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DRUG CLASSES USED IN FORMULATION DESIGN AND DEVELOPMENT OF HIV PREVENTION MICROBICIDES

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ABSTRACT: Topical microbicides have proved to be an important tool for prevention of HIV transmission in women of reproductive age. Large populations studies including CAPRISA 004, VOICE, DREAM and FACTS001 proved 50-60% efficacy could be achieved with good adherence. These studies have shown the success of microbicides to be largely dependent of patient adherence, partner consent, multiple dosing requirement, aesthetic feel and retention in the cervicovaginal mucosa. To improve efficacy and adherence to microbicides, long-acting formulations are now more actively designed and considered in product development. Formulation design has evolved to provide low cost, scalable, discreet and easy to use multipurpose prevention technologies that provide protection against multiple sexual reproductive health issues. Active pharmaceutical ingredients used for microbicides have also evolved from small molecules and first-generation surfactants to large molecules including antimicrobial peptides and neutralising antibodies with broad spectrum efficacy and reduced viral resistance. The ability of novel molecules to inhibit and disrupt multiple sites in the HIV life cycle have shown potential to increase microbicide efficacy from the preclinical and clinical research work done. Good safety profile, sustained drug release and localized effect have been achieved. Controlled drug delivery greatly improves outcomes in HIV prevention but clinical data on safety and efficacy in pregnancy are still lagging. As more innovative intravaginal delivery systems and active molecules are designed the science on their interaction in vaginal microenvironment and microbiome has also led to areas and opportunity for research to improve therapeutic outcomes and drug development for microbicides.

INTRODUCTION: The concept of using a microbicide in a vaginal delivery dosage form for HIV prevention, started gaining traction in the early 90's. As a product category that catered specifically for women it has the potential to promote HIV prevention.

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Numerous studies have shown women to opt for prevention products designed and suited for personal use without consent of a sexual partner [1-3]. This has led to much interest in the development of microbicides for vaginal delivery.

On average, 4,000 adolescent girls and young women acquire HIV every week incidence in Sub-Saharan Africa, only 42% of districts with an inflated HIV incidence rate are currently covered with dedicated prevention programs for adolescent girls and young women [4, 5]. Adolescent and young women have at least three to five times higher

infection rates than the male counterparts [4]. The vaginal route has several distinct advantages for localised or systemic drug delivery. With a large surface area, vasculature, a lymphatic drainage system and the ability to bypass the first pass effect makes it a valuable route for drug delivery [2, 6, 7]. When products are formulated for this route, design considerations have to be made, these include the drug release profile (immediate/controlled), compatibility with vaginal microbiota, environment pH, small volume, anatomical space, safety and tolerability of drug formulation as well as excipients of choice used in product formulation [7, 8].

Traditional dosage form designs like gels, creams and pessaries for vaginal drug delivery are associated with poor retention and distribution caused by drug properties or the self-cleaning mechanisms of the vagina [8]. They have an inability to protect active moieties once they are released into the cervicovaginal mucus. Active moieties are now optimized to achieve sustained drug delivery in vaginal films, intravaginal rings (IVRs) or hydrogels for better efficacy, retention, mucoadhesion.

Microbicide technology targets potential targets for drugs in the HIV life cycle and successfully prevent HIV infection in the vaginal lumen and spreading to the regional lymph nodes and systemic circulation via the epithelial cell lining [2]. Formulations that improve retention, mucoadhesion and reduce rapid drug clearance are key for product development. Active pharmaceutical ingredients employed maybe small or large molecules that are highly potent, with low toxicity and penetrate the cervicovaginal mucosa to prevent HIV infections.

Women still require tailor made products that provide protection from reproductive health risks that are interlinked, these include unintended pregnancies, HIV and other sexually transmitted infections (STIs). Multipurpose prevention technologies (MPTs) have become an evolution from HIV only prevention microbicides to products with combined protection from female sexual reproductive health risks. Acceptance of contraceptive technologies provides an opportunity to increase the uptake of HIV prevention products. The potential challenges for MPTs are the stigma associated by drugs indicated for HIV or STIs in a contraceptive product and the formulation design complexity required for an MPT to achieve efficacy similar to existing contraceptive products while remaining user friendly [2]. This narrative review covers preclinical and clinical work done in developing microbicides from different type of API classes used for HIV prevention.

