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

Screening Visit

Baseline Visit
- Rilpivirine 1200 or 600 mg
- Cervicovaginal Rectal fluid & tissue
- Compartmental PK & explant challenge

Follow-up Visits
- Monthly for up to 6 months
- Cervicovaginal Rectal fluid & tissue
- Compartmental PK & explant challenge

Rilpivirine PK/PD

Rilpivirine PK/PD

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
Integrase inhibitor analogue of dolutegravir

Oral dose $\leq$ 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

Arm A
- Week 2: Cabotegravir oral
- Week 4: Cabotegravir oral
- Week 5: CAB LA 600 mg IM
- Week 6: CAB LA 600 mg IM
- Week 9: CAB LA 600 mg IM
- Week 11: CAB LA 600 mg IM
- Week 17: CAB LA 600 mg IM
- Week 19: CAB LA 600 mg IM
- Week 25: CAB LA 600 mg IM
- Week 27: CAB LA 600 mg IM
- Week 33: CAB LA 600 mg IM
- Week 35: CAB LA 600 mg IM
- Week 41: CAB LA 600 mg IM
- Week 43: CAB LA 600 mg IM
- Week 49: CAB LA 600 mg IM
- Open Label Follow Up

Arm B
- Week 0: Oral placebo
- Week 12: Oral placebo
- Week 24: Oral placebo
- Week 36: Oral placebo
- Week 48: Oral placebo

Key:
- Green: Cabotegravir oral
- Blue: TDF/FTC oral
- Orange: CAB LA IM
- Yellow: CAB LA 600 mg IM
- Light green: Cabotegravir injection
- Dark green: TDF/FTC injection
- Black: Placebo injection

Safety visits:
- Week 0: 0 weeks after each injection
- Week 12: 8 weeks after each injection
- Week 24: 8 weeks after each injection
- Week 36: 8 weeks after each injection
- Week 48: 8 weeks after each injection

Step 1: Oral Phase
Step 2: Injection/Oral Phase
Step 3: Open Label Follow Up
LA Antiretroviral Treatment Trials
LATTE-2 Study Design

**Induction period**

- CAB 30 mg + ABC/3TC for 20 weeks

**Maintenance period**

- CAB 400 mg IM + RPV 600 mg IM Q4W (n=115)
  - CAB loading dose at Day 1
  - CAB loading doses at Day 1 and Week 4
  - CAB 30 mg + ABC/3TC PO QD (n=56)
  - Add RPV PO QD 4 weeks

- CAB 600 mg IM + RPV 900 mg IM Q8W (n=115)

**Weeks**

- Day 1 Randomization 2:2:1
- Week 32 Primary analysis Dosing regimen selection
- Week 48 Analysis Dosing regimen confirmation
- Week 96

**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.**

- Subjects who withdrew after at least 1 IM dose entered the long-term follow-up period.
- 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
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 Week 48 Results

Induction period

Maintenance period

Study visit

Oral CAB induction (ME population)

Oral CAB (n=56)

Q4W IM (n=115)

Q8W IM (n=115)

Proportion of patients with virological suppression, %

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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

How satisfied are you with your current treatment?

- Q8W (n=109): 83%
- Q4W (n=103): 79%
- Oral CAB (n=49): 67%

- 83% 1% 1%
- 79% 1% 4%
- 67% 20% 29%

How satisfied would you be to continue with your present form of treatment?

- Q8W (n=109): 88%
- Q4W (n=103): 85%
- Oral CAB (n=49): 55%

- 88% 1% 1%
- 85% 13% 1%
- 55% 8% 2%

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

Subjects at visit

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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
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

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  - William Spreen
  - David Margolis
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