Learning Objectives

After attending this presentation, learners will be able to describe:

- The latest data on investigational antiretroviral drugs
- The latest information about long-acting antiretroviral drugs
- Antiretroviral agents with new mechanisms of action
Question #1
Which of the following investigational drugs is earliest in clinical development?

1. Cabotegravir
2. EFdA
3. Fostemsavir
4. GS-2607

Newer ART Agents (partial list)

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NRTI
Needs:
• more convenient
• active against drug-resistant viruses
MK-8591 (EFdA)

- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; EFdA
- DNA chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Half-life = 50-60 hours in plasma
- Accumulates in LN, vagina, rectum (animals) Grobler CROI 2017 #435
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Low-dose and parenteral formulations

MK-8591: Activity Against NRTI-Resistant Strains

MK-8591 (EFdA)

- Double-blind, placebo-controlled, 3-panel trial
- HIV- patients
- MK-8591 (or placebo) daily
  5 mg X 6 weeks, 0.75 mg X 4 weeks, 0.25 mg X 4 weeks
- Results:
  - After 2-3 weeks of dosing, MK-8591-TP levels exceeded 1.0 pmol/million cells (similar to 10 mg weekly dosing)
  - Tissue (vaginal, rectal) and PBMC levels adequate
- Conclusion: Low daily doses expected to suppress HIV
- Phase 2b study in rx-naïve of MK-8591 + 3TC + DOR
- Considering weekly dosing regimens
MK-8591 -- Prevention
- MK-8591 3.9 mg/kg weekly was 100% protective in 8 macaques given multiple weekly intrarectal SHIV challenges.
- Follow-up study with lower doses
  - MK-8591: 1.3, 0.43, 0.1 mg/kg weekly (8 macaques/group)
- Results
  - 1.3 mg/kg: all 8 remained uninfected
  - 0.43 mg/kg: all 8 remained uninfected
  - 0.1 mg/kg: 2 of 8 became infected
- Conclusions:
  - MK-8591 protective at low doses
  - Equivalent to 250 µg/week or 10 µg/day in humans

Long-Acting Subdermal Implants: MK-8591 in Animal Studies
- Drug-eluting implants, both bioerodible and non-erodible
- Rats
  - PLA polylactic acid
  - PLGA polylactic-co-glycolic acid
- Non-human primates
  - PLA polylactic acid
  - PLGA polylactic-co-glycolic acid

INSTI
- Needs:
  - more convenient
  - active against INSTI-resistant virus
Cabotegravir (CAB)

- Integrase inhibitor similar to DTG; similar resistance
- Potent in HIV+ individuals (5, 10, 30, 60 mg oral)
- Nanotechnology formulation; SC + IM injections
- T ½ 21-50 days!
- Supports monthly, bimonthly or quarterly dosing
- Safety: ISR (mostly mild) and nodules with SC dosing
- Phase 1, 2, and 3 studies completed

Phase 2b: LATTE-2: IM CAB + IM RPV

- Randomized, open-label, phase 2b, non-inferiority study
- Study population: ART-naïve (N=309)
- Study rx: PO CAB + ABC/3TC X 4 wks, then randomized 2:2:1
- Results (HIV RNA <50 at 96 wks)
  - IM CAB + IM RPV q8 wks – 94%
  - IM CAB + IM RPV q4 wks – 87%
  - PO CAB + ABC/3TC – 84%
- Injection site reactions were nearly universal
  - 97%+ were mild or moderate; lasted a median of 3 days
  - 2 pts (<1%) d/c due to ISR
- Conclusions: IM non-inferior (comparable) to PO; well-tolerated

CAB Phase 3: FLAIR

- Randomized, international, open-label, non-inferiority (∆6%)
- Study population: rx-naïve adults (N=629; 22% women)
- Study rx: ABC/3TC/DTG X 20 wks → CAB + RPV (oral X 4 weeks, then IM monthly) or continue oral DTG regimen
- Results (week 48):
  - 3 VF on LA: 3 Russian (A1)
  - NNRTI and INSTI subs.
  - 3 VF on oral: no resistance
  - ISR ~70% – mild, transient
- Conclusion:
  CAB + RPV non-inferior
**CAB Phase 3: ATLAS**

