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

Prepared by the
Initiative for MPTs (IMPT)

July 2021
Updated September 2022

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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
NICHD	*Eunice Kennedy Shriver* 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. As of July 2022, there are 25 MPTs in the pipeline. [1]

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, initially implemented in 2021, 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). Compounds listed in Tables 1-7 were updated to reflect development status through August 2022. 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 already included in MPT development, as reported in the MPT database [1], as well as 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

Tables 1-7 list the compounds identified through this review. They are organized by STI, in the following order: HIV, HSV-1 & 2, *Chlamydia trachomatis, Neisseria gonorrhoeae,* syphilis, *Trichomonas vaginalis*, and bacterial vaginosis. The following information is provided for each compound, when available: compound classification, mechanism of action, route of administration/formulation, lead research institution and country, source, and additional pertinent information. In some cases, the mechanism of action is not listed if it was not documented in the reference source. Similarly, when the route of administration is not listed it is because it was not documented in the reference source or it is not yet determined, as can be the case for compounds in early preclinical stages of development.

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

Human Immunodeficiency Virus						
Compound	**Classification**	**Mechanism of Action**	**Route of Administration/ Formulation**	**Lead Research Institution, Country**	**Source**	**Additional Information**
Preclinical Development						
AZD5582	SMAC Mimetic		Intravenous injection	Chahroudi, Emory University School of Medicine. USA	IAS 2020	
Cortistatins	Steroid-like alkaloids isolated from marine sponge corticium simplex	Anti-Tat Drug candidate		Valente, Scripts Florida. USA	5R01AI118432-05	
MTI-14	HIV-1 matrix protein inhibitor			Cocklin, Drexel University College of Medicine. USA	8R01AI150491-03	
Clinical Development: Phase 1						
10E8.4/iMab	Broadly neutralizing antibodies (bNAb)		Intravenous or subcutaneous injection	Ho, Columbia University. USA	NCT03875209	Bispecific antibody

GS-2872 (10-1074-LS)	bNab			Gilead Sciences. USA	NCT04811040	Multiple investigations in clinicaltrials.gov
GS-9620 (Vesatolimod)	TLR7 agonist	Immunomudulator	Oral	Gilead Sciences. USA	NCT03060447	
SAR441236	bNab			NIAID Sanofi, USA	NCT03705169	
SHR2150	TLR7 agonist	Immunomodulator	Oral	Jiangsu HengRui Medicine Co., Ltd. China	NCT04802811	
Clinical Development: Phase 2						
Albuvirtide	Antiretroviral	Fusion Inhibitor	Intravenous injection	Frontier Biotech. China	NCT03719664	Approved for use in China
GSK-3640254	Antiretroviral	HIV-1 maturation inhibitor	Oral	Merck. USA	Multiple studies in clinicaltrials.gov PMID: 34996113	
Lefitolimod (MGN1703)	TLR9 agonist	Immunomodulator	Subcutaneous injection	Gilead Sciences. USA	NCT03837756	With 3BNC117 and 10-1074
MK-8507 (islatravir)	Antiretroviral	NRTTI	Oral	Merck. USA	Multiple investigations in clinicaltrials.gov	All clinical studies on hold as of December 2021
Teropavimab (GS-5423, 3BNC117-LS)	bNab			Gilead Sciences. USA	Multiple investigations in clinicaltrials.gov	Long-acting form of 3BNC117
Clinical Development: Phase 3						
Euphorbia Kansui	Traditional Chinese medicine (TCM)	Reactivation of HIV-1 replication in latent cells	Oral	Shanghai Public Health Clinical Center. China	NCT04503928	
GS-6208 (Lenacapavir)	Antiretroviral	Long-acting HIV capsid inhibitor	Subcutaneous injection	Gilead Sciences. USA	PMID: 35544387	CAPELLA Trial Granted European Commission Approval August, 2022
RepHresh Pro-B™	Probiotic		Oral or vaginal	McMaster University. Canada	NCT03837015	

