

FORMULATIONS OF VAGINALLY ADMINISTERED PRODUCTS

FINAL PRESENTATION

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STRATEGIC ANALYSIS,
RESEARCH & TRAINING CENTER

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START OVERVIEW



Leverages leading content expertise from across the University of Washington



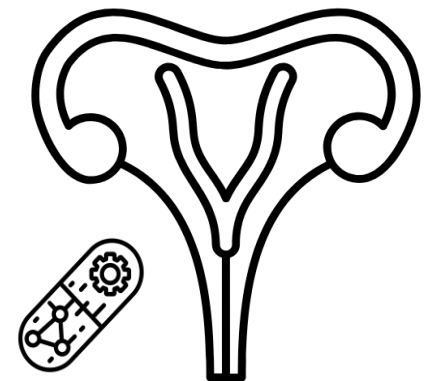
Provides high quality research and analytic support to the Gates Foundation and global and public health decision-makers



Provides structured mentorship and training to University of Washington graduate research assistants

BACKGROUND

- The vagina remains an **understudied** and **under-utilized** route for delivery of therapeutics, particularly for female-specific conditions
- Several Gates Foundation priorities related to women's health may benefit from expansion of vaginal route of administration of therapeutics
- Gates Foundation desires to understand the state of existing research regarding vaginally delivered products and to identify potential partners and collaborators



KEY PROJECT QUESTIONS



What drugs/therapeutics and delivery platforms are most often delivered vaginally in LMICs?



What data are available on the impact of vaginally administered products on the vaginal microbiome and vice versa?



What research is available on user preferences for vaginally-administered products (user and partner perspectives)? How do these preferences influence decision-making?

