Microbicide R&D to **A**dvance HIV Prevention **T**echnologies through **R**esponsive **I**nnovation and e**X**cellence (MATRIX)

R&D Landscape Review 4

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MATRIX
Advancing R&D of Innovative HIV Prevention Products for Women

Abbreviations and acronyms

AECOM	Albert Einstein College of Medicine
ACV	Acyclovir
ATV	Atazanavir
BIC	Bictegravir
bnAB	Broad neutralizing antibodies
BMGF	Bill and Melinda Gates Foundation
mCV-N	modified Cyanovirin-N
CAB	Cabotegravir
CGW	Cis-gender women
CP	Critical Path
CT	Clinical Trial
DFCI	Dana Farber Cancer Institute
DDS	Drug delivery system
DLG	Dolutegravir
DPV	Dapivirine
DP	Dual Purpose
DPP	Dual prevention pill
DVR	Darunavir
EE	Ethinyl estradiol
ENG/ETG	Etonogestrel
EVA	Ethyl Vinyl Acetate
EVG	Elvitegravir
EFV	Efavirenz
GC	Gonorrhea
GRFT	Griffithsin
HCA	Human contraceptive antibodies
HMRI	Houston Methodist Research Institute
HPV	Human Papilloma Virus
HR	Hazard ratio
HSV	Herpes Simplex Virus
ISFI	In situ forming implants
IM	Intra-muscular
ISL	Islatravir
INSTI	Integrase Strand Transfer Inhibitor
IV	Intravenous
LEN	Lenacapavir
LNG	Levonorgestrel

MAP	Microarray Patch
MIT	Massachusetts Institute of Technology
MGT	Male genital tract
MPT	Multipurpose Prevention Technology
NIH	National Institutes of Health
NLC	Nanostructured lipid carrier
NHP	Non-human primates
OD	On demand
Rx	Treatment
PC	Population Council
PCL	Polycaprolactone
PEO	Polyethylene oxide
PGSU	Poly(glycerol sebacate) urethane
PI	Principal Investigator
PrEP	Pre-exposure Prophylaxis
PREG	Pregnancy
PVA	Polyvinyl acetate
Px	Prevention
PU	polyurethane
QGRFT	Q-Griffithsin
QUB	Queen's University Belfast
RAL	Raltegravir
R&D	Research and Development
RPV	Rilpivirine
Rx	Treatment
SC	Sub-cutaneous
ZA	Zinc acetate
ZDV	Zidovudine

Executive Summary

MATRIX Prime is monitoring R&D activities in the HIV prevention and microbicide[1] research space by conducting desktop review of funded R&D on a biannual basis, and by convening a bi-yearly session with other funding groups (i.e., industry, NIH, BMGF), to gather information regarding product development support by other donors and to ensure that changes in the field which could impact MATRIX product development will be considered. Indeed, ongoing R&D research may have a direct or indirect impact on MATRIX Critical Path (CP) products' feasibility or futility.

Our **goals** with these activities are to ensure that Critical Path (CP) R&D work in MATRIX ***complements*** other prevention work in the field and does not have significant overlap with work being conducted by others. One of the key activities for this is a **desktop review of funded R&D prevention activities and publications** on a biannual basis, as described below.

All updates and changes to the scope of this review and the appendix tables are in red text. This review only includes R&D related to bnABs, or monoclonal antibodies for prevention, in so far as the drug delivery system (e.g., ring, film) is relevant for delivery of other types of APIs. This review does not include RNA approaches or HIV vaccines.

The Procedures for desktop review include monitoring:

- Publications/abstracts reviews via PubMed, Bio and Medrxiv, Int'l conferences (i.e., CROI 2023), listserves (i.e., AVAC, Choice agenda, AIDSmap; Fierce pharma) and database review (i.e., AVAC, PrEP watch, IMPT),
- Published reviews, reports and media releases on relevant topics (i.e., HIV PrEP, microbicides, MPTs),
- Current NIH-funded projects (via NIH RePorter),
- Review of funded clinical trials via various websites: clinicaltrials.gov (US), EU clinical trials register (EU) and Wellcome trust funded grants database.

This **fourth desktop review,** for the second half of 2023 includes publications and funded projects identified between mid-June[2] and December 31, 2023, focusing on HIV Prevention/ PrEP, microbicides, and Multi-Purpose Prevention Technologies[3] (MPTs) that include an HIV indication Note: current terminology in MATRIX uses the term "dual purpose" (DP) products, which specifically includes a subset of MPTs with an HIV prevention indication plus a second indication for contraception pursued under MATRIX funding.

Modification from previous reports: We have added a new table (Table 1) in the appendix, with the findings resulting from the clinical trials (CT) databases searched. **Twenty-one CT** were

[1] Microbicide: a drug, chemical, or other substance used to kill microorganisms. The term is used specifically for substances that prevent or reduce the transmission of sexually transmitted diseases, such as HIV.

[2] Because of the delay in posting of new publications on PubMED, this review cycle was started on June 20, 2023, so there would be no missed publications between the first and second half of the year.

[3] Multipurpose Prevention Technology (MPT): a product designed to simultaneously protect against multiple sexual and reproductive health issues, such as HIV and other sexually transmitted infections and unintended pregnancy. A variety of MPT products are under development, including vaginal rings, vaginal and rectal gels, oral pills, implants, and long-acting injectables. Definitions derived from NIH: https://clinicalinfo.hiv.gov/en/glossary

found (active, completed or withdrawn). The products associated with these CTs are also reported in the product tables (2 and 3) in the appendix. Thus, the total number of products/projects summarized below, are only those tallied in the appendix tables 2 and 3.

Key findings from the landscape review (see also tables 1, 2a/3b and 3a/3b in the Appendix):

Summary table of projects identified in landscape review.

Type of projects	N	Active/Ongoing	Currently not active/unknown
HIV Prevention only	41	28*	13
MPTs (including DP products)	34	20**	14
TOTAL	75	48	27

(*) 8 new entries in landscape review # 4; (**) 3 new entries in landscape review # 4

As shown in the summary table above, there are a total of **41 HIV prevention projects**, of which 13 projects are completed, on hold/stopped or of unknown status (5 projects stopped because of safety signal with the API(s) or API development abandoned); and **28 are actively ongoing projects.** These include **eight new entries**:

- Three of the new entries were identified through searches in clinical trials databases (for early-stage clinical trials of new Cab-LA formulations, a new INSTI and two new capsid inhibitors developed by ViiV),
- One new entry for a rectal study of the TAF/EVG insert was identified through a plenary presentation at the 2023 HPTN annual meeting, and confirmation through communication with the PD (CONRAD),
- Four entries were identified through searches of recent NIH awards posted in RePorter. These are to develop:
  - a) prodrugs of TFV and FTC formulated for 3 months injections in membrane-wrapped nanoparticles (NPs) that establish cellular depots for sustained maintenance of inhibitory concentrations of ARVs at primary tissue sites of HIV-1 transmission in the female genital tract and rectum (Boston U, PIs: Reinhard and Markus);
  - b) a novel engineering process to generate small size biodegradable implants (1-4 cm long) with high drug content (=< 85 wt%) using approved APIs, for Rx maintenance (but technology is applicable to PrEP; UNC, PI: Benhabbour);
  - c) 6+ months injectables (nanocrystal suspensions) of a new INSTI (XVIR-110), other INSTIs and NRTIs, with a focus on CMC and IND work prior to a FIH trial (SBIRII for the biotech company EXAVIR https://exavirtherapeutics.com)
  - d) One new R01 was awarded to OCIS to continue the work on their implant with TAF and other prodrugs. This is noted in the table but not indicated as a new entry, as it's the continuation of existing R&D work (Table 2b, row 12).

Active HIV prevention projects (N=28):

- 5 topical products: 1 rectal enema, 1 rectal insert, 2 vaginal rings/device, 1 vaginal drug - eluting fibers.
- 23 systemic products: 10 injectables, 7 implants (removable, bioresorbable, refillable, 3D printed), 1 *in situ* forming implant (ISFI), 2 transdermal MAPs, 2 long-acting oral tablets and one trial with a new INSTI by ViiV (DDS unspecified- but assumed to be for systemic dosing).
- Creating prodrugs to increase the duration of extended release of known APIs seems to be a dominant strategy for PDs currently, both in terms of ongoing funding, new funding and publications in the previous 6 months (i.e. XVIR-110 a prodrug of CAB for ultra-long release).

Drugs investigated (see tables and publications) include:

- New capsid inhibitors and INSTI explored in phase I trials by ViiV
- Reformulation and optimization of the CAB-LA injectable to reach 4 months (and eventually 6-month duration) by ViiV.
- Repurposing ARVs approved for treatment (e.g., saquinavir mesylate, bictegravir, lenacapavir). Specifically, several new publications highlight the potency and favorable PK of LEN for PrEP, including from sexual or IV (parenteral) (S)HIV exposure.
- Synthesis of new nucleoside analogs and reformulation of approved NRTIs (e.g., TFV) for improved vaginal mucosal adhesion of topical products.
- New NRTTI MK8527, an unapproved ARVs for prevention (monthly dosing) by Merck, which is currently in a phase II trial.
- The potent NRTTI islatravir (ISL) continues to generate prevention publications and ongoing funded project(s) despite the API having been withdrawn from the prevention development pipeline by Merck. This is likely due to a combination of factors: a) timeline considerations: ongoing or completed projects with ISL continue to generate new publications, and b) ISL may be used as a model drug for R&D purpose, given its potency and physicochemical characteristics. Furthermore, numerous analogs and prodrugs of ISL have been generated and thus, ISL may remain a useful model drug at the preclinical stage of development l.
- Drugamers to more efficiently deliver multiple small molecules/ARVs (row #4 of MPT table).
- D-peptide entry inhibitor (CPT31) proposed as a 3-month injectable, with a completed phase I trial (and funding ongoing until 2023).
- eCD4-Ig: an antibody-like entry inhibitor that closely mimics HIV-1's obligate receptors, proposed as an injectable.
- The lipo-protein LP-98, a HIV fusion inhibitor, formulated as an injection is investigated in a FIH trial in China.
- Broad spectrum antivirals like GRFT was formulated with silk fibroin, to increase muco-adhesion.
- A publication on a new SC injectable formulation with 3 ARVs for treatment was also noted; this nanoparticle platform technology could be extended to prevention, to efficiently combine and deliver several drugs with divergent physicochemical properties.

This report includes a total of **34 MPT** (inclusive of DP products) **projects**, of which 14 projects are completed, on hold/stopped or of unknown status (5 projects completed, 5 projects of unknown status and 4 projects on hold/seeking funding); and **20 are actively ongoing projects. Three new entries** were identified since July 1, 2023, all three were through publications (article or conference abstracts) by Dr. Karl Malcolm's laboratory at QUB: 2 vaginal rings (one ring for HIV and BV with DPV+ Metronidazole, one ring for HIV and non-hormonal contraception with DPV, Cu, Zinc) and one 2-monthly injection (with Depo Provera+ RPV).

