Learning Objectives
After attending this presentation, participants will be able to:

- Describe why new antiretroviral approaches are needed
- List mechanisms of action of investigational antiretroviral drugs
- Describe how these new drugs and formulations might be incorporated into clinical practice

Goals of Antiretroviral Therapy

- Maintain or restore the health of people living with HIV-1 (PLWHIV) through suppression of HIV-1 replication
- Minimize or eliminate short and long-term adverse effects of the therapy
- Have therapies that are accessible to all PLWHIV
- Prevent transmission of HIV-1 to others via any route of exposure
Why Do We Need New Antiretroviral Agents?

- A 25 year old started on therapy today may need treatment for 6 decades! An infected infant – 8 decades
- Therapy must be incredibly safe, maximally tolerated and include a range of choices
  - Renal, cardiovascular, liver and bone toxicity
  - Safety of ART in pregnancy
  - Therapy options for infants and children
  - Adherence, life chaos, treatment fatigue, tolerability
  - Aging and drug interactions (e.g. CYP 3A4 inhibition)
- TREATMENT GAP - Not all PLWHIV in care are treated
  - Stigma, substance use, mental health, access to clinics, transportation, clinic capacity, country stocks, availability of 3rd line therapy
- HIV-1 resistance will always be with us

Continued Improvement in Currently Available ART Classes

- Doravirine (NNRTI)
  - Fewer side effects (?) and no food or PPI requirements
  - Phase III in naïve patients
- Raltegravir
  - Once daily
- Bictegravir (GS-9883; integrase inhibitor)
  - Single tablet, unboosted, TAF-based
  - Phase III in naïve and switch
- Integrase-based two drug therapy
  - Phase III in switch (DTG or CTG plus RPV)
  - Phase III in naïve in development (DTG plus 3TC)
- MRK-8591 (efoda – NRTI)
  - Long acting oral and injectable (?)
Future Directions: Investigational Approaches to Antiretroviral Therapy

**New NNRTI**

**Doravirine Versus Efavirenz in ART-Naïve Patients**

- Phase 2b study (n=216)
  - HIV RNA >1000 copies/mL
  - CD4 >500 cells/mm³
- Randomized arms
  - DOR 100 mg or EFV 600 mg + FTC/TDF
- Non-success at week 48
  - Doravirine arm (n=18)
  - Efavirenz arm (n=14)
- Discontinuations due to AE
  - Doravirine arm: 3%
  - Efavirenz arm: 6%

**New NNRTI**

**DOR vs. EFV: Clinical Adverse Events**

<table>
<thead>
<tr>
<th>Clinical AEs (%), n (%)</th>
<th>DOR + TDF/FTC (n = 108)</th>
<th>EFV + TDF/FTC (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 AE</td>
<td>87.0</td>
<td>88.9</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>6.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Discontinued due to AEs</td>
<td>2.8</td>
<td>6.3</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>4.9</td>
<td>6.5</td>
</tr>
<tr>
<td>• Nausea</td>
<td>7.4</td>
<td>5.6</td>
</tr>
<tr>
<td>• Headache</td>
<td>6.5</td>
<td>25.9</td>
</tr>
<tr>
<td>• Abnormal dreams</td>
<td>5.6</td>
<td>14.8</td>
</tr>
<tr>
<td>• Insomnia</td>
<td>6.5</td>
<td>2.8</td>
</tr>
<tr>
<td>• Nightmares</td>
<td>8.6</td>
<td>6.3</td>
</tr>
<tr>
<td>• Sleep disorder</td>
<td>6.5</td>
<td>6.5</td>
</tr>
</tbody>
</table>

*Specific AEs occurring in ≥ 5% of pts included.*

**Raltegravir once daily**

**In treatment naïve patients**
Future Directions: Investigational Approaches to Antiretroviral Therapy

Wednesday, August 24, 2016

Joseph J. Eron, Jr, MD

New Integrase Inhibitor
Bictegravir – 10 d Monotherapy

4 participants in each group

100 mg daily dose:
- Half life ~ 20 hours
- IQ = 25
- Peak VL decline = 2.9 log

- Single tablet combination with FTC and TAF
- Phase II studies in naive patients vs. DTG plus TDF/FTC or DTG/ABC/3TC fully enrolled
- Switch study from DRV/r or ATV/r also fully enrolled

Gallant et al ASM Microbe 2016

InSTI based 2-drug therapy
Dolutegravir plus 3TC 48 week data: PADDLE Study

ACTG single arm (N = 120) underway (HIV RNA up to 500,000)
Phase III comparative trial in development

Cahn et al WAC Durban 2016

Maintaining therapy for Life in all PLWHIV

- Adherence
  - Hard to reach populations, substance use, depression, children, adolescents ……
- Life Chaos
  - Travel, dislocation for work or safety, surgery, drug interactions, pill fatigue, patient preference ……

Long acting antiretroviral Therapy!
**Cabotegravir LA and Rilpivirine LA Nanosuspensions**

- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading vs. matrix approaches for lower inj. volumes

**GSK740 300mg/mL**

<table>
<thead>
<tr>
<th>Component</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>CAB1265744</td>
<td>Active</td>
</tr>
<tr>
<td>TMC278</td>
<td>Active</td>
</tr>
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</table>

**TMC278 300mg/mL**

<table>
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<th>Component</th>
<th>Function</th>
</tr>
</thead>
</table>

**Mean Plasma cabotegravir Concentration-Time Profiles Following Single 100-800 mg LAP Doses (200mg/mL nanosuspension)**

Differences observed between split and unsplit dosing

**LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART**

- Multicenter, open-label phase II study
- Primary endpoints: HIV-1 RNA < 50 c/mL by FDA snapshot, PDVF, and safety at maintenance Wk 32

**CAB 400 mg IM + RPV 600 mg IM Q4W** (n = 115)

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

*Pts with HIV-1 RNA < 50 c/mL from Wk 16 to Wk 20 continued to maintenance phase. In snapshot induction analysis, 14 pts had virologic nonresponse and 13 pts had no virologic data in window, including 6 pts who discontinued for AEs or death and 7 pts who discontinued for other reasons.