PRESENTATION **OVERVIEW**



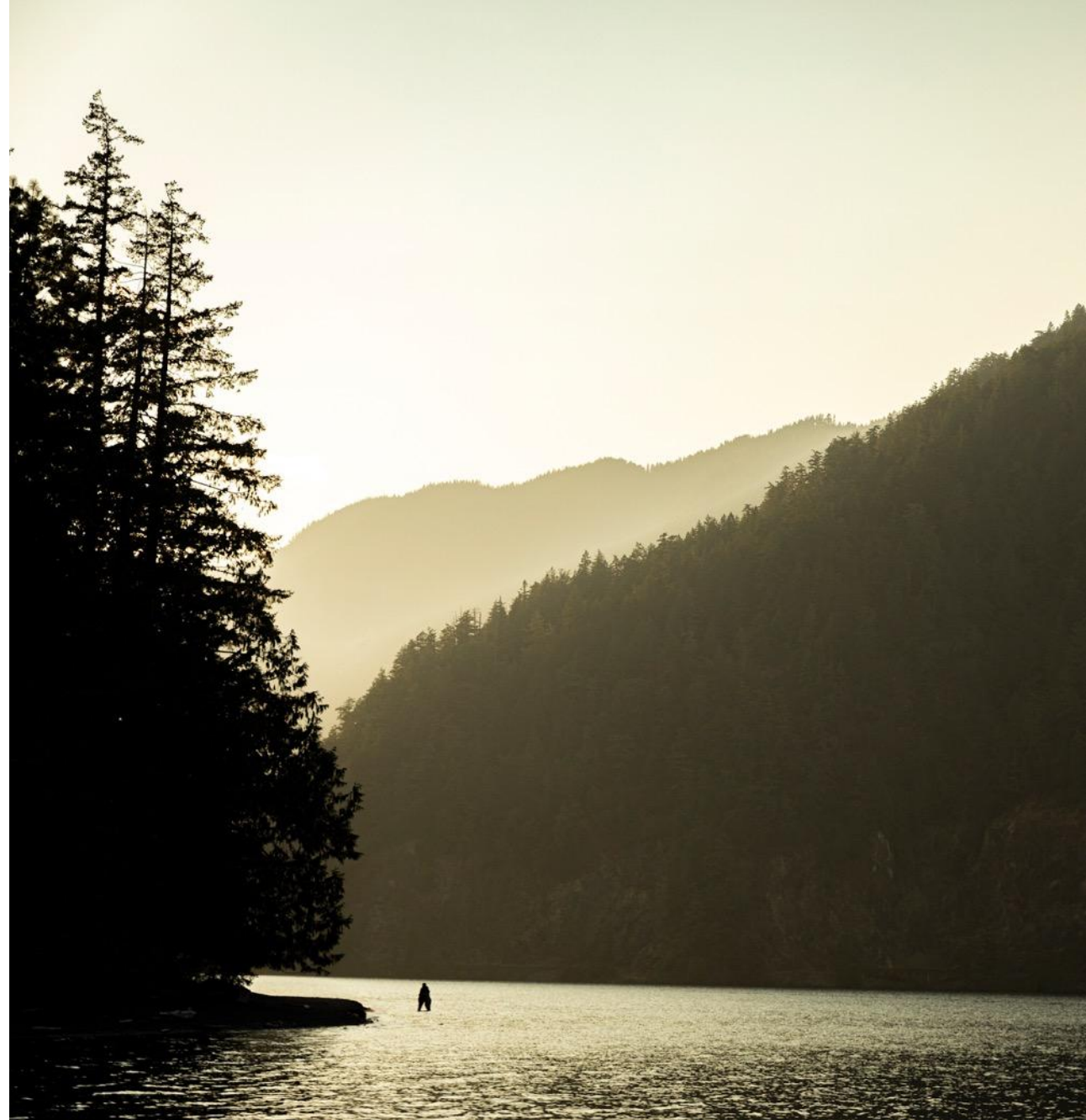
Overview of vaginal drugs & platforms



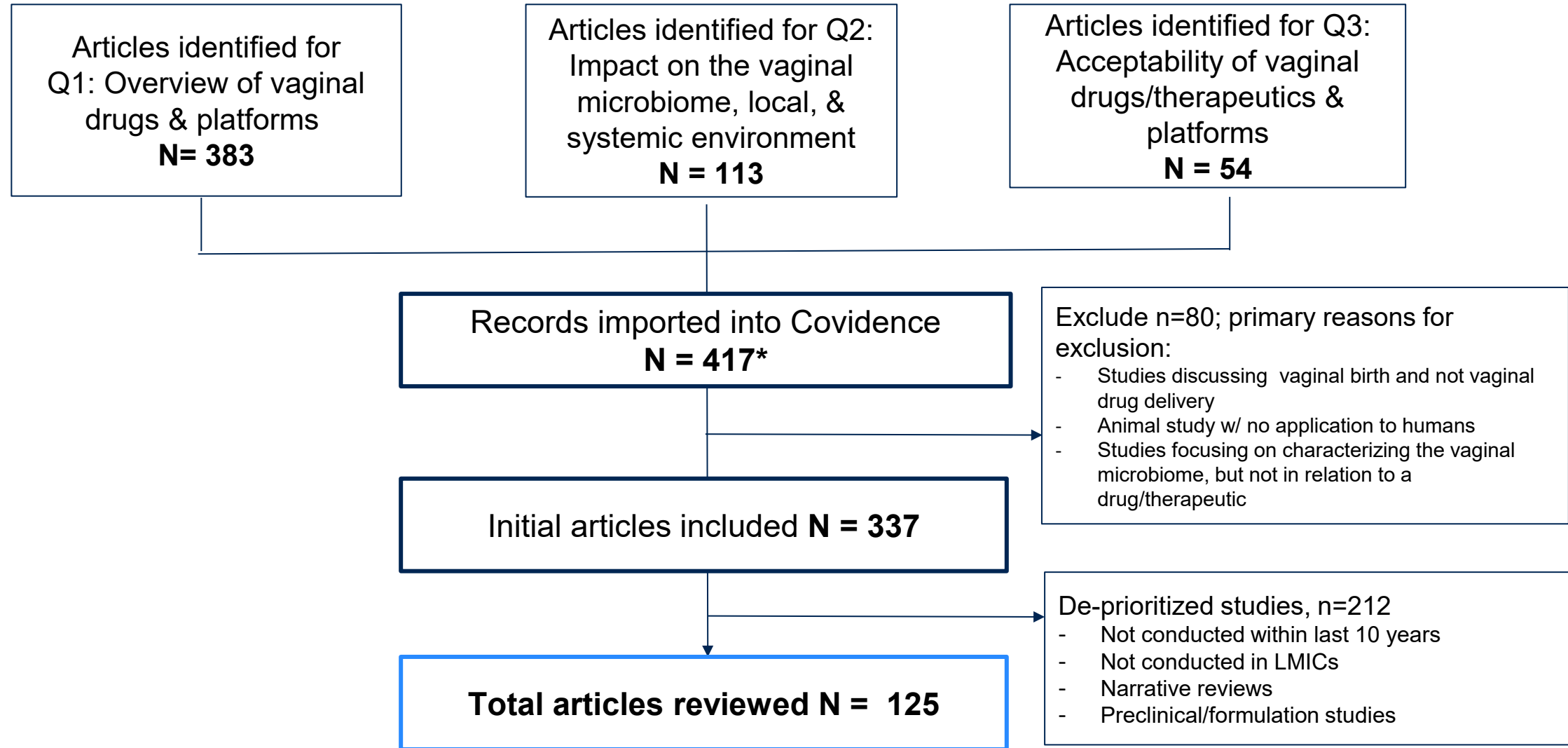
Impact on the vaginal microbiome, local & systemic environment



User and partner preferences of vaginal drugs/therapeutics & platforms

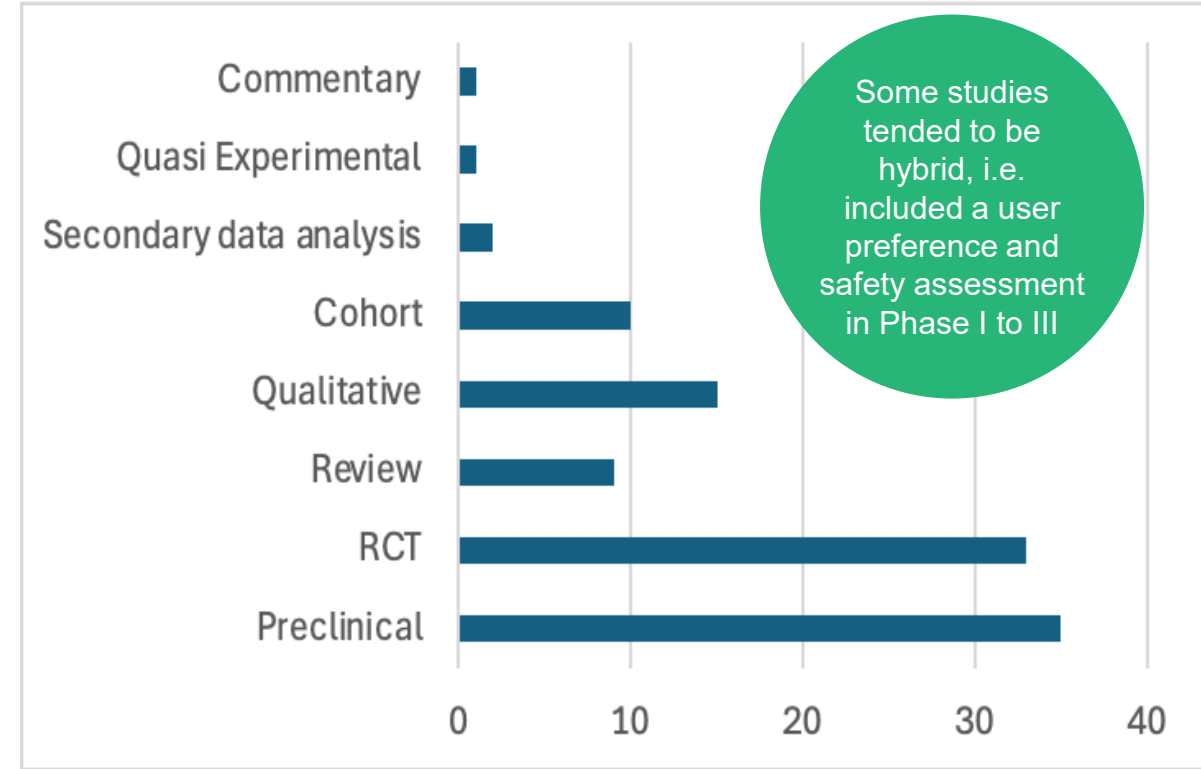
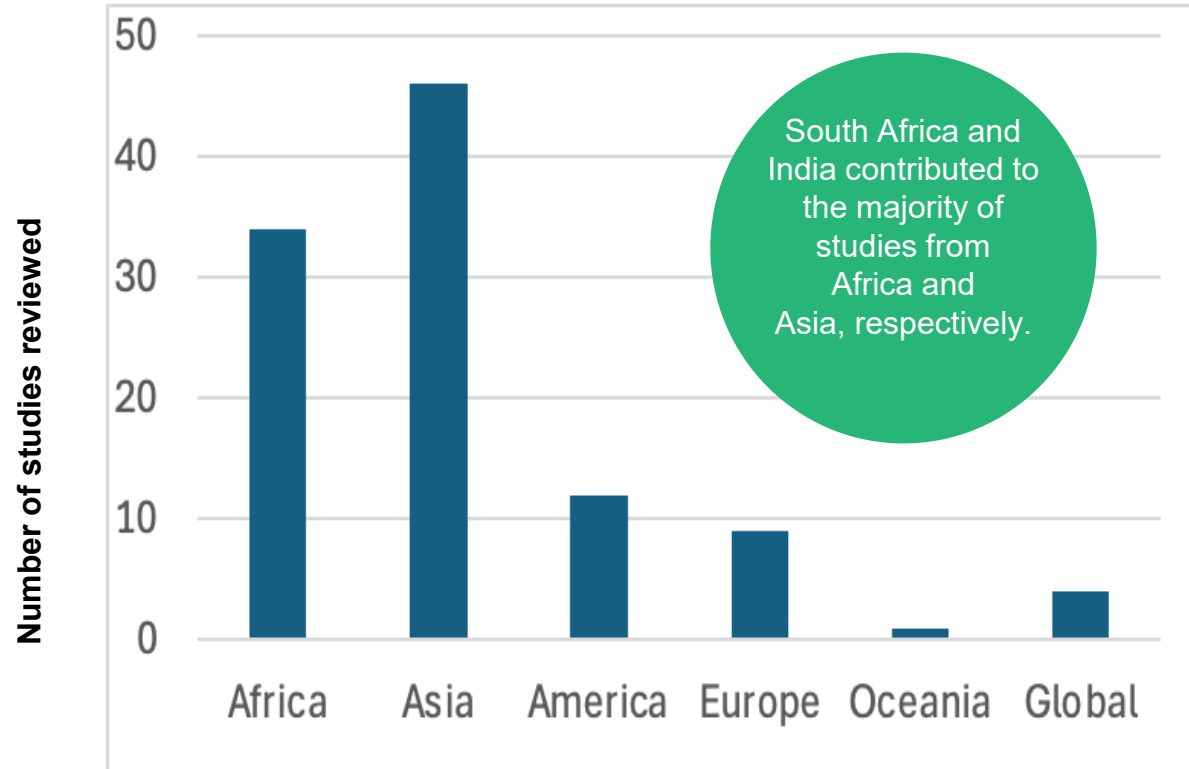


