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

R&D Landscape Review 5

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1. Abbreviations and acronyms

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

IV	Intravenous
LAB	Laboratory
LEN	Lenacapavir
LNG	Levonorgestrel
MAP	Microarray Patch
MI	Maturation Inhibitor
MIT	Massachusetts Institute of Technology
MGT	Male genital tract
MN	Micro-needles
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
PWID	Person Who Inject Drugs
QGRFT	Q-Griffithsin
QUB	Queen's University Belfast
RAL	Raltegravir
R&D	Research and Development
RPV	Rilpivirine
Rx	Treatment
SC	Sub-cutaneous
ZA	Zinc acetate
ZDV	Zidovudine

2. Executive Summary

MATRIX Prime is monitoring R&D activities in the HIV prevention and microbicide[1] research space by conducting desktop reviews 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.

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 noticeable overlap with work being conducted by others. One of the key activities for this is a **desktop review of funded R&D prevention activities and publications** on a biannual basis, as described below.

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

a. Procedures for desktop review include monitoring:

- Publications/abstracts reviews via PubMed, Int'l conferences (i.e., CROI 2024), listserves (i.e., AVAC, Choice agenda, AIDSmap; Fierce pharma) and database review (i.e., AVAC, PrEP watch, IMPT),
- Published reviews, reports and media releases on relevant topics (i.e., HIV PrEP, microbicides, MPTs),
- Current NIH-funded projects (via NIH RePorter),
- Review of funded clinical trials via various websites: clinicaltrials.gov (US), EU clinical trials register and Wellcome trust funded grants database.
- The desktop review does NOT include clinical trials, SEED projects or ISPs directly funded by MATRIX.
- For publications and presentations, authors names are bolded if they are one of the MATRIX PDs, from prime or leads from hubs.

This **desktop review,** for the first half of 2024, includes publications and funded projects identified between January 1 and June 30, 2024, focusing on HIV Prevention/ PrEP, microbicides, and Multi-Purpose Prevention Technologies[2] (MPTs) that include an HIV indication.

Note: current terminology in MATRIX uses the term "dual purpose" (DP) products, which identifies a subset of MPTs consisting of products with active pharmaceutical ingredients that may prevent HIV infection and unplanned/unintended pregnancy.

[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

Twenty five clinical trials (CTs) were found (active, completed or withdrawn), as summarize in Table 1 (in the Appendix). The products associated with these CTs are also reported in the product tables 2 and 3 in the Appendix. Thus, the total number of products/projects summarized below, are only those tallied in Appendix tables 2 & 3.

b. Key findings from the landscape review (see tables 1-3 in the Appendix):

Summary table of projects identified in landscape review.

Type of projects	N	Active/Ongoing	Currently not active/unknown
HIV Prevention only	40	24*	16
MPTs (including DP products)	34	19*	15
TOTAL	74	43	31

(*) no new entries in landscape review # 5

As shown in the summary table above, there are a total of **40 HIV prevention projects**, of which 16 projects are completed, on hold/stopped or of unknown status, and **24 are actively ongoing.** No new entries for HIV prevention projects were found during this review cycle.
This report includes a total of **34 MPT projects** (inclusive of DP products), of which 15 projects are completed, on hold/stopped or of unknown status and **19 are actively ongoing projects.** No new entries for MPT projects were found during this review cycle.

Aside from HIV, the most current other indication(s) among the active MPT projects is to prevent unplanned pregnancy (17 projects); prevent Human Simplex Virus acquisition (HSV; 3 projects), prevent or treat BV (2 projects), GC (2 projects), CT (2 projects) and Human Papilloma Virus (HPV; 1 project).

c. Active HIV prevention projects (N=24):

- 4 topical products:
  - 1 rectal enema,
  - 1 rectal insert,
  - 1 vaginal device,
  - 1 vaginal drug - eluting fibers.
- 20 systemic products:
  - 6 implants (removable, bioresorbable, refillable, 3D printed),
  - 10 injectables,
  - 1 *in situ* forming implant (ISFI),
  - 2 transdermal Microneedle (MN) MAPs,
  - 1 monthly oral tablet.

d. HIV Drugs and DDS investigated, including PD/sponsors:

Clinical phase:

- *CONRAD/EVMS:* is now recruiting for the RITE PrEP trial (implemented by CDC and Emory University) for a multidose rectal safety and PK of their **TAF/EVG** FDI in MSMs. This complements the vaginal focus of the MATRIX project for this CP product. Additionally, several publications in the past 6 months are highlighting the development program of this on-demand product, and an earlier safety trial for rectal use of the FDI (MTN-039).

- *Gilead Sciences*: The company is continuing the PURPOSE program to assess 6-month **LA-LEN injections** in various populations globally. The major breakthrough news in June 2024 was the early stopping of PURPOSE 1 trial among CGW in Africa, with 100% efficacy of LA-LEN and superiority of the injections compared to daily oral PrEP (see press release section).
- *Merck*: is pursuing the clinical program of the monthly oral tablets with the NRTTI **MK8527**.
- *Population Council (and formerly IPM)*: has several ring trials ongoing including a bioequivalence trial with a 3-month **DPV** ring.
- *ViiV Healthcare*: has several new APIs in phase I clinical trials, including **capsid inhibitors** (CAI) taken orally or via injections and **INSTIs** administered via injections. ViiV is also continuing to conduct several trials to characterize and optimize the duration of their **reformulated Cab-LA injections**, including for the best location of the injections in the body (gluteus vs thigh muscles). ViiV is also starting an open-label study (PALISADE) to continue offering 2-month Cab-LA to participants of the HPTN-083 and 084 trials.

Pre-clinical phase:

- Creating **prodrugs** to increase the duration of extended release of known APIs continues to be a dominant strategy for PDs, both in terms of ongoing funding, new funding and publications or presentations in the previous 6 months (e.g., CROI 2024 presentations).
- The repurposing of ARVs approved for treatment for a prevention indication (via prod-drugging or not) is continuing (e.g., saquinavir mesylate, bictegravir, lenacapavir, dolutegravir, raltegravir, tenofovir).
- New APIs are also being characterized for treatment or prevention, including a weekly oral INSTI and a daily protease inhibitor (PI) (which does not require a booster) by Gilead sciences, and several APIs of different drug classes (CAI, INSTI, maturation inhibitor (MI)) by ViiV Healthcare/GSK. We noted a recent publication (including investigators from ViiV and OCIS) describing the advancement through re-formulation of a second-generation MI from oral dosage to long-acting parenteral dosage. A MI Is also being formulated for release from a bioresorbable implant (OCIS, for up to 1 year duration, row #4, Table 2b).

e. Active MPT projects (N=19):

- 13 topical products:
  - 1 intra-uterine system (IUS),
  - 1 fast dissolving insert (FDI),
  - 2 vaginal films,
  - 9 vaginal rings.
- 6 systemic products:
  - 2 injectables,
  - 1 implant refillable,
  - 1 in situ forming implant (ISFI),
  - 2 daily oral tablets (or DPPs).
- The drug delivery systems (DDS) and academic/non-profit groups working on MPTs are similar to those listed for the HIV prevention indication only. Notably, there is a dominance of rings as DDS for MPTs, compared to a dominance of injectables for HIV only products.
- No pharmaceutical company were found to conduct R&D on MPTs, with the exception of Viatris for the Dual Prevention Pill (DPP).
- Drugs investigated for MPTs include both ARVs (e.g., DPV, RPV, TFV/TDF/TAF, FTC, ISL, DTG, CAB) and non-ARV (e.g., Q-GRFT, anti-HIV monoclonal antibodies), and both hormonal (e.g., LNG, EE, Depo-Provera) and non-hormonal (e.g., antibodies, lactic-acid, copper, zinc) for the contraceptive drugs.

- A few clinical trials with MPTs are ongoing or were recently completed, including for a 3-month MPT **DPV/LNG** ring (led by PopC – formerly IPM- and sponsored by NICHD). Additionally, PopC just completed two pilot trials in Zimbabwe and South Africa, of their over-encapsulated DPP.

f. Publications/presentations:

40 recent publications or presentations were identified and are listed below, starting in section 3. They include publications on APIs/ drugs, new formulations, drug delivery systems, preclinical and clinical research, and reviews.

- This landscape review was dominated by research presentations from CROI 2024 (https://www.croiconference.org/wp-content/uploads/sites/2/resources/2024/croi2024-abstract-ebook-v3.pdf -Abstracts from 16 oral or poster presentations were selected). Overall, the focus of presentations and publications, this round, were on the preclinical characterization of novel (or second generation) ARVs, the use of pro-drugs or novel formulation approaches to extend drug delivery from various DDS, and the pre/clinical efficacy of several LA-DDS. We noted:
  a) the ultra-long release and tolerability of ISL from a refillable nanofluidic implant for HIV treatment in SHIV-infected NHPs; (Grattoni's Laboratory (Lab) https://pubmed.ncbi.nlm.nih.gov/38142963/);
  b) presentations at CROI of the formulation of the INSTI BIC as a prodrug for ultra-long-acting injection (6+ months; Gendelman's Lab) or for LA systemic delivery via a MAP (3 weeks, Owen's Lab). A third group (Benhabbour) presented on the release of DTG for over 300 days from an ISFI in mice.
  c) the CAPRISA-018 trial showed proof-of-concept for the 1-year sustained release of TAF in CGW through a removable implant (developed by OCIS); however significant toxicity was also noted (two CROI presentations). TAF and other TFV prodrugs continue to be studied for long-acting release by several PDs;
  d) a robust R&D program at ViiV to pursue longer duration CAB-LA injections over the next few years (several CROI presentations and active trials in clinicaltrial.gov) ;
  e) reassessment of the efficacy of daily oral PrEP in all populations, https://pubmed.ncbi.nlm.nih.gov/38484128/, and specifically in CGW, with imperfect adherence (< 7 doses/ week); https://pubmed.ncbi.nlm.nih.gov/38427359/.
  f) the safety of a first generation MPT ring (DPV/LNG) in CGW https://pubmed.ncbi.nlm.nih.gov/38838028/ ; the safety of the 25mg DPV ring during third trimester pregnancy https://pubmed.ncbi.nlm.nih.gov/38055292/, and the safety of a 3-month TFV ring in CGW: https://pubmed.ncbi.nlm.nih.gov/38444118/.

