New Drugs and Novel Strategies for Antiretroviral Therapy

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe new antiretroviral drugs in development
- Monitor outcomes of studies of new drugs and new strategies for antiretroviral treatment
- Describe potential roles for new antiretroviral drugs and strategies in the treatment of people living with HIV

Slide 3 of 30

Slide #4

Do We Really Need New ARVs?

- Big goals
- Big challenges
  - Treatment for up to 6-8 decades
    - Renal, cardiovascular, liver, bone toxicities
    - Therapy options for infants, children, pregnant women
    - Adherence, life chaos, treatment fatigue, aging
    - Drug interactions (TB and others)
  - HIV resistance will emerge to existing ARVs
    - Especially in regions with limited VL and DR testing

Eron J, CROI 2016

Slide 4 of 30

Slide #5

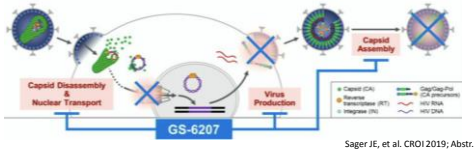
New Antiretroviral Drugs in Development

Slide 5 of 30

Slide #6

GS-6207: A Novel First in Class Capsid Inhibitor

- Active against a broad range of HIV-1 isolates, including those resistant to existing ARV classes
  - Modulates stability and/or transport of capsid complexes; inhibits multiple processes necessary for viral replication
  - Picomolar activity; more potent than current ARVs



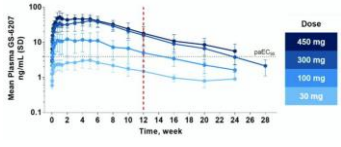
Sager JE, et al. CROI 2019; Abstr. 141

Slide 6 of 30

Slide #7

GS-6207: A Novel First in Class Capsid Inhibitor

- Randomized, blinded, placebo-controlled
  - Phase 1 single ascending SQ dose in healthy volunteers
  - Mean age 35y; 67% male; 72% white
- GS-6207/placebo generally well tolerated
  - No deaths or serious AEs
  - No Grade 4 lab abnormalities or Grade 3 lab abnormalities of clinical relevance
  - Most common AEs were transient injection site reactions



- Prolonged exposures with measureable concentrations for ≥ 24 weeks
- At doses ≥ 100 mg, plasma conc at 12 weeks above the paEC95, supporting every 12 week dosing

Sager JE, et al. CROI 2019; Abstr. 141

Slide 7 of 30

Slide #8

GSK 2838232: A Novel Maturation Inhibitor

- Binds to gag; inhibits last proteolytic cleavage event between p24 capsid (CA) and spacer peptide 1 (SP1)
  - Prior maturation inhibitors had issues with naturally occurring resistance polymorphisms (beviramat) and resistance/GI intolerance (BMS-955176)
  - *In vitro* nanomolar activity; minimal protein binding; inhibits HIV-1 containing the consensus Sp1 polymorphism
  - When co-administered with ritonavir → mean half-life of 34 hours
- Phase 2a study of GSK 2838232 co-administered once daily with cobicistat in HIV-infected adults

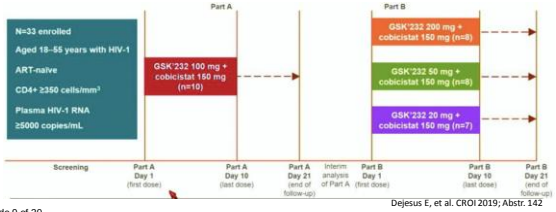
Dejesus E, et al. CROI 2019; Abstr. 142

Slide 8 of 30

Slide #9

GSK 2838232: A Novel Maturation Inhibitor

- Demographics: mean age 35y; 97% men; 61% white; mean BL CD4 416-619 cells/mm^3; mean BL VL 33,829-99,236 copies mL



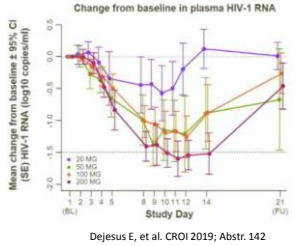
Dejesus E, et al. CROI 2019; Abstr. 142

Slide 9 of 30

Slide #10

GSK 2838232: A Novel Maturation Inhibitor

- Maximal antiviral effect observed in the 200 mg cohort with a mean -1.7 $\log_{10}$ decline in VL
- 2 pts with treatment-emergent A364 A/V mixtures and 1 with phenotypic resistance day 11
- No SAEs or deaths; all AEs Grade 1 or 2 with no specific pattern