METHODOLOGY: This paper used a structured literature search format to formulate a narrative review that also leveraged personal knowledge on the development of topical microbicides with anti-HIV activity. The majority of these products are developed with a direct acting anti-retroviral agents for vaginal delivery in prevention of HIV acquisition alone or in combination for additional clinical indications as MPTs. To identify the specific topical microbicides the authors searched The Initiative for Multipurpose Prevention Technologies (IMPT), the International Partnership for Microbicides (IPM), PubMed, NIAID: National Institute of Allergy and Infectious Diseases databases from 2009 to 2026 using the key search terms: microbicides, multipurpose prevention technologies, pre-exposure prophylaxis, intravaginal delivery and the specific drug class.

The authors also reviewed NIH reporter and ClinicalTrials.gov and analysed information available on any ongoing or recently completed studies not yet published. The inclusion criteria for the work reviewed was analysis of the preclinical/clinical stage of prevention products with anti-HIV activity only or in combination as an MPT used intravaginally. Products under development without any anti-HIV prevention indications were excluded. All authors collated and reviewed research papers and their abstracts, deliberated on the study designs, population samples, objectives and outcomes of each study. The key findings were condensed and tabulated to give brief study description and outcomes.

HIV Life Cycle and Drug Target Sites: The HIV life cycle as depicted in **Fig. 1** consists several from viral entry to replication to new mature virion budding of the host's immune cells and presents potential targets for new drug candidates to be discovered that can prevent or treat infection. Drug development was pioneered from small molecules

with zidovudine becoming the first successful antiretroviral candidate. The science has evolved to different classes of antiretroviral drugs with complex molecules (peptides, antibodies, vaccines) also being developed that can successfully stop viral replication.