  - An special issue of the journal *Pharmaceutics* features several relevant articles for MATRIX (https://www.mdpi.com/journal/pharmaceutics/special_issues/1STR546UJF), including two on the formulation and systemic release of the INSTI CAB through MAPs, and other DDS for extended release or on-demand use that may fill a gap in the HIV prevention field.

- Publications directly relevant to (and/or supporting) MATRIX CP projects (listed in section 3) include one publication on the preclinical development of an extended-release ISL/etonogestrel film (by the UPITT/MWRIF team; https://pubmed.ncbi.nlm.nih.gov/37382422/) and several publications on the TAF/EVG insert, including a review paper by CONRAD (in the special issue of *Pharmaceutics*), a study showing an extended window of PEP protection in NHP to up to 24h with the TAF/EVG FDI (CONRAD/CDC: https://pubmed.ncbi.nlm.nih.gov/38134382/), and the safety

of rectal application of the TAF/EVG inserts in men and women (CONRAD/MTN: https://pubmed.ncbi.nlm.nih.gov/38655842/)

g. Media releases, announcements or reports- Highlights below:

- the **clinical efficacy of semi-annual LEN injections in CGW** was announced through three press releases (1 from Gilead sciences and 2 from the NIH) after early stopping of the PURPOSE 1 trial; Gilead sciences announced the efficacy results of the 6-month LA-LEN injections in CGW and the continuation of clinical research efforts globally. This includes the launch of two new HPTN trials (HPTN 102 and 103) co-funded by NIH.
- There was one press release announcing that Apretude is now approved in Canada and a media article indicating high continuation rate for Cab-LA in Zimbabwe.
- One press release announced a collaboration between the company Exavir and ViiV to further develop ultra long-acting compounds for people at risk or living with HIV.
- Several press releases focused on the DPV ring, including for a licensing agreement to increase supply of rings in Africa, and for the local manufacturing of the DPV in South Africa, and to announce the safety of the DPV in pregnant people.

h. Landscape Summary

- A total of 74 projects have been identified, of which **43 are actively ongoing (24 HIV prevention + 19 MPT projects**).
- Updating the **clinical trial databases** continues to yield key new insights in new products at the clinical stage of evaluation. This includes both Pharma funded trials and non-pharma trials.
- This latest landscape review highlights key progress for MPTs, long-acting and on-demand PrEP products, and various strategies to extend duration of protection for PrEP through improved formulations, pro-drugging of existing APIs and improved platform technologies.
- The most notable news in the past 6 months was the press release from GILEAD for the **100% efficacy of LA-LEN when injected semi-annually in CGW**. This impressive news, however, does not impact directly any of the products in the CP of MATRIX.
- The next call with Pharma and funders will be held in August 2024.
- Next landscape review will be conducted in December 2024.

To conclude, **this landscape review #5 did NOT reveal any significant overlap with current MATRIX critical path products.** Additionally, the progresses noted in the R&D of long-acting prevention approaches, including 6-month products (at the preclinical and clinical stages) suggest the potential benefit for MATRIX to **expand the targeted duration of possible ultra long-acting products to 1 year,** as this remains an unfilled need/gap in the HIV prevention toolbox**.**

3. Review of published literature: Jan1-June 30, 2024

Each citation in this section is followed by a link to the publication in PubMed (when available), and a brief note about the goal or relevance of the publication**.** No notes were written for the review papers and abstracts/presentations from conferences.

- CROI 2024 abstracts are listed in section 3c. Since there was a lot of relevant abstracts presented this year on various classes of ARVs and on formulations and pre-clinical /clinical work (with few or no publications yet), a high level summary of CROI presentations is provided

in itallics in subsection 3a, describing the updates by different classes of ARVs and formulation work.
- 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 for publications and presentations).

Capsid inhibitors (CAI):

- *Summary of Conference (CROI 2024) section 3c: No specific abstracts were selected for this landscape review from CROI 2024 as presentations on lenacapavir at CROI 2024 focused on treatment considerations and characterization of viral resistance to lenacapavir*.

Note: On 20 June 2024, Gilead announced through a press release that the twice-yearly Lenacapavir injections demonstrated 100% efficacy in cis-gender women (from the PURPOSE 1 trial) and superiority to Daily Truvada® for HIV Prevention (see press releases, section 3f).

INSTI:

- *Summary of Conference (CROI 2024), section 3c:*
  - *A new INSTI was described by Gilead science (GS1720) for weekly oral dosage (oral session).*
  - *Several presentations focused on CAB-LA, including an oral presentation by ViiV investigators on the extended dosage of CAB-LA to 4-months, and a poster investigating different body locations for injection (thigh vs gluteal muscles).*
  - *The Exavir company presented a poster on a new CAB-stearate prodrug (XVIR-110) for extended subcutaneous release.*
  - *Investigators from the University of Nebraska also presented a poster on a BIC prod-drug for LA injection (6month or longer).*
  - *University of Liverpool investigators presented a poster on a solid prodrug of BIC for 2-months injections.*
  - *Investigators from UNC presented a poster on an ISFI releasing DTG for over 300 days in mice*.

Maturation inhibitors (MI):

- *Summary of Conference (CROI 2024), section 3c:*
  - *Two posters led by ViiV/GSK at CROI 2024 presented preclinical characterization of two new maturation inhibitors (GSK-3640253 and VH-373993).*
- Publication:

1. Akhavein, N., **Baum, M.M., Gunawardana, M**. *et al.* Parenteral platforms for tunable, long-acting administration of a highly hydrophobic antiretroviral drug. *Sci Rep* **14**, 11573 (2024). https://pubmed.ncbi.nlm.nih.gov/38773172/. *This second-generation MI (GSK8232) is being explored in rats for LA parenteral formulation through suspensions, ionic liquids and subdermal implants*.

NRTI:

- *Summary of Conference (CROI 2024), section 3c:*

- *Investigators from the University of Nebraska presented a poster on creating double ester-prodrugs of TFV for long-acting suppression of HBV.*
- *CAPRISA and OCIS teams had an oral presentation and a poster on CAPRISA-018, the phase I trial of a removable 1-year TAF implant in women in South Africa.*

NRTTI:

- *Summary of Conference (CROI 2024), section 3c:*
  - *an oral presentation and a poster, both led by Merck investigators, presented on the weekly and/or monthly oral dosing and the discovery of their new NRTTI MK8527.*

Protease Inhibitors (PI)*:*

- *See Conference (CROI 2024) section (oral presentation from Gilead sciences).*
- Publication:

2. Mulato A, Lansdon E, Aoyama R, Voigt J, Lee M, Liclican A, Lee G, Singer E, Stafford B, Gong R, Murray B, Chan J, Lee J, Xu Y, Ahmadyar S, Gonzalez A, Cho A, Stepan GJ, Schmitz U, Schultz B, Marchand B, Brumshtein B, Wang R, Yu H, Cihlar T, Xu L, Yant SR. Preclinical characterization of a non-peptidomimetic HIV protease inhibitor with improved metabolic stability. Antimicrob Agents Chemother. 2024 Apr 3;68(4):e0137323. doi: 10.1128/aac.01373-23. Epub 2024 Feb 21. PMID: 38380945; PMCID: PMC10989020. https://pubmed.ncbi.nlm.nih.gov/38380945/. *Gilead sciences has characterized GS-9770, a novel investigational non-peptidomimetic HIV PI with unboosted once-daily oral dosing potential, due to improvements in its metabolic stability and its pharmacokinetic properties in preclinical animal species.*

Drug Delivery Systems (DDS):

- *The articles below and in the "review" section of this landscape review, are part of a special issue in the journal Pharmaceutics on:* ***HIV/AIDS Prevention Formulation Design and Optimization and Its Pharmacokinetic-Pharmacodynamic Evaluation****.* https://www.mdpi.com/journal/pharmaceutics/special_issues/1STR546UJF
- Publications:

3. Vora, L.K.; Tekko, I.A.;Zanutto, F.V.; Sabri, A.; Choy, R.K.M.;**Mistilis, J**.; Kwarteng, P.; Jarrahian, C.;McCarthy, H.O.; Donnelly, R.F. A Bilayer Microarray Patch (MAP) for HIV Pre-Exposure Prophylaxis: The Role of MAP Designs and Formulation Composition in Enhancing Long-Acting Drug Delivery. Pharmaceutics 2024, 16, 142. https://doi.org/10.3390/pharmaceutics16010142. *This research provides an overview of novel strategies aimed at enhancing the efficiency of MAP delivery of micronized cabotegravir sodium (CAB Na) for HIV PrEP.*
4. Kinvig H, Rajoli RKR, Pertinez H, Vora LK, Volpe-Zanutto F, Donnelly RF, Rannard S, Flexner C, Siccardi M, Owen A. Physiologically Based Pharmacokinetic Modelling of Cabotegravir Microarray Patches in Rats and Humans. *Pharmaceutics*. 2023; 15(12):2709. https://doi.org/10.3390/pharmaceutics15122709. *This study aimed to apply physiologically based pharmacokinetic (PBPK) modelling to describe the pharmacokinetics of the dissolving bilayer MAP platform and predict the optimal dosing strategies for a once-weekly cabotegravir MAP*.
5. Kinsale TS, Cottrell ML, Li L, Brand R, Gatto G, Luecke E, Norton C, Krovi A, Dumond JB, Rao G, Yeshwante S, Van Horne B, **van der Straten A,** Kashuba ADM, Johnson LM. Pharmacokinetic Modeling to Guide Preclinical Development of an Islatravir-Eluting Reservoir-Style Biodegradable Implant for Long-Acting HIV PrEP. Pharmaceutics. 2024 Jan

30;16(2):201. doi: 10.3390/pharmaceutics16020201. PMID: 38399255; PMCID: PMC10893066. https://pubmed.ncbi.nlm.nih.gov/38399255/. *This PCL-biodegradable implant is projected to achieve zero-order release of ISL and reach clinical PK above ISL-TP's PrEP efficacy threshold, based on a single-dose subcutaneous ISL dose-ranging pharmacokinetic (PK) study of 0.1, 0.3, and 1 mg/kg in rats.*