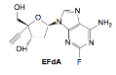
Dejesus E, et al. CROI 2019; Abstr. 142

Slide 10 of 30

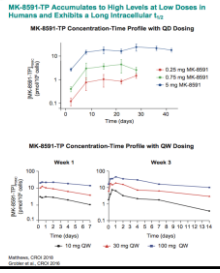
Slide #11

MK-8591: A Novel Nucleoside Reverse Transcriptase Translocation Inhibitor

- NRTTI with unique mechanism of action
- Potent against most resistant mutants; MK-8591-TP IC_{50} for HIV >4-fold lower than other NRTIs
- Long MK-8591-TP intracellular half-life
- Potential for multiple low dose options and high barrier to resistance



EFdA



Grobler JA, et al. CROI 2019; Abstr. 481

Slide #12

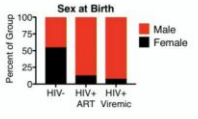
PGT121 Monoclonal Antibody: Therapeutic Activity in HIV-Infected Adults

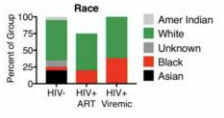
- Human IgG1 mAb targeting V3 env epitope; potent neutralizer of 60-70% of global HIV-1 viruses; active in SHIV-infected monkeys
- First in-human phase 1 safety and dose-ranging (3 – 30 mg/kg) study in HIV(-) and HIV(+) patients
  - HIV-infected pts included those suppressed on ART and viremic not yet on ART
- Safe and well-tolerated; half-life of 23d; 13d in viremic, HIV-infected pts

Stephenson KE, et al. CROI 2019; Abstr. 145LB

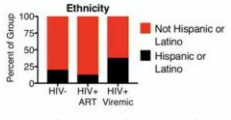
Slide #13

Baseline Demographic Characteristics





	Mean Age (years)	Mean BMI (kg/m2)
HIV-	27	26
HIV+, ART	44	26
HIV+, Viremic	31	25

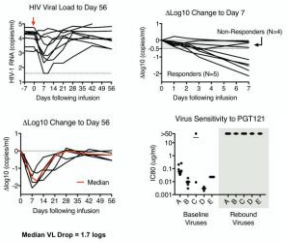


Stephenson KE, et al. CROI 2019; Abstr. 145LB

Slide #14

Therapeutic Activity of PGT121 Monoclonal Antibody in HIV-Infected Adults

- In those with high HIV viral load at baseline (3.3-5.0 log_{10} copies/mL), 4 had no response and 5 were "responders"
- Median VL decline in responders was 1.7 log
  - All rebounded by day 21
  - Baseline virus was sensitive to PGT121 in all; viruses after day 21 were all resistant

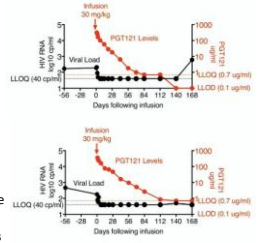


Stephenson KE, et al. CROI 2019; Abstr. 145LB

Slide #15

Therapeutic Activity of PGT121 Monoclonal Antibody in HIV-Infected Adults

- In those with low HIV viral load at baseline (<3.3 log_{10} copies/mL), prolonged antiviral response was seen
  - One pt had VL below LLOQ persisting beyond day 168 but rebounded when no further measurable PGT121
  - Second pt had no rebound virus
  - Viruses were sensitive to PGT121 at baseline and day 168
  - No evidence of enhanced cellular immune responses
  - Longest observed suppression following a single bNAb infusion



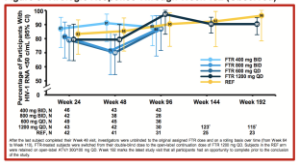
Stephenson KE, et al. CROI 2019; Abstr. 145LB

Slide #16

Fostemsavir (FTR, GSK3684934, BMS663068)

- Prodrug metabolized to temsavir; attachment inhibitor
  - No cross-resistance with other ARVs
  - Phase 2b dose ranging study in ART-experienced pts showed comparable rates of HIV-1 < 50 copies/mL (61-82%) vs. ATV/r (71%) + RAL + TDF at Week 48
  - After Week 48, FTR pts switched to 1200 mg QD + RAL + TDF vs. ATV/r + RAL + TDF continuation
    - Median age 39y; 60% male; 38% White; 30% Black

