Long-acting Treatment with Antiretrovirals

Saye Khoo,
University of Liverpool, UK

Declaration of Interests
www.hiv-druginteractions.org & www.hep-druginteractions.org
Receives sponsorship from AbbVie, Merck, BMS, Janssen, Gilead, ViiV.
Editorial content remains independent.
Research funding, travel grants, speakers bureau from Gilead, AbbVie, ViiV, Merck, Janssen

See https://www.liverpool.ac.uk/translational-medicine/staff/saye-khoo/external-engagement/
• Why long-acting?

• Potency, delivery, pharmacology

• Long-acting Antiretrovirals for Treatment
  - rilpivirine
  - cabotegravir
  - other agents

• PreP

• Real-life challenges
Long – Acting Antiretrovirals

Why ‘long-acting’?

- Improve adherence, convenience (work, travel, etc)
- ‘Fragile’ populations
- Psychological benefit, pill fatigue etc
- Improves bioavailability
- PK ‘smoothing’, reduced variability
- Eliminates food effects
- Eliminates gut-based DDIs
- Improve GI tolerability
- Public health benefits – community VLs, transmissions
Long – Acting Antiretrovirals

- **Terminology**
  - ‘acting’ is not the same as ‘release’ (prolonged, modified, sustained, controlled)

- **Pharmacology**
  - drug potency
  - rational drug combinations
  - physiochemical characteristics, solubility, release characteristics
  - injection volume and drug loading
  - formulation characteristics
  - route of administration s/c, im, iv, oral
  - oral formulation available (lead-in, lead-out, bridging)
  - tissue partitioning (for PreP)
High potency underpins the LA approach
Long – Acting Formulations

CABOTEGRAVIR

- UGT1A1 (minor 1A9) metabolism
- Low DDI potential as victim or perpetrator
- Animal studies support PreP

- Loading dose increased to 600mg im
- Treatment dose 400mg im q 4w
- Q 8w not abandoned

RILPIVIRINE LA

- Terminal T½ 30-90 days (G001)
- CYP3A4 substrate
- Low DDI potential as victim or perpetrator
- Animal studies support PreP

- Loading dose increased to 900mg im
- Treatment dose 600mg im q 4w
- Q 8w not abandoned
Rilpivirine - LA

- Wet bead milling (200nm)
- Different formulations explored (G001)
- sc administration significantly higher rates of ISR
- im administration better tolerated, better absorbed
- Cold chain – particle size and characteristics alter at room temp
- Drug loading 300mg/mL
CAB – PK Characteristics

- 200mg/mL suspension
- PK linear & dose proportional
- Putative MEC 4 x PA-IC₉₀ (0.664μg/mL)
- Drug still detectable a year after a single IM dose

Spreen et al. JAIDS 2014, Aug 21
Spreen. 16th Hep-HIV PK Workshop 2015
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 600 mg IM + RPV 900 mg IM Q8W (n=115)
- CAB 30 mg + ABC/3TC PO QD (n=56)

**Day 1**

- Randomization 2:2:1
- CAB loading dose at Day 1
- CAB loading doses at Day 1 and Week 4

**Week 32**

- Primary analysis
- Dosing regimen selection

**Week 48**

- Analysis
- Dosing regimen confirmation

**Week 96**

- Add RPV PO QD 4 weeks

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.
LATTE-2 Week 48 Results:
HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

**Proportion of patients with virological suppression, %**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Oral CAB induction (ME population)</th>
<th>Oral CAB (n=56)</th>
<th>Q4W IM (n=115)</th>
<th>Q8W IM (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>98%</td>
<td>95%</td>
<td>99%</td>
<td>95%</td>
</tr>
<tr>
<td>W32</td>
<td>91%</td>
<td>94%</td>
<td>94%</td>
<td>91%</td>
</tr>
</tbody>
</table>

**Snapshot success**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Success D1</th>
<th>Success W32</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W-16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W-12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W-8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>W48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Study visit**

- **Induction period**
- **Maintenance period**
HIV-1 RNA <50 c/mL at Week 48: ITT-ME (Snapshot)

