

https://dspace.org/

Innovations in the biomedical prevention diagnosis and service delivery of HIV and other sexually transmitted infections

Remco PH Peters; Beatriz Grinsztejn; Connie Celum; Kenneth H Mayer; Ann Delany-Moretlwe ...

https://hdl.handle.net/10539/48700
WOS

Downloaded from a DSpace repository. https://dspace.org/

Innovations in Sexual and Reproductive Health 3

Innovations in the biomedical prevention, diagnosis, and service delivery of HIV and other sexually transmitted infections

Remco P H Peters, Beatriz Grinsztejn, Connie Celum, Kenneth H Mayer, Jean-Michel Molina, Sinead Delany-Moretlwe, Kenneth Ngure, Sergio Torres-Rueda, Rebecca J Guy, Peter Reiss, Rashida A Ferrand, Rossaphorn Kittiyaowamarn, Linda-Gail Bekker

The interconnectedness of the global HIV and sexually transmitted infection (STI) epidemics necessitates integrated strategies to address both. This Series paper highlights the biological link between HIV and STIs, and describes the successful progress in HIV response versus STI response over the past decades. The concept of undetectable=untransmissible (U=U) in HIV treatment has revolutionised HIV prevention by reducing stigma and promoting early treatment. In line with this approach, we discuss the role of chronic suppressive therapy for herpes simplex virus type 2 and the importance of the accurate diagnosis and treatment of curable STIs to prevent transmission between sexual partners. This Series paper explores the potential of pre-exposure prophylaxis (PrEP) for HIV in different forms (eg, daily oral PrEP, event-driven PrEP, and long-acting injectable PrEP), and highlights the challenges of adherence to daily regimens and the promise of longer-acting agents, such as cabotegravir and lenacapavir. The potential of doxycycline post-exposure prophylaxis for the prevention of bacterial STIs is also discussed, with concerns about antimicrobial resistance. Although vaccine development for HIV and STIs is a key biomedical advance, we discuss the challenges and possibilities of developing effective vaccines, including lessons learnt from previous HIV vaccine trials, the potential of mRNA-based vaccines for herpes simplex virus, ongoing trials for gonorrhoea and chlamydia vaccines, and the impact of existing human papillomavirus and mpox vaccines. Diagnostic innovations emphasise the importance of point-of-care tests for HIV and STIs. This Series paper discusses the benefits, landscape, and pipeline of rapid diagnostic tests (eg, lateral flow tests and molecular assays) and the challenges of implementing these tests in low-resource settings, particularly the need for rapid results to inform clinical decisions, promote convenience, and reduce cost. This Series paper also addresses innovations in service delivery and advocates for integrated and person-centred approaches (eg, differentiated services) that combine HIV and STI services, and highlights the potential of community-based and home-based models to improve access and reduce stigma.

Lancet 2025; 406: 2133–51

This is the third in a **Series** of five papers about innovations in sexual and reproductive health. All papers in the Series are available at thelancet.com/series/sexual-reproductive-health

See **Comment** page 2038

Department of Global HIV, Hepatitis and STI Programmes, World Health Organization, Geneva, Switzerland (R P H Peters PhD); **Evandro Chagas National Institute of Infectious Diseases (INI), Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, Brazil** (B Grinsztejn MD); **Department of Global Health** (Prof C Celum MD, Prof K Ngure PhD) **and Department of Medicine** (Prof C Celum), **University of Washington, Seattle, WA, USA**; **The Fenway Institute, Fenway Health, Boston, MA, USA** (Prof K H Mayer MD); **Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA** (Prof K H Mayer); **Department of Infectious Diseases, Saint-Louis and Lariboisière Hospitals, APHP, University of Paris Cité, INSERM 1342, Paris, France** (Prof J-M Molina MD); **Wits RHI, University of the Witwatersrand, Johannesburg, South Africa** (Prof S Delany-Moretlwe PhD); **School of Public Health, Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya** (Prof K Ngure); **Genesis Analytics, Johannesburg, South Africa** (S Torres-Rueda PhD); **Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, UK** (S Torres-Rueda); **The Kirby Institute, Faculty of Medicine,**

Introduction

As discussed in this *Lancet* Series on innovations in sexual and reproductive health, the global HIV and sexually transmitted infection (STI) epidemics are connected by shared modes of transmission, risk factors, populations, stigma, and discrimination. This Series paper focuses on innovations in the prevention, diagnosis, and service delivery of HIV and STIs. Biologically, STIs increase a person's susceptibility to HIV infection when they are exposed to HIV, and people living with HIV who are not virally suppressed have higher concentrations of HIV in their blood and increased genital tract shedding when co-infected with STIs, thus increasing the infectiousness of HIV.[1]

Although the global response to HIV has progressed over the past decades, responses to other STIs and sexual health have not seen the same progress.[2] Lessons that were learned from the HIV response can be used to strengthen STI programmes and to increase synergy and integration of HIV and STI services. To achieve the WHO's Global Health Sector Strategy's goals to end these epidemics as public health concerns by 2030, it is essential for the global health community to invest in comprehensive strategies for the biomedical prevention, diagnosis, and management of HIV and STIs. This Series paper highlights innovations in reducing the impact of HIV and other STIs, and identifies opportunities for service delivery integration. We review innovations in antimicrobial drug, vaccine, and other prevention technologies for both HIV and STIs, and the progress and gaps in diagnostic approaches. Opportunities for integration highlight the potential value of multipurpose technologies and service delivery innovations that could centre the users of these technologies, thereby having the potential to streamline health systems and health delivery to improve outcomes.

Innovations in antimicrobial-based prevention

In the absence of effective vaccines for HIV or bacterial STIs, antimicrobials have become the mainstay for HIV and STI control. HIV and STI treatments prevent the onwards transmission of infection, and drugs taken as pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) can prevent HIV or STI acquisition. Although antiviral medications for HIV prevention do not reduce the acquisition of other STIs, consequent behavioural changes could occur that reduce or augment

UNSW Sydney, New South Wales, Australia (Prof R J Guy PhD); **Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands** (Prof P Reiss PhD); **Department of Global Health, University of Amsterdam, Amsterdam UMC, Amsterdam, Netherlands** (Prof P Reiss); **Biomedical Research and Training Institute, Harare, Zimbabwe** (Prof R A Ferrand PhD); **Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, UK** (Prof R A Ferrand); **Bangrak Sexually Transmitted Infections Center, Division of AIDS and STIs, Department of Disease Control, Ministry of Public Health, Bangkok, Thailand** (R Kittiyaowamarn MD); **Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa** (Prof L-G Bekker PhD)

Correspondence to: Dr Remco P H Peters, Department of Global HIV, Hepatitis and STI Programmes, World Health Organization, Geneva 1211, Switzerland

petersr@who.int

STI transmission.[3] STI case management is highly effective for the prevention of onwards transmission of STIs, yet the impact of this management on HIV acquisition was inconclusive in three trials in Africa published in the 1990s and early 2000s.[4–7] A randomised controlled trial of strengthened STI syndromic treatment services in the Mwanza region of Tanzania showed a 38% reduction in HIV incidence in communities that received strengthened STI syndromic management (health-care worker training, drug availability, and supervision to ensure quality of care) with community education.[5] In contrast, two Ugandan trials did not show a significant reduction in HIV incidence, with one trial focusing on mass treatment at 10-month intervals combined with health education in Rakai, and the second examining a community-based behavioural intervention (with or without strengthened STI syndromic treatment services) in Masaka.[6,7] Further analysis of these three trial results showed that it was likely population-level differences rather than differences in the intervention that explained the contrasting findings.[4,8] High rates of bacterial STIs were detected in the Mwanza trial and low rates of sexual risk behaviour were reported in the Ugandan trials. Furthermore, the Ugandan HIV epidemic was more advanced than the Tanzanian epidemic during these trials, meaning that a higher proportion of new HIV infections occurred between stable partners without STIs as a cofactor.[8] These trials were conducted before the widespread use of antiretroviral therapy (ART) and prevention. The potency of antiretrovirals in decreasing HIV transmission and acquisition and the increasingly wider use of these treatments makes it now unfeasible to show an independent effect of STI treatment on HIV acquisition.

Treatment as prevention

People with an undetectable HIV viral load due to ART have negligable risk of transmitting HIV to sexual partners.[9] This observation has led to the concept of undetectable=untransmissible (U=U), which has revolutionised HIV programmes by providing further rationale for immediate HIV treatment after diagnosis. People have said how awareness of U=U has reduced internalised stigma, positively impacting their mental health and sexual and reproductive outlook, and has been used in settings with restrictive laws to provide decriminalising evidence of HIV-serodiscordant sexual activities.[10,11] The decreased stigma and enhanced sexual freedom has resulted in more condomless sex between consenting HIV-serodiscordant couples, which could increase the risk of STI acquisition.[11]

The chronic suppressive therapy of herpes simplex virus type 2 (HSV-2) with an antiviral agent such as acyclovir also reduces—but does not completely prevent—the transmission of HSV-2 to sexual partners.[12] Chronic HSV-2 suppressive therapy is not widely available in low-resource settings, and does not reduce HIV acquisition or transmission from a sexual partner who is also living with HIV.[13,14] The hypothesis is that HSV suppressive therapy does not fully resolve associated mucosal genital inflammation.[15] For example, HSV-2 lesions are associated with a dense infiltrate of HSV-2-specific CD8 and CCR5$^+$ CD4 cells that take up to 8 weeks to resolve following short course acyclovir treatment of genital ulcers due to HSV-2.[15]

Accurate diagnosis and appropriate antimicrobial treatment of curable STIs (eg, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and *Treponema pallidum*) ensures high cure rates and prevents onwards transmission. Urethral discharge, vaginal discharge, and genital ulcer are the main syndromes associated with these infections, and syndromic treatment (ie, combination of empirical antibiotics that cover the most likely causes) is the standard of care in most settings. Optimising syndromic management by incorporating diagnostic tests in the algorithm is essential to improve treatment outcomes, reduce unnecessary antibiotic usage, and facilitate targeted partner management.[16] The increased access to and availability of diagnostic STI tests will support the switch from the syndromic to aetiologic treatment of STIs associated with these symptoms, including partner services, and increase the impact of STI treatment and prevention.[17]

However, most STIs are asymptomatic. Consequently, screening with a diagnostic test is required to identify and successfully treat asymptomatic infections. For example, screening for syphilis in pregnant women during antenatal care is strongly recommended by WHO, given its efficacy in preventing vertical HIV transmission and congenital syphilis, and its high cost-effectiveness.[18,19] In contrast to syphilis screening programmes, the benefits of screening programmes for *C trachomatis* and *N gonorrhoeae* vary between settings (high *vs* low prevalence), programme use (uptake, coverage, and reinfection), and population groups (eg, adolescent women, pregnant women, and men who have sex with men [MSM]), with most data about impact coming from high-income settings.[20–22] The value of STI screening among asymptomatic populations is therefore unclear, but, if beneficial, would most likely be in settings with high HIV and STI prevalence, such as among MSM, sex workers, pregnant women, and southern African young women.[23,24] This absence of clarity underpins the need to better understand the local epidemiology and sequelae of these infections globally (see the first paper in this Series[25]).

PrEP

HIV

In the absence of an affordable and effective HIV vaccine, antiretroviral-based prevention options (both before and after exposure) have become key approaches in HIV prevention. Advances in HIV prevention have been seen

in studies such as the landmark global iPrex,[26] African-based PartnersPrEP,[27] the TDF2 study in Botswana,[28] and Bangkok PrEP trials of emtricitabine–tenofovir (FTC-TDF) taken as daily oral PrEP.[29] These trials showed nearly 100% efficacy among the subsets of cisgender women and men, cisgender MSM, transgender women, and people who inject drugs, all of whom had high levels of adherence (table 1). Efficacy has also been shown for event-driven oral FTC-TDF among MSM and transgender women,[30,38] and daily oral FTC–tenofovir alafenamide (TAF) among MSM,[31] yet low adherence to daily FTC-TDF and FTC-TAF led to minimal impact on HIV incidence among cisgender African women in the PURPOSE-1 study.[32]

Despite the high efficacy of daily oral PrEP, real-world effectiveness is substantially lower as there is a strong association between adherence and efficacy. A pooled analysis of 11 studies showed an HIV incidence rate of 0·13 per 100 person-years in the high adherence group, 0·49 per 100 person-years in the high but declining adherence group, and 1·27 per 100 person-years in the consistently low adherence group.[39] Barriers to PrEP use include social stigma, fear of side-effects, long travel to clinics, waiting times, inconvenient clinic operating hours, pill fatigue, product storage, and drug costs.[40,41] The challenges of adherence to daily pill-taking and persistence with oral PrEP might be partly overcome by longer-acting, less frequently dosed PrEP formulations, including the monthly dapivirine ring and long-acting injectable formulations, such as cabotegravir and lenacapavir.

The dapivirine ring had modest efficacy (27% in the ASPIRE trial and 31% in The Ring Study) in two trials of African cisgender women with low use, lower adherence, and no efficacy among women younger than 21 years.[33,34] However, in the MTN-034 and REACH crossover study of the dapivirine ring and daily oral PrEP among women younger than 21 years, adherence to both the dapivirine ring and oral PrEP was high and 67% of participants chose the dapivirine ring after use of each product for 6 months (participants were randomly assigned to the order of product use),[42] indicating that both oral PrEP and the dapivirine ring can be effectively used by young women in the context of access to various adherence support options.