Figure 3. Virologic Response Through Week 192 (Observed)*



Comparable viral suppression and lower overall, cumulative and treatment-limiting AEs vs. ATV/r arm

Thompson M, et al. CROI 2019; Abstr. 483

Slide #17

Update on New Strategies

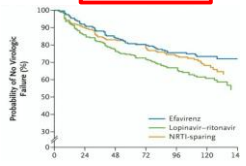
2-Drug Therapy & Novel Formulations

Slide 17 of 30

Slide #18

Are 2-Drug Regimens as Good as 3-Drug Regimens? It Depends…

ACTG A5142



Significantly worse lipid levels (RTV)
NNRTI resistance (66% vs 43%)

- Treatment-naive
  - LPV/r + EFV (A5142)
  - DRV/r + MVC (MODERN)
  - DRV/r + RAL (NEAT-001)*
  - DRV/r + 3TC (ANDES)
- Switch in virally suppressed
  - DRV/r + MVC (MARCH)
  - RAL + ATV (SPARTAN)
  - DRV/r + 3TC (DUAL)
  - ATV/r + 3TC (ATLAS-M, SALT)

Laura Waters, CROI 2019

Slide 18 of 30

Slide #19

Update on 2-Drug Regimens in Clinical Trials

- GEMINI-1 and -2: DTG + 3TC vs DTG + FTC/TDF in treatment naïve patients
  - Week 48: 91% vs 93% HIV-1 RNA < 50 copies/mL; no treatment emergent INSTI or NRTI mutations; DTG + 3TC did not perform as well in CD4 count ≤ 200 cells/mm^3 at baseline
- SWORD-1 and -2: Switch to DTG + RPV vs continue baseline 3-drug ART
  - Week 48: 95% HIV-1 RNA < 50 copies/ml in both groups; Week 100: 3 of 10 with VF in early switch arm had NNRTI resistance
- LATTE-2: CAB/ABC/3TC induction, CAB + RPV vs continue CAB/ABC/3TC
  - Week 32 (48): 94% Q4W vs 95% Q8W vs 91% oral CAB/ABC3TC had HIV-1 RNA < 50 copies/mL

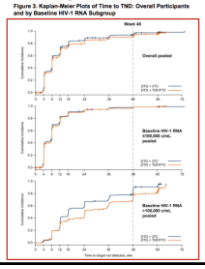
Underwood et al., Glasgow 2018; Abstr. P311; Aboud, AIDS 2018; Abstr. THPEB047; Orkin C, et al. Glasgow 2018; Abstr. P021; Cahn P, et al. AIDS 2018; Abstr. TUAB0106LB; Margolis D, et al. Glasgow 2018; Abstr. P118;

Slide 19 of 30

Slide #20

GEMINI 1 & 2: "Target Not Detected" Abbott Real Time Assay for VL < 40 copies/mL

- Similar proportions of participants in the DTG + 3TC and DTG + TDG/FTC arms had TND by snapshot at all weeks.
  - Numerically higher for 2-drug arm for BL VL > 100,000 copies/mL
- Median time to TND similar for both arms at Week 48
  - Shorter for 2-drug arm for BL VL > 100,000 copies/mL

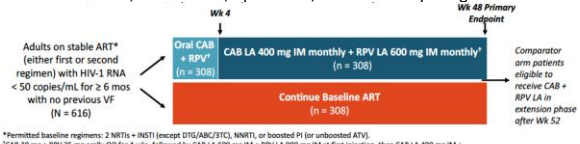


Underwood M, et al. CROI 2019; Abstr. 490

Slide #21

ATLAS: 48 Week Results from Switching to Cabotegravir + Rilpivirine in Virally Suppressed Patients

- Multicenter, randomized, open-label, non-inferiority design

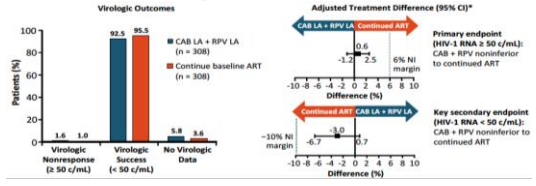


- Primary endpoint: Proportion with HIV RNA ≥ 50 copies/mL at week 48 (FDA snapshot) in ITT-E with 6% non-inferiority margin
  - Median age 42y; 67% male; 68% White; 23% Black

