Injectable Antiretrovirals
The Promise and the Peril

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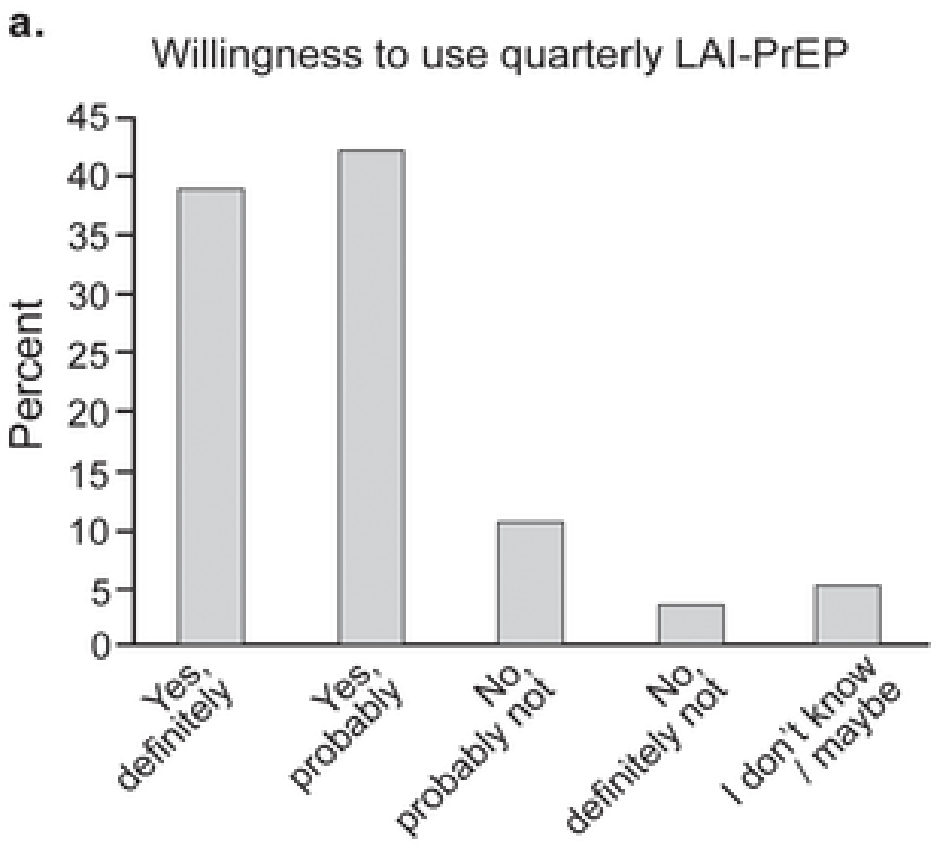
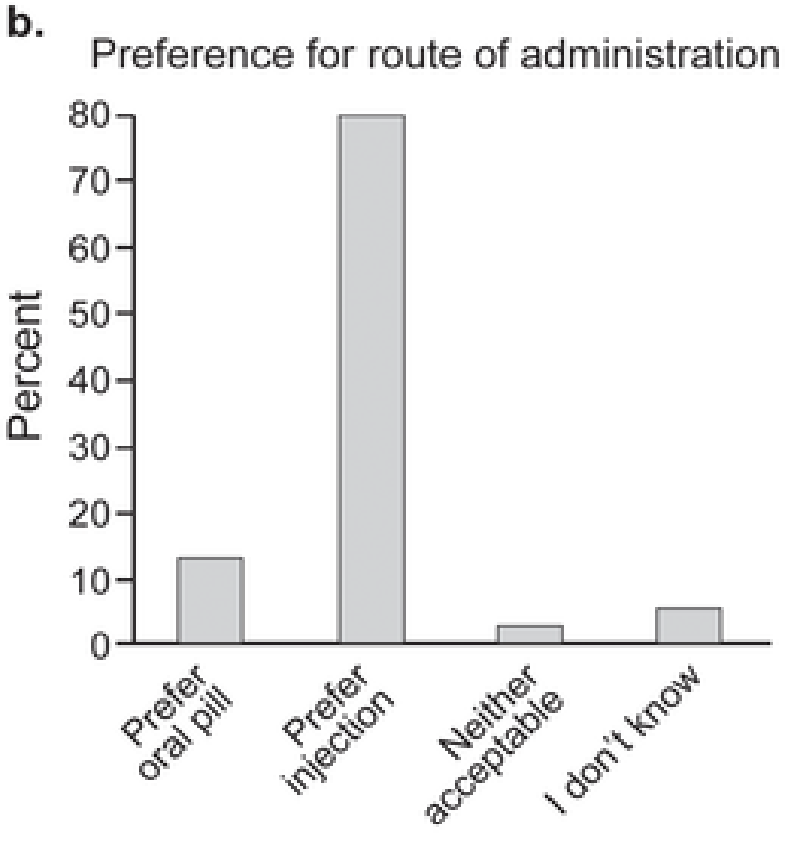
The Promise

Long Acting Formulations

- Have been used to improve adherence and prevent missed doses/treatment fatigue in several therapeutic areas
- Contraception: (Depo Provera)
- Schizophrenia: 6 long-acting antipsychotics available (e.g. risperidone, olanzapine, aripiprazole)
- LA ARV products being developed for PrEP and treatment indications

Acceptability of LA PrEP

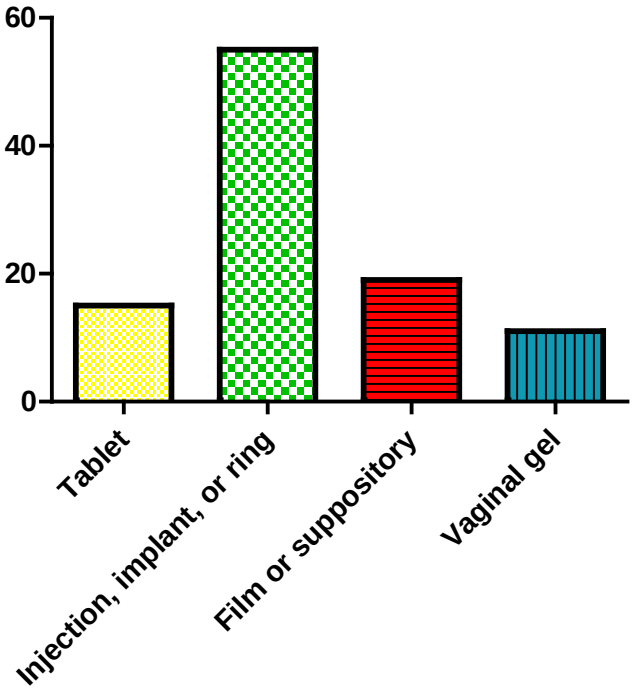




Meyers K et al. PLoS ONE 2014

Prevention Product Preference

- VOICE-D study
- In depth interview (N = 68)
- Women asked to make hypothetical choices about product preference