Aside from HIV, the most current other indication among the active MPT projects is to prevent unplanned pregnancy (18 projects); Herpes Simplex Virus (HSV) prevention is the next most common indication (3 projects), followed by anti-GC indication (2 projects), BV (2 projects), CT (2 projects) and anti- Human Papilloma Virus (HPV) indication (1 project).

Active MPT projects (N=20):

- 14 topical products: 1 intra-uterine system (IUS), 1 fast dissolving insert (FDI), 2 vaginal films, 10 vaginal rings.
- 6 systemic products: 2 injectables, 1 implant refillable, 1 in situ forming implant (ISFI), and 2 daily oral tablets (or DPP).
- The drug delivery forms and groups working on MPTs are similar to those listed for the HIV

prevention indication only. Notably, there is a dominance of rings as DDS for MPTs, compared to a dominance of injectables for single indication products.

- Drugs investigated include both ARVs (e.g., DPV, TFV/TDF/TAF, ISL, DLG) and non-ARV (e.g., Q-GRFT, monoclonal antibodies for HIV prevention), and both hormonal (i.e., LNG, EE) and non-hormonal (e.g., antibodies, copper, zinc) for the contraceptive drugs. New additions include Metronidazole (for BV) and Depo-Provera (for contraception).

Publications/presentations: **40** recent (second half of 2023) publications or presentations were identified and are listed below, starting in section 3. They include publications on APIs/ drugs, new formulations, drug delivery systems, preclinical and clinical research, and reviews.

- This landscape review was dominated by papers and/or research presentations focusing on **preclinical and clinical efficacy of several LA-DDS**. This included:
  a) the efficacy of LEN injection in NHP for sexual or IV exposure,
  b) the flexibility of various body location for LEN injections, allowing users to choose where to be injected,
  c) the revised estimate of CAB-LA efficacy in different population and post-blinded CT phase, along with ex-vivo efficacy for penile infection,
  d) reassessment (upwards) of the efficacy of the DPV ring in a secondary analysis of the ASPIRE trial,
  e) updated estimates of oral PrEP efficacy in CGW with imperfect adherence,
  f) efficacy of ISL implants in NHP models. Notably, a refillable nanofluidic implant achieved 20 months duration of ISL release.
- Another dominant topic was that of **MPTs and multidrug formulations**, with multiple publications on formulations of multiple drugs in rings, implants, ISFI and injectables. One paper also described the TFV film as an MPT (for HIV and HSV2) and another, the formulation of 3 different ARVs with different physicochemical characteristics, in a single injection for treatment.
- New clinical stage publications included that of the DPV ring, shown to be safe and acceptable in third trimester pregnant people and in AGYW.
- Publications directly relevant to MATRIX CP projects include one presentation (by ViiV on their R&D plan) indicating they are developing a 4month CAB-LA injection dosage (anticipated to be approved by 2026) and a 6-month injection (anticipated to be approved in 2030). The TAF/EVG FDI is also being evaluated in a multidose study as a rectal on-demand product.

Eight new relevant **media releases, announcements or reports** were identified:

- Exavir therapeutics press release (August 22, 2023) for the NIAID SBIRII award to advance the ultra-long INSTI XVIR-110 (a prodrug of CAB) into clinical testing.
- Three press releases, were related to new APIs or formulations, one from JHU for a hydrogel injectable to deliver Lamivudine for HIV and HBV, one for the 3-drug combination in an injection to treat HIV, and one for ViiV with their clinical program to extend the duration of CAB-LA and investigate new ultralong prevention products.
- There were 2 press release indicating that the EU approved Apretude, and announcing new trials to evaluate LEN injections for prevention.
- The Population Council announced that the DPV ring is approved in 11 African countries, and they received a new 15-month grant to support the market introduction of the Dapivirine Vaginal Ring in Rwanda and Botswana.

Conclusions:

- A total of 75 projects have been identified, of which **48 are actively ongoing (28 HIV prevention + 20 MPT projects**). Of these, **11 were new project entries** since the landscape review 3 (submitted on July 12, 2023), with 4 being newly funded projects by NIAID (2 implant, 2 injectables). All newly funded projects/grants are highlighted in red and placed at the bottom of the tables in the appendix.
- Searching the **clinical trial databases** (a new activity) yielded key new insights in new products at the clinical stage of evaluation. This included both Pharma funded trials and non-pharma trials.
- This latest landscape review highlights key progress for MPTs and long-acting PrEP products, including new funding and several key publications/presentations demonstrating pre-clinical safety and efficacy and increase options for body location of LEN injections, updated efficacy estimates of several approved PrEP strategies (ring, oral PrEP, CAB-LA) and various strategies to extend duration of protection for PrEP through improved formulations, pro-drugging of existing APIs and improved platform technologies.
- **Directly informing the MATRIX CP projects**, one new clinical trial for rectal use of the TAF/EVG FDI was initiated in the US; several clinical trials (corroborated by a presentation from ViiV to shareholders) indicate that ViiV is significantly investing in extending their LA-prevention strategies through improved formulation of Cab-LA for longer duration of protection, and evaluation of new INSTI and capsid inhibitors. One publication from UNC presents the development of an MPT IVR releasing multiple drugs for HIV and pregnancy prevention (ENG, EE and ISL), using continuous liquid interface production (CLIP™) to fabricate the MPT IVR. This paper is directly informing the development of the MPT IVR with DPV, LNG and Pritelivir, under MATRIX UNC Seed Grant, awarded to the same group.
- Contrary to previous landscape reviews, our most recent findings do result in overlap with CP products in MATRIX. According to a report shared with shareholders, ViiV is extending the duration of Cab-LA through reformulation to a q4M, with expected approval in 2026, and plan to further extend to Q6M by 2030. This is a significant developmental advance for LA CAB which may impact the relative potential impact of the CAB products which are part of the MATRIX CP portfolio as game changers. With the extended duration already achieved for CAB-LA (result pending at CROI 2024), in MATRIX, LA systemic CP products should focus on extending duration of protection beyond 6 months and/or focus on a DPP, providing additional benefits compared to HIV prevention alone. New MPT products were also found, but they are mostly very early in the R&D path, and none directly challenges the DPPs being developed in MATRIX. **Thus, this analysis shows <u>possible significant overlap</u> with current MATRIX critical path products and suggests the need for MATRIX to expand the targeted duration of current CP LA-products, pivot to alternative APIs or prodrugs of existing APIs, or focus on alternative long-acting CAB products that confer additional/ancillary advantages compared to a single indication injectable lasting 4 or 6 months.**
- The fourth call with Pharma and funders will be held in January 2024.
- Next landscape review will be conducted in June 2024.

3. **<u>Review of published literature: July 1-Dec 31, 2023</u>**

Each citation is followed by a link to the publication in PubMed (when available), and a brief note about the goal or relevance of the publication**.** Authors names are bolded if they are one of the MATRIX PDs.

- No notes were written for the review papers and abstracts/presentations from conferences.

- Publications supersede presentations at conferences (so only publications are listed when both are available).
- Publications that are relevant for a specific project entry in the Appendix tables are also linked in the far-right cell of the Appendix tables.

3a. APIs, ARVs and formulation work (sorted by drug class and alphabetical order of first authors' last name).

Capsid inhibitors:

1. Bekerman E, Yant SR, VanderVeen L, Hansen D, Lu B, Rowe W, Wang K, Callebaut C. Long-acting lenacapavir acts as an effective preexposure prophylaxis in a rectal SHIV challenge macaque model. J Clin Invest. 2023 Aug 15;133(16):e167818. doi: 10.1172/JCI167818. PMID: 37384413; PMC10425210. https://pubmed.ncbi.nlm.nih.gov/37384413/
   LEN-treated macaques were challenged with high-dose SHIV 7 weeks after drug administration, and the majority remained protected from infection. This experiment demonstrates effective SHIV prophylaxis in a stringent macaque model at clinically relevant LEN exposures.
2. Subramanian R, Tang J, Zheng J, Lu B, Wang K, Yant SR, Stepan GJ, Mulato A, Yu H, Schroeder S, Shaik N, Singh R, Wolckenhauer S, Chester A, Tse WC, Chiu A, Rhee M, Cihlar T, Rowe W, Smith BJ. Lenacapavir: A Novel, Potent, and Selective First-in-Class Inhibitor of HIV-1 Capsid Function Exhibits Optimal Pharmacokinetic Properties for a Long-Acting Injectable Antiretroviral Agent. Mol Pharm. 2023 Dec 4;20(12):6213-6225. doi: 10.1021/acs.molpharmaceut.3c00626. Epub 2023 Nov 2. PMID: 37917742; PMC10698746. https://pubmed.ncbi.nlm.nih.gov/37917742/
   This article describes the formulation and PK of Lenacapavir (LEN), a picomolar first-in-class capsid inhibitor of human immunodeficiency virus type 1 (HIV-1) with a multistage mechanism of action, and no known cross resistance to other existing antiretroviral (ARV) drug classes.
3. Swanstrom AE, Gorelick RJ, Welker JL, Schmidt F, Lu B, Wang K, Rowe W, Breed MW, Killoran KE, Kramer JA, Donohue D, Roser JD, Bieniasz PD, Hatziioannou T, Pyle C, Thomas JA, Trubey CM, Zheng J, Blair W, Yant SR, Lifson JD, Del Prete GQ. Long-acting lenacapavir protects macaques against intravenous challenge with simian-tropic HIV. EBioMedicine. 2023 Sep;95:104764. doi: 10.1016/j.ebiom.2023.104764. Epub 2023 Aug 23. PMID: 37625266; PMC10470178. https://pubmed.ncbi.nlm.nih.gov/37625266/
   This article shows preclinical efficacy of LEN SC injections against high-dose intravenous challenge with SHIV in the NHP model.

INSTI:

4. Tiboni M, Cespi M, Casettari L, Palmieri GF, Perinelli DR, Bonacucina G. Hydrogel containing mPEG-PLGA nanoparticles for the vaginal delivery of saquinavir mesylate against HIV infection. Eur J Pharm Sci. 2023 Dec 1;191:106599. doi: 10.1016/j.ejps.2023.106599. Epub 2023 Sep 27. PMID: 37774955. https://pubmed.ncbi.nlm.nih.gov/37774955/
   PEG-PLGA nanoparticles, loaded with the INSTI saquinavir mesylate (SQV), were incorporated inside carbopol (C974)-based hydrogel as a vaginally administered prevention or therapeutic treatment for HIV infection
5. Zhang C, Vora LK, Tekko IA, Volpe-Zanutto F, Peng K, Paredes AJ, McCarthy HO, Donnelly RF. Development of dissolving microneedles for intradermal delivery of the long-acting antiretroviral drug bictegravir. Int J Pharm. 2023 Jul 25;642:123108. doi:

10.1016/j.ijpharm.2023.123108. Epub 2023 Jun 8. PMID: 37301241. https://pubmed.ncbi.nlm.nih.gov/37301241/
This describes the formulation of novel bilayer dissolving microneedles (MNs) for the intradermal delivery of long-acting nanosuspensions of bictegravir (BIC) for potential HIV treatment and prevention. MNs were able to intradermally deliver 31% of drug loading from nanosuspension-loaded MNs in the form of drug depots. Release was sustained for 4 weeks in rats.

