Long-Acting Antiretroviral Treatment in relation to the 3rd 90

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Barts Health NHS Trust
I have received:

- Honoraria for lectures and advisory boards
- Travel grants
- Research grants to my institution

From Gilead Sciences, Janssen, MSD and Viiv Healthcare
 Technologies for drug delivery

- Long-acting injection
- Microneedle drug patch
- Subdermal implant
- Oral Nanomedicine
- Wearable infusion pump
- Vaginal ring

1. Lessons from other specialties

2. Long-acting injectable ART

3. Long-acting implantable ART

4. Horizon scanning
What have implantable and injectable drugs done for other specialties?

- CONTRACEPTION
- PSYCHIATRY
- OSTEOPOROSIS
Women prefer long-acting reversible contraception (LARC)

Uptake of contraceptive methods

**US: Contraception method**

- Long-acting
- Other

**Chad: Contraception method**

- Long-acting
- Other

**ECHO trial:** LARC led to low pregnancy rates. Strong justification to improve access

-Peipert et al. Obstet Gynecol 2012; 120:6
-Ononol AS MOAX01013LB  Mexico City July 21-24 2019
-Rattan J Global Health Sci Prac 2016: 4 Suppl 2: S5-S20
What have implantable and injectable drugs done for other specialties?

Adherence to oral bisphosphonates is low and decreases over time.

Once-yearly infusion improves adherence.

Helpful for cognitive impairment, polypharmacy, immobility.

What have implantable and injectable drugs done for other specialties?

Reduces relapse rate and hospitalizations

Improves patient satisfaction

Avoids first pass metabolism, reduces DDIs

Demand for long-acting ART in HIV?

>60% interested in once/month

Interest in New Method by Timing

- **Once/wk**
  - Definitely Would
  - Probably Would
  - Probably Not
  - Definitely Not

- **Once/2wks**
  - Definitely Would
  - Probably Would
  - Probably Not
  - Definitely Not

- **Once/month**
  - Definitely Would
  - Probably Would
  - Probably Not
  - Definitely Not

Adapted from Williams et al Nanomedicine 2012.
Reducing long-term effects and longer treatment intervals important
Score (100 = average importance)

- Reduces long-term effects of HIV medicine on my body
- Longer lasting so I can take treatment less often
- Fewer side effects
- Can take less HIV medicine and get the same effect
- Does not cause DDIs
- Fewer pills each day
- No food restrictions or requirements
- Smaller pill sizes

AE, adverse event; PLHIV, people living with HIV.
Do we really need 3 drugs for 50 years?
Yearly intake of ARV by regimen over 50 years

Once daily single tablet = 17kg

2 monthly injection = 600g
What does LA injectable ART involve?

1. What ATLAS and FLAIR phase III trials show
2. Patient Reported Outcomes
3. What else do we need to know?
4. Planned studies for CAB/RPV
Long-Acting Injectable (LA) ART:
Cabotegravir (CAB) + Rilpivirine (RPV)

- LA: slow release of the active drug or continued absorption of the drug over an extended time
Long Acting injectables - What’s the attraction?

- Infrequent dosing
- Lower overall drug dose
- Prevents poor pill-taking, helps pill fatigue
- Potential for directly observed therapy
- Protects health privacy and treatment related stigma
- Can avoid certain drug interactions eg with mineral supplements like iron, antacids, acid lowering drugs
- **Children**: NO fixed dose oral combinations for children under 25 kg
Long Acting injectables - some key issues

- Not all drugs can be combined
- Must be compatible with small injection volume
- Injection volume is 2ml for each drug
- Must be injected into the buttocks
- Rilpivirine has a cold chain (needs to be stored at -4C)
- What to do about mixed doses
- Long term drug levels at end of dosing interval
- Side effect management as drug cant be removed
Pooled analysis ATLAS and FLAIR studies (wk 48)
No differences in efficacy between oral and injectable ART

Virologic outcomes

*Adjusted for sex and baseline third agent class.

CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.

Overton E IAS MOPEB257 Mexico City July 21-24 2019
Participant Reported Outcomes: Patients preferred LA (ATLAS)

- Several different PRO scores evaluated
- ACCEPT score significantly better after switch to CAB/RPV (all time points)
- Acceptability of ISR’s and pain scored ‘totally/very acceptable’ by 90% and 86%
- Withdrawals due to ISR’s: 4 (1%)
- HIVTSQ score improvements from baseline were significant at week 24 and 44 and met the threshold for the minimally clinically important difference (MCID)
- Preference question: 97% (266/273) of responding participants preferred CAB/RPV*

* ITT group 273/308 had a recorded response to the preference question at week 48; 266/308 86% preferred CAB/RPV.
Long tail: IM CAB drug detectable 48 weeks after single injection

