Long Acting HIV Drugs for Prevention: Data and Potential implementation

Laura Waters
Consultant HIV/GU Medicine
CNWL, Mortimer Market Centre, UK
Content

- Importance of adherence for PrEP
- Vaginal rings
- Injectables
- The future
  - Broadly neutralising antibodies
  - Implants
  - Microneedles
ADHERENCE
Adherence really matters: PrEP

7 Pills Per Week

- 94% Best Protection
- 99% Best Protection

4 Pills Per Week

- 61% Good Protection
- 90% Better Protection

2 Pills Per Week

- 6% Poor Protection
- 76% Good Protection

Adapted from Delany-Moretlwe S. IAS 2018, Amsterdam: Hanscom, JAIDS 2016; Fonner, AIDS 2016
PrEP adherence in trials

• **Daily oral tablets**
  – Adherence to visits may not = adherence to medication
  – Several PrEP trials show reports >> reality

• **Injectables (so far)**
  – Visit = injection = adherence

• **Vaginal rings**....
VAGINAL RINGS
Dapivirine most advanced: two phase 3 RCTs of monthly ring vs placebo

• **ASPIRE**¹ (n=2629)
  – 27% reduction in new HIV in active arm (56% if restricted to >21s with better adherence, no significant reduction in women <21)
  – Similar adverse vents and HIV resistance in both arms

• **RING**² (n=1959)
  – HIV incidence 31% lower in dapivirine group arm (HR 0.69; P=0.04)
  – NNRTI RAMs: 18.2% dapivirine arm vs 16.1%
  – Serious adverse events more common on dapivirine (2.9% vs 0.9%) with no clear pattern

ASPIRE: adherence is not just a pill issue

- Analysis of 1211 women on active product
- Plasma & ring concentrations vs self-report
  - Correlation between PK & self-report BUT....
  - PK non-adherence more frequent than self-report, particularly for 18-21 year olds vs older women
  - 11% 18–21 year olds and 7% of 22+ year olds who rated their ability to keep the ring inserted as good, very good or excellent were non-adherent by PK measures
Two open-label studies at CROI 2018

• **DREAM (RING rollover)**
  – Lower dapivirine concentrations in rings then in RING study & estimated 96% (vs 83% in RING) had used ring for at least some of the preceding 4 weeks
  – HIV incidence 59% lower than predicted

• **HOPE (ASPIRE rollover)**
  – 1299/1407 (92%) eligible accepted the ring rollover
  – HIV incidence 1.9/100PY vs anticipated 4.1/100PY

• **Both completed early 2019, final results awaited**

Tenofovir ring studies

• Animal studies promising
  – Good PK, *slight-moderate increase inflammatory infiltrates*

• **Phase 1 TDF intra-vaginal ring vs placebo trial**
  stopped early when 17/40 women recruited:
  – 8/12 women in TDF arm experienced **grade 1 vaginal ulceration** near the ring at average 32 days into ring use
  – No ulceration in placebo arm (n=5)
  – Higher inflammatory markers in TDF vs placebo arm

• **MTN-038**
  – Phase 1, 90-day study of TDF vs placebo ring; results 2020
Vaginal flora: impact on PK & efficacy

• **TOPICAL: FAME studies**\(^3\)
  - TFV gel: vaginal & plasma concentrations & efficacy reduced by dysbiosis
  - Dapivirine film/gel: concentrations not affected

• **ORAL: PARTNERS-PREP**\(^1\)
  - No impact of vaginal dysbiosis on oral PrEP efficacy

• **DAPIVIRINE VAGINAL RING: ASPIRE trial**\(^2\)
  - No impact of flora on vaginal or plasma concentrations
  - No difference in efficacy by vaginal flora