NRTI:

6. Avlani D, Kumar A, H N S. Development of Dispersible Vaginal Tablets of Tenofovir Loaded Mucoadhesive Chitosan Microparticles for Anti-HIV Pre-Exposure Prophylaxis. Mol Pharm. 2023 Oct 2;20(10):5006-5018. doi: 10.1021/acs.molpharmaceut.3c00288. Epub 2023 Sep 1. PMID: 37656937. https://pubmed.ncbi.nlm.nih.gov/37656937/
   A novel formulation of TDF-loaded bioadhesive chitosan micrparticles was developed and incorporated into vaginal tablets for PrEP.
7. Hou J, Peng Y, Liu B, Zhang Q, Wang JH, Yu W, Chang J. 4'-Ethynyl-2'-deoxy-2'-β-fluoro-2-fluoroadenosine: A Highly Potent and Orally Available Clinical Candidate for the Treatment of HIV-1 Infection. J Med Chem. 2023 Aug 24;66(16):11282-11293. doi: 10.1021/acs.jmedchem.3c00761. Epub 2023 Aug 3. PMID: 37535016. https://pubmed.ncbi.nlm.nih.gov/37535016/
   This describes the synthesis of novel nucleoside analogs, with nanomolar potency, low toxicity, potent inhibitory activities on drug resistant and clinical HIV-1 strains and favorable PK profile in rats.

NRTTI:

8. Kovarova M, Wessel SE, Johnson CE, Anderson SV, Cottrell ML, Sykes C, Cohen MS, Garcia JV. EFdA efficiently suppresses HIV replication in the male genital tract and prevents penile HIV acquisition. mBio. 2023 Aug 31;14(4):e0222422. doi: 10.1128/mbio.02224-22. Epub 2023 Jun 12. PMID: 37306625; PMC10470584 https://pubmed.ncbi.nlm.nih.gov/37306625/
   Using BLT humanized mice, this article showed that productive HIV infection occurs throughout the entire male genital track (MGT) and induces a dramatic reduction in human CD4 T cells compromising immune responses in this organ. Treatment with EFdA (ISL) suppressed HIV replication in all tissues of the MGT, restored normal levels of CD4 T cells and was highly efficient at preventing penile transmission.

Other

9. *Lipoproteins:*
   a. Previous preclinical POC paper: Xue J, Chong H, Zhu Y, Zhang J, Tong L, Lu J, Chen T, Cong Z, Wei Q, He Y. Efficient treatment and pre-exposure prophylaxis in rhesus macaques by an HIV fusion-inhibitory lipopeptide. Cell. 2022 Jan 6;185(1):131-144.e18. doi: 10.1016/j.cell.2021.11.032. Epub 2021 Dec 16. PMID: 34919814. https://doi.org/10.1016/j.cell.2021.11.032.
      LP-98 administrated as a pre-exposure prophylaxis (PrEP) provided complete protection against SHIVSF162P3 and SIVmac239 infections in 51 monkeys via intrarectal, intravaginal, or intravenous challenge.
   b. This RCT is studying LP-98 injection in healthy subjects in a first-in-human clinical study (Investigators and sponsor are from China) – to assess safety and dose escalation. https://clinicaltrials.gov/study/NCT05933824

10. *GRFT:*
    a. Guan W, Zhang N, Bains A, Martinez A, LiWang PJ. Sustained Delivery of the Antiviral Protein Griffithsin and Its Adhesion to a Biological Surface by a Silk Fibroin Scaffold. Materials (Basel). 2023 Aug 9;16(16):5547. doi: 10.3390/ma16165547. PMID: 37629837; PMCID: PMC10456748. https://pubmed.ncbi.nlm.nih.gov/37629837/
    Silk fibroin can be formulated with adhesive properties using the nontoxic polymer hydroxypropyl methylcellulose (HPMC) and glycerol, and that the resulting silk scaffold can both adhere to biological surfaces and release GRFT over the course of at least one week. This work advances the possible use of silk fibroin as an anti-viral vaginal film to prevent infection by sexually transmitted viruses, including HIV-1

New formulations for treatment *(applicable to prevention)*:

11. Perazzolo S, Stephen ZR, Eguchi M, Xu X, Delle Fratte R, Collier AC, Melvin AJ, Ho RJY. A novel formulation enabled transformation of 3-HIV drugs tenofovir-lamivudine-dolutegravir from short-acting to long-acting all-in-one injectable. AIDS. 2023 Nov 15;37(14):2131-2136. doi: 10.1097/QAD.0000000000003706. Epub 2023 Aug 24. PMID: 37650755. https://pubmed.ncbi.nlm.nih.gov/37650755/ *Proof of concept study of a SC drug-combination-nanoparticle injectable dosage form (DcNP) for 3 drugs with disparate physico-chemical properties (tenofovir (T), lamivudine (L), and dolutegravir (D)) . In NHP, all drugs exhibited long-acting profiles in plasma with levels that persisted for 4 weeks above predicted viral-effective concentrations for TLD in combination. Furthermore, the higher intracellular PBMC drug levels relative to plasma for all three drugs suggest that the DcNP platform delivers these ARVs into cells with high efficiency.*

3b. HIV and MPT Preclinical studies:

12. Curley, P.; Hobson, J.; Liptrott, N.; Makarov, E.; Al-khouja, A.; Tatham, L.; David, C.; Box, H.; Neary, M.; Sharp, J.; Pertinez, H.; Meyers, D.; Flexner, C.; Freel Meyers, C.; Poluektova, L.; Rannard, S.; Owen, A. Preclinical Evaluation of Long-Acting Emtricitabine Semi-Solid Prodrug Nanoparticle Formulations. Pharmaceutics 2023, 15(7), 1835; https://pubmed.ncbi.nlm.nih.gov/37514020/
    This describes the preclinical assessment (in mice, rats, rabbits) of semi-solid prodrug nanoparticle (SSPN) LA injectable formulations of emtricitabine (FTC). Drug reached LLOQ after 21-28 days (depending on the species). The combined prodrug/SSPN approach can provide a dramatically extended pharmacokinetic half-life across multiple preclinical species. Species differences in renal clearance of FTC mean that longer exposures are likely to be achievable in humans than in preclinical models.
13. Daly, M.; Wong-Sam, A.; Li, L.; Krovi, A.; Gatto, G.; Norton, C.; Luecke, E.; Mrotz, V.; Forero, C.; Cottrell, M.; Schauer, A.; Gary, J.; Nascimento-Seixas, J.; Mitchell, J.; van der Straten, A.; Heneine, W.; García-Lerma, J.; Dobard, C.; Johnson, L. Pharmacokinetic Study of Islatravir and Etonogestrel Implants in Macaques. Pharmaceutics 2023, 15(12), 2676; https://pubmed.ncbi.nlm.nih.gov/38140017/
    This paper shows that biodegradable MPT implants loaded with ISL and ENG are safe and yield sufficient drug levels to achieve prevention targets in NHPs.
14. Gunawardana M, Remedios-Chan M, Sanchez D, Fanter R, Webster S, Webster P, **Moss JA**, Trinh M, Beliveau M, Ramirez CM, Marzinke MA, Kuo J, Gallay PA, **Baum MM**. Preclinical Considerations for Long-acting Delivery of Tenofovir Alafenamide from Subdermal Implants

for HIV Pre-exposure Prophylaxis. Pharm Res. 2023 Jul;40(7):1657-1672. https://pubmed.ncbi.nlm.nih.gov/36418671/
This article compares three animal models (mice, beagle dogs, and merino sheep) for evaluating TAF implant pharmacokinetics (PK), and recommends use of sheep and mice (and NHP), but not dogs for evaluation of TAF implants.

15. Haeck, C. M., Boyd, P., Dimant, N., Barrail-Tran, A., Gouget, H., Le Grand, R., Desjardins, D., & Malcolm, R. K. (2023). Preclinical development and pharmacokinetic assessment in macaques of a multipurpose long-acting injectable suspension containing medroxyprogesterone acetate for contraception and rilpivirine for HIV prevention. *Journal of Drug Delivery Science and Technology*, *85*, Article 104590. https://doi.org/10.1016/j.jddst.2023.104590.
This study describes the formulation and preclinical development of a new MPT product based on a LA- injectable aqueous suspension formulation combining micronized medroxyprogesterone acetate and a rilpivirine nanosuspension. The combination suspension provided sustained vaginal and systemic exposure of both drugs for over 1 month when injected IM.
16. **Patel SK**, Agashe H, Patton DL, Sweeney Y, Beamer MA, Hendrix CW, Hillier SL, **Rohan LC**. Tenofovir vaginal film as a potential MPT product against HIV-1 and HSV-2 acquisition: formulation development and preclinical assessment in non-human primates. Front Reprod Health. 2023 Aug 10;5:1217835. doi: 10.3389/frph.2023.1217835. PMID: 37638127; PMC10449455. https://pubmed.ncbi.nlm.nih.gov/37638127/
This describes the formulation of a quick release, on demand TFV film for HIV and HSV-2 prevention, with promising in vitro efficacy and favorable PK and safety data in NHPs.
17. Pons-Faudoa FP, Di Trani N, Capuani S, Campa-Carranza JN, Nehete B, Sharma S, Shelton KA, Bushman LR, Abdelmawla F, Williams M, Roon L, Nerguizian D, Chua CYX, Ittmann MM, Nichols JE, Kimata JT, Anderson PL, Nehete PN, Arduino RC, Grattoni A. Long-acting refillable nanofluidic implant confers protection against SHIV infection in nonhuman primates. Sci Transl Med. 2023 Jun 28;15(702):eadg2887. doi: 10.1126/scitranslmed.adg2887. Epub 2023 Jun 28. PMID: 37379369. https://pubmed.ncbi.nlm.nih.gov/37379369/
This paper describes a LA subcutaneous nanofluidic implant that can be refilled trans-cutaneously for sustained release of ISL, which achieved constant ISL concentration in PBMC for over 20 months. ISL-eluting implants conferred 100% protection against SHIV in repeated low dose vaginal or rectal challenges in NHPs, with good tolerability.
18. Young IC, Srinivasan P, Shrivastava R, Janusziewicz R, Thorson A, Cottrell ML, Sellers RS, Sykes C, Schauer A, Little D, Kelley K, Kashuba ADM, Katz D, Pyles RB, García-Lerma JG, Vincent KL, Smith J, **Benhabbour SR**. Next generation 3D-printed intravaginal ring for prevention of HIV and unintended pregnancy. Biomaterials. 2023 Oct;301:122260. doi: 10.1016/j.biomaterials.2023.122260. Epub 2023 Aug 3. PMID: 37549505. https://pubmed.ncbi.nlm.nih.gov/37549505/
Using continuous liquid interface production (CLIP™) to fabricate MPT IVRs in a biocompatible silicone-based resin, Etonogestrel (ENG), ethinyl estradiol (EE), and islatravir (ISL) were loaded into the silicone poly(urethane) IVR. ENG/EE/ISL IVR promoted sustained release of drugs for 150 days in vitro and 14 days in sheep with no product-related AEs. Furthermore, ISL IVR in NHP promoted sustained release for 28 days with ISL-triphosphate levels above the established pharmacokinetic benchmark (50-100 fmol/10^6 PBMCs).
19. Young IC, Pallerla A, Cottrell ML, Maturavongsadit P, Prasher A, Shrivastava R, De la Cruz G, Montgomery SA, Schauer A, Sykes C, Kashuba ADM, **Benhabbour SR**. Long-acting

injectable multipurpose prevention technology for prevention of HIV and unplanned pregnancy. J Control Release. 2023 Nov;363:606-620. doi: 10.1016/j.jconrel.2023.10.006. Epub 2023 Oct 12. PMID: 37797892. https://pubmed.ncbi.nlm.nih.gov/37797892/
This article demonstrated the ability to co-formulate antiretrovirals (CAB or DLV) with contraceptives (ENG or MPT) in an ISFI that was well-tolerated with sustained plasma concentrations up to 90 days in mice.