LITERATURE REVIEW PROCESS



* Duplicate articles identified between Q1, Q2, & Q3 searches

GEOGRAPHIC DISTRIBUTION AND TYPE OF INCLUDED STUDIES

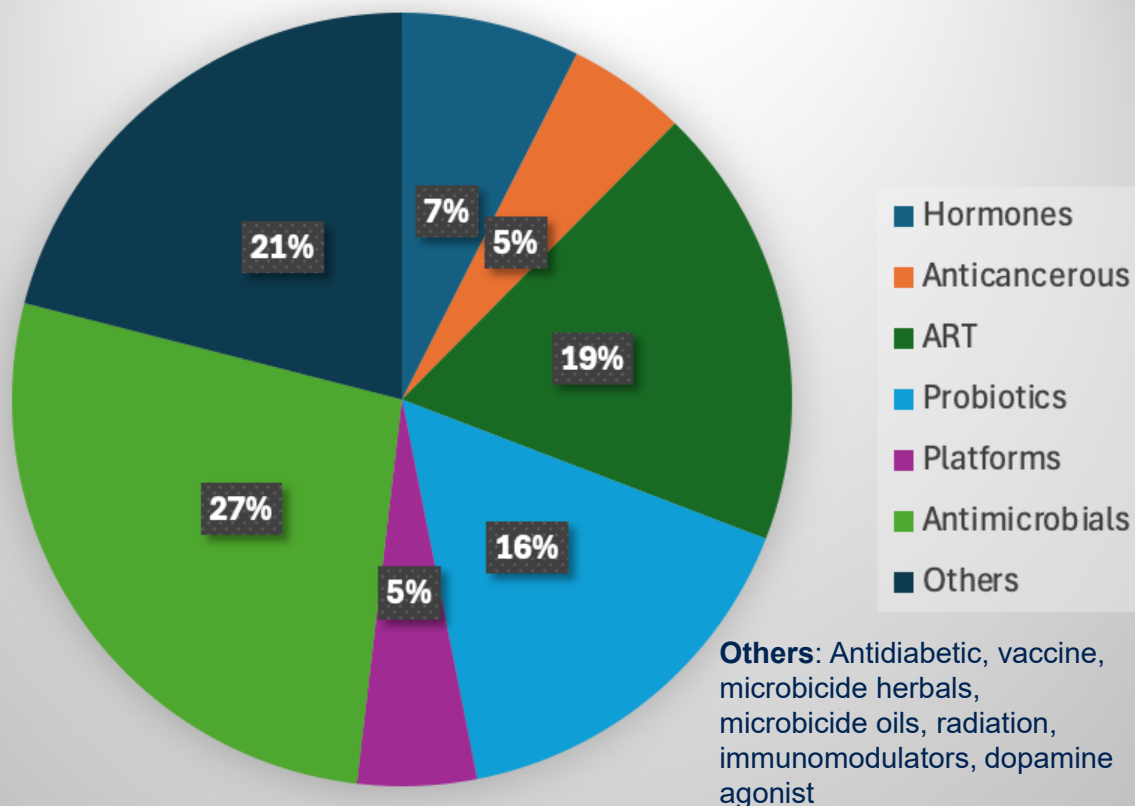


Number of studies reviewed

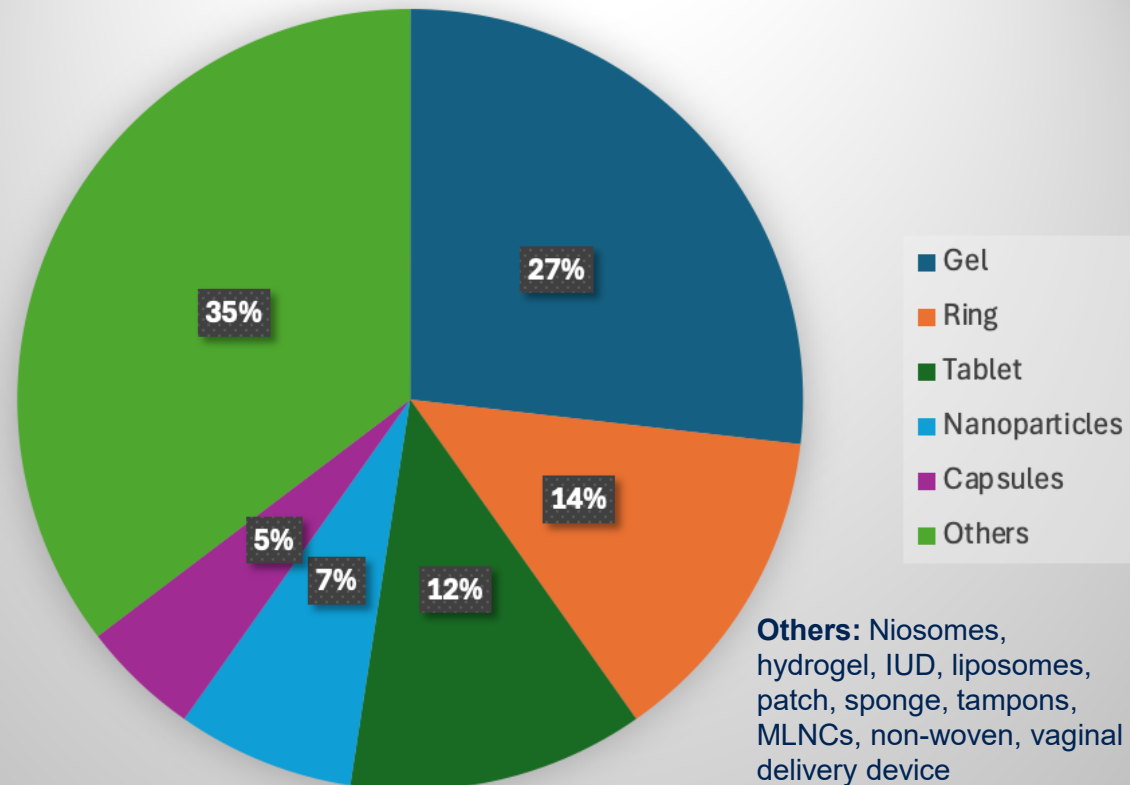
DISTRIBUTION OF DRUGS AND THERAPEUTICS



Drugs and Therapeutics



Platforms



VALIDATED PLATFORMS AND CHARACTERISTICS



PLATFORM	KEY FEATURES
Ring	Ring (usually silicone-based) impregnated with drugs that are released slowly into the vagina. Can be microbicides, contraceptives, etc. Ex: Dapivirine, Bromoncriptine, Estradiol, Etonogestrel
Gel	Semi solid formulation impregnated with drugs and applied usually before coitus. Has lubricant properties. Ex: Tenofovir, Carboplatin, Progesterone, Probiotics
Tablet/pessaries/capsules	Tablets are designed to be inserts whose formulation contains the needed drug. Most are microbicides for STD prevention and treatment. Ex: Metronidazole, 5-Fluorouracil, Clotrimazole, probiotics
Creams	Semi-solid formulation that come in tubes and applied to cover vaginal mucosa. Formulated with oil and water and active drugs. Ex: Clotrimazole, Ketoconazole, Probiotics
Films	Thin, polymer-based sheets that are applied in the vagina and dissolve once in contact with vagina mucosa. Ex: Antibiotics, Nonoxynol-9, Estrogen, other microbicides

BIOAVAILABILITY



01

Most studies did not include data on bioavailability and systemic comparators

02

Vaginal products achieved higher local concentrations & lower plasma concentrations than systemic comparators

03

Majority of sustained release platforms had similar efficacy as oral route

Avlani et al (2024); Xue Wang et al (2021); Milford C et al (2024)

DRUG SAFETY PROFILE



01

Most drugs were safe and well tolerated in clinical trials

02

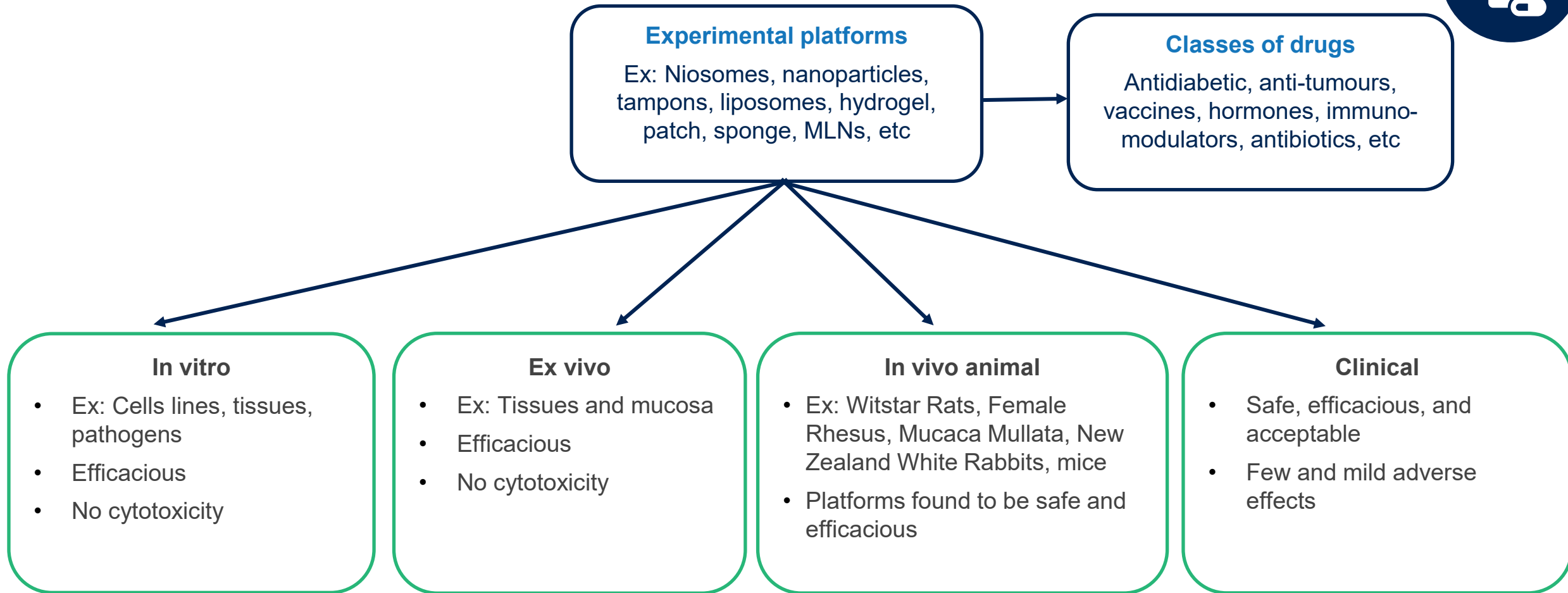
No epithelial damage, inflammation or necrosis in pre-clinical studies

03

Most common adverse effects (vaginal odor, discharge, leakage, cycle control, dryness, loss of sexual desire) in clinical trials were mild

Yuxin Fan et al (2024); Bibon Gill et al (2020); Atujuna M et al (2018); Theresa Delvaux et al (2020); Anna-Ursula Happel et al (2020)

SUMMARY OF EXPERIMENTAL PLATFORMS



Jun Wang et al (2023); Abidin I et al (2020); Eric Amstrong et al (2022); Abd-Esalam WH et al (2021); Uzma Farook et al (2024); Ivay Saha et al (2025); Yiqian Tang et al (2023); Ji Z et al (2017)

VAGINAL DRUGS & DELIVERY PLATFORM TIMELINE



First vaginal antifungals **Monistat** (Miconazole) and **Gyne-Lotrimin** (Clotrimazole), prototype estradiol hormone rings developed, **Dinoprostone** (Prepidil gel, Cervidil insert)

MetroGel (Metronidazole), **Cleocin** (Clindamycin), **Estring** (estradiol vaginal ring), **Crinone** (progesterone vaginal gel), **Clindamycin ovules**, **NuvaRing** (estrogestrel)

Long-acting rings (**Annovera**), **Lactin-V**, probiotic inserts and expanded vaginal probiotics (**Lactobacillus GR-1 & RC-14 vaginal tablets**), **DPV-LNG dual-purpose ring**, **Tenofovir gel** ineffective

1970s

1980s

1990s

2000s

2010s

2020s

OTC antifungal formulations (**Monistat**), intravaginal **Metronidazole & Clindamycin for BV**, **Misoprostol**, early research into controlled-release vaginal drug systems, **Nonxynol-9** spermicides for contraception & HIV prevention

Tenofovir gel in HIV trials, **NuvaRing**, **misoprostol** standard for induction but never approved for vaginal route, **Noxonyl-9** spermicides shown to increase HIV risk

VS-01 vaginal synbiotic insert, bioadhesive vaginal films (**ZB-06 film**, **PSS-based films**, **tinidazole film**), **3-month dapivirine ring**, **MB66 monoclonal antibody vaginal film (Anti-HIV)**, **2G12 film**