Cabotegravir—an integrase strand transfer inhibitor delivered every 2 months by intragluteal injection—was the first long-acting product to be shown to be superior to oral FTC and TDF in trials among MSM and transgender women and highly effective in cisgender women, due to high adherence.[35,36] An implementation study in Uganda and Kenya showed that offering participants a choice of PrEP products with cabotegravir and oral PrEP substantially increased overall PrEP uptake and HIV exposure coverage.[43]

Lenacapavir, a capsid inhibitor, is administered twice yearly by subcutaneous injection. High efficacy and adherence to lenacapavir were shown in the PURPOSE 1 trial of adolescent girls and young women in South Africa and Uganda, with no new HIV infections reported among the 2134 participants who received lenacapavir.[32] In the PURPOSE-2 trial of long-acting lenacapavir for PrEP among cisgender men, transgender women, men, and non-binary people, efficacy was 99·2% with two HIV infections detected in the group of 2195 participants who received lenacapavir.[37] Tolerability issues have been injection site pain, nodules, and redness, but these factors have not been associated with product discontinuation.

It is anticipated that these longer-acting agents could be revolutionary for individuals who struggle with taking daily PrEP, but there are important implementation challenges to long-acting injectable PrEP formulations. One of these concerns could be the long drug tail in which users could be susceptible to becoming infected with resistant HIV when drug levels are subtherapeutic, but this is a hypothetical concern and has not been extensively observed. The potential need for expensive

	Landmark trial	Efficacy in cisgender women	MSM and transgender women	People who inject drugs
Oral daily FTC and TDF	Partners PrEP Study;[27] TDF2 Study;[28] iPrEx;[26] Bangkok Tenofovir Study[29]	75% (Partners PrEP Study; high reduction in HIV incidence among women who took 4–7 doses per week in implementation studies);[27] 62% (TDF2 Study)[28]	44% (73% among men with >90% adherence)	49%
Event-driven FTC and TDF	IPERGAY[30]	Not studied	86%	Not studied
Daily oral FTC and TAF	DISCOVER;[31] PURPOSE-1[32]	HIV incidence did not differ from FTC and TDF and background in low adherence context	Non-inferior efficacy to daily FTC and TDF	Not studied
Dapivirine vaginal ring	MTN-ASPIRE Ring Study;[33] The Ring Study[34]	27% (MTN-ASPIRE Ring Study);[33] 31% (The Ring Study)[34] reduction in HIV incidence	Not applicable	Not studied
Cabotegravir injection	HPTN-083;[35] HPTN 084[36]	88%	66%	Not studied
Lenacapavir injection	PURPOSE-1;[32] PURPOSE-2[37]	100%	96%	Not studied

FTC=emtricitabine. MSM=men who have sex with men. TAF=tenofovir alafenamide. TDF=tenofovir disoproxil fumarate.

Table 1: **Summary of landmark trials of drug-based HIV pre-exposure prophylaxis options**

HIV RNA monitoring to identify acute or breakthrough HIV infections that might be missed by HIV serologic testing is also a concern, although standard antibody and antigen testing approaches are considered sufficient from the public health perspective.[44,45] Barriers to widespread access include high cost, logistical issues, and insurance coverage in high-income countries, and in low-income and middle-income countries (LMICs) these barriers include the low availability and affordability of drugs. Feasibility and acceptability trials are investigating lenacapavir for PrEP among people who use and inject drugs (NCT06101342) and American and European women (NCT06101329 and NCT06513312).

Development of islatravir (a nucleoside reverse transcriptase and translocation inhibitor; NCT04644029; NCT04652700) for monthly oral PrEP was suspended when the antiretroviral was found to decrease subclinical lymphocyte count. As the less frequent dosing of PrEP in a small pill form is believed to be attractive to PrEP users, MK8527 (a nucleoside reverse transcriptase and translocation inhibitor agent; NCT06045507) is being developed for monthly oral PrEP. This drug will enter phase 3 trials in cisgender women and adolescent girls in sub-Saharan Africa (EXPrESSIVE-10; MK-8527-010; NCT07071623) and sexually active individuals at high risk of HIV including MSM, transgender people, and non-binary people (EXPrESSIVE-11; MK-8527-011; NCT07044297). Other topical PrEP options are being developed, including a fast-dissolving TAF and elvitegravir vaginal insert; an intravaginal dapivirine vaginal film and reusable vaginal ring with interchangeable compartments for STI, contraceptive, or HIV prevention inserts;[46] and a tenofovir rectal douche.[47] An intramuscular injection of cabotegravir once every 4 months and an annual intramuscular injection of lenacapavir for PrEP are currently in development.[48,49]

The expanding availability of different forms of HIV PrEP is similar to that of modern contraceptives. The increased variability of HIV PrEP recognises that people might have preferences for different modalities throughout their reproductive or sexual lives. As has been shown in the uptake of different contraceptive options and discussed in the second paper in this Series,[50] when people are given a choice and are able to match their preference to their lifestyle needs, uptake and adherence are increased with improved reproductive outcomes. Emerging evidence suggests that dynamic prevention choices lead to more effective HIV prevention.[51–53]

STIs

Several small studies have shown a potential role for daily doxycycline PrEP in the prevention of STIs.[54,55] An ongoing Canadian trial (DISCO study; CTN 329) of doxycycline PrEP (100 mg daily) versus doxycycline PEP (200 mg post-sex) among MSM and transgender women is assessing the relative efficacy, tolerability, and impact of these prevention approaches on increasing antimicrobial resistance in STIs and other pathogens. The Adolescent Trial Network announced the foXXy doxy study of 200 mg doxycycline once per week compared to on-demand doxycycline PEP and standard of care in cisgender women to start in late 2025 (ATN-173/HPTN-115). PrEP might be more feasible and acceptable to some people than PEP,[56] but the efficacy and effectiveness of these prophylaxes have to be balanced with additional data needed regarding increased antimicrobial resistance in STIs, other pathogens, and the microbiome and the cost-effectiveness of this approach.[57]

PEP

HIV

PEP is a globally accepted and endorsed intervention to prevent the onset of HIV infection in people who are HIV seronegative after they are unexpectedly exposed to HIV. Most guidelines recommend at least 28 days of three antiretroviral agents administered within 72 h of exposure. The efficacy of PEP is derived from a case–control study into zidovudine monotherapy after needlestick injuries in health-care workers.[58] Animal studies and epidemiologic studies in sexual assault and occupational health settings have provided further evidence that PEP is effective, especially if commenced within 72 h after exposure.[59,60] With the advent of safer and more tolerable agents (ie, integrase inhibitors), PEP is more widely recommended than with previous regimens, including after unanticipated sexual exposure.[60] PEP might also be used as a bridging approach to PrEP in cases where recent sexual exposure or symptoms and signs suggest acute HIV infection and initial RNA testing is negative or unavailable, as a three drug PEP regimen is considered more stringent than a two drug PrEP regimen from the perspective of potential antiviral resistance and breakthrough infection. PrEP can then be introduced if the person continues to test as negative for HIV infection.

STIs

Doxycycline has been the antibiotic of choice for STI PEP due to its low cost in generic formulations, safety, tolerability, and high effectiveness against *C trachomatis* and *T pallidum* infection with no reported resistance. Activity against *N gonorrhoeae* is variable due to doxycycline pharmacokinetics and pre-existing resistance levels that vary by geography and explain the different effects observed for doxycycline PEP for *N gonorrhoeae* prevention between studies.[61]

Doxycycline PEP is administered as 200 mg and should be taken within 24 h of condomless sex (maximum within 72 h). Three trials among MSM and transgender women in France and the USA have shown high overall efficacy of 47–66% reduction in incident STIs, with approximately 80% reductions in chlamydia and syphilis, and 17–55% reduction in gonorrhea (table 2).[62–64] Doxycycline PEP was safe and well tolerated, with rare discontinuations

in these studies. Open-label extension data of the DoxyPEP trial have confirmed these findings.[66]

In contrast, the dPEP trial of doxycycline PEP in Kenyan cisgender women did not show efficacy for the prevention of chlamydia, gonorrhoea, and syphilis in the context of high STI rates (overall STI incidence of 27 per 100 person-years).[65] Among a random subset of participants in the doxycycline PEP group, only 58 (29%) of 200 patient hair samples (taken every 3 months) had detectable drug levels, suggesting that low adherence to doxycycline PEP was the most likely cause of the null effect. Women who took part in the trial reported issues with stigma, product storage, lack of awareness about STIs, and forgetting dosing.[65,67] Many of these challenges have also been cited as barriers to daily oral PrEP use for HIV prevention in African women.[40,41] Given the important reproductive health sequelae of STIs among cisgender women, other trials of doxycycline PEP are planned with fixed dosing (eg, once per week in the foXXy doxy study).

An important concern about doxycycline PEP is its impact on the antimicrobial resistance of STIs (eg, *Mycoplasma genitalium*), other pathogens, commensals, and the microbiome and resistome.[68] The DoxyPEP and DoxyVac trials both reported increases in tetracycline resistance in incident *N gonorrhoeae* strains.[63,64] A decrease of *Staphylococcus aureus* colonisation and an increase in doxycycline resistance in those who remained colonised was also observed.[69] Analysis of surveillance data from King County (Washington, USA), showed a rapid increase in tetracycline resistance among MSM following introductions of doxycycline for STI prevention and for chlamydia treatment.[70] This study also observed higher colonisation rates, but below 20%, of tetracycline-resistant Group A streptococcus and *S aureus* among doxycycline PEP users compared with non-users. The clinical significance of these findings remains to be elucidated. Even though doxycycline is not used for the treatment of *N gonorrhoeae*, it is anticipated that the efficacy of doxycycline PEP for *N gonorrhoeae* prevention could wane in doxycycline PEP settings, making it an impermanent solution for this STI, and raising further concerns about the co-selection of antimicrobial resistance.[71] Co-selection refers to the principle that selection for doxycycline resistance might also select for other unrelated antimicrobial drugs (eg, ceftriaxone), as resistance genes can be located close together.[72]

Real-world data on doxycycline PEP use among MSM from early adopter settings showed reductions in chlamydia and syphilis among MSM and transgender women in STI programmes in the USA and Italy.[73–75] Research on the implementation of doxycycline for STI prevention is a high priority in guiding the use of these therapies, establishing effectiveness in different population groups and length of use, and assessing and monitoring antimicrobial resistance in STIs, other common bacteria that have pathogenic potential, and the microbiome.

Vaccines to prevent HIV and other STIs

The ability of vaccines to manage infectious disease outbreaks and epidemics and eradicate diseases has been evident since the development of the smallpox vaccine in 1796. In regions where effective vaccines have been implemented, these vaccines are beginning to have an impact on the prevalence of sexually transmitted infections such as human papillomavirus (HPV) and hepatitis B virus (HBV).

HIV vaccines

The elimination of the HIV epidemic requires an effective, affordable, and deployable preventive vaccine, but this remains elusive.[76] The unsuccessful results of the most recent large-scale efficacy trials have prompted

	Participating population	STI rate or outcome (with doxycycline PEP)	STI rate or outcome (without doxycycline PEP)	Relative risk reduction	Absolute risk reduction
IPERGAY (France, 2015–16)[62]	232 MSM taking HIV PrEP	37·7 per 100 person-years	69·7 per 100 person-years	47% (15 to 67%)	32 per 100 person-years
DoxyPEP (Seattle and San Francisco, 2020–22)[63]	174 MSM and transgender women with HIV who have had a recent bacterial STI	11·8% per 3 months	30·5% per 3 months	52% (17 to 72%)	18·7% per 3 months
DoxyPEP (Seattle and San Francisco, 2020–22)[63]	327 MSM and transgender women taking HIV PrEP who have had a recent bacterial STI	10·7% per 3 months	31·9% per 3 months	66% (49 to 77%)	21·2% per 3 months
DoxyVac (France, 2021–22)[64]	502 MSM taking HIV PrEP who have had a recent bacterial STI	5·6 per 100 person-years	35·4 per 100 person-years	84% (70 to 92%)	30 per 100 person-years
dPEP (Kenya, 2020–22)[65]	449 cisgender women taking HIV PrEP	25·1 per 100 person-years	29·0 per 100 person-years	12% (-29 to 40%)	3·9 per 100 person-years

Recent bacterial STI was defined as any bacterial STI in the previous 12 months. MSM=men who have sex with men. PEP=post-exposure prophylaxis. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection.

Table 2: **Clinical trials of doxycycline PEP for bacterial sexually transmitted infections**

researchers in HIV vaccine development to consider new approaches to developing safe and effective HIV vaccines.[63,77–79] Clinical and laboratory research has moved from the empirical approach of vaccine discovery to a more deductive or experimental medicine approach, which allows for rapid hypothesis testing to support and accelerate the development of better vaccine candidates by taking several key principles into account.

An effective vaccine will need to elicit cross-reactive and potent neutralising antibodies and cellular (CD8 T cell) responses to eliminate HIV virions or intracellular viruses.[80] As the immune system does not naturally mount an effective defence against HIV, an HIV vaccine needs to prompt a preventive immune response from the human immune system that has no natural equivalent. Evidence can be gathered from people with HIV who—following natural infection—produce broadly neutralising antibodies (bNAbs) against HIV, which can counteract a broad array of viral variants.[81] HIV is also highly mutable, and so a vaccine needs to target conserved parts of the viral envelope.

The current new vaccine approach uses a phased process of specific priming and boosting vaccinations to prompt specific B-cell precursors to multiply and then, by modulating these precursors, encourages their maturation into potent bNAb production to give rise to an array of bNAbs.[82] Several early-stage human clinical trials of HIV-vaccine components are under way that use the mRNA vaccine platform, which was popularised during the COVID-19 pandemic. This platform is considered preferable because mRNA vaccines are easier to develop and adjust based on biological findings, which is key to the deductive approach. A complementary strategy that is currently under investigation seeks to promote the development of killer CD8 T cells that might be primed to kill off any immune cells that are not saved from infection by the antibodies.