CAB 5 mg/day PO, $C_{\text{tau}} = 0.6 \mu g/mL$

PA-IC$_{90}$(0.17 $\mu g/mL$)

CAB LA apparent $t_{1/2} \sim 40$ days vs
CAB oral $t_{1/2} \sim 40$ hours

$4 \times$ PA-IC$_{90}$ (0.664 $\mu g/mL$)
Long Tail: IM RPV detectable 12-24 months post single injection

RPV found in plasma and genital fluid 12-24 months post SD LA

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Time since Injection (days)</th>
<th>Rilpivirine concentration* (ng/ml)</th>
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<tbody>
<tr>
<td>1</td>
<td>400</td>
<td>7.5</td>
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<tr>
<td>9</td>
<td>830</td>
<td>1.6</td>
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</table>

*RPV target concentration is 12.2ng/ml

Adapted from McGowan I et al; HIVR4P October 2016
CAB LA tail — women have detectable levels longer than men

Adapted from Landovitz, R et al. HIV R4P, Madrid, 2018. Abstract #OA15.06LB.
Can be given in severe renal impairment and moderate hepatic impairment

Severe renal impairment

Moderate hepatic impairment


TB: LA CAB / RPV cant be given with rifampicin

RIFAMPICIN 600 QD CAB 400 Q4

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Concentration (mg/L)</th>
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<tr>
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<tr>
<td>14</td>
<td>2.0</td>
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<tr>
<td>21</td>
<td>1.5</td>
</tr>
<tr>
<td>28</td>
<td>1.0</td>
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41-46% predicted drop

RIFAMPICIN 600 QD RPV 600 Q4

<table>
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<tr>
<th>Time (days)</th>
<th>Concentration (mg/L)</th>
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<td>0.07</td>
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<td>21</td>
<td>0.05</td>
</tr>
<tr>
<td>28</td>
<td>0.04</td>
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</tbody>
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82% predicted drop

CAB Alone

CAB + 600 mg RIF
TB: CAB can be given with rifabutin

No significant effects on PK predicted

Oral CAB 30mg QD plus Rifabutin 300 mg QD.

<table>
<thead>
<tr>
<th>CAB AUC</th>
<th>CAB $C_{\text{max}}$</th>
<th>CAB $C_{\text{trough}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.79 (0.74, 0.83)</td>
<td>0.83 (0.76, 0.90)</td>
<td>0.74 (0.70, 0.78)</td>
</tr>
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Geometric least squares values of CAB+RBT vs. CAB alone.
Advantages vs disadvantages to LA injectables?
‘Who is the ideal patient for LA CAB/RPV?’
Long-acting Injectables - the logistics

- Monthly or every other month administration: effect on clinic staffing.
- Injection administration: training in Z-track technique; privacy (not like a shot in the arm).
- Clinic visit non-adherence: what steps (proactive or after-the-fact) do you take?
- Costs
  - What is the cost of the drugs?
  - Who pays for the drug?
  - Who provides the drug, and inventory implications?
  - Insurance, administration location and patient co-pays?
- Alternative delivery approaches: pharmacy, home health, mobile units?

The need is to have a delivery approach that is as convenient as the long-acting injectable.
Upcoming/ongoing CAB/RPV studies for HIV treatment

CAB + RPV

- 2 monthly IM: ATLAS 2M (n=1200)
- Children/Adolescents: MOCHA 12-18 (n=150)
- Poor Adherers ACTG 5359
- Implementation study (US): CUSTOMIZE
  - N=135
  - one year single arm study
Implantable devices

Subdermal implant
Implant advantages and disadvantages

Advantages
- Removable at end of treatment and for adverse effects
- Potential to provide therapy for years with a single insertion
  - Inert, non-degradable options available or biodegradable options in development
- Potentially improved and more stable pharmacokinetics
- Palpable under skin indicates receipt of drug

Disadvantages
- Minor sterile medical procedure required for insertion (and removal)
- Palpation will not determine duration of use
- Complicated regulatory environment
- Generic marketplace
Patches and oral nano-formulations

LA microarray patches

- Monthly CAB, weekly RPV
- 30cm²

Oral once/wk drug delivery system
- Testing in swine models
- Drugs DTG CBV RPV

Giardiello M Nature Communications 2016
From lab bench............. to the bed side
Long-acting or extended-release antiretroviral products for HIV treatment and prevention in infants, children, adolescents, and pregnant and breastfeeding women: knowledge gaps and research priorities

Prof Sharon Nachman, MD  Claire L Townsend, PhD  Prof Elaine J Abrams, MD  Moherndren Archary, MBCHB  Prof Edmund Capparelli, PhD  Polly Clayden  et al.  Show all authors

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The future, everywhere!
Thank you

- David Back
- Stephanie Barrett
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- Mark Shaefer
- William Spreen
- John Wong

Emerging information on long acting formulations: www.leapresources.org
QUESTIONS

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