Oral Versus Injectable Delivery, Impact on Adherence/Tolerability

2nd European HIV Forum

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Overview

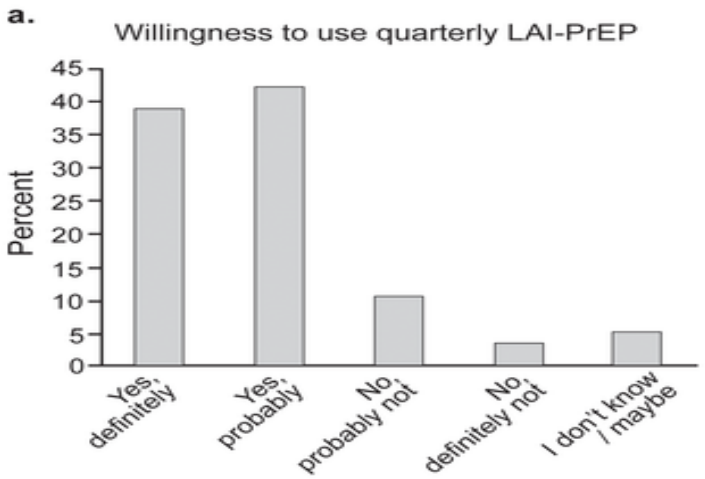
- Why do we need Long-Acting (LA) injectable antiretrovirals?
- Current LA antiretroviral candidates
  - Rilpivirine, cabotegravir, and EFdA
- LA antiretroviral adherence and tolerability
- Looking towards the future

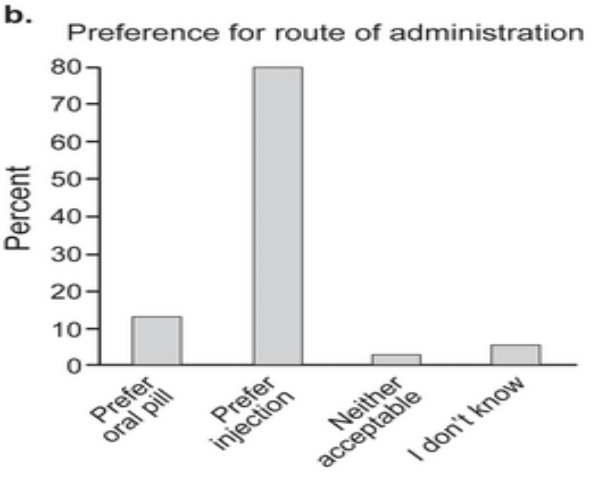
Why Do We Need Long-Acting (LA) Injectable Antiretrovirals?

The Need For LA Antiretrovirals

- Adherence to oral antiretrovirals can be variable
- Special populations
  - Drug and alcohol abuse
  - Psychiatric illness
- Antiretroviral stigma
- Consumer preference

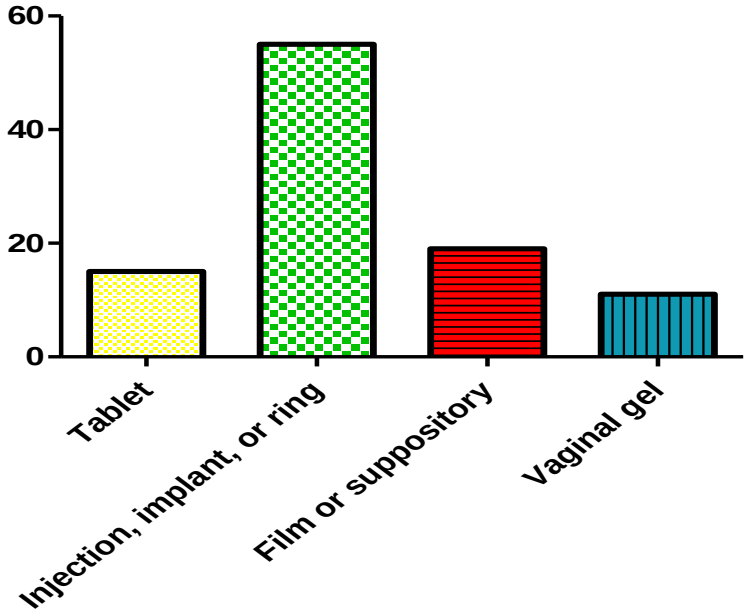
LA Antiretrovirals in MSM





Meyers K et al. PLoS ONE 2014

LA Antiretrovirals in African Women



Luecke EH et al. IAS Vancouver 2015

Uses for LA Antiretrovirals

- Treatment of chronic HIV infection
- Prevention of HIV infection
  - Pre-exposure prophylaxis (PrEP)
  - Post-exposure prophylaxis (PEP)
  - Prevention of mother to child transmission (MCT)
- Current development of LA antiretrovirals is for both treatment and prevention indications

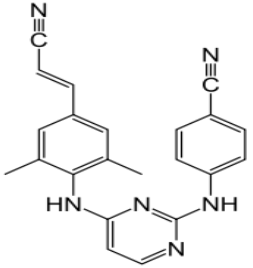
Long-Acting Antiretroviral Candidates

Requirements for LA ARV

- Infrequent dosing (~ 2-3 months)
- Practical injection volume (~ 4mL)
- Stable formulation ideally without cold chain requirements
- Potential LA antiretroviral products
  - TMC278 LA (Rilpivirine)
  - GSK 744 (Cabotegravir)
  - EFdA
  - Monoclonals (Ibalizumab, 3BNC117, 10-1074)

