research and care delivery. France, where PrEP has been authorized and fully reimbursed since 2016, may provide key lessons for CE in the provision of comprehensive, culturally adapted HIV/STI prevention and treatment services.

Community involvement in HIV/AIDS is political and ethical. Community-based organizations (CBOs) such as Gay Men's Health Crisis (US), Terrence Higgins Trust (UK), the Grupo Pela Vidda (Brazil), AIDES (France), or international organizations such as ACT-UP, have historically played important roles in advocating for suitable information on prevention tools and adequate access to health for PLHIV and most-at-risk populations [2-4]. PrEP research is not an exemption [5]. For example, Act Up-Paris and others advocated for the early termination of two PrEP studies due to, among other reasons, the lack of medical services for those who seroconverted on study [6-9]. While implementation of "Good Participatory Practice Guidelines" [10,11] and community advisory boards [12] in research studies are steps forward, further effort is needed to ensure more meaningful CE throughout the entire life course of research studies [13,14]. For example, by building the evidence-base for CE and evaluating its success in meeting community needs [15].

In 2008, AIDES adopted a unique strategy to invest financial and human resources for the creation of a community-based research unit. Working in partnership with research institutions and funding bodies, community-based studies have identified community needs and contributed to the development of innovative and adapted services: rapid HIV testing, educational sessions for injection drug users, and PrEP counselling.

While medical providers may lack the time, skill and/or motivation to address sexual health issues [16,17], CBOs are well-placed to identify the sexual health needs of KP and provide comprehensive and adapted care [18]. The Fenway Community Health Center in Boston provides comprehensive "culturally competent" care [19]. The 56 Dean Street clinic in London offers a succesful well-being programme and an "express" service for self-sampling HIV and STI tests [20]. In Bamako, the CBO ARCAD-SIDA's night sexual health clinic provides testing and treatment services for MSM and sex workers [21]. Finally, results of a community-based testing satisfaction survey conducted by AIDES [22] partially led to the creation of two community-based sexual health structures that integrate sexual and mental health consultations (SPOT Beaumarchais in Paris and SPOT Longchamp in Marseille). Community-based clinical programmes are important examples of how communities and medical professionals may work together to develop and provide effective services.

PrEP provision is an opportunity to provide comprehensive sexual health services, engage individuals on their needs, and to equip them to better evaluate and reduce their HIV/STI risk. AIDES has been a full partner in two PrEP studies: ANRS-Ipergay [23] and ANRS-Prévenir [24,25]. Peer counselling, provided by AIDES counsellors, was constructed collectively with social science researchers (GRePS and Inserm). Based upon individual needs and expectations, discussions go beyond purely medical aspects regarding PrEP to include questions such as "What risks can you identify related to your sex life?" and "Is your sex life as fulfilling as you would like?." Therefore, PrEP is not an end in itself, but rather an opportunity to empower communities regarding sexual health.

As PrEP protects from HIV but not STIs, appropriate and adapted risk reduction methods such as prophylactic antibiotics [26] should be considered. Follow-up appointments, required in the provision of PrEP, allow for STI information, regular screenings and early treatment. However, this regular hospital medical follow-up can represent a barrier, and respondents to a European community-based survey felt that PrEP should be available at community-based health settings or at the general practitioners' [27]. Provision of HIV and STI services outside of traditional medical structures is essential to reach populations who are most exposed and face access barriers. Community-based initiatives such as community-based testing have reached at-risk populations as well as those who have never been tested [18,28] and have identified individuals at an earlier disease stage [29]. More innovative partner notification strategies, such as Check-Out™ developed by the Checkpoint LX in Portugal [30], may be used in the context of PrEP [25].

All communities particularly affected by HIV and STIs must be involved in the development of adapted and inclusive information and programmes regarding provision of PrEP and/or other services (e.g. PEP, STI prophylaxis) which reach KP other than MSM. Regarding transgender people, for example, concerns related to finding "trans-competent" providers and potential interaction with hormones should be addressed [31]. The Thai Red Cross Tangerine Health Center is one example of a community-engaged model providing comprehensive services for transgender women [32]. Women may experience barriers to PrEP, indicating a need for adapted services. Several community-based initiatives are increasingly providing tailored PrEP information to increase awareness among women [33,34]. CE is also critical for the development of adapted and sustainable prevention programmes among sex workers [35,36]. Finally, it is necessary to address stigma related to sexual preferences, drug use, sex work and PrEP use [37-39].

Communities have the knowledge, skills and motivation to provide culturally adapted information and services for PLHIV and KP. Community-based initiatives can and must go further. For example, community-based ART delivery, already implemented in some southern countries [40], needs to be expanded to northern countries. Partnerships between communities and traditional health structures will require the support of governments and international bodies to implement and enforce policies for task shifting in addition to significant funding. We call for a united effort amongst government bodies, health providers, and CBOs to make a comprehensive, positive approach to sexual health for PLHIV and for those most exposed to HIV a reality.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

BS, DRC, RMD, SM and DM conceptualized the commentary. SM and DM provided content on AIDES' community-based approach and activities. BS, DRC, RMD, SM and DM discussed key ideas and concepts forming the basis of this commentary. RMD and DRC reviewed the literature and wrote the manuscript. All authors reviewed and approved the final version.

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