Passive immunisation with bNAbs as a pre-exposure infusion or injection for the prevention of HIV has long been considered. New technology has led to the identification of a new generation of potent bNAbs.[83] These bNAbs target various sites of vulnerability on the HIV envelope and are up to 100% more potent than first-generation antibodies, exhibiting substantial neutralisation breadth against cross-clade HIV-1 strains. Two large efficacy trials in diverse global populations (Antibody Mediated Prevention trials) provided proof-of-concept evidence that this approach could be feasible.[84] Infusions (given every 8 weeks for 48 weeks) of the antibody (VRC01) did not prevent overall HIV-1 acquisition in either trial, but prespecified sub-analyses that focused on VRC01-sensitive HIV isolates provided proof of concept for bNAbs to prevent HIV-1 acquisition.[84] A single bNAb was not sufficiently broad enough to neutralise diverse virus exposure, which suggests that evaluating the efficacy of bNAb combinations or multispecific antibodies is the logical next step in advancing antibodies as an HIV-1 prevention strategy. Trials of multiple antibodies are in early development.

STI vaccines

Given the limitations of current approaches to STI control, such as the inaccessability of diagnostic testing, large burden of asymptomatic infection, and stigma, STI vaccines are crucial for reaching and sustaining the global targets for reducing STI incidence by 2030.[85] Vaccine development for gonorrhoea is a particular priority given the increasing threat of antimicrobial resistance to ceftriaxone, which is the last line of treatment for gonorrhoea. Observational studies with an outer membrane vesicle vaccine against meningococcal serogroup B invasive disease (4CMenB or Bexsero) have shown potential for use as a gonorrhoea vaccine, with reductions in gonorrhoea incidence of 30–40% in vaccinated populations, including among people with HIV.[72,86–88] *Neisseria meningitidis* and *N gonorrhoea* share 80–90% sequence homology, so cross-protection is biologically plausible. Data from oestradiol-treated female mice (*Mus musculus*) models provide additional support for this hypothesis, with an accelerated clearance of *N gonorrhoea* and reduced bacterial load observed in 4CMenB immunised mice.[89] Despite these observations, a trial of 544 MSM without HIV in France did not show a statistically significant reduction in time to first gonorrhoea infection in those who received the vaccine compared with placebo (adjusted hazard ratio 0·78, 95% CI 0·60–1·01).[64] Additional data from women and MSM in diverse settings are awaited, with several phase 3 clinical trials (Australia [NCT04415424 and ACTRN12619001478101]; the USA, Thailand, and Malawi [NCT04350138]; and South Africa [NCT06446752]) are evaluating 4CMenB vaccine for prevention of gonorrhoea, with results expected in 2026. Irrespective of outcome, the data from these trials will provide important insights for gonorrhoea-specific vaccines in pre-clinical development that are about to enter clinical trials.[90]

Although chlamydia vaccines are less advanced in clinical development, a recombinant vaccine against the *C trachomatis* major outer membrane particle is likely to advance to phase 2 trials after it was shown to be safe, well tolerated, and immunogenic against urogenital and ocular chlamydia serovars.[91] Additional studies comparing immune signatures from human and animal models have shown the potential for vaccine-induced antibodies to provide sustained protection against ascending genital infection.[92] Several other vaccines against different antigen targets are in pre-clinical development.[93]

An HSV vaccine could provide notable global health benefits. An estimated 200 million people had at least one symptomatic genital herpes episode in 2020, with herpes estimated to cost US$35 billion in health-care expenditures and productivity loss globally.[94,95] HSV could also account for a third of new HIV infections,

particularly in women and in Africa.[96] Despite previous challenges to vaccine development, two mRNA-based vaccine candidates developed by BioNtech (BNT163) and Moderna (mRNA-1608) have entered phase 1 trials. BNT163 encodes three HSV-2 glycoproteins with the aim of preventing HSV cellular entry and spread and is currently being evaluated for both a prophylactic and therapeutic indication (NCT05432583). The first in human phase 1/2 trial of mRNA-1608 (NCT06033261) has 300 participants from the USA and will establish proof of concept for a therapeutic vaccine to reduce HSV reactivation and recurrence. A therapeutic vaccine with 80% effectiveness (equivalent to daily suppressive therapy with acyclovir) and lifetime protection with 40% coverage of symptomatic individuals could reduce HSV-2 incidence by 30% and HIV incidence by 26% after 40 years, emphasising the potential benefits of these vaccines for both HSV and HIV prevention.[97]

Three vaccines are currently licensed for mpox: modified vaccinia Ankara-BN (eg, Modified Vaccinia Ankara-Bavarian Nordic [MVA-BN] or JYNNEOS and Imvamune or Imvanex), which is a two-dose third-generation smallpox vaccine that is a highly attenuated replication-deficient vaccinia virus vaccine and has been approved in the USA, Canada, and the EU; LC16-KMB (licensed in Japan); and OrthopoxVac (licensed in Russia). Due to the well characterised and sometimes serious adverse effects of first-generation vaccinia virus vaccines, subsequent generations of vaccines were developed to protect laboratory workers who handle orthopoxviruses.[98] These later vaccines were mobilised to protect against mpox during the global mpox outbreak that began in 2022. A second-generation vaccine (ACAM2000) is licensed by the US Food and Drug Administration (FDA) for protection against smallpox based on cross-protective immunity against mpox.

A systematic review of the effectiveness of third-generation mpox vaccines showed 76% effectiveness of single-dose and 82% effectiveness of two doses of the MVA-BN vaccine against mpox, and 67% of any vaccine type against hospitalisation for mpox.[99,100] The real-world effectiveness of the mpox vaccination as a PEP strategy is difficult to establish due to the immortal time bias related to the short incubation period of mpox and challenges in administrating PEP vaccination quickly following mpox exposure.[100,101] Further studies are needed to assess the vaccine effectiveness of PEP (and in other populations, such as children [aged 12 years and younger]), the use of vaccines other than MVA-BN, and to better understand the longevity of vaccine effectiveness, including the need for booster doses.[101]

T pallidum presents unique biological challenges for vaccine design, with no vaccines having reached clinical development.[102] Challenges have included an absence of an optimal animal model and slow replication time of the pathogen. Current efforts are focused on ongoing translational work to identify vaccine targets.

Several sub-Saharan African countries (eg, Kenya, South Africa, and Uganda) have licensed and adopted the bivalent HPV vaccine (Cervarix), which protects against HPV16 and HPV18 genotypes, and the quadrivalent vaccine (Gardasil), which protects against HPV6, HPV11, HPV16, and HPV18 genotypes. These bivalent and quadrivalent prophylactic vaccines, which contain the genotypes that are responsible for about 70% of cervical cancers globally, constitute a breakthrough for primary prevention. Furthermore, the bivalent HPV vaccine offers substantial cross-protection against the HPV31, HPV33, and HPV45 genotypes. A nonavalent vaccine that promotes the immune system to generate antibodies to the nine most common genotypes that cause invasive cervical cancer worldwide could have direct implications for cervical cancer incidence and prevention, and possibly prevent almost 90% of cervical cancers cases worldwide.[103]

WHO recommends including the HPV vaccination in national immunisation programmes in settings where HPV is a public health priority and vaccination is feasible and cost-effective. As of 2025, a total of 149 (76% of WHO member states) countries have introduced HPV vaccination.[104] To eliminate cervical cancer by 2030, the WHO target is to have 90% of girls fully vaccinated with the HPV vaccine by age 15 years.[105] Currently, full-dose coverage is below target at 52% and investment is required.[106] The 2022 WHO recommendation of single-dose vaccination for girls age 9–14 years will go some way to reaching global targets, but questions remain regarding whether a single-dose HPV vaccine will be sufficient for women living with HIV.[107] Gender-neutral immunisation programmes will provide additional protection against other HPV-associated cancers, particularly in settings where screening programmes are sparse or non-existent. A 2023 review concludes that there is strong vaccine efficacy against anal HPV infection and anal intraepithelial lesions in HPV-vaccinated young people (aged 26 years and younger) who do not have HIV.[108]

The opportunity and uses of combining HIV and STI vaccine deployment programmes have been widely suggested. A modelling study has shown the benefit of combining the HPV vaccine with HIV treatment in Kenya, where young women with HIV have a high risk of invasive cervical cancer secondary to persistent HPV infection.[109] There is also a global push to eliminate the vertical transmission of syphilis, HBV, and HIV.

Other prevention options

Medical male circumcision (MMC) provides approximately 60% protection to men against HIV infection and partial protection against some STIs (eg, HSV-2 with 34% reduction).[110–112] Voluntary MMC is a tailored service package that includes foreskin removal, HIV testing and counselling, STI screening and referral, and condom provision. Recent studies have shown that MMC is associated with a reduced risk of STIs in female partners,

including syphilis, chlamydia, cervical cancer and dysplasia, and HSV-2.[113] Although the biological mechanisms behind these protective effects are not well understood, differences in STI prevalence, duration of infection, and microbial clearance could play a role—yet different behavioural characteristics (eg, increased condom use) between circumcised and uncircumcised men cannot be ruled out.[114,115]

Multipurpose prevention technologies

Multipurpose prevention technologies (MPTs) are products designed to simultaneously prevent HIV, other STIs, or pregnancy (discussed in the second, fourth, and fifth papers of this Series).[50,116,117] Multiple studies confirm that many end users prefer MPTs over single prevention technologies, especially MPTs that combine the prevention of HIV and of pregnancy.[118,119]

Over 20 MPT products are in clinical or pre-clinical stages of development, including the dual prevention pill, injectables, vaginal ring, vaginal films, intrauterine devices, implants, vaginal gels, and microarray patches. The most developed of these MPTs are a dual prevention oral pill that combines FTC-TDF as HIV PrEP with an ethinylestradiol–levonorgestrel oral contraception in a 28-day tablet regimen, and tenofovir–levonorgestrel intravaginal rings.[120,121] Safety, acceptability, and tolerability have been shown for both products and the results of ongoing clinical trials are awaited.

The ABC (Abstain, Be faithful, Condomise) campaign was widely promoted in the 1990s when few other biomedical HIV prevention options existed. Over time, condoms have continued to be a primary prevention method in sexual health, and are the only widely accessible MPT that offers dual protection against STIs, HIV, and pregnancy. Several barriers hinder the widespread adoption and consistent use of both male and female condoms, including stigma, misinformation, cultural norms that discourage condom use (especially among young people), and persistent gaps in condom availability in low-resource settings.[122] Additionally, factors such as incorrect use, which can lead to slippage or breakage, contribute to reduced effectiveness. A randomised trial showed that adding water-based lubricants could substantially reduce male latex condom failure rates, particularly among partners who had previously experienced condom failures.[123]

Sex-positive messaging is the preferred public health approach that considers sexuality and pleasure to be a natural, healthy, and integral part of human behaviour and wellbeing.[124] Sex positivity has proven most effective when culturally tailored to different populations.[124] The sex-positive approach combines the absence of physical and emotional harm and risk reduction with the presence of pleasure and meaningful experiences.[124] This approach has been adopted by various HIV and STI programmes to promote engagement and to increase prevention uptake, including the revitalising of condom use.[125,126]

Innovations in diagnosis of HIV and other STIs

Reliable and simple diagnostics are the gateway to the effective prevention and treatment of both HIV and STIs. Improving methods to detect infection means that symptomatic and asymptomatic individuals can be appropriately treated and short-term and long-term complications can be averted. Further benefits include the strengthened antimicrobial stewardship and facilitation of partner services with prevention of onwards transmission to sexual partners. Widespread HIV testing and treatment has substantially reduced the burden of HIV. Prevention for positives is another evidence-based strategy that encourages people with HIV to engage in safer sexual practices, such as including serosorting (ie, selecting sexual partners based on shared HIV status to minimise risk).[127] However, this practice relies on readily available accurate HIV screening or point-of-care testing.[128,129]

Diagnostic test principles

Targeted molecular amplification and antigen and antibody detection are the main technologies used for HIV and STI diagnostics (table 3). The direct detection of microorganism components (eg, nucleic acid and antigens) can provide the earliest diagnosis of HIV and STIs. The indirect detection of infection based on measuring an immune response takes more time as sufficient antibody levels need to be generated, which has been termed the window period. Furthermore, due to the complexity of the immune response, high-quality antibody assays are currently only available for the diagnosis of HIV, HSV, and syphilis.

Diagnostic tests can target single or multiple microorganisms simultaneously. Recent advances have focused on the development of multidisease platform technology and multiplex and combination diagnostic tests, but the widescale distribution of new diagnostics has been limited by cost.[130] These initiatives are driven by clinical relevance (eg, differential diagnosis of the causes of genital discharge), programme synergy, and integration (eg, the elimination of mother-to-child transmission of HIV, syphilis, and HBV), existing infrastructure for other infectious diseases (eg, tuberculosis), feasibility, and affordability.