Ariane van der Straten and the VOICE-D Team

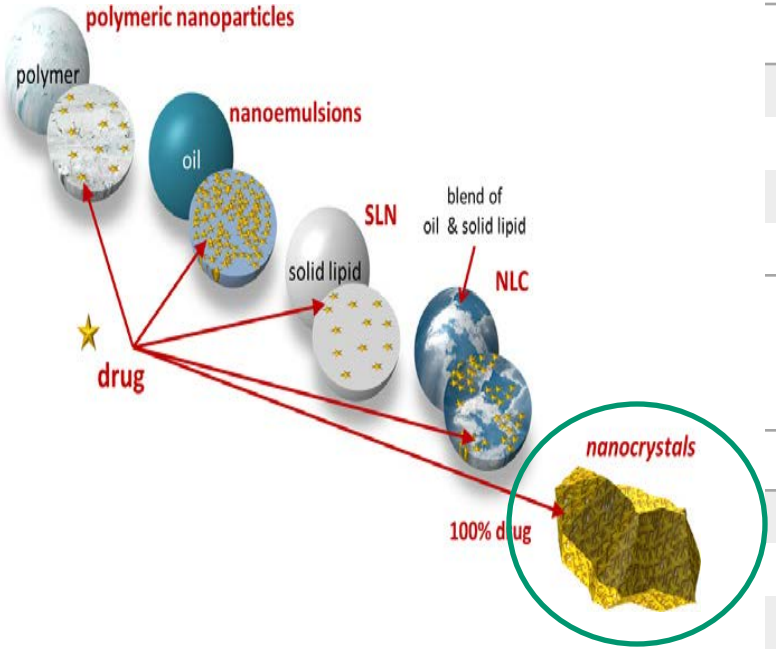
Injectable PrEP

Requirements for LA ARV

- Potency and PK profile allowing infrequent dosing (~ 2-3 months)
- Practical injection volume (~ 4mL)
- Stable formulation ideally without cold chain requirements
- Potential products
  - TMC278 LA (Rilpivirine)
  - GSK 744 (Cabotegravir)
  - Monoclonals (Ibalizumab, 3BNC117, 10-1074)

Nanosuspension Formulations

- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading vs. matrix approaches for lower injection volumes



R H. Müller, et al. European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 1-9

GSK744 200mg/mL

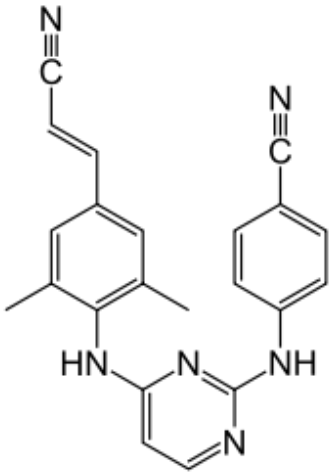
Component	Function
GSK1265744A (d50 ~200 nm)	Active
Mannitol	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

TMC278 300mg/mL

Component	Function
TMC278 (d50 ~200 nm)	Active
Glucose	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

TMC278-LA (Rilpivirine)

- Non Nucleoside Reverse Transcriptase Inhibitor
- Oral rilpivirine licensed as Edurant® for the treatment of chronic HIV infection (25 mg)
- EC_{50}: <0.4 ng/mL
- Plasma trough levels in successful treatment populations: ~70 ng/mL