Both Q8W and Q4W comparable to Oral CAB at Week 48

Met prespecified threshold for concluding IM regimen is comparable to oral regimen (Bayesian Posterior Probability >90% that true IM response rate is no worse than -10% compared to the oral regimen). Observed Bayesian Probabilities: Q8W vs Oral = 99.7%; Q4W vs Oral = 99.4%.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
### Protocol-Defined Virologic Failure (PDVF)

**Maintenance period**

<table>
<thead>
<tr>
<th></th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>Oral CAB (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with PDVF</td>
<td>2 (1%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>INI-r mutations</td>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NRTI-r mutations</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NNRTI-r mutations</td>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- **NNRTI—K103N, E138G, and K238T** (FC RPV=3.3; Etravirine=1.9); **INI—Q148R** (FC CAB=5.1; Dolutegravir=1.38)<sup>c</sup>

- No additional PDVF s beyond W48 on any arm (all subjects through W72)<sup>d</sup>

PDVF: <1.0 log<sub>10</sub> c/mL decrease in plasma HIV-1 RNA by Week 4, OR confirmed HIV-1 RNA ≥200 c/mL after prior suppression to <200 c/mL, OR >0.5 log<sub>10</sub> c/mL increase from nadir HIV-1 RNA value ≥200 c/mL.  
<sup>a</sup>One additional PDVF without treatment-emergent resistance occurred during oral Induction Period due to oral medication non-adherence.  
<sup>b</sup>One PDVF at Week 4: no detectable RPV at Week 4 and Week 8, suggesting maladministration.  
<sup>c</sup>One PDVF at Week 48 at HIV-1 RNA 463 c/mL (confirmed at 205 c/mL).  
<sup>d</sup>Contains data beyond W48.

Margolis et al. AIDS 2016; Durban, South Africa. Abstract THAB0206LB.
## Adverse Events — Maintenance Period

<table>
<thead>
<tr>
<th>ITT-ME population, n (%)</th>
<th>Q8W IM (n=115)</th>
<th>Q4W IM (n=115)</th>
<th>Oral CAB (n=56)</th>
<th>IM subtotal (N=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related AEs, excluding ISRs (≥3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (3)</td>
<td>5 (4)</td>
<td>0</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (2)</td>
<td>4 (3)</td>
<td>1 (2)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>0</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>2 (4)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>3 (3)</td>
<td>0</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Grade 3 and 4 AEs, excluding ISRs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related Grade 3/4 AEs, excluding ISRs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (2)</td>
<td>4 (3)</td>
<td>0</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Serious AEs (none drug related)</td>
<td>8 (7%)</td>
<td>8 (7%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (5%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>AEs leading to withdrawal&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2 (2%)</td>
<td>7 (6%)</td>
<td>1 (2%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Grade 3 and 4 labs&lt;sup&gt;d&lt;/sup&gt;</td>
<td>18 (16)</td>
<td>23 (20)</td>
<td>9 (16)</td>
<td>41 (18)</td>
</tr>
</tbody>
</table>

AE, adverse event; ISR, injection-site reaction. <sup>a</sup>Q8W: influenza-like illness, chills and pain; Q4W: influenza-like illness, rash, depression, and psychosis. <sup>b</sup>one death (epilepsy). <sup>c</sup>Q8W: ISR, ISR/chills/body pain; Q4W: Churg-Strauss vasculitis, hepatitis C, depression, epilepsy, psychosis, rash, and mesenteric vein thrombosis; oral CAB: hepatitis C. <sup>d</sup>Maintenance emergent.
ISRs for CAB LA or RPV LA Over Time

Overall ISR AE Incidence

- 99% of ISRs were mild (82%) or moderate (17%), and 90% resolved within 7 days
- Most common ISR events overall were pain (67%), nodules (7%), and swelling (6%)
- 2/230 subjects (<1%) withdrew as a result of injection reactions (Q8W)

Bars represent incidence of onset ISR events relative to the most recent IM injection visit.
Patient-Reported Outcomes at Week 48: Maintenance Treatment

How satisfied are you with your current treatment?

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

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%

Note: based on observed case data set of subjects who completed Week 48 questionnaires.

