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Sexually transmitted infections among African women: an underrecognized epidemic and an opportunity for combination STI/HIV prevention

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Introduction

An estimated 358 million new cases of the four most common curable sexually transmitted infections (STIs) – the three bacterial pathogens, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum*, plus the parasite *Trichomonas vaginalis* – are acquired worldwide annually.[1–3] Globally, the burden of STIs is greatest in low- and middle-income countries (LMIC), and the overlapping epidemics of HIV and STIs have been recognized since the earliest days of the HIV epidemic.[3–8] The majority of new HIV infections occur in sub-Saharan Africa,[9] and sexually active African women (particularly those under age 30) face disproportionate HIV risk, accounting for more than half of new infections on that continent, and with incidence rates that are often double their male age-mates.[10–12] The consequences of bacterial STIs on sexual and reproductive health can be significant and long-term through sequelae including pelvic inflammatory disease (PID), chronic pelvic pain, tubal infertility, pregnancy complications, fetal and neonatal death, and heightened susceptibility to HIV.[3, 5, 6, 13, 14] These consequences - physical, psychological, and social - of STIs are overwhelmingly borne by women.[15, 16]

Current STI control strategies for women in low- and middle-income countries

In most LMIC, STI prevention efforts are limited to condoms, treatment of symptomatic cases to reduce complications and interrupt transmission, partner notification and treatment,

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and abstinence. For many women in such settings, the impact of those strategies is limited in several ways. First, strategies like partner testing or notification rely heavily or exclusively on partner participation, which may not be feasible; in some instances, these strategies risk intimate partner violence.[17–19] Second, sexual intercourse is often neither predictable nor under the control of many women in LMIC, limiting the impact of STI prevention strategies like condom use or abstinence. Third, standard STI control strategies utilize syndromic management, which relies on the detection of symptomatic cases only and has very limited sensitivity (27–61%) for diagnosis of STIs in women.[20, 21] Indeed, the use of syndromic management strategies creates a management paradox with high rates of untreated asymptomatic STIs and increased potential for selection of resistant organisms and disruption of the vaginal microbiome by low-specificity, broad-spectrum, empiric treatments.[21] Thus, in many LMIC settings, STI control programs, designed principally to prevent sequelae of symptomatic STIs and interrupt transmission when possible, tend to be reactive rather than preventive.

STIs in the context of PrEP

In resource-rich settings, the past decade has seen an unprecedented rise in the incidence of bacterial STIs, with the largest increases among men who have sex with men (MSM), coinciding with the scale-up of pre-exposure prophylaxis (PrEP) for HIV,[22–24] recognition of antiretroviral treatment as prevention (including dissemination of the concept of undetectable = untransmittable [U=U]),[25, 26] increased detection due to increased STI testing, and changing trends in condom use and sexual mixing patterns.[27, 28] Specifically, the role of PrEP in influencing changes in sexual behavior and increased risk for STI acquisition among MSM using PrEP is a source of substantial scientific and public health debate.[22] PrEP reduces incident HIV,[29] but is not expected to prevent bacterial STIs, including gonorrhea, chlamydia, or syphilis, and studies from multiple resource-rich settings have revealed high incidences of these STIs, with low incidence of HIV, among MSM taking PrEP[22, 23, 30] and MSM in general in the PrEP era, although whether and to what degree PrEP has contributed to such rises is not clear. STI control efforts, with a focus on increasing testing, have been reinvigorated for MSM in resource-rich settings, and novel STI interventions for MSM are being developed.[31–33]

Because of shared sexual risk factors, PrEP guidelines include recommendations for regular STI screening for PrEP users, but diagnostic screening is not available in most healthcare settings in many LMIC.[34, 35] Thus, few data are available on rates of curable STIs among women who would benefit from or who have initiated PrEP, although women bear the highest risk of consequences from untreated bacterial STIs; indeed, even in resource-rich settings, very little data are available for STI rates for cisgender women, as most PrEP programs focus on MSM and transgender women.[36, 37] In LMIC, recent data from a limited number of pivotal PrEP studies contribute some of the only information about both STI prevalence and incidence among women in Eastern and southern Africa (Table 1).[38–41] These STI rates (*C. trachomatis* acquisition in excess of 20% per year and *N. gonorrhoeae* greater than 10% per year) in women presenting for PrEP in Africa are extraordinarily high and comparable to those arising during PrEP era among MSM in North America, Australia, and Europe.[42] Thus, even before widespread introduction of PrEP in Africa, women have

reached rates comparable to STI crisis among MSM, and there is concern that rates could increase even further in parallel with PrEP scale-up. Data are not yet available to triangulate PrEP use, behavioral risk compensation, and STI risk among women living in Africa.