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Combined ring preparations

- **Combined TDF + FTC ring**
  - Protective in macaques
  - MTN-038: phase 1, results 2020
- **Phase 2a 90 day safety study in Kenya:**
  - TFV vs TFV/LNG vs placebo
  - Estimated completion July 2019
- **Will TDF concentrations from vaginal ring be impacted by vaginal flora?**
- **Nuvaring promotes lactobacilli-dominated vaginal flora in a population with high BV prevalence**

Crucitti T et al PLOS ONE 13(7): e0201003.
Practical challenges

- Too early to know?
- Adherence
- Safety
- Impact of vaginal flora on NRTI rings
- Impact of topical PrEP on genital tract immunity
  - Dapivirine hydrogel impairs some markers of vaginal innate immunity more than dapivirine film..

- (AT LEAST) THREE CRUCIAL FACTORS:
  - ARV + route + vaginal flora

INJECTABLES
PK & efficacy for injectable HIV PrEP

- **IM RPV discontinued in 2017**
  - Inadequate female genital tract PK & explant suppression

- **IM CAB phase 2**
  - **ECLAIR**: MSM & TGW
  - **HPTN 077**: men & women

- **IM CAB phase 3**
  - **HPTN 083**: MSM & TGW
  - **HPTN 084**: cis-women
HIV-uninfected men and women at low risk for acquiring HIV infection, ages 18 to 65 (n=199)

PrEP: HPTN 077

HPTN 077: cohort 2 met PK targets for male & female participants

Cohort 1
Two 2mL (2x400mg) IM Injections every 12 Weeks

Cohort 2
One 3mL (600mg) IM Injection every 8 Weeks

Median Steady State Trough: ~1.35 ug/mL
% > 1X PA-IC90: ≥95%
% > 4X PA-IC90: ≥80%
HPTN 077: cohort 2 met PK targets for male & female participants

Median Steady State Trough: ~1.35 ug/mL
% > 1X PA-IC90: ≥95%
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Not designed for efficacy, low risk population
ECLAIR

- 12-weekly 5:1 CAB vs placebo after oral lead-in phase (n=127 men at low risk of HIV)
- Injection site reactions common
- PK suboptimal
  - Despite modelling data predicting adequate trough
- 2 new HIV diagnoses
  - 1 in placebo arm
  - 1 in CAB arm 24 weeks after last injection when plasma CAB concentrations undetectable

### HPTN 083: CAB LA 600mg

To Prevent HIV Acquisition in MSM and TGW

Landovitz and Grinsztejn, Protocol Chairs

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Daily oral CAB and TDF/FTC placebo</th>
<th>TDF/FTC and oral CAB placebo</th>
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<td></td>
<td>CAB LA at two time points 4 weeks apart and every 8 weeks thereafter and TDF/FTC placebo</td>
<td>TDF/FTC and injectable placebo at two time points 4 weeks apart and every 8 weeks thereafter</td>
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**Primary Objective:** Reduce HIV Incidence (**non-inferiority**, double blind, double dummy design)

N=4500; Study duration: Enrollment 24-30 months; follow-up ~ 4.5 years

**Enrollment goals:**
- *Minimum* 50% of US enrollment Black MSM (~ 950)
- Overall minimum 10% TGW (~ 450)
- Overall > 50% under age 30

**Results:** 2021
**HPTN 084: CAB LA 600mg**

To Prevent HIV Acquisition in Women
Delaney-Moretlwe and Hosseinipour, *Protocol Chairs*

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**Primary Objective:** Reduce HIV Incidence (*superiority*, double blind, double dummy design)

Study duration: Enrollment 24 months; follow-up up to 4.5 years, N=3200
Patients prefer injectable in ART trials, what about PrEP? HPTN 077

(Chart showing preference distribution in US and non-US groups)

Patient preferences

- Discrete choice studies: efficacy most important
- Non-oral options largely preferred
  - Particularly injectables, rings if multi-purpose
- Questions are based real & estimated attributes
- TRIO: 277 women randomised to placebo PrEP:
  - Monthly ring, monthly IM injection, daily tablet for 1 month then choice of product for 2 months
  - 85% preferred PrEP over condoms
  - 64% chose injections for phase 2
  - Adherence highest for injections

