Updates in HIV therapeutics and prevention

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Agenda

• New Agents, Old Classes
• Novel Therapies
• Updates on long-acting ART
• Updates on dual therapy
• Updates on adverse events
• HIV cure progress
• HIV vaccine progress
• Prevention/Pre-Exposure Prophylaxis
Disclosures

• None
New HIV drugs (from existing classes)
Bictegravir

- Phase III study (1490):
  - bictegravir + tenofovir alafenamide + emtracitabine (BIC/TAF/FTC) vs DTG/TAF/FTC
    - 645 ART-naïve, blinded
    - Non-inferiority at 48 weeks
    - Similar adverse events rates

- Phase III study (1489)
  - BIC/TAF/FTC vs DTG/ABC/3TC (Triumeq)
    - 629 ART-naïve randomized, blinded
      - Non-inferiority at 48 weeks
      - Nausea and neuropsychiatric adverse events higher in DTG/ABC/3TC group


Bictegravir

• *Bictegravir/tenofovir alafenamide/emtracitabine* is under FDA priority review for approval, due February 12, 2018
Doravirine

- NNRTI with fewer CNS adverse effects than EFV
- Can be used in the setting of the most common NNRTI resistance mutations (K103N, Y181C, G190A)
- DRIVE – phase III study
  - 766 participants randomized to 2 NRTIs + doravirine vs. 2 NRTIs + DVR/r
  - Doravirine was non-inferior to DRV/r at 48 weeks
  - Doravirine yielded a more favorable lipid profile than DRV/r

Molina JM et al. (Squires K presenting) Doravirine is non-inferior to darunavir/r in phase 3 treatment-naive trial at week 48. Conference on Retroviruses and Opportunistic Infections (CROI 2017), Seattle, abstract 45LB, 2017.
Doravirine

- **DRIVE-AHEAD**
  - Phase III study evaluating DOR/TDF/3TC vs TDF/FTC/EFV (*Atripla*) in ART-naïve participants
  - DOR-regimen was non-inferior at 48 weeks
  - Fewer neuropsychiatric adverse events with DOR-regimen

- **DRIVE-SHIFT**
  - Phase III study evaluating switch from boosted PI-based regimen to DOR/TDF/3TC
  - Results due March 2018

GS-9131

• NRTI – adenosine nucleotide analogue (like tenofovir)
• Prodrug, converted to active form in lymphocytes
• Minimal renal accumulation or potential for mitochondrial toxicity
• High barrier to resistance, not affected to common NRTI mutations (K65R, M184V, multiple TAMs)
• Low potential for drug-drug interactions

GS-PI1

• Novel PROTEASE INHIBITOR
• More metabolically stable than existing PIs, potentially can be dosed unboosted
• High in vitro barrier to resistance

Novel drug therapies
HIV Capsid Inhibitor

HIV Capsid Inhibitor

- GS-CA1
  - Capsid proteins self-assemble into hexamers, which assemble to form capsid core
  - GS-CA1 binds at interface of two adjacent molecules within a capsid hexamer
  - Interferes with capsid assembly, disassembly, and translocation of viral genetic material into nucleus

GS-CA1

GS-CA1

• High barrier to resistance (and has HIV-2 activity)
• Very long half-life (in rats, a single parenteral administration maintained therapeutic plasma concentrations for >10 weeks)
• Monkey/human PK data are needed
• More potent than available ART

Monoclonal Abs

• Ibalizumab
  – Binds human CD4 receptor (without depleting CD4+ cells)
  – Treatment strategy: Loading dose, then every 2 weeks (with optimized background regimen)
  – Among 40 heavily-treated HIV+ patients on failing regimens, 43% achieved viral suppression at 24 weeks
  – 24 participants continued to 48 weeks; 67% were suppressed <50 copies/mL at 48 weeks
  – Potential for those with highly resistant virus and very limited treatment options


Emu B, et al. 48-Week Safety and Efficacy On-Treatment Analysis of Ibalizumab in Patients with Multi-Drug Resistant HIV-1. IDWeek, San Diego, 2017
Monoclonal Abs