20. Zhao X, Boyd P, Bashi YD, Murphy DJ, McCoy CF, Coulter S, Laverty G, Malcolm RK. Two into one does go: Formulation development of a multipurpose combination vaginal ring releasing dapivirine and metronidazole for prevention of HIV infection and treatment of bacterial vaginosis. Int J Pharm. 2023 Dec 15;648:123572. doi: 10.1016/j.ijpharm.2023.123572. Epub 2023 Nov 4. PMID: 37926178. https://pubmed.ncbi.nlm.nih.gov/37926178/
This preclinical study co-formulated DPV and the antibacterial Metronidazole to treat BV into a silicone elastomer ring with no DDI noted.

3c. Conferences:

21. **IAS Brisbane, AU, 2023:** Cottrell, T. Kinsale[1], L. Li[2], D.F. Cruz[2], C. Norton[2], B. van Horne[1], G. Dobek[3], X. Wang[4], R. Veazey[3], L.M. Johnson: A biodegradable, subcutaneous implant delivery platform to treat HIV for up to 6 months in young children (POSTER TUPEB): https://programme.ias2023.org/Abstract/Abstract/?abstractid=1252
22. **United Kingdom & Ireland Controlled Release Society (UKICRS) 2023**: Xin Shen, Karl Malcolm*, Peter Boyd, Yahya Dallal Bashi, Clare F. McCoy, Xinyu Zhao, Dolores Lamb, Lyann Mitchell, Narender Kumar, Patrick Singer. A multipurpose vaginal ring releasing copper ions, zinc ions and dapivirine for HIV prevention and non-hormonal contraception.https://pure.qub.ac.uk/en/publications/poster-abstract-a-multipurpose-vaginal-ring-releasing-copper-ions
23. **National Contraception Meeting 2023,** Houston Tx: Xin Shen, Peter Boyd, Clare F. McCoy, Yahya Dallal Bashi, Xinyu Zhu, Karl Malcolm. Formulation development of a multipurpose vaginal ring for non-hormonal contraception and HIV prevention. https://pure.qub.ac.uk/en/publications/formulation-development-of-a-multipurpose-vaginal-ring-for-non-ho
24. **ID week conference, October 2023, Poster 1542**. GILEAD assessed various SC body locations for injectable LEN in a Phase I open label, parallel design, single dose, multi cohort study to assess LEN PK and safety when administered at 4 locations (arm, belly, gluteus, thigh). Findings show no safety or PK difference. GILEAD plans to implement user choice in determining which location to receive the injection in HPTN 102, 103 (and some of the other PURPOSE trials, e.g., injection in the thigh for pregnant women in Purpose 1). GILEAD presentation on 12/15/23 during a HPTN102 protocol call.

3d. HIV-PrEP and MPT clinical studies

25. Bunge K, Balkus JE, Fairlie L, Mayo AJ, Nakabiito C, Mgodi N, Gadama L, Matrimbira M, Chappell CA, Piper J, Chakhtoura N, Szydlo DW, Richardson B, Hillier SL. DELIVER: A Safety Study of a Dapivirine Vaginal Ring and Oral PrEP for the Prevention of HIV During Pregnancy. J Acquir Immune Defic Syndr. 2024 Jan 1;95(1):65-73. doi: 10.1097/QAI.0000000000003312. PMID: 38055292. https://pubmed.ncbi.nlm.nih.gov/38055292/ . *In this first safety study of DVR and Oral PrEP in third trimester pregnant people in Africa, both products were found to be safe*

26. Herrera C, Serwanga J, Else L, Limakatso L, Opoka D, Ssemata AS, Pillay AD, Namubiru P, Seiphetlo TB, Odoch G, Mugaba S, Seatlholo P, Alieu A, Penchala SD, Muhumuza R, Alinde B, Petkov S, O'Hagan K, Callebaut C, Seeley J, Weiss H, Khoo S, Chiodi F, Gray CM, Kaleebu P, Webb EL, Martinson N, Fox J; CHAPS. Dose finding study for on-demand HIV pre-exposure prophylaxis for insertive sex in sub-Saharan Africa: results from the CHAPS open label randomised controlled trial. EBioMedicine. 2023 Jul;93:104648. doi: 10.1016/j.ebiom.2023.104648. Epub 2023 Jun 14. PMID: 37327677;PMC10275696. https://pubmed.ncbi.nlm.nih.gov/37327677/
A double dose of either F/TDF or F/TAF given to men once, either 5 or 21 h before ex vivo HIV-challenge provided protection across foreskin tissue.
27. Landovitz RJ, Hanscom BS, Clement ME, Tran HV, Kallas EG, Magnus M, Sued O, Sanchez J, Scott H, Eron JJ, Del Rio C, Fields SD, Marzinke MA, Eshleman SH, Donnell D, Spinelli MA, Kofron RM, Berman R, Piwowar-Manning EM, Richardson PA, Sullivan PA, Lucas JP, Anderson PL, Hendrix CW, Adeyeye A, Rooney JF, Rinehart AR, Cohen MS, McCauley M, Grinsztejn B; HPTN 083 Study Team. Efficacy and safety of long-acting cabotegravir compared with daily oral tenofovir disoproxil fumarate plus emtricitabine to prevent HIV infection in cisgender men and transgender women who have sex with men 1 year after study unblinding: a secondary analysis of the phase 2b and 3 HPTN 083 randomized controlled trial. Lancet HIV. 2023 Dec;10(12):e767-e778. doi: 10.1016/S2352-3018(23)00261-8. Epub 2023 Nov 9. PMID: 37952550. https://pubmed.ncbi.nlm.nih.gov/37952550/
CAB-LA retained high efficacy for HIV prevention in men and transgender women who have sex with men during the first year of open-label follow-up, with a near-identical hazard ratio (HR) for HIV risk reduction between Cab-LA and daily oral PrEP during the first year after unblinding (HR 0.35) compared with the blinded period (HR: 0.31).
28. Marzinke MA, Hanscom B, Wang Z, Safren SA, Psaros C, Donnell D, Richardson PA, Sullivan P, Eshleman SH, Jennings A, Feliciano KG, Jalil E, Coutinho C, Cardozo N, Maia B, Khan T, Singh Y, Middelkoop K, Franks J, Valencia J, Sanchez N, Lucas J, Rooney JF, Rinehart AR, Ford S, Adeyeye A, Cohen MS, McCauley M, Landovitz RJ, Grinsztejn B; HPTN 083 study group. Efficacy, safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir for HIV pre-exposure prophylaxis in transgender women: a secondary analysis of the HPTN 083 trial. Lancet HIV. 2023 Sep 29:S2352-3018(23)00200-X. doi: 10.1016/S2352-3018(23)00200-X. Epub ahead of print. PMID: 37783219. https://pubmed.ncbi.nlm.nih.gov/37783219/
HIV incidence among TGW was 1·80 per 100 py (95% CI 0·73-3·72) in the TDF/FTC group and 0·54 per 100 py (95% CI 0·07-1·95) in the Cab-LA group (hazard ratio 0·34 [95% CI 0·08-1·56]). Cab concentrations did not differ by gender affirming hormone therapy use.
29. Moore M, Stansfield S, Donnell DJ, Boily MC, Mitchell KM, Anderson PL, Delany-Moretlwe S, Bekker LG, Mgodi NM, Celum CL, Dimitrov D. Efficacy estimates of oral pre-exposure prophylaxis for HIV prevention in cisgender women with partial adherence. Nat Med. 2023 Oct 5. doi: 10.1038/s41591-023-02564-5. Epub ahead of print. PMID: 37798438. https://pubmed.ncbi.nlm.nih.gov/37798438/
The authors calculated the adherence-efficacy curve for cisgender women by using HIV incidence and plasma TFV concentration data from three trials (FEM-PrEP, VOICE and Partners PrEP). Two, four and seven pills per week reduced HIV incidence by 59.3% (95% credible interval (CrI) 29.9-95.8%), 83.8% (95% CI 51.7-99.8%) and 95.9% (95% CI 72.6-100%), respectively.

30. Nair G, Celum C, Szydlo D, Brown ER, Akello CA, Nakalega R, Macdonald P, Milan G, Palanee-Phillips T, Reddy K, Tahuringana E, Muhlanga F, Nakabiito C, Bekker LG, Siziba B, Hillier SL, Baeten JM, Garcia M, Johnson S, McClure T, Levy L, Livant E, Jacobson C, Soto-Torres L, van der Straten A, Hosek S, Rooney JF, Steytler J, Bunge K, Parikh U, Hendrix C, Anderson P, Ngure K; REACH Protocol Team. Adherence, safety, and choice of the monthly dapivirine vaginal ring or oral emtricitabine plus tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis among African adolescent girls and young women: a randomised, open-label, crossover trial. Lancet HIV. 2023 Dec;10(12):e779-e789. doi: 10.1016/S2352-3018(23)00227-8. Epub 2023 Oct 25. PMID: 37898146. https://pubmed.ncbi.nlm.nih.gov/37898146/
MTN-034/REACH was a randomized, open-label, phase 2a crossover trial among HIV-negative, non-pregnant adolescent girls and young women aged 16-21 years at four clinical research sites in Africa. No product-related SAEs were found, Similar high adherence was observed in 57% of visits to either product (ring or pills). In the choice period 3, 155 (65%) of 238 participants initially chose the ring, 72 (30%) initially chose oral PrEP, and 11 (5%) chose neither product. During the subsequent 6 months, those choices were quite stable.
31. Stalter RM, Dong TQ, Hendrix CW, Palanee-Phillips T, van der Straten A, Hillier SL, Kiweewa FM, Mgodi NM, Marzinke MA, Bekker LG, Soto-Torres L, Baeten JM, Brown ER; MTN-020/ASPIRE Study Team. Assessing Per-Sex-Act HIV-1 Risk Reduction Among Women using the Dapivirine Vaginal Ring. J Infect Dis. 2023 Dec 14:jiad550. doi: 10.1093/infdis/jiad550. Epub ahead of print. PMID: 38099506. https://pubmed.ncbi.nlm.nih.gov/38099506/
This secondary analysis of data from MTN-020/ASPIRE phase III trial, shows that a Dapivirine release indicative of consistent ring use was associated with a 63% (95% CI: 33-80%) per-sex-act HIV-1 risk reduction in women.
32. Weld ED, McGowan I, Anton P, Fuchs EJ, Ho K, Carballo-Dieguez A, **Rohan LC**, Giguere R, Brand R, Edick S, Bakshi RP, Parsons T, Manohar M, Seigel A, Engstrom J, Elliott J, Jacobson C, Bagia C, Wang L, Al-Khouja A, Hartman DJ, Bumpus NN, Spiegel HML, Marzinke MA, Hendrix CW. Tenofovir Douche as HIV Pre-Exposure Prophylaxis for Receptive Anal Intercourse: Safety, Acceptability, Pharmacokinetics, & Pharmacodynamics (DREAM 01). J Infect Dis. 2023 Nov 29:jiad535. doi: 10.1093/infdis/jiad535. Epub ahead of print. PMID: 38019657, https://pubmed.ncbi.nlm.nih.gov/38019657/
Three TFV rectal douches were evaluated in a phase I trial. All three had high acceptability without toxicity and achieved local tissue TFV-DP concentration higher than oral TDF.