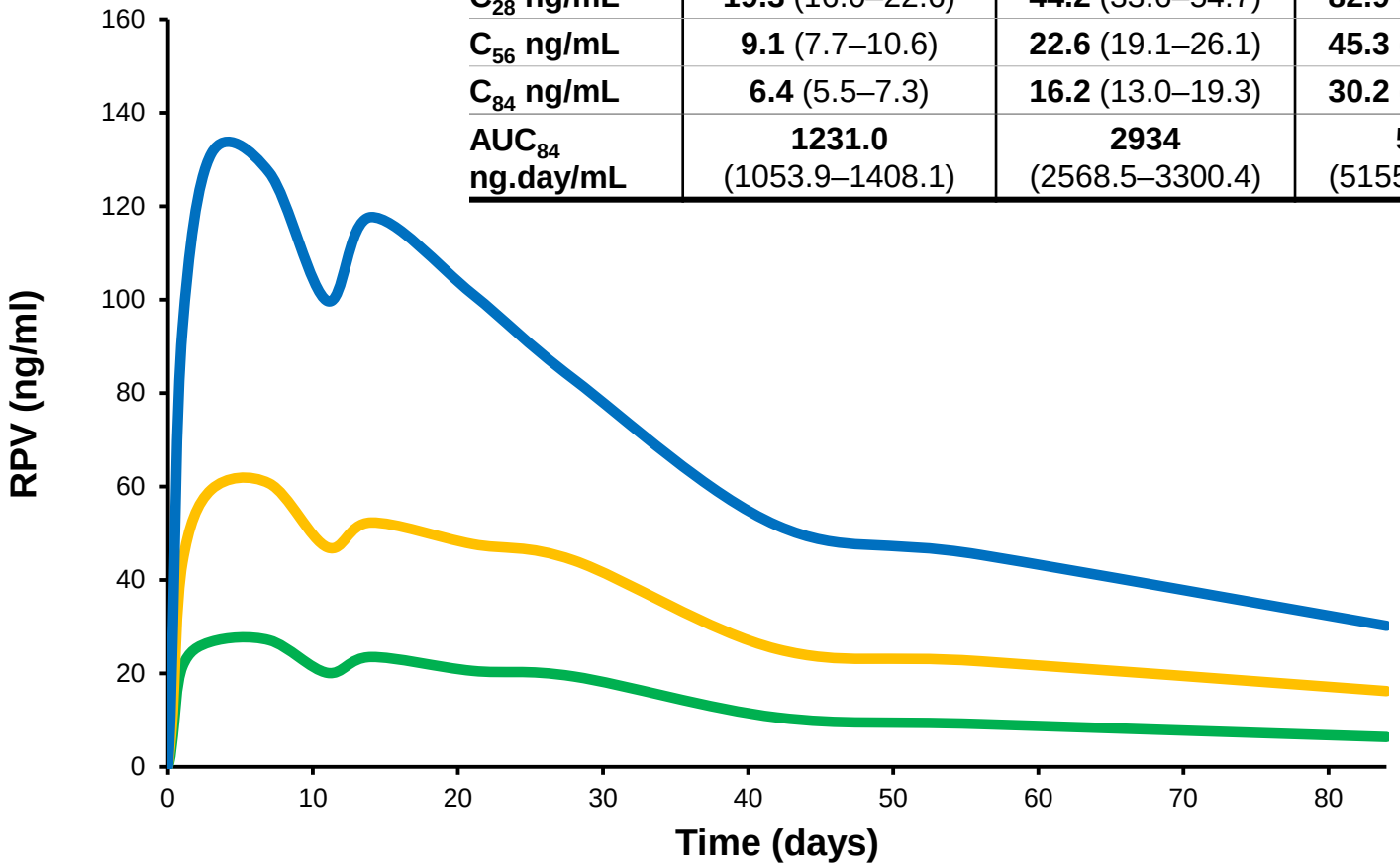
SSAT 040 Phase I Trial

- Study design
  - HIV-negative volunteers, between 18–50 years, low risk for HIV
- Single IM dose
  - 20 women per arm at 300 mg, 600 mg or 1200 mg (n=60)
  - 6 men at 600 mg
- Primary objectives
  - Plasma PK through Day 84 post dose
  - PK in genital tract and rectal fluids/tissues

Jackson A et al. Clinical Pharmacology & Therapeutics 2014

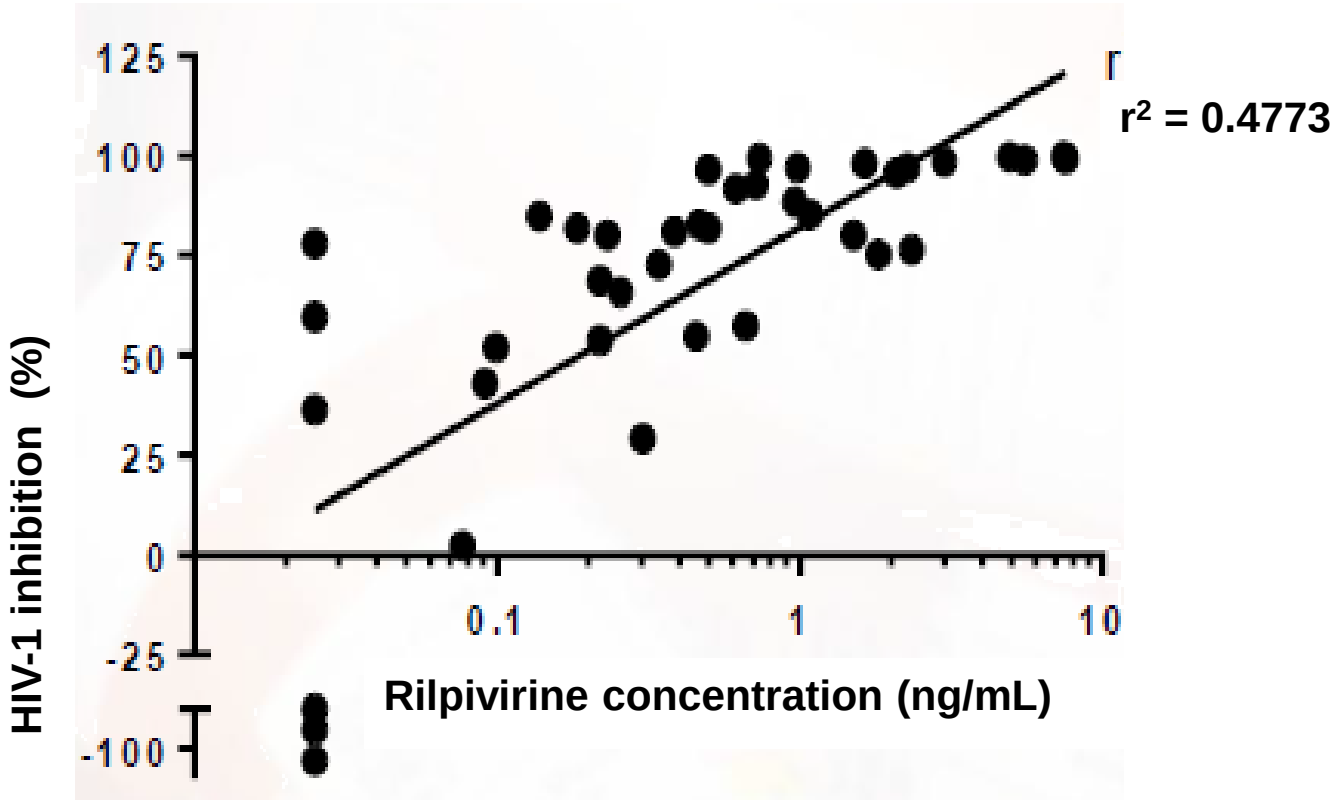
Rilpivirine Levels in Plasma

PK parameter	F 300 mg (n=20)	F 600 mg (n=20)	F 1200 mg (n=20)
C_{max} ng/mL	**33.7** (27.8–39.6)	**81.9** (68.7–95.1)	**160.2** (137.5–182.9)
T_{max} day	**7.9** (4.2–11.5)	**6.0** (3.4–8.6)	**6.2** (4.3–8.1)
C_{28} ng/mL	**19.3** (16.0–22.6)	**44.2** (33.6–54.7)	**82.9** (66.6–99.1)
C_{56} ng/mL	**9.1** (7.7–10.6)	**22.6** (19.1–26.1)	**45.3** (35.8–54.9)
C_{84} ng/mL	**6.4** (5.5–7.3)	**16.2** (13.0–19.3)	**30.2** (23.7–36.6)
AUC_{84} ng.day/mL	**1231.0** (1053.9–1408.1)	**2934** (2568.5–3300.4)	**5981.6** (5155.9–6807.4)