• PRO 140
  – Binds to human CCR5 receptor
  – Potential use as monotherapy in treatment-experienced patients with CCR5-tropic virus
  – Phase 2b trial: 16 patients with CCR5 tropic virus stopped oral ART, received weekly PRO 140 injections
    • 81% (13/16) maintained viral suppression at 40 weeks
    • 63% (10/16) maintained viral suppression at 2 years

Monoclonal Abs

- UB-421
  - Like ibalizumab, binds CD4 (but at a different site)
  - Patients stopped ART, received weekly dosing of UB-421 (N=14) or every other week (N = 15)
  - All remained virally suppressed at 8 and 16 weeks
  - Earlier in development compared to the other monoclonal Abs
Long-acting ART
Cabotegravir LA

• INSTI
• Injectable depot formulation with an elimination half-life of 25–54 days
• Under investigation for both HIV treatment and prevention
• Phase II trial (ÉCLAIR) and HPTN 077 indicate dosing every 8 weeks
• New nano-formulated pro-drug NMCAB demonstrated 300x plasma drug levels at 6-8 weeks


Rilpivirine LA

- NNRTI
- Injectable crystalline nanosuspension with plasma elimination half-life 44-61 days
- Under evaluation for HIV treatment (use in prevention remains indeterminate)
Cabotegravir LA + Rilpivirine LA

- LATTE-2:
  - CAB LA + RVP LA was non-inferior to EVF-containing 3-drug oral regimen
  - Administered every 4 or 8 weeks in ART-experienced participants
  - Sustained plasma drug levels up to 8 weeks

LATTE-2
Cabotegravir LA + Rilpivirine LA

• Background:
  – CAB LA + RVP LA was non-inferior to EVF-containing 3-drug oral regimen (LATTE-1)

• Methods
  – After 20-week induction on oral CAB/ABC/3TC, 286 participants randomized 2:2:1 to:
    • CAB LA 400mg/RPV LA 600mg Q 4 weeks
    • CAB LA 600mg/RPV LA 900mg Q 8 weeks
    • Continue daily oral CAB/ABC/3TC

• Results
  – Viral suppression at 96 weeks:
    • CAB LA 400mg/RPV LA 600mg Q 4 weeks – 87%
    • CAB LA 600mg/RPV LA 900mg Q 8 weeks – 94%
    • Continue daily oral CAB/ABC/3TC – 84%
  – Intermittent IM ART was non-inferior to oral therapy
  – >99% in IM groups reported satisfaction, 78% in oral group reported satisfaction with regimen

Tenofovir alafenamide

- Due to aqueous solubility, unable to formulate as a nano-suspension
- More potent than TDF
- No side effects of bone loss or reduced renal function
- Formulation as subdermal implant in development

MK-8591

• Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
• High, long-lasting (>7 days) concentrations in rat lymphoid tissue, macaque rectal/vaginal tissue
• In HIV+ humans, single oral dose resulted in viral suppression for 10 days
• Potential to suppress ongoing replication of HIV in lymph nodes
• Potential for use as less frequently-dosed PrEP


Elsulfavirine

- Long-acting NNRTI, $T_{1/2} \sim 8$ days
- Phase IIa, randomized, placebo-controlled trial comparing Elsulfavirine + TDF/FTC (N=60) to EFV/TDF/FTC (N=60) in ART-naïve patients
- At 48 weeks, both regimens demonstrated viral and immunologic efficacy
- Elsulfavirine regimen was better tolerated
- Studies evaluating less frequent dosing are pending

HIV-1 Combinectin BMS-986197

- Adnectin, proteins derived from human fibronectin, modified to inhibit highly-conserved regions required for HIV entry
- Multiple inhibitory bindings sites on one molecule, multiple modes of entry inhibition
- $T_{1/2} \sim 30-40$ hours

Other long-acting candidates

- GS-CA1 (capsid inhibitor)
- Ibalizumab
- PRO 140
- UB-421
Dual therapy
Why dual therapy?