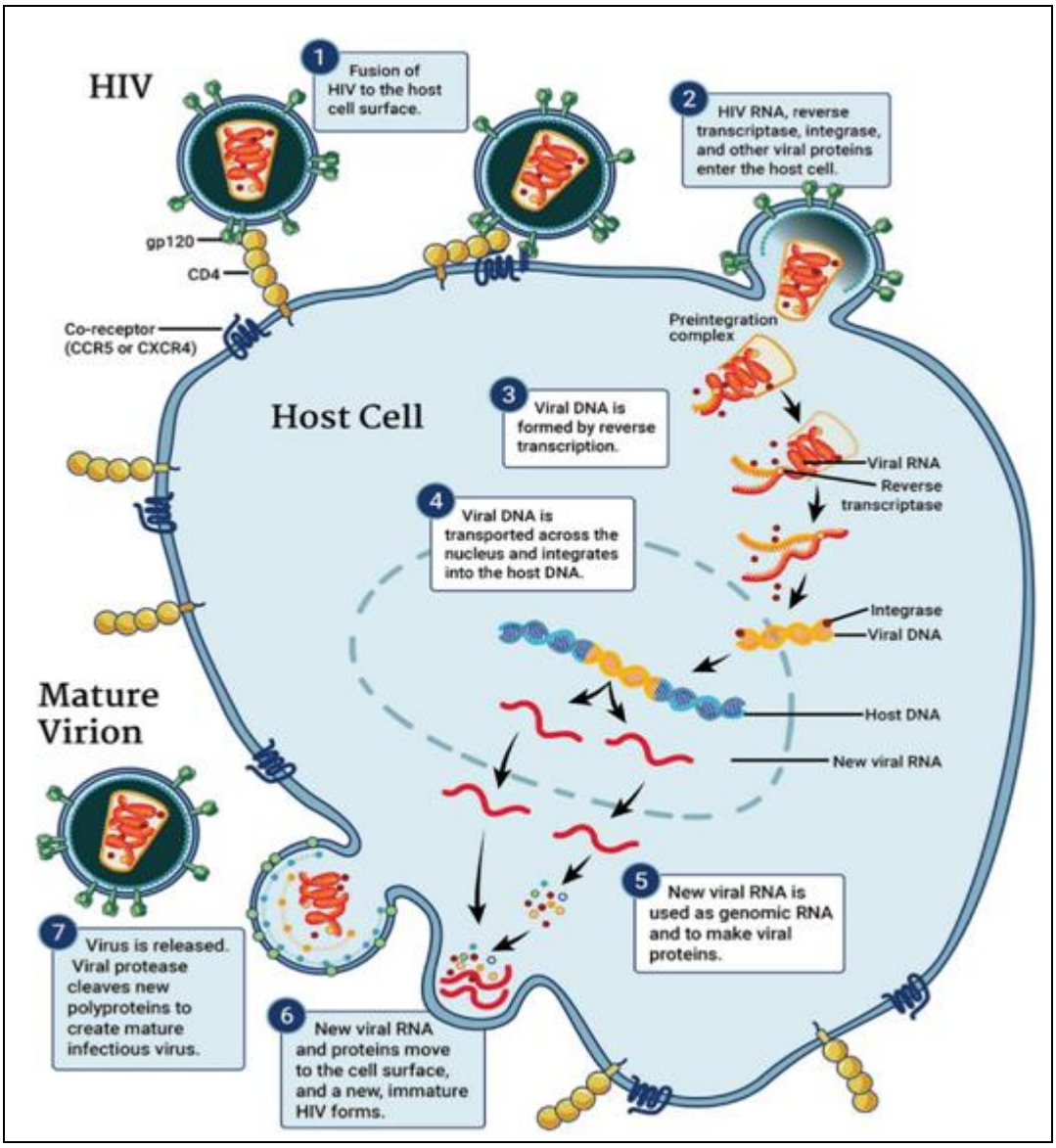

FIG. 1: HIV REPLICATION CYCLE (ADAPTED FROM THE NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NIAD) [9]

Data from drug development work done in developing anti-HIV molecules has shown several potential drug target sites for the inhibition of the retrovirus replication cycle. The molecules may act on one or more steps in the cycle thereby disrupting successful viral replication. This includes inhibition of virus fusion and entry into immune cell, transcription with host RNA, integration into host DNA, assembly of viral proteins and formation of mature virion that released and can infect other target immune cells.

Antiretroviral Drug Classes:

TABLE 1: DRUG CLASSES AND MECHANISMS OF ACTION AGAINST HIV [10]

Class	Mode of action	Examples
Nucleoside reverse transcriptase inhibitors (NRTIs)	Target the action of an HIV enzyme called reverse transcriptase inhibit viral DNA synthesis and lead to chain termination.	Tenofovir, Abacavir, Didanosine, Lamivudine, Stavudine, Zalcitabine, Zidovudine

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Interfere with the reverse transcriptase enzyme by binding directly to it, blocking the reverse transcription process.	Dapivirine, Doravirine, Efavirenz, Etravirine, Nevirapine, Rilpivirine
Nucleoside reverse transcriptase translocation inhibitors	Inhibits HIV reverse transcription by binding to viral DNA and blocking reverse transcriptase translocation on the primer template	Islatravir (EFdA), MK-8527
Integrase inhibitors	Target and block integrase enzymekey to integration and replication of viral DNA in host DNA and inhibit maturation of virion.	Bictegravir, Dolutegravir, Elvitegravir, Raltegravir, Cabotegravir, MK-2048
Entry inhibitors	Stop HIV from entering human cells. There are two types: CCR5 inhibitors and fusion inhibitors	Maraviroc, AMD3100, Enfuvirtide
Protease inhibitors (PIs)	Block the activity of the protease enzyme, which HIV uses to break up large polyproteins into the smaller pieces required for assembly of new viral particles.	Atazanavir, Darunavir, Lopinavir
Capsid inhibitors	Interferes with HIV capsid, a protein shell that protects HIV's genetic material and enzymes needed for replication.	Lenacapavir
Post-attachment inhibitors	Bind to the gp120 portion of the HIV envelope protein that makes up the spikes on the surface of the virus.	Fostemsavir, Ibalizumab, DS003
Booster	'Boost' the effects of protease inhibitors (ritonavir) and other antiretroviral drugs	Ritonavir, Cobicistat

Formulation Development of Microbicides from Different Drug Classes:

