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Expanding the pipeline for multipurpose prevention technologies: compounds with potential activity to prevent or treat HIV and other STIs

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ABSTRACT

Background Continued high incidence of HIV and other STIs, paired with rising antibiotic resistance to a number of existing treatments, warrants the development of new pharmaceutical approaches for STI prevention. Multipurpose prevention technologies (MPTs) offer an innovative approach for expanding HIV/STI prevention. The majority of MPT product candidates currently in development include HIV prevention, while only half include compounds active against non-HIV STIs.

Methods This narrative review focuses on compounds in preclinical development (in vitro and in vivo) through phase 3 clinical trials with activity against one or more of the following infections: HIV, HSV-1, HSV-2, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum*, and *Trichomonas vaginalis.* Bacterial vaginosis is included due to its association with increased risk of STIs. The focus is on compounds with novel mechanisms of action and prophylactic and/or therapeutic potential. Articles published in PubMed between 2011 and 2021, NIH RePorter and conference abstracts and proceedings between 2020 and 2021 were searched. Excluded from the review are compounds that are already being used in MPT product candidates.

Main results There is a growing pipeline of compounds targeting viral STIs, many of which have successfully transitioned from preclinical to clinical stages of development. However, the product development pipeline remains limited for compounds that target bacterial STIs.

Conclusions The paucity of new pharmaceutical approaches for STI prevention, particularly non-HIV STIs, remains a public health gap. Future funding priorities should include STI prevention research. Despite limited attention to STI prevention in the development of MPTs, many research institutions worldwide are working on discoveries of new compounds, exploring new indications for existing drugs or on innovative drug delivery mechanisms. Our findings can be used to connect researchers across the globe to advance the development of compounds that have potential as active pharmaceutical ingredients in future MPTs.

KEY MESSAGES

⇒ Continued high incidence of HIV and STIs in certain regions of the world, paired with rising antibiotic resistance to a number of existing treatments, warrants the development of new pharmaceutical approaches for prevention.
⇒ There is a growing pipeline of compounds targeting viral STIs, while those targeting bacterial STIs remain limited.
⇒ The shortage of new pharmaceutical approaches for STI prevention, particularly non-HIV STIs, remains a significant public health gap.
⇒ Multipurpose prevention technologies (MPTs) offer an innovative approach for expanding HIV/STI prevention.
⇒ As new active pharmaceutical ingredients are identified for STI prevention, our findings underscore the need for a continuously updated database aimed to connect researchers across the globe working on compounds suitable for future MPTs.

INTRODUCTION

The interlinked risks of STIs, including HIV, and unintended pregnancies are significant causes of morbidity and mortality for millions of women of reproductive age worldwide. HIV continues to be a major global public health threat. Adolescent girls and young women in sub-Saharan Africa aged 15–24 years are at particular risk, representing 63% of all new HIV cases in 2021.[1] Non-HIV STIs are on the rise worldwide, and the WHO estimates that more than 1 million STIs are acquired every day globally.[2] Non-HIV STIs are major causes of genital inflammation and have a substantial impact on the female genital mucosa, which is an important biological and physical barrier that forms the first line of defence against invading microorganisms such as HIV.[3] Inflammation in the female genital tract, regardless of the cause, creates an environment that can favour HIV infection.[4] As such, non-HIV STIs are attributed with increasing the risk of HIV acquisition and transmission.[5] Additionally, STIs can cause severe reproductive health complications in women, including stillbirth, preterm birth, infertility and cervical cancer, among others. Many STIs, particularly non-ulcerative infections, are often undiagnosed and may remain untreated for long periods of time.[3] Antibiotic resistance to standard antibiotic drug therapies, as emerging for *Neisseria gonorrhoeae*,[6] poses yet another challenge. According to the WHO, 74 million women living in low-income and middle-income countries have unintended pregnancies every year, leading to 25 million unsafe abortions and 47 000 maternal deaths per year.[7]

Over the last decade, support has grown for multipurpose prevention technologies (MPTs) aimed

to combine the prevention of two or more sexual and reproductive health (SRH) risks into a single product: unintended pregnancies, HIV and/or other STIs. Currently, condoms are still the only multipurpose methods available. An array of new MPTs have entered development, representing diverse delivery approaches and targeted indications. As of December 2022, 28 MPT product candidates are in the pipeline.[8] The majority of these are in early stages of preclinical or clinical development and are primarily focused on combining anti-HIV drugs and hormonal contraceptive drugs into a single product.