• Minimize toxicity
• Minimize drug-drug interactions
• Minimize pill/burden
• Optimize cost effectiveness
Dolutegravir + Rilpivirine

• SWORD 1 & 2
  – Over 1000 treatment-experienced participants randomized to:
    • DTG + RPV
    • Stay on current 3- or 4-drug regimen
  – 95% dolutegravir + rilpivirine group maintained viral suppression at 48 weeks (equivalent to control arm)
  – No clear resistance emergence
  – Potential NRTI and PI-sparing regimen

Dolutegravir + Lamivudine

• ACTG A5353
  – Pilot study on DTG/3TC in ART-naïve
  – 120 participants enrolled
  – 31% with HIV RNA >100,000 cpm
  – At 34 weeks, 96% achieved viral suppression (HIV RNA <50 cpm)

Two large trials currently enrolling to evaluate this regimen vs first line triple therapy regimens in treatment-naïve patients (GEMINI-1 and GEMINI-2)

Taiwo BO, et al. ACTG A5353: A pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA <500,000 copies/ml. IAS 2017: Conference on HIV Pathogenesis, Treatment and Prevention, Paris, France July 23-26 2017
Dolutegravir + Lamivudine

- LAMIDOL
  - 104 treatment-experienced participants switched to dolutegravir + lamivudine
  - 101 maintained viral suppression at 40 weeks

And don’t forget...

- Cabotegravir LA + rilpivirine LA (LATTE-2)
New (and old) adverse effects
Osteopenia/osteoporosis

• Tenofovir disoproxil fumarate (TDF)/Tenofovir alafenamide (TAF) switch study with low BMD

• 214 subjects with low BMD (T-score < -2.0 at the lumbar spine, total hip or femoral neck) switched from TDF to TAF-containing regimen

• At 96 weeks, BMD increased by 2.5% at lumbar spine and hip

• Among 86 with baseline osteoporosis, 23% no longer met criteria

• TDF to TAF switch may be an important treatment strategy in patients with high fracture risk

Osteopenia/osteoporosis

- Zolendronate at time of ART initiation may persistently prevent bone loss
- 63 HIV+ participants randomized to zolendronate vs placebo at ART initiation
- Spine BMD remained 11% higher at 48 weeks in zolendronate arm, and 9-11% higher at 96 and 144 weeks

Cardiovascular disease

• Cumulative treatment with (ritonavir-boosted) darunavir is associated with cardiovascular events (myocardial infarction, stroke, sudden cardiac death or invasive cardiovascular procedure) (IRR 1.59, 95% CI 1.33-1.91)—59% per 5 years of exposure

• 5-year use independently associated with risk of MI (IRR = 1.51; 95% CI, 1.13-2.02) and stroke (IRR = 1.49; 95% CI, 1.08-2.07).

• Possible contributions from dosing or unmeasured cofounder

IRIS

• INSTI use in low CD4 is associated with IRIS
 • The Netherlands
  – Among patients with CD4 <200 cells/µL, INSTI use associated with IRIS (OR 3.25, 95% CI 1.83-5.80)
  – 38% (26/69) who received INSTI vs 16% (47/300) who received another ART class experienced IRIS
 • France
  – Among hospitalized patients with CD4 <200 cells/µL who receive INSTI, IRIS RR 1.99 (95% CI 1.09-3.47)
  – 3% (12/398) who received INSTI and 1.5% (29/1889) who received another ART class experienced IRIS (p=0.05)

Dolutegravir
Less tolerable than we thought?
Dolutegravir
Neuropsychiatric side effects

• Significant CNS adverse effects
  – Insomnia, dizziness, headache, paresthesias, poor concentration, depression

<table>
<thead>
<tr>
<th></th>
<th>Discontinuation due to any adverse event (12-month rate)</th>
<th>Discontinuation due to neuropsychiatric event (12-month rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>7.6%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>7.6%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>3.3%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Among 985 patients who started dolutegravir, 49 stopped due to neuropsychiatric adverse effects.

