Investigational Antiretroviral Strategies and Drugs

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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

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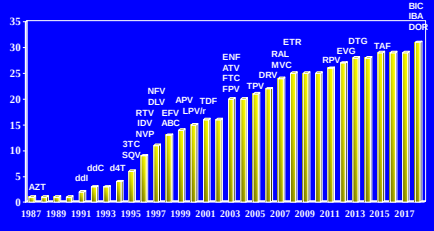
Antiretroviral Drug Approval: 1987 - 2019



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Question #1

Which of the following investigational drugs is earliest in clinical development?

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

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Newer ART Agents (partial list)

	NRTI	NNRTI	PI	EI	II	MI	CI
Phase 3				fostemsavir PRO 140 (leronlimab) UB-421	cabotegravir		
Phase 2	censavudine MK-8591 (EFdA)	elsulfavirine	TMC 310911	cenicriviroc PF-232798		GSK-2838232	GS-6207
Phase 1/2	elvucitabine					GSK-864025	
Pre-clinical	GS-9131						

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NRTI

Needs:

- more convenient
- active against drug-resistant viruses

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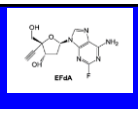
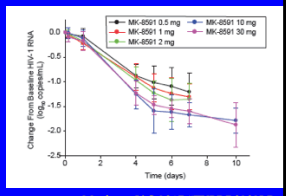
MK-8591 (EFdA)

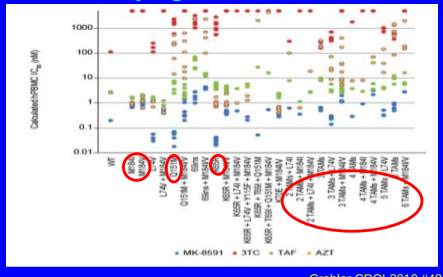


- 4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA
- DNA chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Half-life = 50-60 hours in plasma
- Accumulates in LN, vagina, rectum (animals) Grobler CROI 2017 #435
- Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1,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



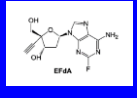
Matthews IAS 2017 #TUPDB0202LB

MK-8591: Activity Against NRTI-Resistant Strains



Grobler CROI 2019 #481

MK-8591 (EFdA)



- Double-blind, placebo-controlled, 3-panel trial
- HIV- participants
- 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

Matthews CROI 2018 #26

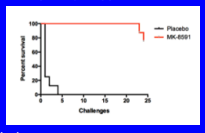
- Phase 2b study in rx-naïve of MK-8591 + 3TC + DOR
- Considering weekly dosing regimens

MK-8591 -- Prevention

- MK-8591 3.9 mg/kg weekly was 100% protective in 8 macaques given multiple weekly intrarectal SHIV challenges

  Markowitz IAS 2017 #MOAX0203LB

- 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

  Markowitz CROI 2018 #89LB

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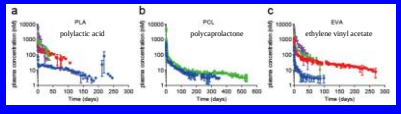
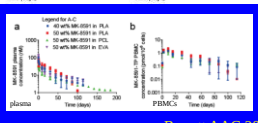
Long-Acting Subdermal Implants: MK-8591 in Animal Studies

Drug-eluting implants, both bioerodible and non-erodible

rats



non-human primates



Barrett AAC 2018;62:e01058-18

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INSTI

Needs:

- more convenient
- active against INSTI-resistant virus

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Cabotegravir (CAB)

- Integrase inhibitor similar to DTG; similar resistance
- Potent in HIV+ individuals (5, 10, 30, 60 mg oral)

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

- Phase 1, 2, and 3 studies completed

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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%**

week 160
→90%
→83%

Margolis Glasgow 2018 #P118

- 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

Eron IAS 2017 #MOAX0205LB; Margolis Lancet 2017;390:1499

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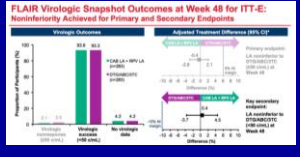
CAB Phase 3: FLAIR

- Randomized, international, open-label, non-inferiority (Δ6%)
- 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

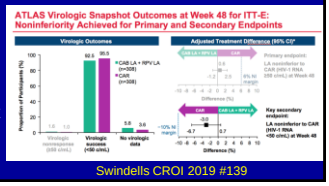


Orkin CROI 2019 #140

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



Swindells CROI 2019 #139

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

Landovitz PLoS Med 2018;15:e1002690

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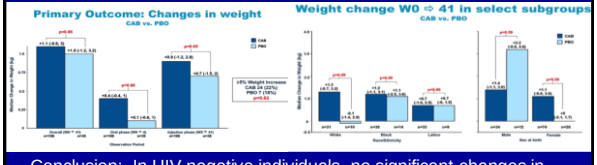
HPTN 077: CAB and Weight Gain

Baseline → Week 41



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

Landovitz CROI 2019 #34

Phase 3 PrEP studies (IM CAB vs. oral TDF/FTC) enrolling.