This narrative review aims to provide a high-level summary of new compounds currently being explored for potential activity against HIV or other STIs that are not yet included in existing MPT candidates. The initial summary review was developed as a report for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and aimed to identify existing efforts and stimulate new research for anti-infective approaches targeting HIV and other STIs that can be combined with contraceptives as new MPTs.[9] The supplementary compound tables developed for this review reveal the extensive amount of research underway in this area by a wide array of researchers around the globe. While the scope of this review is not to provide a systematic and detailed assessment of all listed active pharmaceutical ingredients (APIs) in development and their promise for the targeted infections, it highlights the vast array of work underway in this area by researchers globally. While we attempted to be as comprehensive as possible by searching multiple sources, compound screening and drug development is a rapidly progressing field. Promising compounds may be abandoned at various stages of investigation for unknown reasons, making an accurate accounting of compounds under study difficult at best. This further highlights the need for a comprehensive, continually updated database to advance the field of MPT research, which has been identified as an unmet need by global stakeholders.[10 11]

With the rising cost of drug discovery and development, drug repurposing has become an approach to lowering the cost and time required to bring a product to market.[12] Drug repurposing (also known as drug repositioning, drug reprofiling) is a strategy to identify new indications for approved agents that are outside the scope of the original indication. Such a strategy has the advantage of leveraging the known safety profile of the agent.[12 13] Repurposed drugs are an unexplored source of compounds for MPT development.

STIs are among the most common communicable conditions and affect the health and lives of people worldwide. Thus, their association with HIV transmission and reproductive complications, as well as increases in antibiotic resistance, all underscore the need for innovative prevention approaches including MPTs. The most common way to classify STIs is by the type of causative organism, namely bacterial, viral or parasitic. A second important classification is by clinical presentation. STIs can also be classified by the different mechanisms through which they cause infections and evade immunity.[3] Although STIs are frequently asymptomatic, they can cause: (a) ulcers in genital, anal, oral and perianal tissues (eg, *Treponema pallidum* and *herpes simplex virus* (HSV)), (b) urethral and vaginal discharge (eg, *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Mycoplasma genitalium*) or (c) genital warts (eg, Human Papillomavirus (HPV)).[14–17] In severe cases, STIs can lead to infertility, pregnancy loss, malignancies and other systemic manifestations or infections. Table 1 summarises the current epidemiology of selected STIs and BV, which are the focus of this review.

METHODS

This review provides a summary of drug compounds and/or product candidates that are in preclinical development (in vitro and in vivo) through phase 3 clinical trials with activity against one or more of the infections described in table 1.

Information sources and search strategy

The search strategy for this review, which was initially implemented between March and June 2021, included a number of resources. First, an article search in PubMed using the following search criteria: (1) articles published between 2011–2021; (2) potential search terms including indication (eg, HIV), in vitro, susceptibility, antimicrobial, antibacterial, antiviral, prevention, treatment, repurpose, antibacterial/antimicrobial peptides, probiotic, prebiotic, antiseptic, microbicide and acidifying vaginal agents. Second, the search included a review of the NIH RePorter (reporter.nih.gov) and clinicaltrials.gov databases,