● FDA Approved

● Clinical Trials

● Preclinical Testing

● Off-Label Vaginal Use

● Not Approved / Not Recommended

END OF FIRST SECTION



IMPACT ON VAGINAL MICROBIOME & LOCAL ENVIRONMENT



01

Most documented effects are restorative (especially probiotics following antimicrobial regimens) - reduction in Nugent score, reduced BV-associated anaerobes, rise in *Lactobacillus*

02

Hormones & ARV/MPT rings: generally neutral to mildly supportive of *Lactobacillus* dominance, but evidence limited

03

Future studies need long-term, mechanistic, and comparative platform data to understand not just efficacy but sustainability of vaginal microbiome shifts

SYSTEMIC EFFECTS AND SIDE EFFECTS



- Antibiotics for BV → Lower systemic exposure & fewer systemic AEs than oral route (Brandt et al., 2008)
- Antifungals → Negligible systemic uptake, plasma levels undetectable, systemic side effects rare compared to oral fluconazole (Denison et al., 2020)
- Probiotics → Negligible systemic uptake, systemic labs/AEs similar to placebo (Abbe & Mitchell, 2023)
- ARV rings → Low systemic exposure compared to oral ARVs (Bunge et al. 2015)
- Estradiol rings/creams → Very low systemic hormone levels; safe, local benefit (Krause et al. 2015)
- Contraceptive rings → Deliver systemic hormones, lower exposure than OCPs (Roumen et al. 2008)
- Antibody films → No systemic absorption; safe in Phase I (Politch et al. 2021)
- Bioadhesive films/hydrogels → Early data; localized delivery, little systemic uptake (Subi et al. 2024)

CLINICAL EFFICACY



CLINICAL EFFICACY	DRUG/THERAPEUTIC/PLATFORMS	MEASURE OF IMPACT	AUTHOR, YEAR
	Topical azole antifungals (clotrimazole, miconazole, terconazole)	Mycologic cure; symptom resolution	Denison et al., 2020
	Antibiotics for BV (metronidazole, clindamycin)	Short term Nugent/Amsel cure; 16S/CST shift; drop in BV-anaerobes; pH ↓	Brandt et al., 2008
	Local vaginal estrogen	16S/CST (↑ Lactobacillus, ↓ Gardnerella), pH ↓	Thomas-White et al., 2020; Krause et al., 2015
	Contraceptive vaginal rings (NuvaRing – ENG/EE; Annovera – SA/EE)	Highly effective reversible contraception when used correctly; Pearl Index ~1–2, comparable to COCs but with lower systemic EE exposure	Roumen et al., 2008; Crucitti et al., 2018
	Lactin-V (L. crispatus CTV-05)	Reduced BV recurrence; L. crispatus colonization/engraftment; Nugent 0–3; genital cytokines ↓	Armstrong et al., 2022, 2024
	Dapivirine HIV-prevention ring (monthly)	Phase-III trials show modest HIV risk reduction overall (~27–31%), higher with adherence; VMB impact neutral.	Baeten et al., 2016; Nel et al., 2016; Austin et al., 2021
	Generic probiotics (non-crispatus LBP mixes; oral/vaginal, diverse strains)	Meta-analyses suggest possible benefit (esp. adjunct to antibiotics), but heterogeneity/quality issues keep certainty low	van de Wijgert et al., 2020
	Tenofovir 1% vaginal gel	CAPRISA 004 showed 39% HIV risk reduction with good adherence; VOICE trial failed due to poor adherence	Abdool Karim et al., 2010; Marrazzo et al., 2015
	Nonoxynol-9 microbicide gels	Multiple RCTs: no protection; increased genital lesions and HIV risk with frequent use	Van Damme et al., 2002; Wilkinson et al., 2002

PRECLINICAL EVIDENCE



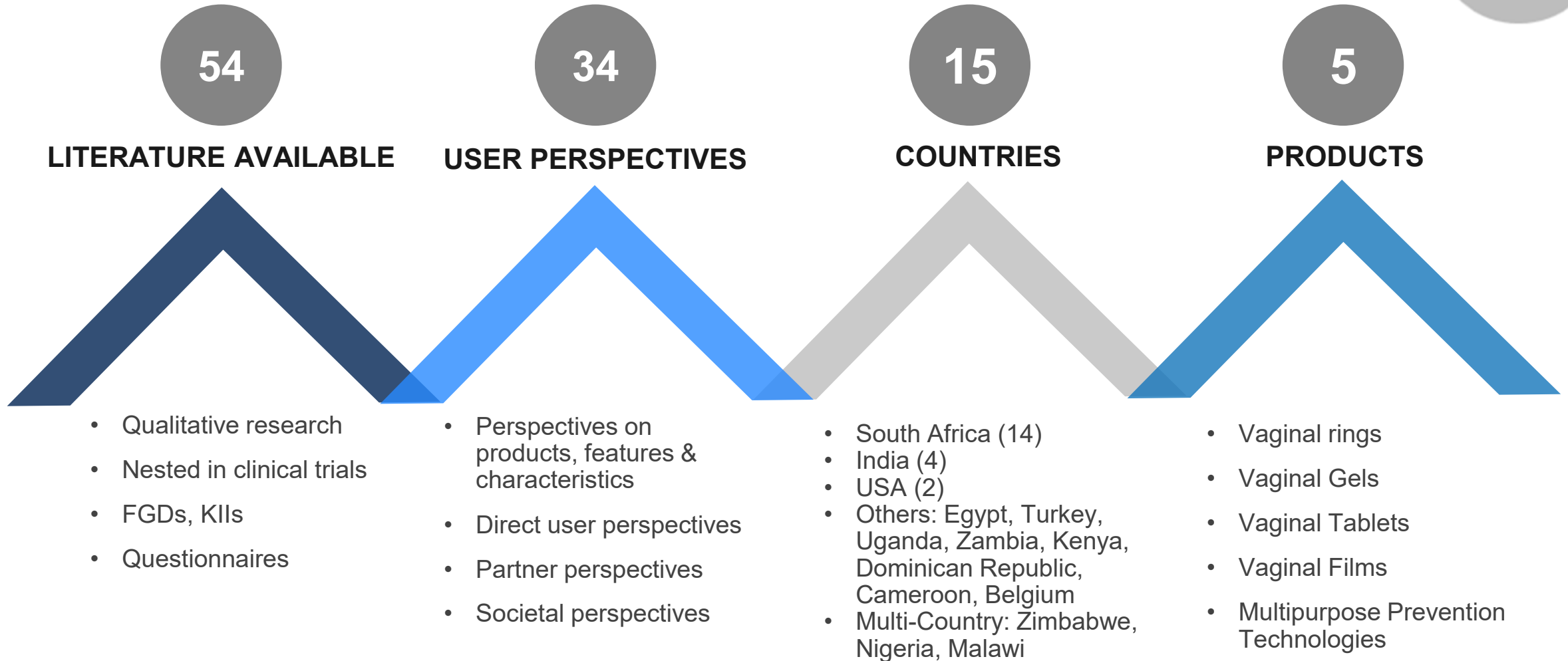
AUTHOR, YEAR	EVIDENCE TYPE	PLATFORM	DRUG/THERAPEUTIC	MEASURE OF IMPACT
Permana et al. 2023	Ex vivo mucosal retention; rat BV infection model	Thermoresponsive hydrogel loaded with gel-flakes	Metronidazole gel-flakes	Sustained release; >8 h tissue retention ex vivo; significant bacterial load reduction in rat BV model
Alqahtani <i>et al.</i> , 2020	In vitro vs 13 WHO N. gonorrhoeae strains; HeLa cell adhesion assay	Chitosan nanoparticles	Drug-free chitosan NPs (intrinsic antimicrobial)	Broad antigonococcal activity (MIC90 0.16–0.31 mg/mL) and reduced gonococcal adhesion to HeLa cells; no ex vivo or in vivo mucosa data reported
Maestrelli <i>et al.</i> , 2018	Ex vivo porcine vaginal mucosa (mucoadhesion); in vitro microbiology vs E. coli	Microspheres	Cefixime	Mucoadhesion/permanence >2 h; entrapment ↑ with loading; release rate correlated with E. coli viability reduction
Campaña-Seoane et al. (2019)	Rat PK study (in vivo)	Mucoadhesive emulsions	Ciprofloxacin water-in-silicone emulsion	Long vaginal residence; measurable ciprofloxacin in uterus & ovary up to 24 h after a single intravaginal dose
Akil <i>et al.</i> , 2014; Li et al. 2019	Ex vivo human ecto/endo-cervical tissue explants; Pigtailed macaque PK + ex vivo tests	Films	Dapivirine + Tenofovir; Dapivirine + Levonorgestrel	↑ DPV tissue accumulation with TFV codelivery; LNG plasma ↑, DPV clearance ↓; evidence of dual-indication advantage
Kim et al. 2017	In vitro release in vaginal fluid simulant	Membranes (pH-responsive)	ARVs / siRNA model nanoparticles	Triggered release at elevated pH (~pH 7): minimal release at pH 4.5, ~60% nanoparticle release at pH 7 over 24 h; biocompatible
Ensign <i>et al.</i> , 2012	In vitro mucus models; mouse HSV challenge model (in vivo)	Nanoparticles (mucus-penetrating, PEGylated)	Antivirals / biologics	Improved mucus penetration; ↑ vaginal retention; protection against HSV infection in mice.
Calvo et al. 2019; Salah et al. 2018	In vitro (Candida albicans); In vitro; rat vaginal candidiasis model (in vivo)	Azole Films/Gels	Tioconazole chitosan-HPMC films; Miconazole microsphere gels	Strong antifungal activity; modulated release; efficacy confirmed in rats.
Nave et al. 2019	In vitro release, preclinical (monkey) PK, early clinical PK/PD	Intravaginal rings	Anastrozole + Levonorgestrel	Multi-drug IVR platform demonstrated sustained release and no DDI between ATZ and LNG in a Phase 2 PK study—illustrates platform versatility