Jackson A et al. Clinical Pharmacology & Therapeutics 2014

Pharmacodynamic Data



Jackson A et al. Clinical Pharmacology & Therapeutics 2014

MWRI-01 Study

Screening Visit

Baseline Visit

Rilpivirine
1200 mg or
600 mg

Female (N=12)
Male (N=6)

Cervicovaginal
Rectal fluid & tissue

Compartmental PK &
explant challenge

FU Visit
+ 1 month

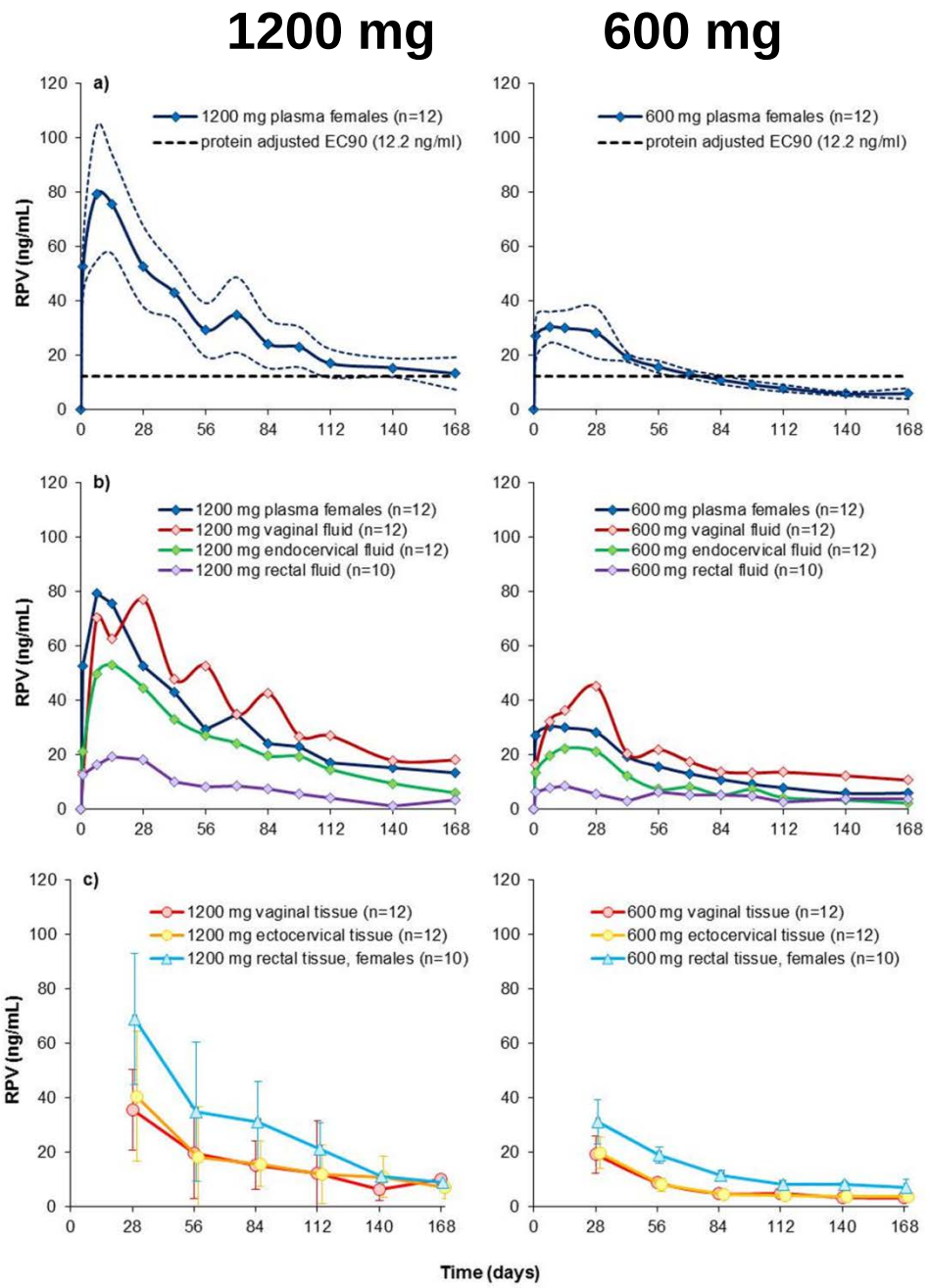
Monthly
FU Visits
+ 2 months to
+ 6 months

