

Prevention Field Landscaping: Update on 4th Desktop Review – June-December 2023

SC March 8, 2024

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Desktop Review

- **Why:**
 - ✓ MATRIX Prime required to monitor R&D activities in the HIV prevention and microbicide research space : Partners Calls + Desktop Review
 - ✓ Desktop prevention landscape review (excluding vaccines & bnAbs): formal report submitted to USAID biannually- 4th review submitted in 1/2024
- **How:**
 - ✓ Publications/abstracts reviews via PubMed, Bio and Medrxiv, conferences websites/attendance, listserves and database review.
 - ✓ Published reviews, reports and media releases on relevant topics
 - ✓ Current NIH-funded projects (via NIH RePorter)
 - ✓ **Clinical trials databases: Clinicaltrials.gov (US), EU CT registry, Wellcome trust (-> 21 relevant clinical studies identified.)**

Key Points/findings

- Several relevant studies and some potential overlap with current MATRIX CP projects were identified.
- 75 projects total (incl. stopped/completed) & **48 active** (HIV PrEP & MPTs)
 - 11 new entries identified this round (8 for HIV, 3 for MPTs)
 - Multi-dose US rectal study of the TAF/EVG insert (RITE-PrEP; CONRAD and CDC)
 - SBIRII (NIAID-funded) for 6+ months injectables nanocrystal suspensions of new prodrugs of NRTIs and INSTIs (e.g. XVIR-110; EXAVIR – Spin off of U of Nebraska)
 - New NIAID R01 to OCIS to continue TAF implant development
 - Pharma updates:
 - **Merck:** initiated phase I trials with new NRTTI MK5827 (\geq QW oral dosing)
 - **ViiV** is extending the duration of Cab-LA through reformulation to a Q4M (anticipated approval in 2026- plan to further extend to Q6M by 2030.)
 - 40 publications/presentations in second half of 2023.

NOTE: aqua highlights = updates available from CROI 2024

Highlights of Projects

# and types of projects	N	Active/ Ongoing	Currently not active/unknown status
HIV Prevention only	41	28*	13
MPTs	34	20**	14
TOTAL	75	48	27