3e. Reviews, commentaries or reports:

33. Chen X, Li J, Kou L, Xie X, Wei D, Li Y. Efficacy and safety of long-acting cabotegravir versus oral tenofovir disoproxil fumarate-emtricitabine as HIV pre-exposure prophylaxis: A systematic review and meta-analysis. Rev Med Virol. 2023 Jul;33(4):e2460. doi: 10.1002/rmv.2460. Epub 2023 May 17. PMID: 37198721. https://pubmed.ncbi.nlm.nih.gov/37198721/
34. Di Perri G. Pharmacological outlook of Lenacapavir: a novel first-in-class Long-Acting HIV-1 Capsid Inhibitor. Infez Med. 2023 Dec 1;31(4):495-499. doi: 10.53854/liim-3104-8. PMID: 38075416; PMCID: PMC10705863. https://pubmed.ncbi.nlm.nih.gov/38075416/
35. Ullah Nayan M, Sillman B, Hasan M, Deodhar S, Das S, Sultana A, Thai Hoang Le N, Soriano V, Edagwa B, Gendelman HE. Advances in long-acting slow effective release antiretroviral therapies for treatment and prevention of HIV infection. Adv Drug Deliv Rev. 2023 Sep;200:115009. doi: 10.1016/j.addr.2023.115009. Epub 2023 Jul 13. PMID: 37451501. https://doi.org/10.1016/j.addr.2023.115009. https://pubmed.ncbi.nlm.nih.gov/37451501/

36. Chien ST, Suydam IT, Woodrow KA. Prodrug approaches for the development of a long-acting drug delivery systems. Adv Drug Deliv Rev. 2023 Jul;198:114860. doi: 10.1016/j.addr.2023.114860. Epub 2023 May 7. PMID: 37160248; PMCID: PMC10498988. https://doi.org/10.1016/j.addr.2023.114860. https://pubmed.ncbi.nlm.nih.gov/37160248/
37. Delany-Moretlwe S, Flexner C, Bauermeister JA. Advancing use of long-acting and extended delivery HIV prevention and treatment regimens. J Int AIDS Soc. 2023 Jul;26 Suppl 2(Suppl 2):e26126. doi: 10.1002/jia2.26126. PMID: 37439079; PMCID: PMC10338994. https://pubmed.ncbi.nlm.nih.gov/37439079/
38. Pezzati, L., Canavesi, G., Rusconi, S. An update on Long-acting agents in HIV therapy. Future Medicine, Published Online: 26 Oct 2023 https://doi.org/10.2217/fvl-2023-0097.
39. Rivera CG, Zeuli JD, Smith BL, Johnson TM, Bhatia R, Otto AO, Temesgen Z. HIV Pre-Exposure Prophylaxis: New and Upcoming Drugs to Address the HIV Epidemic. Drugs. 2023 Dec;83(18):1677-1698. doi: 10.1007/s40265-023-01963-9. Epub 2023 Dec 11. PMID: 38079092. https://pubmed.ncbi.nlm.nih.gov/38079092/
40. de Carvalho, A.C.W.; Paiva, N.F.; Demonari, I.K.; Duarte, M.P.F.; do Couto, R.O.; de Freitas, O.; Vicentini, F.T.M.d.C. The Potential of Films as Transmucosal Drug Delivery Systems. *Pharmaceutics* **2023**, *15*, 2583. https://pubmed.ncbi.nlm.nih.gov/38004562/

3f. Select Press releases, announcements and media:

1. Exavir Therapeutics Receives $3M Award from NIH / NIAID to Advance Ultra-Long-Acting Integrase Inhibitor XVIR-110 (August 22, 2023). https://www.businesswire.com/news/home/20230822179307/en/Exavir-Therapeutics-Receives-3M-Award-from-NIH-NIAID-to-Advance-Ultra-Long-Acting-Integrase-Inhibitor-XVIR-110.
2. European Commission authorizes ViiV Healthcare's Apretude (cabotegravir long-acting and tablets) for HIV prevention. https://www.gsk.com/en-gb/media/press-releases/european-commission-authorises-viiv-healthcare-s-apretude/
3. Could this new hydrogel make HIV therapy more convenient? Delivering Lamivudine over 42 days via a hydrogel to treat HIV and HBV. The research is set to publish in the *Journal of the American Chemical Society*. (JHU press release, Sept 25, 2023) https://www.eurekalert.org/news-releases/1002163
4. Long-acting injectable version of the most popular HIV drug combination is possible. Subcutaneous injectable TLD might be dosed once a month (AIDSMAP sept 26, 2023). https://www.aidsmap.com/news/sep-2023/long-acting-injectable-version-most-popular-hiv-drug-combination-possible?utm_source=AVAC+Email+Updates&utm_campaign=48af62a337-EMAIL_CAMPAIGN_2023_09_29_05_06&utm_medium=email&utm_term=0_-48af62a337-%5BLIST_EMAIL_ID%5D
5. Gilead Sciences Announces New Clinical Trial in Europe to Assess Lenacapavir for HIV Prevention as Part of Landmark Purpose Program (18 October 2023). https://www.gilead.com/news-and-press/press-room/press-releases/2023/10/gilead-sciences-announces-new-clinical-trial-in-europe-to-assess-lenacapavir-for-hiv-prevention-as-part-of-landmark-purpose-program
6. The Population Council was Awarded a 15 months Grand Challenges Canada Grant to Support the Market Introduction of the Dapivirine Vaginal Ring in East and Southern Africa. https://popcouncil.org/media/population-council-awarded-grand-challenges-canada-grant-to-support-the-market-introduction-of-the-dapivirine-vaginal-ring/

7. The Population Council announces that the DPV is approved in 11 African Countries, and that local manufacturing of the ring in SA should bring down the cost (Nov 30, 2023): https://popcouncil.org/media/innovative-hiv-prevention-product-for-women-that-promotes-choice-dapivirine-vaginal-ring-dvr-gains-momentum-across-africa/
8. Viiv announced its' R&D plan in September 2023, which included a program for a q4m injection dosing of CAB for prevention (expecting approval in 2026) and a q6m by end of 2030. See: ViiV Healthcare Meet the Management (gsk.com)

4. Summary of relevant, recently completed, withdrawn or active studies in clinical trials databases (NEW SECTION).

Clinical studies of relevance found in **clinicaltrials.gov** website were added in a new summary table, below. These include 21 trials total, including those led by the 4 MATRIX PDs, but not the MATRIX trials themselves (i.e. MATRIX-001 and 002). Searches included various funders (i.e. NIH and other funders (not pharma) and pharma funders (e.g., GILEAD, Janssen. Merck, ViiV), using broad key words for the searches (i.e. HIV infections; Prevention, Intervention for trials enrolling healthy participants) with a date cut-off of 1/1/2019. We also conducted searches of the **EU CT database** (https://www.clinicaltrialsregister.eu/) 33 clinical trials were identified, but no relevant new trials to be added in the table below, beyond what was listed in clinicaltrials.gov. A search of the **Wellcome trust** grants awarded (https://wellcome.org/grant-funding/people-and-projects/grants-awarded) did not yield any results either.

Of the 21 HIV prevention trials identified in the table below, two trials by Merck with ISL were confirmed as withdrawn. Merck has a new active trial with a novel NRTTI, MK8527, for monthly oral dosing. GILEAD has 3 different trials of LEN ongoing that include CGW (as part of the PURPOSE program), 2 of which are co-funded by NIH via the HPTN. The Population Council has 2 active trials of the [formerly IPM] rings (3-month DPV ring & 3-month MPT ring), and two trials of the oral DPP capsule ongoing. ViiV has 7 trials ongoing, for extended duration Cab-LA injections and other formulations of Cab injectable, 3 trials with new capsid inhibitors, and one with a new INSTI (all in phase I).

Appendix Tables:

1. HIV Prevention Clinical Trials with investigational APIs/DDS by sponsor's alphabetical name– ACTIVE, COMPLETED, WITHDRAWN (since 1/1/2019)

N=21 # trials	DDS	Developer/ SPONSOR	stage	API(s)	Duration	R&D Status (dates)	Notes	NCT number [and links]
1	Rectal insert	CONRAD/ EVMS	Phase II	TAF/EVG	OD	Active-Recruiting	Extended safety, PK/PD assessment after repeated rectal application. Implemented by CDC and Emory U.	https://clinicaltrials.gov/study/NCT06274398
3	SC (abdomen*) injectable - parenteral	GILEAD	Phases II/III	Capsid inhibitor: LEN	6 months	P1- ongoing (2021-2027) P3/HPTN 102 recruiting (2023-2027) P4/HPTN 103 recruiting (2023-2027)	Purpose Program (I-iV). Note: P2 not included as focusing on MSMs. (*) New safety and PK results from phase I trial presented at ID week indicate that injection at 4 different sites can be offered as options (abdomen, arm, gluteus & thigh)	https://clinicaltrials.gov/study/NCT04994509 https://clinicaltrials.gov/study/NCT06101329 https://clinicaltrials.gov/study/NCT06101342
1	Ring	IPM [now PC]	Phase I	DPV	3 months vs 1	Active-Recruiting (2022-2024)	Relative bioavailability study	https://clinicaltrials.gov/study/NCT05416021
1	MPT ring	IPM [now PC]	Phase I/II	DPV & LNG	3 months	Active/FU (2022-2023)	NICHD funded	https://clinicaltrials.gov/study/NCT05041699
2	Rectal douches	JHU, UPenn	Phases I	TFV	OD.	Trials completed	NIAID funded	https://www.clinicaltrials.gov/study/NCT04016233 https://www.clinicaltrials.gov/study/NCT04686279
1	Oral tablets	Merck	Phase III	ISL	1 month	WITHDRAWN (as of 11/24/23)	Impower-022. ISL for PrEP abandoned -	https://clinicaltrials.gov/study/NCT04644029
1	Implant	Merck	Phase II	ISL	1 year	WITHDRAWN (as of 11/24/23)	ISL for implants abandoned	https://clinicaltrials.gov/study/NCT05115838
1	Oral	Merck	Phase II	NRTTI: MK8527	1 month	Recruiting (2023-2025)		https://clinicaltrials.gov/study/NCT06045507
1	injectable	Navigen	Phase I	CPT31	3 months	Completed	NIAID funded	https://www.clinicaltrials.gov/study/NCT04672083
1	Oral DPP capsule	Pop C	Cross-over study	TDF/FTC+COC	daily	Active-recruiting (2022-2023)	Adherence, preference and acceptability of, DPP vs 2 pills in Joburg, SA	https://clinicaltrials.gov/study/NCT04778527

