

# Compounds with Potential Activity to Prevent or Treat HIV and Other Sexually Transmitted Infections: A Landscape Review

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Prepared by the  
Initiative for MPTs (IMPT)



## Key Abbreviations

Abbreviation	Definition
ALL	Acute lymphocytic leukemia
AML	Acute myeloid leukemia
Anti-Tat	Trans-Activator of transcription
API	Active pharmaceutical ingredient
ART	Antiretroviral therapy
BCL-2	B-cell lymphoma-2
bNab	Broadly neutralizing antibodies
BSAA	Broad-spectrum antiviral agents
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
DNase	Deoxyribonuclease
FDA	Food and Drug Administration
FDI	Fast dissolving insert
GnRH	Gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HSV-1	Herpes simplex virus - 1
HSV-2	Herpes simplex virus - 2
IL-8	Interleukin-8
IMPT	Initiative for Multipurpose Prevention Technologies
IVR	Intravaginal ring
mAB	Monoclonal antibody
MDR	Multidrug resistant
MPT	Multipurpose prevention technologies
NICHHD	<i>Eunice Kennedy Shriver</i> National Institute of Child Health and Human Development
NRTI	Nucleoside reverse transcriptase inhibitor
NRTTI	Nucleoside reverse transcriptase translocation inhibitor
SAMHD1	Sterile alpha motif and histidine-aspartic acid domain containing protein 1
SMAC	Second mitochondrial-derived activator of caspases
SRH	Sexual and reproductive health
STI	Sexually transmitted infection
PHI	Public Health Institute
TCM	Traditional Chinese medicine

TLR	Toll-like receptor
UCSF	University of California San Francisco

## Introduction

An array of multipurpose prevention technologies (MPTs) are in development for the prevention of two or more sexual and reproductive health (SRH) risks: unintended pregnancies, human immunodeficiency virus (HIV) and/or other sexually transmitted infections (STIs). MPTs currently in development are tracked annually and updated in an online MPT product development pipeline database. [1] As of July 2021, there are 27 MPTs in the pipeline.

The Initiative for MPTs (IMPT)[2], a product-neutral global collaboration that advances the field of MPTs, was founded in 2009 by researchers, policymakers, funders, and advocates working across the spectrum of women's global health to help facilitate strategic thinking for MPT development. With support from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), in 2019 the IMPT facilitated a process to inform strategic actions for advancing non-hormonal MPTs. [3] A priority action area, which emerged from this process, is to identify and stimulate research for anti-infective approaches targeting HIV and other STIs that can be combined with contraceptives as MPTs. To further stimulate MPT innovation and connect researchers working on compounds that have the potential to become active pharmaceutical ingredients (APIs) in future MPTs, this review aims to summarize the anti-infective agents in development with activity against HIV or other STIs.

Inflammation in the female genital tract, regardless of the cause, creates an environment that favors HIV replication and infection. [4] 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 defense against invading microorganisms such as HIV. [5] As such, non-HIV STIs are implicated in increasing the risk of HIV acquisition and transmission.[6] Additionally, STIs can cause severe reproductive health complications in women, including stillbirth, preterm birth, infertility, cervical cancer among others. Many STIs, particularly non-ulcerative infections, are often missed and may remain untreated for long periods of time. [5] Antibiotic resistance to standard antibiotic drug therapies, as emerging for *Neisseria gonorrhoeae* [6], poses yet another challenge.

STIs can be classified in several ways, most commonly 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. [5] Although STIs are frequently asymptomatic, they can cause (a) ulcers in genital, anal, oral, and perianal tissues (e.g., *Treponema pallidum*, *herpes simplex virus* [HSV]), (b) urethral and vaginal discharge (e.g., *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Mycoplasma genitalium*), or (c) genital warts (e.g., HPV). 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 and low rates of treatment all underscore the need for innovative prevention approaches including MPTs. The focus of this assessment is on HIV and other STIs that are associated with increased risk of HIV, namely: *HSV-1* and *HSV-2*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, bacterial vaginosis, *Treponema pallidum*, and *Trichomonas vaginalis*. [4, 8, 9, 10, 11]

## Methodology

This review focuses on MPT product candidates that are in later preclinical development (*in vitro* and *in vivo*) through Phase 3 clinical trials with activity against one or more of the following STIs: HIV, HSV-1, HSV-2, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum*, *Trichomonas vaginalis*, and bacterial vaginosis. The search strategy included a number of avenues. First, an article search in PubMed using the following search criteria: i) articles published between 2011-2021; ii) potential search terms including indication (e.g., 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 and clinicaltrials.gov databases 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; CROI (Conference on Retroviruses and Opportunistic Infections); IAS (International AIDS Society); and ECCMID (European Congress of Clinical Microbiology and Infectious Diseases). For drug candidates in multiple parallel stages of development, the most recent findings or clinical trial was included to minimize redundancy.