- Randomized, international, open-label, non-inferiority (Δ6%)
- Study population: adults with VS on 2 NRTI + PI, NNRTI, or INSTI regimens (N=616; 33% women)
- Study rx: continue ART or change to CAB + RPV (oral X 4 weeks, then IM monthly)
- Results (week 48):
  - 3 VF: 2 Russian (A/A1)
    • NNRTI and INSTI subs.
  - ISR ~70% – mild, transient
- Conclusion: CAB + RPV non-inferior

**CAB – Prevention: HPTN 077**

- Phase 2a randomized, double-blind, placebo-controlled
- Study pop: low-risk HIV- participants (N=199); median age 31, 66% women, 34% men
- Study meds: 3:1 to oral CAB X 4 wks then CAB IM 800 mg q12 weeks or 600 mg q8 wks (or placebo)
- Results:
  - ISR more common with CAB (34%) vs. PBO (2%); 1.5% d/c'ed
  - No other differences in safety/tolerability
  - drug troughs lower with CAB 800 q12 wks
- Conclusion: CAB 4 wk oral → 600 mg IM q8 wks optimal

**HPTN 077: CAB and Weight Gain**

Conclusion: In HIV-negative individuals, no significant changes in weight on CAB (vs. placebo) over 41 weeks

Phase 3 PrEP studies (IM CAB vs. oral TDF/FTC) enrolling.
Question #2
Which of the following new HIV drug classes is farthest along in clinical development?

1. Attachment inhibitor
2. Capsid inhibitor
3. CXCR4 antagonist
4. Maturation inhibitor

Entry Inhibitors

Needs:
• Novel mechanism of action
• More convenient dosing

HIV Entry Inhibitors

Adapted from Moore JP, PNAS 2003;100:10598-10602.
Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Prodrug of tesamivir (TMR)
- Inhibits CD4 binding by binding to gp120
- PK suggests daily dosing without boosting
- Phase 1 dose-escalation over 8 days
  - 5 doses (4 with RTV)
  - up to 1.5 log cps/ml ↓
  - ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms

Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Phase 2b: modestly rx-experienced, screened for susceptibility (IC_{50} <100 nM) (N=251)
  - Study rx: TDF + RAL + 4 FTR doses: 400 mg bid, 800 mg bid, 600 mg qd or 1200 mg qd (vs. ATV/r)
  - Week 48: 61-82% VL <50; dose then ↑ to 1200 mg qd
  - Week 96: 61% VL <50 (MITT)

- No TDF or ATV resistance; 6 on FTR developed RAL resistance; 13 with available phenotypes showed ↓ susceptibility to temsavir and 7 had substitutions in gp120

Fostemsavir (FTR): Oral Attachment Inhibitor

BRIGHTE (Phase 3): heavily rx-experienced, NOT screened for susceptibility (N=272 with 1-2 remaining ART classes randomized to FTR 600 mg bid or placebo; 99 with no remaining ART classes non-randomized)

- day 8 (primary endpoint): mean HIV RNA Δ: -0.2 log (placebo) vs. -0.8 cpg/ml (FTR) (p<0.0001)
- then, optimized background ART
- wk 48: VL <40: 54% (randomized) vs. 38% (non-randomized)
- Comparable results by gender
- FDA “breakthrough status” July 2015
- Planned filing for approval 2019
New Mechanisms of Action

HIV Maturation Inhibitors (MI)

- **Bevirimat** – phase 2
  - ~50% of treatment-experienced patients had no response due to polymorphisms in gp120
  - McCallister 2008 XVII HIV Drug Resistance Conference #8
- **GSK 3532795/BMS-955176** – phase 2b
  - TDF/FTC + '795: 76-83% <40 cps/ml
  - GI intolerance
- **GSK 2838232** – phase 2a
  - '232 + cobicistat: up to ↓1.7 log cps/ml at 10 days
  - DeJesus CROI 2019 #142
- **GSK 3640254** – phase 1 pending; phase 2 starting
HIV Capsid Inhibitors

Capsid Inhibitor: GS-6207

- Potent antiretroviral activity: EC$_{50}$ 140 pM in PBMC
- Active across all tested subtypes
- Resistant variants have low fitness
- High clearance and solubility → very long $\frac{1}{2}$ life: 30–43 days
- Phase 1 single SQ dose (vs. placebo) in HIV- (10/group)
  - Doses: 30, 100, 300, 450 mg
  - Prolonged exposure ($\geq$24 wks)
  - 3 highest doses >prot-adjusted-EC$_{95}$ at 12 wks
- Phase 1 in HIV+ underway

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- Division of AIDS, NIAID, NIH
- The patient volunteers!