*aHIV Treatment Satisfaction Questionnaire status version (HIVTSQs).*
Pharmacokinetics

Mean plasma RPV ± SD, ng/mL

Week
Q4W
Q8W
PA-IC90
25 mg PO Cτ

Pharmacokinetics

Mean plasma CAB ± SD, μg/mL

Week
Q4W
Q8W
PA-IC90
10 mg PO Cτ
30 mg PO Cτ

Cτ, trough concentration; PA-IC90, protein binding–adjusted 90% inhibitory concentration; SD, standard deviation.

- Both Q4W and Q8W steady state exposures approximate once-daily oral dosing
Do LA formulations reduce inter-patient variability?

LA formulations appear to be as variable in terms of PK as their oral counterparts:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral PK variability (AUC CV%)</th>
<th>LA PK variability (AUC CV%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone</td>
<td>36%</td>
<td>40%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>26%</td>
<td>50%</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>52%</td>
<td>34%</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>39%</td>
<td>52%*</td>
</tr>
<tr>
<td>Cabotegravir</td>
<td>27%</td>
<td>39%</td>
</tr>
</tbody>
</table>

What are the mechanisms for drug absorption following depot administration?
**CAB LA: Factors influencing drug exposure**

<table>
<thead>
<tr>
<th>Gender</th>
<th>BMI 50&lt;sup&gt;th&lt;/sup&gt; Percentile (10&lt;sup&gt;th&lt;/sup&gt;, 90&lt;sup&gt;th&lt;/sup&gt;) (kg/m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Mean Estimate of Ka LA (h&lt;sup&gt;-1&lt;/sup&gt;) by BMI Quantile (Relative Difference from 50% Ka LA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Male</td>
<td>26.8 (22.8, 30.3)</td>
<td>0.00114 (1.35) ↑35%</td>
</tr>
<tr>
<td>Female</td>
<td>26.3 (21.7, 30.4)</td>
<td>0.000407 (1.43) ↑43%</td>
</tr>
</tbody>
</table>

Population PK model (oral N=346; LA N=121)
Two compartment model
Covariate analysis (stepwise): age, gender, race, BMI, BSA, weight, HIV status, route, injections/dose
Gender & BMI retained as significant covariates in final model

Ford et al. ICAAC 2014; Abstr H-645
LA Formulations for PreP

- What is the plasma target? how does this differ from treatment targets?
- What is the tissue penetration? differences from oral TDF
- PK considerations long ‘tail’
CAB for PreP: Proof of Concept in NHPs

Rectal

Drug + virus challenges
Washout
CAB LA  CAB LA
8/8 protected

Weekly SHIV 162p3 50xTCID50 Intrarectal Challenge in Male Rhesus Macaques
(viral challenge weekly 0-7)

Aviremic (%)

0 2 4 6 8 10 12 14 16 18 20

Weeks post first challenge

8/8 infected p < 0.0001

Vaginal

Drug + virus challenges
Washout
CAB LA  CAB LA
8/8 protected

SHIV 162p3 300xTCID50 Intravaginal Challenge in Female Rhesus Macaques, with DMPA
(viral challenge Week 1, 5 and 7)

Aviremic (%)

0 2 4 6 8 10 12 14 16 18 20 22 24

Weeks

4/4 infected p = 0.0003

Vaginal

Drug + virus challenges
Washout
CAB LA  CAB LA  CAB LA

SHIV 162p3 50xTCID50 Intravaginal Challenge in Female Pigtail Macaques, no DMPA
(biweekly viral challenges x 22)

Aviremic (%)

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30

Weeks

p = 0.0005

Andrews et al. 20th CROI 2013
Andrews et al. 21st CROI 2014
Radzio et al. 21st CROI 2014
CAB for prevention – NHP Challenge Model

**Rectal Challenge**

- Plasma [CAB]
  - >3x PAIC$_{90}$ – 100% protection
  - >1x PAIC$_{90}$ – 97% protection

Andrews et al. Science 2014, March

**Vaginal Challenge**

- Plasma GSK744
  - Untreated (no drug)
  - Plasma CAB Concentration (µg/mL)