3b. HIV and MPT Preclinical Studies:

6. Massud I, Nishiura K, Ruone S, Holder A, Dinh C, Lipscomb J, Mitchell J, Khalil GM, Heneine W, García-Lerma JG, et al. Weekly Oral Tenofovir Alafenamide Protects Macaques from Vaginal and Rectal Simian HIV Infection. *Pharmaceutics*. 2024; 16(3):384. https://doi.org/10.3390/pharmaceutics16030384. *In NHP, a weekly TAF dose of 27.4mg/kg had a protective efficacy of 94% with vaginal SHIV challenges, and a protective efficacy of 80% with rectal SHIV challenges. For vaginal protection, this dose equates to a weekly human dose of 450mg (vs 25mg /day for treatment). A previous study during the development of TAF showed that daily doses of up to 600mg were well tolerated in humans. The authors conclude a weekly dose of TAF may protect women from vaginal acquisition of HIV.*
7. Makarova N, Singletary T, Peet MM, Mitchell J, Bachman S, Holder A, Dinh C, Lipscomb J, Agrahari V, Mendoza M, Pan Y, Heneine W, **Clark MR**, García-Lerma JG, **Doncel GF,** Smith JM. Extended Postexposure Protection Against Vaginal Simian/Human Immunodeficiency Virus Infection With Tenofovir Alafenamide Fumarate/Elvitegravir Inserts in Macaques. J Infect Dis. 2024 Jun 14;229(6):1791-1795. doi: 10.1093/infdis/jiad599. PMID: 38134382. https://pubmed.ncbi.nlm.nih.gov/38134382/. *This NHP study shows that FDI vaginal application 8 hours or 24 hours after SHIV exposure maintains high efficacy (94.4% and 77.2%, respectively), potentially extending the protective window by TAF/EVG inserts for on-demand prophylaxis in women*.
8. Mainella V, Morrow M, Brooks K, Bushman L, Abdelmawla F, Nerguizian D, Choi YJ, Patton D, Cosgrove Sweeney Y, **Patel SK**, Anderson P, **Rohan L**. Intracellular Islatravir-Triphosphate in Dried Blood Spots and Peripheral Blood Mononuclear Cells from Pig-Tailed Macaques. AIDS Res Hum Retroviruses. 2024 May;40(5):227-230. doi: 10.1089/AID.2023.0059. Epub 2023 Sep 12. PMID: 37382422. https://pubmed.ncbi.nlm.nih.gov/37382422/. *This study evaluated the relationship between intracellular islatravir-triphosphate (ISL-TP) in paired peripheral blood mononuclear cells (PBMCs) and dried blood spots (DBS) using pig-tailed macaques (PMs) who were dosed with one vaginal extended-release ISL-etonogestrel film for a period of 31 days.*
9. Pons-Faudoa FP, Di Trani N, Capuani S, Facchi I, Wood AM, Nehete B, DeLise A, Sharma S, Shelton KA, Bushman LR, Chua CYX, Ittmann MM, Kimata JT, Anderson PL, Nehete PN, Arduino RC, Grattoni A. Antiviral potency of long-acting islatravir subdermal implant in SHIV-infected macaques. J Control Release. 2024 Feb;366:18-27. doi: 10.1016/j.jconrel.2023.12.031. Epub 2023 Dec 29. PMID: 38142963; PMCID: PMC10922355. https://pubmed.ncbi.nlm.nih.gov/38142963/. *Intended as a HIV treatment indication, the constant ISL release from a subdermal LA nanofluidic implant, with higher potency than daily or weekly oral dosing, achieved significant viral load reduction in SHIV-infected macaques.*
10. Zhang C, Wu Y, Hutton ARJ, Hidayat Bin Sabri A, Hobson JJ, Savage AC, McCarthy HO, Paredes AJ, Owen A, Rannard SP, Donnelly RF. Systemic delivery of bictegravir and tenofovir alafenamide using dissolving microneedles for HIV preexposure prophylaxis. Int J Pharm. 2024 Jun 6:124317. doi: 10.1016/j.ijpharm.2024.124317. Epub ahead of print.

PMID: 38851410. https://pubmed.ncbi.nlm.nih.gov/38851410/. *Two dissolving microneedle patches (MNs) containing either bictegravir (BIC) or tenofovir alafenamide (TAF) solid drug nanoparticles (SDNs) were developed for systemic delivery of a novel ARV regimen for potential HIV prevention. PK studies in rats demonstrated that BIC MNs achieved sustained release for 3 weeks*.

3c. Conferences (CROI March 3-6, 2024): https://www.croiconference.org/wp-content/uploads/sites/2/resources/2024/croi2024-abstract-ebook-v3.pdf

11. Russ P. Carstens, Yash Kapoor, Ryan Vargo, Arinjita Bhattacharyya, Graigory, Garrett, Jean-Francois Denef, Kemira Naidoo, Liliana Preotescu, Richard, Kaplan, Mohammed Rassool, Johannes Lombaard, Randolph P. Matthews, S. Aubrey Stoch, Marian Iwamoto, Gillian Gillespie. *Single Dose Administration of MK-8527, a Novel nRTTI, in Adults With HIV-1* (Oral, Abstract #115).
12. Carl J. Fichtenbaum, Mezgebe Berhe, Jose Bordon, Jacob P. Lalezari, Godson Oguchi, Gary Sinclair, Furong Wang, Brie Falkard, Haeyoung Zhang, Eva Mortensen, Jared Baeten, Moti Ramgopal. *Antiviral Activity, Safety, and Pharmacokinetics of GS-1720: A Novel Weekly Oral InSTI* (Oral, Abstract #116).
13. Tanuja N. Gengiah, Quarraisha Abdool Karim, Lara Lewis, Ishana Harkoo, **Leila E. Mansoor**, Johara Khan, Zainab Kharva, Nqobile Myeni, Natasha. Samsunder, **Marc M. Baum, John A. Moss**, Catherine Hankins, Bruno Pozzetto, James F. Rooney, Salim S. Abdool Karim. *Phase I Safety, Tolerability and Pharmacokinetics of Tenofovir Alafenamide Implants in African Women* (Oral Abstract #123).
14. Kelong Han, Ronald D'Amico, Jörg Sievers, Darin Brimhall, Brian Spears, Dale Taylor, David Dorey, Paul Benn, Lisa Morgan, Randa Hareedy, Gilda Bontempo, Max Lataillade, William Spreen. *Phase I Study of Cabotegravir Long-Acting Injectable Formulations Supports ≥4-Monthly Dose Interval* (Oral, Abstract #130).
15. Xiaochun Han, Ron Aoyama, Jacob Cha, Aesop Cho, Ana Z. Gonzalez, Salman, Jabri, Michael Lee, Albert C. Liclican, Ryan McFadden, Andrew Mulato, Zach E., Newby, Jie Xu, Johannes Voigt, Lianhong Xu, Hong Yang. *Discovery of GS-9770: A Novel Unboosted Once Daily Oral HIV Protease Inhibitor.* (Poster, Abstract #637).
16. Usman Arshad, Joanne Sharp, Megan Neary, Joanne Herriott, Edyta Kijak,Eduardo Gallardo-Toledo, Paul Curley, Helen Cox, Eleanor Barlow, James J.Hobson, Andrew B. Dwyer, Jonathan Massam, Steve Rannard, Andrew Owen. *Preclinical Pharmacokinetics of a Novel Long-Acting Bictegravir Solid Injectable in Rats* (Poster, Abstract #653).
17. Srijanee Das, Weimin Wang, Samiksha Raut, Murali Ganesan, Grace A. Bybee,Nam Thai Hoang Le, Howard E.Gendelman, Natalia A. Osna, Larisa Poluektova,Benson Edagwa. *Monthslong HBV Suppression by TFV Double Ester Prodrugs* (Poster, Abstract #739)
18. Tanuja N. Gengiah, Craig J. Heck, Lara Lewis, **Leila E. Mansoor**, Ishana Harkoo, Diana Chetty, Nqobile Myeni, **Marc M. Baum, John A. Moss**, James F. Rooney, Catherine Hankins, Bruno Pozzetto, Quarraisha Abdool Karim, Salim S. Abdool Karim. *CAPRISA 018 Trial: Acceptability of Tenofovir Alafenamide Implants for HIV PrEP in African Women* (Poster Abstract #1136).
19. Kelong Han, Ronald D'Amico, William Spreen, Susan Ford. Model-Based Comparison of Cabotegravir Pharmacokinetics Following Thigh and Gluteal Injections (Poster, #617)
20. Arthur Cai, Jason Perry, Jerry L. Jeffrey, Tom White, Samit Joshi, Brian Wynne. *Next-Generation Maturation Inhibitor GSK3640254 Showed Broad Spectrum Potency Without MI Resistance.* (Poster, Abstract #634).

21. Brian P. Kearney, Brady Sillman, Howard E. Gendelman, Benson Edagwa, Leigh Ann Burns-Naas3, Alborz Yazdi. *Cabotegravir Stearate (XVIR-110), an InSTI Prodrug, Provides Ultra-Long Acting Cabotegravir Exposure* (Poster, Abstract #656)
22. Thy Le, Isabella C. Young, Craig Sykes, Amanda P. Schauer, Mackenzie Cottrell, Angela D. Kashuba, **S. Rahima Benhabbour**. *Safety and Pharmacokinetics of Ultra-Long-Acting Dolutegravir In-Situ Forming Implant* (Poster, Abstract #1137).
23. Brian McAuliffe, Paul Falk, Ira Dicker, Susan Jenkins, Jean Simmermacher, Mark Krystal. *The Preclinical Profile of Maturation Inhibitor VH3739937*. (Poster, Abstract # 633).
24. Mohammad Ullah Nayan, Ivana Massud, Srijanee Das, Brady Sillman,Brandon Hanson, Arpan Acharya, Tiancheng Edwards, Richard Haalan, Siddappa N. Byrareddy, Gerardo Garcia-Lerma, Walid Heneine, Charles W.Dobard, Howard E. Gendelman, Benson Edagwa. *Shape-Shifting Tail Decay Is the Pharmacokinetic Profile of an Ultra-Long Acting Bictegravir Prodrug* (Poster, Abstract # 654)
25. Izzat Raheem, Kerry Fillgrove, Gregory O'Donnell, Jonathan Patteson, Shih Lin, Goh, Carolyn Bahnck-Teets, Qian Huang Ernest Asante-Appiah, Min Xu, Steve S.Carroll, Jay A. Grobler, Jeffrey Hale, Ming-Tain Lai, Vinay Girijavallabhan, Tracy L. Diamond. *Discovery of MK-8527: A Long-Acting HIV-1 Nucleoside Reverse Transcriptase Translocation Inhibitor* (Poster, Abstract #638).
26. Ruohui Zheng, Ken Ho, Edward J. Fuchs, Alex Carballo-Diguez, **Lisa C. Rohan**, Rebecca Giguere, Rhonda M. Brand, Stacey Edick, Rahul P. Bakshi,Teresa L. Parsons, Cindy E. Jacobson, Christina Bagia, Lin Wang, Mark Marzinke, Craig W. Hendrix. *Safety and PK/PD of a Tenofovir Rectal Douche Administered in Different Sequences, DREAM-03* (Poster, Abstract #612).