Compartment

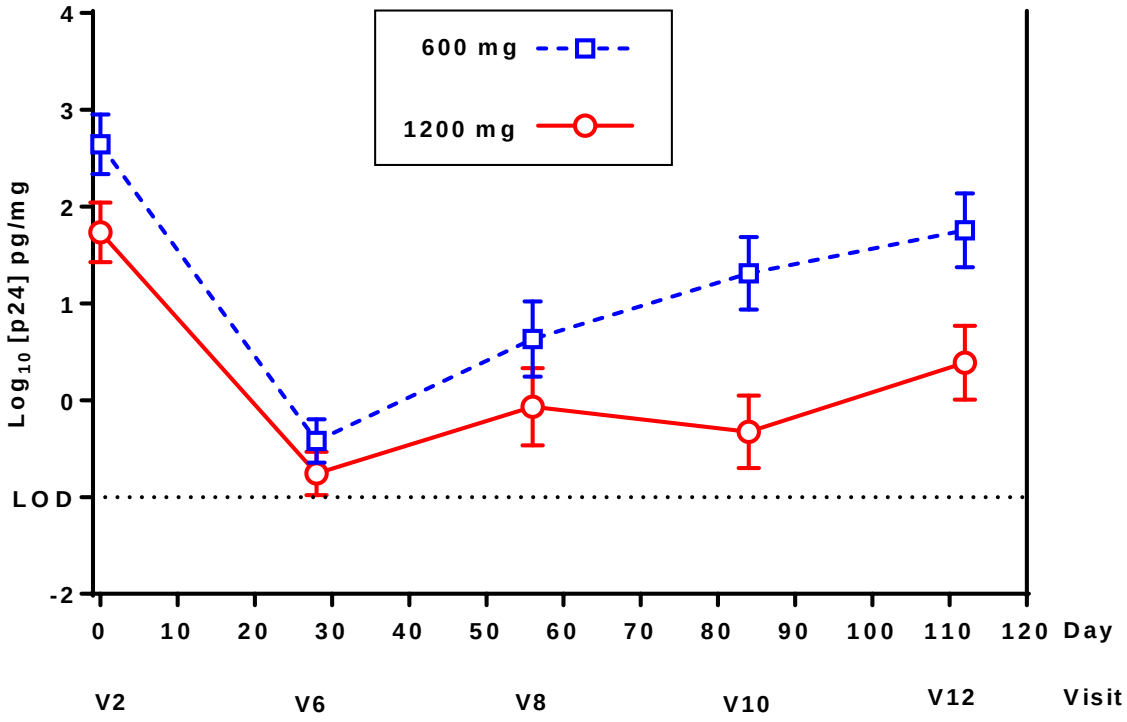
Plasma

Cervicovaginal & rectal fluid

Cervicovaginal & rectal tissue



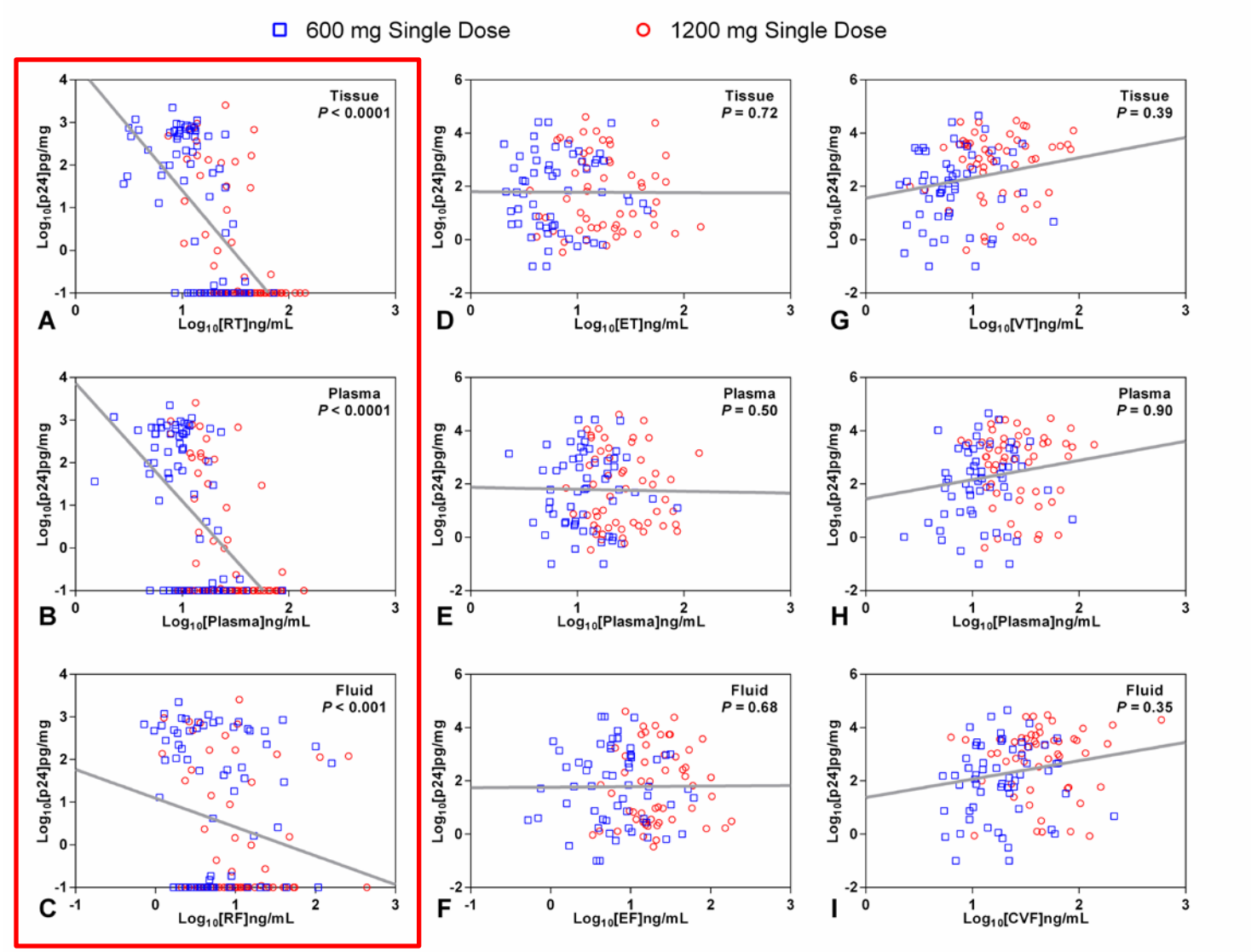
MWRI-01 Explant Data



Dose Effect *P* = 0.0009
Visit Effect *P* <0.0001
Dose*Visit Interaction *P* = 0.2131

