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

R&D Landscape Review 2

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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
BMGF	Bill and Melinda Gates Foundation
CAB	cabotegravir
CP	Critical Path
DFCI	Dana Farber Cancer Institute
DDS	Drug delivery system
DLG	Dolutegravir
DPV	dapivirine
DVR	Darunavir
EE	ethinyl estradiol
ENG/ETG	etonogestrel
EVA	Ethyl Vinyl Acetate
EVG	elvitegravir
EFV	efavirenz
GRFT	Griffithsin
HCA	Human contraceptive antibodies
ISFI	in situ forming implants
LEN	Lenacapavir
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
PI	Principal Investigator
PrEP	Pre-exposure Prophylaxis
PREG	Pregnancy
PVA	Polyvinyl acetate
Px	Prevention
PU	polyurethane
QUB	Queen's University Belfast
RAL	Raltegravir
R&D	Research and Development
RPV	Rilpivirine
SC	Sub-cutaneous
ZA	Zinc acetate

Executive Summary

MATRIX Prime is monitoring R&D activities in the HIV Prevention research space by conducting desktop review of funded R&D on a bi-annual basis, and by convening a 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., IAS 2022), 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 second desktop review for 2022 includes publications and funded projects identified between July 1 and December 31, 2022, focusing on HIV Prevention/ PrEP, Multi-purpose prevention technologies (MPTs) that include an HIV indication and microbicides. This review did not include R&D related to bnABs or RNA approaches for prevention, nor vaccines.

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

We have 29 entries for **HIV prevention projects** (with 6 projects completed, on hold or stopped). These include two new entries for NIAID funded projects: one new project since June 2022- for the University of Louisville to develop 3D bio-printed silicone scaffold devices for vaginal insertion for a BV indication, and one (previously overlooked) entry from University of Florida to optimize the combination of a broad and potent HIV-1 entry inhibitor and a tunable hydrogel that significantly extends the in vivo half-life of this inhibitor, and that would be delivered via an injectable.

- 7 topical products: 1 rectal enema, 4 vaginal rings, 1 project with vaginal drug - eluting fibers and 1 (new) project with 3D bio-printed silicone scaffold devices.
- 22 systemic products: 8 injectables, 9 implants (removable, bioresorbable, refillable, 3D printed, osmotic pump), 1 in situ forming implant (ISFI), 2 transdermal MAPs, 2 long-acting oral tablets.
- Several projects identified new APIs, 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 used for treatment (e.g bictegravir, rilpivirine),
    - New ARVs for prevention usage (e.g., Islatravir, a NRTTI, lenacapvir, and a D-peptide capsid inhibitor, other capsid inhibitors, entry inhibitors). Of note a press release from Merck indicated that the pursue of Islatravir for prevention purpose is being abandoned.

    - Creation of prodrugs with improved physico-chemical and safety characteristics (e.g., for dolutegravir, raltegravir, atazanavir, other protease inhibitors, NNRTIs, etc.)
    - Drugamers to more efficiently deliver multiple small molecules/ARVs.,
    - Small molecules HIV entry inhibitors (smCMC) delivered using a Pod-IVR,
    - SAMT-247, a nucleocapsid protein (NCp7) inhibitor delivered with a pod-IVR.
    - 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.
  - Several projects with novel drug delivery systems (DDS) were identified through new publications or NIH RePorter, including 3 projects proposing 3-D printing to develop a) a biodegradable implant or b) a "biocage" (a third project for 3D printing of a ring is also listed under the MPTs), and the new 3D bio-printed silicone scaffold devices. Additionally, a publication described the 3D printing of an intrauterine device, and an intravaginal ring for HSV prevention. Other new DDS identified include an IUD (listed in the MPT table), a multivalent oral DDS for extended gastric residence, an implantable osmotic pump (R&D stopped).
  - Several review papers and/or research articles discussed a) the effect (or lack of thereof) of PrEP products on the microbiome, b) natural products/biologics including lectins. One paper identified a lectin from the leaves of a bitter melon.
  - Publications directly relevant to MATRIX CP projects include one publication describing the efficacy of QGRFT against vaginal candidiasis in a mouse model, another described the lack of rectal protection from carrageenan gel for anal HPV acquisition. Two publications showed high vaginal and rectal efficacy of the TAF/EVG FDI in the NHP model.
  - Two different publications describe full preclinical efficacy and phase I safety of ISL implants (one removable and one refillable).
- 28 entries were found for **MPTs**, all with an HIV indication (with 9 projects completed, on hold, stopped or of unknown status). One new entry since June 2022 was added for a NIAID-funded project that propose to combine copper (for contraception) and ARVs (unspecified) in an IUD, at the University of Washington. The most current other indication was to prevent unplanned pregnancy (21 projects); HSV prevention was the next most common indication (15 projects), followed by anti HPV indication (4 projects).
  - The 22 topical products include: 1 rectal enema, 2 intra-uterine devices/system (IUS), 2 fast dissolving inserts (FDIs), 3 vaginal films, 5 vaginal gels, 9 vaginal rings.
  - The 6 systemic products include: 1 injectable, 2 implants (1 removable, 1 bioresorbable), 1 in situ forming implant (ISFI), 1 transdermal microarray patch (MAP), and 1 daily oral tablet (the dual prevention pill or DPP).
  - The drug delivery formats and groups working on MPTs are similar to those listed for the HIV prevention indication only.
  - Drugs investigated include both ARVs (e.g. TFV, 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 (i.e. antibodies) for the contraceptive drugs.

- 57 recent (July through December 2022) publications were identified and are listed below, starting in section 3. They include publications on APIs and drugs, drug delivery systems, preclinical and clinical research, and review papers.
- 8 new relevant media release were identified:
    - Two on the Population Council for the acquisition of the dapivirine ring and other women-centered HIV prevention tools from IPM.
    - Three on CAB-LA /Apretude:
        - Access to generic version of Apretude in 90 countries.
        - Zimbabwe is the first African nation to approve Apretude.
        - The EMA validates ViiV marketing authorization for CAB-LA.
    - One on the PrEP Ring and Cab-LA: Uganda approves both PrEP options.
    - Merck announced a new treatment program with lower dose of ISL- It also announced it will stop the monthly oral ISL pill (and other ISL DDS) for PrEP.
    - Gilead announced FDA approval of Sunlenca (lenacapavir injectable) for-people-living-with-multidrug-resistant-HIV.

Conclusions:

- The landscape analysis highlighted significant progress for long-acting PrEP products, including two ISL implants (one at the preclinical stage and one in phase I), showing excellent PK, safety and NHP efficacy. Nevertheless, these do not result in overlap with CP products in MATRIX given that Merck is abandoning ISL for prevention. 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.**
- Second call with Pharma and funders will be held in January 2023
- Next landscape review will be conducted in June 2023

3. **Review of published literature July 1, 2022-December 31, 2022**

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).

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

Entry/Fusion inhibitor:

1. Andrianov AM, Nikolaev GI, Shuldov NA, Bosko IP, Anischenko AI, Tuzikov AV. Application of deep learning and molecular modeling to identify small drug-like compounds as potential HIV-1 entry inhibitors. J Biomol Struct Dyn. 2022 Oct;40(16):7555-7573. doi: 10.1080/07391102.2021.1905559. Epub 2021 Apr 15. PMID: 33855929. https://pubmed.ncbi.nlm.nih.gov/33855929/ .
   Note: computational chemistry approach was used to identify three new HIV entry inhibitors-(for CD-4 binding). No experimental research was done to test their antiviral properties and potency.

2. 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://pubmed-ncbi-nlm-nih-

gov.ucsf.idm.oclc.org/34919814/
Note: Two HIV fusion-inhibitory lipopeptides (LP-97 and LP-98) were designed with highly potent, long-acting antiviral activity. These were tested as monotherapy and resulted in reduced viral loads in SHIV infected Rhesus monkey and allowed maintenance of long-term viral suppression. LP-98 administrated as PrEP provided complete protection in 51 monkeys via intrarectal, intravaginal, or intravenous challenge.