ECLAIR: CAB persists in a minority 52W after last injection

Ford et al. HIVR4P 2016; Chicago, IL. Abstract OA12.06LB.
Unanswered questions

• What will happen with delayed or missed doses?
• Covering the PK tail?
  – How long? TDM guided?
  – What with?
• Acceptability of long-term IM injections
• Impact of BMI
• Impact of additional IM injections
• Practicalities & costs of service delivery
THE FUTURE
• Rilpivirine dissolving microarray patches
• ‘Self-limiting’ but what will the tail be?
• Will the patch size be practical?
Implants

• Lots of preclinical work
  – TAF
  – Cabotegravir
  – Multipurpose implants possible

• Macaque studies of TAF/FTC implant:
  – Sustained delivery 83 days, preventative tenofovir levels within 3 days, refillable transcutaneously

Design of an Implant for Long-Acting HIV Pre-Exposure Prophylaxis: Input from South African Health Care Providers

Emily A. Krogstad, Elizabeth T. Montgomery, Millicent Atujuna, Alexandra M. Minnis, Shannon O'Rourke, Khatija Ahmed, Linda-Gail Bekker, and Ariane van der Straten
Broadly neutralising antibodies

• **Promising PrEP efficacy in animal studies**
  – Rectal, vaginal & penile exposure

• **Risk of resistance with ‘monotherapy’**
  – Combinations crucial

CONCLUSIONS
Concerns: a non-exhaustive list

1. Safety in pregnancy
   – e.g. CAB signal in animal studies

2. Drug-drug interactions
   – e.g. modelled impact of rifampicin + LA CAB at CROI 2019

3. Systemic exposure with topical methods
   – e.g. low concentrations of dapivirine in breast milk & low plasma concentrations of tenofovir following enema

4. Impact of topical methods on mucosa
   – Nonoxynol-9, lubricants
Long-acting ART: it’s a journey

ART

IMI 1-2 monthly

Less frequent IM, SC & PO drugs

Implants
Long-acting PrEP: are we heading in the wrong direction?

- Short-acting, dual function topical
- Long-acting oral, vaginal rings
- Implants & injectables
Why?!

- **For some immediate short acting PrEP preferable?**
  - Risk is not continuous
  - Event-based methods may limit toxicity
  - Short-acting methods may limit resistance

- **Link PrEP with higher risk sexual practices?**
  - Lubricant
  - Rectal douches: men reporting RAI in last 3/12 80% doused before, 27% after, 98% reported high likelihood of using an HIV-prevention douche: PrEP dissolvable in tap water with rapid onset of action ideal??
  - **IS THIS A DREAM?!**

Development of rectal enema as microbicide (DREAM)

• **DREAM: TDF enema murine studies**
  – Vehicle characteristics crucial (e.g. osmolality)

• **DREAM 01: single pre-sex TDF rectal douche**
  – 98% currently douching & 94% not currently douching would definitely or probably try a microbicide douche
  – Significantly lower plasma exposure than oral
  – Similar colon TFV-DP levels after 1 dose to 7 days consecutive rectal tenofovir gel
  – From 1 to 24 hours after dosing, median colon cell TFV-DP concentrations exceeded target inhibitory concentrations
  – Effective in ex vivo replication analyses

My dream future

• **Non-treatment agents**
  – Vaginal ring delivery HIV CCR5 inhibitor 5P12-RANTES in sheep (could this be combined with contraception?)

• **Intelligent implants**
  – Drug release adjusted to plasma concentrations
  – Option for immediate shut down without removal
  – Individualised concomitant medication
    • Depot contraception
    • STI treatment (in-built RPR monitoring?!)
Thank you!

lwaters@nhs.net
@drlaurajwaters