Table 1 Overview of epidemiology of selected STIs and BV

STI	Brief summary of current epidemiology
HIV	► 1.5 million people worldwide became newly infected with HIV in 2021. ► The WHO African Region accounts for almost 60% of new HIV infections globally.[19]
Herpes Simplex Virus (HSV)	► An estimated 13% of people globally ages 15–49 years are infected with genital herpes caused by HSV-2. ► Women are infected with HSV-2 nearly two times more than men. ► Worldwide, it is estimated that 67% of people under the age of 50 years are infected with HSV-1.[28]
Chlamydia trachomatis	► The most prevalent bacterial STI worldwide. ► 128 million new cases of *C. trachomatis* infection in 2020. ► Highest prevalence (3.2%) among persons aged 15–49 years. ► *C. trachomatis* infection most commonly occurs in females and is a leading cause of cervicitis and infertility.[29 30]
Neisseria gonorrhoeae	► The second most common bacterial STI. ► 82.4 million new cases worldwide in 2020.[20 31]
Treponema pallidum (syphilis)	► There were approximately 6.3 million new cases of syphilis globally in 2019.[27] ► Among women in the USA, rates of infection increased by nearly 179% between 2015 and 2019.[32 33] ► More than half a million total cases of congenital syphilis globally in 2016, resulting in over 200 000 stillbirths and neonatal deaths.[34]
Trichomonas vaginalis	► With 156 million infections annually, trichomoniasis is the most common non-viral STI globally.[2] ► Often asymptomatic but is associated with increased risk for preterm birth, cervical cancer and HIV acquisition.
Bacterial vaginosis (BV)	► BV is a common infection of the female reproductive tract with a prevalence of up to 30% of all women of reproductive age globally.[22 35] ► Although not an STI, women with BV are at increased risk for STIs, such as HIV, *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*, *M. genitalium*, HPV, and HSV-2.[22]

which are listings of publicly funded research and ongoing registered clinical trials. Third, recent conference abstracts for 2020–2021 were included in the search from the following conferences and annual meetings: American Society of Microbiology; Infectious Diseases Society of America; STI & HIV World Congress; Conference on Retroviruses and Opportunistic Infections); International AIDS Society; and European Congress of Clinical Microbiology and Infectious Diseases. Compounds listed in online supplemental tables 1–7 were further updated to reflect development status through August 2022. For drug candidates in multiple parallel stages of development, the most recent findings or clinical trials were included to minimise redundancy. Repurposed drugs with demonstrated activity against STIs were also included as part of our review.

While our search is an attempt to be as comprehensive as possible, the focus is on compounds with novel mechanisms of action and prophylactic and/or therapeutic potential. Excluded from the review are compounds that are already included in the MPT product development database,[8] vaccine candidates, older studies of potentially abandoned compounds without further data beyond 2011 and gene therapy approaches. Since the focus of the review includes prevention of HIV and other STIs, in order to narrow the scope of the search, antibiotic compounds studied solely for treatment were not included. In the results section, we aim to summarise general classifications of existing compounds, and in the supplemental tables, we provide select references for each compound.

RESULTS

HIV

The majority of APIs under consideration for HIV include antiretroviral agents in various stages of clinical development, immunomodulating agents or passive immunisation strategies with monoclonal antibodies (mAbs) or broadly neutralising antibodies (bnAbs). The number of HIV clinical trials is vast, with multiple studies of the same agents, often paired with combinations of drugs from other classes. Common drug regimens include combinations of different mAbs or bnAbs, passive immunisation agents paired with antiretroviral agents or antiretroviral agents paired with immunomodulating or chemotherapeutic agents. Unfortunately, a rate-limiting factor for all these agents is toxicity, and the long-term tolerability of these agents still remains to be seen. Furthermore, data from recent trials suggest the need to assess efficacy of a broader, more potent combination of antibodies due to innate resistance and diversity of HIV strains.[18]

Online supplemental table 1 includes promising agents from the following drug classes:

1. mAbs and bnAb preventing HIV infection by blocking entry into cells.
2. Toll-like receptor agonists that activate the innate and adaptive immune system.
3. Repurposed antineoplastic agents for cancer chemotherapy and immunotherapy.

