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

R&D Landscape Review 3

SUBMISSION DATE:

V1.1 July 28, 2023

PERIOD OF REVIEW:

January 1-June 30, 2023

SUBMITTED TO:

United States Agency for International Development (USAID), Cooperative Agreement Number 7200AA22CA00002

SUBMITTED BY:

Magee-Womens Research Institute and Foundation

Prepared by Ariane van der Straten, PhD

PEPFAR

USAID FROM THE AMERICAN PEOPLE

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
CP	Critical Path
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
HSV	Human Simplex Virus
ISFI	In situ forming implants
ISL	Islatravir
INSTI	Integrase Strand Transfer Inhibitor
LEN	Lenacapavir
LNG	Levonorgestrel
MAP	Microarray Patch
MIT	Massachusetts Institute of Technology
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
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.

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)

This **third desktop review** for the first half of 2023 includes publications and funded projects identified between January 1 and June 30, 2023, focusing on HIV Prevention/ PrEP, microbicides, and Multi-Purpose Prevention Technologies[2] (MPTs) that include an HIV indication (note that 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 pursued under MATRIX funding, such as contraception.)

All updates and changes to the appendix tables are in red text. Note that 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.

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

Modification from previous reports: We have recategorized the products reported in the Appendices to separate projects that a) are completed, have been paused/on hold (e.g., while seeking additional funding), stopped or whose R&D status is unknown to us, from b) products where this is evidence that the products are actively being developed.

[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] 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

Summary table of projects identified in landscape review.

Type of projects	N	Active/Ongoing	Currently not active/unknown
HIV Prevention only	34	23*	11
MPTs (including DP products)	30	18**	12
TOTAL	64	41	23

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

As shown in the summary table above, there are a total of **34 HIV prevention projects**, of which 11 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 **23 are actively ongoing projects.** These include **three new entries**. Two of the entries were identified through recent publications from Queen's University Belfast (QUB), one for a Microarray Patch (MAP) releasing the ARV bictegravir (BIC) and the other for an *in situ* forming implant (ISFI) with an innovative formulation where a prototype ARV (zidovudine) is combined (covalently conjugated) with a peptide for rapid hydrogel formation, and long-acting drug release is achieved via hydrolysis of the covalent bond under physiologic conditions. Both these research activities were funded in the UK/Europe. The third new entry (previously on hold) is a NIAID project funded in 2020- for the company Osel, Inc. to develop a Live Biotherapeutic Product (LBP) in the form of an on-demand vaginal tablet. The LBP is secreting Cynanovirin-N (mCV-N) a potent HIV entry inhibitor derived from the algae cyanobacterium. Of note, Osel's main indication is improved vaginal health due to vaginal colonization by *Lactobacillus.*

Active HIV prevention projects:

- 5 topical products: 1 rectal enema, 2 vaginal rings/device, 1 vaginal drug - eluting fibers and 1 (newly identified) project with a vaginal tablet LBP.
- 19 systemic products: 7 injectables, 6 implants (removable, bioresorbable, refillable, 3D printed), 2 *in situ* forming implant (ISFI), 2 transdermal MAPs, 2 long-acting oral tablets.
- Several projects identified new APIs for their DDS (e.g., bictegravir, MK8527), used model drugs as proof of concepts (e.g., zidovudine) and were optimizing the new APIs and/or creating prodrugs to increase the duration of extended release. Drugs investigated (see table and publications) include:
    - Repurposing ARVs approved for treatment (e.g., bictegravir, lenacapavir),
    - New unapproved ARVs for prevention usage (e.g., MK8527, a NRTTI). Of note: there are no official announcement from Merck indicating that the pursue of MK8527 for prevention purpose is actively ongoing, but last partner's call in 2023 suggested this has been initiated.
    - The potent NRTTI islatravir (ISL) continues to generate prevention publications and newly 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, as well.

- Creation of prodrugs with improved physicochemical and safety characteristics (e.g., for dolutegravir, raltegravir, atazanavir, other protease inhibitors, NNRTIs…)
- Drugamers to more efficiently deliver multiple small molecules/ARVs (see new MPT entry with NIAID funding in row #5 of MPT table)
    - Small molecule HIV entry inhibitor (mCV-N) delivered using a LBP in the form of an on-demand vaginal tablet.
- D-peptide entry inhibitor (CPT31) proposed as a 3-month injectable,
- eCD4-Ig: an antibody-like entry inhibitor that closely mimics HIV-1's obligate receptors, proposed as an injectable.

There are a total of **30 MPT** (inclusive of DP products) **projects**, of which 12 projects are completed, on hold/stopped or of unknown status (4 projects completed, 5 projects of unknown status and 3 projects on hold/seeking funding); and **18 are actively ongoing projects. Three new entries** were identified since Jan 1, 2023: a NIAID-funded project that proposes to combine etonogestrel (for contraception) and islatravir (for PrEP) as drugamers in a nanofluidic refillable implant (NanoMPI), at the Houston Methodists Research Institute (HMRI) and University of Washington. The second new entry (previously overlooked) is a NIAID project funded since 2020- to UMass which proposes to develop a vaginal ring with TDF (for HIV PrEP) and a monoclonal antibody to prevent Gonorrhea (GC). The third new entry is an ongoing internally funded project from the Population Council and Medicines360 for a daily dual prevention pill (DPP) with TAF/FTC (for HIV PrEP) and LNG/EE (for contraception), which is being developed concurrently to the Viatris DPP (using TDF/FTC and LNG/EE). Aside from HIV, the most current other indication among the active MPT projects is to prevent unplanned pregnancy (17 projects); Human Simplex Virus (HSV) prevention is the next most common indication (5 projects), followed by anti-GC indication (3 projects) and anti- Human Papilloma Virus (HPV) indication (2 projects).

Active MPT projects:

- 13 topical products: 1 intra-uterine system (IUS), 1 fast dissolving insert (FDI), 2 vaginal films, 1 vaginal gel, 8 vaginal rings.
- 5 systemic products: 1 injectable, 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.
- Drugs investigated include both ARVs (e.g. 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) for the contraceptive drugs. The one new addition to this list is the ISL-ENG drugamer in the newly funded nanoMPI (refillable implant).

Publications/presentations: 37 recent (January through June 30, 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 review papers.