McGowan I et al. HIV R4P 2014

MWRI-01 PK/PD



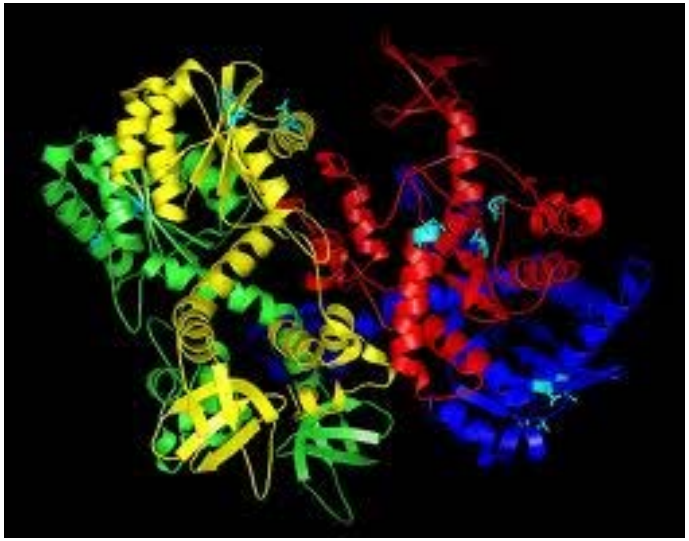
Rectal Cervical Vaginal

Rilpivirine Development

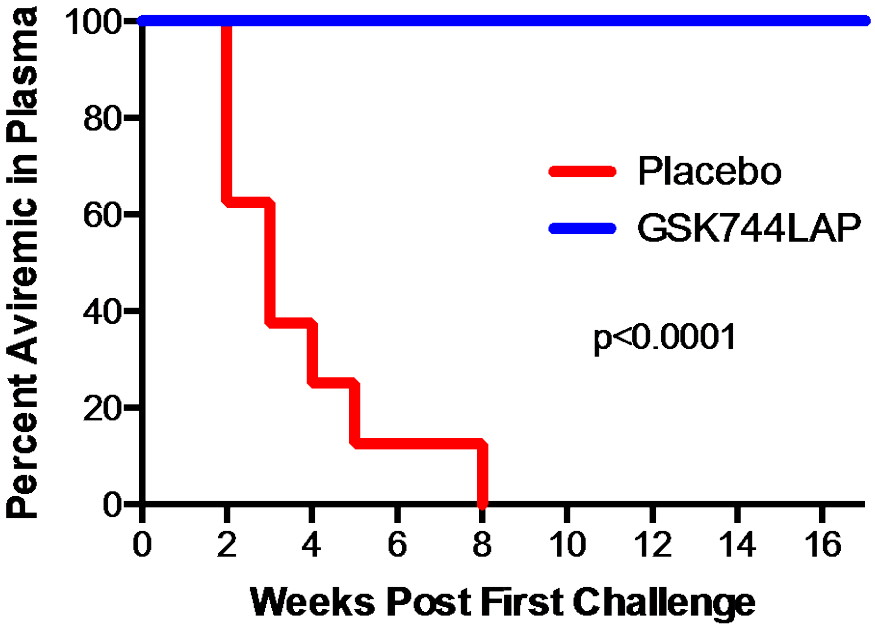
- Complete MWRI-01 multiple dosing phase
  - 1200 mg every 2 months
- Complete Phase 2 evaluation
  - HPTN-076
- Rilpivirine unlikely to advance to Phase 3 development for prevention
  - Resistance and cold-chain requirement
  - Failure to suppress explant infection
- Also being developed for Rx indication

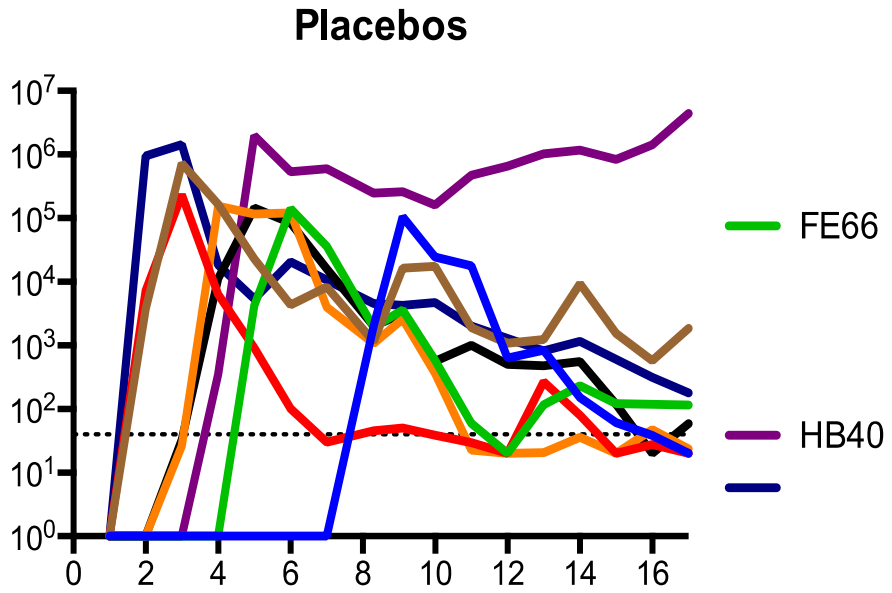
GSK 744 (Cabotegravir)

- Integrase inhibitor
- Analogue of dolutegravir
- Oral dose ≤ 30mg
- IC_{50}: 0.22 nmol/L
- Highly protein bound
- PA IC_{90}: 166ng/mL
- LA formulation has 200 mg/mL