Rilpivirine LA

- NNRTI licensed as Edurant® for the treatment of chronic HIV infection (25 mg)
- PA EC_{90}: 12.2 ng/mL
- Plasma trough levels in successful treatment populations: ~70 ng/mL
- Formulation: 300 mg / mL
- PrEP doses evaluated
- 300 - 1200 mg QD & Q8 weeks



Rilpivirine LA Trials

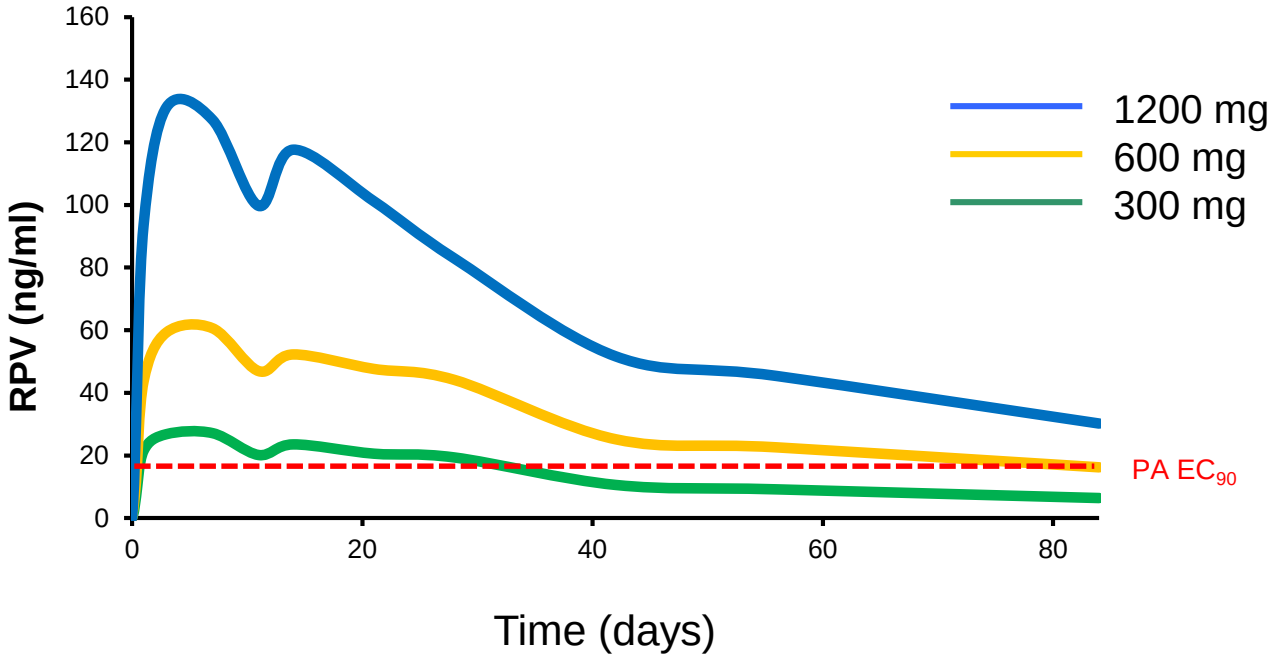
- Treatment
  - LATTE-2 study
- Prevention
  - SSAT 040 Phase 1 study
  - MWRI-01 Phase 1 study
  - HPTN 076 Phase 2 study

SSAT 040 Phase I Trial

- Study design
  - HIV-negative volunteers at 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 objective
  - Characterize plasma, genital and rectal PK

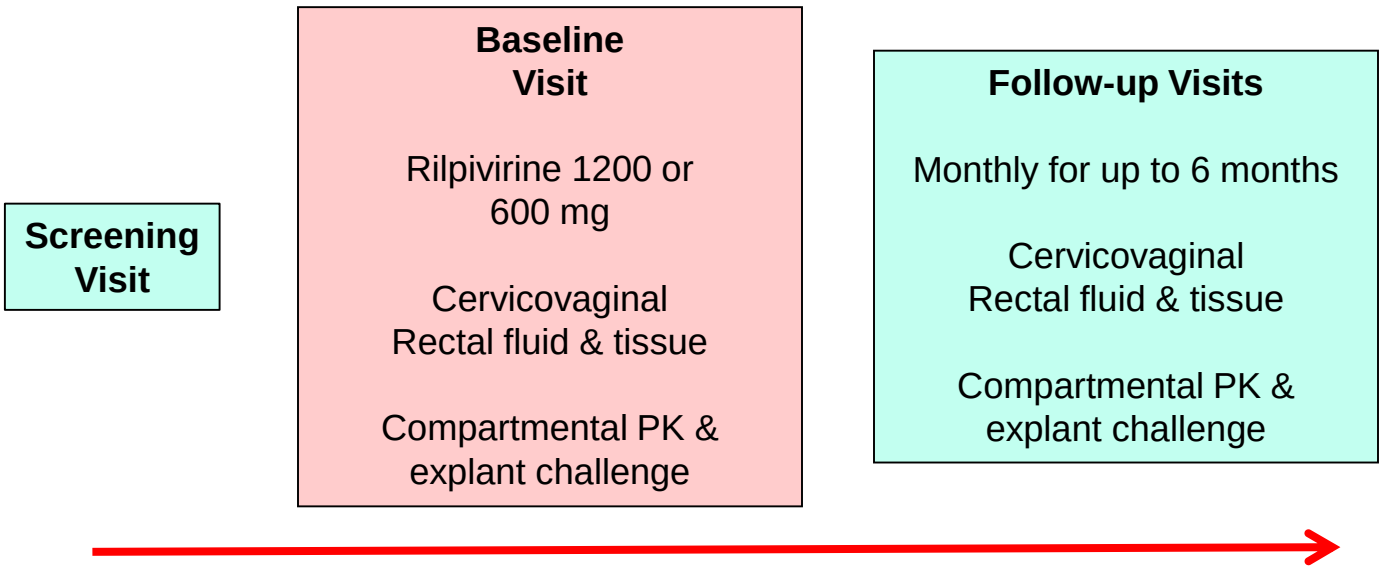
Jackson A et al. Clinical Pharmacology & Therapeutics 2014