- This landscape review was dominated by papers and/or research presentations focusing on preclinical efficacy of several LA-DDS including a) the efficacy of ISL implants, CAB-ISFI and LEN injectables in NHP models b) new or ongoing strategies to extend the duration of protection through chemical modification of drugs or modification of APIs, and c) new compounds that may also prevent non-HIV STIs.

- Two papers explored a) drug toxicity with TAF releasing implants and discussed the relevance of the DDS itself (surface area and directionality of drug release) and local tissue concentration of drug as important considerations in drug-product performance, and b) a preclinical and mathematical modelling approach to better understand drug-drug interactions (both synergism and antagonism).
- Publications directly relevant to MATRIX CP projects include one publication and one presentation on the safety and favorable PK profile of the TAF/EVG FDI for rectal and vaginal use, and one presentation suggesting that women may have protection from injectable CAB-LA for 3 months, and a publication on a CAB ISFI which demonstrated extended duration of drug release (beyond 6 months).
- One publication describes safety and favorable PK of 3-month MPT TFV or TFV/LNG rings in women.

13 new relevant **media releases** were identified:

- Two (older) press releases from 2021 were identified for MPT implants being developed by private companies, with funding from the BMGF: one from Inflammasome Therapeutics (using ISL), and one from Titan Pharmaceuticals based on their platform technology which has been commercialized for the long-acting treatment of opioid addiction, called PRONEURA®. The APIs were not specified.
- Two press releases from vaccines trials (favorable preclinical data from Intranasal GC vaccine) and futility results from the MOSAICO trial of an HIV vaccine.
- Announcement that generic versions of CAB-LA will be produced in LMICs.
- Initial real-world data from uptake of the DPV ring vs Oral PrEP shows preference for the ring in Zimbabwe and HIV incidence similar to oral PrEP, especially in rural settings.
- 6 press releases and media articles of direct relevance from presentations at the CROI 2023 conference. These include press releases about the safety of the DPV ring during pregnancy and breastfeeding, the PK data supporting quarterly injections of CAB-LA in cis-gender women, the safety and acceptability of the FDI for rectal use, and the ineffectiveness of Doxy-PrEP in a trial among women in Kenya.

Conclusions:

- A total of 64 projects have been identified, of which **41 are actively ongoing (23 HIV prevention + 18 MPT projects**). Of these, 6 were new project entries since the landscape review 2 (submitted on Jan 18, 2023), but only one is a newly funded project by NIAID (the refillable MPT implant). Additionally, for increased clarity we have separated in the Appendix tables the 41 active projects from the 23 not currently active or whose status is unknown (11 HIV prevention +12 MPT projects).
- This latest landscape analysis (#3) highlighted significant progress for long-acting PrEP products, including new funding, and several key publications/presentations demonstrating pre-clinical safety and efficacy (i.e. LEN efficacy with SC injectables, CAB efficacy and > 6 month duration with CAB-ISFI and two papers showing ISL efficacy with a biodegradable implant and a refillable implant, respectively); prolonged duration of protection to 3 months, for cis-gender women injected with CAB-LA (from CROI 2023). Additionally, one publication showed safety and favorable PK and acceptability for 2 MPT rings (TFV and TFV/LNG rings) in Kenya.
- Directly informing the MATRIX CP projects, one publication describes the favorable PK, safety and acceptability of the TAF/EVG FDI inserted vaginally in women and one presentation (from CROI 2023) describes the same positive findings for rectal application (of 1 or 2 FDIs) in men and women. Furthermore, another presentation (from CROI 2023)

highlighted the extended duration of protection of the FDI post vaginal sex (for PEP) in the NHP model.

- Nevertheless, our most recent findings do not result in overlap with CP products in MATRIX. Indeed, the recent publications of preclinical efficacy with ARVs are with different formulations (e.g., ISFI), APIs (LEN or ISL) or target durations than the MATRIX CP products. Notably, the CAB ISFI which demonstrated preclinical efficacy in NHP, is an alternative delivery system that has solved the target duration problem of the CAB hydrogel depot (sustained release well over the 4xPA90 for >6months). But the ISFI has other regulatory challenges to consider (i.e., leaving solvent, size and number of nodules persisting subcutaneously). Of note one project entry (Project Horizon table 2b #4) was identified in 2023 as having the same two APIs for the dual-purpose hydrogel injectable (CAB and LNG) as the MATRIX CP project, however based on discussions with CONRAD the target duration is different for the USAID (6 months) and NIH funded projects (3 months). Also, importantly, with new DDS and APIs showing preclinical protection for extended duration, and indications that CAB-LA may afford protection to women for 3-months, in MATRIX, LA systemic CP products should focus on extending duration of protection beyond 3 months. New MPT products were also found, but they are mostly very early in the R&D path. **Thus, this analysis shows no significant overlap with current MATRIX critical path products.**

- The third call with Pharma and funders will be held in August 2023.
- Next landscape review will be conducted in December 2023.

3. **Review of published literature: Jan 1-June 30, 2023**

Each citation is followed by a link to the publication in PubMed, and a brief note about the goal or relevance of the publication (no notes written for the review papers and abstracts/presentations from conferences). Also, 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. Huang et al., (CROI 2023[3]) Abstract 100: LENACAPAVIR INHIBITS VIRION MATURATION BY BLOCKING FORMATION OF CAPSID PENTAMERS. https://www.iasusa.org/wp-content/uploads/2023/04/april-2023.pdf

INSTI:

2. Haaland RE, Fountain J, Martin A, Dinh C, Holder A, Edwards TE, Lupo LD, Hall L, Conway-Washington C, Massud I, García-Lerma JG, Kelley CF, Heneine WM. Pharmacology of boosted and unboosted integrase strand transfer inhibitors for two-dose event-driven HIV prevention regimens among men. J Antimicrob Chemother. 2023 Feb 1;78(2):497-503. doi:

[3] All CROI 2023 abstracts will have the same link to the conference book of abstracts (then search for the abstract number): https://www.iasusa.org/wp-content/uploads/2023/04/april-2023.pdf

10.1093/jac/dkac419. PMID: 36512383; PMCID: PMC1016126. https://pubmed.ncbi.nlm.nih.gov/36512383/. *This paper assessed elvitegravir- and bictegravir-containing regimen for on demand PrEP in Men. To better understand INSTI distribution and inform dosing selection the authors compared the pharmacology of two-dose boosted elvitegravir and unboosted bictegravir regimens in MSM. Differing elvitegravir and bictegravir tissue distribution may result in variable mucosal and systemic antiviral activity and can inform dosing strategies for event-driven HIV prevention.*