Protease inhibitors:

3. Gurumukhi VC, Bari SB. Quality by design (QbD)-based fabrication of atazanavir-loaded nanostructured lipid carriers for lymph targeting: bioavailability enhancement using chylomicron flow block model and toxicity studies. Drug Deliv Transl Res. 2022 May;12(5):1230-1252. doi: 10.1007/s13346-021-01014-4. Epub 2021 Jun 10. PMID: 34110597. https://pubmed.ncbi.nlm.nih.gov/34110597/
Note: the goal of this paper was to fabricate the protease inhibitor Atazanavir (ATV)-loaded nanostructured lipid carriers (NLCs) employing quality by design (QbD) approach to address the challenges of ATV's bioavailability and its safety after oral administration (it has liver toxicity).

4. Ma L, Wen J, Dong B, Zhou J, Hu S, Wang J, Wang Y, Zhu M, Cen S. Design and Evaluation of Novel HIV-1 Protease Inhibitors Containing Phenols or Polyphenols as P2 Ligands with High Activity against DRV-Resistant HIV-1 Variants. Int J Mol Sci. 2022 Nov 16;23(22):14178. doi: 10.3390/ijms232214178. PMID: 36430656; PMCID: PMC9697080. https://pubmed.ncbi.nlm.nih.gov/36430656/
Note: the goal of this paper is to develop new inhibitors of multidrug resistant HIV, including variants that are resistant to the protease inhibitor Darunavir. The group designed and synthesized a new series of HIV-1 protease inhibitors, including two that exhibited potent enzymatic inhibitory activity in the low picomolar range, and one inhibitor showed excellent activity against the Darunavir-resistant HIV-1 variant in vitro.

5. Okafor SN, Angsantikul P, Ahmed H. Discovery of Novel HIV Protease Inhibitors Using Modern Computational Techniques. Int J Mol Sci. 2022 Oct 12;23(20):12149. doi: 10.3390/ijms232012149. PMID: 36293006; PMCID: PMC9603388. https://pubmed.ncbi.nlm.nih.gov/36293006/
Note: discovery of new protease inhibitors identified via in silico analysis. The paper also examined for potential cytochrome interactions of a variety of licensed protease inhibitors.

6. A M Subbaiah M, Subramani L, Ramar T, Desai S, Sinha S, Mandlekar S, Kadow JF, Jenkins S, Krystal M, Subramanian M, Sridhar S, Padmanabhan S, Bhutani P, Arla R, Meanwell NA. Improving Drug Delivery While Tailoring Prodrug Activation to Modulate C_{max} and C_{min} by Optimization of (Carbonyl)oxyalkyl Linker-Based Prodrugs of Atazanavir. J Med Chem. 2022 Aug 25;65(16):11150-11176. doi: 10.1021/acs.jmedchem.2c00632. Epub 2022 Aug 11. PMID: 35952307. https://pubmed.ncbi.nlm.nih.gov/35952307/
Note: Using the HIV-1 protease inhibitor atazanavir (ATV), the goal of this paper was to design new prodrugs to enhance the systemic drug delivery of ATV.

Integrase strand transfer inhibitors (INSTI):

7. Priya Dharshini K, Ramya Devi D, Banudevi S & Vedha Hari B. Narayanan. In-vivo pharmacokinetic studies of Dolutegravir loaded spray dried Chitosan nanoparticles as milk admixture for paediatrics infected with HIV. *Sci Rep* **12**, 13907 (2022). https://doi.org/10.1038/s41598-022-18009-x
https://www.nature.com/articles/s41598-022-18009-x
Note: New formulation for dolutegravir (DTV) intended for pediatric use via the oral route, to improve its solubility. DTG-loaded Chitosan nanoparticles (NPs) were synthesized utilizing spray drying technology. The in vivo oral bioavailability studies were conducted in Balb-C mice and the bioavailability of the NPs was compared to pure DTG.

8. Deodhar S, Sillman B, Bade AN, Avedissian SN, Podany AT, McMillan JM, Gautam N, Hanson B, Dyavar Shetty BL, Szlachetka A, Johnston M, Thurman M, Munt DJ, Dash AK, Markovic M, Dahan A, Alnouti Y, Yazdi A, Kevadiya BD, Byrareddy SN, Cohen SM, Edagwa B, Gendelman HE. Transformation of dolutegravir into an ultra-long-acting parenteral prodrug formulation. Nat Commun. 2022 Jun 9;13(1):3226. doi: 10.1038/s41467-022-30902-7. PMID: 35680875; PMCID: PMC9184486. https://pubmed.ncbi.nlm.nih.gov/35680875/
Note: Ultra-long-acting integrase strand transfer inhibitors were created by screening a library of monomeric and dimeric dolutegravir (DTG) prodrug nanoformulations. This led to an 18-carbon chain modified ester prodrug nanocrystal (coined NM2DTG) with the potential to sustain yearly dosing after a single parenteral injectable.

9. Mandarino A. Modifying dolutegravir to PrEPare for long life. Commun Biol. 2022 Nov 7;5(1):1193. doi: 10.1038/s42003-022-04114-0. PMID: 36344610; PMCID: PMC9640719. https://pubmed.ncbi.nlm.nih.gov/36344610/
Note: commentary on #8, Deodhar et al., above.

10. Khuroo T, Mohamed EM, Dharani S, Immadi S, Nutan MTH, Lu D, Ali HI, Khan MA, Rahman Z. In-Situ Implant Formulation of Laurate and Myristate Prodrugs of Dolutegravir for Ultra-Long Delivery. J Pharm Sci. 2022 Aug;111(8):2312-2321. doi: 10.1016/j.xphs.2022.03.007. Epub 2022 Mar 14. PMID: 35296412. https://pubmed.ncbi.nlm.nih.gov/35296412/
Note: the goal for this work was to synthesize prodrugs of dolutegravir (DTG) for ultra-long delivery purpose, combining prodrug and drug delivery approach. The prodrugs and drug were formulated into in-situ implant using biodegradable polymer. In vitro release achieved 77 days with only 60% of API released.

Capsid inhibitors:

11. Ji X, Li J, Sharma PP, Jiang X, Rathi B, Gao Z, Hu L, Kang D, De Clercq E, Cocklin S, Liu C, Pannecouque C, Dick A, Liu X, Zhan P. Design, Synthesis and Structure-Activity Relationships of Phenylalanine-Containing Peptidomimetics as Novel HIV-1 Capsid Binders Based on Ugi Four-Component Reaction. Molecules. 2022 Sep 14;27(18):5995. doi: 10.3390/molecules27185995. PMID: 36144727; PMCID: PMC9502897. https://pubmed.ncbi.nlm.nih.gov/36144727/
Note: 18 novel phenylalanine derivatives of a capsid-inhibitor were synthesized via the Ugi four-component reaction. These exhibited in vitro anti-HIV activity at the low-micromolar-level.

12. Jiang X, Sharma PP, Rathi B, Ji X, Hu L, Gao Z, Kang D, Wang Z, Xie M, Xu S, Zhang X, De Clercq E, Cocklin S, Pannecouque C, Dick A, Liu X, Zhan P. Discovery of novel 1,2,4-triazole

phenylalanine derivatives targeting an unexplored region within the interprotomer pocket of the HIV capsid protein. J Med Virol. 2022 Dec;94(12):5975-5986. doi: 10.1002/jmv.28064. Epub 2022 Aug 18. PMID: 35949003.
https://pubmed.ncbi.nlm.nih.gov/35949003/
Note: this paper describes the discovery of a novel HIV-capsid inhibitor.

13. Zhang X, Sun L, Xu S, Shao X, Li Z, Ding D, Jiang X, Zhao S, Cocklin S, Clercq E, Pannecouque C, Dick A, Liu X, Zhan P. Design, Synthesis, and Mechanistic Study of 2-Pyridone-Bearing Phenylalanine Derivatives as Novel HIV Capsid Modulators. Molecules. 2022 Nov 7;27(21):7640. doi: 10.3390/molecules27217640. PMID: 36364467; PMCID: PMC9658817. https://pubmed.ncbi.nlm.nih.gov/36364467/
Note: this paper describes the synthesis of a novel series of 2-pyridone-bearing phenylalanine derivatives as HIV capsid modulators, that have activity against HIV-1 and HIV-2.