(*) 8 new entries for HIV Prevention only

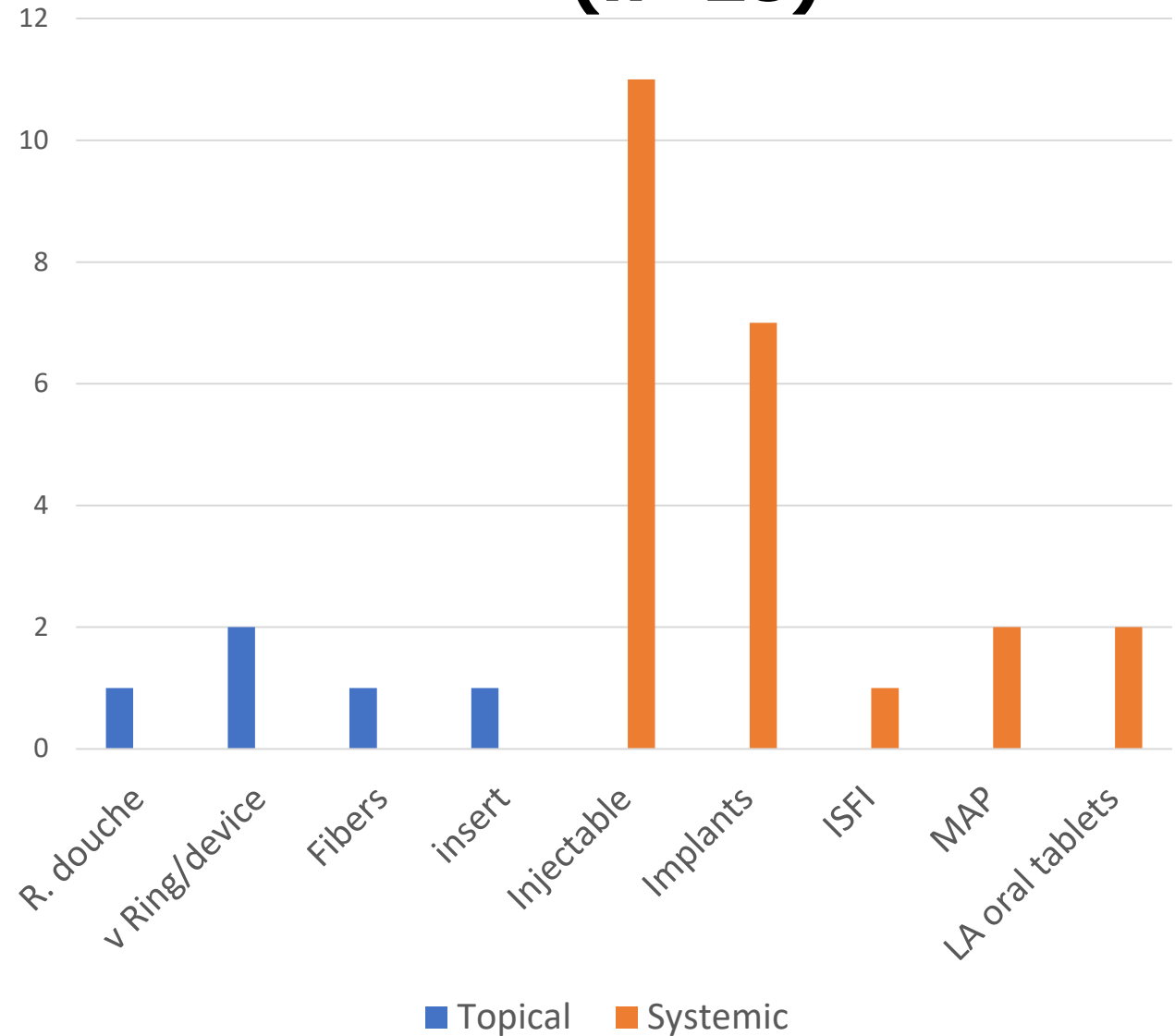
(**) 3 new entries for MPTs

HIV Prevention only

- Twenty-three systemic DDS
- Five topical products
- Majority of LA DDS

- 10+ projects at clinical stage (FIH to phase III)
- 6 projects with prodrugging approaches (excluding TAF)
- 3 projects use non-ARV drugs

Active projects- distribution (n=28)