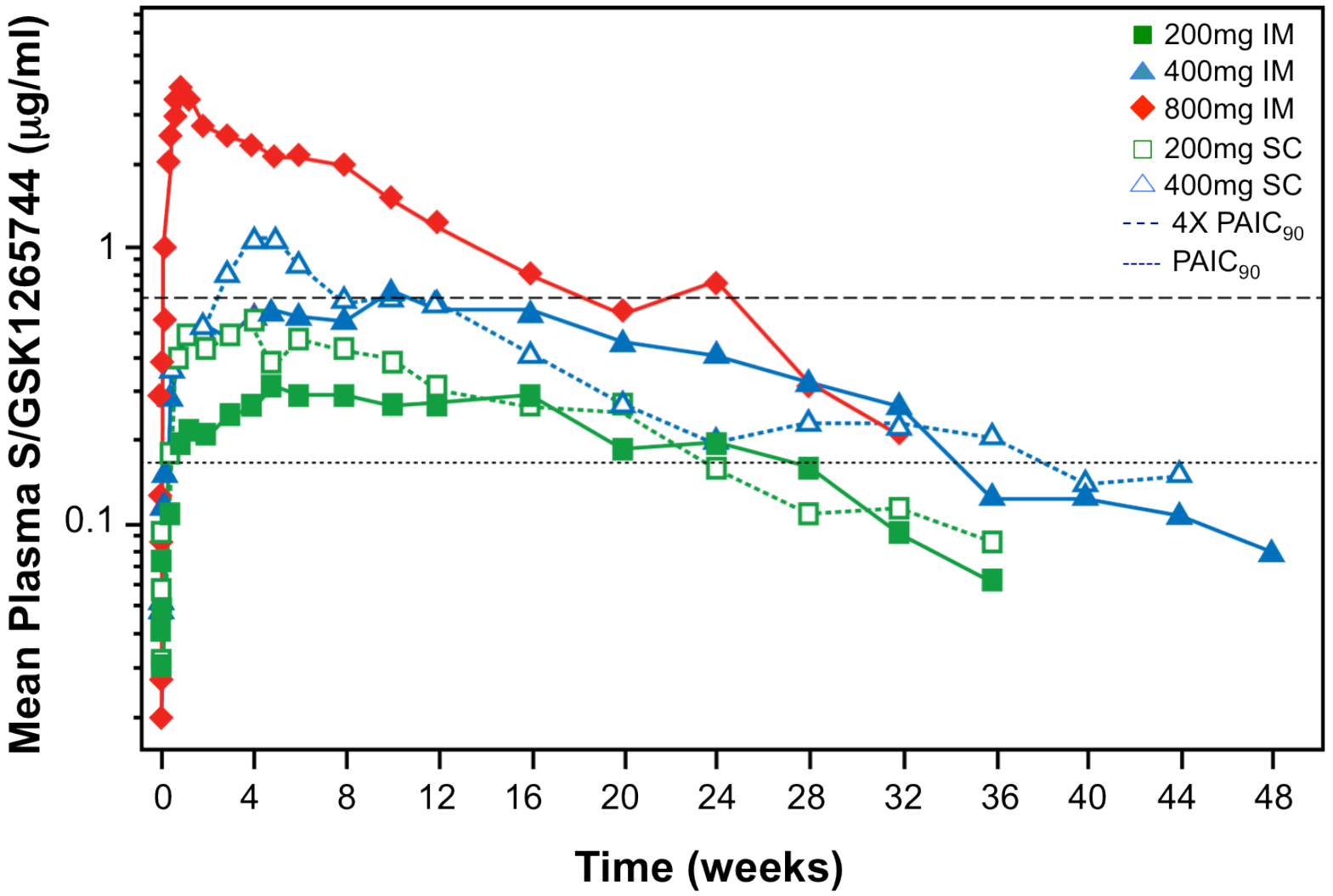
Non Human Primate Study





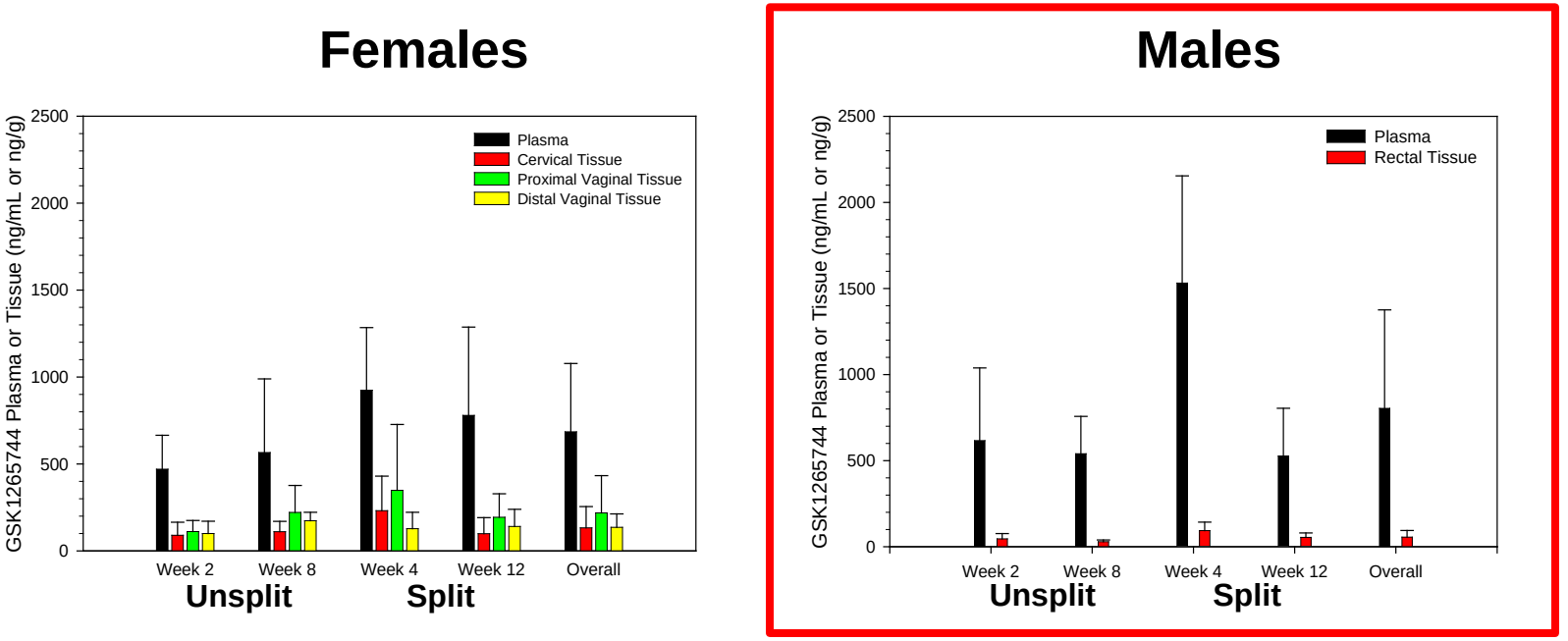
Andrews CD et al. Science 2014

PK Profile of Cabotegravir



W. Spreen, et al, 19th IAC July 2012. Abstract TUPE040

Tissue Concentration Analysis



- Median split, unsplit (range) individual tissue:plasma ratios were
  - 0.16, 0.20 (NQ – 0.40) in cervical tissue
  - 0.19, 0.28 (NQ – 0.70) in vaginal tissue
  - NQ, 0.08 (NQ – 0.20,0.10) in rectal tissue

Cabotegravir Development

- Phase 1

  Multiple Phase 1 safety studies completed*

- Phase 2
  - HPTN-077
    - Brazil, Malawi, South Africa, and the US
    - Currently enrolling
- Phase 3
  - HPTN-083
    - In development