RTI and NNRTIs:

14. Gao S, Cheng Y, Song S, Song L, Zhao F, Xu S, Kang D, Sun L, Gao P, De Clercq E, Pannecouque C, Liu X, Zhan P. Chemical space exploration around indolylarylsulfone scaffold led to a novel class of highly active HIV-1 NNRTIs with spiro structural features. Eur J Med Chem. 2022 Aug 5;238:114471. doi: 10.1016/j.ejmech.2022.114471. Epub 2022 May 20. PMID: 35640327. https://pubmed.ncbi.nlm.nih.gov/35640327/.
Note: the goal of this paper is to describe the design and synthesis of novel NNRTIs. Two of the compounds displayed 30- and 16-fold potency improvement compared to nevirapine and zidovudine and comparable potency to efavirenz and etravirine. Notably, the introduction of spiro rings may both reduce the cytotoxicity and greatly improve the selectivity index of these new NNRTIs.
15. Weising S, Weber S, Schols D, Meier C. Triphosphate Prodrugs of the Anti-HIV-Active Compound 3'-Deoxy-3'-fluorothymidine (FLT). J Med Chem. 2022 Sep 22;65(18):12163-12175. doi: 10.1021/acs.jmedchem.2c00665. Epub 2022 Sep 13. PMID: 36099330.
https://pubmed.ncbi.nlm.nih.gov/36099330/
Note: this is a pro-drugging approach to reduce the toxicity of FLT (3'-Fluoro-3'-deoxythymidine) a highly potent RTI that was abandoned due to high toxicity. The paper describes various triphosphate prodrugs of FLT.

16. Zhao LM, Wang S, Pannecouque C, De Clercq E, Piao HR, Chen FE. Discovery of novel biphenyl-substituted pyridone derivatives as potent non-nucleoside reverse transcriptase inhibitors with promising oral bioavailability. Eur J Med Chem. 2022 Oct 5;240:114581. doi: 10.1016/j.ejmech.2022.114581. Epub 2022 Jun 30. PMID: 35797898.
https://pubmed.ncbi.nlm.nih.gov/35797898/
Note: this paper describes the optimization of an FDA-approved NNRTI, doravirine, to increase oral bio-availability, potency and decrease toxicity.

17. Zheng R, Valicherla GR, Zhang J, Nuttall J, Silvera P, Marshall LJ, Empey PE, Rohan LC. Transport and Permeation Properties of Dapivirine: Understanding Potential Drug-Drug Interactions. *Pharmaceutics*. 2022; 14(9):1948.
https://doi.org/10.3390/pharmaceutics14091948
Note: Concomitant use of the DPV ring and miconazole (MIC) altered DPV pharmacokinetic profile. This paper explored whether or not DPV transport and permeation contributed to

the observed DPV-miconazole (MIC) interaction. The findings from this paper suggest that the DPV-MIC interaction is not due to the five transporters examined here, altered tight junction integrity, nor altered tissue permeability.

Maturation inhibitors:

18. Alicia Regueiro-Ren, Sing-Yuen Sit, Yan Chen, Jie Chen, Jacob J. Swidorski, Zheng Liu, Brian L. Venables, Ny Sin, Richard A. Hartz, Tricia Protack, Zeyu Lin, Sharon Zhang, Zhufang Li, Dauh-Rurng Wu, Peng Li, James Kempson, Xiaoping Hou, Anuradha Gupta, Richard Rampulla, Arvind Mathur, Hyunsoo Park, Amy Sarjeant, Yulia Benitex, Sandhya Rahematpura, Dawn Parker, Thomas Phillips, Roy Haskell, Susan Jenkins, Kenneth S. Santone, Mark Cockett, Umesh Hanumegowda, Ira Dicker, Nicholas A. Meanwell, and Mark Krystal. The discovery of GSK3640254, a next generation inhibitor of the HIV-1 Maturation. Journal of Medicinal Chemistry, 2022, *65* (18), 11927-11948. DOI: 10.1021/acs.jmedchem.2c00879 https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c00879

    Note: this paper describes the discovery of a GSK maturation inhibitor which is now in Phase 3 trials ---so not really a new API.

Others: biologics including Lectins

19. Coleman MI, Khan M, Gbodossou E, Diop A, DeBarros K, Duong H, Bond VC, Floyd V, Kondwani K, Montgomery Rice V, Villinger F, Powell MD. Identification of a Novel Anti-HIV-1 Protein from *Momordica balsamina* Leaf Extract. Int J Environ Res Public Health. 2022 Nov 18;19(22):15227. doi: 10.3390/ijerph192215227. PMID: 36429944; PMCID: PMC9690441. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9690441/
    Note: Discovery and characterization of a new lectin derived from the leaves of the bitter melon M. balsamina*, used by Senegalese healers as a part of a plant-based treatment for HIV/AIDS infections*.

20. Kim HI, Kim GN, Yu KL, Park SH, You JC. Identification of Novel Nucleocapsid Chimeric Proteins Inhibiting HIV-1 Replication. Int J Mol Sci. 2022 Oct 15;23(20):12340. doi: 10.3390/ijms232012340. PMID: 36293198; PMCID: PMC9604505. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9604505/
    Note: the paper describes the development of improved antiviral proteins that specifically binds viral RNA. Two novel Nucleocapsid fused chimeric proteins displayed novel mechanisms of anti-HIV effects by inhibiting both HIV-1 transcription and packaging.

21. Nabeta HW, Lasnik AB, Fuqua JL, Wang L, Rohan LC, Palmer KE. Antiviral lectin Q-Griffithsin suppresses fungal infection in murine models of vaginal candidiasis. Front Cell Infect Microbiol. 2022 Oct 18;12:976033. doi: 10.3389/fcimb.2022.976033. PMID: 36329822; PMCID: PMC9623022. https://pubmed.ncbi.nlm.nih.gov/36329822/
    Note: The goal of this study was to evaluate the efficacy of a prototype Q-GRFT dosage form in prophylactic and therapeutic murine models of vaginal candidiasis, through microbiologic, histopathologic, and immune studies. Findings shows that Q-GRFT has significant preventive and therapeutic activity in vaginal candidiasis, potentially offering additional benefit as a microbicide for prevention of HIV-1 and HSV-2 transmission.

22. Nittayananta W, Promsong A, Levy C, Hladik F, Chaitaveep N, Ungphaiboon S, Tewtrakul S, Satthakarn S. Microbicide Containing Ellagic Acid Can Inhibit HIV-1 Infection. Molecules. 2022 Nov 16;27(22):7941. doi: 10.3390/molecules27227941. PMID: 36432041; PMCID: PMC9695535. https://pubmed.ncbi.nlm.nih.gov/36432041/
Note: Ellagic Acid is a polyphenol found in numerous fruits and vegetables, which was formulated as a gel. The study found that either in solution or in a gel form, Ellagic Acid inhibits HIV infection without adverse effects on target cells in vitro. Thus, gel containing EA can be tested as a new microbicide against HIV infection.