NRTIs and NNRTIs: Tenofovir (TFV) has been formulated into different intravaginal products that have under human trials and preclinical development as HIV and multipurpose prevention products as shown in **Table 2**. The drug terminates chain elongation of HIV-1 virus by competitive inhibition of deoxyadenosine 5'-triphosphate stopping viral replication and has activity against hepatitis B virus as well [11]. Low toxicity and safety are dependent on a low affinity for the hosts DNA polymerase [12]. The molecule is available in pro-drug forms of tenofovir disoproxil (TDF) or alafenamide (TAF) that increase oral bioavailability, and is phosphorylated into tenofovir diphosphate via a bi-phosphorylation process [11].

A microbicidal product was formulated with tenofovir intravaginal gel that generated great interest but the drug had limited efficacy in inflamed conditions around the genital area and unpredictable mucosal penetration and pharmacokinetics [13]. A case control analysis that tested topical tenofovir in women (CAPRISA 004, VOICE, and FACTS001) showed that protection against HIV ranged from 50-60%, when product adherence was high [13, 14]. Product efficacy was largely dependent on patient adherence that was affected by leakiness, required multiple dosing, and vaginal wetting that caused discomfort for sexual partner. This work showed great potential and impact and sparked interest in development of HIV prevention microbicides that empower the end user with a localized product tailor made for their use.

TABLE 2: PIPELINE OF NRTIS AND NNRTIS FOR KEY MICROBICIDES DEVELOPED

Product type	Drug development stage	Reference
Tenofovir vaginal film	Preclinical assessment in non-human primates for prevention of HIV-1 and HSV-2 infection. Safe in macaques with repeated exposure for 2 weeks as evidenced by minimal perturbation to tissues, microbiome, neutrophil influx, and pH. Higher TFV prodrug and bisphosphate form concentrations in vaginal tissues were achieved with the film in comparison to the gel	Patel *et al.*, 2023[15]
Tenofovir/acyclovir intravaginal ring (IVR)	Preclinical assessment *in-vivo* PK studies in rabbits and sheep for dual prevention of HIV-1 and HSV-2 infection. The devices showed preliminary safety and exhibited sustained release of both drugs independently and in a controlled fashion over the 28-day studies. Pod design used for IVR achieved target drug levels for potential prevention of HIV-1 and HSV	Moss *et al.*, 2012[16]
Tenofovir/DS003 vaginal gel	Limited information available. Early preclinical work. Potential dual HIV prevention mechanism.	Rosenberg and Devlin, 2012[17]
mAb 2C7 + TDF IVR	Proposed long acting MPT for dual prevention of HIV and gonorrhoea (mAb 2C7) early preclinical. Monoclonal antibody (MAb) 2C7 recognizes a lipooligosaccharide epitope expressed by most clinical *Neisseria gonorrhoeae* isolates and mediates complement-dependent bactericidal activity.	Parzych *et al.*., 2021[18]

	Rapid and prolonged MAb 2C7 expression attenuated gonococcal colonization at 8 days as well as 65 days post administration providing protection against gonococcal infection in a mouse model	
Novel mAb contraceptive + TDF IVR	Preclinical phase non-hormonal polyvalent mAb for prevention of pregnancy blocks sperms motility and movement through vaginal mucous and access to egg fertilization. MPT for prevention of HIV and pregnancy	Shrestha *et al.*, 2020[19]
TAF+ acyclovir (ACV) + etonogestrel (ENG) + ethinyl estradiol (EE) long acting IVR pod	Preclinical phase pharmacokinetic evaluation, product designed for prevention HIV, HSV and hormonal contraception. Prolonged release over 5 weeks in pigtailed macaques achieved systemic levels of ENG and EE to suppress reproductive cycle and vaginal tissue concentrations of TAF and ACV to inhibit HIV and HSV infections	Smith *et al.*, 2017[20]
TAF + elvitegravir vaginal insert	Phase 1 PK, PD and safety study for MPT developed for HIV and HSV prevention. Topical delivery achieved high drug concentrations in vaginal mucosa for up to 24 hours and 7 days post-dosing. Safe and highly acceptable	Thurman *etal.*, 2023[21]
Tenofovir/ dapivirine IVR	Preclinical phase. Segmented polyurethane IVR formulation for dual action of 2 anti-HIV drugs with different hydrophobic properties for 30 day sustained intravaginal drug release	Johnson *et al.*, 2010[22]
Tenofovir+ levonorgestrel IVR	Clinical Phase 2a studies evaluating safety, PK and pharmacodynamics. Phase 1 studies with 138 participants showed 90-day PK window ring delivered high concentration of TFV, LNG caused changes in cervical mucus, sperm penetration, and ovulation compatible with contraceptive efficacy	Thurman *et al.*, 2022[23]
Dapivirine 25mg IVR	Long-acting intravaginal ring made from flexible silicone polymer for once-a-month use. Recommended by WHO for preexposure prophylaxis of HIV acquired vaginal intercourse for women. A main study conducted in almost 2,000 women from 18 years of age in sub-Saharan Africa showed that 4.2% of women who used Dapivirine Vaginal Ring 25 mg became infected after two years of treatment, compared with 6.4% of women who used placebo (a vaginal ring not releasing any medicine). This means that Dapivirine. Vaginal Ring 25 mg lowered the chances of being infected with HIV-1 by over a third (35.1%)	Nel *et al.*, 2016[24]