Herpes simplex virus

The available medications used to treat symptoms of HSV do not provide a cure and will have to be taken indefinitely. The most effective of these medications are antivirals including acyclovir, famciclovir and valacyclovir.[19] A number of new agents with activity against HSV have entered the development pipeline and could have potential as an MPT component (online supplemental table 2):

1. mAbs targeting envelope glycoprotein D inhibiting viral entry and cell-to-cell transmission.
2. Traditional Chinese medicines, such as flavonoid isolated from the root of *Scutellaria baicalensis* Georgi, which demonstrate inhibition of HSV-1 viral replication.
3. Dietary supplements that act as immunomodulators.
4. Antifungal and antiseptic agents that demonstrate inhibition of HSV-1 viral replication.
5. Antiviral agents, including broad-spectrum antiviral agents.

Chlamydia trachomatis

At present, the only commercially available treatment options for *C. trachomatis* infection include systemic antibiotics. Doxycycline is under investigation for both postexposure prophylaxis and pre-exposure prophylaxis in men who have sex with men and transgender women. However, doxycycline is contraindicated in pregnancy and young children, and treatment options are limited, making it a less attractive option for some cisgender women.

As shown in online supplemental table 3, six new APIs active against *C. trachomatis* are in development, with microbicides and herbal supplements making up the majority of compounds under study, for example:

1. Microbicides inhibiting infection by blocking attachment and entry.
2. Herbal and dietary supplements with anti-inflammatory properties.
3. Lactoferrin, known for its antimicrobial and anti-inflammatory properties.
4. Repurposed agents with potential antimicrobial properties.

Neisseria gonorrhoeae

The treatment of gonococcal infections is complicated by the rapidly changing antimicrobial susceptibility patterns of *N. gonorrhoeae*, raising concerns about the eventual development of untreatable gonococcal infections with serious SRH consequences.[20]

According to the Centers for Disease Control and Prevention (CDC), currently there are few antibiotic options left that are simple, well studied, well tolerated and highly effective.

Compounds in development with activity against gonorrhoea are largely in preclinical stages of development and are all orally administered repurposed drugs. As noted in online supplemental table 4, some examples include:

1. Methyldopa and carbamazepine, which is already approved by the U.S. Food and Drug Administration (FDA) as an antihypertensive and anticonvulsant, and acetazolamide, a carbonic anhydrase inhibitor also approved by the FDA as an anticonvulsant.
2. Salicylamide, which is an analgesic and antipyretic drug already approved by the FDA for aches and pains and shows limited effect on the microbiome.
3. Fenamic acid compounds, which are non-steroidal anti-inflammatory drugs that also show limited effect on microbiome.
4. Auranofin, a gold compound that is bactericidal in combination with antibiotics, with activity against both chlamydia and multidrug-resistant gonorrhoea.

Treponema pallidum

Penicillin continues to be the gold standard for the treatment of all stages of syphilis. While resistance has developed to second-line therapies such as azithromycin, penicillin remains active

against *T. pallidum*. As a result, few new approaches have been identified for treatment or prevention of syphilis (online supplemental table 5).

Trichomonas vaginalis

Standard antimicrobial treatments are limited to nitroimidazole derivatives (metronidazole and secnidazole). Drug resistance has been observed but remains poorly understood. Newer studies suggest a symbiotic association with *Trichomonas vaginalis* virus, but its role in affecting the severity of symptoms and effectiveness of antimicrobial treatments remains unclear.[21]

A number of agents are available in the development pipeline (online supplemental table 6).[22] Although many of them are in preclinical stages of development, they could have potential as an MPT component:

1. Antiseptic agents like boric acid or 1% zinc sulfate.
2. Proteasome inhibitors such as the clinically approved cancer drugs ixazomib and carmaphycin-17 show activity against trichomonad infections.
3. Gold compounds such as auranofin, a repurposed agent approved for rheumatoid arthritis.
4. Benznidazole such as ipronidazole and dimetridazole is potentially active against *T. vaginalis*.
5. Disulfiram and its metabolite ditiocarb.
6. Hybrid compounds such as nitaxozanide-N-methylbenzimidazole, 1H-1,2,3-triazole-tethered metronidazole-isatin conjugates and metronidazole-chalcone conjugates.
7. Synthetic compounds such as 2H-indazole derivatives.
8. Nanotechnology-based agents as nano-emulsion (*Micana cordifolia*) and polymeric nanoparticles (chitosan).