N=21 # trials	DDS	Developer/ SPONSOR	stage	API(s)	Duration	R&D Status (dates)	Notes	NCT number [and links]
1	Oral DPP capsule	Pop C	Cross-over study	TDF/FTC+COC	daily	Completed (2022-2023)	Acceptability and preference in Chitungwiza, Zim.	https://clinicaltrials.gov/study/NCT04778514
1	IM (gluteus) injectable-parenteral	ViiV	Phase I	CAB-LA	Not specified.	Not recruiting (yet) (2023-2025)	PK study comparing 2 formulations (F&G)-	https://clinicaltrials.gov/study/NCT06033547
1	SC Injectable	ViiV	Phase I	CAB-LA	2 months, 4 months or more	Active-Recruiting (2022-2024)-	Compares different CAB loadings (200 vs 400 mg/ml), formulations (w/ or w/o hyaluronidase) duration & routes of administration (Sc vs IM)	https://clinicaltrials.gov/study/NCT05418868
1	SC vs IM injectable	ViiV	Phase I (w/ active control)	CAB-LA 400mg/ml	2 months or more	Completed (2020-2023)	Safety, PK of SC (abdominal) vs IM (gluteal) and 400 vs 200mg/ml CAB-LA) w/ or w/o anti-inflammatory drugs and/or hyaluronidase	https://clinicaltrials.gov/study/NCT04484337
1	SC or IM Injectable	ViiV	Phase I	NEW capsid inhibitors: VH4004280 VH4011499	Ultralong-Not specified	Active-Recruiting (2023-2026)-	Participants followed up to w52. Oral administration explored also in phase II for treatment	https://clinicaltrials.gov/study/NCT06012136
1	Oral	ViiV	Phase I (FIH)	NEW capsid inhibitor: VH4011499	Not specified (assuming daily)	Completed (2021-2023)	Safety, PK study in healthy volunteers. First: Single ascending dose; Next: multiple ascending doses for DDI with Midazolam	https://clinicaltrials.gov/study/NCT05393271
1	Oral	ViiV	Phase I (FIH)	NEW capsid inhibitor: VH4004280	Not specified (assuming daily)	Completed (2022-2023)	Safety, PK study in healthy volunteers. First: Single ascending dose; Next: multiple ascending doses for DDI with Midazolam	https://clinicaltrials.gov/study/NCT05163522
1	Not specified	ViiV	Phase I (FIH)	INSTI: VH4524184	Not specified	Active-recruiting (2022-2023)	Safety, PK study in healthy volunteers. First: Single ascending dose; Next: multiple ascending doses for DDI and effect on CYP3A activity	https://clinicaltrials.gov/study/NCT05631704

2a. HIV Prevention Projects – COMPLETED, STOPPED or STATUS UNKNOWN (* all changes in table are in red text)

N= 13	DDS	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	References publication and/or NIH RePorter link
1	IM injectable parenteral	Viriom/NWU	phase 1	Elsufavirine-NNRTI VM1500A-LA	1 month	Unknown*	PI: E. Smolyarchuk, first Moscow State Medical University, Russia (approved for oral dosage)	https://pubmed.ncbi.nlm.nih.gov/28940154/ https://classic.clinicaltrials.gov/ct2/show/NCT03706911
2	Removable Implant (EVA)- SC	MSD	phase 1	NRTTI: ISL	1+year	Stopped for PrEP due to safety signal. Unknown status	PI unknown, MSD. Project withdrawn from Clinicaltrials.gov see table 1	https://pubmed.ncbi.nlm.nih.gov/36450129/ https://www.merck.com/news/merck-to-initiate-new-phase-3-clinical-program-with-lower-dose-of-daily-oral-islatravir-in-combination-with-doravirine-for-treatment-of-people-with-hiv-1-infection/
3	Implant-Removable - SC	NWU	preclinical	INSTI: CAB	??	Completed-searching for additional funding.	NHP study completed - PI: Hope, NIAID 2015-2022	https://www.sciencedirect.com/science/article/abs/pii/S0168365920307483 https://reporter.nih.gov/project-details/9728861
4	osmotic pump- -SC	Intarcia	preclinical	exenatide; TAF	6 mo-1year	Stopped due to toxicity of TAF in animal models.	Company is bankrupt. Medici system. PI: Unknown	https://pubmed.ncbi.nlm.nih.gov/33913760/
6	Injectable-parenteral	UW	preclinical	TAF	??	Unknown- see new entry #5 for MPT implant	Drugamers described in proceedings from BMGF TAF workshop. PI: Stayton, BMGF	https://pubmed.ncbi.nlm.nih.gov/33913760/
7	Hydrogel-forming MAP transdermal	QUB	preclinical	CAB-sodium salt	~ 1 month	Completed-	Target duration not achieved PI: unknown, USAID	https://pubmed.ncbi.nlm.nih.gov/?term=35738464,35658545&format=abstract
8	Ring (PU)-vaginal	AECOM	clinical-phase I	TDF	1 month	Stopped due to safety signals	PI: Herold, NIAID 2018-2023.	https://www.sciencedirect.com/science/article/abs/pii/S2352301819301456
9	Ring - vaginal	NWU	preclinical	NRTI: IQP-0528	1 month?	Stopped.	IQP0528 not further supported by IMQUEST for Px PI: Kiser, NIH	https://pubmed.ncbi.nlm.nih.gov/28770490/
10	Ring - vaginal	Tulane U	preclinical	DLG, SAMT (nucleocapsid protein inhibitor)	1 month	Completed-failure to protect and safety signal in NHP	PI: Veazey NIAID 2017-2022 SAMT-247 Drug Originator is Daniel Appella, from NIDDK.	https://reporter.nih.gov/project-details/10071116
11	Biocage--SC	diverse academics (GW, CNMC,	preclinical	Multiple, neuro-drugs	Theoretically tunable to needed duration	NIMH and NCATS funding completed in 2023. Unknown status	3D printed small biodegradable device (can be delivered via 22G needle) for direct implantation in target tissues (E.g., brain). PI: Torii,	https://pubmed.ncbi.nlm.nih.gov/29247175/ US patent. Application No. 62/554,680 (per publication)

		yale, U Mass..)					Masaaki, NIMH (2017-2023), NCATS (2016-2023)	
12	In situ forming implant (ISFI)- -SC	UNC	preclinical	ISL, CAB and other drugs incl for TB	>6 months	Completed (end date Aug 31, 2023)	PI: Garcia, NIAID 2018-2023 **5R01AI140799-05**	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9911691/ https://reporter.nih.gov/project-details/10468909
13	Tablet, vaginal	Osel, Inc.	Preclinical& preparation for FIH trial	recombinant L. jensenii with mCV-N	OD	Completed (end date July 2023)	PI Lagenaur NIAID 2020-2023. Live biotherapeutic product secreting modified cyanovirin-N	https://reporter.nih.gov/search/cKoXtRxn2U2IgmOggFNymg/project-details/10223989

2b. HIV Prevention Projects – Ongoing (* all changes in table are in red text, new entries at the bottom of the table. Overlap[4] grading with the CP products is indicated in the first column by the following color coding: no overlap (no color), some potential overlap (yellow), moderate/significant overlap (orange))

N=28	DDS	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	References publication and/or NIH RePorter link
1	injectable - parenteral	GILEAD	phase III	Capsid inhibitor: LEN	6 months	Ongoing	PURPOSE program (1-4) GILEAD PIs (unknown) HPTN102/P3, PI: Adimora, NIAID & GILEAD- Activated	https://clinicaltrials.gov/ct2/show/NCT04994509 https://www.jci.org/articles/view/167818 See Table 1
2	injectable-parenteral	UW	Phase I focused on Rx	LPV, RTV, TFV nano-particle suspension (TLC-ART 101)	??	Ongoing. FIH trial initiated May 2023 – End in 2025 (N=16) All gender ppts, not living with HIV	Targeted LA- combination ARV Therapy (TLC-ART) Program - New platform to stabilize insoluble & soluble ARVs together in a nanosuspension- RX focused; applicable to Px PIs: Bender Ignacio and Ho, NIAID 2019-2024 **5U01AI148055-03**;	https://reporter.nih.gov/search/tqIyle6FM02SXTyegdlPdg/project-details/10234129 https://pubmed.ncbi.nlm.nih.gov/37650755/ https://depts.washington.edu/tlcart/ https://classic.clinicaltrials.gov/ct2/show/NCT05850728
3	Implant bioerodible.	QUB	Preclinical	model hydrophobic	> 6 months	Unknown	3D printed implant. PI: unknown, funding: Academy	https://www.tandfonline.com/doi/full/10.1080/10717544.2022.2057620

[4] Overlap considerations: a) DDS, b) API/Drug(s) and 3) Target/Actual duration are used to consider whether a reported product overlaps with a CP product under development by MATRIX. Non-MATRIX identified products that are only identical for one of these three factors are not identified as overlapping. Potential overlap is assigned if the API(s) are identical and a second factor is similar (or identical) to a CP product in MATRIX. Moderate/Significant overlap is assigned when all 3 factors are similar/identical to a CP product in MATRIX.