Fusion and Entry Inhibitors: This class has small molecules and peptides that stop entry of HIV into human cells by inhibition of CCR5 receptors, targetHIV-1 envelope glycoprotein gp120/gp41, or fusion into host's cells. Topical microbicides designed should be applied topically within minutes to hours of the virus crossing the vaginal lumen to achieve maximum efficacy. Combination with other ARV drug classes can potentially extend the therapeutic window. Griffithsin (GRFT) an algae derived lectin shows effective broad-spectrum activity in blocking viral entry to host cells, through crosslinking and aggregation to terminal mannose residues on viral glycoprotein (gp120) [7]. It is also active against HSV-2 and HCV. Maraviroc is a broad spectrum CCR5 receptor inhibitor with in vitro anti-HIV activity displayed against many clinical isolates and resistant strains. Entry inhibitors include polyanions that are negatively charged showed good *in-vitro* anti-HIV efficacy but are much more effective against the positively charged CXCR4 mechanism than CCR5-using (R5-tropic) viruses that are used for HIV infection and transmission into host cells [25]. Polyanions include cellulose sulfate, dextran sulfate, carageenan and PRO-2000 are capable of binding to the HIV envelope and preventing cellular infection but have not improved effective in HIV prevention clinical trials for the topical microbicides [25, 26]. Lectins including GRFT and cyanovirin are high effective against HIV infections *in-vitro* with similar mechanism as highlighted before. Cyanovirin is a 101 amino-acid protein produced by the cyanobacterium *Nostoc ellipsosporum* [25] and was developed as topical gel microbicide in preclinical stages in NHP models for potential prevention of rectal and vaginal HIV transmission [27]. **Table 3** gives a brief summary of the work done in developing microbicides and MPTs in this class.

TABLE 3: VAGINAL PRODUCTS WITH FUSION INHIBITORS DEVELOPED FOR HIV PREVENTION

Product type	Drug development stage	Reference
Griffithsin (GRFT) + carrageenan fast dissolving	Preformulation stage, insert displays good physicochemical properties for friability, osmolality, disintegration, hardness, low moisture content, and	Lal *et al.*, 2018[28]