- >4x PAIC$_{90}$ – 98% protection
- 1-4x PAIC$_{90}$ – no protection

Spreen et al CROI 2015 966LB
## CAB for PreP: Tissue Partitioning

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Non-Human Primates Mean Ratio T:P (range)</th>
<th>Human Subjects@ 400mg&lt;sup&gt;a&lt;/sup&gt; Median Ratio T:P (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagina</td>
<td>0.15 (0.06 – 0.23)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.19; 0.28 (NQ – 0.7)</td>
</tr>
<tr>
<td>Cervix</td>
<td>0.14 (0.08 – 0.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.16; 0.20 (NQ – 0.4)</td>
</tr>
<tr>
<td></td>
<td>0.09 (NQ – 0.2)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>0.13 (0.05 – 0.31)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NQ; 0.08 (NQ – 0.2)</td>
</tr>
<tr>
<td></td>
<td>0.21 (0.08 – 0.54)&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

---

<sup>a</sup> Single 400mg IM dose (1x 400mg or 2x 200mg): n=8 females; n=8 males (Spreen, JAIDS, 2014)

<sup>b</sup> Single 50mg/kg IM dose: n=6 female pigtail macaques, no DMPA (JG Garcia-Lerma, personal communication)

<sup>c</sup> Repeat 50mg/kg (n=8) IM doses in female rhesus macaques, with DMPA (Andrews, 21st CROI, 2014)

<sup>d</sup> Repeat 10mg/kg (n=8) or 30 mg/kg (n=4) IM doses in male rhesus macaques (Andrews, Science, 2014)

---

**Studies used variety of CAB doses and sampling times**
RPV-LA: Genital/Rectal fluid PK
MWRI-01

b) 

1200 mg vaginal fluid (n=12)
1200 mg endocervical fluid (n=12)
1200 mg rectal fluid, females (n=10)

600 mg vaginal fluid (n=12)
600 mg endocervical fluid (n=12)
600 mg rectal fluid, females (n=10)

RPV-LA: Tissue PK
MWRI-01

RPV (ng/mL)

Time (days)

1200 mg vaginal tissue (n=12)
1200 mg ectocervical tissue (n=12)
1200 mg rectal tissue, females (n=10)

600 mg vaginal tissue (n=12)
600 mg ectocervical tissue (n=12)
600 mg rectal tissue, females (n=10)

Real-life Challenges - 1

- **Injection related**
  - ISR
  - needle fatigue
  - consistency & reproducibility of injections
  - children, low BMI
  - gender-based differences

- **Pharmaceutical**
  - formulations and co-formulations
  - variability – BMI, gender, pharmacogenetic
  - cold chain
  - scalability, affordability
  - implementation and health system capacity
  - alignment with allied interventions (LA contraceptives)
Real-life Challenges - 2

- **Clinical**
  - Patient selection
  - Lead-in, lead-out, bridging scenarios
  - Missed dosing
  - Managing DDIs
  - New Clinical Events
    - Pregnancy, contraception,
    - epilepsy, TB (Rif - CAB ↓59%, RPV ↓80% after oral dosing)
    - liver/renal failure,
    - cardiac event,
    - cancer, surgery, etc, etc

- **PreP**
  - what is the prevention target?
  - stopping PreP
MWRI-01: Persistence of RPV LA

- Initially 600 vs 1200mg single dose
- Rollover to multi-dose
- RPV detected in 7/7 (100%) of plasma samples collected a mean of 541 days after single exposure to 1200mg LA
- RPV also detected in endocervical and vaginal fluid
- RPV not detected in cervical/vaginal/rectal tissue
Current and Future Studies

Treatment

- RPV-LA CAB
  - LATTE
  - LATTE-2
  - FLAIR
  - ATLAS
  - 8% women

PreP

- CAB
  - HPTN 077
  - ECLAIR
  - CAPRISA 014
  - HPTN 083
  - 60% women
  - MSM
  - 100% women
  - MSM / TGW

- RPV-LA
  - SSAT 040
  - HPTN 076
  - MWRI-01
Other LA candidates

**Albuvirtide**
- Peptide fusion inhibitor
- Conjugates to serum albumin
- T½ 11d
- Low CNS/genital tract penetration
- Once-weekly IV with LPVr
- TALENT data to be presented in Glasgow

**Nevirapine**
- Developed for HIV prevention in breastfeeding infants
- s/c administration in rats

**Atazanavir/ritonavir**
- Concentrates in cells
- May be encased in folate polymers for macrophage targeting

Cortez et al, AAC 2015;59:59
Puligujja et al. Nanomedicine 2013;9:1263
Wu et al. ICAAC 2012 H-554
MK-8591 (EFdA)