Rilpivirine Levels in Plasma



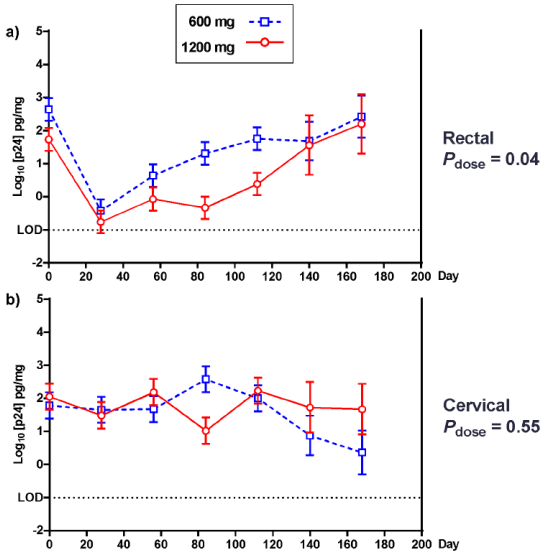
Jackson A et al. Clinical Pharmacology & Therapeutics 2014

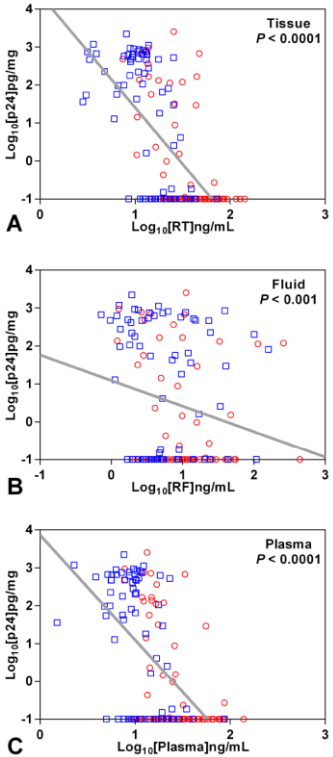
MWRI-01 Study



McGowan I et al. Lancet HIV 2016

Rilpivirine PK/PD





McGowan I et al. Lancet HIV 2016

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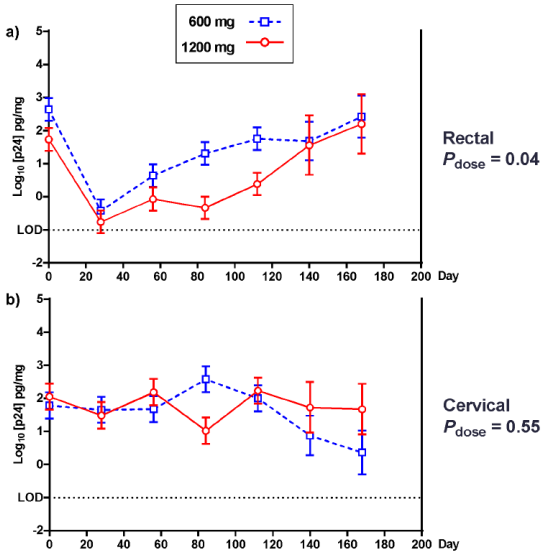
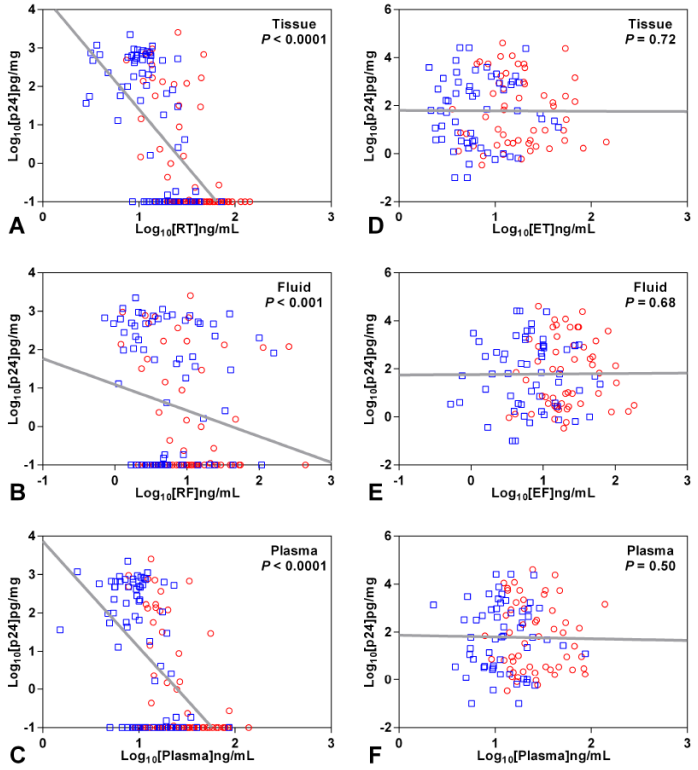
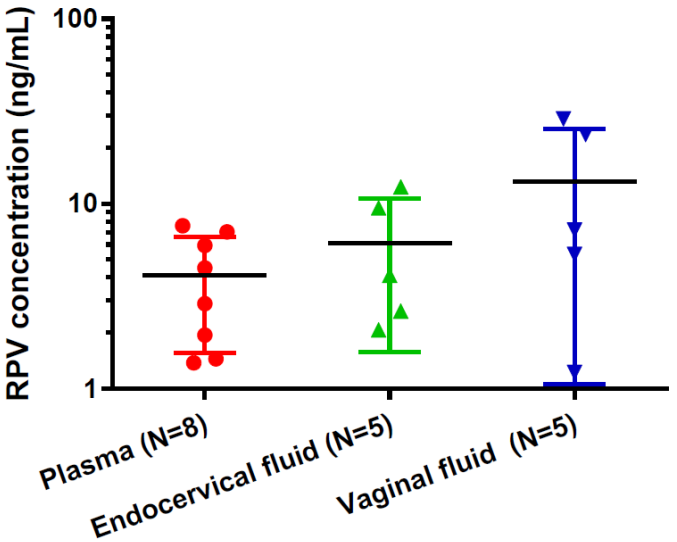




McGowan I et al. Lancet HIV 2016

Half Life of Rilpivirine LA

- RPV was detectable in 7/7 (100%) of plasma samples collected a mean of 541 days after single dose exposure to 1200 mg of RPV LA



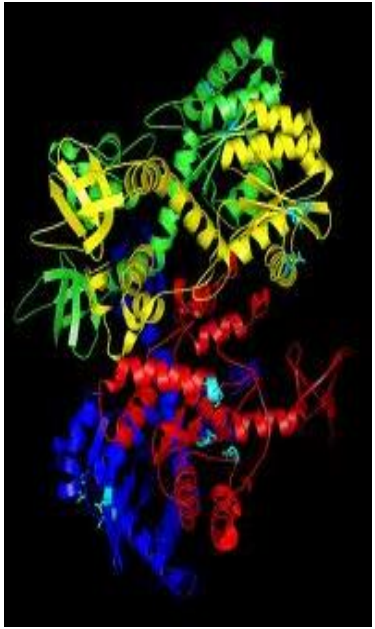
McGowan I et al. AIDS 2016

HPTN 076

- Phase 2 study of the safety and acceptability of rilpivirine LA in women
- 136 women enrolled in the US, South Africa, and Zimbabwe
- Oral run in phase followed by six injections of 1200 mg of rilpivirine LA
- Study closed to accrual and ongoing

Cabotegravir

- Integrase inhibitor analogue of dolutegravir
- Oral dose ≤ 30mg
- Highly protein bound
  - PA IC_{90}: 166ng/mL
- Formulation: 200 mg/mL
- Dosing in evolution
  - PrEP: 600-800 Q8/12 weeks
  - Treatment: 600 mg Q8 weeks



Cabotegravir LA Trials

- Treatment
  - LATTE-2 study
- Prevention
  - Phase 1 studies
  - ÉCLAIR Phase 2A study
  - HPTN 077 Phase 2 study
  - HPTN 083 Phase 3 study