Point-of-care tests

Point-of-care (POC) diagnostic tests for HIV and STIs have several advantages over laboratory testing, which is often the standard of care.[131] Rapid POC test results can provide immediate diagnosis, impact treatment decisions, and trigger follow-up laboratory testing. Furthermore, POC testing increases accessibility, as most tests can be performed in settings without a laboratory and by non-laboratory staff. Key benefits are the scale-up of testing programmes, inclusion of remote and vulnerable populations, and mitigation of existing infrastructure and logistic barriers and challenges.[132]

Some platforms also provide the opportunity for integrated multipurpose testing. For maximum impact in LMICs, POC tests should meet the REASSURED criteria: Real-time connectivity; Ease of specimen collection; Affordable; Sensitive; Specified; User-friendly; Rapid and robust; Equipment free and environmentally friendly; and Deliverable to the end-user.[133]

Lateral flow assays that provide a result within 15 min have been instrumental in the global HIV response, with over 500 million tests performed annually. Important technical advancements over the years have been the expansion of antibody type detected from IgG (first generation) to the inclusion of IgM (second generation), IgA (third generation), and p24 antigen (fourth and fifth generation) resulting in increased sensitivity and reduced window period.[134] The subsequent integration of lateral flow assays in global and country guidelines resulted in the large-scale implementation of routine HIV testing. The advent of long-acting injectable PrEP has introduced the complication that the administration of single antiretroviral agents as PrEP in the face of asymptomatic acute HIV infection could lead to the suppression of HIV antibody seroconversion and masked infections (ie, clinically silent infections with unusually low or undetectable viral load and diminished antibody production) now called the LEVI (Long-acting Early Viral Inhibition) syndrome.[135] This concern has led to some regulatory bodies requiring that HIV nuclear antigen testing should precede injectable PrEP. The added cost and complexity of this is not feasible or cost-effective in most LMIC settings. Recently, WHO has recommended a public health approach to HIV testing using HIV rapid diagnostic tests for people starting or continuing to use long-acting injectable PrEP.[136]

Syphilis lateral flow assays detect IgM and IgG antibodies, but these take time to mount to detectable levels, meaning that a negative test does not rule out syphilis in symptomatic individuals. As with the history of HIV POC tests, developments in syphilis antibody tests focus on increasing test sensitivity and reducing the window period.[137] Lateral flow assays for *N gonorrhoeae* and *T vaginalis* detect microbial antigens rather than antibodies, and provide direct and rapid evidence of infection.[138,139] The sensitivity of these assays is lower than the sensitivity of a nucleic acid amplification test, but meets the WHO target product profile criteria for a useful test in settings that do not have access to laboratory testing. Sensitivity is higher in symptomatic than asymptomatic people, suggesting that the usefulness of these lateral flow assays is predominantly for the optimisation of syndromic management.[139,140] Therefore, despite their slightly lower performance characteristics, lateral flow assays can be an invaluable tool in settings with poor or no access to laboratory-based technologies.

Molecular tests have become available in recent years, including POC HIV viral load testing and HIV DNA PCR tests for early infant diagnosis. Implementation of these

	Molecular test	Antigen test	Antibody test	Microscopy	Antimicrobial resistance test
Bacteria					
Chlamydia trachomatis	NAAT	DFA not used (low sensitivity)	ELISA not done (low sensitivity)	Not done (difficult to visualise)	Not indicated
Haemophilus ducreyi	NAAT	Not available	Not available	Not done (low sensitivity)	Culture and AST; NGS including WGS
Mycoplasma genitalium	NAAT	Not available	Not available	Not done (difficult to visualise)	Targeted PCR; NGS including WGS
Neisseria gonorrhoeae	NAAT	Lateral flow assay	Not available	Gram-stained smear of urethral discharge; vaginal discharge smear not done (low sensitivity)	Culture and AST; NGS including WGS
Treponema pallidum	NAAT	Not available	*T pallidum*-specific antibodies (eg, enzyme immunoassay, chemiluminescent assay, and *T pallidum* haemagglutination assay); lipoidal antibodies (eg, rapid plasma reagin test or venereal disease research laboratory)	Darkfield examination of lesion exudate	Targeted PCR; NGS including WGS
Protozoa					
Trichomonas vaginalis	NAAT	Lateral flow assay	Not available	Wet mount examination of vaginal smear	Culture and AST; NGS including WGS
Viruses					
Herpes simplex virus type 1 and 2	NAAT	Not done (low sensitivity)	ELISA for purpose of latent infection screening	Not done	Target PCR; NGS including WGS
HIV	NAAT	Lateral flow assay	Lateral flow assay	Not done	NGS including WGS

AST=antimicrobial susceptibility testing. DFA=direct fluorescence assay. ELISA, enzyme-linked immunosorbent assay. NAAT=nucleic acid amplification test. NGS=next-generation sequencing. WGS=whole-genome sequencing.

Table 3: **Diagnostic tests for HIV and sexually transmitted infections in clinical practice**

HIV tests at POC has shown positive impact on clinical and public health outcomes.[141] For STIs, three FDA-cleared POC tests are available for the molecular detection of *C trachomatis*, *N gonorrhoeae*, and *T vaginalis*. Binx health io CT/NG assay, and the Visby Medical Sexual Health test provide rapid (<30 min) and reliable results, but the assay cost is a barrier to widespread use in LMICs.[142,143] Xpert CT/NG and Xpert TV have been used in many research studies in LMICs showing good and reliable performance for in-facility and near-patient testing.[144,145] However, the time to results (<90 min) of this assay is generally considered too long to impact on treatment decisions in symptomatic patients and for asymptomatic people to wait for their results.[145,146] Additional barriers to widespread use in low-resource settings are the cost, electricity dependence, and other requisites (eg, requirement for bench space and waste management). There is a substantial pipeline of rapid molecular tests for *N gonorrhoeae* and *C trachomatis*, some of these combined with *T vaginalis* detection, that is largely built on technology developed for COVID-19, but most of these tests are in the pre-clinical stages of development and clinical performance evaluation data are not yet available.

Gaps exist in the diagnostics pipeline for HIV and STIs (table 4). Driving factors include cost, infrastructure and equipment dependency, turnaround time, and the benefits of multiplex testing for aetiological diagnosis of STI-associated syndromes. There are also key diagnostic gaps in syphilis, especially the lack of diagnostic tests to reliably distinguish between active and previous syphilis in asymptomatic individuals and to confirm or exclude active syphilis in exposed newborns. A focus in HIV research will be on the performance of current and new (eg, microfluidic and nanofluidic HIV tests) diagnostic tests in the context of long-acting HIV PrEP. Another expansion in this field is the development of a lateral flow test (Genital InFlammation Test) to detect cytokine biomarkers for the identification of genital inflammation associated with STIs or bacterial vaginosis.[147]

Which HIV and STI tests should be used, in which combination, and at what frequency to have an impact on

	Current limitations	Diagnostic gap
Treatment of patients with genital discharge		
Microscopy for *Neisseria gonorrhoeae* in men	Low sensitivity in women; not widely available due to skill and infrastructure	Affordable rapid test with high sensitivity and specificity; preferably multiplex for *Chlamydia trachomatis* and *N gonorrhoeae;* possibly combined with *Trichomonas vaginalis;* inclusion of antimicrobial resistance markers for *N gonorrhoeae* would be preferable
Lateral flow assay for *N gonorrhoeae* and *T vaginalis*	Lower sensitivity compared with NAAT	As above
NAAT for *C trachomatis*, *N gonorrhoeae*, and *T vaginalis*	High cost; not affordable in LMICs; infrastructure requirement and electricity dependency	As above
Treatment of patients with genital ulcer		
Darkfield microscopy	Not widely available due to skill and health and laboratory infrastructure	Affordable rapid test with high sensitivity and specificity; preferably multiplex with *Treponema pallidum* and HSV-1 and HSV-2; *Haemophilus ducreyi* for populations at risk in endemic settings
Treponemal antibody detection	Insufficient sensitivity to rule out syphilis	As above
Management of newborns who are symptomatic and have been exposed to syphilis		
Not available	Not available	Affordable rapid test that reliably provides diagnosis of *T pallidum* infection in symptomatic and exposed newborns
Screening asymptomatic individuals for curable STIs		
Lateral flow assay for *N gonorrhoeae* and *T vaginalis*	Lower sensitivity than for NAAT and lower than in symptomatic people	Affordable rapid test with high sensitivity and specificity; preferably multiplex for *C trachomatis* and *N gonorrhoeae*; possibly combined with *T vaginalis*
NAAT for *C trachomatis*, *N gonorrhoeae*, and *T vaginalis*	High cost; not affordable in LMICs; health infrastructure requirement and electricity dependency	As above
Screening asymptomatic individuals for viral STIs		
Lateral flow assay for treponemal antibody detection	Not informative in people with previous infection (antibody persistence); cannot be used in newborns who have been exposed to syphilis (maternal antibodies)	Affordable rapid test for *T pallidum* that can be used regardless of previous syphilis history; affordable rapid antibody test that distinguishes between active and previous *T pallidum* infection; affordable rapid test that reliably provides diagnosis of *T pallidum* infection in asymptomatic but exposed newborns
Multiplex test for *T pallidum*, HIV, and hepatitis B and C virus antibodies	Not available	Affordable rapid multiplex test combining HIV and *T pallidum* with hepatitis B virus and hepatitis C virus

HSV=herpes simplex virus. LMIC=low-income and middle-income country. NAAT=nucleic acid amplification test. STI=sexually transmitted infection.

Table 4: **Diagnostic gaps for point-of-care STI tests**

significant reproductive health outcomes (eg, pelvic inflammatory disease and infertility) remain topics for implementation research. The worldwide adoption of HIV PrEP has brought this into sharp focus with the need for guidance and ongoing improvement in available diagnostics.

Artificial intelligence for diagnosis of HIV and other STIs

Artificial intelligence (AI) initiatives have been developed for settings that do not have access to diagnostic tests and to triage diagnostic test strategies (table 5).[148–158] For example, a machine learning generated telephone application could distinguish between mpox and

	Data source and population	Purpose and methods	Findings
HIV			
Koh et al (2024)[148]	Not available	ChatGPT (version 3·5) was instructed to answer frequently asked questions by people with HIV and counsel about ART; questions were derived based on the combined experience of HIV clinicians and pharmacists; the accuracy and appropriateness of responses were assessed qualitatively and compared with the most recent WHO and other HIV management guidelines	This study deemed that ChatGPT answered all questions accurately and comprehensively; ChatGPT provided detailed answers on treatment options (eg, single-pill regimens and injectables), the timing of ART initiation with considerations for individual preferences and readiness to start, and adherence and side-effects; ChatGPT also recognised warnings (eg, abacavir hypersensitivity reaction and potential drug–drug interactions); ChatGPT accurately described treatment as prevention
Cheah et al (2024)[149]	14 participants evaluated the acceptability of an AI-based chatbot	Beta testing of this study aimed to test the feasibility and acceptability of an AI chatbot in promoting the uptake of HIV testing and PrEP in MSM	The majority of participants (13 of 14; 93%) reported that the chatbot was useful and provided comprehensive information on HIV testing and PrEP (performance expectancy); around 79% of respondents reported that they would continue to use the chatbot, and 14 (100%) respondents felt that the chatbot was easy to use due to its simple, straightforward design and quick, friendly responses (effort expectancy); 13 (94%) participants rated the overall chatbot quality as high, and 14 (100%) respondents would refer the tool to others
Seboka et al (2023)[150]	The dataset was made of historical patient data (eg, demographics, clinical, and laboratory data) from an ART registry database in Ethiopia (2907 patients aged 15 years and older)	8 machine learning classifier algorithms were trained on historical patient data to predict viral load from patient data	The models used in this study were able to correctly predict viral load (ie, suppressed or detectable) with 78– 96% accuracy and CD4 classification (<200 cells per mL) with 79% accuracy; the eXtreme gradient boosting classifier had 96% accuracy and the random forest classifier had 95% accuracy in viral load prediction, and the gradient boosting classifier was the most accurate (79%) for predicting participants with a CD4 cell count <200 cells per mL
Roche et al (2024)[151]	The dataset included images of blood-based HIV rapid tests from 1500 adult clients of 20 private pharmacies in Kisumu, Kenya who purchased products indicative of sexual activity; the training set had 6074 images and the testing set had 5000 images	This study assessed the AI-based interpretation of HIV self-testing results using photographs of tests uploaded to a web-based platform; the determinations of HIV test results by an expert panel were used as ground truth; a total of 854 HIV test images were of sufficient quality to be interpreted by the AI algorithm	The AI algorithm showed 100% sensitivity (ie, true positives) and 98·8% specificity (ie, 7 negative tests were classified as positive and 3 as indeterminant); pharmacy clients (93·2% specificity) and providers (97·7% specificity) did not interpret HIV test results as accurately as the AI algorithm; the AI tool could be used to support differentiated HIV service delivery and with human interpreters to improve the accuracy of interpreting HIV test results
STIs			
Nadarzynski et al (2024)[152]	A chatbot was evaluated in minoritised ethnic groups (n=548; 54% were women, 66% were Black, average age of 30 years) recruited via social media platforms using relevant hashtags (eg, #BlackSexualHealth)	This study investigated the impact of CASA on the intentions for sexual health screening, attitudes about screening, and level of information disclosure in minoritised ethnic groups and the subsequent use of the chatbot for booking STI screening (screening intentions *vs* demographic and behavioural risk factors for STI and HIV)	CASA had a statistically significant positive effect on screening intentions, concerns about STIs, and attitudes towards sexual health screening (p<0·001); attitudes regarding CASA were generally positive but differed by race and ethnicity (Asian participants had the highest score, followed by Black participants, and then Latino participants), current STI symptoms, native language, and condom use; around 11% booked appointments directly through the chatbot, 72% of whom were from minoritised ethnic groups; CASA appeared to foster an environment conducive to changing behavioural intentions, highlighting the potential for use in digital health interventions
Koh et al (2024)[153]	Not available	ChatGPT (version 3·5) was evaluated as a tool to improve access to knowledge on STIs; ChatGPT was instructed to answer STI questions from three domains: general risk factors, access to care and diagnosis, and management of STIs and HIV PrEP; responses were compared with the US Centers for Disease Control and Protection STI guidelines	ChatGPT responses were mainly concise and accurate; for STI prevention, ChatGPT recommended measures such as safe sex practice and HPV vaccination but failed to recommend HIV PrEP; when individuals queried about symptoms, ChatGPT advocated for testing; for treatment, ChatGPT consistently conveyed the importance of testing and follow-up testing for sexual partners but was inconsistent on conveying the importance of testing for other STIs
Elder et al (2021)[154]	The dataset was made of structured data from patients aged 15 years and older who acquired an incident STI diagnosis in 2008–15 in MA, USA	Machine learning models (including over 180 variables) were developed to assess whether routine data could predict the risk of acquiring at least 1 or 2 additional STIs diagnoses 1 or 2 years after initial diagnosis (ie, risk of recurrence); a sensitivity analysis incorporated health department surveillance data to assess whether improving the accuracy of identifying STI cases improved model performance	8723 incident episodes of laboratory-confirmed gonorrhoea, chlamydia, or syphilis were identified between 2008 and 2015; the best performing model was Bayesian additive regression trees (AUC=0·75), but this model showed poor balance between sensitivity and positive predictive value, possibly owing to the low rate of recurrence (11·3% for 1 repeat diagnosis and 2·6% for ≥2 repeat diagnoses); incorporating health department surveillance data did not affect cross-validated AUC-receiver operating characteristic; the machine learning models did not differentiate well between patients with and without repeat STIs diagnoses