STI prevention in the setting of rising antibiotic resistance

Rising antimicrobial resistance is a global threat. Multi-drug resistant *N. gonorrhoeae* is a prominent example of this growing international public health issue, with 66% of countries reporting some resistance to extended-spectrum cephalosporins between 2009–2014, and risk of untreatable cases in the near future - based on the forecast of diffuse resistance to beta-lactams, macrolides, and tetracyclines.[43–47] In addition to mounting fears over multi-drug resistant gonorrhea, there are now hints of drug resistance in other curable STIs, including syphilis and *Mycoplasma genitalium*.[48–51] Importantly, and in contrast, *C. trachomatis* has never been reported to express resistance, but is theoretically possible based on rare *Chlamydia suis* resistance documented in pigs.[52–54] In sub-Saharan Africa, antimicrobial resistance data are more sparse but the few data that exist suggest rates of resistance to first line empiric therapies as high as other settings (Table 2).[43–45, 55–59] New antibiotics are in development and under evaluation for the treatment of *N. gonorrhoeae* infections with varying success.[60–62] In the era of rising resistance, new prevention and treatment approaches are needed, particularly ones that limit resistance-inducing antibiotic exposure.

Strategies for STI prevention: opportunities for STI/HIV combination prevention for women

The global epidemic of STIs in women demands new prevention approaches for curable STIs through timely diagnosis and treatment of women and their partners, with abstinence or condom use during treatment to prevent reinfection by partners, or by averting infections in the first place. New strategies are emerging that offer opportunities for research and program delivery of combination STI/HIV prevention (Table 3).[21, 63–68]

Point-of-care testing

In resource-rich settings, etiologic screening with high-sensitivity testing done on asymptomatic individuals is the backbone of STI control, detecting the bulk of infections that result in ongoing STI dissemination.[69, 70] Even in such settings there are important limitations to screening, including laboratory result turnaround time, loss to follow up, reinfection, and the fact that testing is principally about secondary prevention.[71] While high-sensitivity nucleic acid amplification tests revolutionized STI diagnosis, usually such testing is costly and requires specialized laboratory facilities. The use of point-of-care (POC) STI testing has the potential to improve access to STI screening as well as detection and prevention of antibiotic resistant infections through POC molecular detection of key mutations and immediate treatment of specific pathogens.[72, 73] POC testing could thus be useful for both LMIC and resource-rich settings. Early POC assays lacked sensitivity and did not generate substantial enthusiasm.[74, 75] In contrast, a ‘near POC’ machine, Cepheid GeneXPert, has recently been validated for POC molecular testing for *N. gonorrhoeae* and

C. trachomatis with high sensitivity (97.4–98.7%) and specificity (99.4–99.9%).[76–78] GeneXPert macines are already widely available in LMICs for diagnosis of *Mycobacterium tuberculosis,* but the high cost per test (approximately $16/test) and 90 minute wait time are important limitations for its use.[79] Newer POC technology by binx health (formally Atlas Genetics) with faster (less than 30 minute) time to results was recently validated with modestly lower sensitivity (84%) and high specificity (99%) for detecting *C. trachomatis* in a pilot analysis,[80] with plans to release a combined, rapid POC test for *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, and *M. genitalium*. In addition to advances in POC testing, ongoing trials of binx health rapid tests for home-use provides encouraging possibility for LMIC if affordable. To scale screening for asymptomatic but pathogenic STIs in LMIC, real-time, sensitive STI tests,[73] standardized self testing strategies,[72] and cost-effectiveness studies are needed. In addition, bulk purchase guarantees and price negotiations by donors, which facilitated widespread use of HIV self-testing, and implementation studies incorporation of diagnostic STI testing in resource-constrained settings are needed.

Expedited partner therapy (EPT)

The high incidence of STIs in heterosexual women is likely due in part to reinfection,[81] indicating that syndromic management is insufficient for treating asymptomatic cases and cases in sexual partners. One way reinfection can be addressed is through partner treatment; however, getting partners to present to clinic is a global challenge. Expedited partner therapy (EPT) or provider-assisted partner therapy are proven solutions.[64, 82] EPT, in which patients who have a diagnosed STI are supplied with additional treatment to deliver to their partner(s), is recognized in the US as a useful public health strategy when treating male partners of women with chlamydia or gonorrhea.[31, 83] One small study in South Africa found high rates of acceptability and successful reduction of *C. trachomatis*, *N. gonorrhoeae*, and *T. vaginalis*,[78] and recent studies completed in several African countries have found EPT and partner notification to be acceptable with on-going trials exploring impact on STI recurrence.[84]