3d. HIV-PrEP and MPT clinical studies

27. Marrazzo J, Tao L, Becker M, Leech AA, Taylor AW, Ussery F, Kiragu M, Reza-Paul S, Myers J, Bekker LG, Yang J, Carter C, de Boer M, Das M, Baeten JM, Celum C. HIV Preexposure Prophylaxis with Emtricitabine and Tenofovir Disoproxil Fumarate Among Cisgender Women. JAMA. 2024 Mar 1. doi: 10.1001/jama.2024.0464. Epub ahead of print. PMID: 38427359. https://pubmed.ncbi.nlm.nih.gov/38427359/. *Data were pooled from 11 F/TDF PrEP post-approval studies conducted in 6 countries that included 6296 cisgender women aged 15 to 69 years conducted from 2012 to 2020. Overall HIV incidence was 0.72 per 100 person-years; individuals with consistently daily or consistently high adherence (4-6 doses/week) to oral PrEP experienced very low HIV incidence.*
28. Achilles SL, Kelly CW, Hoesley CJ, Blithe DL, Brown J, Richardson BA, Devlin B, Hendrix CW, Poloyac SM, Marzinke MA, Gundacker H, Singh D, Piper JM, Johnson S, Steytler J, Chen BA; MTN-030/IPM 041 and MTN-044/IPM 053/CCN019 Protocol Teams for the Microbicide Trials Network and the Contraceptive Clinical Trials Network. Phase 1 randomized trials to assess safety, pharmacokinetics, and vaginal bleeding associated with use of extended duration dapivirine and levonorgestrel vaginal rings. PLoS One. 2024 Jun 5;19(6):e0304552. doi: 10.1371/journal.pone.0304552. PMID: 38838028; PMCID: PMC11152307. https://pubmed.ncbi.nlm.nih.gov/38838028/. *This study presents the pooled results of two phase I trials of the 3-month MPT silicone ring containing 200mg DPV and 320mg LNG. The extended duration DPV/ LNG rings were well tolerated with DPV concentrations in plasma and cervicovaginal fluid exceeding concentrations observed in previous DPV ring efficacy studies, when used continuously. Genital DPV concentrations had a short half-life and were thus not well sustained following ring removal. LNG concentrations in plasma were comparable with other efficacious LNG-based contraceptives.*

29. Riddler SA, Kelly CW, Hoesley CJ, Ho KS, Piper JM, Edick S, Heard F, **Doncel GF,** Johnson S, Anderson PL, Brand RM, Kunjara Na Ayudhya RP, Bauermeister JA, **Hillier SL,** Hendrix CW. A Phase 1 Clinical Trial to Assess the Safety and Pharmacokinetics of a Tenofovir Alafenamide/Elvitegravir Insert Administered Rectally for HIV Prevention. J Infect Dis. 2024 Apr 24:jiae211. doi: 10.1093/infdis/jiae211. Epub ahead of print. PMID: 38655842.. https://pubmed.ncbi.nlm.nih.gov/38655842/. *This study assessed rectal administration of one and two TAF/EVG inserts in 23 male and female participants. Rectal administration of the inserts achieved high rectal tissue concentrations of EVG and TFV-DP with low systemic drug exposure and demonstrable ex vivo inhibition of HIV infection for 72 hours.*

30. Weld ED, McGowan I, Anton P, Fuchs EJ, Ho K, Carballo-Dieguez A, **Rohan LC**, Giguere R, Brand R, Edick S, Bakshi RP, Parsons T, Manohar M, Seigel A, Engstrom J, Elliott J, Jacobson C, Bagia C, Wang L, Al-Khouja A, Hartman DJ, Bumpus NN, Spiegel HML, Marzinke MA, Hendrix CW. Tenofovir Douche as HIV Preexposure Prophylaxis for Receptive Anal Intercourse: Safety, Acceptability, Pharmacokinetics, and Pharmacodynamics (DREAM 01). J Infect Dis. 2024 Apr 12;229(4):1131-1140. doi: 10.1093/infdis/jiad535. PMID: 38019657; PMCID: PMC11011183. https://pubmed.ncbi.nlm.nih.gov/38019657/. *Three tenofovir rectal douches were studied in 21 HIV-negative MSMs. All 3 tenofovir douches achieved tissue tenofovir-diphosphate concentrations and colorectal antiviral effect exceeding oral TDF and with lower systemic tenofovir.*
31. Landovitz RJ, Tao L, Yang J, de Boer M, Carter C, Das M, Baeten JM, Liu A, Hoover KW, Celum C, Grinsztejn B, Morris S, Wheeler DP, Mayer KH, Golub SA, Bekker LG, Diabaté S, Hoornenborg E, Myers J, Leech AA, McCormack S, Chan PA, Sweat M, Matthews LT, Grant R; Global F/TDF PrEP Study Team. HIV-1 Incidence, Adherence, and Drug Resistance in Individuals Taking Daily Emtricitabine/Tenofovir Disoproxil Fumarate for HIV-1 Pre-Exposure Prophylaxis: Pooled Analysis From 72 Global Studies. Clin Infect Dis. 2024 Mar 14:ciae143. doi: 10.1093/cid/ciae143. Epub ahead of print. PMID: 38484128. https://pubmed.ncbi.nlm.nih.gov/38484128/. *Seventy-two prospective studies of daily oral F/TDF PrEP were conducted to evaluate HIV-1 incidence, drug resistance, adherence, and bone and renal safety in diverse settings, among a total of 17,274 participants, demonstrating that F/TDF is safe and highly effective, even with less than daily dosing, in diverse clinical settings, geographies, populations, and routes of HIV-1 exposure.*
32. Liu AY, Gundacker H, Richardson B, Chen BA, Hoesley C, **van der Straten A**, Brown A, Beamer M, Robinson J, Jacobson CE, Scheckter R, **Bunge K**, Schwartz J, Thurman A, Piper JM, Marzinke MA; MTN-038 Protocol Team for the Microbicide Trials Network. Phase 1 randomized pharmacokinetic and safety study of a 90-day tenofovir vaginal ring in the United States. J Int AIDS Soc. 2024 Mar;27(3):e26223. doi: 10.1002/jia2.26223. PMID: 38444118; PMCID: PMC10935712. https://pubmed.ncbi.nlm.nih.gov/38444118/ . *Fourty nine HIV-negative US participants were enrolled into a phase 1, placebo-controlled trial of a 90-day ring containing 1.4 grams (g) TFV. The TFV ring was well-tolerated, acceptable and exceeded target cervical tissue concentrations through day 56, but TFV levels declined thereafter, requiring additional studies to better characterize TFV release from the ring and the optimal duration of ring use*.
33. **Bunge K,** Balkus JE, Fairlie L, Mayo AJ, Nakabiito C, Mgodi N, Gadama L, Matrimbira M, Chappell CA, Piper J, Chakhtoura N, Szydlo DW, Richardson B, **Hillier SL**. DELIVER: A Safety Study of a Dapivirine Vaginal Ring and Oral PrEP for the Prevention of HIV During Pregnancy. J Acquir Immune Defic Syndr. 2024 Jan 1;95(1):65-73. doi: 10.1097/QAI.0000000000003312. PMID: 38055292.

https://pubmed.ncbi.nlm.nih.gov/38055292/. *In MTN-042, 307 female participants in third trimester pregnancy used either the monthly dapivirine ring or daily oral PrEP with TDF/FTC. Adverse pregnancy outcomes and complications were uncommon when ring and TDF/FTC were used, suggesting a favorable safety profile for both prevention products.*

34. Parikh UM, Penrose KJ, Heaps AL, Sethi R, Goetz BJ, Szydlo D, Chandran U, **Palanee-Phillips T**, Mgodi NM, Baeten JM, Mellors JW; MTN-025/HOPE Study Team. Brief Report: HIV Drug Resistance Assessment Among Women Who Seroconverted During the MTN-025/HOPE Open-Label Extension Dapivirine Vaginal Ring Trial. J Acquir Immune Defic Syndr. 2024 Jan 1;95(1):35-41. doi: 10.1097/QAI.0000000000003308. PMID: 37732881; PMCID: PMC11042691. https://pubmed.ncbi.nlm.nih.gov/37732881/ *NNRTI resistance among 38 women who seroconverted during the HOPE trial (MTN-025) was infrequent and selection of DPV-specific mutations was not detected*.