3b. Review publications or reports:

23. Agrahari, V., Sharon M. Anderson, M. Melissa Peet, Andrew P. Wong, Onkar N. Singh, Gustavo F. Doncel & Meredith R. Clark (2022) Long-acting HIV Pre-exposure Prophylaxis (PrEP) approaches: Recent advances, emerging technologies and development challenges, Expert Opinion on Drug Delivery, DOI: 10.1080/17425247.2022.2135699 https://pubmed.ncbi.nlm.nih.gov/36252277/

24. Amblard F, Patel D, Michailidis E, Coats SJ, Kasthuri M, Biteau N, Tber Z, Ehteshami M, Schinazi RF. HIV nucleoside reverse transcriptase inhibitors. Eur J Med Chem. 2022 Oct 5;240:114554. doi: 10.1016/j.ejmech.2022.114554. Epub 2022 Jun 20. PMID: 35792384. https://pubmed.ncbi.nlm.nih.gov/35792384/

25. Castillo-Mancilla JR, Anderson PL. (editorial/review) Long-acting injectable Cabotegravir: How drug concentrations could help guide patient management. Br J Clin Pharmacol. 2022 Oct;88(10):4384-4386. doi: 10.1111/bcp.15410. Epub 2022 Aug 16. PMID: 35971819. https://pubmed.ncbi.nlm.nih.gov/35971819/

26. Flexner C. The future of long-acting agents for preexposure prophylaxis. Curr Opin HIV AIDS. 2022 Jul 1;17(4):192-198. doi: 10.1097/COH.0000000000000735. PMID: 35762373; PMCID: PMC9467455. https://pubmed.ncbi.nlm.nih.gov/35762373/

27. Lantz AM, Nicol MR. Translational Models to Predict Target Concentrations for Pre-Exposure Prophylaxis in Women. AIDS Res Hum Retroviruses. 2022 Dec;38(12):909-923. doi: 10.1089/AID.2022.0057. Epub 2022 Oct 25. PMID: 36097755 https://pubmed.ncbi.nlm.nih.gov/36097755/

28. Naik S, Kumar S. Lectins from plants and algae act as anti-viral against HIV, influenza and coronaviruses. Mol Biol Rep. 2022 Dec;49(12):12239-12246. doi: 10.1007/s11033-022-07854-8. Epub 2022 Sep 22. PMID: 36138301; PMCID: PMC9510388. https://pubmed.ncbi.nlm.nih.gov/36138301/

29. Parikh UM, Koss CA, Mellors JW. Long-Acting Injectable Cabotegravir for HIV Prevention: What Do We Know and Need to Know about the Risks and Consequences of Cabotegravir Resistance? Curr HIV/AIDS Rep. 2022 Oct;19(5):384-393. doi: 10.1007/s11904-022-00616-y. Epub 2022 Sep 16. PMID: 36112336; PMCID: PMC9508028. https://pubmed.ncbi.nlm.nih.gov/36112336/

30. Zhao AV, Crutchley RD, Guduru RC, Ton K, Lam T, Min AC. A clinical review of HIV integrase strand transfer inhibitors (INSTIs) for the prevention and treatment of HIV-1 infection.

Retrovirology. 2022 Oct 22;19(1):22. doi: 10.1186/s12977-022-00608-1. PMID: 36273165; PMCID: PMC9588231. https://retrovirology.biomedcentral.com/articles/10.1186/s12977-022-00608-1

31. Compounds with Potential Activity to Prevent or Treat HIV and Other Sexually Transmitted Infections**:** Landscape review, updated 9/ 2022 (https://theimpt.org/compounds-with-potential-activity-to-preventor-treat-hiv-and-other-sexually-transmitted-infections-a-landscape-review/.

3c. HIV Preclinical studies of DDS:

32. Benhabbour (presenter)/ Maturavongsadit et al.**,** (IAS 2022, e-poster): In vitro release and in vivo pharmacokinetics of antiretroviral drugs from ultra-long-acting polymeric implants: towards better outcomes for HIV prevention and treatment. https://programme.aids2022.org/Search/Search?search=novel%2BAPI
Note: Presents In-situ forming implants (ISFIs) and polymeric solid implants (PSIs) loaded with CAB or 3TC. Implants can accommodate ARVs of distinct physicochemical properties and exhibited near identical plasma drug concentrations for both CAB and 3TC when administered at equivalent doses.

33. de Carvalho Rodrigues V, Guterres IZ, Savi BP, Silva IT, Fongaro G, Salmoria GV. 3D-Printed EVA Devices for Antiviral Delivery and Herpes Virus Control in Genital Infection. Viruses. 2022 Nov 11;14(11):2501. doi: 10.3390/v14112501. PMID: 36423110; PMCID: PMC9696101. https://pubmed.ncbi.nlm.nih.gov/36423110/
Note: Application is for Herpes, not HIV, but drug delivery system is interesting. 3D printed EVA devices with different acyclovir amounts (0, 10, and 20 wt.%) were manufactured by fused filament fabrication in 2 different geometries, an IUD, and an intravaginal ring. In vitro release of the drug was demonstrated for 80 days.

34. 3Dobard CW, Peet MM, Nishiura K, Holder A, Dinh C, Mitchell J, Khalil G, Pan Y, Singh ON, McCormick TJ, Agrahari V, Gupta P, Jonnalagadda S, Heneine W, Clark MR, García-Lerma JG, Doncel GF. Single dose topical inserts containing tenofovir alafenamide fumarate and elvitegravir provide pre- and post-exposure protection against vaginal SHIV infection in macaques. EBioMedicine. 2022 Nov 21;86:104361. doi: 10.1016/j.ebiom.2022.104361. Epub ahead of print. PMID: 36423375; PMCID: PMC9691909. https://pubmed-ncbi-nlm-nih-gov.ucsf.idm.oclc.org/36423375/
Note: this paper shows the vaginal efficacy of a single dose EVG/TAF FDI in NHP for PrEP or PEP.

35. Gatto GJ, Krovi A, Li L, Massud I, Holder A, Gary J, Mills P, Mitchell J, Luecke E, Demkovich ZR, Heneine W, García-Lerma JG, Marzinke MA, Brand RM, Dobard CW, Johnson LM, Van Der Straten A. Comparative Pharmacokinetics and Local Tolerance of Tenofovir Alafenamide (TAF) From Subcutaneous Implant in Rabbits, Dogs, and Macaques. Front Pharmacol. 2022 Jul 19;13:923954. doi: 10.3389/fphar.2022.923954. PMID: 35928266; PMCID: PMC9343794. https://www.frontiersin.org/articles/10.3389/fphar.2022.923954/full
Note: This paper describes the preclinical performance of biodegradable TAF implants in 3 animal species. Sustained release of TAF was achieved for the pre-specified duration of time, but active implants resulted in local adverse events proximal to the implant ranging in severity from mild to moderate and included dermal inflammation and necrosis, across all

species.

36. Kretschmer M, Ceña-Diez R, Butnarasu C, Silveira V, Dobryden I, Visentin S, Berglund P, Sönnerborg A, Lieleg O, Crouzier T, Yan H. Synthetic Mucin Gels with Self-Healing Properties Augment Lubricity and Inhibit HIV-1 and HSV-2 Transmission. Adv Sci (Weinh). 2022 Nov;9(32):e2203898. doi: 10.1002/advs.202203898. Epub 2022 Sep 14. PMID: 36104216; PMCID: PMC9661867. https://pubmed.ncbi.nlm.nih.gov/36104216/
Note: bovine submaxillary mucins (BSMs) were assembled into "mucus-like" gels (5%, wt/v) by dynamic covalent crosslinking reactions. BSM gels trap HIV-1 by binding to the envelope glycoprotein gp120 and suppress cytokine production during viral exposure. The gels may offer promise for further development as personal lubricants that can limit viral transmission.

37. Kinvig H, Cottura N, Lloyd A, Frivold C, Mistilis J, Jarrahian C, Siccardi M. Evaluating Islatravir Administered Via Microneedle Array Patch for Long-Acting HIV Pre-exposure Prophylaxis Using Physiologically Based Pharmacokinetic Modelling. Eur J Drug Metab Pharmacokinet. 2022 Nov;47(6):855-868. doi: 10.1007/s13318-022-00793-6. Epub 2022 Sep 30. PMID: 36178586. https://pubmed.ncbi.nlm.nih.gov/36178586/
Note: This study aimed to utilize physiologically based pharmacokinetic (PBPK) modelling to predict the pharmacokinetics resulting from ISL administered via Microneedle Array Patch (MAP) and to identify key MAP characteristics required to sustain effective concentrations over extended dosing intervals. The integrated intradermal PBPK model outlined optimal MAP dose and nanoparticle release rates for effective ISL-TP concentrations up to 12 months.

38. Makarova N, Singletary T, Peet MM, Mitchell J, Holder A, Dinh C, Agrahari V, Mendoza M, Pan Y, Heneine W, Clark MR, García-Lerma JG, Smith JM, Doncel GF. Pharmacokinetics and efficacy of topical inserts containing tenofovir alafenamide fumarate and elvitegravir administered rectally in macaques. EBioMedicine. 2022 Nov 4;86:104338. doi: 10.1016/j.ebiom.2022.104338. Epub ahead of print. PMID: 36343572; PMCID: PMC9643401. https://pubmed.ncbi.nlm.nih.gov/36343572/
Note: This paper demonstrates the rectal efficacy of one TAF/EVG insert in NHPs, and the increased protection conferred by a second rectal dose of the insert. These results highlight the high efficacy of TAF/EVG inserts as topical on-demand rectal PrEP, as well as the need for appropriate drug coverage in the deep rectum and colon to achieve high protection.