Periodic presumptive STI treatment

Periodic presumptive STI treatment has been tested in a number of settings, in different ways. Several trials have tested periodic empiric therapy for STIs among female sex workers in LMIC, often as a strategy to reduce acquisition of HIV.[65, 85, 86] Community level interventions with periodic mass treatment for STIs have also been evaluated; these found limited effects on the incidence of HIV but showed some reductions in STIs.[87–91] A systematic review of data from studies done in 10 countries across Africa and Asia reported that periodic presumptive therapy could result in a 40–60% reduction in *N. gonorrhoeae* and a 47–62% reduction in *C. trachomatis*.[92] WHO recommends time-limited periodic presumptive STI treatment for sex worker populations with high STI prevalence;[93] however, neither mass treatment nor presumptive therapy have been implemented at scale due to concerns about lack of specificity and risk of generation of antibiotic resistance.[92]

Doxycycline post-exposure prophylaxis

A recent open-label clinical trial randomized 232 MSM taking PrEP for HIV prevention in France (IPERGAY) to take 200 mg doxycycline as an STI post-exposure prophylaxis (PEP) following condomless sex versus no doxycycline, finding a 47% relative reduction in new bacterial STIs with doxycycline PEP.[67] The reduction was as a result of large decreases in new cases of *C. trachomatis* (70%) and *T. pallidum* (73%). There was no reduction in *N. gonorrhoeae*, perhaps in part due to high levels of tetracycline resistance in Europe. These results have spurred global debate about the potential role of antibiotic PEP for STI prevention.[94] The use of antibiotics to prevent infections is an established intervention – for example, doxycycline is used after tick exposure in areas of high Lyme disease prevalence and as malaria or leptospirosis prophylaxis for travelers.[95–97] Trials of doxycycline PEP are being launched among MSM on PrEP and MSM living with HIV[98] to provide additional data on effectiveness and antimicrobial resistance. There are several upcoming trials of doxycycline PEP in US, France, and Australia[99] as well as one trial among Kenyan women.[100] Use of doxycycline PEP has potential for efficacy in populations with high chlamydia incidence and sequelae, such as women in LMIC. It is not yet known if doxycycline will be accepted, tolerated, and effective as a post-exposure prophylaxis for sexually active African women and the impact on antimicrobial resistance. These concerns about potential benefits and risks of doxycycline PEP are reminiscent of concerns raised in the early days of PrEP development (Table 4). On the other hand, similar to acceptability and importance of emergency contraception for women to reduce the risk of unwanted pregnancies,[101, 102] if doxycycline is demonstrated to have high effectiveness, safety, and acceptability, it could be a significant female-controlled intervention to reduce risk of STIs.

STI vaccines

Vaccine development for STIs is an international priority outlined in the WHO global roadmap in 2013; however, no vaccines are currently available to prevent bacterial STIs.[103] Early stages of *N. gonorrhoeae* and *C. trachomatis* vaccine development are ongoing, [104–108] and a *C. trachomatis* vaccine is entering phase 2 trials. Interestingly, a recent retrospective analysis of persons who presented with any type of STI in New Zealand found that those who had received a *Neisseria meningitidis* B vaccine had a 31% reduction in *N. gonorrhoeae* compared to those who had not received the meningitis vaccine.[68] Recent evaluation of immune response in mice following meningococcal vaccination indicates that attenuated outer membrane vesicle vaccines elicit gonococcal antibodies.[68, 109] These intriguing results, which need replication in other settings and with more controlled study designs, suggest that licenced meningococcal B vaccines containing outer membrane antigen could have the potential to modestly reduce gonorrhea rates and suggests the possibility for a gonococcal specific vaccine in the future.[110]

PrEP roll out is an opportunity for improving STI services

PrEP will continue to scale up to meet international targets for ending the HIV epidemic, [111, 112] and given the high rates of bacterial STIs in Africa, treating and preventing STIs will continue to be relevant even as longer-acting PrEP formulations become available. The STI epidemic must be addressed and PrEP roll-out provides an opportunity to impact both

HIV and STI rates in sexually active African women. PrEP users are an ideal population for STI prevention efforts – they have demonstrated engagement in prevention, have high risk for STI exposure, have regular encounters with clinical services, take medication for prevention, and ideally could undergo periodic STI screening as part of PrEP services. Since 2017, several African countries have developed national PrEP guidelines for young women, and many additional African countries are expected to follow. International donor funds have generally not supported public health implementation of STI services integrated within HIV treatment and prevention programs, but the opportunity may be ripe now. Integration of PrEP and STI prevention within comprehensive sexual health care services are needed for greater program efficiency both to improve STI control but could also have benefits for identification and retention of potential PrEP candidates.

Conclusion

At a time of rising STI incidence and STI antibiotic resistance rates, traditional approaches to STI control are unlikely to be sufficient in controlling these epidemics. Young women are at risk for severe, lasting effects from pelvic inflammation, including infertility, chronic pelvic pain, or pregnancy complications. In sub-Saharan Africa, sexually active young women have a very high prevalence of asymptomatc bacterial STIs in addition to HIV, with significant risk of long-term reproductive health consequences. There is an urgent need to address this syndemic in young African women. New strategies for detection, treatment, and prevention of STIs should be emphasized in research and policy, and the current increase in promotion and availability of PrEP creates an important and timely opportunity to introduce combination STI/HIV prevention.

