Investigational Drugs for HIV

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Financial Relationships With Commercial Entities

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Learning Objectives

After attending this presentation, learners will be able to:

- Discuss the latest data on investigational HIV drugs in existing classes (nRTI, NNRTI, II)
- Learn about investigational HIV drugs in new classes (CD4 attachment inhibitors, maturation inhibitors, capsid inhibitors)
Antiretroviral Drug Approval: 1987 - 2017

Newer ART Agents (partial list)

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NRTI Needs:
- more convenient
MK-8591 (EFdA)

- 4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- 1/2 life (150-160 hours)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Accumulates in LN, vagina, rectum (animals)
- Grobler CROI 2017 #435
- Low-dose and parenteral formulations

MK-8591 Parenteral Formulations Release Effective Drug Levels for >180 days

- Grobler CROI 2016 #58
- Friedman CROI 2016 #437LB
- Grobler CROI 2017 #435

MK-8591 -- Prevention

- MK-8591 (vs. placebo) given to male macaques weekly by oral gavage up to 14 weeks
- 6 days after dosing, macaques exposed to intrarectal SHIV (until infection or a total of 12 challenges)
- Conclusion: Supports the potential for PrEP in humans

Markowitz IAS 2017 #MOA0203LB
**NNRTI**

Needs:
- Less toxicity and better tolerability
- Active against NNRTI-resistant viruses
- Fewer drug interactions

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**Doravirine (DOR; MK-1439)**

- Investigational NNRTI
- Pre-clinical
  - Potent at low milligram dose
  - Metabolized by CYP3A4; not a CYP450 inhibitor or inducer
  - Active in vitro against viral strains with:
    - K103N
    - Y181C
    - G190A
    - E101K
    - E138K
    - K103N/Y181C

Let AAD 2014;38:1652-1665

- Phase 1: Scharmann AIDS 2016;30:57-63
- Phase 2: EFV: Gatell JIAS 2016;17:19532

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**Doravirine (DOR) – Phase 3: DRIVE-FORWARD**

Phase 3, multicenter, double-blind, placebo-controlled randomized study

Study population: Rx-naïve, VL >1000, no GT resistance to study drugs (N=769)

Study treatment: 2 NRTIs + [DOR 100 mg vs. DRV 800 mg/RTV 100 mg]

Protocol-defined virologic failure: DOR 19 (6%) vs. DRV 24 (8%) → No drug resistance

Discontinuation due to AE: DOR 2% vs. DRV 3%

Lipids: L with DOR (chol -1, triglyc -3 mg/dL) and L with DRV (chol +18, triglyc +22)

Molina CROI 2017 #40LB
**Doravirine (DOR) – Phase 3: DRIVE-AHEAD**

- **Study population:** Rx-naïve, VL $\geq$ 1000, no GT resistance to study drugs (N=728)
- **Study treatment:** TDF/FTC/DOR 100 mg vs. TDF/FTC/EFV

**Protocol-defined virologic failure:**
- DOR 22 (6%) vs. EFV 14 (4%)
- Drug resistance: DOR 2% vs. EFV 3%
- Discontinued due to reasons other than VF: DOR 10% vs. EFV 14%
- Dizziness: DOR 9% vs. EFV 37%; Sleep disorders DOR 12% vs. EFV 26%

**Bictegravir (BIC)**

- **INVI (Bictegravir)**
  - **In vitro EC50 0.75 nM against wt clinical isolates of HIV-1 and -2**
  - **T1/2 18 hours (once-daily); no PK boosting required**
  - No inhibition or induction of CYP3A4 or UGT – low potential for drug interactions
  - Phase 1 Gallant JAIDS 2017;75:61-66
  - Phase 2 (vs. DTG). San Lancet HIV 2017;4:e154-e160

**INSTI**

- Needs:
  - Active against INSTI-resistant virus
  - More convenient

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Bictegravir (BIC): Phase 3

- Phase 3, double-blind, active-controlled study
- Study population: Rx-naïve, VL $\geq$ 500, GFR $\geq$ 50, HLA-B*5701 neg (N=645)
- Study treatment: TAF/FTC/BIC vs. ABC/3TC/DTG
- Results:

Bictegravir (BIC): Phase 3

- Phase 3, double-blind, active-controlled study
- Study population: Rx-naïve, VL $\geq$ 500, GFR $\geq$ 30 (N=645)
- Study treatment: TAF/FTC/BIC vs. TAF/FTC+DTG
- Results:

Cabotegravir (CAB)