Triptolide Wilfordii	TCM	Anti-inflammatory	Oral	Peking Union Medical College Hospital. China	NCT03403569	
Other Clinical Development						
10-1074	mAb			Capparelli, UCSF. USA	CROI 2021	
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 injection	Vigon, Institute of Health Carlos III. Spain	IAS 2020	Adjunct to ART Repurposed agent FDA approved for various cancers
Nilotinib	Tyrosine kinase inhibitor		Intravenous injection	Vigon, Institute of Health, Carlos III. Spain	IAS 2020	Adjunct to ART Repurposed agent. FDA approved for CML
Triptorelin acetate	GnRH analogue	Reduce HIV reservoir	Intramuscular injection	Immune System Regulation AB. Sweden	NCT03536234	Repurposed agent. FDA approved for various indications
UB-421	mAb	CD4 Attachment Inhibitor		UnitedBioPharma. China	NCT04406727	
Venetoclax	Antineoplastic; BCL-2 inhibitor		Oral	Cummins, Mayo Clinic. USA	CROI 2021	Repurposed agent. FDA approved AML, CLL
VTC01LS	Monoclonal antibody (mAb)			Capparelli, UCSF. USA	CROI 2021	

Table 2. Compounds with Potential Activity to Prevent or Treat Herpes Simplex Virus 1 & 2

Herpes Simplex Virus 1 & 2						
Compound	**Classification**	**Mechanism of Action**	**Route of Administration /Formulation**	**Lead Research Institution, Country**	**Source**	**Additional Information**
Preclinical Development						
AqMol	Dietary supplement	Immunomodulator		Lien Co. Ltd. Japan	PMID: 26814058	A queous extract of Moringa oleifera
ASP2151(amenamevir)	Antiviral	Herpes helicase-primase inhibitor	Oral	Himaki T, University of Toyama. Japan	PMID: 22155691	Approved for use in Japan
Baicalein	TCM	Flavonoid isolated from the root of Scutellaria baicalensis Georgi. Inhibits HSV-1 viral replication.		Lou, Jinan University, Guangzhou. China	PMID: 33354504	Active against HSV-1, available as a supplement
Bortezomib (Velcade®, PS-341)	Proteasome inhibitor	Halt nucleocapsid transport to the nucleus	Intravenous or subcutaneous injection	Nicola, Washington State University. USA	PMID: 31088925	Repurposed agent. FDA approved for multiple myeloma and mantle cell lymphoma
Calcium spirulan (Ca-SP)	Antiviral sulfated polysaccharide of the Spirulina platensis microalgae extract (SPME)	Ca-SP inhibited HSV-1 attachment and penetration	Topical cream	Reich, Hamburg, Germany	PMID: 26341274	
Cetylpyridinium chloride (CPC)	Antiseptic	Inhibits viral replication		Millennium Institute on Immunology and	PMID: 32423887	Repurposed drug. Used in numerous oral hygiene

				Immunotherapy. Chile		products to reduce bacteria
Ciclopirox	Antifungal agent	Inhibits viral replication	Topical	Bernier & Morrison, St. Louis University School of Medicine. USA	PMID: 29908958	Repurposed drug. FDA approved topical antifungal
Emetine	BSAA			Anderson, Umeå University, Sweden	PMID: 31635418	Repurposed antiviral agents
G1-S4 or G2-S16	Dendrimers	Microbicide	Topical	Muñoz-Fernández. Gregorio Marañón Health Research Institute (liSGM). Spain	PMID: 27274240 PMID: 31040662	Also active against HIV
Hu-mAb#33	mAb	mAb targeting envelope glycoprotein D inhibiting viral entry and cell-to-cell transmission		Clementi, Milan. Italy	PMID: 28396205	
Niclosamide	BSAA			Anderson, Umeå University. Sweden	PMID: 31635418	Repurposed antiviral agents
Obatoclax	BSAA			Anderson, Umeå University. Sweden	PMID: 31635418	Repurposed antiviral agents
Shilajit, Humic acid	Ayurvedic medicine	Mechanism unclear, potential virus inactivation and interference of viral attachment		Lemba, University of Torino. Italy	PMID: 25792012	
Thymol	Monoterpene		Topical	Sharifi-Rad, Zabol University. Iran	PMID: 28886313	Extract of Thymus vulgaris
	TCM	Potential source for HSV-1 therapy		Wi, Jinan University. China	PMID: 30347851	Individual extracts: Lychee flower;