3. Marzinke, M. et al., (CROI 2023, Abstract 159) CABOTEGRAVIR PHARMACOLOGY IN THE BACKGROUND OF DELAYED INJECTIONS IN HPTN 084. *See also* media article: https://www.aidsmap.com/news/feb-2023/good-news-women-and-prep-quarterly-dosing-may-work?utm_source=conference+news-english&utm_medium=email&utm_campaign=2023-02-23
4. Eshleman, S. et al., (CROI 2023, Abstract 160): THE LEVI SYNDROME: CHARACTERISTICS OF EARLY HIV INFECTION WITH CABOTEGRAVIR FOR PrEP

NRTTI:

5. Squires, K. et al., (CROI 2023 Abstract 192): EFFECT OF ISLATRAVIR ON TOTAL LYMPHOCYTE AND LYMPHOCYTE SUBSET COUNTS.
6. MK8527: this is an analog to ISL that Merck has been developing by MERCK to replace ISL. The clinical program with MK8527 for treatment is continuing, with one completed trial (N=17) for treatment https://clinicaltrials.gov/ct2/show/results/NCT03615183, and a phase I trial (N=20) in treatment naïve individuals started in 2022 (N=20). Anticipated completion of the second trial is for 10/2023:https://www.avac.org/trial/mk-8527-004 https://www.clinicaltrials.gov/ct2/show/NCT05494736?term=NCT05494736&draw=2&rank=1. There is only sparse public information on Merck's plans for treatment (and none for prevention) with this analog: https://www.pharmaceutical-technology.com/data-insights/mk-8527-merck-human-immunodeficiency-virus-hiv-infections-aids-likelihood-of-approval/

7. 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 Jun 12:e0222422. doi: 10.1128/mbio.02224-22. Epub ahead of print. PMID: 37306625. https://pubmed.ncbi.nlm.nih.gov/37306625/. *This paper presents an innovative approach to evaluate the prevention of penile HIV transmission, through a new in vivo model that uses BLT humanized mice. The authors show that antiretroviral treatment with Islatravir (EFdA) suppresses HIV replication in all tissues of the male genital tract, restores normal levels of CD4 T cells and thus, should be highly efficient at preventing penile transmission*.

Entry/Fusion inhibitor

8. He L, Wang C, Zhang Y, Chong H, Hu X, Li D, Xing H, He Y, Shao Y, Hong K, Ma L. Broad-spectrum anti-HIV activity and high drug resistance barrier of lipopeptide HIV fusion inhibitor LP-19. Front Immunol. 2023 May 15;14:1199938. doi: 10.3389/fimmu.2023.1199938. PMID: 37256122; PMCID: PMC10225588. https://pubmed.ncbi.nlm.nih.gov/37256122/ *This in vitro study with 47 HIV clinical isolates of Lipopeptide-19, a HIV fusion inhibitor (LP-19), suggests that LP-19 has broad-spectrum anti-HIV activity, and high drug resistance barrier.*

Other:

9. Gallay PA, Ramirez CM, Baum MM. Acute antagonism in three-drug combinations for vaginal HIV prevention in humanized mice. Sci Rep. 2023 Mar 21;13(1):4594. doi: 10.1038/s41598-023-31695-5. PMID: 36944714; PMCID: PMC10030891. https://www.nature.com/articles/s41598-023-31695-5
BLT humanized mice were used to measure the in vivo efficacy against HIV-1 of single and combination antiviral compounds applied vaginally, coupled with data analysis using a mathematical model to study the dose-effect characteristics. Unexpectedly, strong antagonism was observed in drug combinations composed of TDF-FTC coupled with a third agent using a different mode of action against (e.g., the INSTI EVG or the viral membrane-disrupting peptide C5A). The antagonistic effect was remedied when TDF was omitted from the regimen. The authors provide a translational template for the preclinical, rational, and systematic evaluation of drug combinations for the prevention of HIV-1.

3b. Reviews or reports:

10. 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. https://pubmed.ncbi.nlm.nih.gov/37160248/

11. Overmars, R.J., Zoë Krullaars & Thibault Mesplède (2023). Investigational drugs for HIV: trends, opportunities and key players, Expert Opinion on Investigational Drugs, 32:2, 127-139, DOI: 10.1080/13543784.2023.2178415. https://doi.org/10.1080/13543784.2023.2178415

12. Young Holt B, Hemmerling A, Moore S, Yang K. Expanding the pipeline for multipurpose prevention technologies: compounds with potential activity to prevent or treat HIV and other STIs. Sex Transm Infect. 2023 May;99(3):203-207. doi: 10.1136/sextrans-2022-055647. Epub 2023 Mar 6. PMID:36878691. https://pubmed.ncbi.nlm.nih.gov/36878691/

3c. HIV and MPT Preclinical studies:

13. Bekerman E, Yant SR, Vander Veen LA, Hansen D, Lu B, Rowe W, Wang KW, Callebaut C. Long-acting lenacapavir acts as an effective pre-exposure prophylaxis in a rectal SHIV challenge macaque model. J Clin Invest. 2023 Jun 29:e167818. doi: 10.1172/JCI167818. Epub ahead of print. PMID: 37384413. https://www.jci.org/articles/view/167818
This paper is a proof of concept that LEN can offer safe and effective long-lasting HIV prophylaxis (published after the CROI 2023 presentation). Using a single high-dose rectal SHIV challenge in the NHP mode to acquire the precise knowledge of plasma drug exposure at the time of challenge, LEN administration reduced the rate of infection per exposure by more than 2-fold (compared to the untreated animals) and was fully protective against SHIV acquisition at plasma LEN levels above the NHP-adjusted C-trough concentrations targeted with twice-yearly formulations of LEN in the clinic.