ÉCLAIR Study

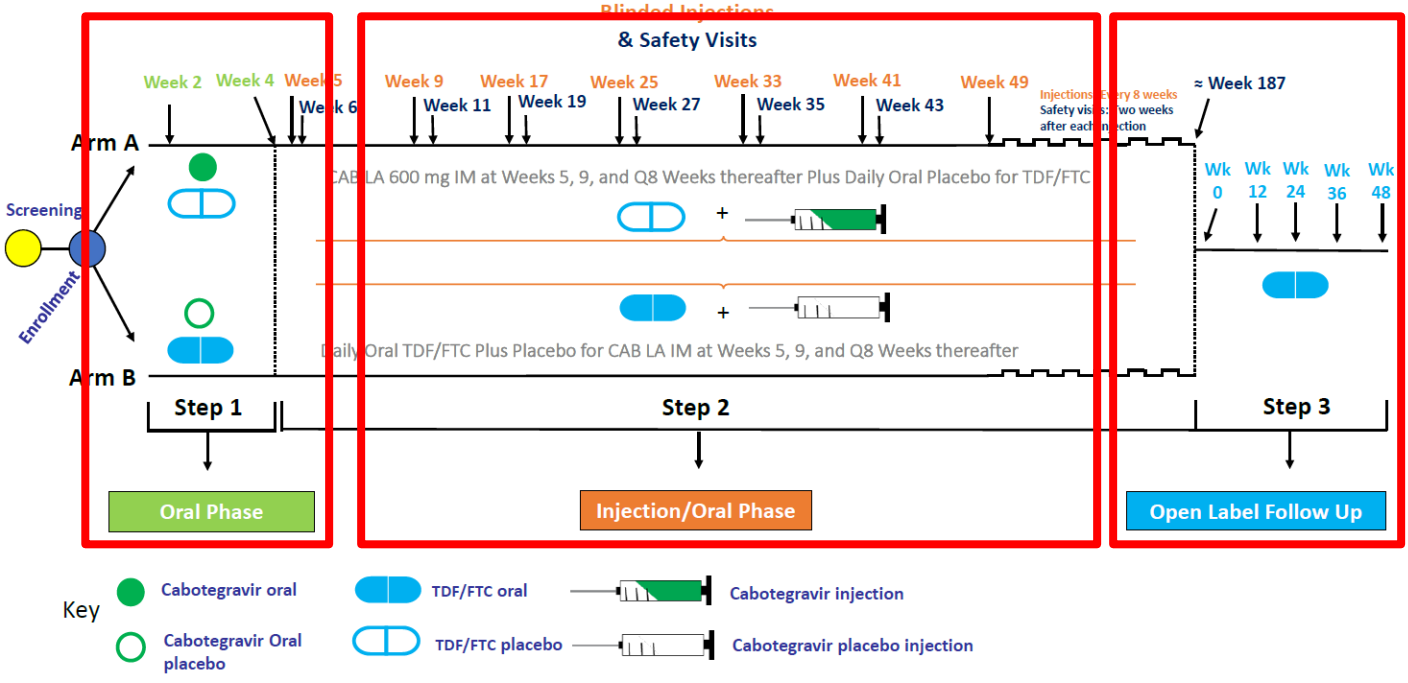
- Phase 2A study in which 127 HIV-uninfected participants were randomized to receive cabotegravir or placebo (5:1)
- Oral cabotegravir (30mg) or matching placebo tablet for four weeks followed by 800mg cabotegravir LA or placebo dosed once every 12 weeks for three cycles.

Markowitz M et al. CROI 2016

HPTN 077 Study

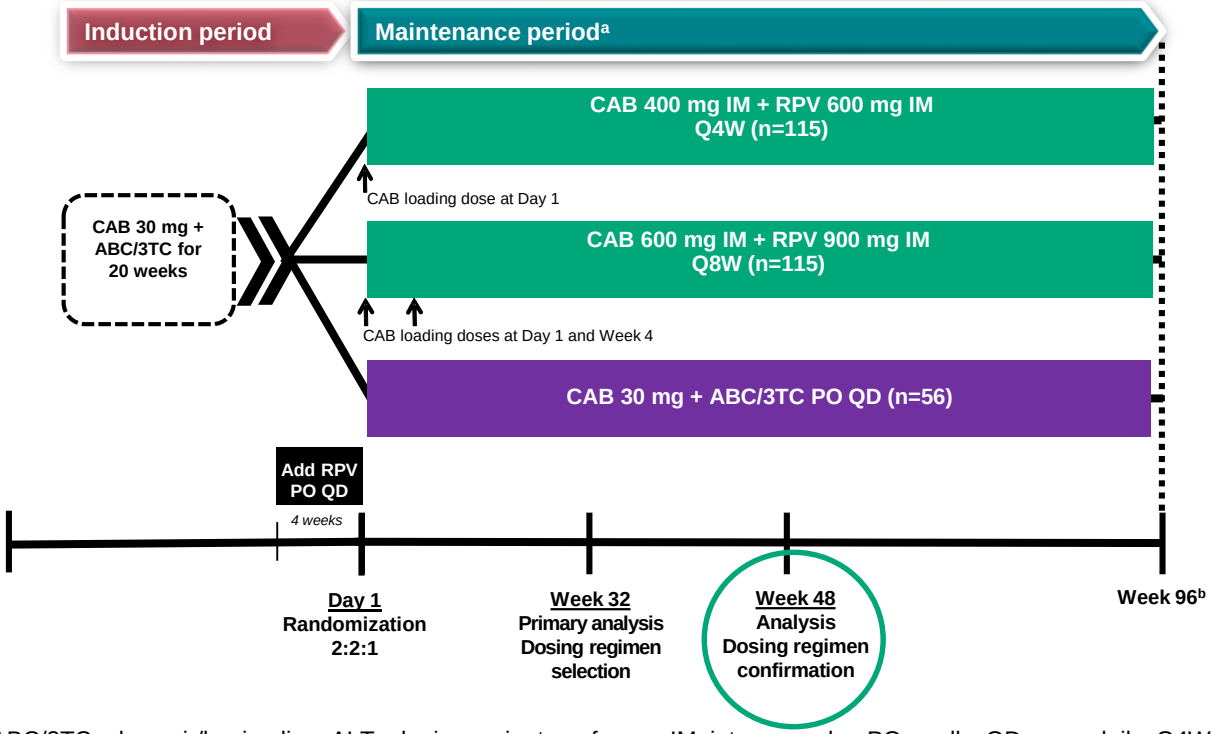
- Phase 2A evaluation of cabotegravir LA in low risk men and women
- Trial sites in the US, Brazil, Malawi, and South Africa
- Four week oral run in followed by IM injections
  - Cohort 1: 800 mg Q12 weeks x 3
  - Cohort 2: 600 mg x 2 Q4 weeks then 600 mg x 3 Q8 weeks
- Current status: closed to accrual