39. Massud I, Krovi A, Nishiura K, Ruone S, Li L, Holder A, Gary J, Mills P, Mitchell J, Khalil G, Pan Y, Luecke E, Gatto G, Heneine W, Garcia-Lerma JG, Johnson L, van der Straten A, Dobard C. Safety and efficacy of a biodegradable implant releasing tenofovir alafenamide for vaginal protection in a macaque model. J Antimicrob Chemother. 2022 Oct 28;77(11):2964-2971. doi: 10.1093/jac/dkac252. PMID: 35913838. https://pubmed.ncbi.nlm.nih.gov/35913838/
Note: This paper demonstrates the complete protection against vaginal SHIV infection with two implants releasing a total of 0.7 mg of tenofovir alafenamide per day, it also identified TFV-DP concentrations in PBMCs associated with complete vaginal protection. However, adverse local toxicity and necrosis near the TAF implant site were observed in all animals.

40. Fernanda P. Pons-Faudoa, Nicola Di Trani, Simone Capuani, Jocelyn Nikita Campa-Carranza, Bharti Nehete, Suman Sharma, Kathryn A. Shelton, Lane R. Bushman, Farah Abdelmawla, Martin Williams, Laura Roon, David Nerguizian, Corrine Ying Xuan Chua, Michael M. Ittmann, Joan E. Nichols, Jason T. Kimata, Peter L. Anderson, Pramod N. Nehete, Roberto C. Arduino, Alessandro Grattoni. Ultra-long-acting refillable nanofluidic implant confers full protection against SHIV infection in non-human primates bioRxiv 2022.12.15.520646; doi: https://doi.org/10.1101/2022.12.15.520646. https://www.biorxiv.org/content/10.1101/2022.12.15.520646v1
Note: This paper describes a titanium-made refillable ISL implant which was 100% protective against rectal and vaginal challenge in NHPs, with the "protective" drug levels achieved after 1 day and lasting for 20 months (without a refilling needed). There were mild local reaction (but no systemic toxicity) and no change in CD4 counts.

41. Shen et al., 2022. Poster abstract: Multipurpose vaginal rings for HIV prevention and non-hormonal contraception. https://pure.qub.ac.uk/en/publications/poster-abstract-multipurpose-vaginal-rings-for-hiv-prevention-and
Note: This presentation described the development of a vaginal ring that can provide sustained release of both DPV and Cu/Zn to simultaneously prevent HIV infection and unintended pregnancy (with a non-hormonal contraceptive).

42. Vartak R, Jablonski J, Deore B, Mediouni S, Sanhueza CA, Valente ST, Patel K. Bictegravir nanomicelles and anionic pullulan loaded vaginal film: Dual mechanistic pre-exposure prophylaxis (PrEP) for HIV. Int J Biol Macromol. 2022 Nov 30;221:416-425. doi: 10.1016/j.ijbiomac.2022.08.211. Epub 2022 Sep 6. PMID: 36075305. https://pubmed.ncbi.nlm.nih.gov/36075305/
Note: BCT-loaded PLGA-PEG polymeric nanomicelles (for sustained release) were incorporated into PVA/pullulan-based film matrix. In vitro, the film was safe and significantly inhibited HIV-1 replication.

43. Volpe-Zanutto F, Vora LK, Tekko IA, McKenna PE, Permana AD, Sabri AH, Anjani QK, McCarthy HO, Paredes AJ, Donnelly RF. Hydrogel-forming microarray patches with cyclodextrin drug reservoirs for long-acting delivery of poorly soluble cabotegravir sodium for HIV Pre-Exposure Prophylaxis. J Control Release. 2022 Aug;348:771-785. doi: 10.1016/j.jconrel.2022.06.028. Epub 2022 Jun 25. PMID: 35738464. https://pubmed.ncbi.nlm.nih.gov/35738464/
Note: this study examined hydrogel-forming microarray patches using cyclodextrin to increase the solubility of hydrophobic ARVs, like cabotegravir.

44. Xiao P, Gumber S, Marzinke MA, Hoang T, Myers R, Date AA, Hanes J, Ensign LM, Wang L, Rohan LC, Cone R, Fuchs EJ, Hendrix CW, Villinger F. Hypo-osmolar rectal douche tenofovir formulation prevents simian/human immunodeficiency virus acquisition in macaques. JCI Insight. 2022 Dec 8;7(23):e161577. doi: 10.1172/jci.insight.161577. PMID: 36477356. https://pubmed.ncbi.nlm.nih.gov/36477356/
Note: this is a NHP rectal challenge study demonstrating the efficacy of the TFV-hypo-osmolar rectal douche to prevent rectal HIV acquisition.

45. Yeruva T, Lee CH. Enzyme Responsive Delivery of Anti-Retroviral Peptide via Smart Hydrogel. AAPS PharmSciTech. 2022 Aug 24;23(7):234. doi: 10.1208/s12249-022-02391-w.

PMID: 36002705.
https://pubmed.ncbi.nlm.nih.gov/36002705/
Note: a stimuli-sensitive hydrogel formulation that intravaginally delivers HIV-1 entry inhibitor (enfuvirtide) upon being exposed to a specific protease was developed. The PEG-based hydrogel was found to have suitable physicochemical properties for an intravaginal formulation of the Prostate-Specific Antigen (PSA) substrate-linked ARVs and was safe towards vaginal epithelium in vitro. It was capable of delivering enfuvirtide with effective concentrations to achieve vaginal prevention from HIV-1 infection.

46. Young, I et al., (IAS, 2022, e-poster): In vivo pharmacokinetics and safety in mice for ultra-long-acting injectable, biodegradable, and removeable in-situ forming implant with cabotegravir for HIV prevention.
https://programme.aids2022.org/Search/Search?search=novel%2BAPI
Note: the presentation shows sustained CAB release kinetics in mice for 90 days with plasma levels well above the 4X PA-IC90 in a well-tolerated and safe ISFI formulation.

3d. HIV-PrEP clinical studies

47. Austin MN, Meyn LA, Avolia HA, Petrina MA, Cosentino LA, Alphonse C, Chen BA, Bunge K, Noguchi L, Beigi R, Squires K, Hillier SL. Impact of Dapivirine and Placebo Vaginal Rings on the Microbiota of Adolescent, Lactating, and Postmenopausal Females. J Infect Dis. 2022 Jun 15;225(12):2208-2218. doi: 10.1093/infdis/jiab590. PMID: 34865071; PMCID: PMC9200158. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9200158/
Note: In this secondary analysis of MTN trials conducted in US adolescents, lactating, and postmenopausal females, vaginal microbiota was assessed prior to and after ring use, and between dapivirine and placebo ring users. The study found that DVR use was associated with minimal changes in the vaginal microbiota that are likely not clinically significant.

48. Benn, P et al., IAS 2022 (poster). A study evaluating the safety, tolerability, and pharmacokinetics of a high-concentration (CAB 400mg/ml) cabotegravir long-acting injectable formulation following subcutaneous and intramuscular administration in healthy adult participants. https://programme.aids2022.org/Abstract/Abstract/?abstractid=6276
Note: This presentation assessed a high-concentration (CAB400mg/mL) formulation that was developed to support less frequent dosing and/or potential self-administration via subcutaneous or thigh injectables.

49. Dabee S, Mugo N, Mudhune V, McLellan-Lemal E, Peacock S, O'Connor S, Njoroge B, Nyagol B, Thurman AR, Ouma E, Ridzon R, Wiener J, Haugen HS, Gasper M, Feng C, Allen SA, Doncel GF, Jaspan HB, Heffron R; Kisumu Combined Ring Study Team. Genital microbiota of women using a 90-day tenofovir or tenofovir and levonorgestrel intravaginal ring in a placebo controlled randomized safety trial in Kenya. Sci Rep. 2022 Jul 14;12(1):12040. doi: 10.1038/s41598-022-13475-9. PMID: 35835755; PMCID: PMC9283538.https://pubmed.ncbi.nlm.nih.gov/35835755/
Note: This secondary analysis of a phase I trial investigated the influence of 90 days continuous-delivery of TFV intravaginal rings with/without levonorgestrel (LNG) on the genital microbiota of Kenyan women, and concluded that TFV/LNG and TFV rings did not adversely affect the genital microbiota and are safe to use.