		by direct (blocking viral attachment/absorption/ penetration/replication) or indirect (reducing the susceptibility to HSV-1 or regulating autophagy) antiviral activities				Moringa oleifera; Ventilago denticulata; Antrodia camphorata mycelia; Nelumbo mucifera; Tripterygium hypoglaucum; Ocimum basilicum; Almond skin; Yin Chen Hao Tang (YCHT); Stephania cepharantha; Houttuynia cordata
Clinical Development: Phase 1						
BTL TML HSV				Beechtree Labs, Inc. USA	PMID: 35142535	
SADBE Squaric Acid Dibutyl Ester			Topical solution	Squarex, LLC. USA	PMID: 32289388	Repurposed drug. Used to treat dermatologic conditions
UB-621	mAb	Long-acting mAb binds to HSV envelope glycoprotein B	Subcutaneous injection	United BioPharma, Taipei Veterans General Hospital. Taiwan	NCT04714060	
Clinical Development: Phase 2						
HDIT101	mAb		Intravenous; topical	Heidelberg Immuno Therapeutics. Germany	NCT04539483	
VDO gel		Viral suppression	Topical gel	Yung Shin Pharm. Ind. Co., Ltd. Taiwan	NCT02207881	
Clinical Development: Phase 3						
Ionic zinc (Zicam®),	Zinc salt	Inhibits viral replication	Topical	Riley, University of New Mexico. USA	NCT00809809	Homeopathic cold remedy

Homeopathic Zinc gluconate						
Pritelivir	Antiviral agent	Inhibits viral replication by inhibiting the viral helicase-primase enzyme complex	Oral	AiCuris Anti-infective CURES. Germany	NCT03073967	

Table 3. Compounds with Potential Activity to Prevent or Treat *Chlamydia trachomatis*

Chlamydia trachomatis						
Compound	**Classification**	**Mechanism of Action**	**Route of Administration/ Formulation**	**Lead Research Institution, Country**	**Source**	**Additional Information**
Preclinical Development						
Baicalin	Anti-inflammatory	inhibits TLR2/4 signaling pathway to block infection		Zhongliang, Wuhan First Hospital, Wuhan. China	PMID: 21612566	Available as herbal supplement
Biochanin A	Isoflavone phytoestrogen	Growth inhibition	Buccal	Vuorela, University of Helsinki. Finland	PMID: 25514140	Found in red clover, cabbage, alfalfa
DS-96	Microbicide	Inhibits attachment and entry by binding lipopolysacchide	Vaginal	Hefty, University of Kansas. USA	PMID: 24663021	
INP0341	Microbicide	Salicylidene acylhydrazide compound; mechanism of action unclear	Vaginal gel	Pederson, University of California, Irvine. USA	PMID: 25356686	Also demonstrates activity against HSV and HIV

Lactoferrin	Iron binding cationic glycoprotein	Inhibits entry; anti-inflammatory		Valenti, University of Rome, La Sapiena. Italy	PMID: 28094551	
Nafamostat mesylate	Serine protease inhibitor	Inhibits chlamydial intracellular growth	Intravenous	Chen, Second Xiangy Hospital, Central South University, Changsah, Hunan. China	PMID: 32712115	Repurposed drug. Approved in Japan for treatment of pancreatitis

Table 4. Compounds with Potential Activity to Prevent or Treat *Neisseria gonorrhoeae*

Neisseria gonorrhoeae						
Compound	**Classification**	**Mechanism of Action**	**Route of Administration/ Formulation**	**Lead Research Institution, Country**	**Source**	**Additional Information**
Preclinical Development						
Acetazolamide	Carbonic Anhydrase Inhibitor		Oral	Flaherty, Purdue University. USA	PMID: 33765392	Repurposed drug. FDA approved as an anticonvulsant
Auranofin	Gold compound	Bacteri cidal 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
Fenamic acid compounds (tolfenamic acid, flufenamic acid, and	Nonsteroidal anti-inflammatory drugs		Oral	Saleem, Purdue University. USA	PMID: 32393483	Repurposed drugs. Limited effect on microbiome

meclofenamic acid)						
Methyldopa and carbama-zepine	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