insert	viscosity on dissolving in simulated vaginal fluid. Product stable over 6 months. IC_{50} for antiviral activities against HIV and HPV retained in vitro for anti-HIV (TZM-bl) and anti-HPV cell-based assays.	
GRFT + carrageenan vaginal gel	Phase 1 clinical trial a (0.1% GRFT in a carrageenan (CG) gel investigation of PK, PD, safety, immunogenicity after single dose and daily dosing for 2 weeks. GRFT concentrations in cervicovaginal fluids achieved inhibit HIV and HPV activity from lavage samples *in-vitro*. No significant adverse events and cervicovaginal proinflammatory responses were recorded	Teleshova *et al.*, 2022 [29]
Dapivirine/maraviroc vaginal gel	Preformulation stage, physicochemical testing for pH, viscosity, osmolality and *in-vitro* drug release. *In-vitro* TZM-bl assays confirmed improved anti-HIV synergistic effect for combination product. Effectively blocked HIV infection in explant challenge using human ectocervical and colorectal tissue and safe.	Dezzuti *et al.*, 2015[30]
Dapivirine/maraviroc IVR	Phase 1 safety, PK and PD study done. Tissue dapivirine concentrations were 1,000 times greater than plasma concentrations and single drug rings had more stable pharmacokinetics. Dapivirine, and not maraviroc, demonstrated concentration-dependent inhibition of HIV-1 infection in cervical tissue. Formulation improvement required for increased maraviroc drug concentrations in tissue and achieve sustained drug release	Chen et al.,2015[31]
DS003 IVR	Preformulation stage, ethylvinylacetate IVR with 40% drug loading changes in drug crystallinity or polymer structure affected drug release rate on storage at low temperatures, macaque animal study could not differentiate drug released *in-vivo*, from loaded concentration in IVR on insertion and after removal	Malcolm et al., 2021[32]
Theaflavin derivatives (TFmix) vaginal gel	Late stage preformulation, >50% *in-vitro* drug release in 3 hours peaking at 9 hours low *in-vitro* cytotoxicity, low cervicovaginal irritation and inflammation in rabbit vaginal tissue, concentrations higher than 10^5-fold over its *in-vitro* anti-HIV IC_{50} value, did not cause significant vaginal irritation in the rabbit model, once daily intravaginal application for 14 days achieved tissue drug concentration>6 hours/application potentially for once daily application or 12 h before/after sexual intercourse in human use	Yang et al., 2012[33]
Carrageenan-based gel (Carraguard)	In the Phase 3 randomised, double-blind, placebo-controlled trial done in South Africa the microbicide was not effective in HIV prevention, it was safe, acceptable and was used in 42.1% of the sexual acts by study participants. A total of 6202 participants, who were randomly assigned by a block randomisation scheme to Carraguard (n=3103) or placebo (methylcellulose [n=3099]), were instructed to use one applicator of gel plus a condom during each vaginal sex act	Skoler-Karpoff et al., 2008[34]

Integrase Inhibitors: Integrase inhibitors are highly effective in blocking viral replication in treatment naïve and drug-resistant strains by inhibiting the integrase enzyme viral DNA strand transfer and integration into host DNA [35]. They can also bind to a non-active site of the enzyme and block conformational changes required to catalyse the strand transfer process [36]. In addition, integrase enzymes play an important role in proper virion maturation as it interacts with the viral RNA genome to ensure encapsulation of ribonucleoprotein complexes within the protective capsid core that can also be inhibited [37, 38]. The barrier to drug resistance, safety and efficacy of this class has led to development of drugs used in current combination oral tablets prevention and treatments based on dolutegravir, bictegravir and long-acting injectables with cabotegravir. Interest has also been generated in investigating their potential topical use for HIV prevention as summarised in **Table 4.**

TABLE 4: PHASE 1 AND PRECLINICAL STUDIES OF MICROBICIDES WITH INTEGRASE INHIBITORS

Product type	Drug development stage	Reference
MK-2048 IVR	Phase 1 safety and PK study of MK-2048/MK-2048a, formulations were safe and tolerated over 28-day use. Drug concentrations in cervical tissue did not inhibit HIV in ex-plant tissue challenge test in a dose dependent manner due to poor drug penetration or efflux transport out of tissue, inadequate loading dose in the IVR and drug concentration for dose-response curve	Hoesley *et al.*, 2019[39]
MK-2048 vaginal films	Phase 1 safety and PK study for two vaginal formulations, proof of concept study to determine whether an extended-release vaginal film can deliver drug for seven days	Bunge, 2023[40]

MK-2048 nanoparticle in vaginal film	Preclinical study for formulation development, drug release, *in-vitro* toxicity, *ex-vivo* permeability and *in-vivo* PK study in macaques, safe in *in-vitro* and *in-vivo*, prolonged drug release for NPs, penetration, retention and reduced efflux in *ex-vivo* permeability model	Tong *et al.*, 2022[41]
Raltegravir vaginal gel	-Macaques animal PK study (Preclinical), maximum drug concentration in vaginal fluid and tissue achieved with 3-5 hours of administration. Drug concentrations achieved potentially provide protection from HIV infection in vaginal and rectal tissue	Nishiura *et al.*, 2021[42]