14. Cohen, J., Dennis Shull & Stephanie Reed (2023) Co-delivery of an HIV prophylactic and contraceptive using PGSU as a long-acting multipurpose prevention technology, Expert Opinion on Drug Delivery, 20:2, 285-299, https://doi.org/10.1080/17425247.2023.2168642
Traditional polymers encounter challenges delivering multiple drugs with dissimilar physiochemical properties. Poly(glycerol sebacate) urethane (PGSU) is a cured

bioresorbable elastomer that offers an alternative option that successfully delivers hydrophilic EFdA (ISL) alongside hydrophobic LNG. This article presents the formulation, design, and characterization of PGSU implants co-delivering EFdA and LNG. The authors of this paper are employees of Secant group, a PA-based company with expertise in biomaterials for medicine: https://secant.com/drug-delivery/

15. Coulter SM, Pentlavalli S, Vora LK, An Y, Cross ER, Peng K, McAulay K, Schweins R, Donnelly RF, McCarthy HO, Laverty G. Enzyme-Triggered l-α/d-Peptide Hydrogels as a Long-Acting Injectable Platform for Systemic Delivery of HIV/AIDS Drugs. Adv Healthc Mater. 2023 Mar 7:e2203198. doi: 10.1002/adhm.202203198. Epub ahead of print. PMID: 36880399. https://pubmed.ncbi.nlm.nih.gov/36880399/ *This work is a proof-of-concept, that a HIV/AIDS long-acting drug delivery ISFI can be developed using an enzyme responsive peptide hydrogel system. This paper presents an alternative ISFI platform to deliver a model antiretroviral drug (zidovudine) over a month. The formulation is a self-assembling ultrashort d or l-αpeptide hydrogelator, covalently conjugated to zidovudine via an ester linkage. Drug release, via hydrolysis of the ester linkage, progress under physiological conditions and persisted in rats over 35 days*.

16. Daly, M. et al., (CROI 2023, Abstract 989):VAGINAL PrEP EFFICACY OF BIODEGRADABLE ISLATRAVIR IMPLANTS IN MACAQUES. https://www.croiconference.org/abstract/vaginal-prep-efficacy-of-biodegradable-islatravir-implants-in-macaques/
17. Makarova, N. et al. (CROI 2023, Abstract 990): EXTENDED POST-EXPOSURE PROTECTION AGAINST SHIV VAGINAL INFECTION WITH TAF/EVG INSERTS
18. 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 is a proof of concept that ISL can offer safe and effective long-lasting HIV prophylaxis (published after the CROI 2023 presentation). The paper describes ISL-eluting implants which maintained preventative concentration of ISL in plasma and ISL-TP (the active metabolite) in PBMC for over 20 months in rhesus macaques. The implants were well tolerated (mild local tissue inflammation and no sign of systemic toxicity) and were 100% protective in male or female macaques against low dose repeat SHIV challenge vaginally or rectally.*
19. Pons-Faudoa FP, Di Trani N, Capuani S, Hernandez N, Wood AM, Nehete B, Niles J, Shelton KA, Kezar S, Bushman LR, Chua CYX, Ittmann MM, Anderson PL, Nehete PN, Arduino RC, Nichols JE, Grattoni A. Changes in local tissue microenvironment in response to subcutaneous long-acting delivery of tenofovir alafenamide in rats and non-human primates. J Control Release. 2023 Jun;358:116-127. doi: 10.1016/j.jconrel.2023.04.037. Epub 2023 Apr 29. PMID: 37120032. https://pubmed.ncbi.nlm.nih.gov/37120032/ *This paper explores the basis for TAF's local toxicity when delivered via different types of subcutaneous implants. The authors explored 3 forms of TAF (free base, fumarate salt and freebase with urocanic acid) released from their refillable nanofluidic implants in the rat and NHP models. All forms of TAF produced chronic local inflammation. Importantly, the level of foreign body response was tightly correlated with local TAF tissue concentration. Further, regardless of the degree of FBR, the fibrotic capsule (FC) surrounding the implants*

did not interfere with drug diffusion and systemic delivery. These findings may partially explain why implants with a larger drug release surface area exhibited more severe AE (including necrosis and ulceration) as compared to the pores/ports from the nanofluidic implant. A key finding was that for drugs eliciting an inflammatory tissue response, release direction with respect to the body (and skin surface) can determine implant tolerability or rejection.

20. Young, I.C., Massud, I., Cottrell, M.L. *et al.* Ultra-long-acting in-situ forming implants with cabotegravir protect female macaques against rectal SHIV infection. *Nat Commun* **14**, 708 (2023). https://doi.org/10.1038/s41467-023-36330-5. *This paper describes the release of CAB from ISFI above protective benchmarks for more than 6 months. In female rodent and NHP, CAB ISFIs showed no signs of toxicity or chronic inflammation. In macaques, median plasma CAB concentrations exceed established PrEP protection benchmarks within 3 weeks and confer complete protection against repeated rectal SHIV challenges. Modelling suggests that 3ml injections would confer protection in humans for over 5 months*.
21. Young, I.C.; Thorson, A.L.; Shrivastava, R.; Sykes, C.; Schauer, A.P.; Cottrell, M.L.; Kashuba, A.D.M.; Benhabbour, S.R. Dose-Ranging Plasma and Genital Tissue Pharmacokinetics and Biodegradation of Ultra-Long-Acting Cabotegravir InSitu Forming Implant. Pharmaceutics 2023, 15, 1487.https://pubmed.ncbi.nlm.nih.gov/37242729/. *This paper characterizes CAB ISFI pharmacokinetics (PK) in mice by assessing the effect of dose and number of injections on CAB PK, time to completion of CAB release and polymer degradation, long-term genital tissue PK, and CAB PK tail after implant removal. CAB concentrations in plasma were above the benchmark for protection for 11-12 months with proportionality between dose and drug exposure. CAB ISFI exhibited high concentrations in vaginal, cervical, and rectal tissues for up to 180 days.*
22. 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 Jun 8;642:123108. doi: 10.1016/j.ijpharm.2023.123108. Epub ahead of print. PMID: 37301241. https://pubmed.ncbi.nlm.nih.gov/37301241/. *This paper describes novel bilayer dissolving microneedles (MNs) for the transdermal delivery of long-acting delivery of the ARV bictegravir (BIC) as coarse drug or nanosuspension. Dissolving MNs exhibited favorable mechanical and insertion ability in the human skin simulant Parafilm® _M and excised neonatal porcine skin. After a single application in rats (for 24h), both coarse BIC and BIC nanosuspensions achieved sustained release, maintaining plasma concentrations above human therapeutic levels (162 ng/mL) for 4 weeks. However, calculation for scaling up in humans would only achieve relevant BIC plasma concentration over 7 days, with an acceptable size patch (~<29cm2).*