While our search is an attempt to be as comprehensive as possible, the focus is on compounds with novel mechanisms of action and therapeutic potential. Excluded from the review are compounds that are currently already included in MPT development as reported in the MPT database [1], vaccine candidates, older studies without further data beyond 2011, gene therapy approaches, and compounds in very early preclinical stages. As the focus of the review was on the prevention of HIV and other STIs, antibiotic compounds studied solely for treatment were not included.

## Findings

Table 1. Compounds with Potential Activity to Prevent or Treat HIV and Other STIs

Human Immunodeficiency Virus						
API (or agent)	Agent Classification	Mechanism of Action	Delivery Type	Lead Research Institution, Country	Source	Additional Information
<b>Pre-clinical Development</b>						
AZD5582	SMAC Mimetic		Intravenous	Chahroudi, Emory University School of Medicine. USA	IAS 2020	
MTI-14	HIV-1 matrix protein inhibitor			Cocklin, Drexel University College of Medicine. USA	8R01AI150491-03	
Cortistatins	Steroid-like alkaloids isolated from marine sponge corticium simplex	Anti-Tat Drug candidate		Valente, Scripts Florida. USA	5R01AI118432-05	
<b>Clinical Development: Phase 1</b>						
TMB-365 (ibalizumab)	mAB	Anti-CD4 mAB	Intravenous	TaiMed Biologics, Taiwan	NCT04027387	
10E8.4/iMab	bNAb	Bispecific antibody	Intravenous or subcutaneous	Ho, Columbia University. USA	NCT03875209	Bispecific antibody
SAR441236	bNab	Tri-specific bNAB		NIAID Sanofi, USA	NCT03705169	
GS-5423 (3BNC117-LS)	bNab			Gilead Sciences. USA	NCT04811040	Multiple investigations in <a href="http://clinicaltrials.gov">clinicaltrials.gov</a>
GS-2872 (10-1074-LS)	bNab			Gilead Sciences. USA	NCT04811040	Multiple investigations in <a href="http://clinicaltrials.gov">clinicaltrials.gov</a>

GS-9620 (Vesatolimod)	TLR7 agonist	Immune activation	Oral weekly	Gilead Sciences. USA	NCT03060447	
SHR2150	TLR7 agonist	Immune activation	Oral	Jiangsu HengRui Medicine Co., Ltd. China	NCT04802811	
<b>Clinical Development: Phase 2</b>						
MK-8507 (islatravir)	Antiretroviral	NRTI	Oral	Merck. USA	CROI 2021	Multiple investigations in <a href="http://clinicaltrials.gov">clinicaltrials.gov</a>
Albuvirtide	Antiretroviral	Fusion Inhibitor	Intravenous	Frontier Biotech. China	NCT04560569	
BMS-986001	Antiretroviral	NRTI	Oral daily	Bristol-Myers Squibb. USA	PMID: 26762988	
Lefitolimod	TLR9 agonist	Immune activation	Subcutaneous injection	Gilead Sciences. USA	NCT03837756	
<b>Clinical Development: Phase 3</b>						
GS-6208 (Lenacapavir)	Antiretroviral	Long-acting HIV capsid inhibitor	Subcutaneous injection	Gilead Sciences. USA	NCT04150068	CAPELLA Trial
Euphorbia Kansui	TCM	Reactivation of HIV-1 replication in latent cells	Oral	Shanghai Public Health Clinical Center. China	NCT04503928	
RepHresh Pro-B™	Probiotic		Oral or vaginal	McMaster University. Canada	NCT03837015	
<b>Other Clinical Development</b>						
VTC01LS and 10-1074	mAB			Capparelli, UCSF. USA	CROI 2021	
UB-421	mAB	CD4 Attachment Inhibitor		UnitedBioPharma. China	NCT04406727	
Dasatinib	Tyrosine kinase inhibitor	Inhibition of SAMHD1 phosphorylation, preventing virus reactivation	Oral	Vigon, Institute of Health Carlos III. Spain	CROI 2021	Adjunct to ART FDA approved for ALL. CML
Imatinib	Tyrosine kinase inhibitor		Intravenous	Vigon, Institute of Health Carlos III. Spain	IAS 2020	Adjunct to ART Repurposed agent FDA approved for various cancers