(Table 5 continues on next page)

	Data source and population	Purpose and methods	Findings
(Continued from previous page)			
Soe et al (2024)[155]	The dataset consisted of 4913 clinical images of genital lesions (1583 STI images and 3330 non-STI images) and metadata from MSHC (Melbourne, Australia)	This study evaluated two binary classification models to differentiate STIs from non-STIs based on clinical images of genital lesions; one model was a CNN trained on images only and the other was an integrated model that combined images and patient metadata	Although the image-only model had acceptable performance (AUC=0·859), the image and metadata model achieved a statistically significantly higher AUC (0·893; p<0·01), outperforming the image-only model; of 21 metadata labels extracted from protected health information, integrating demographic and dermatological metadata led to the largest improvement in the performance of the image and metadata model
HIV and other STIs			
Latt et al (2024)[156]	The dataset included demographic, behavioural, and diagnostic data from 216 252 HIV, 227 995 syphilis, 262 599 gonorrhoea, and 320 355 chlamydia consultations at MSHC (Melbourne, Australia)	An AI-based risk assessment tool (MySTIRisk) was used to estimate infection risk scores with Youden's Index to determine optimal cutoffs for determining people who were at high risk of HIV and other STIs in a clinical setting; MySTIRisk uses machine learning models trained on demographic, behavioural, and diagnostic data to estimate risk scores from 0 to 1, where 1 is the highest risk	The high-risk score cutoffs were predicted as follows: HIV (86·0% sensitivity), syphilis (77·6% sensitivity), gonorrhoea (78·3% sensitivity), and chlamydia (68·8% sensitivity); high-risk groups identified using these thresholds accounted for 85% of HIV, 78% of syphilis, 78% of gonorrhoea, and 69% of chlamydia cases; the odds of HIV or STI positivity were statistically significantly higher in the high-risk group than non-high-risk groups across all infections; the determined thresholds could assist in identifying individuals for screening and prevention
Mpox			
Soe et al (2023)[157]	The dataset included 86 mpox and 1565 non-mpox images from MSHC (Melbourne, Australia), 260 images gathered from the internet using data scraping and verified by pathologists, and 277 mpox images from the Kaggle dataset for external validation; after augmentation, 902 additional mpox images were included	This study developed and evaluated an AI-based tool to differentiate mpox lesion images from other skin lesions seen in a sexual health clinic; the study assessed six deep learning architectures using a hold-out testing set and external validation; generalisability and robustness were improved using 5-fold cross-validation	The DenseNet-121 model outperformed other models (AUC=0·928) and had 84·8% accuracy; cropping images in the external validation set to the region of interest significantly improved the performance of all models, increasing the AUC of the DenseNet-121 model to 0·982; this approach increased the correct classification of mpox images from 79% (55 of 70) to 94% (66 of 70); in the external validation dataset, ResNet-18 (AUC=0·990, accuracy=94·7%) and DenseNet-121 (AUC=0·982, accuracy=92·6%) had the highest performance
Thieme et al (2023)[158]	After deduplication and image filtering, the dataset had 676 images of mpox skin lesions and 138 522 non-mpox images, representing both people from across the globe and various body regions; images were acquired from public sources and clinical images of confirmed mpox cases from Stanford University Medical Center (California, USA)	This study developed and evaluated an image-based deep CNN (MPXV-CNN) to identify skin lesions caused by mpox; the dataset was split into training (n=518, exclusively laboratory-confirmed cases), testing (n=158), and internal validation sets (80:20 split training:validation); cross validation was performed five times; data augmentation was used to overcome issues related to imbalanced class distribution (mpox *vs* non-mpox images)	The sensitivity of MPXV-CNN was 91·0% (AUC=0·966) for the testing cohort and 83·0% (AUC=0·967) for the validation cohort; the sensitivity was 89·0% in the prospective cohort; MPXV-CNN performed well in classifying mpox versus acute and chronic skin lesions, and across various skin tones and body regions; the lowest performance was in Fitzpatrick type III skin (ie, light to medium), with higher false positive rates in darker skin tones (ie, Fitzpatrick types V and VI); a web-based app was developed to guide patients in using the CNN
Mpox and other STIs			
Tan et al (2024)[159]	An existing AI-based tool was trained on 5000 images from a global population (n=2600 with penis pathologies such as syphilis, HSV, and HPV; n=2400 without) and subsequently trained on 1000 mpox-related images and 1000 images of penises without mpox (n=600 with no skin pathologies and n=400 with mimickers)	The HeHealth smartphone app, which is an existing digital screening tool for STIs, was adapted to screen for symptomatic mpox using AI; after training, internal validation of the tool included calculating specificity using a dataset comprising 100 patient observations who received a risk score of at least 80% (high likelihood of mpox) and sensitivity based on 100 patient observations who received a risk score of 40% or less (unlikely to be mpox)	After refining the tool based on user feedback, an internal validation study showed that the AI-based symptom checker tool had high specificity (87%) and sensitivity (90%) for symptomatic mpox; issues around generalisability were addressed by being inclusive of all skin colours, training the tool on other areas of the body, and training the model to focus on colour-neutral skin atypicalities

AI=artificial intelligence. ART=antiretroviral therapy. AUC=area under the curve. CASA=chatbox-assisted self-assessment. CNN=convolutional neural network. HPV=human papillomavirus. HSV=herpes simplex virus. MSHC=Melbourne Sexual Health Centre. MSM=men who have sex with men. PrEP=pre-exposure prophylaxis. STI=sexually transmitted infection.

Table 5: **Advances in AI in HIV and STI care**

non-mpox causes of genital ulcer lesions.[157] Other applications are risk stratification based on machine learning to guide testing strategies, and to interpret laboratory results (eg, improve accuracy of HIV rapid testing).[160] Although these applications have been successfully designed, evaluation of clinical application is crucial to inform usability and acceptability. Machine learning that includes all skin types is important for use, as seen in an mpox ulcer application that was successfully evaluated in the USA but had unclear performance results in central Africa. Furthermore, important medicolegal questions need to be addressed about the use of these applications in practice, including legal accountability, confidentiality, and data storage. AI is only one aspect of the oncoming digital health revolution.

Innovations in HIV and STI service delivery

The HIV field supported by WHO and the International AIDS Society first introduced differentiated service delivery in the context of person-centred ART, with an aim of ensuring that people with HIV are retained in care and virally suppressed for both individual and public health benefit. Differentiated service delivery is a client-centred approach that simplifies and adapts HIV services across the cascade in ways that better serve the needs of people with HIV and reduces avoidable burdens to the health-care

system.[161] Differentiated service delivery suggests that country programmes can choose the who, what, where, and how of HIV treatment delivery.[162] This serves to not only provide quality, person-centred care, but also to find efficiencies within the health system, especially in countries with large treatment programmes.[161]

With the advent of more prevention options (eg, long-acting PrEP), this service delivery approach has now been extended to prevention.[163] Country programmes can choose which prevention package to offer and which prevention components can be offered together. The effective integration of HIV and STI services within health-care systems provides an important opportunity to address both epidemics synergistically. In recent years, focus has increasingly shifted from facility-based to community-based and home-based models of care (figure). Out-of-facility services can be delivered through community-based and outreach programmes, in non-clinical facilities, and at specific venues (eg, mobile clinics).[164] These services can be more convenient, discrete, and potentially less stigmatising, which might remove barriers to access and reach marginalised groups at higher risk of HIV than facility-based services would.[165] Other examples include rapid service sexual and HIV health clinics that emphasise self-testing, self-care, and rapid diagnosis and offer same day treatment.[166] Integration of other services might be included in these models, such as HIV and STI testing alongside menstrual health and contraceptive services, or in combination with mpox vaccination.[167]

In a 2023 systematic review, 96 studies provided data on effectiveness, acceptability, feasibility, barriers, facilitators, economic evaluation, and social harms of concurrent HIV and STI testing.[168] The review found poor concurrent HIV and STI testing among people who had already been diagnosed with an STI or who had symptoms of STIs. Additionally, concurrent HIV and STI testing among those tested for STIs varied substantially according to the testing location, country income level, and region of the world. A few potential reasons for these observations include differences in national STI-related policies, lack of standard operation procedures, clinician-level factors, poor awareness and adherence to HIV indicator condition-guided HIV testing, and stigma associated with HIV compared with other curable STIs. However, strengthened sexual and reproductive health services (eg, STI screening) could increase the demand for HIV prevention services and vice versa.[169,170]

On a service level, the provision of services, ease of access, stigmatising features, privacy and confidentiality, and bureaucracy were barriers. Service factors that improved ease of access included the implementation of a dual HIV and syphilis testing strategy, express testing services for people at low risk of HIV and STIs, and convenient testing locations. Internet-based HIV and STI testing—either through self-collection or allowing clients to present to designated specimen collection sites—that is integrated with existing clinic-based services increased HIV testing rates. Clients being tested or diagnosed with STIs at both general practitioner and STI clinics also felt that a routine offer of HIV testing would increase testing uptake. Raising awareness of sexual health in a non-judgemental and professional manner and maintaining confidentiality was reported to increase trust and improve the acceptability of HIV testing. Additionally, positive sex messaging shifts away from risk-based approaches, focusing on pleasure, consent, and empowerment. This messaging promotes sexual health as part of overall wellbeing, encourages informed choices and routine STI care, and helps reduce stigma through open and respectful communication.

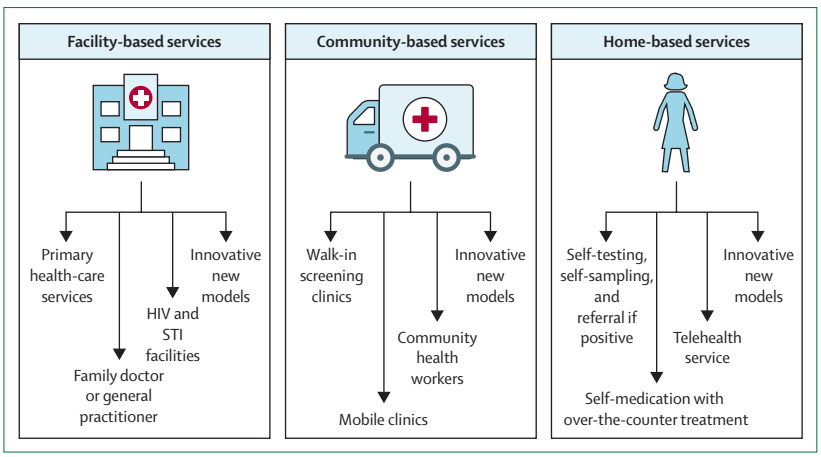


Figure: **HIV and STI service delivery models**
Advances in service delivery, with traditional approaches shown on the left (ie, facility-based services) moving through out-of-facility services in the middle to home-based services on the right. STI=sexually transmitted infection.

The routine offer of HIV testing in antenatal settings and emergency departments has been implemented successfully in many countries, and rapid POC HIV testing has markedly increased concurrent HIV and STI testing. This approach has now been expanded to broader sexual and reproductive health services in some countries, such as South Africa.[169,170] The integration of HIV testing into standard STI care protocols, including PrEP services, has resulted in more consistent programme performance across clinics.

Home-based testing as part of self-care includes self-testing (eg, for HIV testing), self-sampling (eg, for *C trachomatis* and *N gonorrhoeae* testing), and self-treatment of symptoms using over-the-counter obtained medication (eg, from a pharmacy or retail outlet, unregulated distribution channels, or online); these approaches are often supported by mobile apps on mobile phones. These services might be offered as a telehealth tool (ie, to provide screening and medical consultation from a distance) or through direct-to-consumer models, where medical professionals are not typically involved.[171] In direct-to-consumer models, consumers independently acquire the medication or testing device or submit a

sample to a non-medical laboratory, receiving the test results directly and bypassing traditional clinical oversight.[172] Home-based testing services could remove geographical inequalities in access, offer autonomy and privacy, and address concerns about confidentiality and stigma.[173,174] This provision of care needs to be balanced against concerns about the lack of appropriately licensed professionals, quality of testing, linkage to care for those with positive results, and low regulatory and antimicrobial stewardship oversight.