Broadly Neutralizing Antibodies (bNAbs): The mechanism action for bNAbs targets and binds to conserved epitopes on the HIV viral envelope proteins and fusion to host cell thereby neutralizing the virus and activating immune mediated to engulf and destroy infected cells [43]. The antigen binding fragments of bNAbs can be designed to target different virus strains to give broad spectrum activity and increased potency against HIV [44, 45]. Extensive preclinical work is currently being done for different therapeutics applications including passive immunisation, treatment and prevention in HIV. The most commonly used drug delivery method investigated is for intravenous use, but emergence of novel delivery systems is an area of interest for localized intravaginal delivery [47]. Different bioengineering techniques used to antigen surface and bNAbs can extend half-life for prolonged circulation (8-12 weeks), improve potency and increase safety [43, 44]. Research on bNAbs has not provided evidence of superior efficacy compared to small molecules used in ART or prevention [45].

TABLE 5: MICROBICIDE FORMULATIONS DEVELOPED FOR INTRAVAGINAL DELIVERY OF BROADLY NEUTRALIZING ANTIBODIES

Product type	Drug development stage	Reference
Single-chain aerosolised mRNA-encoded bnAbs	Preclinical work on vaginal explant tissue of macaques, protection against SHIV/HIV strains observed. IgM multimers potent against multiple SHIV strains and viral neutralization	Joo *et al.*, 2025b[48]
VRC01 vaginal gel	Preclinical study in humanised mouse model, Protection observed in HIV challenge test when gel was applied an hour before viral exposure	Veselinovic *et al.*, 2012[49]
Anti-N-glycans/V3 loop HIV-1 bNAb 10-1074 vaginal gel	Repeated cell-associated SHIV162P3 vaginal challenge in non-human primates, low infection rate and transmission in vaginal mucosa achieved	Suphaphiphat *et al.*, 2023[50]
Ovine immunoglobulin G (ov-IgG) IVR	Sustained drug delivery of IgG and IgA mAbs over 2 weeks, ovine immunoglobulin G (ov-IgG) as a model for IgG and IgA human monoclonal antibodies. *In-vitro* release studies showed potential delivery of mAbs using IVRs	Gunawardana *et al.*, 2014[51]
VRC01-N IVR	PK and safety study for intravaginal delivery in macaques' model, controlled drug delivery over 21 days with no adverse reactions. Concentration range of 0.3 to 10 μg ml^{-1} IgG achieved in vaginal fluid over 21 days	Zhao *et al.*, 2017[52]
MABGEL (2F5, 4E10 and 2G12)	A randomized, double-blind, placebo-controlled clinical phase 1 trial with 28 women. Gel (2.5g) applied day for 12 days and sufficient concentrations to prevent HIV infection observed up to 8 hours after administration, formulations were safe and compatible with vaginal flora, the bNAb 2G12 exhibited more rapid elimination from the human vagina than 4E10 and 2F5, likely due to poor stability of 2G12 in acidic human vaginal secretions	Morris *et al.*, 2014[53]
MB66 film	A Phase I clinical trial to assess the safety, pharmacokinetics (PK), and ex vivo efficacy of single and repeated doses (once daily) of MB66 was done, antibody concentration reached maximum at level an hour after dosing in vaginal secretions and remained high after 24 hours, repeated dosing maintained elevated concentration for the antibodies, the product was safe and well tolerated	Politch *et al.*, 2021[54]
2G12 vaginal gel	Double-blind, placebo-controlled, randomized, dose-escalation phase I safety study of a single vaginal administration of P2G12 was carried out in healthy female subjects. P2G12 was detectable in vaginal secretions 8 hours after administration though potential degradation to samples occurred during cold chain transport and handling. No systemic levels of antibody were detected. The product was safe and well tolerated	Ma *et al.*, 2015[55]