END OF SECOND SECTION



OVERVIEW OF USER AND PARTNER PREFERENCES

1. What research is available on user preferences?
2. How do these preferences influence decision-making?



PERSPECTIVES OF VAGINAL DRUG PRODUCTS



GENERAL PERSPECTIVES			
Vaginal Rings	Long-acting protection Discrete Reduced dosing frequency ¹		Hygiene concerns Partner comfort during sex
Vaginal Tablets & Pessaries	Dispersibility Discreetness Ease of use Portability	Muco-adhesion	
Vaginal Gels	Lubrication Control during sex Cream color preferred ²	Stickiness Leakage Odor ² Viscosity (thickness)	Messy, inconvenient, short-acting
Films and Multipurpose Prevention Technologies	Cap shaped films preferred ³ MPTs favored for dual purpose		Square shape of films least liked ³

¹[Atujuna et al, 2018](#)

²[Joglekar et al 2007](#)

³[Laborde ND et al, 2018](#)

DIRECT USER PERSPECTIVES



DIRECT USER PERSPECTIVES		
Core Preferences	Desired long protection, Discretion, Peace of mind. Invisibility Autonomy	Sexual independence was also stigmatized in some cases
Sexual activity context	Enhanced sexual pleasure	Relationship safety, Risk of intimate partner violence (IPV), Partner trust.
Overall experiences	Lubrication Ease of insertion	Odor Excess lubrication Partner disapproval

¹[Duby et al, 2017](#)

²[Laborde ND et al, 2018](#)

PARTNER PERSPECTIVES



PARTNER PERSPECTIVES			
Mixed reactions	Protection Pleasure enhancing	Mixed support Altered vaginal stage, e.g wetness had mixed reviews	Partner discomfort led to demands for removal.
Influence on adherence	Partner acceptance increased willingness to use product.		Negative reactions (discomfort, suspicion, or IPV) deterred adherence.
Disclosure	Discreetness favored for those wanting to keep a secret.	Varied perspectives on disclosure to partners	Disclosure was strategic – either to avoid suspicion or failure to disclose for fear of IPV.

¹[Duby et al, 2017](#)

²[Laborde ND et al, 2018](#)

SOCIETAL PERSPECTIVES



SOCIETAL PERSPECTIVES		
Cultural and relational context	Products associated with sexual pleasure for men (tightening, dryness, heat) were highly valued¹. Some women prized independent use	Women's comfort often deprioritized². Some women rejected products due to associations with promiscuity or deceit.
HIV related Stigma		Partner disapproval; fear of stigma if seen accessing HIV services to access microbicides or vaginal products³
Fear, Intimate Partner Violence and Safety		Women sometimes discontinued use due to threats, conflict, or violence tied to partner discovery.

¹[Duby et al, 2017](#)

²[Laborde ND et al, 2018](#)

³[Atujuna et al, 2018](#)

DECISION MAKING FACTORS



Acceptability → Satisfaction → Adherence → Continuation

Product Attributes & Clinical Effectiveness

Vaginal drugs and product attributes from both a pharmaceutical and user perspective influenced product uptake & **acceptability** (odor, protective effect).



Discretion, Autonomy & Empowerment

Users focus on discretion, autonomy, and **satisfaction** influenced use of product (ease of insertion, comfort, control).



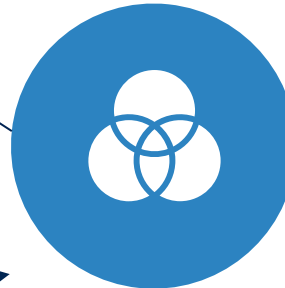
Partner Dynamics and Relational Safety

Emphasis on the partner's sexual experience, approval and trust influenced adherence to the product.(fear of discovery)



Social, Cultural and Economic Context

Stigma, peer and provider influence, economic dependence and affordability, significantly shaped **continued** use of the product.



SPOTLIGHT ON SOUTH AFRICA



PREFERRED PLATFORMS

Vaginal Ring & HIV Vaccine: long protection, discretion, and reduced dosing frequency.