Other: STI prevention clinical studies

35. Haaland RE, Fountain J, Edwards TE, Dinh C, Martin A, Omoyege D, Conway-Washington C, Kelley CF, Heneine W. Pharmacokinetics of single dose doxycycline in the rectum, vagina, and urethra: implications for prevention of bacterial sexually transmitted infections. EBioMedicine. 2024 Mar;101:105037. doi: 10.1016/j.ebiom.2024.105037. Epub 2024 Feb 29. PMID: 38428259; PMCID: PMC10910237. https://pubmed.ncbi.nlm.nih.gov/38428259/. *This study examined vaginal, rectal and urethral doxycycline concentrations in men and women to better inform STI prevention. Eleven male and nine female participants participated in the study, showing that doxycycline efficiently distributes to the rectum, vagina and urethra.*

3e. Reviews, commentaries or reports:

36. Senneker T. Drug-drug interactions between gender-affirming hormone therapy and antiretrovirals for treatment/prevention of HIV. Br J Clin Pharmacol. 2024 Jun 12. doi: 10.1111/bcp.16097. Epub ahead of print. PMID: 38866600. https://pubmed.ncbi.nlm.nih.gov/38866600/
37. Owuor S, Kimani M, Kaplan R. The future of PrEP: novel long-acting HIV prevention agents for adolescent women. Pan Afr Med J. 2024 Mar 4;47:102. doi: 10.11604/pamj.2024.47.102.36052. PMID: 38766564; PMCID: PMC11101307. https://pubmed.ncbi.nlm.nih.gov/38766564/
38. **Peet MM, Agrahari V, Clark MR, Doncel GF.** Preclinical and Early Clinical Development of Tenofovir Alafenamide/Elvitegravir Topical Inserts for Effective On-Demand Vaginal and Rectal HIV Prevention. Pharmaceutics. 2024 Mar 1;16(3):348. doi: 10.3390/pharmaceutics16030348. PMID: 38543242; PMCID: PMC10974834. https://pubmed.ncbi.nlm.nih.gov/38543242/
39. Nayan MU, Panja S, Sultana A, Zaman LA, Vora LK, Sillman B, Gendelman HE, Edagwa B. Polymer Delivery Systems for Long-Acting Antiretroviral Drugs. Pharmaceutics. 2024 Jan 28;16(2):183. doi: 10.3390/pharmaceutics16020183. PMID: 38399244; PMCID: PMC10892262. https://pubmed.ncbi.nlm.nih.gov/38399244/
40. Tam EH, Peng Y, Cheah MXY, Yan C, Xiao T. Neutralizing antibodies to block viral entry and for identification of entry inhibitors. Antiviral Res. 2024 Apr;224:105834. doi: 10.1016/j.antiviral.2024.105834. Epub 2024 Feb 17. PMID: 38369246. https://pubmed.ncbi.nlm.nih.gov/38369246/

3f. Select Press releases, announcements and media:

1. New Licensing Agreement Set To Double HIV Vaginal Ring Supply in Africa (Devex, 02/2024)
2. UK guide to PrEP now online: major update (2024). https://i-base.info/htb/47180
3. South Africa Company Set To Manufacture HIV Prevention Ring (AVAC, march 1 2024)
4. Vaginal Ring and Oral Pre-Exposure Prophylaxis Found Safe for HIV Prevention Throughout Pregnancy (3/5/2024 press release from MTN at CROI)
5. Health Canada approves Apretude for PrEP: https://www.catie.ca/catie-news/health-canada-approves-apretude-the-first-long-acting-injectable-for-hiv-prevention?utm_source=AVAC+Email+Updates&utm_campaign=cfd7aba553-EMAIL_CAMPAIGN_2024_05_17_03_41&utm_medium=email&utm_term=0_-cfd7aba553-%5BLIST_EMAIL_ID%5D
6. Guardian (5/27/2024): Celebrities join campaigners in call for cheaper version of 'gamechanger' HIV drug for poorer countries. Open letter to GILEAD, inc: https://peoplesmedicines.org/wp-content/uploads/2024/05/Gilead-Open-Letter_May-2024.pdf
7. NIH announces the start of 2 trials with injectable LEN: https://www.nih.gov/news-events/news-releases/us-clinical-trials-begin-twice-yearly-hiv-prevention-injection
8. Exavir Therapeutics and ViiV Healthcare have joined forces to develop groundbreaking ultra-long-acting HIV compounds for individuals living with HIV or at risk of acquiring the virus (Press release 5/22/2024): https://bitperfect.pe/en/exavir-therapeutics-and-viiv-healthcare-partner-to-revolutionize-hiv-treatment/ [bitperfect.pe]
9. Gilead's press release (6/20/24): Twice-Yearly Lenacapavir Demonstrated 100% Efficacy and Superiority to Daily Truvada® for HIV Prevention. https://www.gilead.com/news-and-press/press-room/press-releases/2024/6/gileads-twiceyearly-lenacapavir-demonstrated-100-efficacy-and-superiority-to-daily-truvada-for-hiv-prevention?utm_source=AVAC+Email+Updates&utm_campaign=8a22e715f0-EMAIL_CAMPAIGN_2024_03_26_12_52_COPY_01&utm_medium=email&utm_term=0_-3d24179dba-%5BLIST_EMAIL_ID%5D.
10. NIH press release (6/26/24): https://www.niaid.nih.gov/news-events/nih-statement-preliminary-efficacy-results-twice-yearly-lenacapavir-hiv-prevention?utm_campaign=+61149283&utm_content=&utm_medium=email&utm_source=govdelivery&utm_term= The PURPOSE 1 study enrolled over 5,300 cisgender adolescent girls and young women ages 16-26 in South Africa and Uganda to evaluate injectable lenacapavir and daily oral emtricitabine/tenofovir alafenamide (F/TAF) for PrEP. Semi-annual LEN injections was 100% efficacious, demonstrating superiority of LA-LEN over background HIV incidence and over once-daily Truvada. Furthermore, lenacapavir was generally well-tolerated and safe.
11. CAB-LA Enjoys High Continuity Rates Among PrEP Users In Zimbabwe (Health times 6/25/2024)**:** https://healthtimes.co.zw/2024/06/25/cab-la-enjoys-high-continuity-rates-among-prep-users-in-zimbabwe/?utm_source=AVAC+Email+Updates&utm_campaign=f723ff8619-EMAIL_CAMPAIGN_2024_06_28_03_55&utm_medium=email&utm_term=0_-f723ff8619-%5BLIST_EMAIL_ID%5D

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

Clinical studies of relevance found in **clinicaltrials.gov** website are presented in the summary table 1. These include 28 trials total, with 5 new entries since the previous Landscape Review

(LR-4). Of those, 12 trials are completed, stopped or of unknown status. One trial is sponsored by one of the MATRIX PDs (CONRAD/EVMS); none of the MATRIX trials are included here (i.e. MATRIX-001, 002 and 003). Searches included public funders (i.e. NIH and other funders (not pharma) and pharma funders (e.g., GILEAD, Janssen. Merck, ViiV), using broad key words for the searches (i.e. HIV infections; Prevention, Intervention for trials enrolling healthy participants) with a date cut-off of 1/1/2019. No additional relevant trials were found through searching the **EU CT database** (https://www.clinicaltrialsregister.eu/) or the **Wellcome trust** grants awarded (https://wellcome.org/grant-funding/people-and-projects/grants-awarded).

- CONRAD/EVMS is actively recruiting for a trial assessing multiple rectal doses of their TAF/EVG insert, with the CDC and Emory University.
- GILEAD had an early stop of the blinded phase of PURPOSE 1 (LEN-LA and TAF/FTC in cisgender women in Africa) due to high (100%) efficacy of the 6-month injectable (see press releases). The trial is continuing unblinded. PURPOSE 2 (pivotal trial for MSMs and TG people) is ongoing. Two additional trials of LEN-LA in the U.S. are actively recruiting (P3/HPTN-102 among CGW and P4/HPTN-103 among persons who inject drugs (PWID)). These are co-funded by NIH via the HPTN.
- Another HPTN trial (HPTN-106) to assess safety, acceptability and preference of the rectal douche (vs on-demand oral PrEP) is close to activation.
- Merck's trial with MK8527 (a novel NRTTI), for monthly PrEP oral dosing is now in follow-up phase, with completion anticipated by 12/2024.
- The Population Council has two active trials of the [formerly IPM] rings (3-month DPV ring & 3-month MPT ring), and two trials of the oral DPP capsule that were recently completed. PopC also recently completed a cross-over trial to assess the impact of different outer diameters of the ring on ring adherence and acceptability in U.S couples.
- ViiV has at least 8 trials started or ongoing, including a new study (called PALISADE, not recruiting yet) to continue providing CAB-LA to those who participated in HPTN-083 and HPTN-084. Other trials are assessing extended duration Cab-LA injections and other formulations of Cab injectable, a new capsid inhibitor (taken orally or by SC injections), and a new SC-injected INSTI (all in phase I).

5. Appendix Tables:

1. HIV Prevention Clinical Trials with investigational APIs/DDS by sponsor's alphabetical name (Review since 1/1/2019)–COMPLETED, WITHDRAWN/UNKNOWN and ACTIVE (* all changes in table are in red text)

N=28 # trials	DDS	PD/ Sponsor	stage	API(s)	Duration	R&D Status-dates	Notes	NCT number [and links]
1	Insert-Rectal	CONRAD/ EVMS	Phase II-	TAF/EVG	OD	Active-Recruiting 1/2024-12/2024	RITE PrEP: Extended safety, PK/PD after repeated dosing. Implemented by CDC & Emory U.	https://clinicaltrials.gov/study/NCT06274398
3	Injectable-SC parenteral	GILEAD	Phases II/III	CAI: LEN	6 months	• P1- Active/FU 2021-2024 Blinded phase stopped. • P3/HPTN-102 & P4/HPTN-103 Active / Recruiting: 2023-2027.	PURPOSE Program I-IV. Early efficacy results for P1 announced June 2024. Note: P2 not included as focusing on MSMs/TG people.	https://clinicaltrials.gov/study/NCT04994509 https://clinicaltrials.gov/study/NCT06101329 https://clinicaltrials.gov/study/NCT06101342
1	Ring	IPM / PopC	Phase I	DPV	3-month vs 1	Active/FU 2022-2024	Relative bioavailability study	https://clinicaltrials.gov/study/NCT05416021
1	MPT ring	IPM / PopC	Phase II	DPV & LNG	3 months	Active/Recruiting: 2022-2024	NICHD funded	https://clinicaltrials.gov/study/NCT05041699
3	Rectal douches	JHU, UPenn	Phases I	TFV	OD	• 2 trials completed. • HPTN 106: Active/ not recruiting yet.	NIAID funded. HPTN 106 not listed in NCT yet – Protocol training done.	https://www.clinicaltrials.gov/study/NCT04016233 https://www.clinicaltrials.gov/study/NCT04686279
1	Oral tablets	Merck	Phase III	ISL	1 month	WITHDRAWN (as of 11/24/23)	Impower-022. ISL for PrEP abandoned -	https://clinicaltrials.gov/study/NCT04644029
1	Implant	Merck	Phase II	ISL	1 year	WITHDRAWN (as of 11/24/23)	ISL for implants abandoned	https://clinicaltrials.gov/study/NCT05115838
1	Oral	Merck	Phase II	NRTTI: MK8527	1 month	Active/FU: 2023-12/2024	Alternative to ISL for prevention	https://clinicaltrials.gov/study/NCT06045507
1	injectable	Navigen	Phase I	CPT31	3 months	Completed	NIAID funded	https://www.clinicaltrials.gov/study/NCT04672083
2	Oral DPP capsule	PopC	Cross-over studies	TDF/FTC+ COC	Daily	• Active/FU: 2022-2024. • Completed:2022-2023	Both studies (in RSA and Zimbabwe) completed per preliminary results shared at CROI 2024 and HPTN annual meeting	https://clinicaltrials.gov/study/NCT04778527 https://clinicaltrials.gov/study/NCT04778514
1	IVRs of various diameters	Pop C	Cross-over study	Placebos (non-medicated)	30 days	Completed:2023	Study to assess impact of various external diameter sizes of IVRs on adherence in couples.	https://clinicaltrials.gov/study/NCT05128136