Nilotinib	Tyrosine kinase inhibitor		Intravenous	Vigon, Institute of Health, Carlos III. Spain	IAS 2020	Adjunct to ART Repurposed agent. FDA approved for CML
Venetoclax	Antineoplastic; BCL-2 inhibitor		Oral	Cummins, Mayo Clinic. USA	CROI 2021	Repurposed agent. FDA approved AML, CLL
Triptorelin acetate	GnRH analogue	Reduce HIV reservoir	Intramuscularly injection monthly	Immune System Regulation AB. Sweden	NCT03536234	Repurposed agent. FDA approved for various indications
GSK-3640254	Antiretroviral	HIV-1 maturation inhibitor	Oral	Merck. USA	CROI 2021	Multiple studies in clinicaltrials.gov
Triptolide Wilfordii	TCM	Anti-inflammatory	Oral	Peking Union Medical College Hospital. China	NCT03403569	

## Herpes Simplex Virus 1 & 2

API (or agent)	Agent Classification	Mechanism of Action	Delivery Type	Lead Research Institution, Country	Source	Additional Information
<b>Pre-clinical Development</b>						
Hu-mAb#33	mAB	mAb targeting envelope glycoprotein D inhibiting viral entry and cell-to-cell transmission		Clementi, Milan. Italy	PMID: 28396205	
Baicalein	TCM	Flavonoid isolated from the root of <i>Scutellaria baicalensis</i> Georgi. Inhibits HSV-1 viral replication.		Lou, Jinan University, Guangzhou. China	PMID: 33354504	Active against HSV-1, available as a supplement
	TCM	Potential source for HSV-1 therapy by direct (blocking viral		Wi, Jinan University. China	PMID: 30347851	Individual extracts: Lychee flower; Moringa oleifera; Ventilago



		attachment/absorption/penetration/replication) or indirect (reducing the susceptibility to HSV-1 or regulating autophagy) antiviral activities				denticulata; Antrodia camphorata mycelia; Nelumbo mucifera; Tripterygium hypoglaucum; Ocimum basilicum; Almond skin; Yin Chen Hao Tang (YCHT); Stephania cepharantha; Houttuynia cordata
AqMol (aqueous extract of Moringa oleifera)	Dietary supplement	Immunomodulator		Lien Co. Ltd. Japan	PMID: 26814058	
ASP2151 (ame namevir)	Antiviral	Herpes helicase-primase inhibitor	Oral	Himaki T, University of Toyama. Japan	PMID: 22155691	Approved for use in Japan in 2017
Obatoclax	BSAA			Anderson, Umeå University. Sweden	PMID: 31635418	Repurposed antiviral agents
Emetine	BSAA			Anderson, Umeå University, Sweden	PMID: 31635418	Repurposed antiviral agents
Niclosamide	BSAA			Anderson, Umeå University. Sweden	PMID: 31635418	Repurposed antiviral agents
Bortezomib (Velcade®, PS-341)	Proteasome inhibitor	Halt nucleocapsid transport to the nucleus		Nicola, Washington State University. USA	PMID: 31088925	Repurposed agent. FDA approved for multiple myeloma and mantle cell lymphoma
Calcium spirulan (Ca-SP)	Antiviral sulfated polysacchari	Ca-SP inhibited HSV-1 attachment and penetration	Topical (cream)	Reich, Hamburg, Germany	PMID: 26341274	