3d. HIV-PrEP and MPT clinical studies

23. Anderson PL, Marzinke MA, Glidden DV. Updating the adherence-response for oral F-TDF for PrEP among cisgender women. Clin Infect Dis. 2023 Jan 16:ciad021. doi: 10.1093/cid/ciad021. Epub ahead of print. PMID: 36645796. https://pubmed.ncbi.nlm.nih.gov/36645796/. *When using intra-erythrocytic TFV-DP data from the FTC/TDF arms of HPTN 038 and 084, ~ 99% efficacy was achieved at lower adherence threshold for men (in HPTN 083), equivalent to 2+ doses/week, compared with daily dosing in HPTN-084 (women), suggesting that higher adherence is necessary for women vs. men with oral PrEP.*

24. Brown, B.P., Feng, C., Tanko, R.F. *et al.* Copper intrauterine device increases vaginal concentrations of inflammatory anaerobes and depletes lactobacilli compared to hormonal options in a randomized trial. *Nat Commun* **14**, 499 (2023). https://doi.org/10.1038/s41467-023-36002-4. *Among 218 women enrolled into a substudy of the ECHO Trial, participants randomized to Cu-IUD exhibit elevated bacterial diversity, increased cytokine concentrations, and decreased relative abundance of lactobacilli after one and six months of use, relative to enrollment and other hormonal contraceptive options (DMPA and LNG implants). Total bacterial loads of women using Cu-IUD increase 5.5 fold after six months, predominantly driven by increases in the concentrations of several inflammatory anaerobes. Furthermore, growth of L. crispatus (MV-1A-US) is inhibited by Cu2+ ions below biologically relevant concentrations, in vitro. These findings on the vaginal environment may have implications for MPTs using Copper for their contraceptive indication.*
25. *Bunge, K et al.,* (CROI 2023 Abstract 127): DELIVER: A SAFETY STUDY OF A DAPIVIRINE VAGINAL RING AND ORAL PrEP DURING PREGNANCY
26. Franzén Boger M, Benhach N, Hasselrot T, Brand RM, Rohan LC, Wang L, McGowan I, Edick S, Ho K, Meyn L, Matoba N, Palmer KE, Broliden K, Tjernlund A. A topical rectal douche product containing Q-Griffithsin does not disrupt the epithelial border or alter $CD4^+$ cell distribution in the human rectal mucosa. Sci Rep. 2023 May 9;13(1):7547. doi: 10.1038/s41598-023-34107-w. PMID: 37161022; PMCID: PMC10169179. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10169179/.*For topical on demand products applied rectally, it is critical to preserve an intact rectal epithelium and avoid an influx of mucosal HIV target cells with such product use. This phase 1 clinical trial evaluated application of a topical rectal douche product containing Q-Griffithsin (Q-GRFT). Colorectal tissue samples were obtained via sigmoidoscopy at baseline, 1 and 24 h after single-dose exposure in 15 healthy volunteers. the rectal epithelium and CD4+ cell distribution remained unchanged following topical application of Q-GRFT. In situ visualization of HIV susceptibility markers at mucosal sites could be useful to complement standard product safety assessments.*
27. Mugo NR, Mudhune V, Heffron R, Thomas KK, McLellan-Lemal E, Njoroge B, Peacock S, O'Connor SM, Nyagol B, Ouma E, Ridzon R, Wiener J, Isoherranen N, Erikson DW, Ouattara LA, Yousefieh N, Jacot TA, Haaland RE, Morrison SA, Haugen HS, Thurman AR, Allen SA, Baeten JM, Samandari T and Doncel GF (2023) Randomized controlled phase IIa clinical trial of safety, pharmacokinetics and pharmacodynamics of tenofovir and tenofovir plus levonorgestrel releasing intravaginal rings used by women in Kenya. Front. Reprod. Health 5:1118030. doi: 10.3389/frph.2023.1118030. https://www.frontiersin.org/articles/10.3389/frph.2023.1118030/full. *The paper presents the primary findings from a Phase IIa placebo-controlled RCT among 27 Kenyan women, which showed that a 3-month TFV/LNG or TFV-only vaginal ring were safe and well tolerated. Steady state geometric mean amount (SSGMC) of plasma or vaginal TFV (collected via swabs) were comparable in both ring groups. Serum LNG SSGMC was 241 pg/ml in users of the TFV/LNG ring. In vitro, cervico-vaginal fluids in active ring users displayed elevated anti-HIV-1 and anti-HSV2 activities (compared to placebo rings). These findings suggest the potential for MPT clinical efficacy of the TFV/LNG ring.*
28. Owor, M. et al., (CROI 2023 Abstract 785): DAPIVIRINE RING SAFETY AND DRUG DETECTION IN BREASTFEEDING MOTHER-INFANT PAIRS.
29. Riddler, S. et al., (CROI 2023 Abstract 164) SAFETY AND PK/PD OF A TENOFOVIR ALAFENAMIDE/ELVITEGRAVIR INSERT ADMINISTERED RECTALLY.

30. Sachdeva R, Kumar N, Brache V, Friedland BA, Plagianos M, Zhang S, Kizima L, Cochon L, Tabar AST, Blanc A, Merkatz RB. New approaches for developing biomarkers of hormonal contraceptive use. Sci Rep. 2023 Jan 5;13(1):245. doi: 10.1038/s41598-022-24215-4. PMID: 36604469; PMCID: PMC9816169. https://pubmed.ncbi.nlm.nih.gov/36604469/. *Liquid chromatography-tandem mass spectrometry (LC–MS/MS) was used to measure serum/urine LNG and medroxyprogesterone acetate (MPA). Results suggest urine sampling can be used to identify a biomarker of LNG and MPA use.*
31. Thurman AR, Ouattara LA, Yousefieh N, Anderson PL, Bushman LR, Fang X, Hanif H, Clark M, Singh O, Doncel GF. A phase I study to assess safety, pharmacokinetics, and pharmacodynamics of a vaginal insert containing tenofovir alafenamide and elvitegravir. Front Cell Infect Microbiol. 2023 Apr 19;13:1130101. doi: 10.3389/fcimb.2023.113010. PMID: 37153145; PMCID: PMC10154607. https://pubmed.ncbi.nlm.nih.gov/37153145/. *In this phase I RCT trial, a single vaginal application of a TAF/EVG FDI was safe, well tolerated (all product-related AEs were mild) and acceptable. The insert rapidly delivered TAF, which converted into TFV, and EVG, yielding high concentrations in vaginal fluid by 4h after dosing (first time point evaluated). high tissue concentrations of EVG were measured at 4 and 24h post-dosing, followed by high TFV-DP concentrations 24-72h post dosing. A single dose of TAF/EVG inserts met PK benchmarks, with PK data supporting an extended window of high mucosal protection. PD modeling supports mucosal protection against both HIV-1 and HSV-2.*
32. Donnell, D., , Fei Gao, James P. Hughes, Brett Hanscom, Lawrence Corey, Myron S. Cohen, Srilatha Edupuganti, Nyaradzo Mgodi, Helen Rees, Jared M. Baeten, Glenda Gray, Linda-Gail Bekker, Mina Hosseinipour, Sinead Delany-Moretlwe. Counterfactual estimation of efficacy against placebo for novel PrEP agents using external trial data: example of injectable cabotegravir and oral PrEP in women. JIAS 2023, 26: e26118. https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.26118. *Using counterfactual placebo methodology, CAB-LA in HPTN-084 showed an estimated risk reduction of 92.8%–94.7% for women. The counterfactual placebo estimates of oral FTC/TDF efficacy ranged from 15% to 40%, in the context of modest adherence to oral PrEP in HPTN 084. Counterfactual placebo rates of HIV acquisition derived from external trial data in similar locations and time can be used to support estimates of placebo-based efficacy of a novel HIV prevention agent.*