Table 5. Compounds with Potential Activity to Prevent or Treat Syphilis

Syphilis (*Treponema pallidum*)						
Compound	**Classification**	**Mechanism of Action**	**Route of Administration/ Formulation**	**Lead Research Institution, Country**	**Source**	**Additional Information**
Preclinical Development						
Gallium maltolate (GaM)	Antibacterial agent	Disrupts DNA synthesis	Topical and oral	Arthur M. Baca; IT-ENDs. USA	PMID: 30601824	

Table 6. Compounds with Potential Activity to Prevent or Treat *Trichomonas vaginalis*

Trichomonas vaginalis						
Compound	**Classification**	**Mechanism of Action**	**Route of Administration/ Formulation**	**Lead Research Institution, Country**	**Source**	**Additional Information**
Pre-clinical Development						

1H-1,2,3-triazole-tethered metronidazole-isatin conjugates	Hybrid compounds	Antiprotozoal properties against *Trichomonas vaginalis*		Kumar, 2018	PMID: 30425970	
2H-indazole derivatives	Synthetic compounds such as	Antiprotozoal properties against against *Trichomonas vaginalis*		Perez-Villanueva, 2017. Rodriguez-Villar, 2021.	PMID: 29088121 PMID: 33917871	
Ammonium salts of carbamodithioic acid	Microbicide	Inhibition of free thiols and cysteine proteases of T. vaginalis	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	
Chitosan	polymeric nanoparticles	Antiprotozoal properties against against *Trichomonas vaginalis*		Pradines, 2015	PMID: 25319099	
Diazocyclobutenes		Activity against *Trichomonas vaginalis*		Clemson University	1P20GM146584	

Disulfiram, ditiocarb		activity against *Trichomonas vaginalis*		Bouma, 1998	PMID: 10052908	
Ipronidazole, Dimetridazole	Benznidazole	activity against *Trichomonas vaginalis*		Meneses-Marcel, 2018	PMID: 29589477	
Ixazomib, Carmaphycin-17 (CP-17)	Proteasome inhibitors	activity against *Trichomonas vaginalis*		O'Donoghue 2019. University of California, San Diego	PMID: 31451503 5R01AI158612	Clinically approved cancer drugs
Metronidazole-chalcone conjugates	Hybrid compounds	Antiprotozoal properties against *Trichomonas vaginalis*		Anthwal, 2014	PMID: 24727243	
Micana cordifolia	nano-emulsion	Antiprotozoal properties against against *Trichomonas vaginalis*		Vazini, 2017	PMID: 29114138	
Nitaxozanide-N-methylbenzimidazole	Hybrid compounds	Antiprotozoal properties against *Trichomonas vaginalis*		Soria-Arteche, 2013	PMID: 24183540	
Clinical Development: Phase 2						
Auranofin	Gold compound	Blocks the activity of microbial thioredoxin reductases (TrxR), critical enzymes	Topical	Reed, UC San Diego. USA Eckmann, Lars, UC San Diego. USA	5U01AI110435-03; 5R21AI119459-02	Repurposed agent. FDA approved to treat rheumatoid arthritis

		involved in maintaining protein function and combating oxidative damage				
Other Clinical Development						
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.
Boric Acid	Acidifying antimicrobial agent		Vaginal capsule	Ross, University Hospitals Birmingham NHS Foundation Trust. UK	PMID: 29223972	Review of boric acid for *Trichomonas vaginalis*
Dequalinium chloride (Vaginal DQC, Fluomizin)	Antiseptic agent	Disturbance of cell permeability; loss of enzymatic activity	Vaginal tablets	Mendling W. German Center for Infections in Gynecology and Obstetrics, Wuppertal. Germany	PMID: 26506926	
Lactoferrin	Iron-binding cationic glycoprotein	Antibacterial, antifungal, antiviral, and antiparasitic activity	Vaginal	Mastromarino, Paola. Italy	PMID: 29545798	Review article. Also active against other STIs
Mentha crispa: Giamebil®	Antiparasitic used in traditional medicine		Oral tablets	Moraes, Federal University of Ceará. Brazil	PMID: 22350328	