	de of the Spirulina platensis microalgae extract (SPME)					
Shilajit, Humic acid	Ayurvedic medicine	Mechanism unclear, potential virus inactivation and interference of viral attachment		Lemba, University of Torino. Italy	PMID: 25792012	(note, two compounds that are similar)
Thymol			Topical	Sharifi-Rad, Zabol University. Iran	PMID: 28886313	
Ciclopirox	Antifungal agent	Inhibits viral replication	Topical	Bernier & Morrison, St. Louis University School of Medicine. USA	PMID: 29908958	Repurposed drug. FDA approved topical antifungal
Cetylpyridinium chloride (CPC)	Antiseptic	Inhibits viral replication		Millennium Institute on Immunology and Immunotherapy. Chile	PMID: 32423887	Repurposed drug. Used in numerous oral hygiene products to reduce bacteria
G1-S4 or G2-S16	Dendrimers	Branched nanoparticles developed as microbicide	Topical	Muñoz-Fernández. Gregorio Marañón Health Research Institute (IISGM). Spain	PMID: 27274240 PMID: 31040662	Activity against HIV
<b>Clinical Development: Phase 1</b>						
SADBE Squaric Acid Dibutyl Ester			Solution administered topically	Squarex, LLC. USA	NCT02965781	Repurposed drug. Used to treat dermatologic conditions

BTL TML HSV				Beechtree Labs, Inc. USA	NCT01902303	Note, this study was completed in 2013. No results posted.
UB-621	mAB		Subcutaneous injection	United BioPharma, Taipei Veterans General Hospital. Taiwan	NCT02346760; NCT04714060	
<b>Clinical Development: Phase 2</b>						
VDO gel		Viral suppression	Gel	Yung Shin Pharm. Ind. Co., Ltd. China	NCT02207881	
HDIT101	mAB		Intravenous; topical	Heidelberg Immuno Therapeutics. Germany	NCT04165122; NCT04539483	
Pritelivir Ointment	Antiviral agent	Inhibits viral replication by inhibiting the viral helicase-primase enzyme complex	Topical	AiCuris Anti-infective CURES. Germany	NCT02871492; NCT01047540; NCT01658826	
Trifluridine	Antiviral agent	Interferes with viral replication	Topical	NIAID. USAID	NCT01902303	Repurposed drug. FDA approved eyedrop for HSV now being investigated for treatment of HSV at other mucocutaneous openings (nasal, oral, vaginal, anal)
<b>Clinical Development: Phase 3</b>						
Ionic zinc (Zicam®), Homeopathic	Zinc salt	Inhibits viral replication	Topical	Riley, University of New Mexico. USA	NCT00809809	Homeopathic cold remedy

Zinc gluconate						
Pritelivir	Antiviral agent	Inhibits viral replication by inhibiting the viral helicase-primase enzyme complex	Oral	AiCuris Anti-infective CURES. Germany	NCT0307967	

<b>Chlamydia trachomatis</b>						
API (or agent)	Agent Classification	Mechanism of Action	Delivery Type	Lead Research Institution, Country	Source	Additional Information
<b>Pre-clinical Development</b>						
Nafamostat mesylate	Serine protease inhibitor	Inhibits chlamydial intracellular growth	Intravenous	Chen, Second Xiangy Hospital, Central South University, Changshah, Hunan. China	PMID: 32712115	Repurposed drug. Approved in Japan for treatment of pancreatitis
INP0341	Microbicide	Salicylidene acylhydrazide compound	Vaginal gel	Pederson, University of California, Irvine. USA	PMID: 25356686	Activity against HSV and HIV
Baicalin	Anti-inflammatory	inhibits TLR2/4 signaling pathway to block infection		Zhongliang, Wuhan First Hospital, Wuhan. China	PMID: 21612566	Available as herbal supplement
Lactoferrin	Iron binding cationic glycoprotein	Inhibits entry; anti inflammatory		Valenti, University of Rome, La Sapiena. Italy	PMID: 28094551	
Biochanin A	Isoflavone	Growth inhibition	Buccal	Vuorela, University of Helsinki. Finland	PMID: 25514140	
DS-96	Microbicide		Vaginal	Hefty, University of Kansas. USA	PMID: 24663021	
<b>Clinical Development: Phase 2</b>						