Swindells S, et al. CROI 2019; Abstr. 139

Slide #22

Atlas: Virologic Outcomes at Week 48

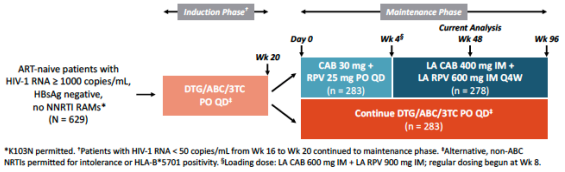


- 2 of 3 pts in CAB + RPV arm with VF had baseline NNRTI RAMs
- 95% of drug-related AEs were Grade 1 or 2; no drug-related SAEs, hypersensitivity or DILI; ISRs mild, most resolved within < 7d

Swindells S, et al. CROI 2019, Abstr. 139

Slide #23

FLAIR: Week 48 Results of Switching to CAB + RPV Following Oral Induction Vs. Continuing DTG/ABC/3TC



*K103N permitted. †Patients with HIV-1 RNA < 50 copies/mL from Wk 16 to Wk 20 continued to maintenance phase. ‡Alternative, non-ABC NRTIs permitted for intolerance or HLA-B*5701 positivity. §Loading dose: LA CAB 600 mg IM + LA RPV 900 mg IM; regular dosing begun at Wk 8.

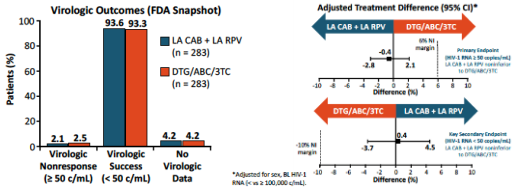
- Primary endpoint: Proportion with HIV RNA ≥ 50 copies/mL at week 48 (FDA Snapshot) with 6% noninferiority margin
  - Median age 34y; 78% male; 74% White; 18% Black

Orkin C, et al. CROI 2019; Abstr 140 LB

Slide 23 of 30

Slide #24

FLAIR: Week 48 Virologic Outcomes in ITT-E Population



- Confirmed VF: n=3 per arm; emergent NNRTI, INSTI resistance in all CAB + RPV failures; no resistance in DTG/ABC/3TC failures

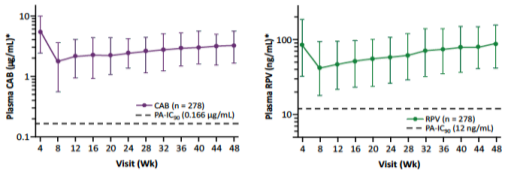
Orkin C, et al. CROI 2019; Abstr 140 LB

Slide 24 of 30

Slide #25

FLAIR: Week 48 Virologic Outcomes in ITT-E Population

- Plasma concentrations with IM CAB and RPV similar to effective PO regimens



- 94% of AEs were Grade 1 or 2, no drug-related hypersensitivity or DILI, 1 SAE (monoarticular arthritis); ISR most common AE; 99% Grade 1 or 2 most resolved in ≤ 7d

Orkin C, et al. CROI 2019; Abstr 140 LB

Slide 25 of 30

Slide #26

Where does 2-drug therapy fit?

- Clinical benefit in reducing toxicity…
  - Bone, renal toxicity (TDF)
  - Cardiovascular toxicity (ABC)
  - Mitochondrial toxicity of other NRTIs
  - Improved patient satisfaction
- Reduced cost?
  - Study visit frequency, monitoring
  - Supplies for injections
- But…
  - Underlying HBV
  - Adherence; delayed/missed doses
  - Drug-drug interactions (PI/r-, RPV-, INSTI-based 2-drug regimens)
  - Barrier to resistance (RPV-, RAL-based 2-drug regimens)
  - Toxicity
    - CNS, weight gain, neural tube defect (DTG)
    - Lipids (PI/r)

Slide 26 of 30

Slide #27

Where does 2-drug therapy fit?