N=28 # trials	DDS	PD/ Sponsor	stage	API(s)	Duration	R&D Status-dates	Notes	NCT number [and links]
1	IM injectable	ViiV	open label study	Cab-LA	2-months	Active/ Not yet recruiting: 2024-2027	PALISADE: follow up to HPTN-083 and HPTN-084.	https://clinicaltrials.gov/study/NCT06134362
1	IM injectable	ViiV	Phase I	CAB-LA	Not specified	Active/ Recruiting: 2023-2025	PK study comparing 2 formulations (F&G)-	https://clinicaltrials.gov/study/NCT06033547
1	SC Injectable	ViiV	Phase I	CAB-LA	2 months, 4 months or more	Active-Recruiting: 2022-2027	Compares different CAB loadings (200 vs 400 mg/ml), formulations (w/ or w/o hyaluronidase) duration & Sc vs IM administration.	https://clinicaltrials.gov/study/NCT05418868
1	SC vs IM injectable	ViiV	Phase I w/ active control	CAB-LA 400mg/ml	2 months or more	Completed: 2023	Safety, PK of SC (abdominal) vs IM (gluteal) and 400 vs 200mg/ml CAB-LA +/- anti-inflammatory drugs and/or hyaluronidase.	https://clinicaltrials.gov/study/NCT04484337
1	SC or IM Injectable	ViiV	Phase I	CAI: VH4004280 VH4011499	Ultralong-Not specified	Active/Recruiting: 2023-2026	Participants followed up to w52. Oral administration explored also in phase II for treatment.	https://clinicaltrials.gov/study/NCT06012136
2	Oral	ViiV	Phases I	CAI: VH4011499	Not specified (daily?)	• Completed: 2023 • New trial: Active/Recruiting: 4/2024- 6/2024	• Safety, PK : 1) Single ascending dose; 2) Multiple ascending doses: DDI w/ Midazolam •New trial: Drug bioavailability /effect of food	https://clinicaltrials.gov/study/NCT05393271 https://clinicaltrials.gov/study/NCT06368986
1	Oral	ViiV	Phase I (FIH)	CAI: VH4004280	Not specified (daily?)	Completed: 2023	Safety, PK study in healthy volunteers. 1) Single ascending dose; 2) multiple ascending doses for DDI with Midazolam	https://clinicaltrials.gov/study/NCT05163522
2	SC injections	ViiV	Phase I (FIH)	INSTI: VH4524184	Not specified	Active/ Recruiting: 2022-2028	Safety, PK study in healthy volunteers. First: Single ascending dose; Next: multiple ascending doses for DDI & CYP3A activity.	https://clinicaltrials.gov/study/NCT05631704 https://clinicaltrials.gov/study/NCT06310551
1	SC injections	ViiV	Phase I Open label	VH4524184 & Loestrin	Not specified	Active-recruiting: 3/2024-8/2024	DDI between SC administered INSTI and COC (Loestrin) in healthy females.	https://clinicaltrials.gov/study/NCT06310616
1	Oral	Viriom	Phase I	Elpida NNRTI	Weekly	Unknown	No updates since 2019 API is elsulfavirine or VM1500	https://clinicaltrials.gov/study/NCT03730311

(*) alternative injection locations possible

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

N=16	DDS	PD	stage	API(s)	Duration	R&D Status	Notes incl. PI, funding source	References
1	Biocage--SC	GW, CNMC, yale, U Mass..)	preclinical	Multiple, neuro-drugs	Theoretically tunable to needed duration	NIMH and NCATS funding completed in 2023. Unknown status	3D printed small biodegradable device (can be delivered via 22G needle) for direct implantation in target tissues (E.g., brain). PI: Torii, Masaaki, NIMH (2017-2023), NCATS (2016-2023)	https://pubmed.ncbi.nlm.nih.gov/29247175/ US patent. Application No. 62/554,680 (per publication)
2	Implant- SC Removable	OCIS, CAPRISA	Phase 1	NRTI TAF	1 year	Trial completed, Closing up other activities	CAP-018. PI: Abdool Karim, Registration # PACTR201809520959443 SAMRC, EDCTP, NRF	https://pubmed.ncbi.nlm.nih.gov/34992111/J10 https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3584 See CROI 2024, #13 and #18
3	Implant (EVA)- SC Removable	MSD	Phase 1	NRTTI: ISL	1+year	Stopped for PrEP due to safety signal. Unknown status	PI unknown, MSD. Project withdrawn from Clinicaltrials.gov see table 1	https://pubmed.ncbi.nlm.nih.gov/36450129/ https://www.merck.com/news/merck-to-initiate-new-phase-3-clinical-program-with-lower-dose-of-daily-oral-islatravir-in-combination-with-doravirine-for-treatment-of-people-with-hiv-1-infection/
4	Implant- SC Removable -	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
5	Implant -SC Osmotic pump-	Intarcia	Preclinical	exenatide; TAF	6 mo-1year	Stopped due to toxicity of TAF in animal models.	Company declared bankruptcy. Medici system. PI: Unknown	https://pubmed.ncbi.nlm.nih.gov/33913760/
6	In situ forming Implant (ISFI)- -SC	UNC	preclinical	ISL, CAB and other drugs incl for TB	>6 months	Completed- End date Aug 31, 2023.	PI: Garcia, NIAID 2018-2023 5R01AI140799-05	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9911691/ https://reporter.nih.gov/project-details/10468909
7	Injectable- IM- 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

8	Injectable-parenteral	Navigen	clinical	CPT31 -D-peptide Entry inhibitor	target 3 months	Completed	PI: Madani, NIAID 2017-6/2024-5R01AI134494-05 Phase I trial completed	https://www.newswise.com/articles/long-acting-injectable-drug-could-strengthen-efforts-to-prevent-treat-hiv?sc=rsgt https://reporter.nih.gov/project-details/10174715 https://www.clinicaltrials.gov/study/NCT04672083 and table 1
9	Injectable-parenteral	UW	preclinical	TAF	??	Unknown- see new entry #4 for MPT implant	Drugamers described in proceedings from BMGF TAF workshop. PI: Stayton, BMGF	https://pubmed.ncbi.nlm.nih.gov/33913760/
10	MAP/MN hydrogel-forming 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
11	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
12	Ring - vaginal	NWU	preclinical	NRTI: IQP-0528	1 month?	Stopped when funding ended.	IQP0528 not further supported by IMQUEST for Px PI: Kiser, NIH	https://pubmed.ncbi.nlm.nih.gov/28770490/
13	Ring - vaginal	Tulane U	preclinical	DTG, 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
14	Pod Ring-vaginal	Dana Farber (DFCI)	preclinical	CD4 mimetic compound	?	Funding Ended 6/30/2024	Entry inhibitor -irreversibly interferes with HIV ENV binding to CD4 PI: Madani, NIAID 2011-2024 5R01AI134494-05	https://reporter.nih.gov/project-details/10174715
15	Tablet, vaginal	Osel, Inc.	Preclinical& preparation for FIH trial	recombinant L. jensenii with mCV-N	OD	Completed	PI Lagenaur NIAID 2020-2023. Live biotherapeutic product secreting modified cyanovirin-N	https://reporter.nih.gov/search/cKoXtRxn2U2IgmOgqFNymg/project-details/10223989
16	Tablet-Oral - enteral	Lyndra LYNX™ platform	Preclinical	Undisclosed	7 days-1 month	Unknown	No longer mention HIV as a target indication on their website. https://lyndra.com/pipeline/ PI: unknown	https://www.nature.com/articles/s41467-017-02294-6

2b. HIV Prevention Projects by DDS name – Ongoing (* all changes in table are in red text, new entries at the bottom of the table)

