Investigational Antiretroviral Drugs

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Financial Relationships With Commercial Entities

• Dr. Gulick has no relevant financial affiliations to disclose. (Updated 04/27/17)

Learning Objectives

After attending this presentation, learners will be able to:

• Identify new investigational HIV drugs in existing mechanistic classes
• Identify new investigational HIV drugs in new mechanistic classes
• Describe the latest clinical data on investigational HIV drugs
Which investigational class of HIV drugs is farthest along in development?

1. Capsid inhibitor
2. CD4 attachment inhibitor
3. CD8 agonist
4. RNase H inhibitor
5. Maturation inhibitor

Newer ART Agents (partial list)

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<tr>
<th>Phase</th>
<th>NRTH</th>
<th>NNRTI</th>
<th>PI</th>
<th>Entry/Link</th>
<th>II</th>
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Los Angeles, California: April 28, 2017
Which investigational HIV drug is being investigated for both treatment and prevention?
1. bictegravir
2. cabotegravir
3. doravirine
4. fostemsavir
5. ibalizumab

NRTI

Needs:
• More convenient
MK-8591 (EFdA)

- 4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA
- Non-obligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Accumulates in LN, vagina, rectum (animals)
- Low-dose formulations

NNRTI

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

  Lai AAC 2014;38:1052-1063

Doravirine (DOR): Phase Ib

Double-blind, randomized, placebo-controlled
Study population: HIV+, treatment-naïve (N=18)

Schurmann AIDS 2016;30:57-63

Doravirine (DOR) – Phase 2

Randomized, double-blind, 2-part study
Study population: Rx-naïve participants; VL >1000, CD4 >100 (N=216)

Drug-related AEs: 31% (DOR) vs. 56% (EFV)

Los Angeles, California: April 28, 2017
Doravirine (DOR) – Phase 3

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]

Participants with protocol-defined virologic failure: DOR 19 (5%) vs. DRV 24 (6%) * NS drug resistance
Discontinued due to AE: DOR 2% vs. DRV/r 3%
Lipids decreased with DOR (chol -1, triglyc -3 mg/dL), increased with DRV/r (chol +18, triglyc +22)

INSTI

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

Bictegravir (GS-9883): In vitro
• 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
Bictegravir (GS-9883): Phase 1

- Study population: HIV+, naïve/off ART X >12 wks, no prior INSTI, VL 10K-400K, CD4 >200 (N=20)

Gallant, ASM Microbe 2016, abstract #415

Bictegravir (GS-9883): Phase 2

- Study population: Rx-naïve, VL >1000, CD4 >200, HBV/HCV neg (N=98)
- Study rx: TAF/FTC + [BIC or DTG] (2:1 randomization)
- Phase 3 studies in progress: TAF/FTC/BIC Sax CROI 2017 #41

adverse events and lab abnormalities similar; no drug resistance detected

Cabotegravir (CAB, GSK 1265744)

- 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 or quarterly dosing
- Safety: ISR (all mild) and nodules with SC dosing

Spreen JACS 2014;67:481
LATTE-2: CAB + RPV IM Maintenance

Phase 2b multicenter, parallel group, open-label study
Study population: Rx-naïve individuals (N=309)

LATTE-2: Virologic Suppression

LATTE-2: Injection Site Reactions

- Most common ISR events overall were pain (57%), swelling (7%), and nodules (8%)
- Number of subjects reporting ISRs decreased over time, from 86% (Day 1) to 33% (Week 24)
- 2/233 subjects withdrew due to a result of injection reactions (CINV)
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
- First participant enrolled 12/16!

Entry Inhibitors

Needs:
- Novel mechanism of action
- More convenient dosing

HIV Entry Inhibitors

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

- Prodrug of tamsivir
- Inhibits CD4 binding by binding to gp120
- PK suggest QD or BID dosing without boosting
- ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms; screened by baseline IC50


tamsivir

Nettles JID 2012;206:1002

Fostemsavir: Phase 2b

Phase 2b, randomized, controlled, partially blinded (n=168 doses) Study pop: Rx-experienced (≥ 1 wk on ≥ 1 ART), IC50 <100 nM for 529 (N=254)

Lalezari Lancet HIV 2015;2:e427-37 and Thompson Antivir Ther (epub 12/16)

Fostemsavir: Phase 2b Efficacy

- Week 48 VL <50:
  - MITT: 61-82% (fostemsavir) vs. 71% (ATV/r)
  - Observed: 77-95% (fostemsavir) vs. 88% (ATV/r)

DeJesus CROI 2016 #472

Thompson Antivir Ther (epub 12/16)
Fostemsavir: Phase 2b Safety

Ibalizumab: HIV Entry Inhibitor

• Monoclonal antibody; IV, IM, 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 #TuPE0058
• Phase 2b Khanlou IDSA 2011 #LB9
  Rx-experienced; 3-class resistance, (N=113)

Ibalizumab: 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, +ibalizumab 800 mg IV day 7, +OBR day 14, +ibalizumab IV day 21 and q 2 wks
  – 24 wks
• FDA: orphan drug; breakthrough designation
Albuvirtide (ABT): HIV Fusion Inhibitor

- 1/2-life = 11-12 d \(\Rightarrow\) weekly IV dosing
- Pilot study:
  - ART-naïve, VL 5K-1M, CD4 >350 (N=20)

56%

Albuvirtide (ABT): HIV Fusion Inhibitor

- TALENT
  - Test Albuvirtide in Treatment-Experienced Patients
  - Phase 3 – Second-line therapy following VF on a first-line ART regimen (N=389)
  - Study ex: LPV/r bid + [2 NRTI or IV ABT]
  - Planned interim analysis; ½ of study participants (n=175) on study X 48 wks:
    - VL <50: 66% (NRTI) vs. 80% (ABT)
    - \(\Rightarrow\) non-inferiority
    - In 5 pts on ABT with VL >500 \(\Rightarrow\) no resistance
  - Wu Glasgow 2016 #O335

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