Neuropsychiatric AEs leading to discontinuation more frequently seen in:
• Women (HR = 2.64; 95% CI, 1.23-5.65, p = 0.012)
• Age >60 years (HR = 2.86; 95% CI, 1.42-5.77, p = 0.003)
• DTG + ABC (HR = 2.42; 95% CI, 1.38-4.24, p = 0.002)
Dolutegravir
Neuropsychiatric side effects

• The Quintiles IMS database (pharmacy and medical claims records)
• 54,151 HIV+ patients on DTG, EVG, RAL (2006-2016)
• Outcomes: insomnia/sleep disturbance, depression
• Insomnia/sleep disturbance events
  – significantly higher for patients treated with DTG vs EVG (IRR 1.21 [95% CI 1.09-1.33, p<0.001]), but not DTG vs RAL
• Incident depression
  – significantly higher for patients treated with DTG vs EVG (IRR 1.18 [95% CI 1.09-1.27, p <0.001]), but not DTG vs RAL

Wohl D, et al. Selected CNS outcomes among INSTI antiretrovirals. IDWeek, San Diego, 2017
Dolutegravir
Neuropsychiatric side effects

OPERA cohort

- 11,539 HIV+ participants who received DTG, RAL, EVG, EFV, RPV, DVR between 1/2013 – 8/2015
- No significant differences in incident psychiatric disorders between participants taking DTG and participants taking any of the other drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug discontinuation ≤14 days after incident psychiatric disorder diagnosis (%)</th>
<th>p-value (reference: DTG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG</td>
<td>0.3</td>
<td>--</td>
</tr>
<tr>
<td>RAL</td>
<td>1.7</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EVG</td>
<td>0.8</td>
<td>p=0.04</td>
</tr>
<tr>
<td>EFV</td>
<td>2.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>RPV</td>
<td>1.0</td>
<td>p=0.006</td>
</tr>
<tr>
<td>DRV</td>
<td>1.0</td>
<td>p=0.006</td>
</tr>
</tbody>
</table>

Dolutegravir
Neuropsychiatric side effects

• OPERA cohort
  – Baseline anxiety more likely in participants on DTG than EFV, DRV, or RPV (all \( p<0.001 \)).
  – Baseline depression more likely in participants on DTC than EFV, RPV, or EVG (all \( p<0.0001 \)).
  – Baseline insomnia more likely in participants on DTG than EFV, DRV, RPV, or EVG (all \( p<0.0001 \)).

Figure 2. History of psychiatric diagnoses at baseline by anchor agent

Dolutegravir
Weight gain

• 495 HIV+, virally suppressed patients on EFV/TDF/FTC at VUMC
  – 136 switched to INSTI-containing regimen
    • 58 containing DTG
    • 21 containing RAL
    • 42 containing ELV
  – 34 switched to PI-containing regimen
  – 325 remained on EFV regimen

• Those switched to INSTI-containing regimen gained significantly more weight at 18 months than those that stayed on initial regimen
  – +2.9kg vs +0.9kg, p=0.003
  – Non-significantly higher weight gain among DTG group (+5.3kg) vs RAL/ELV group (+2.8kg)

HIV Cure
HSCT

• 55yoM with HIV since 1990, B-cell ALL diagnosed 2013 underwent allogeneic HSCT with wild-type CCR5 donor
• Complicated by pneumocystis pneumonia, GVHD
• Noted to have reduced HIV DNA, undetectable HIV RNA in gut biopsies, and HIV antibody levels
• 2 years post-HSCT, he underwent observed ART interruption, remained undetectable for 287 days
HIV Vaccine
HIV Vaccine

• BCN02-Romi (NCT02616874)
  – Single arm, proof-of-concept study
  – Combination of HIV vaccination and HIV reservoir activation
  – 15 participants with HIV, undetectable for >3 years
    • Received immunization and 3 weekly doses of romidepsin (histone deacetylase inhibitor)
    • Stopped ART unless HIV RNA >2,000 copies/mL
    • FOUR have remained off ART for 22 weeks
  – Demonstrated POST-TREATMENT CONTROL

Histone Deacetylase Inhibitors

• “SHOCK AND KILL” approach to purging HIV reservoirs

HIV Vaccine

• Antibody-Mediated Prevention (AMP)
  – Utilizing a broadly-neutralizing anti-HIV antibody (VRC01)
  – VRC01 can neutralize 90% of HIV-1 isolates
  – Clinical trial HVTN 703/HPTN 085 is enrolling now
    • Randomized to VRC01 30mg/kg, 10mg/kg, or placebo
    • Ten infusions, once every 8 weeks
  – Implication is a long-lasting HIV prevention strategy

https://ampstudy.org/
HIV Vaccine

• APPROACH
  – Mosaic vaccine (Ad26.Mos.HIV.)
    • Induces immunologic responses to multiple HIV clades
  – 66% protection in macaque models
  – Phase 2a, 393 participants enrolled
    • All have developed anti-HIV antibody responses

NCT02315703. clinicaltrials.gov. Accessed October 9, 2017
Pre-Exposure Prophylaxis
Pre-Exposure Prophylaxis

• Out of 1.2 million individuals at high risk for HIV
  – 136,000 are receiving TDF/FTC
    • Up from 80,000 the previous year
Tenofovir Alafenamide (TAF)?