- Novel mechanism of action (prevents translocation)
- Potent ($EC_{50}$ 0.2nM in PBMCs)
- Intracellular MK8591-TP $T_1/2$ 103h
- 1 x 10mg po reduced HIV VL by -1.67 log over 10d
- Suitable for once-weekly oral dosing
- Parenteral formulations >180d extended release after single injection in rats

Grobler et al. CROI 2016; Boston, MA. Abstract 98 & Friedman CROI 2016; Boston, MA. Abstr 437
# MK-8591 (EFdA)

<table>
<thead>
<tr>
<th></th>
<th>MK-8591</th>
<th>Zidovudine</th>
<th>Tenofovir</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>M184I (n = 5)</td>
<td>3.9 ± 0.4</td>
<td>0.37 ± 0.04</td>
<td>0.58 ± 0.03</td>
<td>&gt;123</td>
</tr>
<tr>
<td>M184V (n = 5)</td>
<td>5.0 ± 0.9</td>
<td>0.44 ± 0.21</td>
<td>0.60 ± 0.11</td>
<td>&gt;79</td>
</tr>
<tr>
<td>K65R (n = 7)</td>
<td>0.16 ± 0.04</td>
<td>0.39 ± 0.14</td>
<td>1.7 ± 0.4</td>
<td>11 ± 7</td>
</tr>
<tr>
<td>K65R + M184I/V (n = 7)</td>
<td>2.1 ± 0.3</td>
<td>0.42 ± 0.22</td>
<td>1.3 ± 0.3</td>
<td>&gt; 69</td>
</tr>
<tr>
<td>L74V (n = 3)</td>
<td>0.21 ± 0.07</td>
<td>0.38 ± 0.10</td>
<td>0.54 ± 0.08</td>
<td>1.6 ± 0.6</td>
</tr>
<tr>
<td>L74V + M184V (n = 2)</td>
<td>2.3 ± 0.4</td>
<td>0.20 ± 0.05</td>
<td>0.37 ± 0.11</td>
<td>&gt; 69</td>
</tr>
<tr>
<td>Q151M (n = 5)</td>
<td>0.25 ± 0.11</td>
<td>84 ± 78</td>
<td>1.9 ± 0.8</td>
<td>11 ± 8</td>
</tr>
<tr>
<td>Q151M + M184I/V (n = 6)</td>
<td>3.1 ± 2.5</td>
<td>71 ± 95</td>
<td>1.1 ± 0.5</td>
<td>&gt; 69</td>
</tr>
<tr>
<td>3 TAMs + L74V (n = 4)</td>
<td>1.2 ± 0.4</td>
<td>12 ± 11</td>
<td>1.4 ± 0.5</td>
<td>4.1 ± 1.6</td>
</tr>
<tr>
<td>3TAMs + M184I/V (n = 8)</td>
<td>11 ± 5</td>
<td>34 ± 54</td>
<td>1.6 ± 0.7</td>
<td>&gt; 69</td>
</tr>
</tbody>
</table>

- MK-8591 and TFV pro-drugs have complementary resistance profiles
  - MK-8591 hyperactive against K65R / TFV hyperactive against M184 mutants
- TAMs confer low level resistance (< 4-fold) to MK-8591
  - M184I/V resistance is additive with TAMs
Long-Acting Antiretrovirals - Summary

- An unquestionably exciting development with potential to impact on treatment and prevention

- Generally high acceptance in subjects selected for multi-dosing studies

- Who should we consider this for? adherence, multiple co-morbidities, etc

- Real-life challenges need to be anticipated more data on women DDIs cannot necessarily be imputed from oral dosing studies
Acknowledgements

University of Liverpool
David Back
Andrew Owen
Marco Siccardi
Laura Else
Deirdre Egan
Alieu Amara
Sara Gibbons
Sujan Dilly Penchala
Laura Dickinson
Alessandro Schipani
Henry Pertinez

St Stephens AIDS Trust
Marta Boffito
Akil Jackson

Chelsea and Westminster Hospital

Magee Women’s Research Institute & University of Pittsburgh
Ian McGowan
Ross Cranston
Charlene Dezutti
Jarrett Engstrom