EVO100		pH-buffering, acidity-maintaining gel (pH 3.5) containing lactic acid, citric acid, potassium bitartrate	Intravaginal	Evoform Inc. USA	NCT03107377	
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<b><i>Neisseria gonorrhoeae</i></b>						
<b>API (or agent)</b>	<b>Agent Classification</b>	<b>Mechanism of Action</b>	<b>Delivery Type</b>	<b>Lead Research Institution, Country</b>	<b>Source</b>	<b>Additional Information</b>
<b>Pre-clinical Development</b>						
Methyldopa and carbamazepine	Antihypertensive and anticonvulsant		Oral	Jennings, Griffith University, Southport, Queensland, Australia	PMID: 32127453	Repurposed drug. FDA approved as antihypertensive and anticonvulsant. Active against MDR gonorrhea
Salicylamide	Analgesic and antipyretic drug	Synergistic antibacterial activity with known agents	Oral	Saleem, Purdue University. USA	PMID: 31570391	Repurposed drug. FDA approved for minor aches and pains. Limited effect on microbiome
Acetazolamide	Carbonic Anhydrase Inhibitor		Oral	Flaherty, Purdue University. USA	PMID: 33765392	Repurposed drug. FDA approved as an anticonvulsant
Fenamic acid compounds (tolfenamic acid, flufenamic acid, and meclofenamic acid)	Nonsteroidal antiinflammatory drugs		Oral	Saleem, Purdue University. USA	PMID: 32393483	Repurposed drugs. Limited effect on microbiome

Auranofin	Gold compound	Bacteriocidal in combination with antibiotics. Reduction of IL-8	Oral	Saleem, Purdue University. USA	PMID: 32221472	Repurposed drug. FDA approved for rheumatoid arthritis. Active against Chlamydia and MDR gonorrhea. Limited effect on microbiome
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<b><i>Trichomonas vaginalis</i></b>						
API (or agent)	Agent Classification	Mechanism of Action	Delivery Type	Lead Research Institution, Country	Source	Additional Information
<b>Pre-clinical Development</b>						
Ammonium salts of carbamodithioic acid	Microbicide	Inhibition of free thiols	Topical	Gupta, Central Drug Research Institute. India	PMID: 26706422	
Anti-CD52g mABs	mABs	Targets male-reproductive tract-specific antigen, CD52g that is present on both sperm and STI pathogens in semen		Anderson, Boston University. USA	5R01HD095630-04	
<b>Clinical Development: Phase 2</b>						
Auranofin	Gold compound	Blocks the activity of microbial thioredoxin reductases (TrxR), critical enzymes involved in	Topical	Reed, UC San Diego. USA  Eckmann, Lars, UC San Diego. USA	5U01AI110435-03;  5R21AI119459-02	Repurposed agent. FDA approved to treat rheumatoid arthritis

		maintaining protein function and combating oxidative damage				
<b>Other Clinical Development</b>						
Lactobacilli	Part of host microbiome		Intravaginal	Mastromarino, Paola. Italy	PMID: 29545798	Review article. Also active against other STIs
Lactoferrin	Iron-binding cationic glycoprotein	Antibacterial, antifungal, antiviral, and antiparasitic activity	Intravaginal	Mastromarino, Paola. Italy	PMID: 29545798	Review article. Also active against other STIs
Boric Acid	Acidifying agent		Vaginal capsule	Ross, University Hospitals Birmingham NHS Foundation Trust. UK	PMID: 29223972	Review of boric acid for <i>Trichomonas vaginalis</i>
1% Zinc sulfate	Antimicrobial		Vaginal douche	Kim, Inje University, Busan. South Korea.	PMID:26522122	Case series used for metronidazole-resistant trichomonas with and without tinidazole.
Mentha crispa: Giamebil®	Antiparasitic used in traditional medicine		Oral tablets	Moraes, Federal University of Ceará. Brazil	PMID: 22350328	
Zataria multiflora	Group of plants containing saponins, caffeic acid resin, tannin, resonates, and	Antimicrobial antifungal, antiseptic, and antiworm properties re antimicrobial	Topical cream	Jahed, Dezful University of Medical Science. Iran	PMID: 26266260	

	2.6% volatile oil. Active ingredients of volatile oil include thymol and carvacrol	properties. Carvacrol is antiseptic and antifungal, and thymol is antiseptic and antiworm				
Dequalinium chloride (Vaginal DQC, Fluomizin)	Antiseptic agent	Quaternary ammonium compound	Vaginal tablets	Mending W. German Center for Infections in Gynecology and Obstetrics, Wuppertal. Germany	PMID: 26506926	
Pluronic F127	Thermosensitive hydrogel	Block parasitic mobility to reduce acquisition of infection.	Topical vaginal gel	Bouchemal, Université Paris-Saclay. France	PMID: 31713413	