3e. Reviews of clinical studies:

33. Durham SH, Milam A, Waer D, Chahine EB. Cabotegravir: The First Long-Acting Injectable for HIV Preexposure Prophylaxis. Ann Pharmacother. 2023 Mar;57(3):306-316. doi: 10.1177/10600280221102532. Epub 2022 Jul 1. PMID: 35778802. https://pubmed.ncbi.nlm.nih.gov/35778802/
34. Dohadwala S, Politch JA, Barmine JH, Anderson DJ. A Brief History and Advancement of Contraceptive Multipurpose Prevention Technology (cMPT) Products. Open Access J Contracept. 2023 Jun 13;14:83-94. doi: 10.2147/OAJC.S375634. PMID: 37332341; PMCID: PMC10276588. https://pubmed.ncbi.nlm.nih.gov/37332341/
35. Fonner, Virginia; Ridgeway, Kathleen; van der Straten, Ariane; Lorenzetti, Lara; Dinh, Nhi; Rodolph, Michelle; Schaefer, Robin; Schmidt, Heather-Marie; Nguyen, Van Thi Thuy; Radebe, Mopo; Peralta, Hortencia; Baggaley, Rachel. Safety and efficacy of long-acting injectable cabotegravir as preexposure prophylaxis to prevent HIV acquisition. AIDS 37(6):p 957-966, May 1, 2023. | DOI: 10.1097/QAD.0000000000003494. https://pubmed.ncbi.nlm.nih.gov/36723489/

36. Lu and Haddad, Commentary: Multipurpose prevention technologies—What about sexually transmitted infections? Front. Reprod. Health, 02 June 2023
Sec. HIV and STIs Volume 5 - 2023 | https://doi.org/10.3389/frph.2023.1158528
37. Landovitz, R.J., Scott, H. & Deeks, S.G. Prevention, treatment and cure of HIV infection. *Nat Rev Microbiol* (2023). https://doi.org/10.1038/s41579-023-00914-1

3e. Select Press releases and media:

1. Inflammasome Therapeutics announced in 2021 that they received funding from the BMGF to develop a MPT implant: https://www.inflam.com/images/pdfs-doc/Inflammasome_to_Develop_Dual_Sustained_Release_HIV-Prevention_and_Birth_Control_Implant.pdf

2. Titan Pharmaceuticals also received funding from the BMGF in 2021 to develop a MPT implant (APIs not specified) using their platform implant technology PRONEURA: https://www.titanpharm.com/news/press-releases/detail/259/titan-pharmaceuticals-receives-funding-to-develop)

3. Intravacc Announces Favorable Preclinical Data for its Candidate Intranasal Gonorrhea Vaccine Avacc 11 (Jan 16, 2023): https://www.prnewswire.com/news-releases/intravacc-announces-favorable-preclinical-data-for-its-candidate-intranasal-gonorrhea-vaccine-avacc-11-301722085.html

4. JandJ MOSAICO vaccine trial stopped for futility (January 18, 2023) https://www.fiercebiotech.com/biotech/jj-packs-hiv-vaccine-after-failing-phase-3-trial?utm_medium=email&utm_source=nl&utm_campaign=LS-NL-FiercePharma+Tracker&oly_enc_id=4768I1067634H7I and https://www.jnj.com/janssen-and-global-partners-to-discontinue-phase-3-mosaico-hiv-vaccine-clinical-trial?utm_source=AVAC+Email+Updates&utm_campaign=f35b021248-EMAIL_CAMPAIGN_2021_08_31_11_20_COPY_01&utm_medium=email&utm_term=0_6fd730be57-f35b021248-130145473

5. Medicines Patent Pool signs sublicences with Aurobindo, Cipla and Viatris to produce generic versions of ViiV Healthcare's innovative long-acting HIV prevention medicine. https://medicinespatentpool.org/news-publications-post/medicines-patent-pool-signs-sublicences-with-aurobindo-cipla-and-viatris-to-produce-generic-versions-of-viiv-healthcares-innovative-long-acting-hiv-prevention-medicine

6. Generic for CAB-LA to be produced locally in South Africa via Cipla: https://bhekisisa.org/health-news-south-africa/2023-05-09-the-anti-hiv-injection-will-be-made-in-sa-it-could-cost-between-r600-and-r800-a-pop/?utm_source=AVAC+Email+Updates&utm_campaign=9e7239ba6a-EMAIL_CAMPAIGN_2023_05_12_08_05&utm_medium=email&utm_term=0_-9e7239ba6a-%5BLIST_EMAIL_ID%5D

7. https://www.aidsmap.com/news/may-2023/dapivirine-vaginal-ring-shows-comparable-hiv-risk-rate-oral-prep
Early real-world data from Zimbabwe on the dapivirine vaginal ring shows a similar rate of new HIV acquisitions between women using the ring and oral PrEP, Jabulani Mavudze of Population Solutions For Health in Harare told the INTEREST 2023 conference in Maputo, Mozambique. The study also found that more rural than urban women preferred the ring, and that more women continued to use the ring for several months. (May 12, 2023).