- Integrase inhibitor similar to DTG; similar resistance
- Potent in HIV+ individuals (5, 10, 30, 60 mg oral)
  - Margolis EACS 2013; Spreen HIV Clin Trials 2013:14:192
- 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
  - Spreen JAIDS 2014;67:481
LATTE-2: IM CAB + RPV  96 weeks
- Randomized, open-label, phase 2b, non-inferiority study
- Study pop: ART-naïve (N=309)
- Study rx: PO CAB + ABC/3TC X 4 wks, then randomized 2:2:1
- Results:
  - 96 wks
- Conclusions: IM non-inferior (comparable) to PO; well-tolerated
- Phase 3 studies evaluating IM q4 wks

Cabotegravir (CAB) – Prevention: HPTN 077
- Phase 2a randomized, double-blind, pbo-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 PBO)
- 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 q8wks optimal

HPTN 083: PrEP with TDF/FTC oral vs. CAB IM
- Study population: Adult MSM and TGW, at high-risk for HIV acquisition (N=4500)
  - High risk
  - any non-condom receptive anal intercourse (RAI)
  - >5 partners
  - stimulant drug use
  - rectal or urethral STI in past 6 months
- Study regimen: TDF/FTC daily oral vs. CAB q2 month injections
  - double-blind, double-dummy design
- Design: non-inferiority, efficacy study
- Now enrolling!
Entry Inhibitors

Needs:
• Novel mechanism of action
• More convenient dosing

HIV Entry Inhibitors

Fostemsavir: Oral HIV Attachment Inhibitor

• Prodrug of temsavir
• Inhibits CD4 binding by binding to gp120
• PK suggest QD (or BID) dosing without boosting
• Phase 1 dose escalation: Nettles JID 2012;206:1002
  – Up to 1.5 log viral ↓
  – ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms

• Drug interactions
  – None with OCP: Magee IAS 2017 #BPB20138
  – No sign drug interactions with methadone, buprenorphine: Borsky IAS 2017 #BPB10308
Fostemsavir: Phase 2b Efficacy

- Phase 2b, randomized, controlled, partially blinded (to dose)
- Study pop: Rx-experienced (≥1 wk on ≥1 ART); IC₅₀ <100 nM for fostemsavir (N=254)
- Study rx: RAL + TDF + [fostemsavir 4 doses or ATV/r]
- Week 48 VL <50: MITT: 61-82% (fostemsavir) vs. 71% (ATV/r)

- Week 96:
  - FDA “Breakthrough Status” 7/15
  - Phase 3 in rx-experienced enrolled

Ibalizumab (IBA): HIV Entry Inhibitor

- Monoclonal antibody; IV, SC
- Binds to CD4 receptor
- Dosing every 1-4 weeks
- Phase 1a Kuritzkes JID 2004;189:286
- Phase 1b Jacobson AAC 2009;53:450
- Phase 2a Norris IAS 2006 #TaPE0058
- Phase 2b Khanlou IDSA 2011 #LB9

  Rx-experienced; 3-class resistance; (N=113)
  - baseline susceptibility to IBA not different for those with drug resistance to NRTIs, NNRTIs, PI, 3i, ENF or MVC

  Weinheimer IAS 2017 #MOPEB0352

Ibalizumab (IBA): HIV Entry Inhibitor

- Phase 3
  - Study population: VL>1000, on ART >6 months, 3-class resistance, ≥1 sensitive drug (N=40)
  - Study treatment: continue ART, +IBA 800 mg day 7, +OBR day 14, +IBA day 21 and q 2 wks → 24 wks

  Lalezari IDWeek 2016 #LB6
  Lewis CROI 2017 #449LB

  FDA: orphan drug; breakthrough designation
HIV Maturation Inhibitors (MI)

- Protease Maturation Inhibitor
- Immature virus
- Mature virus
- Untreated
- Treated with Maturation inhibitor
- Protease

Capsid Inhibitor

- EC_{50} 140 picomolar in PBMC, Active across all tested subtypes, resistant variants, low fitness

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- HIV Prevention Trials Network (HPTN)
- Division of AIDS, NIAID, NIH

- The patient volunteers!
Cornell HIV Clinical Trials Unit

Director: Marshall Glesby, MD   Co-Director: Tim Wilkin, MD
Investigators: Leah Burke, MD, Kristie Marks, MD, Mary Vogler, MD
Study Coordinators: Karris Ham, NP, Valery Hughes, NP, Todd Stroberg, RN, Louise Walke, RN
Program Director: Glenn Sturge
Multiple Staff Members!

Question and Answer Period

• Use the microphones or Q-cards for questions
• If you are participating via the live webcast, please email your questions to RWCCwebcast@iasusa.org