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Table 1.

High STI rates among sexually active African women (18 to 25 years old) in three PrEP cohorts

	Chlamydia trachomatis	**Neisseria gonorrhoeae**
MTN-020/ASPIRE (n= 2692) (phase III microbicide trial) S. Africa, Zimbabwe, Zambia, Malawi and Uganda	Prevalence = 12% Incidence = 27% per 100 person-years	Prevalence = 4% Incidence = 11% per 100 person-years
HPTN 082 (n=434) (PrEP demonstration project) S. Africa and Zimbabwe	Prevalence = 29% Incidence = 33% per 100 person-years	Prevalence = 8% Incidence = 14% per 100 person-years
POWER (n=284) (PrEP implementation project) S. Africa and Kenya	Prevalence = 26% Incidence = 53% per 100 person-years	Prevalence = 10% Incidence = 20% per 100 person-years

Note: Syphilis prevalence was <2% in these studies, with incidence <5% per 100 person-years – emphasizing that the burden of STIs in this population is cervical infections.

Table 2.

Neisseria gonorrhoeae antimicrobial resistance prevalence in various African countries

Country	Cephalosporins	Fluoroquinolones	Azithromycin	Tetracyclines
Ghana[45,57]	<0.1%	74%	6–30%	100%
Kenya[43, 45,55]	11%	50%	2%	97%
Madagascar[57,58]	0.1–5%	71–100%	<0.1%	94%
Malawi[57]	<0.1%	71–100%	6–30%	77%
South Africa[44,45,56,57]	0.1–5%	69%	6–30%	83%
Uganda[45,59]	0.1–5%	71–100%	71–100%	97%

Table 3.

Summary of new intervention opportunities for the prevention of sexually transmitted bacterial infections.

Intervention	Potential impact	Key evidence
Point-of-care testing	Increased access and frequency of testing, improved return of results and initiation of treatment	A cross-sectional cohort, (n=705)[21] found improved case finding and management of STIs in Rwandan women with or without symptoms with addition of point-of-care STI testing to risk screening algorithm
Expedited partner therapy	Secondary prevention through decreased reinfection	Two large RCT (n=1787)[63] and (n=931)[64] in the USA demonstrated a reduced risk of reinfection with patient-delivered partner treatment compared to referral
Periodic presumptive treatment	Secondary prevention through increased treatment of asymptomatic infections, potentially some primary prevention benefit with early dosing	A randomized, double-blind trial among Kenyan female sex workers (n=341)[65] found a reduced incidence of *N. gonorrhoeae*, *C. trachomatis*, and *T. vaginalis* with a single monthly azithromycin dose
Doxycycline post-exposure prophylaxis	Primary prevention of *C. trachomatis* and *T. pallidum*, less for *N. gonorrhoeae* expected given widespread resistance to tetracyclines globally	A pilot (n=30)[66] of daily doxycycline in HIV+ MSM in USA followed by an RCT (n=232)[67] of PrEP taking MSM in France, which found significant reduction of STIs (*C. trachomatis* and *T. pallidum*) with single dose doxycycline as post-exposure prophylaxis
STI vaccination	Primary prevention, with candidates in preclinical and clinical development	One retrospective case-control study (n=14730)[68] found 31% reduction in gonorrhea following *Neisseria meningitidis B* vaccine

Table 4.

Parallels between questions relevant to HIV PrEP and to doxycycline PEP – balancing benefits, risks, and costs

PrEP for HIV prevention (circa 2007–2010, with some ongoing today)	Question	Doxycycline PEP for STI prevention (in 2019)
Can PrEP prevent HIV? What about in women?	**Efficacy**	Can doxycycline PEP prevent STIs? What about in women?
Is PrEP safe? Is it safe if women become pregnant? Does it cause sexual disinhibition?	**Safety**	Is doxycycline PEP safe to use? Does it cause sexual disinhibition?
Is PrEP an acceptable strategy for at-risk individuals/ populations?	**Acceptability**	Is doxycycline PEP an acceptable strategy for at-risk individuals/ populations, particularly African women?
Will women adhere to PrEP?	**Adherence**	Will women take doxycycline PEP?
Will HIV resistance develop? Will resistance undermine PrEP's benefits at the population level?	**Resistance**	Will antibiotic resistance develop as a result of doxycycline PEP? Will resistance undermine benefits at the population level and contribute to growing global antimicrobial resistance?
Is PrEP cost-effective? Is it affordable?	**Costs**	What are the costs of doxycycline PEP on top of PrEP? Is it cost-effective?