N=24	DDS	PD	stage	API(s)	Duration	R&D Status	Notes incl. PI, funding source	References
1	Enema/ Douche-rectal	JHU	phase I/II	TFV	OD	Ongoing	DREAMS trials completed, see table 1 PI: Hendrix, HPTN 106, NIH (Not recruiting yet)	https://grantome.com/grant/NIH/U19-AI113127-01 https://pubmed.ncbi.nlm.nih.gov/36477356/ https://pubmed.ncbi.nlm.nih.gov/38655842/ https://pubmed.ncbi.nlm.nih.gov/38019657/
2	Fibers-based microbicide - drug eluting-vaginal	UW	preclinical	INSTI: RAL prodrug	OD- 2 weeks	Ongoing	PI: Woodrow; NIAID 2019-2025. Aims to identify ARV(s) that are compatible with the Nano-spun fibers. 5R01AI145483-05	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7591136/ https://pubmed.ncbi.nlm.nih.gov/37160248/ https://reporter.nih.gov/project-details/10576394
3	Insert (FDI), rectal	CONRAD	Phase II	TAF/EVG	OD	Ongoing	RITE-PrEP study initiated. Led by CDC and Emory (PK/PD assessment after repeated rectal application)	HPTN 2023 annual meeting, plenary session and Table 1
4	Implant -SC bioresorbable	OCIS	preclinical	maturation inhibitor (DFH-1160005)	=<1 year	Ongoing	PI: Moss; NIAID 2020-2025 5R01AI154561-04	https://reporter.nih.gov/project-details/10669021
5	Implant -SC removable	OCIS	Next gen Preclinical	TAF and 2 new pro-drug formulations	6 mo-1year	Ongoing	PI: Baum; NIAID 2021-2026 5R01AI162151-03 NIAID 2023-2027 1R01AI172541-01A1	https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10654774 https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10617540 https://pubmed.ncbi.nlm.nih.gov/35581262/ https://pubmed.ncbi.nlm.nih.gov/36418671/
6	Implant- SC bioerodible (PCL)	RTI	preclinical	TAF, ISL, BIC, others	7-12 months	Ongoing	PI: Johnson; USAID funding (Completed); NIAID 2020-2025 (LAPIS): 5R01AI152713-04. NIAID 2020-2024 (AMBER): 5R01AI154549-04. NICHD 2020-2025 (DAISY): 5R33AI149499-05 .	https://reporter.nih.gov/project-details/10581520 https://reporter.nih.gov/project-details/10799633 https://reporter.nih.gov/project-details/10663830 https://www.frontiersin.org/articles/10.3389/fphar.2022.923954/full

N=24	DDS	PD	stage	API(s)	Duration	R&D Status	Notes incl. PI, funding source	References
								https://pubmed.ncbi.nlm.nih.gov/35913838/
7	Implant bioerodible	UNC	Preclinical	For Rx maintenance	LA- Unclear duration	Ongoing	Applicable to PrEP PI: Benhabbour, NIAID 2023-2027 1R01AI176949-01A1.	https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10759149
8	Implant- SC refillable NanoDDI (Titanium) -	HMRI	preclinical	ISL	2 years	Ongoing	NanoDDI comprises a newly patented nanofluidic membrane, and ports for rapid, minimally invasive transcutaneous drug refilling. PI: Grattoni; NIAID 2022-2027 5R01AI165372-02	https://pubmed.ncbi.nlm.nih.gov/38142963/ 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/search/fLniIlRd4kG_7zK3sq-lkQ/project-details/10843229
9	Implant--SC bioerodible. (PEO coated w/ PCL)	QUB	Preclinical	model hydrophobic drug: olanzapine	> 6 months	Ongoing?	3D printed implant. PI: unknown; funding: Academy of medical sciences, Wellcome Trust.	https://www.tandfonline.com/doi/full/10.1080/10717544.2022.2057620 https://pubmed.ncbi.nlm.nih.gov/36509226/
10	Injectable-SC parenteral	GILEAD	phase III	CAI: LEN	6 months	Ongoing	PURPOSE program (1-4) P1 halted early for efficacy. PI: Swaminathan HPTN102/P3, NIAID/GILEAD - Active/Recruiting	https://clinicaltrials.gov/ct2/show/NCT04994509 https://www.jci.org/articles/view/167818 See Table 1 and Press releases #10 & #11
11	Injectable-parenteral	UW	Phase I/ FIH- focused on Rx	LPV, RTV, TFV nano-particle suspension (TLC-ART 101)	??	Ongoing	Trial May 2023 –2025 (N=16) All gender healthy ppts. Targeted LA- combination ARV Therapy (TLC-ART) Program - New platform to stabilize insoluble & soluble ARVs together in a nanosuspension- RX focused; applicable to Px. PIs: Bender Ignacio and Ho, NIAID 2019-2024 5U01AI148055-03.	https://reporter.nih.gov/search/tqIyle6FM02SXTyegdlPdg/project-details/10234129 https://pubmed.ncbi.nlm.nih.gov/37650755/ https://pubmed.ncbi.nlm.nih.gov/38382809/ https://depts.washington.edu/tlcart/ https://classic.clinicaltrials.gov/ct2/show/NCT05850728

N=24	DDS	PD	stage	API(s)	Duration	R&D Status	Notes incl. PI, funding source	References
12	Injectable-parenteral	U Florida	preclinical	eCD4-Ig antibody-like molecule	6 months	Ongoing	Broad/potent HIV-1 entry inhibitor & a tunable hydrogel. PI: Farzan; NIAID 2020-2025 7R01AI154989-05	https://reporter.nih.gov/project-details/10841186
13	Injectable-IM parenteral	U Nebraska	Preclinical-Focused on Rx	NRTI and INSTI (e.g DTG) prodrugs converted into nanocrystal formulation for LA delivery	6 months	Ongoing	Use of prodrug nanocrystals for sustained release via IM injection. PIs: Edagwa & Gendelman; NIAID 2019-2024 5R01AI145542-05	https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10652403 https://pubmed.ncbi.nlm.nih.gov/37451501/ https://pubmed.ncbi.nlm.nih.gov/35680875/ See CROI 2024, #17 and #24
14	Injectable-parenteral	U Nebraska	preclinical	DTG, FTC, TFV, BIC, others	up to 1 year	Ongoing	LASER-ART: chemical modification of existing ARVs for extended release. 3 patents listed on RePorter. PI: Gendelman; NIAID 2021-2026 5R01AI158160-03	https://pubmed.ncbi.nlm.nih.gov/34531390/ https://reporter.nih.gov/project-details/10597017
15	Injectable parenteral (Nanocrystal suspension)	EXAVIR therapeutics, inc https://exavirtherapeutics.com/	Preclinical SBIRII (CMC and IND enabling studies)	INSTI XVIR-110 From website: CAB, TAF, DTG-	≥6 months	Ongoing	Company's spin off from Gendelman's group. PI: Gunzer-Toste; NIAID 2023-2026; **1R44AI179564-01**	https://reporter.nih.gov/project-details/10764186 https://www.nature.com/articles/s41467-021-25690-5 https://www.science.org/doi/full/10.1126/sciadv.ade9582 https://www.nature.com/articles/s41467-022-30902-7 https://www.nature.com/articles/s41467-021-23668-x See CROI 2024, #21
16	Injectable-parenteral	Boston U	prelcinical	Prodrug of TFV and FTC	3 month or more?	Ongoing	Membrane-wrapped nanoparticles (NPs) that establish cellular depots for sustained maintenance of inhibitory concentrations of ARVs at primary tissue sites of HIV-1 transmission in the FGT & rectum. PIs: Reinhard and Markus; NIAID (2023-2027) 1R01AI175068-02	https://reporter.nih.gov/project-details/10811673 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11064779/

N=24	DDS	PD	stage	API(s)	Duration	R&D Status	Notes incl. PI, funding source	References
17	Injectable-SC or IM parenteral	ViiV	clinical	CAB (various formulations)	4 (and 6) months	Ongoing	R&D plan announced by ViiV (Sept 2023), listings in Clinical trials.gov	ViiV Healthcare Meet the Management (gsk.com) &Table 1 CROI 2024, #14 & 19
18	Injectable-SC or IM and Oral	ViiV	clinical	Capsid inhibitors VH4004280 & VH4011499	unspecified	Ongoing	R&D plan announced by ViiV (Sept 2023), and in Clinical trials.gov	ViiV Healthcare Meet the Management (gsk.com) & Table 1
19	Injectable-SC	ViiV	clinical	INSTI: VH4524184	unspecified	Ongoing	R&D plan announced by ViiV (Sept 2023), and in Clinical trials.gov	ViiV Healthcare Meet the Management (gsk.com) & Table 1
20	ISFI hydrogel-Injectable parenteral	QUB	preclinical	ZDV (prototype) + d-peptide	?	Ongoing?	PI: Unknown; funding: EPSRC, the Wellcome Trust, the MRC & Invest NI.	https://pubmed.ncbi.nlm.nih.gov/36880399/
21	MAP/MN transdermal	QUB	preclinical	INSTI: Bictegravir	~ 1 month	Ongoing?	PI: Donelly; funding: EPSRC Wellcome Trust	https://pubmed.ncbi.nlm.nih.gov/37301241/
22	MAP/MN-transdermal	PATH/ QUB	preclinical	RPV and other ARVs (CAB, LEN)	7 D-1 Mo	Ongoing	Current Funding focused on Pediatric Rx PIs: Choy & Donnelly; NIAID 2020-2025 5R33AI149642-05	https://pubmed.ncbi.nlm.nih.gov/36224503/ https://www.microneedlesconference.com/ https://doi.org/10.3390/pharmaceutics16010142 https://reporter.nih.gov/search/p95CUX_DpEuMUTElg1y-xA/project-details/10811689

N=24	DDS	PD	stage	API(s)	Duration	R&D Status	Notes incl. PI, funding source	References
23	Tablets- Oral enteral	MSD	Clinical phase 2a	MK8527 (NRTTI)	1 month	Ongoing	PI: unknown. Study completion anticipated in 12/2024	https://clinicaltrials.gov/study/NCT06045507 & table 1 See CROI 2024, #11
24	Vaginal devices- 3D-printed silicone scaffold	U of Louisville	preclinical	BV- No direct HIV indication: phased-release of antibiotic and probiotic agents	LA (unclear duration)	Ongoing	BV indication- 3D printing and computational modeling to design LA topical products. PI: Frieboos, H. NIAID 2022-2027 1R01AI168475-03	https://reporter.nih.gov/search/ttU8bGUDGkOFi3qd-vWenw/project-details/10765687 https://pubmed.ncbi.nlm.nih.gov/37076014/ https://pubmed.ncbi.nlm.nih.gov/38182058/