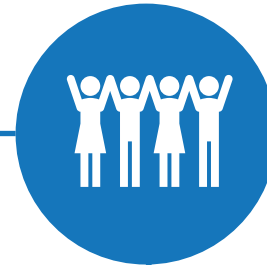
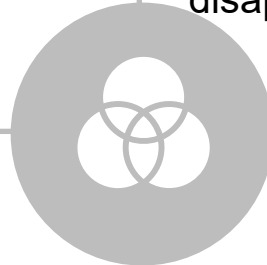
Oral Capsule > Vaginal Spray: sprays seen as messy, smelly, difficult to use



MOTIVATIONS & BARRIERS

Motivations: Peace of mind, autonomy, HIV protection, discreet use, and low daily burden.

Barriers: Fear of partner violence, abandonment, accusations of infidelity, or disapproval.



DECISION MAKING

High perceived benefits - protection
Peer influence
Accessibility
Affordability



“I noticed a difference before I had the ring and after I had the ring.”¹

‘I am not going to have sex with you and I am not going to give you any of my money because you are using drugs that I do not understand.’

PARTNER & SOCIETAL PERSPECTIVES

Varied Reactions: Ranged from supportive to opposed, often shaped by misconceptions (illness, promiscuity, infertility, “witchcraft”)².

Negative Responses: Some men reported discomfort during sex, complaints of smell, or used opposition as control.

Trust, Awareness & Disclosure: varied



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RELATIONSHIP OUTCOMES

Conflict & Violence patterns: Product use became a source of quarrels, mistrust, jealousy, or accusations of adultery.

Supportive outcomes: Disclosure and male partner involvement sometimes fostered cooperation

Sexual experience : varied

¹Laborde ND et al, 2018

²Hartmann et al, 2019

FACILITATORS AND BARRIERS TO PRODUCT USE



FACILITATORS



Long term protection; discreet use, no need for partner negotiation; protection during unplanned or forced sex; female control.



Fewer systemic side effects and effectiveness.



Comfort, ease of applicator use, similarity to natural secretions, discretion with partners, minimal leakage



Autonomy, empowerment and minimal interference with sexual activity.

BARRIERS



Product-related barriers: user comfort during use, and retention/adherence issues, including leakage, odor, irritation, insertion/removal difficulty,



Partner barriers: interference with sex or menses, and the need for repeated dosing or risk of detection, disapproval, violence.



Socio-economic barriers – access, affordability, stigma

USER PERSPECTIVES EVIDENCE



AUTHOR, YEAR	EVIDENCE TYPE	PERSPECTIVE	THEMES
Duby et al 2017 - <i>Achieving the optimal vaginal state: using vaginal products and study gels in Uganda, Zimbabwe, and South Africa.</i>	Qualitative research – Focus Group Discussions (FGDs) & Semi-structured interviews	Direct users - findings from the VOICE-D/MTN-003D study with women from Zimbabwe, Uganda and South Africa, previously enrolled in the VOICE/MTN-003 trial	The perceived positive effects of the gel on women's libido was described as beneficial for the maintenance of sexual relationships, enhancing male partner sexual satisfaction. Gel use resulted in: 1) Lubrication – positive aspect but negative if excessive as it would lead to unwanted disclosure/ IPV 2) Tightening – mixed reviews 3) Drying – gel lubrication was short lived
Laborde et al 2018 - <i>Impact of the Dapivirine Vaginal Ring on Sexual Experiences and Intimate Partnerships of Women in an HIV Prevention Clinical Trial: Managing Ring Detection and Hot Sex.</i>	Qualitative data - In depth interviews and FGDs	Direct users – women participants' sexual experiences while wearing the ring during MTN-020/ASPIRE were analyzed.	Overall, their main impression was that sex was not impacted by the ring. However, the data suggested that a woman's primary concerns in this regard were: (1) threat of discovery, or making sure her partner did not accidentally discover the ring; (2) creating hot sex and maintaining male pleasure; and (3) her own experience of the ring.
Morar et al 2023 - <i>Male partner opinions of the dapivirine vaginal ring used during an open-label extension HIV prevention trial in KwaZulu-Natal, South Africa</i>	Qualitative analysis FGDs	Partner perspectives - four focus group discussions with 18 male partners of phase III trial participants at two sites in KwaZulu-Natal, South Africa.	Most (97%, n=17) male partners were supportive of ring use by their partners. 1) Rural male partners' greater preference for ring use disclosure 2) Assertion that male partners were supportive of the ring, research, and study procedures but they wanted to be actively engaged; 3) Several male partners remained concerned that the ring would empower women to have more sexual freedom.
Laborde et al 2018 - <i>Perceptions of the "Fabric" – An exploratory study of a novel multi-purpose technology among women in Sub Saharan Africa</i>	FGDs - in South Africa, Uganda & Zimbabwe, women who had used vaginal products in previous trials.	General perspectives - Participants asked to feel a sample of electrospun nanofiber (the fabric), see how it dissolves, and give feedback on shape, size and other attributes & compare the fabric to vaginal gel and film.	Women generally reacted positively to the idea of multipurpose technologies, highlighting the utility of having a single product to prevent both HIV and pregnancy. 1) Liked the capped tube shape best, followed by the circle, and the square least, due to ease of insertion and they did not like the hard edges of the square 2) Preferred the smaller size of the fabric prototypes 3) Prefer a product that would last for a week or longer over a shorter acting product. 4) Preferred the product to dissolve as quickly as possible to get immediate protection and to avoid detection by male partners.

END OF THIRD SECTION



GAPS IDENTIFIED

01

Limited insights from many LMIC settings, most studies were from India & South Africa

02

Limited studies assessing pharmacokinetics (including bioavailability), microbiome, and biomarkers

03

Short follow-up horizons, especially for novel interventions

04

Limited studies focusing on user or male partner perspectives



FUTURE OPPORTUNITIES

01

Conduct studies in other LMICs to obtain a diversity of perspectives across various settings

02

Integrate microbiome and host immune profiling to illuminate mechanisms, support personalized approaches, and guide product optimization

03

Advance mucoadhesive, non-antibiotic, natural compound–based formulations, and MPTs

04

Prioritize acceptability and real-world implementation, co-designing with communities