Bacterial vaginosis

In women with BV, the vaginal microbiome is in a highly diverse anaerobic state with diminished amounts of endogenous *Lactobacillus* strains. While not an STI, women with BV are at increased risk of STI and HIV acquisition.[23] Available treatments are currently limited to standard antibiotics such as metronidazole and clindamycin, but pathogens associated with BV (such as *Gardnerella vaginalis, Prevotella* and *Atopobium vaginae*) often recolonise the genital tract within months. Recurring disease is common and impacts the quality of life and sexual relationships.[24 25]

As noted in online supplemental table 7, new treatment approaches for the prevention of recurrent BV are currently in various stages of preclinical and clinical development:

1. Antiseptic biofilm disruptors designed to break up BV-associated biofilms of clustered bacteria resistant to standard antibiotics (eg, Dnase, amphoteric tenside, vaginolysin inhibitor, octinedine dihydrochloride, glycerol monolaureate, boric acid).
2. Acidifiers delivered through vaginal gels, fast-dissolving inserts or vaginal rings intended to lower the vaginal pH to levels associated with healthy vaginal microbiota (eg, l-lactic acid, citric acid, galactoarabian polyglucoronic acid crosspolymer, Carbopol 974P).
3. Monoclonal antibodies trapping BV-associated pathogens.
4. Live biotherapeutic products containing lactobacilli strains, often adjuvant to a standard antibiotic treatment for BV, to replenish vaginal *Lactobacillus* strains and optimise vaginal microbiota (eg, *L. rhamnosus* GR-1 and DSM 14870 and Lcr35, *L. reuteri* RC-14, *L. gasseri* DSM 14869 and *L. crispatus* CTV-05 and IP 174178).

DISCUSSION

This review suggests that the paucity of new pharmaceutical approaches for STI prevention remain a significant public health gap.[26] This public health threat is further exacerbated by the lack of new antibiotics in development for treatment of infection. This is despite continuously high rates of STIs globally and their well-researched linkages to increased risk of HIV infection, as well as emerging antibiotic resistance to a number of existing treatments. In recent years, there has been limited research for new prevention strategies of bacterial STIs, such as chlamydia, gonorrhoea and syphilis, while there has been a greater focus on viral STIs such as HIV, HSV-1 and HSV-2. Similarly, limited research has been conducted to identify potential new APIs for syphilis prevention despite high global morbidity and mortality rates resulting from congenital syphilis.[27] Additionally, the recognition of syphilis as a global health problem is reflected in the WHO-led initiative for the elimination of maternal-to-child transmission of HIV and syphilis as a global health priority.

Our review also found that a greater number of compounds targeting viral indications, namely HIV and HSV-1 and HSV-2, have successfully transitioned from preclinical to clinical stages of development. However, the product development pipeline remains limited for compounds that target bacterial STIs and for those that could be used as potential MPT components in combination with contraceptives. This may be a reflection of current funding priorities in STI prevention research.

Our review identified many compounds in development at a wide array of research institutions globally. As this is a narrative review rather than a systematic review of all the compounds in development, there are limitations. Among these is that the focus of the review was on compounds listed in English language publications and other relevant data sources. As such, additional regionally developed compounds and opportunities for collaborative research on MPTs may exist.

Lastly, our findings revealed preliminary results about many compounds that were subsequently no longer pursued for reasons that are unclear. These findings highlight an unmet need to create an open-source database for the purposes of identifying promising compounds and to connect investigators conducting research in the MPT field.

CONCLUSION

Despite the limited attention to STI prevention in the development of new pharmaceutical approaches suitable for MPTs, many research institutions worldwide are working on discoveries of new compounds, exploring new indications for existing drugs, or on innovative drug delivery mechanisms. As a field, we need to improve collaborations between these often isolated efforts by providing better options for the identification of potential synergies.

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