8. Press releases and media articles from presentations at CROI 2023:
    a. AIDSMAP: Injectable PrEP: good news for women as quarterly dosing may work. https://www.aidsmap.com/news/feb-2023/good-news-women-and-prep-quarterly-dosing-may-work?utm_source=conference+news-english&utm_medium=email&utm_campaign=2023-02-23
    b. https://www.mtnstopshiv.org/news/no-safety-concerns-seen-use-dapivirine-vaginal-ring-during-third-trimester-pregnancy-according
    c. https://www.mtnstopshiv.org/news/study-suggests-dapivirine-vaginal-ring-safe-use-hiv-prevention-during-breastfeeding
    d. https://www.aidsmap.com/news/feb-2023/promising-new-prep-method-undergoes-first-safety-study-anal-sex
    e. https://www.mtnstopshiv.org/news/fast-dissolving-insert-found-safe-shows-promise-method-preventing-hiv-through-anal-sex
    f. Doxy PEP Does Not Lower Risk of STIs in Cisgender Women: https://www.medscape.com/viewarticle/988659

Appendix Tables:

1a. HIV Prevention Projects – COMPLETED, STOPPED or STATUS UNKNOWN (* all changes in table are in red text)

N= 11	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	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	preclinical	Multiple, neuro-drugs	Theoretica	NIMH and NCATS funding	3D printed small biodegradable device (can be	https://pubmed.ncbi.nlm.nih.gov/29247175/

		(GW, CNMC, yale, U Mass..)			lly tunable to needed duration	completed in 2023. Unknown status	delivered via 22G needle) for direct implantation in target tissues (E.g., brain). PI: Torii, Masaaki, NIMH (2017-2023), NCATS (2016-2023)	US patent. Application No. 62/554,680 (per publication)

1b. HIV Prevention Projects – Ongoing (* all changes in table are in red text)

N=23	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	https://clinicaltrials.gov/ct2/show/NCT04994509 https://www.jci.org/articles/view/167818
2	Injectable-parenteral	U Nebraska	preclinical	DLG prodrug	up to 1 yr.	Ongoing	18-carbon chain modified ester prodrug nanocrystal- for sustained release via IM injectable in rats & NHP. PI: Gendelman, NIAID (2019-2024; 2021-2026) and NIMH	https://pubmed.ncbi.nlm.nih.gov/35680875/ Multiple grants including: https://reporter.nih.gov/search/4tRb8l3UVU20sJ2Ev-E3ew/project-details/10421426 And https://reporter.nih.gov/search/4tRb8l3UVU20sJ2Ev-E3ew/project-details/10597017
3	injectable-parenteral	UW	FIH/ clinical	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: Collier and Ho, NIAID 2019-2024;	https://reporter.nih.gov/search/tqIyle6FM02SXTyegdlPdg/project-details/10234129 https://reporter.nih.gov/project-details/9733109 https://classic.clinicaltrials.gov/ct2/show/NCT05850728
4	Implant bioerodible. (PEO coated w/ PCL) -SC	QUB	Preclinical	model hydrophobic drug: olanzapine	> 6 months	Unknown	3D printed implant. PI: unknown, funding: Academy of medical sciences, Wellcome Trust	https://www.tandfonline.com/doi/full/10.1080/10717544.2022.2057620
5 New Entry	MAP transdermal	QUB	preclinical	Bictegravir	~ 1 month	Ongoing? (new publication in 6/2023)	PI: Donelly; funding: EPSRC Wellcome Trust	https://pubmed.ncbi.nlm.nih.gov/37301241/
6 New Entry	Injectable ISFI	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/

N=23	DDS	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	References publication and/or NIH RePorter link
	hydrogel-parenteral							
7	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	https://reporter.nih.gov/project-details/10841186
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	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- Phase I trial completed 2/2023	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://classic.clinicaltrials.gov/ct2/show/NCT04672083
10	Removable Implant- SC	OCIS, CAPRISA	Phase 1	NRTI TAF	1 year	Trial completed, publication pending.	CAP-018. PI: Abdool Karim, SAMRC, EDCTP, NRF (end 12/2023)	https://pubmed.ncbi.nlm.nih.gov/34992111/J10 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	https://reporter.nih.gov/search/a71vYCzPO0ylXUPZu8M8Cw/project-details/10458685
12	Removable Implant -SC	OCIS	Next gen Preclinical + phase I/II	TAF and new pro-drug formulations	1year	Ongoing	PI: Baum; NIAID 2021-2026 and 2023-2027	https://reporter.nih.gov/project-details/10449318 https://reporter.nih.gov/search/yJeldSyO4Ei5rDD8l8nehw/project-details/10617540 https://pubmed.ncbi.nlm.nih.gov/35581262/

N=23	DDS	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	References publication and/or NIH RePorter link
13	Implant-bioerodible (PCL) -SC	RTI	preclinical	TAF, ISL, BIC, others	7-12 months	Ongoing	NHP studies completed with TAF and ISL PI: Johnson, USAID (completed); NIAID (2020-2025), NICHD (2020-2025).	https://reporter.nih.gov/project-details/10348177 https://reporter.nih.gov/search/zaeac07k30aOzz8tjq2E3Q/project-details/10242929 https://reporter.nih.gov/project-details/10546217 https://pubmed.ncbi.nlm.nih.gov/35913838/ https://www.frontiersin.org/articles/10.3389/fphar.2022.923954/full
14	Implant-Refillable (Titanium) -SC	HMRI	preclinical	TAF and FTC; ISL	60 + days->20 months	Ongoing	PI Grattoni: NIGMS 2018-2023; NIAID 2016-2022; 2022-2027	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/ https://reporter.nih.gov/project-details/10093084
15	In situ forming implant (ISFI)- -SC	UNC	preclinical	ISL, CAB and other drugs incl for TB	>6 months	Ongoing (end date Aug 31, 2023)	PI: Garcia, NIAID 2018-2023	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9911691/ https://reporter.nih.gov/project-details/10468909
16	Oral tablets-enteral	MSD	clinical	ISL or MK8527 (NRTTI)	monthly	ISL development Stopped for PrEP. Initiation of R&D with Back up API	PI: unknown. Merck may be reinitiating development with MK8527	https://www.pharmaceutical-technology.com/data-insights/mk-8527-merck-human-immunodeficiency-virus-hiv-infections-aids-likelihood-of-approval/