<b>Bacterial vaginosis</b>						
<b>API (or Agent)</b>	<b>Agent Classification</b>	<b>Mechanism of Action</b>	<b>Delivery Type</b>	<b>Lead Research Institution, Country</b>	<b>Source</b>	<b>Additional Information</b>
<b>Pre-clinical Development</b>						
Pathogen-trapping antibodies	mAB	Pathogen-trapping monoclonal antibodies (mABs) in vaginal mucus (pathogen- and mucin-binding)	IVR with embedded sustained release polymeric vaginal capsules	Moench, Mucommune, LLC. USA	1R41AI122472	Technology could also specifically target other pathogens



Amphora + QGRFT	L-lactic Acid, citric acid, and potassium bitartrate  Griffithsin (lectin)	Lowering pH, antimicrobial activity	Fast dissolving insert (FDI)	Angsantikul, Population Council. USA	5R01AI150324	BV/contraceptive/ HSV-2 (Amphora)  Anti-HIV/ HSV-2 (GRFT, Amphora)
LA- Releasing IVR	Lactic Acid, 30-day IVR	Lowering vaginal pH	IVR	Cone, Mucommune LLC. USA	1R43AI157652	Formulation and release work
Synthetic Antimicrobial Peptides (AMPs)	Sugar-based non-cytotoxic cationic amphiphiles	Targeting gram-variable <i>Gardnerella vaginalis</i> and its biofilm		Sinko, Rutgers University. USA	PMID: 24566190	
DNase	DNase	Biofilm disruptor targeting <i>Gardnerella vaginalis</i> and B <i>Streptococcus</i> biofilms	Vaginal Gel	Ratner, New York University. USA	7R33AI098654	
Cocoampho propionate	Amphoteric tenside	Surfactant, Biofilm disruptor	Vaginal pessary	Wagner-Döbler, Helmholtz Centre for Infection Research. Germany	PMID: 28903767	
Retrocycline (RC-101)	Antimicrobial peptide, Vaginolysin inhibitor	Biofilm disruptor, targeting <i>Gardnerella vaginalis</i>		Ratner. New York University. USA	PMID: 22855857	

Subtilisin	Antimicrobial peptide	Biofilm disruptor, targeting <i>Gardnerella vaginalis</i>		Chikindas. The State University of New Jersey. USA  Rajan. The State University of New Jersey. USA	PMID: 23024575 PMID: 27111438 PMID: 24566190	
Cystine-uptake inhibitors	Cystine-uptake inhibitors	Block growth of <i>Lactobacillus iners</i>		Bloom, Harvard University. USA	IDweek2020: 1207 poster abstract	combined with standard antibiotic treatment
<b>Clinical Development: Phase 1</b>						
EcoVag®	<i>L. gasseri</i> , <i>L. rhamnosus</i>	Probiotic, optimizing vaginal microbiome	Vaginal capsules	Skaraborg Hospital, Sweden	NCT02295579	
<i>Lactobacilli rhamnosus GR-1</i> <i>Lactobacilli reuteri RC-14</i>	<i>Lactobacilli rhamnosus GR-1</i> <i>Lactobacilli reuteri RC-14</i>	Probiotic, optimizing vaginal microbiome	Vaginal capsules	Kimberly-Clark Corporation. USA	NCT02139839	
RepHresh Pro-B™ + Estring® Vaginal Ring	<i>Lactobacilli rhamnosus GR-1</i> <i>Lactobacilli reuteri RC-14</i> , 17 beta-estradiol	Probiotic + hormonal contraceptive  optimizing vaginal microbiome	Vaginal/oral capsules + IVR	McMaster University, Canada	NCT03837015	
Multi-Gyn® ActiGel	Galactoarabinan Polyglucuronic Acid Crosspolymer	Lowering vaginal pH	Acidifying vaginal gel	BioClin BV. Netherlands	NCT04807842	