N=28	DDS	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	References publication and/or NIH RePorter link
	(PEO coated w/ PCL) -SC			drug: olanzapine			of medical sciences, Wellcome Trust	https://pubmed.ncbi.nlm.nih.gov/36509226/
4	MAP transdermal	QUB	preclinical	INSTI: Bictegravir	~ 1 month	Ongoing? (new publication in 6/2023)	PI: Donelly; funding: EPSRC Wellcome Trust	https://pubmed.ncbi.nlm.nih.gov/37301241/
5	Injectable ISFI hydrogel parenteral	QUB	preclinical	ZDV (prototype) + d-peptide	?	Ongoing? (new publication in 6/2023)	PI Unknown; funding: EPSRC, the Wellcome Trust, the MRC & Invest NI	https://pubmed.ncbi.nlm.nih.gov/36880399/
6	injectable parenteral	U Florida	preclinical	eCD4-Ig antibody-like molecule	6 months	Ongoing	To optimize the combination of a broad/potent HIV-1 entry inhibitor & a tunable hydrogel to extend the in vivo half-life of this inhibitor. PI: Farzan, M. NIAID 2020-2025 **7R01AI154989-05**	https://reporter.nih.gov/project-details/10841186
7	IM Injectable-parenteral	U Nebraska	Preclinical-Focused on Rx	NRTI and INSTI (e.g DLG) prodrugs converted into nanocrystal formulation for LA	6 months	Ongoing	18-carbon chain modified ester prodrug nanocrystal- for sustained release via IM injectable in rats & NHP. PIs: Edagwa, and Gendelman NIAID 2019-2024; 5R01AI145542-05	https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10652403 https://pubmed.ncbi.nlm.nih.gov/37451501/ https://pubmed.ncbi.nlm.nih.gov/35680875/
8	Injectable-parenteral	U Nebraska	preclinical	DLG, FTC, TFV, others	up to 1 year	Ongoing	LASER-ART: chemical modification of existing ARVs for extended release. 3 patents listed on RePorter. PI: Gendelman, NIAID 2021-2026 **5R01AI158160-03**	https://pubmed.ncbi.nlm.nih.gov/34531390/ https://reporter.nih.gov/project-details/10597017
9	Injectable-parenteral	Navigen	clinical	CPT31 -D-peptide Entry inhibitor	target 3 months	Ongoing	PI: Madani, NIAID 2017-2024- **5R01AI134494-05** Phase I trial completed	https://www.newswise.com/articles/long-acting-injectable-drug-could-strengthen-efforts-to-prevent-treat-hiv?sc=rsgt https://reporter.nih.gov/project-details/10174715 https://www.clinicaltrials.gov/study/NCT04672083 and table 1
10	Removable Implant- SC	OCIS, CAPRISA	Phase 1	NRTI TAF	1 year		CAP-018. PI: Abdool Karim,	https://pubmed.ncbi.nlm.nih.gov/34992111/J10

N=28	DDS	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	References publication and/or NIH RePorter link
						presentation at CROI 2024 pending.	SAMRC, EDCTP, NRF (end 12/2023). Trial completed,	https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3584
11	bioresorbable implant -SC	OCIS	preclinical	maturation inhibitor (DFH-1160005)	=<1 year	Ongoing	PI: Moss; NIAID 2020-2025 **5R01AI154561-04**	https://reporter.nih.gov/project-details/10669021
12 new grant	Removable Implant -SC	OCIS	Next gen Preclinical	TAF and 2 new pro-drug formulations	6 mo-1year	Ongoing	PI: Baum; NIAID 2021-2026 **5R01AI162151-03** and NIAID 2023-2027 **1R01AI172541-01A1**	https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10654774 https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10617540 https://pubmed.ncbi.nlm.nih.gov/35581262/ https://pubmed.ncbi.nlm.nih.gov/36418671/
13	Implant-bioerodible (PCL) -SC	RTI	preclinical	TAF, ISL, BIC, others	7-12 months	Ongoing	Several grants from NIAID or NICHD PI: Johnson, USAID funding (completed); NIAID (2020-2025) LAPIS: **5R01AI152713-04.** NIAID (2020-2024) **AMBER: 5R01AI154549-04**, NICHD (2020-2025) DAISY: **5R33AI149499-04** .	https://reporter.nih.gov/project-details/10581520 https://reporter.nih.gov/project-details/10663830 https://reporter.nih.gov/project-details/10594581 https://www.frontiersin.org/articles/10.3389/fphar.2022.923954/full https://pubmed.ncbi.nlm.nih.gov/35913838/
14	Implant-Refillable (Titanium) -SC- NanoDDI	HMRI	preclinical	ISL	2 years	Ongoing	PI Grattoni: NIGMS 2018-2023; NIAID 2022-2027 5R01AI165372-02 NanoDDI comprises a newly patented nanofluidic membrane, and ports for rapid, minimally invasive transcutaneous drug refilling	https://reporter.nih.gov/search/0QLLolLF1kWs6-YgNUdB_Q/project-details/10481727 https://www.sciencedirect.com/science/article/abs/pii/S0168365918304711 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7590004/ https://pubmed.ncbi.nlm.nih.gov/33997267/

N=28	DDS	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	References publication and/or NIH RePorter link
								https://reporter.nih.gov/project-details/10093084
15	Oral tablets-enteral	MSD	Clinical phase 2a	MK8527 (NRTTI)	1 month	Back up API to ISL	PI: unknown. Merck has re-initiated development with MK8527	https://clinicaltrials.gov/study/NCT06045507, see table 1
16	Tablets LYNX™ platform-enteral	Lyndra	preclinical	undisclosed	7 days-1 month	Ongoing	Focused on Rx but can work for Px; GILEAD funding for HIV indication; https://lyndra.com/pipeline/ PI: unknown	https://www.nature.com/articles/s41467-017-02294-6
17	Enema/ douche-rectal	JHU	phase I/II	TFV	OD	Ongoing	DREAMS trials completed, see table 1 PI: Hendrix, HPTN 106, NIH (protocol development stage)	https://grantome.com/grant/NIH/U19-AI113127-01 https://pubmed.ncbi.nlm.nih.gov/36477356/
18	MAP-transdermal	PATH/QUB	preclinical	RPV and other ARVs (CAB, LEN)	7 D-1 Mo	Ongoing	Current Funding focused on Pediatric Rx (e.g., with LEN) PIs: Choy (PATH & Donnelly, R (QUB) NIAID 2020-2025 **5R33AI149642-04**	https://pubmed.ncbi.nlm.nih.gov/36224503/ Posters presented at 2023 https://www.microneedlesconference.com/
19	Pod ring-vaginal	Dana Farber (DFCI)	preclinical	CD4 mimetic compound	?	Ongoing	Entry inhibitor -irreversibly interferes with HIV ENV binding to CD4 PI: Madani, NIAID 2011-2024 **5R01AI134494-05**	https://reporter.nih.gov/project-details/10174715
20	Fibers-based microbicide - drug eluting-vaginal	UW	preclinical	INSTI: RAL prodrug	OD- 2 weeks	Ongoing	PI: Woodrow; NIAID 2019-2024. Aims to identify ARV(s) that are compatible with the Nano-spun fibers. **5R01AI145483-05**	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7591136/ https://pubmed.ncbi.nlm.nih.gov/37160248/ https://reporter.nih.gov/project-details/10576394
21	3D-printed silicone scaffold devices-vaginal	U of Louisville	preclinical	BV- Not specifically for HIV indication	LA (unclear duration)	Ongoing	BV indication- 3D printing and computational modeling to design LA topical products. PI: Frieboos, H. NIAID 2022-2027 **1R01AI168475-01**	https://reporter.nih.gov/search/ttU8bGUDGkOFi3qd-vWenw/project-details/10420527 https://pubmed.ncbi.nlm.nih.gov/37076014/

N=28	DDS	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	References publication and/or NIH RePorter link
22 new Entry	Biodegradable implant	UNC	Preclinical	Grant is for Rx maintenance, but applicable to PrEP	LA (unclear duration)	New award	PI: Benhabbour, NIAID 2023-2027**1R01AI176949-01A1**	https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10759149
23 New entry	Nanocrystal suspension-Injectable (parenteral)	EXAVIR therapeutics, inc https://exavirtherapeutics.com/	preclinical	INSTI **XVIR-110**. From website: CAB, TAF, DLG-	LA (6 months+)	SBIRII (CMC and IND enabling studies)	Companyy collaborates with Gendelman's group. PI: Gunzer-Toste, NIAID 2023-2026;**1R44AI179564-01**	https://reporter.nih.gov/project-details/10764186 https://www.nature.com/articles/s41467-021-25690-5 https://www.science.org/doi/full/10.1126/sciadv.ade9582 https://www.nature.com/articles/s41467-022-30902-7 https://www.nature.com/articles/s41467-021-23668-x
24 New Entry	Injectable (parenteral)	Boston U	prelcinical	Prodrug of TFV and FTC	3 month or more?	New award	membrane-wrapped nanoparticles (NPs) that establish cellular depots for sustained maintenance of inhibitory concentrations of ARVs at primary tissue sites of HIV-1 transmission in the FGT & rectum. Reinhard and Markus NIAID (2023-2027) **1R01AI175068-01A1**	https://reporter.nih.gov/project-details/10711555
25 New Entry	Injectable (parenteral) SC or IM	ViiV	clinical	CAB (various formulations)	4 (and 6) months	Ongoing	R&D plan announced by ViiV (Sept 2023), and listings in Clinical trials.gov	ViiV Healthcare Meet the Management (gsk.com) and table 1
26 New Entry	Oral and Injectable (SC or IM)	ViiV	clinical	NEW capsid inhibitors: VH4004280 and VH4011499	unspecified	Ongoing	R&D plan announced by ViiV (Sept 2023), and listings in Clinical trials.gov	ViiV Healthcare Meet the Management (gsk.com) and table 1
27 New Entry	Unspecified	ViiV	clinical	New INSTI: VH4524184	unspecified	Ongoing	R&D plan announced by ViiV (Sept 2023), and listings in Clinical trials.gov	ViiV Healthcare Meet the Management (gsk.com) and table 1
28 New Entry	FDI, rectal	CONRAD	Clinical	TAF/EVG	OD	Ongoing	RITE-PrEP study initiated. Led by CDC and Emory (PK/PD assessment after repeated rectal application)	HPTN 2023 annual meeting, plenary session and table 1

3a. MPTs including an HIV indication (stopped/ completed project or unknown) (* all changes in table are in red text-)

N =14	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
1	FDI- vaginal	HSV, PREG	IPM, now PC	preclinical	DPV, LNG, ACV	8h	Paused; (Haddad pers. comm)	PI: Unknown.	https://pubmed.ncbi.nlm.nih.gov/27163243/
2	Gel- Vivagel (dendrimer)-vaginal	HSV, HPV, BV	Starpharma	preclinical	SPL7013 (astodrimer sodium)	30 days	Unknown if program still active.	PI: Jeremy Paull. A product was licensed in the Pacific rim for BV, based on Vivagel.	https://reporter.nih.gov/project-details/7490395
3	Gel (TFV) vaginal	HSV	CONRAD	clinical	TFV 1%	BAT 24	Stopped: poor adherence/in-effectiveness in FACTS-001 trial	PI: Unknown.	https://pubmed.ncbi.nlm.nih.gov/20643915/ https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30428-6/fulltext
4	Gel (TFV/ACV) vaginal	HSV	SRI Int'l	preclinical	TFV, ACV	24h	Inactive (lack of funding).	PI: Shankar, G.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4538522/
5	Gel MCZ vaginal	HSV, HPV	PC	clinical	CG, MIV-150, Zinc Acetate	24h (daily or OD)	On pause	PI: Unknown.	https://pubmed.ncbi.nlm.nih.gov/27552154/
6	Implant bioerodible (PCL)-SC	PREG	RTI	preclinical	TAF or ISL, LNG or EE	7-12 months	Completed	PI: Johnson, USAID (SCHIELD). NHP studies completed. Not considered for CP in MATRIX.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4468722/ https://www.croiconference.org/abstract/vaginal-prep-efficacy-of-biodegradable-islatravir-implants-in-macaques/
7	Enema-rectal	Hepatitis, HSV	U of Louisville	clinical	Q-GRFT	OD	Completed- New publication in 2023	gel abandoned in favor of enema for anal sex- PI: Palmer, NIAID	https://pubmed.ncbi.nlm.nih.gov/31792342/ https://pubmed.ncbi.nlm.nih.gov/37161022/
8	MAP-transdermal	PREG	QUB, PATH	preclinical	CAB_ progestin (norelgestromin)	7 days- 1 month	Completed	PI: Unknown, USAID. Not considered for CP in MATRIX.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6809612/
9	IUS-Intrauterine	PREG	CONRAD	preclinical	Cu + EVG	1 year	Unknown if program sill active. Grant is Completed	PI: Unknown.	https://www.conrad.org/what_we_do/product_development/ https://reporter.nih.gov/project-details/9249465