*Jackson A and McGowan I Current Opinion HIV and AIDS 2015

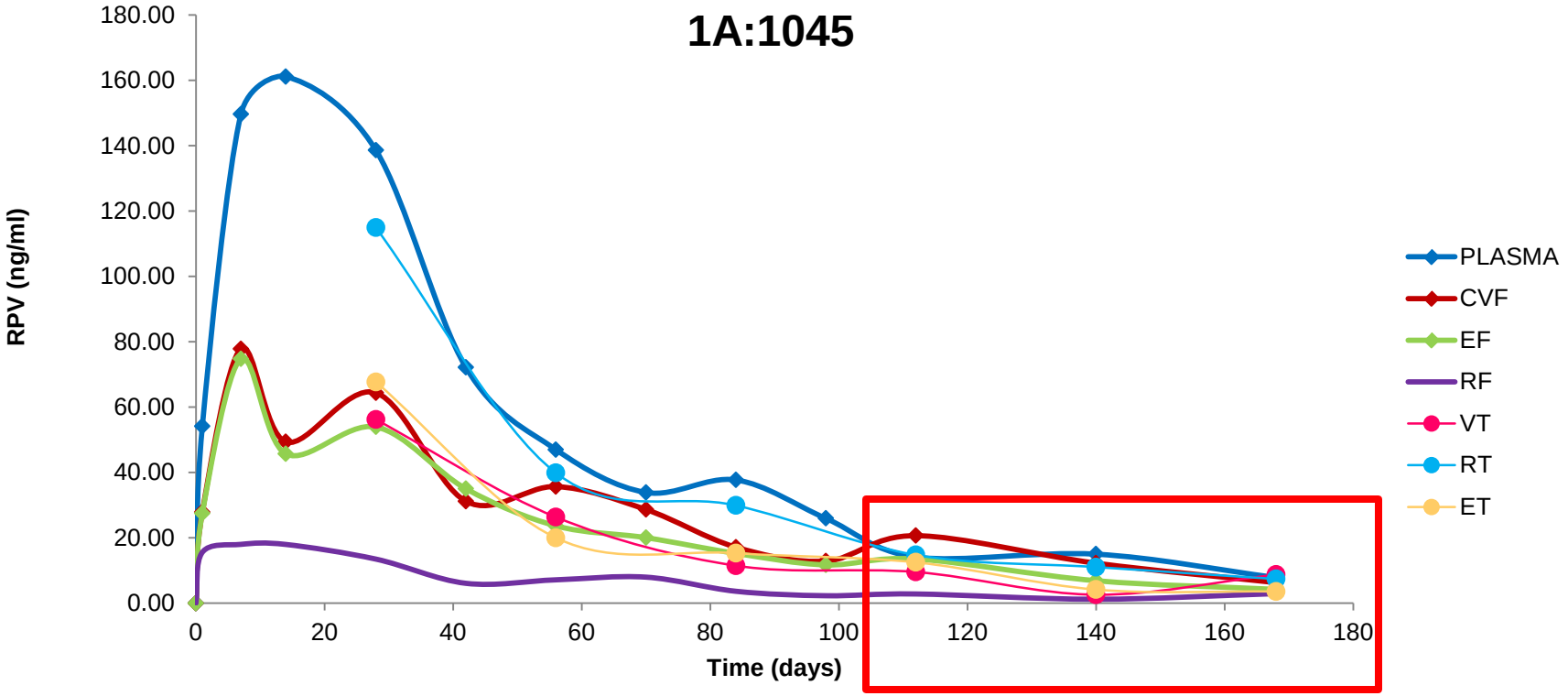
The Perils

The Perils of LA PrEP

- Safety
- Acceptability
- Adherence
- Pharmacokinetics
- Resistance
- Operational complexity

Pharmacokinetics

The PK Tail



Female participant receiving a single 1200 mg dose of rilpivirine

→ ?

Resistance

- HIV infection during periods of subtherapeutic drug exposure may result in the development of resistance
- NNRTI resistance seen in a SSAT040 study participant who received a 300 mg dose of rilpivirine and who seroconverted
- Loss to follow-up during implementation may generate large pool of vulnerable individuals

Operational Complexity

One month
oral run in phase

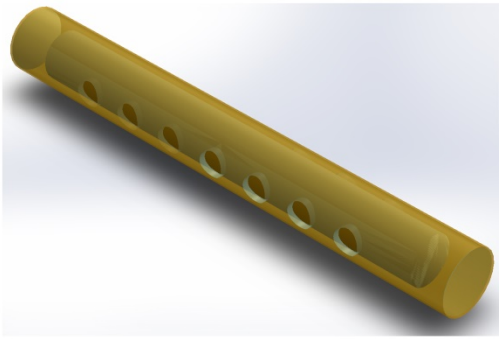
Exposure to
LA PrEP every
2-3 months
Two IM injections

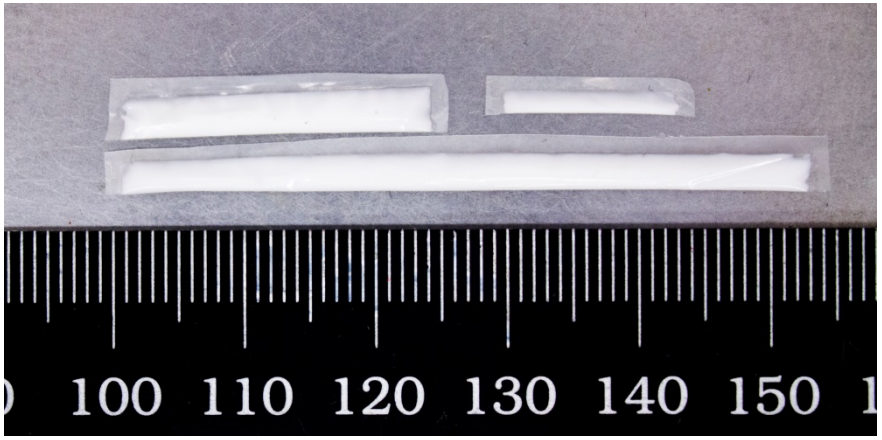
PrEP
Cessation

12 months of
Oral PrEP

Implantable Products

Implantable Formulations





Tenofovir alafenamide implant

Gunawardana M et al.
Antimicrob Agents Chemother 2015

Van der Straten A
USAID Grant
In Progress

Summary

- GSK744 and TMC278 have progressed through Phase1 studies
  - Generally safe and acceptable but ISR common
- Efficacy signals seen for both products
  - GSK744: NHP model
  - TMC278: Explant model
- Phase 2 studies ongoing
- Phase 3 GSK744 study planned

Acknowledgements

- Janssen R & G
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Thank You