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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

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Entry Inhibitors

Needs:

- Novel mechanism of action
- More convenient dosing

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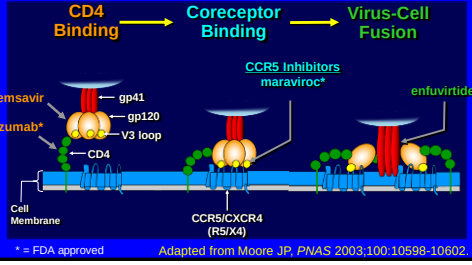
HIV Entry Inhibitors



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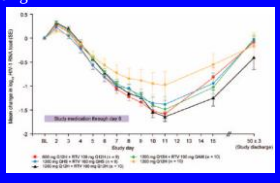
* = FDA approved

Adapted from Moore JP, *PNAS* 2003;100:10598-10602.

Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Prodrug of **temsavir (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



Nettles JID 2012;206:1002

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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)

    Thompson Antivir Ther 2017;22:215
  - 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

    Latilliade JAIDS 2018;77:299
  - Week 192: "comparable rates of virologic suppression" to ATV/r

    Thompson CROI 2019 #483

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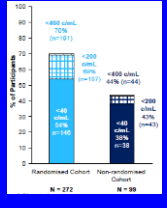
Fostemsavir (FTR): Oral Attachment Inhibitor

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 cps/ml (FTR) (p<0.0001)
- then, optimized background ART
- wk 48: VL <40: 54% (randomized) vs. 38% (non-randomized) Aberg/Ackerman Glasgow 2018 #344
- Comparable results by gender Quercia CROI 2019



- FDA "breakthrough status" July 2015
- Planned filing for approval 2019

New Mechanisms of Action

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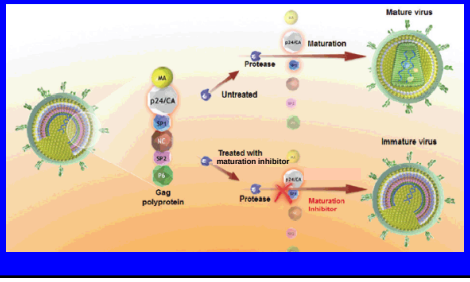
HIV Maturation Inhibitors (MI)



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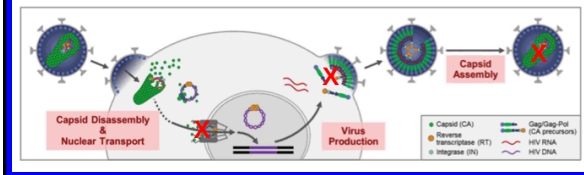
HIV Maturation Inhibitors

- **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 Morales-Ramirez PLoS One 2018;13:e0205368
- **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



Sager CROI 2019 #142

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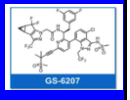
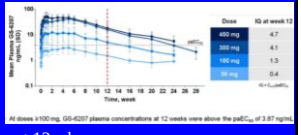
Capsid Inhibitor: GS-6207

- Potent antiretroviral activity: EC_{50} 140 pM in PBMC
- Active across all tested subtypes
- Resistant variants have low fitness
- ↓ clearance and solubility → very long ½ life: 30-43 days
- Phase 1 single SQ dose (vs. placebo) in HIV- (10/group)
  - Doses: 30, 100, 300, 450 mg
  - Prolonged exposure (≥24 wks)
  - 3 highest doses >prot-adjusted-EC_{95} at 12 wks
- Phase 1 in HIV+ underway


GS-6207



Sager CROI 2019 #480

Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Cornell Medicine
- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network (HPTN)
- Division of AIDS, NIAID, NIH

- The patient volunteers!

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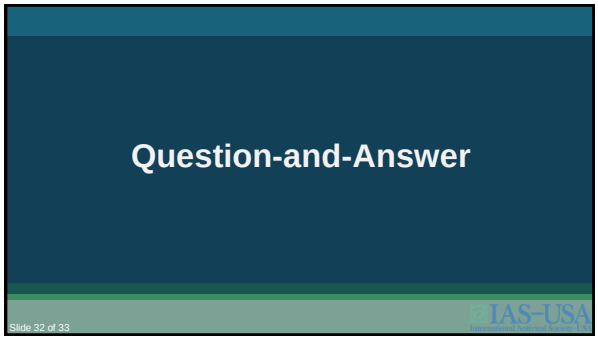
Question-and-Answer
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