**Wk 1**

**Induction Phase**

**Maintenance Phase**

| ART-naive HIV-infected pts with CD4+ cell count > 200 cells/mm³ (n = 206) |
| CAB 30 mg PO + ABC/3TC PO QD |
| CAB 30 mg PO QD + ABC/3TC |

| Week 32 primary analysis data snapshot |
| CAB 30 mg PO + RPV 500 mg IM Q4W (n = 205) |
| CAB 30 mg PO + RPV 500 mg IM q12w (n = 205) |
| CAB 30 mg PO + RPV 500 mg IM q16w (n = 205) |

Phase III — suppression on oral therapy, every 4 week injections.

**4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA) MK8591**

- EFdA (MK-8591) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- Sub-nanomolar potency in vitro and prolonged suppression of SIV in macaque model
- Prolonged persistence of triphosphate form in PBMC and macrophage
- Potential for once weekly dosing
- Long-acting formulations under development

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2. Murphey-Corb et al. AAC 56:4707-12; 2012
Antiretroviral Therapy: The Next Generation?

- Implantable (and removable) combination antiretrovirals
- Vectored delivery of combinations of antibody-based therapy or protein based therapy
RESISTANT HIV-1 WILL ALWAYS BE WITH US

Four to eight decades of therapy
Previous exposure to suboptimal treatment in the developed world
Limited monitoring of virologic response world-wide
Transmitted drug resistance

Settings with Viral load Monitoring and Multiple Treatment Options and Past Sub-optimal ART

Viremic patients with multi-drug resistant HIV-1

Patients currently suppressed on therapy That have multi-drug resistant HIV-1

Resistance in the Developing World

- Second-line study: NNRTI/NRTI first line virologic failure – 15 countries – majority of participants from Africa or Asia
  - Baseline resistance - 492 participant samples

Published Online January 28, 2015 – Abstract 503
New Agents for Resistant HIV-1

- Integrase Inhibitors
  - Bictegravir
- N(t)RTI
  - TAF (approved)
  - EFdA (4'-ethynyl-2-fluoro-Z'-deoxyadenosine) (Phase I-II)
- NNRTI
  - Doravirine (Phase III)

Maturation Inhibitors
- BMS 911576 (Phase II)
- Attachment inhibitors
  - BMS 663068 + 626529 (Phase III)
- Monoclonal antibodies
  - Broadly virus neutralizing
  - Targeting entry receptors
    - GalNAc
    - VRC01

New Targets: e.g. LEDGF, combination entry, additional maturation sites, HIV-1 RNA processing.

Integrase Inhibitor Activity Against Resistant Variants in Vitro

Kirsten White, Tomas Cihlar and Michael D. Miller
ASM Microbe 2016

Activity of NRTI vs. Resistant variants
Fold change

Grobler et al ASM Microbe 2016
Maturation Inhibitors (MIs): BMS-955176 Mode of Action

- **Gag polyprotein**

**Untreated**
- Mature virus
- BMS-955176 Maturation Inhibitor

**Treated with BMS-955176**
- Immature virus

BMS-955176: Median Change in HIV-1 RNA over Time

HIV Entry Inhibitors

AI438011: BMS-663068 Attachment Inhibitor Monotherapy Substudy: Mean Change in HIV-1 RNA from Baseline*
Attachment Inhibitor – Clinical Development
BMS-663068

- HIV-1 variants have a range of susceptibility
  - In Phase IIB study 6% had a BMS-626529 IC_{50}>100 nM at screening
- Phase IIB study in participants with limited resistance
  - Attachment Inhibitor (over a range of doses) plus RAL and TDF had similar activity over 48 weeks to ATV/r plus RAL plus TDF
- Phase III study: highly ARV-experienced pts with MDR HIV
  - If at least one fully active ARV then
    - BMS-663068 600 mg or placebo BID for 8 days with no change in background ART followed by BMS-663068 600 mg BID for 48 weeks or longer with optimized background
  - If no fully active ARV then
    - BMS-663068 600 mg BID for 48 weeks or longer with optimized background therapy

BROADLY NEUTRALIZING ANTIBODIES
Can they be harnessed as therapy?

Combined Antibodies: Improved Potency and Breadth


Fraction of HIV-1 strains neutralized

- 2 mAbs > 98% coverage

- WR07
- PG9
- V31328
- PG9 + V31328
- 2 mAb Combinations
- 3 mAb Combinations
- 4 mAb Combination

HIV-1 discovered
ZDV monotherapy
ZDV/3TC
Triple Drug Therapy
The Integrase Era
Long Acting Formulations
Antiretroviral Therapy: The Future