Overview

- A brief history of oral/LA PrEP research
- Integration of mucosal assays into oral/LA PrEP research
- Lessons learned about the performance and utility of mucosal assays in oral/LA PrEP trials
Oral PrEP
Oral PrEP

- Oral PreP with either TDF or TDF/FTC has been evaluated in eight Phase 2B/3 trials with evidence of efficacy in multiple populations
- Limited mucosal sampling has focused primarily on compartmental PK assays
- Ongoing Phase 1/2 studies have more extensive mucosal sampling
Oral PrEP Timeline

- **2010**
  - iPrEx (TDF/FTC)

- **2012**
  - FEM-PrEP (TDF/FTC)
  - TDF2 (TDF/FTC)
  - Partners PrEP (TDF, TDF/FTC)
  - Bangkok Tenofovir Study (TDF)

- **2013**
  - Bangkok Tenofovir Study (TDF)

- **2015**
  - VOICE (TDF, TDF/FTC)
  - PROUD (TDF/FTC)
  - Ipergay (TDF/FTC)
  - HPTN-069 (Maraviroc, FTC, TDF)
  - CHARM-03 (Maraviroc)
Mucosal Assays in Oral PrEP

- RMP-02/MTN-006 (single dose TDF)
  - Compartmental PK
  - Mucosal safety including flow cytometry
  - Explant infection

- HPTN-069
  - CCR5 genotype
  - Compartmental PK
  - GALT flow cytometry
  - Explant infection
- Early detection of FTC in rectal tissue at high concentrations similar to HIV-infected patients on ART
- TFV is only detectable at 24h post drug intake at high concentrations
Long Acting (LA) PrEP
LA PrEP

- LA antiretrovirals are being developed for treatment and prevention indications
- Goal is to circumvent adherence challenges associated with the use of oral antiretrovirals
- LA Platforms
  - Injectable agents (rilpivirine and cabotegravir)
  - Implantable device (multiple preclinical leads)
<table>
<thead>
<tr>
<th>Candidate</th>
<th>Class of Drug</th>
<th>Current Stage of development</th>
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<tbody>
<tr>
<td>Rilpivirine</td>
<td>NNRTI</td>
<td>Licensed for treatment of HIV infection</td>
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<tr>
<td>Dapivirine</td>
<td>NNRTI</td>
<td>Phase 3</td>
</tr>
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<td>Tenofovir alafenamide</td>
<td>NRTI</td>
<td>Phase 3</td>
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<td>Cabotegravir</td>
<td>INSTI</td>
<td>Phase 2</td>
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<td>Elvitegravir</td>
<td>INSTI</td>
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<td>VRC01</td>
<td>Monoclonal antibody</td>
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<td>5P12-RANTES</td>
<td>CCR5 antagonist</td>
<td>Preclinical</td>
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<tr>
<td>Griffithsin</td>
<td>Lectin</td>
<td>Preclinical</td>
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Rilpivirine LA Timeline

- 2007: Rilpivirine (Phase 1)
- 2009: Rilpivirine (Phase 1)
- 2011: Rilpivirine (Phase 1)
- 2012: SSAT040 Rilpivirine (Phase 1)
- 2013: Rilpivirine Cabotegravir (Phase 1)
- 2015: MWRI-01 Rilpivirine (Phase 1)
- 2015: HPTN-076 Rilpivirine (Phase 2)
- 2015: LATTE-2 Rilpivirine Cabotegravir (Phase 2B)
Cabotegravir LA Timeline

2012
Cabotegravir (Phase 1)

2013
Rilpivirine Cabotegravir (Phase 1)

2014
Cabotegravir (Phase 1)

2015
ÉCLAIR Cabotegravir (Phase 2A)

2015
LATTE-2 Cabotegravir Rilpivirine (Phase 2B)

2015
HPTN-077 Cabotegravir (Phase 2A)

2015
HPTN-083 Cabotegravir (Phase 2B/3)
Cabotegravir Compartmental PK

<table>
<thead>
<tr>
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<th>Plasma or Tissue (ng/mL or ng/g)</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td></td>
<td>500</td>
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<td></td>
<td>1000</td>
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<td></td>
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<tr>
<td></td>
<td>2000</td>
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<tr>
<td></td>
<td>2500</td>
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Plasma | Rectal Tissue

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tissue / Plasma Ratio Unsplit, Split</th>
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<tr>
<td>Cervical</td>
<td>0.16, 0.20</td>
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<tr>
<td>Vaginal</td>
<td>0.19, 0.28</td>
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<tr>
<td>Rectal</td>
<td>NQ, 0.08</td>
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Unsplit Split
NHP Cabotegravir Data

Andrews CD et al. Science 2014
Mucosal Assays in LA PrEP

- Rilpivirine studies
  - SSAT040 & MWRI-01
  - Compartmental PK
  - Explant infection
  - Rectal fluid PD

- Cabotegravir studies
  - Compartmental PK
Implantable PrEP

- Products still in preclinical phase of development


Thin film polymer device. PK data in rats anticipated in 2015. Ariane van der Straten USAID grant
Lessons Learned
Lessons Learned

- **Oral PrEP**
  - Very limited mucosal assays in completed oral PrEP studies
  - More extensive data being generated in ongoing studies (HPTN-069 & CHARM-03)

- **LA PrEP**
  - Compartmental PK and explant challenge data available for rilpivirine (SSAT040 & MWRI-01 Studies)
  - Limited PK data for cabotegravir
Summary

- Oral PrEP established as safe and effective form of HIV prevention
  - Mucosal assays of limited value unless evaluating new drug classes in Phase 1/2 studies

- Mucosal assays may be of significant benefit in the development of LA injectable and implantable PrEP
  - Compartmental PK
  - Explant infection studies
Acknowledgements

The Microbicide Trials Network is funded by the National Institute of Allergy and Infectious Diseases (UM1AI068633, UM1AI068615, UM1AI106707), with co-funding from the National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health.