N =14	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
10	Film_ARV nanoparticle - vaginal	HSV	U of Porto	preclinical	EFV + TFV	24h (daily)	Unknown	PI: Unknown, funding via Portugal & EU (FCT, FEDER, POCI COMPETE 2020,)	https://pubmed.ncbi.nlm.nih.gov/27664327/
11	Reservoir Ring (PU)- vaginal	HSV	CONRAD	clinical	TFV	90 days	Unknown	PI: Mugo, CDC & USAID funding PI: Liu, MTN-038 https://mtnstopshiv.org/research/studies/mtn-038	Liu, CROI 2022 (link unavailable)- MS under review https://www.frontiersin.org/articles/10.3389/frph.2023.1118030/full
12	Ring (PU reservoir segmented)- vaginal	HSV, PREG	CONRAD	clinical	TFV, LNG	90 days	Unknown	PIs: Doncel and Clark, CDC & USAID. see row above for publication	https://www.conrad.org/news/news_items/conradandcdccollaborateonstudyofintravaginalringsreleasingtfvwithandwithoutlnginkenya.html https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199778
13	PPCM-Gel vaginal	CT, GC, HPV, HSV, PREG	YASO therapeutics	Preclinical & early clinical	polyphenylene carboxymethylene	OD	FDA placed Phase 1 trial on a partial hold.	IND submitted 5/2023. PI: Weitzel, NICHD 2022-2023 **1R43HD109101-01**	https://pubmed.ncbi.nlm.nih.gov/32469052/ https://reporter.nih.gov/project-details/10483274
14	Ring- pod- (silicone) vaginal	HSV, PREG	Auritech	preclinical	TAF/ or TDF/FTD, ACV and ENG/EE	1 month	Completed	PI: Smith, NIAID (2018-2023) **5R33AI136008-05**	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0185946 https://reporter.nih.gov/project-details/10378141

3b. **MPTs including an HIV indication (ongoing)** (* all changes in table are in red text, new entries at the bottom of the table; Overlap[4] grading with the CP products are indicated in the first column by the following color coding: no overlap (no color), some potential overlap (yellow), moderate/significant overlap (orange).

N =20	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
1	LA-FILM-vaginal	PREG	MWRIF	preclinical	ISL (or Prodrug) + progestins	1 month	Ongoing	PI: Rohan, LATCH NIAID 2019-2025 **5R33AI142687-05**	https://reporter.nih.gov/project-details/10545302
2	Film_mAB cocktail-vaginal	PREG	Boston U + MAPP	Preclinical/ clinical	MB66 (anti HIV) + ZB-06 (contraceptive)	OD (24h)	Ongoing	PI: Anderson, P50 and subprojects NICHD 2018-2026 **2P50HD096957-05**	https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003495 https://pubmed.ncbi.nlm.nih.gov/36870409/ https://reporter.nih.gov/search/2_RtMItIvESsrlrKXx1tXg/project-details/10532090
3	Injectable Hydrogel-parenteral- SC	PREG	EVMS/ CONRAD	preclinical	CAB+ LNG	3 mo	Ongoing	PI: Clark. Project Horizon, NIAID 2019-2024 **5R33AI142685-05**. Switched from DLG to CAB	https://reporter.nih.gov/project-details/10546210 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9639748/
4.	nanofluidic refillable implant (NanoMPI)- SC	PREG	HMRI and UW	preclinical	etonogestrel (ENG) and islatravir (ISL) drugamer	2 years	Awarded in 3/2023	PIs: Grattoni and Stayton, NIAID (2023-2028) **1R01AI167659-01A1**	https://reporter.nih.gov/search/t0FXMGGdiE622_eUszaw7g/project-details/10619811
5	In Situ forming implant (ISFI)	PREG	UNC	preclinical	DLG, RPV, CAB, other	6 months	Ongoing	PI: Benhabbour. NIAID 2021-2026 **5R01AI162246-03**	https://pubmed.ncbi.nlm.nih.gov/34216767/ https://reporter.nih.gov/project-details/10392508 https://pubmed.ncbi.nlm.nih.gov/35745761/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9911691/ (crf Young Feb 2023)
6	Insert (FDI)-vaginal	BV, CT, GC, PREG	PC	preclinical	AMPHORA, Q-GRFT	OD	Ongoing	PI: Angsantikul. NIAID 2020-2025 **5R01AI150324-04**	https://reporter.nih.gov/search/vNSHP2pULUitSm8f8ITfaA/project-details/10569037

N =20	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
7	IUD - Intrauterine	PREG	UW	preclinical	Copper + ARVs or prodrugs (unspecified)	Up to 3 years	Ongoing	PI: Woodrow NIAID 2020-2025 **5R01AI150325-04**	https://reporter.nih.gov/project-details/10675641 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9081257/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9277594/
8	DPP- enteral	PREG	Viatris, (PC)	clinical	TDF/FTC, LNG/EE	24h (daily)	Ongoing-	Note: pilot bioequivalence (BE) completed. Confirmatory BE planned in 2024 (CIFF, CHAI, BMGF funding)- PI: Haddad, HPTN- 104, NIAID	https://www.frontiersin.org/articles/10.3389/frph.2021.682689/full#:~:text=A%20dual%20prevention%20pill%20(DPP,into%20the%20hands%20of%20women https://www.prepwatch.org/dual-prevention-pill/
9	DPP- enteral	PREG	PC/ Medicines 360	Pre-clinical & clinical	TAF /FTC, LNG/EE	24h (daily)	Ongoing (PC internal funding)	works on an over-encapsulated DPP and a TAF DPP. PI: Haddad- See table 1	https://popcouncil.org/project/dual-prevention-pill-for-the-prevention-of-hiv-and-unintended-pregnancy/
10	Core Sheath Ring -vaginal	PREG	IPM/PC	clinical	DPV, LNG	90 days	Ongoing- Requested onboarding in MATRIX (NPR)	PI: Steytler phase I/II IPM 056 / CCN019B (NICHD) through 12/2023	https://www.avac.org/trial/ipm-056-ccn019b https://clinicaltrials.gov/study/NCT05041699 and table 1
11	Non-hormonal CZL Ring vaginal	HSV, HPV, PREG	PC (+ QUB, WCMC)	preclinical	Non hormonal APIs Copper, Zinc and lactide	30 days	Ongoing	PI: Haddad P50 grant and sub-projects, NICHD 2021-2026 **5P50HD106793-03**	https://www.sciencedirect.com/science/article/pii/S0168365915006252 https://reporter.nih.gov/project-details/10700065
12	Ring- pod (silicone) - vaginal	PREG	PC	preclinical	Q-GRFT, ETG, EE	90 days	Ongoing	PI: Teleshova, NIAID 2020-2025. **5R01AI150360-04** Also tests 3 diameters of rings.	https://reporter.nih.gov/project-details/10600151 https://www.popcouncil.org/research/an-intravaginal-ring-containing-etonogestrel-ethinyl-estradiol-and-qgriffit

N =20	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
13	Non hormonal Ring_pod - vaginal	HSV, CT, PREG	MB, OCIS, Plante Biotech, UMass UNC, Mucomune	preclinical	mAB 2C7, TDF	30 days	Ongoing	PI: Baum, NICHD 2020-2025. **5R01HD101344-04** The contraceptive mAB relies on sperm immobilization	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8868023/ https://reporter.nih.gov/project-details/10588268
14	Non hormonal Ring_ capsule vaginal	PREG	Mucomune	preclinical	mAB cocktail-HCA+VRC01+N6	1 month +	Ongoing	PI: Kushiro. NICHD-2021-2024. **5R44HD097063-03** 2 mABs against HIV+ HCA	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8640842/ https://reporter.nih.gov/project-details/10381449
15	CLIP 3D printed ring- vaginal	HSV, PREG.	UNC	preclinical	DPV/pritelivir/ LNG or ISL/ENG/EE	1-3 months	Ongoing	PI: Benhabbour. NIAID 2019-2024. **5R01AI150358-05** (CLIP™) 3D printing allows to engineer ring in one step for multidrug release	https://reporter.nih.gov/project-details/10308467 you tube: https://www.youtube.com/watch?v=NCq2_yMpUfk https://pubmed.ncbi.nlm.nih.gov/37549505/
16	Ring- vaginal	GC	UMass/ OCIS	preclinical	TDF and mAb 2C7 (against GC)	Unspecified	ongoing	PI: Ram NIAID 2020-2024 **5R33AI136007-05**	https://reporter.nih.gov/search/a71vYCzPO0ylXUPZu8M8Cw/project-details/10378501
17	Ring-vaginal	PREG	OCIS	Preclinical	ARV (not specified) & mAb for sperm agglutination	30 days	ongoing	PI: Baum NICHD 2020-2025 5R01HD101344-04	https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10588268
18 New Entry	Ring Vaginal	BV	QUB	Preclinical	DPV+ Metronadizole	Unspecified	unspecified	Malcolm's group . Funder unspecified in publication.	https://www.sciencedirect.com/science/article/pii/S0378517323009936?via%3Dihub https://doi.org/10.1016/j.ijpharm.2023.123296
19 New Entry	Ring Vaginal, with Non-hormonal contraceptive	PREG	QUB	preclinical	DPV, Cu, Zinc	Unspecified	In vitro study. Unspecified	Malcom's group funding unspecified in conference abstract	https://pure.qub.ac.uk/en/publications/poster-abstract-a-multipurpose-vaginal-ring-releasing-copper-ions

N =20	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
									https://pure.qub.ac.uk/en/publica rmulation-development-of-a-multipurpose-vaginal-ring-for-non
20 New Entry	MPT injectable	PREG	QUB	Preclinical	Depo Provera+ RPV	Up to 2 months	NHP study	WHO funding	https://doi.org/10.1016/j.jddst.2023.104590