N= 23	DDS	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	References publication and/or NIH RePorter link
17	Tablets LYNX™ platform-enteral	Lyndra	preclinical	undisclosed	7 days-1 month	Ongoing	focused on Rx but can work for Px; GILEAD involved for HIV indication; https://lyndra.com/pipeline/ PI: unknown	https://www.nature.com/articles/s41467-017-02294-6
18	Enema/ douche-rectal	JHU	phase I/II	TFV	OD	Ongoing	PI: Hendrix, HPTN 106, NIH (protocol development stage)	https://grantome.com/grant/NIH/U19-AI113127-01 https://pubmed.ncbi.nlm.nih.gov/36477356/
19	MAP-transdermal	PATH/QUB	preclinical	RPV and other ARVs (CAB, LEN)	7 D-1 Mo	Ongoing	USAID (past). Current Funding focused on Pediatric Rx (e.g., with LEN) PIs: R. Donelly (QUB); R Choy (PATH) NIAID (2020-2025)	https://www.sciencedirect.com/science/article/pii/S0168365918306370?via%3Dihub Posters presented at 2023 https://www.microneedlesconference.com/
20	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	https://reporter.nih.gov/project-details/10174715
21	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	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7591136/ https://reporter.nih.gov/project-details/10576394
22	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	https://reporter.nih.gov/search/tU8bGUDGkOFi3qd-vWenw/project-details/10420527
23 New entry	Tablet-vaginal	Osel, Inc.	Preclinical/ FIH	recombinant L. jensenii with mCV-N	OD	ongoing	PI Lagenaur NIAID 2020-2023. Live biotherapeutic product (LBP) secreting potent HIV entry inhibitor, modified cyanovirin-N	https://reporter.nih.gov/search/cKoXtRxn2U2IgmOgqFNymg/project-details/10223989

2a. **MPTs including an HIV indication (stopped/ completed project or unknown)** (* all changes in table are in red text)

N =12	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	On Pause (Haddad personal 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 =12	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 through Portugal and EU (FCT, FEDER, COMPETE 2020, POCI)	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 NIAID (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 and 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

2b. **MPTs including an HIV indication (ongoing)** (* all changes in table are in red text)

N =18	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 program NIAID 2019-2024	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	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	PPCM-Gel vaginal	CT, GC, HPV, HSV, PREG	YASO therapeutics	Preclinical and early clinical	polyphenylene carboxymethylene	OD	Ongoing. IND submitted 5/2023 (pers. communication Weitzel)	PI: Weitzel, NICHD 2022-2023.	https://pubmed.ncbi.nlm.nih.gov/32469052/ https://reporter.nih.gov/project-details/10483274
4	Injectable Hydrogel-parenteral- SC	PREG	EVMS/CONRAD	preclinical	CAB+ LNG	3 mo	Ongoing	PI: Clark. Project Horizon, NIAID 2019-2024. Note: Project switched from DLG to CAB	https://reporter.nih.gov/project-details/10546210 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9639748/
5. NEW entry	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)	https://reporter.nih.gov/search/t0FXMGGdiE622_eUszaw7g/project-details/10619811
6	In Situ forming implant (ISFI)	PREG	UNC	preclinical	DLG, RPV, CAB, other	6 months	Ongoing	PI: Benhabour. NIAID 2021-2026	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)
7	Insert (FDI)-vaginal	BV, CT, GC, PREG	PC	preclinical	AMPHORA, Q-GRFT	OD	Ongoing	PI: Angsantikul. NIAID 2020-2025	https://reporter.nih.gov/project-details/10395456

N =18	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
8	IUD - Intrauterine	PREG	UW	preclinical	Copper + ARVs (unspecified)	??	Ongoing	PI: Woodrow NIAID 2020-2025	https://reporter.nih.gov/project-details/10460638 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9081257/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9277594/
9	DPP- enteral	PREG	Viatris, (PC)	clinical	TDF/FTC, LNG/EE	24h (daily)	Ongoing-	Note: delays in starting clinical study given challenges to establishing bioequivalence 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/
10 NEW entry	DPP- enteral	PREG	PC/ Medicines 360	Pre-clinical and clinical	TAF/FTC, LNG/EE	24h (daily)	Ongoing (PC internal funding)	works on an over-encapsulated DPP and a TAF DPP. PI: Haddad	https://popcouncil.org/project/dual-prevention-pill-for-the-prevention-of-hiv-and-unintended-pregnancy/
11	Core Sheath Ring -vaginal	PREG	IPM/PC	clinical	DPV, LNG	90 days	Ongoing- requested onboarding in MATRIX (NPR)	PI: Steyton phase I/II IPM 056 / CCN019B (NICHD) through 2023	https://www.avac.org/trial/ipm-056-ccn019b
12	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	https://www.sciencedirect.com/science/article/pii/S0168365915006252 https://reporter.nih.gov/project-details/10324914
13	Ring- pod- (silicone) vaginal	HSV, PREG	Auritech	preclinical	TAF/ or TDF/FTD, ACV and ENG/EE	1 month	Ongoing	NHP studies completed. PI: Smith, NIAID R33 active (2018-2023)	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0185946 https://reporter.nih.gov/project-details/10378141
14	Ring- pod (silicone) - vaginal	PREG	PC	preclinical	Q-GRFT, ETG, EE	90 days	Ongoing	PI: Teleshova, NIAID 2020-2025. Will also test 3 different diameters of rings.	https://reporter.nih.gov/project-details/10394426 https://www.popcouncil.org/research/an-intravaginal-ring-

N =18	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
									containing-etonogestrel-ethinyl-estradiol-and-qgriffit
15	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. The non-hormonal contraceptive mAB relies on sperm immobilization	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8868023/ https://reporter.nih.gov/project-details/10359111
16	Non hormonal Ring_ capsule vaginal	PREG	Mucomune	preclinical	mAB cocktail-HCA+VRC01+N6	1 month +	Ongoing	PI: Kushiro. NICHD-2021-2024. 2 mABs against HIV+ HCA	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8640842/ https://reporter.nih.gov/project-details/10381449
17	CLIP 3D printed ring- vaginal	HSV, PREG.	UNC	preclinical	DPV/pritelivir/ LNG or ISL/ENG/EE	?	Ongoing	PI: Benhabbour. NIAID 2019-2024. Continuous liquid interface production (CLIP™) 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
18 new entry	Ring- vaginal	GC	UMass/ OCIS	preclinical	TDF and mAb 2C7 (against GC)	Unspecified	ongoing	PI: Ram NIAID 2020-2024	https://reporter.nih.gov/search/a71vYCzPO0ylXUPZu8M8Cw/project-details/10378501