HPTN-083 Study



LA Antiretroviral Treatment Trials

LATTE-2 Study Design



ABC/3TC, abacavir/lamivudine; ALT, alanine aminotransferase; IM, intramuscular; PO, orally; QD, once daily; Q4W, every 4 weeks; Q8W, every 8 weeks; ULN, upper limit of normal. [a]Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period. [b]Subjects can elect to enter Q4W and Q8W LA Extension Phase beyond Week 96.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

EFdA

- Potent nucleoside RTI derived from soy
- 10 mg dose associated with 1.64 log reduction in viral load
- Allows for once weekly dosing
- $T^{1/2}$ in PBMC 103 hours
- LA formulation might last 1 year

Adherence and Tolerability of LA Antiretrovirals

Adherence to LA Antiretrovirals

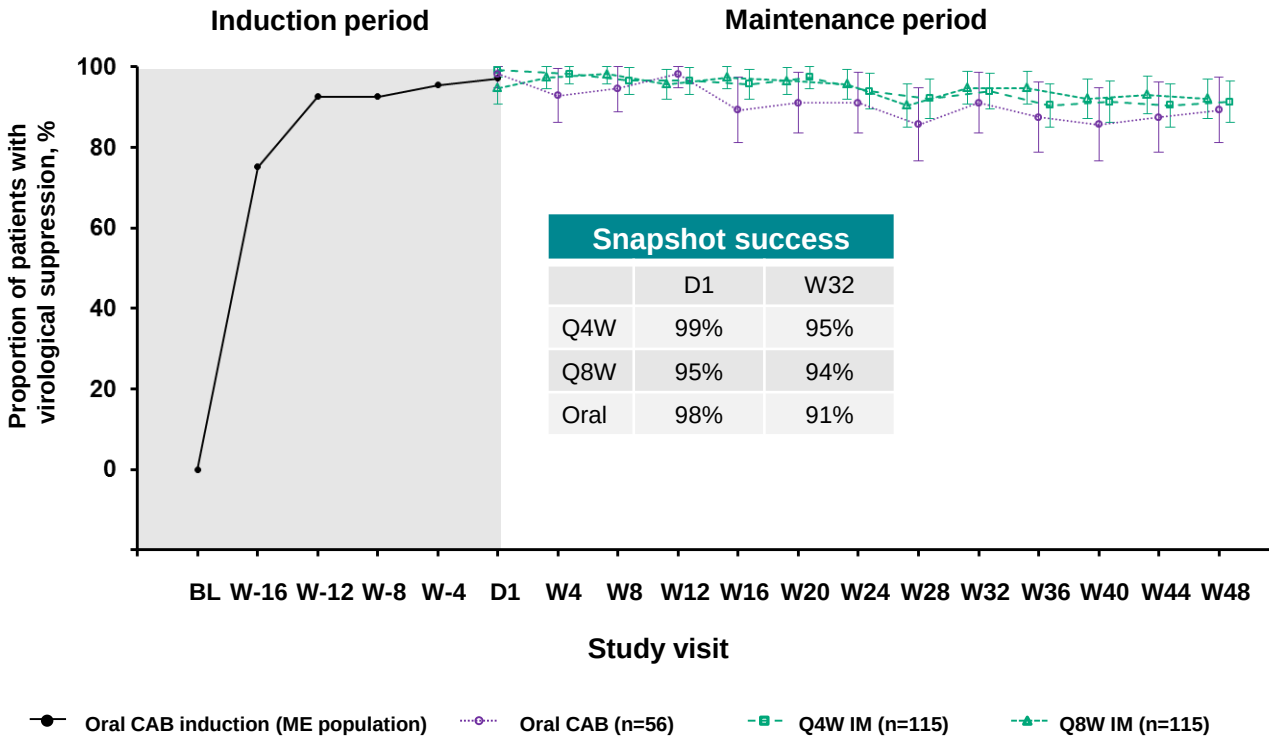
- Rilpivirine LA and cabotegravir LA have only been evaluated in the context of clinical trials
- Adherence data may vary in the real world and be influenced by treatments indication
  - Treatment versus prevention
- Adherence may be better when LA antiretrovirals are used for treatment

The Patient's Perspective

- *It seems to me that it's much better because you simply **don't have to worry about anything**. If you go on a trip, you don't have to bring your pills or take anything at all along. It's just that. You come once a month and you're done. You follow your "**normal life**". You come once a month. **You get the shot and it's over.** You don't have to be thinking everyday …oh I forgot to take the pill. Or …when did I take it last... You just don't worry about anything. In reality, taking the pill everyday keeps it present [HIV]…you have it more present…and the shot is just once a month…you remember it when you come in and the rest of the time you **can basically forget it**.*-Spain, MSM

LATTE-2 Study

LATTE-2 Week 48 Results



Snapshot success

	D1	W32
Q4W	99%	95%
Q8W	95%	94%
Oral	98%	91%

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.