Pluronic F127	Thermosensitive hydrogel	Block parasitic mobility to reduce acquisition of infection.	Topical vaginal gel	Bouchemal, Université Paris-Saclay. France	PMID: 31713413	
Zataria multiflora	Group of plants containing saponins, caffeic acid, resin, tannin, resonates, and 2.6% volatile oil. Active ingredients of volatile oil include thymol and carvacrol	Antimicrobial, antifungal, antiseptic, and antiworm properties. Carvacrol is antiseptic and antifungal, and thymol is antiseptic and antiworm	Topical cream	Jahed, Dezful University of Medical Science. Iran	PMID: 26266260	

Table 7. Compounds with Potential Activity to Prevent or Treat Bacterial Vaginosis

Bacterial vaginosis						
Compound	**Classification**	**Mechanism of Action**	**Route of administration/ Formulation**	**Lead Research Institution, Country**	**Source**	**Additional Information**
Pre-clinical Development						
Cocoampho propionate	Amphoteric tenside	Surfactant, Biofilm disruptor	Vaginal pessary	Wagner-Döbler, Helmholtz Centre for Infection Research. Germany	PMID: 28903767	

Cystine-uptake inhibitors	Cystine-uptake inhibitors	Block growth of *Lactobacillus iners*		Bloom, Harvard University. USA	IDweek2020: 1207 poster abstract	combined with standard antibiotic treatment
DNase	DNase	Biofilm disruptor targeting *Gardnerella vaginalis* and B *Streptococcus* biofilms	Vaginal gel	Ratner, New York University. USA	7R33AI098654	
HBCA2	Casein-derived milk-borne antimicrobial peptide	Inhibitor of *Gardnerella vaginalis*		Matrubials, Inc. USA	1R43AI165105	
Lactic Acid		Acidifying agent	Vaginal / Intravaginal ring	Cone, Mucommune LLC. USA	1R43AI157652	Formulation and release work
Pathogen-trapping antibodies (MM008)	mAb	Pathogen-trapping monoclonal antibodies (mABs) in vaginal mucus (pathogen- and mucin-binding)	Vaginal / Intravaginal ring with embedded sustained release polymeric vaginal capsules	Moench, Mucommune, LLC. USA	1R41AI122472 1R43HD105277	Technology could also specifically target other pathogens
Retrocycline (RC-101)	Antimicrobial peptide, Vaginolysin inhibitor	Biofilm disruptor, targeting *Gardnerella vaginalis*		Ratner. New York University. USA	PMID: 22855857	
Subtilosin	Antimicrobial peptide	Biofilm disruptor, targeting *Gardnerella vaginalis*		Chikindas. The State University of New Jersey. USA	PMID: 23024575 PMID: 27111438 PMID: 24566190	

				Rajan. The State University of New Jersey. USA		
Synthetic Antimicrobial Peptides (AMPs)	Sugar-based non-cytotoxic cationic amphiphiles	Targeting gram-variable *Gardnerella vaginalis* and its biofilm		Sinko, Rutgers University. USA	PMID: 24566190	
Clinical Development: Phase 1						
Carbopol 974P		Lowering vaginal pH	Acidifying vaginal gel RepHresh™	Haas, Indiana University. USA	NCT00545181	
D-Lactic Acid	L-lactic Acid	Lowering vaginal pH	Vaginal / intravaginal ring	Verstraelen, Ghent University. Belgium	NCT02314429	
Galactoarabinan Polyglucoronic Acid Crosspolymer		Lowering vaginal pH	Acidifying vaginal gel Multi-Gyn® ActiGel	BioClin BV. Netherlands	NCT04807842	
GDA 001 food additive		Lowering vaginal pH	Vaginal tablet Gedea Pessary pHyph	Gedea Biotech AB. Sweden	NCT04640922	
L. gasseri, L. rhamnosus	Probiotic	Optimizing vaginal microbiome	Vaginal capsules EcoVag®	Skaraborg Hospital. Sweden	NCT02295579	
Lactobacilli rhamnosus GR-1 Lactobacilli reuteri RC-14	Probiotic	Optimizing vaginal microbiome	Vaginal capsules	Kimberly-Clark Corporation. USA	NCT02139839	
Lactobacilli rhamnosus GR-1 Lactobacilli reuteri RC-14, 17 beta-estradiol	Probiotic + hormonal contraceptive	Optimizing vaginal microbiome	Vaginal/oral capsules + vaginal ring RepHresh Pro-B™ +	McMaster University. Canada	NCT03837015	