Antimicrobial Peptides: Antimicrobial peptides (AMPs) are found in the mucosal lining of the female reproductive tract and play an important in immunomodulation and antimicrobial effect against different pathogens. Peptides typically contain short chain length amino-acid sequence synthesized through chemical or biological pathways for development of therapeutics or vaccines [56]. Their physiological role is associated with different conditions including pelvic inflammatory disease, fertility and spermicidal effects, shaping microbiota, maintaining normal reproduction and pregnancy. Naturally occurring AMPs also occur in bacteria, plants, breast milk and animals and can be used as a template to develop designed AMPs for topical delivery for HIV prevention and for MPTs [57]. Several mechanisms of action exist that explain AMP activity against HIV, which include viral entry inhibition due to AMPs membrane active properties, lipid clustering of the HIV envelope, binding to glycoproteins to stop viral entry and inhibit cDNA viral replication 12 hours after infection [57, 58]. Designed AMPs are able to block different mechanisms in the HIV life cycle most notable is LL-37 a human cathelicidin that damages the viral envelope, is a competitive inhibitor for CCR5 and CXCR4 viral binding and the HIV reverse transcriptase enzyme. It also shows activity against other pathogens that affect the female reproductive tract and is spermicidal potentially working as an MPT [59].

Lactobacillus Biotherapeutics: Lactobacilli occur in vaginal milieu that regulate the microbiome and maintain ideal pH (<4.5) by releasing lactic acid and hydrogen peroxide as a chemical barrier to infection, and provide a physical barrier to prevent dysbiosis, vaginosis and pathogens from infecting the vaginal mucosa [60]. The main substrate for lactobacilli is glycogen produced by epithelial cells in response oestrogen stimulation. Lactobacilli biotherapeutics contain microorganism from the lactobacillus family that are modified for application in prevention or treatment of infections. A vaginal tablet MucoCept-CVN© was formulated from recombinant *Lactobacillus jensenii* strain that can produce modified cyanovirin-N (mCV-N) an effective HIV entry inhibitor. In animal studies using macaques a fast-dissolving tablet of the formulation achieved 83% colonization after administration at day 14 and day [61].

A phase 1 study has been designed for dosing scale, safety, colonization, change in microbiota and PK with a randomized double-blind placebo-controlled study [62].

CONCLUSION: Microbicides have been developed from the 1990s for prevention of HIV transmission and multipurpose use in contraception and pathogens that affect the female reproductive tract. The field was pioneered with the development of detergents and acidifiers that failed to show safety and efficacy in phase 3 trials. Pivotal success for use of antiretrovirals in microbicides was discovered with the development of tenofovir 1% gel that reduced HIV acquisition by 39% in women under CAPRISA 004 trial. Tenofovir showed good efficacy in gel formulation but poor adherence to daily dosing for the gel changed formulation strategy to products that improve retention, sustained drug delivery, and are user friendly with the emergence of IVRs and films among other dosage forms. The Dapivirine IVR has been developed for once-a-month use and showed a 56% reduction in HIV acquisition in real world settings when consistently used among women 21 years or older in the ASPIRE trial [24]. MPTs have expanded to address sexual and reproductive health challenges other than HIV transmission in combination products and represent majority of microbicides in the drug development pipeline.

Active pharmaceutical ingredients developed for microbicides has evolved from small molecules and first-generation surfactants, to repurposing ARVs used in treatment, antimicrobial peptides, and neutralising antibodies with broad spectrum efficacy and reduced viral resistance. The ability of novel molecules to inhibit and disrupt multiple sites in the HIV life cycle have shown potential to increase microbicide efficacy from preclinical and phase 1 clinical work, good safety profile and localized effect has been achieved. Product design and testing consider safety in pregnant women if they are to use the product as well in special study post approval stages as in the case dapivirine IVR. Low-cost scalable formulations have the potential to improve accessibility to user populations for MPTs with controlled intravaginal drug delivery for APIs in sufficient vaginal fluid and tissue concentrations that exhibit protective action against HIV infections and other pathogens in the female

reproductive tract. The challenges faced in drug development, formulation science and human use of microbicides continue to innovation in the drug class for products with better safety profiles, efficacy, microbiome compatibility and user friendliness.

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