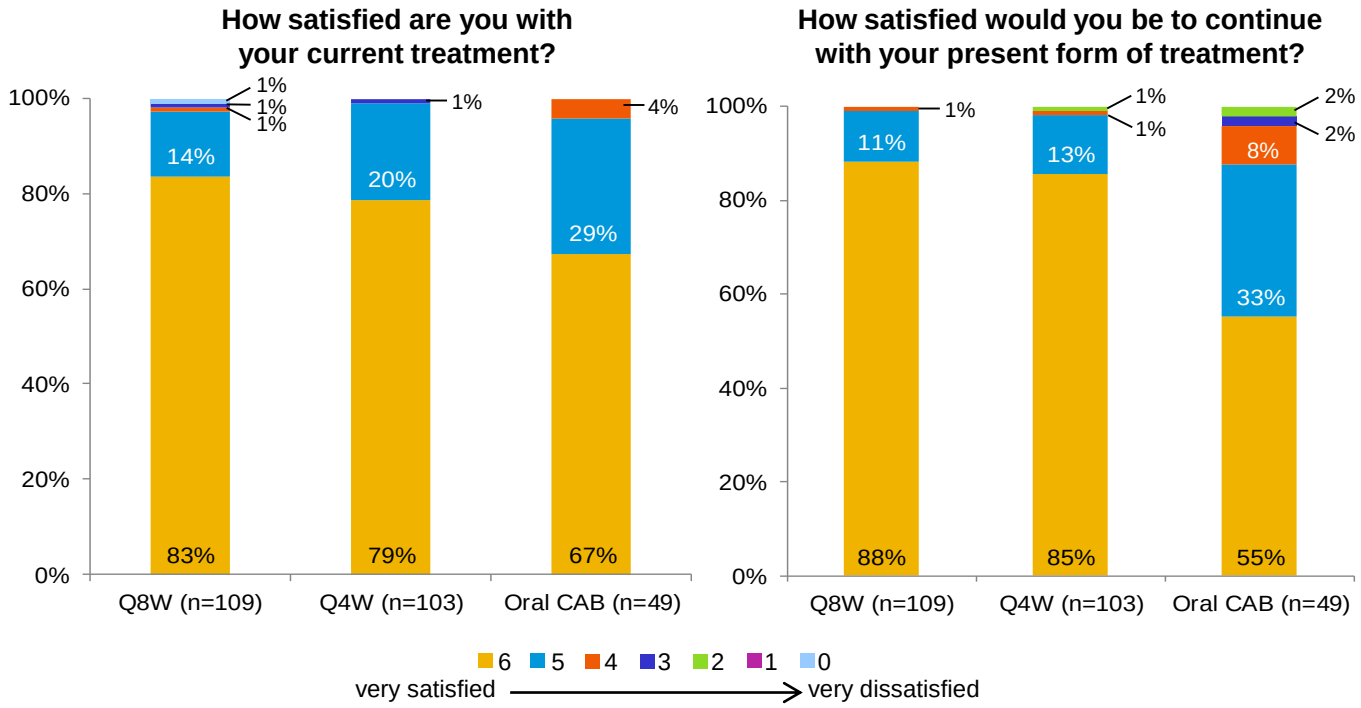
Tolerability of LA Antiretrovirals

MWRI-01 Study

- Participants reported acceptable levels of anxiety related to injections
- Anxiety was significant lower among women than men
- Barriers to uptake
  - Costs and potential side effects
  - Fear of needles not a major concern