05

Include male partner perspectives and engagement to improve acceptability

06

Expand long-term evaluation and value chain integration



THANK YOU



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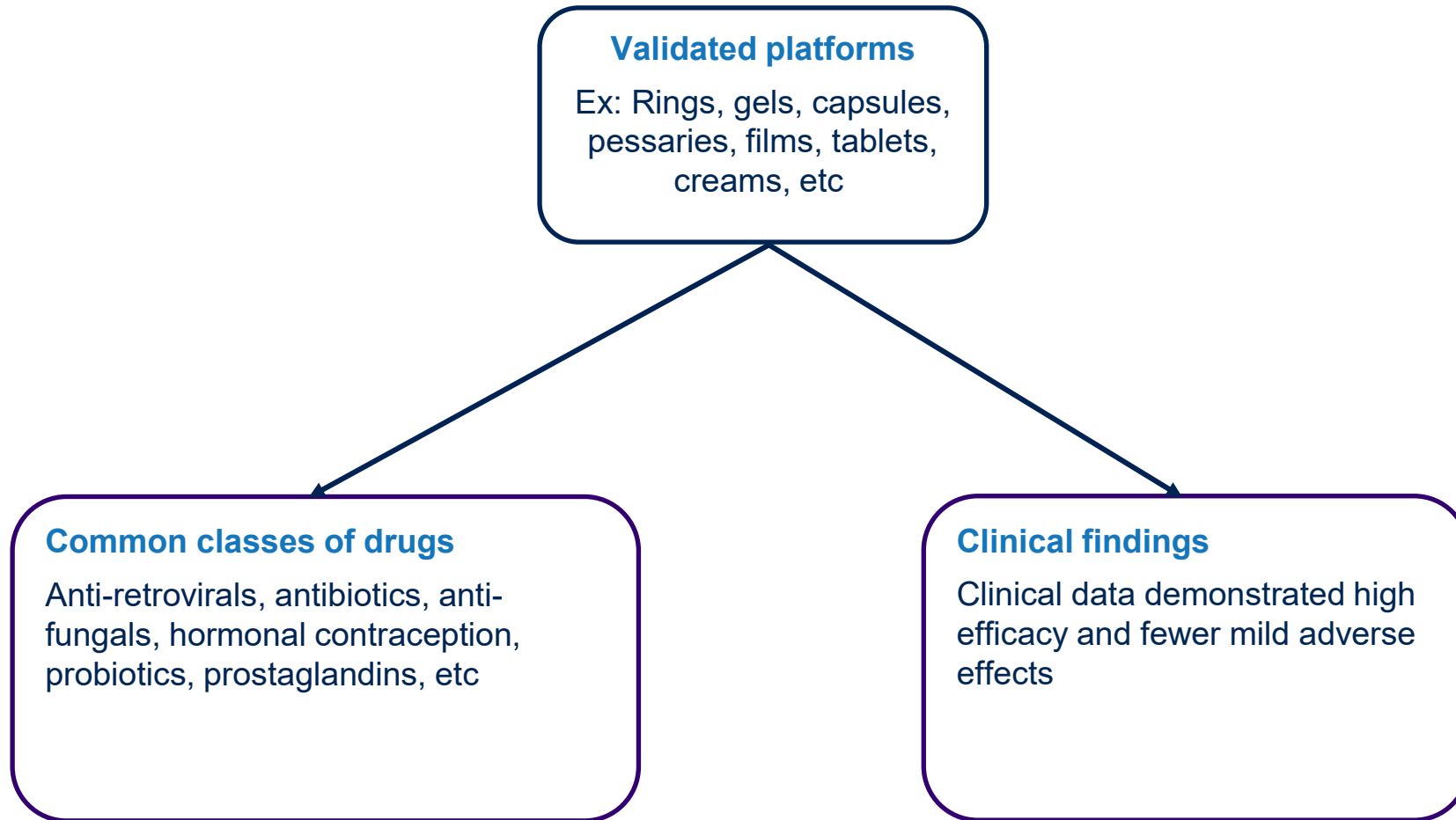
APPENDIX

Impact on Vaginal Microbiome

Summary Table

Class	Drugs / Products	Typical Platforms	Effect (summary)	Key Gaps / Limitations
Antibiotics	Metronidazole, Clindamycin, Ornidazole, Secnidazole	Vaginal gel, cream, pessary, ovule	Restorative (↓ BV, ↓ Nugent, ↑ Lactobacillus short-term)	High recurrence; limited long-term microbiome data
Probiotics / LBPs	Lactin-V (L. crispatus), RepHresh® Pro-B®, EcoVag, Gynophilus	Vaginal capsule, tablet, gel, powder applicator	Restorative (↑ Lactobacillus, ↓ BV recurrence when colonized), Lactin-V showed longer term colonization of L. crispatus	Colonization variable; durability not established
Hormones	Estradiol, Estring®, NuvaRing® (etonogestrel+EE)	Intravaginal rings	Restorative (some ↑ Lactobacillus)	Few RCTs; microbiome endpoints inconsistently measured
Antiretroviral microbicides	Dapivirine vaginal ring	Intravaginal rings	Neutral (no significant disruption)	Most trials not designed for microbiome outcomes
Antifungals	Nystatin + Iodoquinol, Fluconazole (limited data)	Vaginal tablets/ovules	Restorative (return to healthy flora in BV/Candida studies)	Sparse microbiome sequencing; mostly Candida endpoints
Acidifiers / pH modulators	Lactic acid, sucrose gel; nutraceuticals (pea protein, grape seed extract)	Vaginal gels, tablets	Mixed (lactic acid restorative; some nutraceuticals disruptive)	Limited/experimental; mechanisms unclear

SUMMARY OF RESEARCH AND DEVELOPMENT



Regulatory Approvals



- Most of the active drugs tested in the trials have regulatory approval by FDA, EMA or WHO PQ
- However, most of the delivery platforms do not have approval for vaginal delivery and therefore studies were testing them to apply for approval

Other platforms

Niosomes, topical agent (non-specified), brachtherapy, creams, films, hydrogel, IUD, liposomes, nanocapsules, nanofibers, non-woven vaginal delivery device, patch, pessary, rosehip oil, sponge, suppository, suspension, tampons, Thixotropic mixed lipid nanoconstructs(MLNCs), vaginal applicator, vaginal microbiota transplantation

Other drugs

Antidiabetic(1), vaccine(1), sucrose(1), spermicide(1), sildenafil citrate(1), sesame seed oil(1), radiation(1), prostaglandins(2), PP/Gs/La(1), phytochemical(1), nitrate(1), nanomedicine(1), immunomodulator(1), chamomile(1), dopamine(1), anti-viral(1)

Summary on User and Partner Preferences

User Perspectives	Acceptability hinges on balancing discretion, dosing convenience, and sensory attributes (odorless, non-leaky, easy insertion, unnoticeable during sex). Many changed preferences after use, indicating that actual product experience (comfort, ease of insertion, lack of interference with daily life) outweighed theoretical preferences.
Partner Perspectives	Male perceptions act as a gatekeeper to sustained use; partner education and engagement could improve acceptance and adherence. Acceptability is not just pharmacological, it is embedded in cultural norms, gender power dynamics, and safety considerations.

Acceptability → Satisfaction → Adherence → Continuation (demonstrated in multiple studies).

Systemic Effects & Comparators



- Route/formulation comparisons:
 - Vaginal vs oral metronidazole/clindamycin (systemic exposure far lower vaginally)
 - Vaginal vs oral/topical antifungals (azole suppositories show negligible systemic vs oral fluconazole)
- Device vs systemic contraceptives:
 - NuvaRing/Annovera vs combined oral contraceptives (COCs) and contraceptive patch (lower systemic EE exposure with rings)
- Prevention platforms:
 - Dapivirine rings vs oral PrEP (systemic ARV levels markedly lower with rings, reducing systemic toxicity risk).
 - Tenofovir vaginal gel vs oral TDF/FTC PrEP (minimal plasma TFV, efficacy tied to genital levels)
- Hormonal vaginal estrogen vs systemic HRT:
 - Low-dose vaginal estradiol yields negligible systemic estradiol compared to oral/transdermal systemic hormone therapy.
- Placebo/vehicle arms:
 - Gel/film/ring placebo comparators assessed for systemic absorption (none expected), with AEs and labs benchmarked to active arms.

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