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

N =15	DDS	Other indications	PD	Stage	APIs	Duration	R&D Status	Notes:	References
1	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/
2	Film_ARV nanoparticle- vaginal	HSV	U of Porto	preclinical	EFV + TFV	24h (daily)	Completed	PI: Unknown, funding via Portugal & EU (FCT, FEDER, POCI COMPETE 2020)	https://pubmed.ncbi.nlm.nih.gov/27664327/
3	FDI-vaginal	HSV, PREG	IPM, now PC	preclinical	DPV, LNG, ACV	8h	Paused; (Haddad pers. comm)	PI: Unknown.	https://pubmed.ncbi.nlm.nih.gov/37161022/
4	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
5	Gel (TFV) vaginal	HSV	CONRAD	clinical	TFV 1%	BAT 24	Stopped: poor adherence/in-effectiveness in FACTS-001 trial	PI: Rees, H.	https://pubmed.ncbi.nlm.nih.gov/20643915/ https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30428-6/fulltext
6	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/
7	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/
8	Gel- PPCM vaginal	CT, GC, HPV, HSV, PREG	YASO therapeutics	Preclinical & early clinical	polyphenylene carboxymethylene	OD	FDA placed Phase 1 trial on a partial hold.	IND submitted 5/2023. PI: Weitzel, NICHD 2022-2023 1R43HD109101-01	https://pubmed.ncbi.nlm.nih.gov/32469052/ https://reporter.nih.gov/project-details/10483274
9	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-

N =15	DDS	Other indications	PD	Stage	APIs	Duration	R&D Status	Notes:	References
									islatravir-implants-in-macaques/
10	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
11	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/
12	Ring (PU Reservoir)-vaginal	HSV	CONRAD	clinical	TFV	90 days	Unknown	PI: Mugo, CDC & USAID funding PI: Liu; NIAID MTN-038	https://pubmed.ncbi.nlm.nih.gov/38444118/ https://www.frontiersin.org/articles/10.3389/frph.2023.1118030/full
13	Ring (PU reservoir segmented) -vaginal	HSV, PREG	CONRAD	clinical	TFV, LNG	90 days	Unknown	PIs: Doncel & Clark, CDC & USAID.	https://www.conrad.org/news/news_items/conradandcdccollaborateonstudyofintravaginalringsreleasingtfvwithandwithoutlnginkenya.html https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199778
14	Ring (silicone pod)-vaginal	HSV, PREG	Auritech	preclinical	TAF/ or TDF/FTD, ACV and ENG/EE	1 month	Completed	PI: Smith; NIAID 2018-2023 5R33AI136008-05	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0185946 https://reporter.nih.gov/project-details/10378141
15	Ring (Non hormonal)-vaginal	PREG	Mucomune	preclinical	mAB cocktail-HCA+VRC01+N6	1 month +	Completed/ Inactive per IMPT database	PI: Kushiro, K. NICHD-2021-2024. 5R44HD097063-03	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8640842/ https://reporter.nih.gov/project-details/10381449

3b. **MPTs including an HIV indication by DDS name (ongoing)** (* all changes in table are in red text, new entries at the bottom of the table)

N=19	DDS	Other indications	PD	Stage	APIs	Duration	R&D Status	Notes:	References
1	LA-FILM-vaginal	PREG	MWRIF	preclinical	ISL (or Prodrug) + progestins	1 month	Ongoing	PI: Rohan; LATCH NIAID 2019-2025 5R33AI142687-06	https://reporter.nih.gov/project-details/10580096 https://pubmed.ncbi.nlm.nih.gov/37382422/
2	Film (mAB cocktail) vaginal	PREG	Boston U + MAPP	Preclinical/ clinical	ZB-06	OD (24h)	Ongoing	PI: Anderson, P50 and subprojects NICHD 2018-2026 2P50HD096957-06	https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003495 https://pubmed.ncbi.nlm.nih.gov/36870409/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10967333/ https://reporter.nih.gov/search/Sm6mvJwvLU2nuKZ7L6KiNg/project-details/10695240
3	Injectable Hydrogel-SC parenteral	PREG	EVMS/ CONRAD	preclinical	CAB+ LNG	3 months	Ongoing	PI: Clark; Project Horizon. NIAID 2019-2025 5R33AI142685-05.	https://reporter.nih.gov/project-details/10546210 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9639748/
4.	Implant- SC refillable (NanoMPI)	PREG	HMRI and UW	preclinical	etonogestrel (ENG) and islatravir (ISL) drugamer	2 years	Ongoing	PIs: Grattoni & Stayton; NIAID 2023-2028 1R01AI167659-01A1	https://reporter.nih.gov/search/t0FXMGGdiE622_eUszaw7g/project-details/10817794 https://pubmed.ncbi.nlm.nih.gov/38142963/
5	In Situ forming implant (ISFI)	PREG	UNC	preclinical	DTG, RPV, CAB, other	6 months	Ongoing	PI: Benhabbour; NIAID 2021-2026 5R01AI162246-04	https://pubmed.ncbi.nlm.nih.gov/34216767/ https://reporter.nih.gov/project-details/10793533 https://pubmed.ncbi.nlm.nih.gov/35745761/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9911691/
6	Insert-vaginal	BV, CT, GC, PREG	PC	preclinical	AMPHORA, Q-GRFT	OD	Ongoing	PI: Angsantikul; NIAID 2020-2025 5R01AI150324-05	https://reporter.nih.gov/search/vNSHP2pULUitSm8f8ITfaA/project-details/10772045

N=19	DDS	Other indications	PD	Stage	APIs	Duration	R&D Status	Notes:	References
7	IUD - Intrauterine	PREG	UW	preclinical	Copper + ARVs or prodrugs (unspecified)	Up to 3 years	Ongoing	PI: Woodrow; NIAID 2020-2025 5R01AI150325-04	https://reporter.nih.gov/project-details/10675641 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9081257/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9277594/
8	Tablet (DPP)- Oral enteral	PREG	Viatris, (PC)	clinical	TDF/FTC, LNG/EE	24h (daily)	Ongoing-	Confirmatory bioequivalence study to be completed in 2024 (CIFF, CHAI, BMGF funding)- PI: Haddad, HPTN- 104, NIAID	https://www.frontiersin.org/articles/10.3389/frph.2021.682689/full#:~:text=A%20dual%20prevention%20pill%20(DPP,into%20the%20hands%20of%20women https://www.prepwatch.org/dual-prevention-pill/
9	Tablet (DPP)- Oral enteral	PREG	PC/ Medicines 360	Pre-clinical & clinical	TAF /FTC, LNG/EE	24h (daily)	Ongoing?	TAF DPP. PI: Haddad-	https://popcouncil.org/project/dual-prevention-pill-for-the-prevention-of-hiv-and-unintended-pregnancy/
10	Ring- Core Sheath vaginal	PREG	IPM/PC	clinical	DPV, LNG	90 days	Ongoing-	PI: Steytler phase I/II IPM 056 / CCN019B (NICHD) through 12/2024	https://www.avac.org/trial/ipm-056-ccn019b https://clinicaltrials.gov/study/NCT05041699 See Table 1
11	Ring- Non-hormonal (CZL) vaginal	HSV, HPV, PREG	PC (+ QUB, WCMC)	preclinical	Non hormonal APIs Copper, Zinc and lactide	30 days	Ongoing	PI: Haddad; P50 grant and sub-projects, NICHD 2021-2026 5P50HD106793-03	https://www.sciencedirect.com/science/article/pii/S0168365915006252 https://reporter.nih.gov/project-details/10700065
12	Ring- (pod silicone) EEQ vaginal	PREG	PC	preclinical	Q-GRFT, ETG, EE	90 days	Ongoing	PI: Teleshova; NIAID 2020-2025. 5R01AI150360-05. Also tested 3 diameters of rings.	https://reporter.nih.gov/project-details/10798184 See Table 1 https://www.popcouncil.org/research/an-intravaginal-ring-containing-etonogestrel-ethinyl-estradiol-and-qgriffit
13	Ring- pod - Non hormonal vaginal	HSV, CT, PREG	MB, OCIS, Plante Biotech,	preclinical	mAB 2C7, TDF	30 days	Ongoing	The contraceptive mAB relies on sperm immobilization	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8868023/

N=19	DDS	Other indications	PD	Stage	APIs	Duration	R&D Status	Notes:	References
			UMass UNC, Mucomune					PI: Baum; NICHD 2020-2025. 5R01HD101344-05	https://reporter.nih.gov/project-details/10805424
14	Ring-CLIP 3D printed vaginal	HSV, PREG.	UNC	preclinical	DPV/pritelivir/ LNG or ISL/ENG/EE	1-3 months	Ongoing	PI: Benhabbour; NIAID 2019-2024. 5R01AI150358-05 (CLIP™) 3D printing.	https://reporter.nih.gov/project-details/10752633 you tube: https://www.youtube.com/watch?v=NCq2_yMpUfk https://pubmed.ncbi.nlm.nih.gov/37549505/
15	Ring- vaginal	GC	UMass/ OCIS	preclinical	TDF and mAb 2C7 (against GC)	Unspecified	ongoing	PI: Ram NIAID 2020-2024. 5R33AI136007-05	https://reporter.nih.gov/search/a71vYCzPO0ylXUPZu8M8Cw/project-details/10378501
16	Ring-vaginal	PREG	OCIS/UNC	Preclinical	ARV (not specified) & mAb for sperm agglutination	30 days	ongoing	PI: Baum NICHD 2020-2025. 5R01HD101344-05	https://reporter.nih.gov/search/ukGHVfvUxkm4cqnFmjVZxQ/project-details/10805424
17	Ring vaginal	BV	QUB	Preclinical	DPV+ Metronadizole	Unspecified	Ongoing?	Malcolm's group. Funding unspecified in publication.	https://www.sciencedirect.com/science/article/pii/S0378517323009936?via%3Dihub https://doi.org/10.1016/j.ijpharm.2023.123296
18	Ring Vaginal, with Non-hormonal contraceptive	PREG	QUB	Preclinical In vitro study.	DPV, Cu, Zinc	Unspecified	Ongoing?	Malcom's group funding unspecified in conference abstract	https://pure.qub.ac.uk/en/publications/poster-abstract-a-multipurpose-vaginal-ring-releasing-copper-ions https://pure.qub.ac.uk/en/public rmulation-development-of-a-multipurpose-vaginal-ring-for-no
19	injectable	PREG	QUB	Preclinical (NHP)	Depo Provera+ RPV	Up to 2 months	Ongoing?	WHO funding	https://doi.org/10.1016/j.jddst.2023.104590