Gedea Pessary pHyph	GDA 001 food additive	Lowering vaginal pH	Vaginal tablet	Gedea Biotech AB, Sweden	NCT04640922	
RepHresh™	Carbopol 974P	Lowering vaginal pH	Acidifying vaginal gel	Haas, Indiana University. USA	NCT00545181	
Octenidine	Octenidine Dihydrochloride	Biofilm disruptor		Swidsinski, Humboldt University Berlin, Germany	PMID: 25245669	
D-Lactic Acid IVR	L-lactic Acid	Lowering vaginal pH	IVR	Verstraelen, Ghent University, Belgium	NCT02314429	
<b>Clinical Development: Phase 2</b>						
LACTIN-V	<i>L. crispatus</i> CTV-05	Probiotic, optimizing vaginal microbiome	Powder in vaginal applicator	Cohen, UC San Francisco Osel Inc. USA	NCT02766023	
<i>L. rhamnosus</i> DSM 14870 <i>L. gasseri</i> DSM 14869	<i>L. rhamnosus</i> DSM 14870 <i>L. gasseri</i> DSM 14869	Probiotic, optimizing vaginal microbiome	Vaginal capsule	Marcotte. Karolinska Institutet at Karolinska University Hospital Huddinge. Sweden.	Pan African Clinical Trial Registry PACTR2018040033 27269	
Monolaurin	Glycol-based glycerol monolaurate (GML)	Surfactant with antimicrobial activity	Vaginal Gel	Winokur, University of Iowa	NCT02709005	
TOL-463	Boric Acid, non-azole vaginal anti-infective drug	Biofilm disruptor	Vaginal Insert	Marrazzo, University of Alabama	NCT03930745	

Trimo-San	Oxyquinoline sulfate		Vaginal pessary	Meriwether, University of New Mexico. USA	NCT01471457	Side effects irritation, from the 1970s, spermicide Vaginal wash
<b>Clinical Development: Phase 3</b>						
Gynophilus®	<i>L. rhamnosus</i> Lcr35®	Probiotic, optimizing vaginal microbiome	Vaginal capsules	Laboratories Lyocentre, France	NCT01160796	
EVAFLORE® PHYSIOFLOR®	<i>L. crispatus</i> IP 174178	Probiotic, optimizing vaginal microbiome	Vaginal capsule	Institut Alfred-Fournier, France  IPRAD PHARMA Bohbot 2018	PMID: 29196153	
Fluomizin	Dequalinium Chloride	Quaternary ammonium compound, antiseptic	Vaginal tablet	Weissenbacher, Medinova AG. Switzerland.	NCT01125410	

### Syphilis (*Treponema pallidum*)

API (or Agent)	Agent Classification	Mechanism of Action	Delivery Type	Lead Research Institution, Country	Source	Additional Information
<b>Pre-clinical Development</b>						
Gallium maltolate (GaM)	Antibacterial agent	Disrupts DNA synthesis	Topical and oral	Arthur M. Baca; IT-ENDs. USA	PMID: 30601824	

## Discussion

This review aims to summarize compounds in development with activity against HIV and other STIs that have the potential to become active pharmaceutical ingredients (APIs) in future MPTs. Further, this also aims to connect researchers and product developers working across the areas of HIV and STI prevention and contraception to explore possible collaborations and to further stimulate MPT innovation.

Despite high rates of STIs globally and their linkages to increased risk of HIV infection, as well as antibiotic resistance to a number of existing treatments, pharmaceutical approaches for STI prevention remain a significant gap. Our findings suggest that in recent years there has been little research for prevention of bacterial STIs, with a stronger focus on viral STIs such as HIV, HSV-1 and HSV-2. Further, little research has been done to identify potential new APIs for syphilis prevention despite increasing rates of congenital syphilis and recognition of syphilis as a global health problem, as reflected in the WHO-led initiative for the elimination of maternal-to-child transmission (EMTCT) of HIV and syphilis as a global health priority. As the focus of our review is on prevention of HIV and other STIs, for this search we removed standard antibiotics often related to STI treatment in order to narrow the scope. Our review also clearly suggests that some indications, namely HIV and HSV-1 & 2, include more compounds that have successfully moved into clinical stages of development, likely also reflecting funding priorities for STI prevention research.

In summary, our review identified many compounds in development for HIV, HSV-1& HSV-2 at a wide array of research institutions globally. However, the product development pipeline remains limited for compounds suitable for prevention of other STIs as potential MPT components in combination with contraceptives. A detailed vetting process of prioritizing compounds for further funding and development by experts and stakeholders is not within the current scope of this review, but materials developed by the IMPT for MPT development can serve as a tool for such a process. [3, 12, 13, 14]

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