- Achieves high intracellular concentrations, but lower plasma and tissue concentrations than TDF
  - 13-fold lower than TDF in rectal tissues
  - 11-fold lower than TDF in cervicovaginal fluid

Due to low plasma and tissue concentrations, TAF’s use in PrEP is uncertain

Tenofovir Alafenamide (TAF)?

• However...
  – An animal study suggests efficacy
    • 6 macaques received TAF/FTC before and after rectal weekly exposure of SHIV or up to 19 weeks
    • 6 macaques received placebo
  
  • None of the 6 receiving TAF/FTC acquired SHIV, while all 6 receiving placebo did

Cabotegravir LA

• Integrase inhibitor with long half-life
• Long acting, depot-controlled nanosuspension has an even longer half-life (25-54 days)
• Use as PrEP in phase 2 trials:
  – Oral lead-in
  – Will likely need every 2 months (6 injections/year)
  – Injection site reactions common
  – Most patients still preferred this over daily oral PrEP

Rilpivirine LA

• MWRI-01 trial
  – 8 women and 4 men randomized to varying doses (600mg, 1200mg, or 1200mg at 0 months, 2 months, 4 months)
  – Ex vivo explant infection model
    • Rectal tissue: infection inhibited 4 months after last injection
    • Cervical tissue: infection inhibited 2 months after first injection
MK-8591

- Nucleoside reverse transcriptase translocation inhibitor (NRTTI)
- High, long-lasting (>7 days) concentrations in rat lymphoid tissue, macaque rectal/vaginal tissue
- Weekly dosing with MK-8591 (N=8) vs placebo (N=8) in macaques
  - All subjected to repeated intra-anal exposure to SHIV
  - After 12 weeks, all in control group were infected with SHIV, 0 in MK-8591 group were infected
Pharmacy-Driven PrEP Initiatives

• “One-Step PrEP” in Seattle, WA
• Pharmacist provides screening, counseling and provision of PrEP under the remote oversight of physician
• Between 2015-2016, initiated PrEP in 245 patients, 43% without a PCP
• Retention was 75%
• Financially sustainable for pharmacy

Walgreen’s

• As of 7/2017, select sites offer PrEP counseling, STI screening, and Truvada® provision
• Sites are those with existing Walgreens Healthcare Clinics with APNs, PAs
• Sites include:
  – Cincinnati, Cleveland, Columbus, Dallas, Denver, Kansas City, Knoxville, Las Vegas, Louisville, Memphis, Nashville, Orlando, Philadelphia, Phoenix, Tucson, Washington D.C., and Wichita.
• [https://www.walgreens.com/topic/scheduler/hiv-prep.jsp](https://www.walgreens.com/topic/scheduler/hiv-prep.jsp)
STI Prophylaxis

• Among participants in IPERGAY
  – 232 randomized to doxycycline 200mg PO x1 up to 72 hours after sex vs. placebo
  – After median 8.7 month follow-up
    • 70% (7 vs. 21) fewer chlamydial infections in doxycycline arm
    • 73% (3 vs. 10) fewer syphilis infections in the doxycycline arm
    • No effect on gonorrhea (22 infection in doxycycline arm, 25 in control arm)

• PARTNER
  – European prospective study of ~900 sero-discordant partners in which the HIV+ partner is undetectable, representing 58,000 condomless sex acts
  – No transmissions were observed.

• OPPOSITES ATTRACT
  – prospective study from Australia, Thailand and Brazil of 343 gay, sero-discordant partners representing 12,000 condomless sex acts.
  – No transmissions were observed.


Thank you!

Questions?