50. Han K, Baker M, Lovern M, Paul P, Xiong Y, Patel P, Moore KP, Seal CS, Cutrell AG, D'Amico RD, Benn PD, Landovitz RJ, Marzinke MA, Spreen WR, Ford SL. Population pharmacokinetics of cabotegravir following administration of oral tablet and long-acting intramuscular injectable in adult HIV-1-infected and uninfected subjects. Br J Clin Pharmacol. 2022 Oct;88(10):4607-4622. doi: 10.1111/bcp.15439. Epub 2022 Jul 4. PMID: 35695476; PMCID: PMC9543358. https://pubmed.ncbi.nlm.nih.gov/35695476/
Note: This study aimed to characterize cabotegravir population pharmacokinetics using data from phase 1, 2 and 3 studies and evaluate the association of intrinsic and extrinsic factors with pharmacokinetic variability. The population pharmacokinetic model can be used to inform dosing strategies and future study designs.

51. Ho K, Dominguez-Islas C, Szydlo D, Edick S, Macagna N, Riddler SA, Brand RM, Jacobson CE, Kramzer L, Kunjara Na Ayudhya RP, Piper J, Marzinke MA, Bauermeister J, Nuttall J, Hillier SL, Hendrix CW. MTN-033: a Phase 1 Study Comparing Applicator versus "as Lubricant" Delivery of Rectal Dapivirine Gel. Antimicrob Agents Chemother. 2022 Oct 18;e0081622. doi: 10.1128/aac.00816-22. https://pubmed.ncbi.nlm.nih.gov/36255254/
Note: the MTN-033 trial assessed DPV gel intrarectally using an applicator or self-administered on an artificial phallus as lubricant . There were no safety concerns associated with use of DPV gel and participants reported finding it easy to use. However, lower DPV exposure in plasma and lack of quantifiable DPV in rectal tissue indicate that higher potency, concentration, and longer half-life ARVs with optimized formulations will be needed to achieve protective tissue concentrations.

52. Kumar, et al., IAS 2022 e-poster: Injectable site reaction experience in clinical studies of people using lenacapavir for HIV treatment.
https://programme.aids2022.org/Abstract/Abstract/?abstractid=6805
Note: People with HIV using subcutaneous LEN, reported that ISRs were generally mild to moderate, rarely leading to discontinuation, and decreased in frequency with subsequent injectable. Most ISRs resolved within days, while induration and nodules gradually improved over months but were generally not visible or painful.

53. Laurie C, El-Zein M, Tota JE, Khosrow-Khavar F, Tellier PP, Coutlée F, de Pokomandy A, Franco EL; LIMIT-HPV study group. Efficacy of a carrageenan gel in preventing anal human papillomavirus (HPV) infection: interim analysis of the Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV) randomised controlled trial. Sex Transm Infect. 2022 Jun;98(4):239-246. doi: 10.1136/sextrans-2021-055009. Epub 2021 Jun 17. PMID: 34140405. https://pubmed.ncbi.nlm.nih.gov/34140405/
Note: This interim analysis of a trial among MSMs (LIMIT-HPV) shows a lack of rectal protection against HPV in MSMs using CG gel and increased AEs in those using CG gel (versus placebo). The outcome is HPV (not HIV) but may be relevant for HIV PrEP and MPT products using CG as well.

54. Matthews RP, Zang X, Barrett SE, Koynov A, Goodey A, Heimbach T, Weissler VL, Leyssens C, Reynders T, Xu Z, Rottey S, Vargo R, Robertson MN, Stoch SA, Iwamoto M. A Randomized, Double-Blind, Placebo-Controlled, Phase 1 Trial of Radiopaque Islatravir-Eluting Subdermal Implants for Pre-exposure Prophylaxis Against HIV-1 Infection. J Acquir Immune Defic Syndr. 2022 Nov 29. doi: 10.1097/QAI.0000000000003135. Epub ahead of print. PMID: 36450129.

https://pubmed.ncbi.nlm.nih.gov/36450129/
Note: these are the primary results of a 12-week phase I trial conducted by Merck with their ISL implant. Safety and tolerability, as well as PK for islatravir parent and islatravir triphosphate from plasma and PBMCs, were assessed.

55. Mazibuko-Motau, N., Sobia, P., Xu, J. *et al.* Vaginal microbial shifts are unaffected by oral pre-exposure prophylaxis in South African women. *Sci Rep* **12**, 16187 (2022). https://doi.org/10.1038/s41598-022-20486-z
Notes: This study investigated the impact of daily oral TDF in combination with emtricitabine for PrEP on the vaginal microbiota of South African women.

56. Thurman AR, Brache V, Cochon L, Ouattara LA, Chandra N, Jacot T, Yousefieh N, Clark MR, Peet M, Hanif H, Schwartz JL, Ju S, Marzinke MA, Erikson DW, Parikh U, Herold BC, Fichorova RN, Tolley E, Doncel GF. Randomized, placebo controlled phase I trial of the safety, pharmacokinetics, pharmacodynamics and acceptability of a 90 day tenofovir plus levonorgestrel vaginal ring used continuously or cyclically in women: The CONRAD 138 study. PLoS One. 2022 Oct 10;17(10):e0275794. doi: 10.1371/journal.pone.0275794. PMID: 36215267; PMCID: PMC9550080.
https://pubmed.ncbi.nlm.nih.gov/36215267/
Note: these are the primary results of a phase I trial with TFV/LNG IVRs. Most TFV/LNG IVR users reported no change in menstrual cycles or fewer days of and/or lighter bleeding. All IVRs were safe. Active rings delivered high TFV concentrations locally. LNG caused changes in cervical mucus, sperm penetration, and ovulation compatible with contraceptive efficacy.

57. Yu Y, Bigos KL, Marzinke MA, Landovitz RJ, McCauley M, Ford S, Hendrix CW, Bies RR, Weld ED; HPTN 077 Study Team. A population pharmacokinetic model based on HPTN 077 of long-acting injectable cabotegravir for HIV PrEP. Br J Clin Pharmacol. 2022 Oct;88(10):4623-4632. doi: 10.1111/bcp.15477. Epub 2022 Aug 14. PMID: 35949044.
https://pubmed.ncbi.nlm.nih.gov/35949044/
Note: Cabotegravir pharmacokinetics, like those of other long-acting depot preparations, exhibit variability between individuals and between injectable occasions. The aim of this study is to describe the population pharmacokinetics of long-acting cabotegravir (CAB-LA), to facilitate a variety of future clinically relevant simulations to inform the optimal use of CAB-LA.