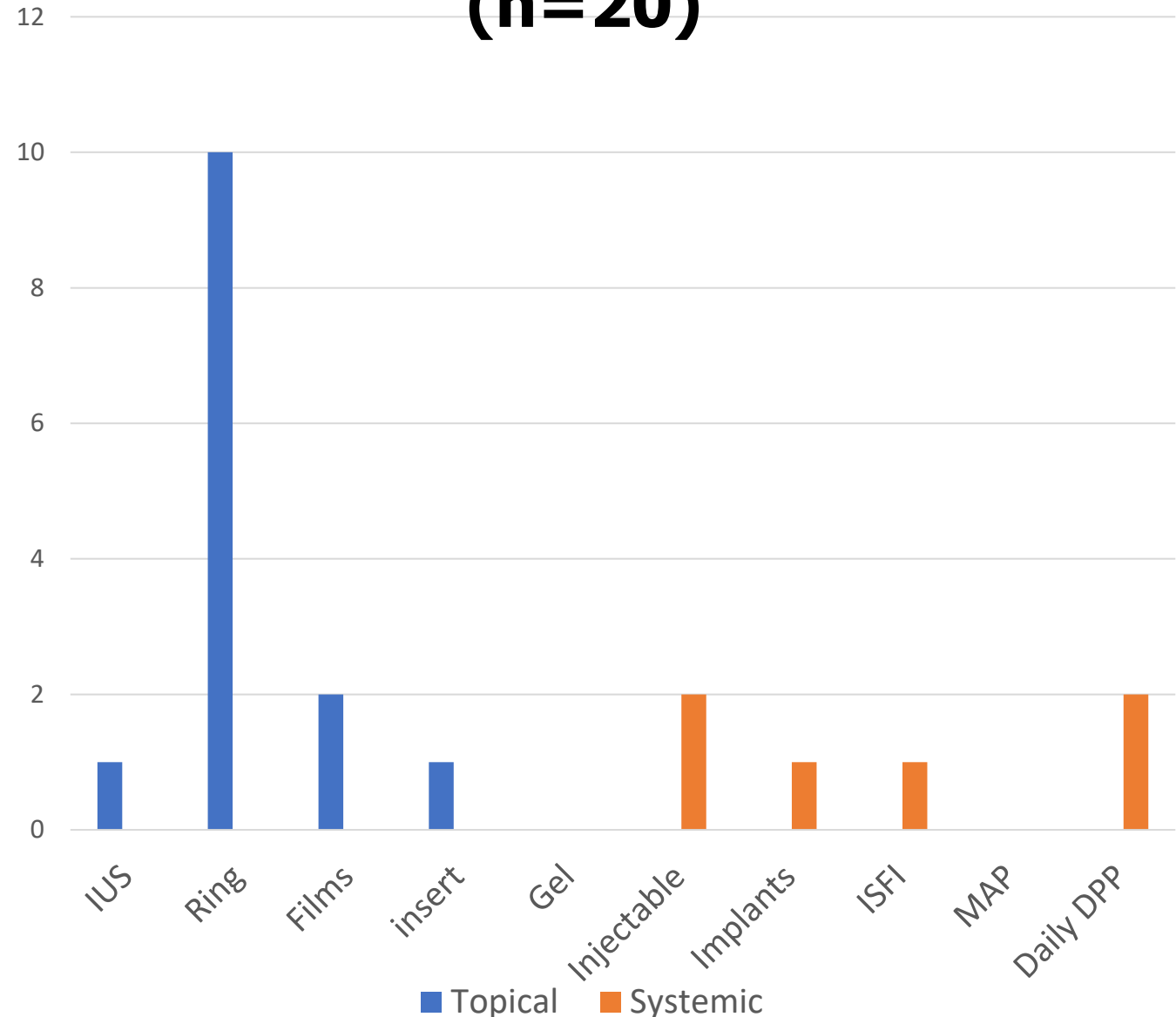
Types of APIs used in HIV-PrEP DDS

- INSTIs (CAB, BIC, RAL, new ViiV INSTIs) & ULA-CAB (4+M)
- Capsid inhibitors(Cis) (LEN + new CIs from ViiV)
- New NRTTI MK8527 (replacing ISL for Px)
- ISL-related publications still prevalent (model drug in preclinical studies for Px, and for Rx)
- Other APIs: drugamers, D-peptide entry inhibitor, CD4 mimetic compounds and IG, fusion inhibitor, maturation inhibitors,
- Non-ARVs: GRFT (+ silk fibroin for increased film mucoadhesion)

MPT projects

- Fourteen are topical products
 - 10 ring projects
- Six systemic LA-DDS
- 4 projects at (early) clinical stage
- **Prevention indications:**
 - HIV- all 20 (by definition)
 - Pregnancy: 18 projects
 - HSV: 3 projects
 - GC/NG: 2 projects
 - HPV: 1 project
 - BV: 2 projects

Active MPT projects distribution (n=20)



Types of APIs used in MPTs

- **HIV Prevention:**

- NNRTI: DPV, RPV
- NRTIs (TFV, TDF, TAF, FTC)
- NRTTI (ISL)
- INSTI (DTG, CAB)

- **Non-ARVs:**

- GRFT and QGRFT
- mABs

- **Pregnancy prevention:**

- Hormonal: LNG, EE, ETG, DMPA
- Non-hormonal: mABs, copper, zinc, acid buffering agents

- **Other indications:**

- Metronidazole (BV)
- Pritelivir (HSV)
- GRFT and QGRFT (viral STIs)

40 publications/presentations thru 12/31

- Preclinical and clinical efficacy of LA-DDS :
 1. Efficacy of LEN injection in NHP for sexual or IV exposure,
 2. Options for various body location for LEN SC injections,
 3. Efficacy of CAB-LA in OLE & ex-vivo efficacy for penile infection
 4. Reassessment (upwards) of the efficacy of the DPV ring in a secondary analysis of the ASPIRE trial,
 5. Updated estimates of oral PrEP efficacy in cisgender women with imperfect adherence
 6. Efficacy of ISL implants in NHP models.

Con't

- MPTs and multidrug formulations:

1. Formulations of multiple drugs in rings, implants, ISFI and injectables.
2. One paper described an on-demand TFV film as an MPT (for HIV and HSV2)
3. Formulation of 3 different ARVs with different physicochemical characteristics, in a single injection for treatment.