Conclusion

The HIV and STI epidemics are linked together in epidemiological, behavioural, and biological ways. It is therefore imperative that sexual health programmes are developed and implemented that offer various prevention, diagnostic, and treatment options for different populations and include comprehensive HIV and STI care.

Innovation and research have been key components and drivers of the global HIV response. Different ART regimens and HIV prevention options have been developed based on individual values and preferences and have focused on addressing individual and system-related barriers to successful use. Long-acting treatment options, which can offer an increased duration of activity and improved ease of use, are a major step towards equitable access and use if implementation issues and cost challenges can be addressed. Furthermore, given the scale of the HIV programme, service delivery models will continue to evolve with a focus on self-care, person-centredness, and differentiated care. It is essential that these approaches are designed with an inductive approach (ie, driven by end users, the community, and service providers) and maintain regulatory and quality assurance oversight. In that light, further development of MPTs, digital technologies, and AI will likely play a major role.

Unlike in HIV research, innovations in the STI field have been sparse over the past two decades. Doxycycline PEP is the first efficacious biomedical intervention to offer to people who have had recent bacterial STIs, and needs additional research among cisgender women and to evaluate the selection of antimicrobial resistance. The development of affordable diagnostic tests (preferably used at point of care) is imperative to reduce the burden of infection and associated complications, but effective vaccines will be required to end both the HIV and STI epidemics. The present size and diversity of the diagnostic and vaccine pipelines is encouraging, although most products are still in the early stages of development. Investment in these pipelines is imperative to advance the field of HIV and STI innovation. Questions on how and if these innovations (ie, interventions, products, and diagnostics) are integrated at a service level to ensure optimal health system use, better user experience, and cost-effective and favourable HIV and sexual health outcomes need to be resolved by well-constructed health service research.

Ultimately, given the real-world effectiveness of existing interventions and in the context of increasing global health challenges, the successful development of HIV and STI vaccines is essential to end these epidemics as a global health threat. Major progress has been made to date, but continued investment, commitment, and support for innovation towards optimised integration is an ongoing imperative.

Contributors

RPHP and L-GB wrote the first draft with inputs from all authors. All authors reviewed the draft and final versions of the manuscript.

Declaration of interests

CC receives institutional funding from the Gates Foundation and the National Institutes of Health (NIH); and receives consulting fees from Merck and ViiV Healthcare as scientific advisor. KHM receives institutional research grants from Gilead, Merck, GSK, Moderna, and ViiV Healthcare; receives royalties from a textbook from McGraw-Hill; has received financial compensation from Up-to-date for educational writing; and has held a position as an advisory board member for Gilead Sciences. JM-M receives institutional funding and consulting fees from Merck, ViiV Healthcare, and Gilead. KN receives institutional grants from the Gates Foundation, NIH, and Merck Investigator Studies Programme; has received honoraria for conference summaries for Clinical Care Options; and holds a position as a member of the Data Safety and Monitoring Board for the FP-Plus study. RJG receives institutional funding from Cepheid and SpeeDx. PR receives institutional funding from Gilead Sciences, Merck, and ViiV Healthcare; has received consulting fees from Gilead Sciences and ViiV Healthcare; and has participated on the NIH Data and Safety Monitoring Board for HIV vaccine trials. LG-B has received honoraria from Merck, Gilead Sciences, ViiV Pharmaceuticals, and Cepheid. All other authors declare no competing interests.

Acknowledgments

This work was funded by an unrestricted educational grant from the Gates Foundation (INV-064094).

References

1 Cohen MS, Council OD, Chen JS. Sexually transmitted infections and HIV in the era of antiretroviral treatment and prevention: the biologic basis for epidemiologic synergy. *J Int AIDS Soc* 2019; **22** (suppl 6): e25355.

2 Peters RPH. Leaving no one behind: sexually transmitted infections in Africa. *Sex Transm Dis* 2024; **51:** 626–27.

3 Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 recommendations of the International Antiviral Society-USA panel. *JAMA* 2023; **329:** 63–84.

4 Mayaud P, Mabey D. Approaches to the control of sexually transmitted infections in developing countries: old problems and modern challenges. *Sex Transm Infect* 2004; **80:** 174–82.

5 Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995; **346:** 530–36.

6 Wawer MJ, Sewankambo NK, Serwadda D, et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. *Lancet* 1999; **353:** 525–35.

7 Kamali A, Quigley M, Nakiyingi J, et al. Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *Lancet* 2003; **361:** 645–52.

8 Corbett EL, Steketee RW, ter Kuile FO, Latif AS, Kamali A, Hayes RJ. HIV-1/AIDS and the control of other infectious diseases in Africa. *Lancet* 2002; **359:** 2177–87.

9 Broyles LN, Luo R, Boeras D, Vojnov L. The risk of sexual transmission of HIV in individuals with low-level HIV viraemia: a systematic review. *Lancet* 2023; **402:** 464–71.

10 Grace D, Stewart M, Blaque E, et al. Challenges to communicating the undetectable equals untransmittable (U=U) HIV prevention message: healthcare provider perspectives. *PLoS One* 22; **17:** e0271607.

11 Okamoto EE, Anam FR, Batiste S, et al. Ending AIDS as a public health threat: the imperative for clear messaging on U=U, viral suppression, and zero risk. *Lancet HIV* 2024; **11:** e783–90.

12 Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004; **350:** 11–20.

13 Mujugira A, Magaret AS, Celum C, et al. Daily acyclovir to decrease herpes simplex virus type 2 (HSV-2) transmission from HSV-2/HIV-1 coinfected persons: a randomized controlled trial. *J Infect Dis* 2013; **208:** 1366–74.

14 Celum C, Wald A, Hughes J, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; **371:** 2109–19.

15 Zhu J, Koelle DM, Cao J, et al. Virus-specific CD8+ T cells accumulate near sensory nerve endings in genital skin during subclinical HSV-2 reactivation. *J Exp Med* 2007; **204:** 595–603.

16 Wi TE, Ndowa FJ, Ferreyra C, et al. Diagnosing sexually transmitted infections in resource-constrained settings: challenges and ways forward. *J Int AIDS Soc* 2019; **22** (suppl 6)**:** e25343.

17 Tuddenham S, Hamill MM, Ghanem KG. Diagnosis and treatment of sexually transmitted infections: a review. *JAMA* 2022; **327:** 161–72.

18 Silke F, Earl L, Hsu J, et al. Cost-effectiveness of interventions for HIV/AIDS, malaria, syphilis, and tuberculosis in 128 countries: a meta-regression analysis. *Lancet Glob Health* 2024; **12:** e1159–73.

19 Rodriguez PJ, Roberts DA, Meisner J, et al. Cost-effectiveness of dual maternal HIV and syphilis testing strategies in high and low HIV prevalence countries: a modelling study. *Lancet Glob Health* 2021; **9:** e61–71.

20 Grennan T, Tan DHS. Benefits of opportunistic screening for sexually transmitted infections in primary care. *CMAJ* 2021; **193:** E566–67.

21 Kenyon C, Herrmann B, Hughes G, de Vries HJC. Management of asymptomatic sexually transmitted infections in Europe: towards a differentiated, evidence-based approach. *Lancet Reg Health Eur* 2023; **34:** 100743.

22 Esra RT, Johnson LF. Modelling the impact of screening for chlamydia and gonorrhoea in youth and other high-prevalence groups in a resource-limited setting. *Int J Public Health* 2020; **65:** 413–23.

23 Michalow J, Hall L, Rowley J, et al. Prevalence of chlamydia, gonorrhoea, and trichomoniasis among male and female general populations in sub-Saharan Africa from 2000 to 2024: a systematic review and meta-regression analysis. *EClinicalMedicine* 2025; **83:** 103210.

24 Davies EP, Tsuboi M, Evans J, Rowley J, Korenromp EL, Clayton T, Chico RM. A global meta-analysis of gonorrhoea and chlamydia prevalence among men who have sex with men from 2000 to 2022. *Int J STD AIDS* 2025; **36:** 611–21.

25 Grulich AE, Mercer C, Sturro B, et al. Partial progress in sexual and reproductive health and rights: the influence of sociocultural, behavioural, structural, and technological changes on epidemiological trends. *Lancet* 2025; **406:** 2100–18.

26 Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363:** 2587–99.

27 Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367:** 399–410.

28 Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012; **367:** 423–34.

29 Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2013; **381:** 2083–90.

30 Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015; **373:** 2237–46.

31 Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet* 2020; **396:** 239–54.

32 Bekker LG, Das M, Abdool Karim Q, et al. Twice-yearly lenacapavir for daily F/TAF for HIV prevention in cisgender women. *N Engl J Med* 2024; **391:** 1179–92.

33 Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. *N Engl J Med* 2016; **375:** 2121–32.

34 Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention. *New Engl J Med* 2016; **375:** 2133–43.

35 Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. *N Engl J Med* 2021; **385:** 595–608.

36 Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. *Lancet* 2022; **399:** 1779–89.

37 Kelley CF, Acevedo-Quinones M, Agwu AL, et al. Twice-yearly lenacapavir for HIV prevention in men and gender-diverse persons. *N Engl J Med* 2025; **393:** 1261–76.

38 Irie WC, Nicol MR, Clement M, et al. Event-driven PrEP beyond cisgender men who have sex with men. *Lancet HIV* 2025; **12:** e143–53.

39 Marrazzo J, Tao L, Becker M, et al. HIV preexposure prophylaxis with emtricitabine and tenofovir disoproxil fumarate among cisgender women. *JAMA* 2024; **331:** 930–37.

40 Walensky RP, Baden LR. The real PURPOSE of PrEP: effectiveness, not efficacy. *N Engl J Med* 2024; **391:** 1246–47.

41 Zhang J, Li C, Xu J, et al. Discontinuation, suboptimal adherence, and reinitiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis. *Lancet HIV* 2022; **9:** e254–68.

42 Ngure K, Browne EN, Reddy K, et al. Correlates of adherence to oral and vaginal pre-exposure prophylaxis (PrEP) among adolescent girls and young women (AGYW) participating in the MTN-034/REACH trial. *AIDS Behav* 2024; 28: 2990–3000.

43 Kakande ER, Ayieko J, Sunday H, et al. A community-based dynamic choice model for HIV prevention improves PrEP and PEP coverage in rural Uganda and Kenya: a cluster randomized trial. *J Int AIDS Soc* 2023; **26:** e26195.

44 Marzinke MA, Fogel JM, Wang Z, et al. Extended analysis of HIV infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. *Antimicrob Agents Chemother* 2023; **67:** e0005323.

45 Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. *N Engl J Med* 1997; **337:** 1485–90.

46 Agrahari V, Anderson SM, Peet MM, et al. Long-acting HIV pre-exposure prophylaxis (PrEP) approaches: recent advances, emerging technologies, and development challenges. *Expert Opin Drug Deliv* 2022; **19:** 1365–80.

47 PEPFAR, USAID. MATRIX: a USAID project to advance the research and development of innovative HIV prevention products for women. 2022. https://www.prepwatch.org/wp-content/uploads/2022/09/about-matrix.pdf (accessed Feb 23, 2025).

48 Han K, D'Amico R, Sievers J, et al. Phase I study of cabotegravir long-acting injectable formulations supports ≥4-monthly dose interval. Conference on Retroviruses and Opportunistic Infections; March 3–6, 2024 (abstract 130).

49 Jogiraju V, Pawar P, Yager J, et al. Pharmacokinetics and safety of once-yearly lenacapavir: a phase 1, open-label study. *Lancet* 2025; **405:** 1147–54.

50 Anderson DJ, Bearak JM, Grimstad FW, et al. Biomedical innovations in contraception: gaps, obstacles, and solutions for sexual and reproductive health. *Lancet* 2025; **406:** 2119–32.

51 Kabami J, Koss CA, Sunday H, et al. Randomised trial of dynamic choice HIV prevention at antenatal and postnatal care clinics in rural Uganda and Kenya. *J Acquir Immune Defic Syndr* 2024; **95:** 447–55.

52 Ayieko J, Balzer LB, Inviolata C, et al. Randomized trial of "dynamic choice" patient-centered interventions for mobile persons with HIV in east Africa. *J Acquir Immune Defic Syndr* 2024; **95:** 74–81.

53 Kakande ER, Ayieko J, Sunday H, et al. A community-based dynamic choice model for HIV prevention improves PrEP and PEP coverage in rural Uganda and Kenya: a cluster randomized trial. *J Int AIDS Soc* 2023; **26:** e26195.

54 Ontario HIV Treatment Network. Doxycycline prophylaxis for the prevention of bacterial sexually transmitted infections (STIs): doxyPrEP and doxyPEP. 2024. https://www.ohtn.on.ca/wp-content/uploads/2024/11/RR183-doxycycline-prep-pep.pdf (accessed Feb 23, 2025).

55 Grant JS, Stafylis C, Celum C, et al. Doxycycline prophylaxis for bacterial sexually transmitted infections. *Clin Infect Dis* 2020; **70:** 1247–53.

56 Grennan T, Mohammed S, Edward J, et al. A pilot, randomized controlled trial of dual daily HIV and sexually transmitted infection pre-exposure prophylaxis using tenofovir disoproxil fumarate/emtricitabine and doxycycline in gay, bisexual and other men who have sex with men and transgender women: the DuDHS Study. *Clin Infect Dis* 2025; published online Jan 30. https://doi.org/10.1093/cid/ciaf043.