3d. Press releases and media:

1. Population Council acquires the dapivirine ring and other women-centered HIV prevention from IPM.
https://www.popcouncil.org/news/population-council-acquires-the-monthly-dapivirine-ring-and-other-woman-cen
https://www.ipmglobal.org/content/population-council-acquires-monthly-dapivirine-ring-and-other-woman-centered-hiv-prevention
Oct 4, 2022: Population Council Completes Asset Purchase Agreement from the International Partnership for Microbicides, Acquiring the Monthly Dapivirine Ring and Other HIV Prevention Technologies
https://www.popcouncil.org/news/population-council-completes-asset-purchase-agreement-from-the-internationa

2. Access to generic version of Apretude in 90 countries: https://www.aidsmap.com/news/jul-2022/viiv-healthcare-allow-90-countries-access-generic-versions-hiv-prevention-shot

3. Merck: announces a new treatment program with lower dose of ISL- Stops the monthly oral ISL pill for PrEP: 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/

4. Zimbabwe Becomes First African Nation To Approve HIV Prevention Drug https://www.theguardian.com/global-development/2022/oct/20/zimbabwe-approves-hiv-prevention-drug-cabotegravir?utm_source=AVAC+Email+Updates&utm_campaign=f08fcb93d9-EMAIL_CAMPAIGN_2022_10_21_09_24&utm_medium=email&utm_term=0_6fd730be57-f08fcb93d9-130145473. (the Guardian)

5. European Medicines Agency Validates ViiV Healthcare's Marketing Authorisation Application for Cabotegravir Long-Acting Injectable for HIV Prevention https://www.spotlightnsp.co.za/2022/11/09/sa-expected-to-begin-piloting-hiv-prevention-shot-in-early-2023/

6. The Ministry of Health has approved the use of dapivirine vaginal ring (DRV) and long acting injectable cabotegravir (CAB-LA) as additional optional drugs for preventing HIV/Aids infection in Uganda. https://www.monitor.co.ug/uganda/news/national/government-approves-new-hiv-injectable-drug-4013554

7. Sunlenca® (lenacapavir) Receives FDA Approval as a First-in-Class, Twice-Yearly treatment Option for People Living With Multi-Drug Resistant HIV https://www.businesswire.com/news/home/20221221005541/en/ https://www.gilead.com/news-and-press/press-room/press-releases/2022/12/sunlenca-lenacapavir-receives-fda-approval-as-a-firstinclass-twiceyearly-treatment-option-for-people-living-with-multidrug-resistant-hiv

Appendix tables:

1. HIV Prevention projects

N= 29	Drug delivery system (DDS)	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	refs, publication and/or NIH RePorter link (if link doesn't work paste it into browser)
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.avac.org/trial/purpose-3-hptn-102
2	injectable parenteral	Viriom/NWU	phase 1	NNRTI VM1500A	1 month?	Ongoing	developed in Russia for Rx (approved in oral dosage)	https://pubmed.ncbi.nlm.nih.gov/28940154/ Paste link into browser: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2020/1430_0_Murphy_00473.pdf
3	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 and NIMH	https://pubmed.ncbi.nlm.nih.gov/35680875/ Multiple grants including: https://reporter.nih.gov/search/vZal4np7ika09TFKy_8XBA/project-details/10368947
4	injectable-parenteral	UW	FIH/ clinical	LPV, RTV, TFV	??	Ongoing	Targeted LA- combination ARV Therapy (TLC-ART) Program - New platform to stabilize insoluble a& soluble ARVs together in a nanosuspension- RX focused; applicable to Px PIs: Collier and Ho, NIAID 2019-2023;	https://reporter.nih.gov/project-details/9983588 https://reporter.nih.gov/project-details/9733109
5	Injectable-parenteral	UW		TAF	??	Unknown	Drugamers described in proceedings from BMGF TAF workshop. PI: Stayton, BMGF	https://pubmed.ncbi.nlm.nih.gov/33913760/

N= 29	Drug delivery system (DDS)	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	refs, publication and/or NIH RePorter link (if link doesn't work paste it into browser)
6 New entry	injectable parenteral	U Florida	preclinical	eCD4-Ig	6 months	Ongoing	To optimize the combination of a broad and potent HIV-1 entry inhibitor and a tunable hydrogel that significantly extends the in vivo half-life of this inhibitor. PI: Farzan, M. NIAID 2020-2025	https://reporter.nih.gov/project-details/10401854
7	Injectable-parenteral	U Nebraska	preclinical	DLG, FTC, TFV, others	up to 1 year	Ongoing	LASER-ART: chemical modification of existing ARVs for extended release. PI: Gendelman, NIAID 2021-2026	https://pubmed.ncbi.nlm.nih.gov/34531390/ https://reporter.nih.gov/project-details/10391567
8	Injectable-parenteral	Navigen	clinical	CPT31 -D-peptide Entry inhibitor	target 3 months	Ongoing	PI: Madani, NIAID 2017-2023	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
9	Removable Implant (EVA)- SC	MSD	phase 1	NRTTI: ISL	1+year	Stopped. See Merck's Press release	PI unknown, MSD	https://pubmed.ncbi.nlm.nih.gov/34608329/ 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/
10	bioresorbable implant - SC	OCIS	preclinical	maturation inhibitor (DFH-1160005)	0.5-1 year	Ongoing	PI: Moss; NIAID 2020-2025	https://reporter.nih.gov/project-details/10249347

N= 29	Drug delivery system (DDS)	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	refs, publication and/or NIH RePorter link (if link doesn't work paste it into browser)
11	Removable Implant -SC	OCIS	Preclinical + phase I/II	TAF	1+year	Ongoing	CAP-018. PI: Abdool Karim, SAMRC, EDCTP, NRF (end dec 2022) PI: Baum; NIAID 2021-2026	https://pubmed.ncbi.nlm.nih.gov/34992111/J10 https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3584 https://reporter.nih.gov/project-details/10449318 https://pubmed.ncbi.nlm.nih.gov/35581262/
12	Implant-bioerodible (PCL) -SC	RTI	preclinical	TAF, ISL, BIC, others	7-12 months	Ongoing	NHP studies completed with TAF and ISL PI: Johnson, USAID; NIAID NICHD.	https://www.sciencedirect.com/science/article/abs/pii/S0168365921005502?via%3Dihub https://reporter.nih.gov/project-details/10348177 https://reporter.nih.gov/search/zaeac07k30aOzz8tjq2E3Q/project-details/10242929 https://reporter.nih.gov/project-details/10546217 https://www.frontiersin.org/articles/10.3389/fphar.2022.923954/full https://pubmed.ncbi.nlm.nih.gov/35913838/
13	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://www.sciencedirect.com/science/article/abs/pii/S0168365918304711 https://reporter.nih.gov/search/0QLLolLF1kWs6-YgNUdB_Q/project-details/10481727 https://www.biorxiv.org/content/10.1101/2022.12.15.520646v1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7590004/ https://pubmed.ncbi.nlm.nih.gov/33997267/ https://reporter.nih.gov/project-details/10093084

N= 29	Drug delivery system (DDS)	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	refs, publication and/or NIH RePorter link (if link doesn't work paste it into browser)
14	Implant-Removable - SC	NWU	preclinical	INSTI: CAB	??	Completed- Grant Ended- PI 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
15	osmotic pump- -SC	Intarcia	preclinical	exenatide; TAF	6 mo-1year	Stopped due to toxicity of TAF in animal models.	Medici system. Publication is a review where Intarcia system is described. PI: Unknown	https://pubmed.ncbi.nlm.nih.gov/33913760/
16	Implant, bioerodible. (PEO coated w/ PCL membrane) -SC	QUB	Preclinical	model hydrophobic drug: olanzapine	> 6 months	Unknown	3D printed implant PI: unknown, Academy of medical sciences, Wellcome Trust	https://www.tandfonline.com/doi/full/10.1080/10717544.2022.2057620
17	Biocage--SC	diverse academics (CNMC, yale, U of M..)	preclinical	multiple/neuro-drugs	Theoretically tunable to needed duration	Unknown	3D printed small biodegradable device (can be delivered via 22G needle) for direct implantation in target tissues (E.g. brain) PI: unknown, NCATS, NIH	https://pubmed.ncbi.nlm.nih.gov/29247175/
18	In situ forming implant (ISFI)- -SC	UNC	preclinical	ISL and other drugs incl for TB	Unknown	Ongoing	Publication is for *Mtb.* PI: Garcia, NIAID 2018-2023	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9360445/ https://reporter.nih.gov/project-details/10468909
19	Oral tablets-enteral	MSD	clinical	ISL (NRTTI)	monthly	Stopped. See Merck press release.	PI: unknown.	https://www.avac.org/infographic/future-arv-based-prevention
20	Tablets (gastric-residence)-enteral	MIT, Lyndra	preclinical	DLG, RPV, CAB	7 days	Unknown	focused on Rx but can work for Px; GILEAD involved for HIV indication; https://lyndra.com/ PI: unknown, BMGF, NIH	https://www.nature.com/articles/s41467-017-02294-6
21	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/