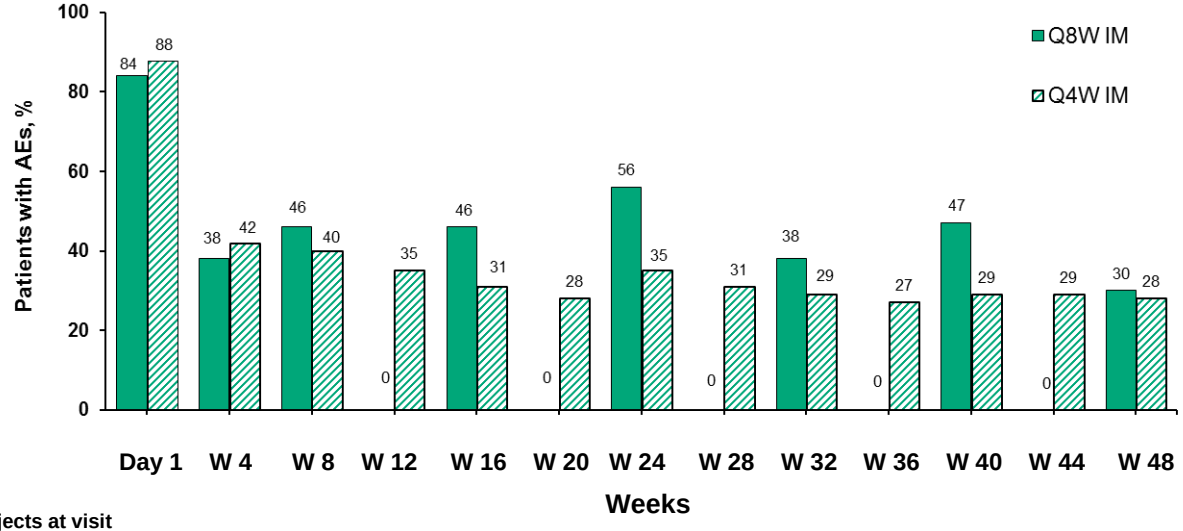
McGowan I et al. AIDS 2016

Reported Outcomes at Week 48



LATTE-2 study: Margolis D et al. AIDS 2016

Injection Site Reactions

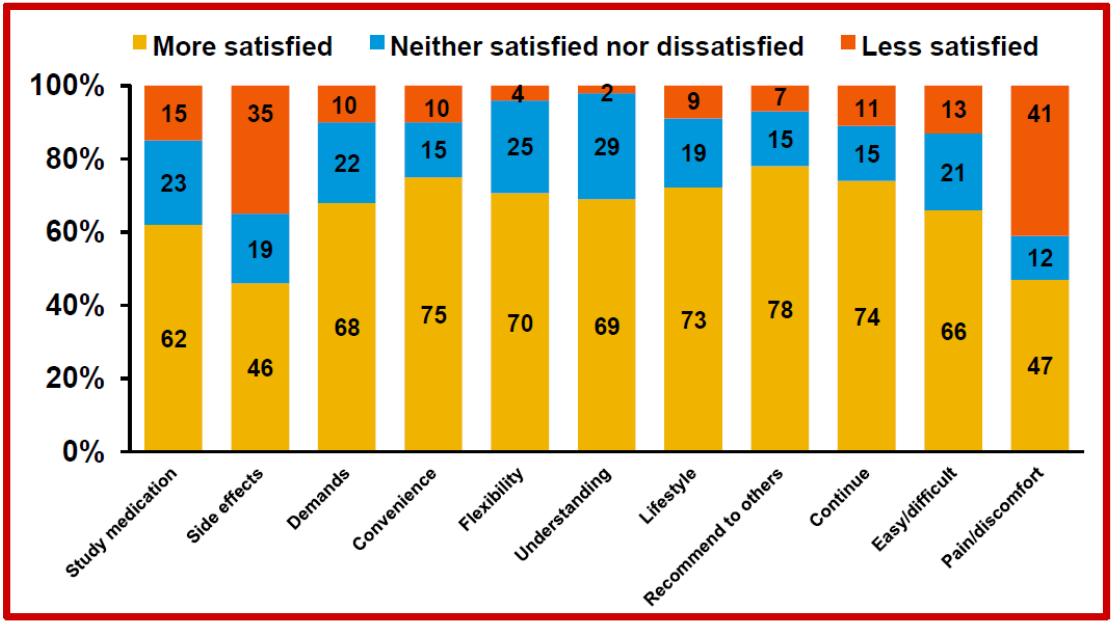


Subjects at visit

	Day 1	W 4	W 8	W 12	W 16	W 20	W 24	W 28	W 32	W 36	W 40	W 44	W 48
Q8W IM	115	115	114	113	113	113	113	112	112	112	112	112	111
Q4W IM	115	115	115	114	112	111	109	109	108	107	106	105	104

LATTE-2 study: Margolis D et al. AIDS 2016

LA Versus Oral Antiretrovirals



Éclair study: Murray M et al. CROI 2016

ÉCLAIR Study Acceptability Data

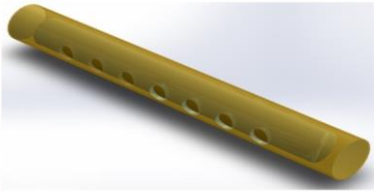
"I'm thinking why not do injectable PrEP because there could be that one night where you're not even planning for that, you're like oh wait I have to take pills for a week before I even consider doing this. Because for men who have sex with men, being spontaneous is there. The hookup culture is so prevalent, where I think it's just smarter to take injectable PrEP." -MSM, SF

"Oh totally, especially if they're already on PrEP, on Truvada, I would definitely recommend this as an alternative. And the fact that they don't have to remember to take it every day, I think would make a big difference and people probably don't need to be convinced very hard, or very much, to make the switch". - MSM, SF

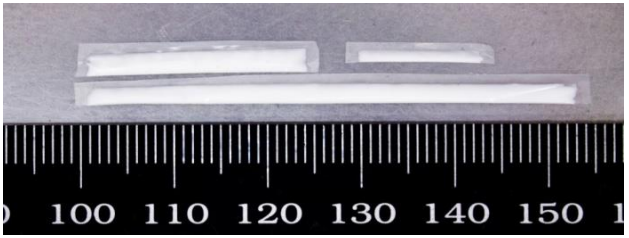
Kerrigan D et al. AIDS 2016

Looking Towards the Future

Implantable LA Antiretrovirals



Tenofovir alafenamide silicone tubing implant[1]



Tenofovir alafenamide biodegradable implant[2]

[1]Gunawardana M et al. Antimicrob Agents Chemother 2015
[2]Schlesinger EB et al. Pharm Res 2016

Summary

- LA antiretroviral therapy being developed for both treatment and prevention indications
- Acceptability profile supports further development of LA antiretrovirals
- May play a critical role in de-stigmatizing use of antiretroviral therapy and helping individuals with adherence challenges

Acknowledgements

- ViiV Healthcare / GSK
  - William Spreen
  - David Margolis
  - Alex Rinehart
- Janssen R & D
  - Peter Williams