57 Klausner JD. A new choice for doxycycline prophylaxis. *Clin Infect Dis* 2025; published online Jan 29. https://doi.org/10.1093/cid/ciaf044.

58 Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. *N Engl J Med* 1997; **337:** 1485–90.

59 Irvine C, Egan KJ, Shubber Z, Van Rompay KK, Beanland RL, Ford N. Efficacy of HIV postexposure prophylaxis: systematic review and meta-analysis of nonhuman primate studies. *Clin Infect Dis* 2015; **60** (suppl 3)**:** S165–69.

60 Mayer KH, Allan-Blitz LT. Post-exposure prophylaxis to prevent HIV: new drugs, new approaches, and more questions. *Lancet HIV* 2023; **10:** e816–24.

61 Schroder D, Cherdtrakulkiat T, Doanh LH, et al. Exceedingly high levels of tetracycline resistance in *Neisseria gonorrhoeae* in eight WHO Enhanced Gonococcal Antimicrobial Surveillance Programme countries in three WHO regions, 2021–2024—doxycycline post-exposure prophylaxis will unlikely impact gonorrhoea burdens. *J Antimicrob Chemother* 2025; **80:** 1291–95.

62 Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. *Lancet Infect Dis* 2018; **18:** 308–17.

63 Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure doxycycline to prevent bacterial sexually transmitted infections. *N Engl J Med* 2023; **388:** 1296–306.

64 Molina JM, Bercot B, Assoumou L, et al. Doxycycline prophylaxis and meningococcal group B vaccine to prevent bacterial sexually transmitted infections in France (ANRS 174 DOXYVAC): a multicentre, open-label, randomised trial with a 2 × 2 factorial design. *Lancet Infect Dis* 2024; **24:** 1093–104.

65 Stewart J, Oware K, Donnell D, et al. Doxycycline prophylaxis to prevent sexually transmitted infections in women. *N Engl J Med* 2023; **389:** 2331–40.

66 Luetkemeyer AF, Donnell D, Cohen SE, et al. Doxycycline to prevent bacterial sexually transmitted infections in the USA: final results from the DoxyPEP multicentre, open-label, randomised controlled trial and open-label extension. *Lancet Infect Dis* 2025; published online March 24. https://doi.org/10.1016/S1473-3099(25)00085-4.

67 Stewart J, Oware K, Donnell D, et al. Objective assessment of doxycycline post-exposure prophylaxis use among cisgender women in Kenya. Poster presentation. Conference on Retroviruses and Opportunitis Infections, 2024.

68 Chu VT, Glascock A, Donnell D, et al. Impact of doxycycline post-exposure prophylaxis for sexually transmitted infections on the gut microbiome and antimicrobial resistome. *Nat Med* 2025; **31:** 207–17.

69 Mittelstaedt R, Kanjilal S, Helekal D, et al. *Staphylococcus aureus* tetracycline resistance and co-resistance in a doxycycline postexposure prophylaxis-eligible population. *medRxiv* 2024; published online Aug 22. https://doi.org/10.1101/2024.08.22.24312434 (preprint).

70 Soge OO, Thibault CS, Cannon CA, et al. Potential impact of doxycycline post-exposure prophylaxis on tetracycline resistance in *Neisseria gonorrhoeae* and colonization with tetracycline-resistant *Staphylococcus aureus* and Group A streptococcus. *Clin Infect Dis* 2025; published online Feb 28. https://doi.org/10.1093/cid/ciaf089.

71 Reichert E, Grad YH. Effects of doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections on gonorrhoea prevalence and antimicrobial resistance among men who have sex with men in the USA: a modelling study. *Lancet Microbe* 2024; **5:** 100926.

72 Vanbaelen T, Manoharan-Basil SS, Kenyon C. Doxycycline postexposure prophylaxis could induce cross-resistance to other classes of antimicrobials in *Neisseria gonorrhoeae*: an in-silico analysis. *Sex Transm Dis* 2023; **50:** 490–93.

73 Traeger MW, Leyden WA, Volk JE, et al. Doxycycline post-exposure prophylaxis and bacterial sexually transmitted infections among individuals using HIV preexposure prophylaxis. *JAMA Intern Med* 2025; **185:** 273–81.

74 Sankaran M, Glidden DV, Kohn RP, et al. Doxycycline post-exposure prophylaxis and sexually transmitted infections trends. *JAMA Intern Med* 2025; **185:** 266–72.

75 Raccagni AR, Diotallevi S, Lolatto R, et al. DoxyPEP: real-life effectiveness in a cohort of men who have sex with men in Milan, Italy. *Lancet Infect Dis* 2025; **25:** e1–3.

76 Fauci AS. An HIV vaccine is essential for ending the HIV/AIDS pandemic. *JAMA* 2017; **318:** 1535–36.

77 Gray GE, Bekker LG, Laher F, et al. Vaccine efficacy of ALVAC-HIV and bivalent subtype C Gp120-MF59 in adults. *N Engl J Med* 2021; **384:** 1089–100.

78 Gray GE, Mngadi K, Lavreys L, et al. Mosaic HIV-1 vaccine regimen in southern African women (Imbokodo/HVTN 705/HPX2008): a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Infect Dis* 2024; **24:** 1201–12.

79 Johnson & Johnson. Johnson & Johnson and global partners to discontinue phase 3 Mosaico HIV vaccine clinical trial. Aug 31, 2023. https://www.jnj.com/johnson-johnson-and-global-partners-announce-results-from-phase-2b-imbokodo-hiv-vaccine-clinical-trial-in-young-women-in-sub-saharan-africa (accessed Feb 23, 2025).

80 Ahmed Y, Tian M, Gao Y. Development of an anti-HIV vaccine eliciting broadly neutralizing antibodies. *AIDS Res Ther* 2017; **14:** 50.

81 Liu Y, Cao W, Sun M, Li T. Broadly neutralizing antibodies for HIV-1: efficacies, challenges and opportunities. *Emerg Microbes Infect* 2020; **9:** 194–206.

82 Sanders RW, Moore JP. Progress on priming HIV-1 immunity. *Science* 2024; **384:** 738–39.

83 Julg B, Barouch DH. Neutralizing antibodies for HIV-1 prevention. *Curr Opin HIV AIDS* 2019; **14:** 318–24.

84 Corey L, Gilbert PB, Juraska M, et al. Two randomized trials of neutralizing antibodies to prevent HIV-1 acquisition. *N Engl J Med* 2021; **384:** 1003–14.

85 WHO. Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030. 2022. https://www.who.int/publications/i/item/9789240053779 (accessed Feb 23, 2025).

86 Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. *Lancet* 2017; **390:** 1603–10.

87 Abara WE, Bernstein KT, Lewis FMT, et al. Effectiveness of a serogroup B outer membrane vesicle meningococcal vaccine against gonorrhoea: a retrospective observational study. *Lancet Infect Dis* 2022; **22:** 1021–29.

88 Wang B, Giles L, Andraweera P, et al. Effectiveness and impact of the 4CMenB vaccine against invasive serogroup B meningococcal disease and gonorrhoea in an infant, child, and adolescent programme: an observational cohort and case-control study. *Lancet Infect Dis* 2022; **22:** 1011–20.

89 Leduc I, Connolly KL, Begum A, et al. The serogroup B meningococcal outer membrane vesicle-based vaccine 4CMenB induces cross-species protection against *Neisseria gonorrhoeae*. *PLoS Pathog* 2020; **16:** e1008602.

90 Lyu Y, Choong A, Chow EPF, et al. Vaccine value profile for *Neisseria gonorrhoeae*. *Vaccine* 2024; **42:** S42–69.

91 Pollock KM, Borges ÁH, Cheeseman HM, et al. An investigation of trachoma vaccine regimens by the chlamydia vaccine CTH522 administered with cationic liposomes in healthy adults (CHLM-02): a phase 1, double-blind trial. *Lancet Infect Dis* 2024; **24:** 829–44.

92 Olsen AW, Rosenkrands I, Jacobsen CS, et al. Immune signature of chlamydia vaccine CTH522/CAF01 translates from mouse-to-human and induces durable protection in mice. *Nat Commun* 2024; **15:** 1665.

93 Poston TB. Advances in vaccine development for *Chlamydia trachomatis*. *Pathog Dis* 2024; **82:** ftae017.

94 Harfouche M, AlMukdad S, Alareeki A, et al. Estimated global and regional incidence and prevalence of herpes simplex virus infections and genital ulcer disease in 2020: mathematical modelling analyses. *Sex Transm Infect* 2025; **101:** 214–23.

95 Chaiyakunapruk N, Lee SWH, Kulchaitanaroaj P, et al. Estimated global and regional economic burden of genital herpes simplex virus infection among 15–49 year-olds in 2016. *BMC Glob Public Health* 2024; **2:** 42.

96 Looker KJ, Welton NJ, Sabin KM, et al. Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction analysis using published epidemiological data. *Lancet Infect Dis* 2020; **20:** 240–49.

97 Stone J, Looker KJ, Silhol R, et al. The population impact of herpes simplex virus type 2 (HSV-2) vaccination on the incidence of HSV-2, HIV and genital ulcer disease in South Africa: a mathematical modelling study. *EBioMedicine* 2023; **90:** 104530.

98 Riedel S. Smallpox and biological warfare: a disease revisited. *Proc Bayl Univ Med Cent* 2005; **18:** 13–20.

99 Wolff Sagy Y, Zucker R, Hammerman A, et al. Real-world effectiveness of a single dose of mpox vaccine in males. *Nat Med* 2023; **29:** 748–52.

100 Pischel L, Martini BA, Yu N, et al. Vaccine effectiveness of 3rd generation mpox vaccines against mpox and disease severity: a systematic review and meta-analysis. *Vaccine* 2024; **42:** 126053.

101 Rosen JB, Arciuolo RJ, Pathela P, et al. JYNNEOS effectiveness as post-exposure prophylaxis against mpox: challenges using real-world outbreak data. *Vaccine* 2024; **42:** 548–55.

102 Waugh S, Cameron CE. Syphilis vaccine development: aligning vaccine design with manufacturing requirements. *Hum Vaccin Immunother* 2024; **20:** 2399915.

103 Soldan K, Elliss-Brookes L, Sasieni P. The impact of HPV vaccination program on CIN3 and cervical cancer incidence in England. 2022. https://www.hpvworld.com/articles/the-impact-of-hpv-vaccination-program-on-cin3-and-cervical-cancer-incidence-in-england/ (accessed Feb 23, 2025).

104 WHO. WHO expands guidance on sexually transmitted infections and reviews country progress on policy implementation. July 26, 2025. https://www.who.int/news/item/26-07-2025-who-expands-guidance-on-sexually-transmitted-infections-and-reviews-country-progress-on-policy-implementation (accessed Sept 9, 2025).

105 WHO. Global HIV, Hepatitis and STIs Programmes. https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/strategies/global-health-sector-strategies (accessed Sept 9, 2025).

106 WHO. HPV dashboard. 2025. https://www.who.int/teams/immunization-vaccines-and-biologicals/diseases/human-papillomavirus-vaccines-(HPV)/hpv-clearing-house/hpv-dashboard (accessed Feb 23, 2025).

107 WHO. Human papillomavirus vaccines: WHO position paper (2022 update). 2022. https://www.who.int/publications/i/item/who-wer9750-645-672 (accessed Feb 23, 2025).

108 Wei F, Alberts CJ, Albuquerque A, Clifford GM. Impact of human papillomavirus vaccine against anal human papillomavirus infection, anal intraepithelial neoplasia, and recurrence of anal intraepithelial neoplasia: a systematic review and meta-analysis. *J Infect Dis* 2023; **228:** 1496–504.

109 Liu G, Mugo NR, Bayer C, et al. Impact of catch-up human papillomavirus vaccination on cervical cancer incidence in Kenya: a mathematical modeling evaluation of HPV vaccination strategies in the context of moderate HIV prevalence. *EClinicalMedicine* 2022; **45:** 101306.

110 Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med* 2005; **2:** e298.

111 Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007; **369:** 643–56.

112 Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; **369:** 657–66.

113 Davis S, Toledo C, Lewis L, Maughan-Brown B, Ayalew K, Kharsany ABM. Does voluntary medical male circumcision protect against sexually transmitted infections among men and women in real-world scale-up settings? Findings of a household survey in KwaZulu-Natal, South Africa. *BMJ Glob Health* 2019; **4:** e001389.

114 Morris BJ, Hankins CA, Banerjee J, et al. Does male circumcision reduce women's risk of sexually transmitted infections, cervical cancer and associated conditions? *Front Public Health* 2019; **7:** 4.

115 Grund JM, Bryant TS, Jackson I, et al. Association between male circumcision and women's biomedical health outcomes: a systematic review. *Lancet Glob Health* 2017; **5:** e1113–22.

116 Meyer-Rather G, Jamieson L, Mudimo E, et al. Who pays and what pays off in sexual and reproductive health? A review of the cost and cost-effectiveness of interventions and implications for future funding and markets. *Lancet* 2025; **406:** 2152–67.

117 Mayer KH, Beyrer C, Cohen MS, et al. Challenges and opportunities in developing integrated sexual and reproductive health programmes. *Lancet* 2025; **406:** 2168–94.

118 Little KM, Hanif H, Anderson SM, Clark MR, Gustafson K, Doncel GF. Preferences for long-acting PrEP products among women and girls: a quantitative survey and discrete choice experiment in Eswatini, Kenya, and South Africa. *AIDS Behav* 2024; **28:** 936–50.