N= 29	Drug delivery system (DDS)	Developer	stage	API(s)	Duration	R&D Status	Notes: (including PI & funding source)	refs, publication and/or NIH RePorter link (if link doesn't work paste it into browser)
22	MAP-transdermal	PATH/QUB	preclinical	RPV nanosuspension	7 D-1 Mo	Ongoing	ex vivo porcine study & in vivo rat study	https://www.sciencedirect.com/science/article/pii/S0168365918306370?via%3Dihub
23	Hydrogel-forming MAP transdermal	QUB	preclinical	CAB-sodium salt	~ 1 month		cyclodextrin complexation used to solubilize the hydrophobic API, PI: unknown, USAID	https://pubmed.ncbi.nlm.nih.gov/?term=35738464,35658545&format=abstract
24	Ring (PU)-vaginal	AECOM	clinical-phase I	TDF	1 month	Stopped due to AEs	PI: Herold, NIAID 2018-2023.	https://www.sciencedirect.com/science/article/abs/pii/S2352301819301456
25	Ring - vaginal	NWU	preclinical	NRTI: IQP-0528	1 month?	Stopped. IQP0528 not further supported by IMQUEST for Px	Tested in NHP. PI: Kiser, NIH	https://pubmed.ncbi.nlm.nih.gov/28770490/
26	Ring - vaginal	Tulane	preclinical	DLG, SAMT-247 (nucleocapsid protein inhibitor)	3 months	Ongoing	PI: Veazey NIAID 2017-2022 SAMT-247 Drug Originator is Daniel Appella, from NIDDK.	https://reporter.nih.gov/project-details/10071116
27	Pod ring-vaginal	Dana Farber (DFCI)	preclinical	CD4 mimetic compound	?	Ongoing	Entry inhibitor -irreversibly interferes with HIV ENV binding to CD4 PI: Madani, NIAID 2011-2023	https://reporter.nih.gov/project-details/10174715
28	Fibers-based microbicide - drug eluting-vaginal	UW	preclinical	INSTI: RAL prodrug	OD- 2 weeks	Ongoing	PI: Woodrow; R012019-2024, NIAID. Grant is 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/10359034
29 New entry	3D bioprinted silicone scaffold devices-vaginal	U of Louisville	preclinical	BV- Not specifically for HIV indication	LA (unclear duration)	New award-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

2. MPTs including an HIV indication

N =28	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
1	Injectable Hydrogel-parenteral	PREG	EVMS	preclinical	DLG+ LNG	3 mo. +	Ongoing	PI: Clark. Project Horizon, NIAID 2019-2024.	https://reporter.nih.gov/project-details/10546210 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9639748/
2	Implant-(EVA)- SC	PREG	Merck	clinical	ISL, ENG	1+year	Stopped. See Merck Press release	PI: unknown.	Grobler, LEAP Conference 2020 (link unavailable). LEAP link: https://longactinghiv.org/topics
3	Implant bioerodible (PCL)-SC	PREG	RTI	preclinical	TAF or ISL, LNG or EE	7-12 months	Unknown	PI: Johnson, USAID (SCHIELD). NHP studies completed. Not considered for CP in MATRIX.	https://www.sciencedirect.com/science/article/abs/pii/S0168365921005502?via%3Dihub
4	In Situ forming implant (ISFI)	PREG	UNC	clinical	DLG, RPV, 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/ AIDS 2022 (link not available)
5	DPP- enteral	PREG	Viatris, (PC)	clinical	TDF/FTC, LNG/EE	24h (daily)	Ongoing	PI: Haddad, HPTN 104, NIAID PC also works on an over encapsulated pill.	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/
6	Enema-rectal	Hepatitis, HSV	U of Louisville	clinical	Q-GRFT	OD	Stopped; gel abandoned in favor of an enema for anal intercourse-	PI: Palmer	https://pubmed.ncbi.nlm.nih.gov/31792342/ https://reporter.nih.gov/project-details/9276572

N =28	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
7	MAP-transdermal	PREG	QUB, PATH	preclinical	Cab_ progestin (norelgestromin)	7 days- 1 month	Ongoing	PI: Unknown., USAID. Not considered for CP in MATRIX.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6809612/
8	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
9	Core Sheath Ring - vaginal	PREG	IPM/PC	clinical	DPV, LNG	90 days	Ongoing	PI: Steyton phase I/II IPM 056 / CCN019B (NICHD) through 2023	https://www.avac.org/trial/ipm-056-ccn019b
10	Reservoir Ring (PU)-vaginal	HSV	CONRAD	clinical	TFV	90 days	Unknown	PI: Mugo, Funding unknown. PI: Liu NIAID (MTN-038) https://mtnstopshiv.org/research/studies/mtn-038	Mugo, R4P 2021 (link unavailable) Liu, CROI 2022 (link unavailable)
11	Ring (PU reservoir segmented)-vaginal	HSV, PREG	CONRAD	clinical	TFV, LNG	90 days	Unknown	PIs: Doncel and Clark, USAID	https://www.conrad.org/news/news_items/conradandcdccollaborateonstudyofintravaginalringsreleasingtfvwithandwithoutlnginkenya.html https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199778
12	Ring vaginal	HSV, HPV, PREG	PC	preclinical	LNG, CG, MIV-150, ZA	28 days	Ongoing	PI: Haddad P50 contraceptive program grant funded via 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

N =28	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
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-containing-etonogestrel-ethinyl-estradiol-and-qgriffit
15	non hormonal Ring_pod mAB+TDF vaginal	HSV, CT, PREG	MB, OCIS, Plante Biotech, U of Mass UNC, Mucoimmune	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 mAB cocktail- vaginal	PREG	Mucomune	preclinical	HCA+VRC01+N6	1 month +	Ongoing	PI: Kushiro. NICHD-2021-2023. 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	Film_ARV nanoparticles- vaginal	HSV	U of Porto	preclinical	EFV + TFV	24h (daily)	Unknown	PI: Unknown, funding unknown	https://pubmed.ncbi.nlm.nih.gov/27664327/
19	LA-FILM- vaginal	PREG	MWRIF	preclinical	ISL (-Pro) + progestin	1 month	Ongoing	PI: Rohan, LATCH program NIAID 2019-2024	https://reporter.nih.gov/project-details/10545302
20	Film_mAB vaginal	HSV, PREG	MAPP	clinical	MB66	24h	Stopped. R&D on other antibodies supported by Mucommune	PI: Andersen.	https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003495

N =28	DDS	other indications	Developer	stage	APIs	Duration	R&D Status	Notes: (including PI & funding source)	Ref, publication and/or NIH RePorter link
21	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
22	FDI- vaginal	HSV, PREG	IPM	preclinical	DPV, LNG, ACV	8h	Unknown	PI: Unknown.	https://pubmed.ncbi.nlm.nih.gov/27163243/
23	Gel- Vivagel (dendrimer)-vaginal	HSV, HPV, BV	Starpharma	preclinical	SPL7013 (astodrimer sodium)	30 days	Unknown if program sill active.	PI: Jeremy Paull. A product was licensed in the Pacific rim for BV, based on Vivagel.	https://reporter.nih.gov/project-details/7490395
24	Gel (TFV) vaginal	HSV	CONRAD	clinical	TFV 1%	BAT 24	Stopped: poor adherence/ineffectiveness 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
25	Gel (TFV/ACV) vaginal	HSV	SRI Int'l	preclinical	TFV, ACV	24h	Program inactive (lack of funding).	PI: Shankar, G.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4538522/
26	PPCM-Gel vaginal	CT, GC, HPV, HSV, PREG	YASO therapeutics	Preclinical and early clinical	polyphenylene carboxymethylene	OD	ongoing	PI: Weitzel, M. NICHD (2022-2023)	https://pubmed.ncbi.nlm.nih.gov/32469052/ https://reporter.nih.gov/project-details/10483274
27	Gel MCZ vaginal	HSV, HPV	PC	clinical	CG, MIV-150, Zinc Acetate	24h (daily or OD)	Inactive (lack of funding)	PI: Unknown.	https://pubmed.ncbi.nlm.nih.gov/27552154/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4468722/
28 New entry	IUD - Intrauterine	PREG	UW	preclinical	Copper + ARVs (unspecified)	Unspecified (duration of the IUD)	Ongoing	PI: Woodrow NIAID 2020-2025	https://reporter.nih.gov/project-details/10460638 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9081257/ delayed release manuscript — Available May 1, 2023) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9277594/