- Other:

1. DPV ring, shown to be safe and acceptable in third trimester **pregnant people** and in AGYW (**MTN-042**; MTN-034)

CROI 2024 update



Clinical: New APIs for Px and/or Rx

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- a. [125] **GILEAD: new INSTI (GS-1720)** for \geq **QW** administration:
2 phase I conducted in HIV(-) and HIV (+) persons, respectively.
- $t_{1/2}$ life 9.4 days
 - Dose range (50-1350mg)- 450mg and 900mg doses have potent anti HIV activity (in HIV+ persons) and are well tolerated
- a. [115, 129 & 638] **Merck: new NRTTI (MK8527): QW** for Rx and Px .
Studies assessed single and multiple ascending doses.
- Single (0.5-200mg) and multiple doses (5-40mg) well tolerated
 - MK-8527 TP values for doses ranging from 5-200mg were all above PK threshold (0.2pmol/ 10^6 PBMC)
- b. [633 & 6344] **GSK/ViiV new maturation inhibitors (MI)** GSK3640254 & VH3739937) focused on Rx (dosage and frequency not described)-
potential for Px as well.

Con't: New DDS, optimized duration/administration & new populations

- a. [123] **CAPRISA/OCIS: FIH trial of TAF implant (CAP-018)**
- Demonstrated sustained drug release for ~1 year (48w) w/o drug dumping
 - Tolerability problematic (31% of implants w/early removal) but high reported acceptability
 - PK level did not reach target (36 fmol/10⁶) in most women (85%) even with 2 implants
- a. [130] **ViiV: Extended (Q4M) CAB release in new ULA IM formulation**
- Findings support move towards a ≥ 4 month dosage
 - IM (gluteus) better tolerated than SC (belly) – further evaluation for SC dosage needed
 - IM dosage has shorter $\frac{1}{2}$ life than SC (but predicted to be 2x longer $\frac{1}{2}$ life than CAB-LA)
 - Currently still figuring out IM dosage (800mg/2ml- \rightarrow 1600 mg/3ml)
- b. [617] **ViiV: assessment of CAB-LA PK following thigh vs gluteal injections**
- Difference in release rate and PK profiles by gender and sites of injections
- c. [168]: **MTN-042: Safety of DVR in pregnancy** across 2nd & 3rd trimesters

Preclinical stage studies

- a. [1137] **UNC: ULA ISFI with DTG** was safe and released drug (zero order release) for **>300 days** (and continuing) over target concentration (4x PA-IC90) in mice .
- b. [656] **Exavir: ULA injection (1 year) of XVIR110** (CAB stearate prodrug) in rats & dogs, releasing above PK target levels.
- c. [654] **UNMC: ULA injection (6-mo to 1yr) of BIC prodrug** (XVIR-130 and 131) in rats and NHP. XVIR-131 displays a short PK tail.
- d. [653] **U of Liverpool: LA-BIC solid injection (42 days) w/** sustained therapeutic concentration in rats

Other MPT/PrEP/PEP highlights from CROI

- [1139] **PopC: Over-encapsulated DPP pill** pilot cross-over study in Zimbabwe: ~2/3 preferred the DPP over 2 pills; also DPP adherence was higher (w/ sequence effect).
- [170] **Women's benchmark study**: established PK benchmarks for oral PrEP protection in non-pregnant and pregnant women.
- [612] **JHU: DREAM-03 rectal douche** : assessed different douche sequences. importance to finish with a medicated (TFV) douche if multiple douches are used prior to sex.
- No evidence that STIs interfere with **efficacy of Cab-LA among men**(in HPTN-083)
- **DoxyPEP**: overwhelming evidence of benefits to decrease CT and syphilis (not so for GC, in part because of high prevalence of drug resistant GC): both individual and population wide benefits.
- **PEP**: highly under-utilized, need broader access

Acknowledgements

This program was made possible by the generous support of the American people through the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the U.S. Agency for International Development (USAID).

The contents in this presentation are those of the presenter and do not necessarily reflect the view of the U.S. President's Emergency Plan for AIDS Relief, the U.S. Agency for International Development or the U.S. Government.