			Estring® Vaginal Ring			
Lactoferrin	Prebiotic protein		Vaginal pessary	St George's, University of London. UK	NCT05434104	
Octenidine	Octenidine Dihydrochlor-ide	Biofilm disruptor		Swidsinski, Humboldt University, Berlin. Germany	PMID: 25245669	
Clinical Development: Phase 2						
D005	n/a	n/a	Vaginal mousse	Pharmiva AB. Glasgow, Scotland	NCT04489290	
L. crispatus CTV-05	Probiotic	optimizing vaginal microbiome	Powder in vaginal applicator LACTIN-V	Cohen, UC San Francisco Osel Inc. USA	NCT02766023	
L. rhamnosus DSM 14870 *L. gasseri* DSM 14869	Probiotic	optimizing vaginal microbiome	Vaginal capsule	Marcotte. Karolinska Institutet at Karolinska University Hospital Huddinge. Sweden.	Pan African Clinical Trial Registry PACTR201804003327269	
Monolaurin	Glycol-based glycerol monolaurate (GML)	Surfactant with antimicrobial activity	Vaginal gel	Winokur, University of Iowa. USA	NCT02709005	
TOL-463	Boric Acid, non-azole vaginal anti-infective drug	Biofilm disruptor	Vaginal insert	Marrazzo, University of Alabama. USA	NCT03930745	

Trimo-San	Oxyquinoline sulfate		Vaginal pessary	Meriwether, University of New Mexico. USA	NCT01471457	Side effects irritation, from the 1970s, spermicide Vaginal wash
Umeta-mimi	Probiotic	Optimizing vaginal microbiome	Oral probiotic	Peking University Shenzhen Hospital. China	NCT04771728	
Clinical Development: Phase 3						
Fluomizin	Dequalinium Chloride	Quaternary ammonium compound, antiseptic	Vaginal tablet	Weissenbacher, Medinova AG. Switzerland.	NCT01125410	
L. crispatus IP 174178	Probiotic	Optimizing vaginal microbiome	Vaginal capsule EVAFLORE® PHYSIOFLOR®	Institut Alfred-Fournier. France IPRAD PHARMA Bohbot 2018	PMID: 29196153	
L. rhamnosus Lcr35	Probiotic	Poptimizing vaginal microbiome	Vaginal capsule Gynophilus®	Laboratories Lyocentre. France	NCT01160796	

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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Acknowledgments

This report was prepared by Bethany Young Holt and Susanna Moore (IMPT), Katherine Yang (UCSF School of Pharmacy), and Anke Hemmerling (UCSF Bixby Center for Global Reproductive Health). We give special thanks to Sheila Mohebbi (UCSF School of Pharmacy) and Hannah Rubens (IMPT) for their contributions to this review.

We would like to express our gratitude to those who offered their time and valuable insights in the framing of and finalization of this assessment: Travis Kent, James Kiarie, Daniel Johnston, Logan Nickels, Ina Park, Joseph Romano, and Teodora Wi.

The Initiative for Multipurpose Prevention Technologies (IMPT) is a project of CAMI Health, a social impact organization dedicated to improving the health of women and their families worldwide. CAMI Health is housed at the Public Health Institute (PHI). This work was made possible by the generous support of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) through an interagency agreement with the United States Agency for International Development (USAID), cooperative agreement number AID-OAA-A-16-00045. Support was also provided by the California Prevention Training Center (CAPTC). The contents of this report are the sole responsibility of the IMPT, CAMI Health, PHI and co-authors, and do not necessarily reflect the views of USAID, NICHD, CAPTC or the United States Government.