- Clini… toxic…
  - Bo…
  - Ca…
  - Mi… NR…
  - Im…
- Redu…
  - St…
  - Supplies for injections

The Pozniak Paradox

Staff	1000 'stable' patients 30-minute clinic visits	Patients
Booking Prescribing Administering Chasing DNA	ORAL: 2 visits/year = 1000 clinic hours	Time Convenience Confidentiality Tolerability
	INJECTABLE: 6 visits/year = 3000 clinic hours	

…doses
…, RPV-,
…s)
…RAL-
…e defect
- Lipids (PI/r)

Slide 27 of 30

Slide #28

Cost-Effectiveness of Long-Acting ART

- CEPAC computer simulation study comparing:
  - Daily oral 3-drug therapy
  - LA ART in pts with multiple prior ART failures
  - LA ART in pts failing first-line ART
  - LA ART for ART-naïve pts
- LA ART increased overall life expectancy by 0.15-0.24 years (0.51-0.89 years in poorly adherent pts)
- LA ART cost-effective at annual drug cost of $40-$70K, $26-$31K, and $24-$27K, respectively, vs. $25-$28K for daily oral ART

Table 2. Survival Benefits of Long-Acting Antiretroviral Therapy

	Life Expectancy (y, Undiscounted)		Quality-Adjusted Life Expectancy (QALYs, Discounted 3%/Year)	
Clinical Role of Long-Acting ART	Overall	Patients With Adherence in Lowest 20%	Overall	Patients With Adherence in Lowest 20%
Daily oral ART only	23.72	13.53	12.89	8.52
Patients with multiple prior failures	23.87	14.04	12.95	8.71
Second-line therapy	23.90	14.17	12.97	8.80
Initial therapy for treatment-naive	23.96	14.42	13.01	8.95

Ross EL, et al. Clin Infect Dis 2015; 60:1102

Slide 28 of 30

Slide #29

Current Recommendations for 2-Drug ART

- DHHS Guidelines October 2018: "Consider when ABC, TAF & TDF cannot be used or are not optimal"
  - DTG + 3TC
  - DRV/r + 3TC
  - DRV/r once daily + RAL twice daily if viral load < 100,000 copies/mL and CD4 > 200 cells/mm^3
- IAS-USA Recommendations 2018:
  - For initial therapy → "…only recommended in the rare situations in which a patient cannot take ABC, TAF, or TDF"
  - Switch in the setting of viral suppression → "…can be used in patients with no prior virologic failure or transmitted drug resistance"

www.aidsinfo.nih.gov/guidelines; Saag MS, et al. JAMA 2018

Slide 29 of 30

Slide #30

Novel Formulations

- Novel long-acting drug eluting subcutaneous implant
  - TAF subcutaneous implant: Simulation suggested ≥ 0.6 mg/d eluted from the implant would be needed to provide TFV-DP concentrations above target in PBMCs; predicted lower exposure in cervical and rectal tissue
- Nanoparticle long-acting injectable pro-drug formulations
  - FTC: 2 formulations given IM to mice followed by 7d HIV challenge → 100% protection for both; 100% protection after 14d for one formulation
  - Cabotegravir: 2nd generation CAB prodrug nanoformulation → 10-fold improvement in PK; safe; sustained activity ~6mos; retained and slowly released by macrophages

Rajoli RKR et al., CROI 2019; Abstr. 487; Curley P, et al. CROI 2019; Abstr. 488; Kulkarni TA, et al. CROI 2019; Abstr. 489

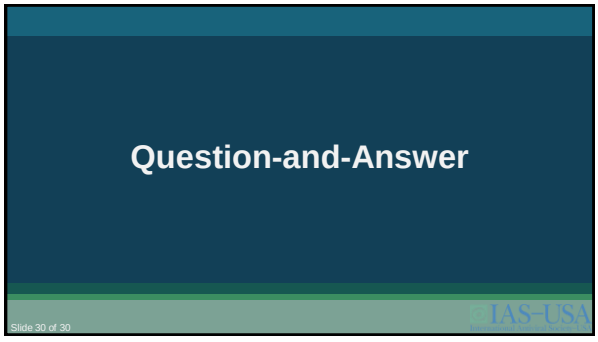
Slide 30 of 30

Slide #31

Summary

- The pipeline for development of novel investigational ARVs and research evaluating novel regimens and strategies is relatively robust and offer:
  - Comparable or improved activity compared to many current first line regimens
  - Improved tolerability
  - Improved resistance profiles
- The promise of novel long-acting injectable or implant formulations
  - Fewer drugs; fewer pills; potentially lower cost; less drug resistance?

Slide 31 of 30


Question-and-Answer
Slide 30 of 30
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