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

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
New Antiretroviral Drugs in Development

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

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 pEC95, supporting every 12 week dosing
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 (bevirimat) 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

GSK 2838232: A Novel Maturation Inhibitor

- Demographics: mean age 35y; 97% men; 61% white; mean BL CD4 416-619 cells/mm³; mean BL VL 33,829-99,236 copies mL

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
MK-8591: A Novel Nucleoside Reverse Transcriptase Translocation Inhibitor

- NRTTI with unique mechanism of action
- Potent against most resistant mutants; MK-8591-TP IC50 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

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

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

Baseline Demographic Characteristics

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<thead>
<tr>
<th></th>
<th>Mean Age (years)</th>
<th>Mean BMI (kg/m2)</th>
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<tbody>
<tr>
<td>HIV-</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>HIV- ART</td>
<td>44</td>
<td>26</td>
</tr>
<tr>
<td>HIV+, Viremic</td>
<td>31</td>
<td>25</td>
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Stephenson KE, et al. CROI 2019; Abstr. 145LB
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

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

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 (63-82%) 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

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

Thompson M, et al. CROI 2019; Abstr. 483
Update on New Strategies
2-Drug Therapy & Novel Formulations

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

- Treatment-naive
  - LPV/r + EFV (A5142)
  - DRV/r + RAL (NEAT-001)

- Switch in virally suppressed
  - DRV/r + MVC (MARCH)
  - DRV/r + 3TC (ANDES)
  - DRV/r + ATV (SPARTAN)
  - ATV/r + 3TC (ATLAS-M, SALT)

ACTG A5142

Significantly worse lipid levels (RTV) NNRTI resistance (66% vs 43%)
Laura Waters, CROI 2019

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/mm³ 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% Q4W vs 91% Q8W vs 91% oral CAB/ABC/3TC had HIV-1 RNA < 50 copies/mL

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 + TDF/FTC arm 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

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

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

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

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

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
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)

Where does 2-drug therapy fit?

The Pozniak Paradox

- Staff
  - Booking
  - Prescribing
  - Administering

- Patients
  - ORAL: 2 visits/year = 1000 clinic hours
  - INJECTABLE: 6 visits/year = 3000 clinic hours

- Time
  - Convenience
  - Confidentiality
  - Tolerability

- Reduced:
  - Sts
  - Supplies
  - Injections

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
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

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


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?
Question-and-Answer