119 Minnis AM, Etima J, Musara P, et al. Couples' preferences for 2 in 1 multipurpose prevention technologies to prevent both HIV and pregnancy: results of a discrete choice experiment in Uganda and Zimbabwe. *AIDS Behav* 2022; **26:** 3848–61.

120 Thurman AR, Brache V, Cochon L, et al. Randomized, placebo controlled phase I trial of the safety, pharmacokinetics, pharmacodynamics and acceptability of a 90 day tenofovir plus levonorgestrel vaginal ring used continuously or cyclically in women: the CONRAD 138 study. *PLoS One* 2022; **17:** e0275794.

121 Mugo NR, Mudhune V, Heffron R, et al. Randomized controlled phase IIa clinical trial of safety, pharmacokinetics and pharmacodynamics of tenofovir and tenofovir plus levonorgestrel releasing intravaginal rings used by women in Kenya. *Front Reprod Health* 2023; **5:** 1118030.

122 Brandt AM. No magic bullet: a social history of venereal disease in the United States since 1880—35th anniversary edition, 2nd edn. Oxford University Press, 2020.

123 Gabbay MB, Thomas J, Gibbs A, Hold P. A randomized crossover trial of the impact of additional spermicide on condom failure rates. *Sex Transm Dis* 2008; **35:** 862–68.

124 Nimbi FM, Galizia R, Rossi R, et al. The biopsychosocial model and the sex-positive approach: an integrative perspective for sexology and general health care. *Sex Res Soc Policy* 2022; **19:** 894–908.

125 Dehlin JM, Stillwagon R, Pickett J, Keene L, Schneider JA. #PrEP4Love: an evaluation of sex-positive HIV prevention campaign. *JMIR Public Health Surveill* 2019; **5:** e12822.

126 Curley CM, Rosen AO, Mistler CB, Eaton LA. Pleasure and PrEP: a systematic review of studies examining pleasure, sexual satisfaction, and PrEP. *J Sex Res* 2022; **59:** 848–61.

127 Fisher JD, Smith L. Secondary prevention of HIV infection: the current state of prevention for positives. *Curr Opin HIV AIDS* 2009; **4:** 279–87.

128 Villa-Rueda AA, Onofre-Rodríguez DJ, Churchill S, Ramírez-Barajas F, Benavides-Torres RA. Multilevel elements associated with HIV serosorting for sexual encounters: a scoping literature review. *Cien Saude Colet* 2021; **26:** 2183–94.

129 Siegler AJ, Sullivan PS, Khosropour CM, Rosenberg ES. The role of intent in serosorting behaviors among men who have sex with men sexual partnerships. *J Acquir Immune Defic Syndr* 2013; **64:** 307–14.

130 Karellis A, Naeem F, Nair S, et al. Multiplexed rapid technologies for sexually transmitted infections: a systematic review. *Lancet Microbe* 2022; **3:** e303–15.

131 Chitneni P, Owembabazi M, Muyindike W, et al. Sexually transmitted infection point-of-care testing in resource-limited settings: a narrative review guided by an implementation framework. *Sex Transm Dis* 2023; **50:** e11–16.

132 de Vos L, Daniels J, Gebengu A, et al. Implementation considerations for a point-of-care *Neisseria gonorrhoeae* rapid diagnostic test at primary healthcare level in South Africa: a qualitative study. *BMC Health Serv Res* 2024; **24:** 43.

133 Land KJ, Boeras DI, Chen XS, Ramsay AR, Peeling RW. REASSURED diagnostics to inform disease control strategies, strengthen health systems and improve patient outcomes. *Nat Microbiol* 2019; **4:** 46–54.

134 Alexander TS. Human immunodeficiency virus diagnostic testing: 30 years of evolution. *Clin Vaccine Immunol* 2016; **23:** 249–53.

135 Landovitz RJ, Delany-Moretlwe S, Fogel JM, et al. Features of HIV infection in the context of long-acting cabotegravir preexposure prophylaxis. *N Engl J Med* 2024; **391:** 1253–56.

136 WHO. Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis. 2025. https://www.who.int/publications/i/item/9789240111608 (accessed Aug 30, 2025).

137 Pham MD, Wise A, Garcia ML, et al. Improving the coverage and accuracy of syphilis testing: the development of a novel rapid, point-of-care test for confirmatory testing of active syphilis infection and its early evaluation in China and South Africa. *EClinicalMedicine* 2020; **24:** 100440.

138 Peters RPH, Klausner JD, Mazzola L, et al. Novel lateral flow assay for point-of-care detection of *Neisseria gonorrhoeae* infection in syndromic management settings: a cross-sectional performance evaluation. *Lancet* 2024; **403:** 657–64.

139 Gaydos CA, Klausner JD, Pai NP, Kelly H, Coltart C, Peeling RW. Rapid and point-of-care tests for the diagnosis of *Trichomonas vaginalis* in women and men. *Sex Transm Infect* 2017; **93:** S31–35.

140 Martin K, Dauya E, Dziva Chikwari C, et al. Evaluation of a novel point-of-care lateral flow assay screening for *Neisseria gonorrhoeae* infection among pregnant women in Zimbabwe. *PLOS Glob Public Health* 2025; **5:** e0003839.

141 Luo R, Fong Y, Boeras D, Jani I, Vojnov L. The clinical effect of point-of-care HIV diagnosis in infants: a systematic review and meta-analysis. *Lancet* 2022; **400:** 887–95.

142 Van Der Pol B, Gaydos CA. A profile of the binx health *io* molecular point-of-care test for chlamydia and gonorrhea in women and men. *Expert Rev Mol Diagn* 2021; **21:** 861–68.

143 Morris SR, Bristow CC, Wierzbicki MR, et al. Performance of a single-use, rapid, point-of-care PCR device for the detection of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*: a cross-sectional study. *Lancet Infect Dis* 2021; **21:** 668–76.

144 Riddell MA, Vallely LM, Mengi A, et al. Point-of-care testing and treatment of sexually transmitted and genital infections to improve birth outcomes in high-burden, low-resource settings (WANTAIM): a pragmatic cluster randomised crossover trial in Papua New Guinea. *Lancet Glob Health* 2024; **12:** e641–51.

145 Mdingi MM, Peters RPH, Gigi R, et al. Same-day treatment following point-of-care sexually transmitted infection testing in different healthcare settings in South Africa. *Clin Infect Dis* 2023; **76:** 1699–700.

146 Martin K, Olaru ID, Buwu N, et al. Uptake of and factors associated with testing for sexually transmitted infections in community-based settings among youth in Zimbabwe: a mixed-methods study. *Lancet Child Adolesc Health* 2021; **5:** 122–32.

147 Ramboarina S, Crucitti T, Gill K, et al. Novel point-of-care cytokine biomarker lateral flow test for the screening for sexually transmitted infections and bacterial vaginosis: study protocol of a multicentre multidisciplinary prospective observational clinical study to evaluate the performance and feasibility of the Genital InFlammation Test (GIFT). *BMJ Open* 2024; **14:** e084918.

148 Koh MCY, Ngiam JN, Yong J, Tambyah PA, Archuleta S. The role of an artificial intelligence model in antiretroviral therapy counselling and advice for people living with HIV. *HIV Med* 2024; **25:** 504–08.

149 Cheah MH, Gan YN, Altice FL, et al. Testing the feasibility and acceptability of using an artificial intelligence chatbot to promote HIV testing and pre-exposure prophylaxis in Malaysia: mixed methods study. *JMIR Hum Factors* 2024; **11:** e52055.

150 Seboka BT, Yehualashet DE, Tesfa GA. Artificial intelligence and machine learning based prediction of viral load and CD4 status of people living with HIV (PLWH) on anti-retroviral treatment in Gedeo zone public hospitals. *Int J Gen Med* 2023; **16:** 435–51.

151 Roche SD, Ekwunife OI, Mendonca R, et al. Measuring the performance of computer vision artificial intelligence to interpret images of HIV self-testing results. *Front Public Health* 2024; **12:** 1334881.

152 Nadarzynski T, Knights N, Husbands D, et al. The impact of chatbot-assisted self assessment (CASA) on intentions for sexual health screening in people from minoritised ethnic groups at risk of sexually transmitted infections. *Sex Health* 2024; **21:** SH24058.

153 Koh MCY, Ngiam JN, Tambyah PA, Archuleta S. ChatGPT as a tool to improve access to knowledge on sexually transmitted infections. *Sex Transm Infect* 2024; **100:** 528–31.

154 Elder HR, Gruber S, Willis SJ, et al. Can machine learning help identify patients at risk for recurrent sexually transmitted infections? *Sex Transm Dis* 2021; **48:** 56–62.

155 Soe NN, Yu Z, Latt PM, et al. Evaluation of artificial intelligence-powered screening for sexually transmitted infections-related skin lesions using clinical images and metadata. *BMC Med* 2024; **22:** 296.

156 Latt PM, Soe NN, Xu X, et al. Identifying individuals at high risk for HIV and sexually transmitted infections with an artificial intelligence-based risk assessment tool. *Open Forum Infect Dis* 2024; **11:** ofae011.

157 Soe NN, Yu Z, Latt PM, et al. Using AI to differentiate mpox from common skin lesions in a sexual health clinic: algorithm development and validation study. *J Med Internet Res* 2024; **26:** e52490.

158 Thieme AH, Zheng Y, Machiraju G, et al. A deep-learning algorithm to classify skin lesions from mpox virus infection. *Nat Med* 2023; **29:** 738–47.

159 Tan RKJ, Perera D, Arasaratnam S, Kularathne Y. Adapting an artificial intelligence sexually transmitted diseases symptom checker tool for mpox detection: the HeHealth experience. *Sex Health* 2024; **21:** SH23197.

160 Turbé V, Herbst C, Mngomezulu T, et al. Deep learning of HIV field-based rapid tests. *Nat Med* 2021; **27:** 1165–70.

161 Grimsrud A, Bygrave H, Doherty M, et al. Reimagining HIV service delivery: the role of differentiated care from prevention to suppression. *J Int AIDS Soc* 2016; **19:** 21484.

162 Ehrenkranz P, Grimsrud A, Rabkin M. Differentiated service delivery: navigating the path to scale. *Curr Opin HIV AIDS* 2019; **14:** 60–65.

163 Grimsrud A, Wilkinson L, Delany-Moretlwe S, et al. The importance of the how: the case for differentiated service delivery of long-acting and extended delivery regimens for HIV prevention and treatment. *J Int AIDS Soc* 2023; **26** (suppl 2): e26095.

164 Ford N, Eshun-Wilson I, Ameyan W, et al. Future directions for HIV service delivery research: research gaps identified through WHO guideline development. *PLoS Med* 2021; **18:** e1003812.

165 Bien CH, Muessig KE, Lee R, et al. HIV and syphilis testing preferences among men who have sex with men in South China: a qualitative analysis to inform sexual health services. *PLoS One* 2015; **10:** e0124161.

166 Motsieloa L, Phalane E, Phaswana-Mafuya RN. Differentiated service delivery model in improving HIV treatment outcomes among female sex workers in Gauteng province of South Africa: a Protocol Paper. *Methods Protoc* 2024; **7:** 89.

167 Chikwari CD, Simms V, Kranzer K, et al. Evaluation of a community-based aetiological approach for sexually transmitted infections management for youth in Zimbabwe: intervention findings from the STICH cluster randomised trial. *EClinicalMedicine* 2023; **62:** 102125.

168 Saleem K, Ting EL, Loh AJW, et al. Missed opportunities for HIV testing among those who accessed sexually transmitted infection (STI) services, tested for STIs and diagnosed with STIs: a systematic review and meta-analysis. *J Int AIDS Soc* 2023; **26:** e26049.

169 Mullick S, Cox LA, Martin CE, Fipaza Z, Ncube S. Comparing the integration of syndromic versus etiological management of sexually transmitted infections into HIV pre-exposure prophylaxis services for adolescent girls and young women, in South Africa. *J Adolesc Health* 2023; **73:** S67–72.

170 Shahmanesh M, Chimbindi N, Busang J, et al. Effectiveness of integrating HIV prevention within sexual reproductive health services with or without peer support among adolescents and young adults in rural KwaZulu-Natal, South Africa (Isisekelo Sempilo): 2 × 2 factorial, open-label, randomised controlled trial. *Lancet HIV* 2024; **11:** e449–60.

171 Melendez JH, Hamill MM, Armington GS, Gaydos CA, Manabe YC. Home-based testing for sexually transmitted infections: leveraging online resources during the COVID-19 pandemic. *Sex Transm Dis* 2021; **48:** e8–10.

172 Exten C, Pinto CN, Gaynor AM, Meyerson B, Griner SB, Van Der Pol B. Direct-to-consumer sexually transmitted infection testing services: a position statement from the American Sexually Transmitted Diseases Association. *Sex Transm Dis* 2021; **48:** e155–59.

173 Gilbert M, Salway T, Haag D, et al. A cohort study comparing rate of repeat testing for sexually transmitted and blood-borne infections between clients of an internet-based testing programme and of sexually transmitted infection clinics in Vancouver, Canada. *Sex Transm Infect* 2019; **95:** 540–46.

174 Rahib D, Delagreverie H, Gabassi A, et al. Online self-sampling kits to screen multipartner MSM for HIV and other STIs: participant characteristics and factors associated with kit use in the first 3 months of the MemoDepistages programme, France, 2018. *Sex Transm Infect* 2021; **97:** 134–40.

Copyright © 2025 Elsevier Ltd. All rights reserved, including those for text and data mining, AI training, and similar technologies.