CROI 2017 Highlights
What’s New in Antiretrovirals (Part 2)
Ann Collier, MD
High interest globally in DTG-based regimens
- U.S. Drug “du jour”
- 1st line for ART start in Brazil
- Generic FDC of DTG/TAF/3TC coming to RLS

DTG monotherapy (as a switch strategy) is sub-optimal

Dual drug regimens of interest (some non-inferior)
- DTG + rilpivirine (SWORD)
- CAB + rilpivirine (open-label 144 wk extension of LATTE)
- DRV/r + 3TC (>1000 pts in Europe, non-inferior to 3-drugs)
- DTG + 3TC phase 3 studies underway
- Multiple questions: durability of response, residual viremia, reservoirs, inflammation, cost
Desirable Characteristics for “Ideal ART”

- Lower doses/simpler regimens
- Lower costs
- Better Rx for pediatrics & adolescents
- More FDCs
- More “universal” regimens (globally for all populations)
  - Less drug-drug interactions (e.g. with rifampin)
  - Better safety in pregnancy & with breast-feeding
  - Safer ARVs if co-morbidities
- Better resistance profiles
Novel ARVs in Development: New Class

- **HIV Capsid inhibitor** (GS-CA1)
  - Inhibits HIV at *multiple* steps in life cycle
    - Inhibits disassembly
    - Prevents core assembly (non-infectious virus)
  - Potent inhibition: all clades, multi-resistant HIV
    - EC$_{50}$ 60-140 picomolar
  - Binding site highly conserved, mutations with serial passage
  - *PK data in rats (SQ)* suggest potential for monthly dosing

*Potential for low-dose, long-acting, drug with new mechanism active against MDR strains of HIV*

Drugs in *Early* Development

**GS-9131 (NRTI)**
- Potent against NRTI resistant viruses (e.g. m184V, multiple TAMs, T69 insert)
- $\text{IC}_{50}$ 2.3 μM (HIV-1 and HIV-2)
- No inhibition of gamma polymerase (less toxicity potential?)

*Potential for daily dosing*

**GS-PI1 (PI)**
- Active against PI-resistant clinical isolates
- Slow metabolism: liver microsomes 4% vs 83-92% other PIs
- $T_{1/2}$ in rats/dogs: 13-14 hr vs <30min for other PIs

*Potential for unboosted PI with daily dosing*

K White; J Link, CROI 2017
Bictegravir (GS-9883)

- Potent integrase inhibitor (EC$_{95}$ 11.4 nM)
- Active against ISTI resistant isolates
- 70% oral bioavailability (no boosting)
- 99% protein binding (no CNS penetration)
- T$_{1/2}$ 18 hr without “boosting”
- Metabolism: CYP3A4 & UGT1A1; Inhibits OCT2
- Needs to be staggered by 2 hr from antacids
Bictegravir Phase II Study

Double-blind, randomized 2:1 BIC 75 mg vs DTG (with FTC+TAF)
- 91 ARV-naïve: 90% men, 37% BI, CD4 444, VL 4.5 log_{10}
- AEs similar (nausea 12%); Lab AEs: mild ↑CPK, AST; ↓glucose
- Inhibits tubular secretion (OCT2); small eGFR↓

Conclusions:
High efficacy, safe, well-tolerated
Phase III studies ongoing
Optimized FDC
BIC 50 mg/FTC/TAF

P Sax, CROI 2017;
Novel NNRTI: Phase 3 Results

**Doravirine** (MK-1439)
- Phase III, randomized 1:1, placebo-controlled, multi-national
- DOR 100 mg vs DRV/r with 2 NRTIs (TDF/FTC or ABC/3TC)
- HIV RNA<50 at 48 wk FDA snapshot; 10% non-inferiority
- 771 ARV-naïve pts: 85% male, 20%Bl, RNA 4.4 log_{10}, CD4 420, 30% non-clade B
- Similar discontinuation rates (2% due to AEs)
- AEs generally similar
- DOR: Better lipid profiles

J-M Molina, K Squires et al, CROI 2017
Conclusions:
New, safe, potent once daily NNRTI
Plan for: DOR/TDF/FTC FDC
Overview of Long-acting Antiretrovirals (1)

- Patients more enthusiastic than health-care workers
- Potential for infrequent dosing
  - DOT?
  - Better health privacy?
  - Strategy to combat pill fatigue?
  - Increased adherence?
- Example of injectable/implantable contraceptives
- Multiple Issues:
  - Injectable vs implants?
  - Injection volume, # of injections/dose
  - PK issues: Need for oral lead-in, PK “tail” & resistance potential
  - Management of AEs
Long-acting Antiretrovirals (continued)

- Multiple drugs & strategies in different development stages
  - Early stage compounds (GS-CA1 & MK-8591)
  - Monoclonal antibodies
  - Modification of existing ART (3TC; dolutegravir)
  - Nanoformulations (potential to decrease doses & costs)
  - Targeted Long-Acting Combination ART (TLC-ART)
    - 3-4 drugs in a lipid nano-suspension
    - prolonged plasma & LN conc. with SQ injection in preclinical studies

Schematic of TLC-ART 101

Drug in Early Development

MK-8591 (EFdA)

- Novel mechanism of action: nucleoside reverse translocation inhibitor
- Potent anti-HIV effects
  - PBMC EC$_{50}$ 0.2 nM; active vs HIV-1, HIV-2, MDR strains
  - CROI 2016: Phase I single dose -1.6 log$_{10}$ HIV RNA at 7 days
- Preclinical Results
  - Rapid distribution to LNs in rats (3x higher conc. in LN than blood out to 24 hrs)
  - NHP once weekly dosing (conc. similar in PBMC, vagina, rectum)
- Potential for Rx, Prevention, Oral, Injectable

J Grobler, CROI 2017
Monoclonal Antibodies

• PRO140 for Treatment
  - Humanized monoclonal Ab (targets CCR5)
  - Optional long-term monoRx extension with 2, 1mL SQ injections weekly
  - Of 16: 10 still on (93-106 wks), 5 VF, 1 moved
  - At 2 yrs: VL<1 copy in 7/10 (rest 4-19 copies/mL)
  - “Well tolerated”, no d/c 2° AEs, no anti-PRO140 Abx
  - Ongoing Phase III monoRx study underway

• Broadly-neutralizing monoclonal Abs for “cure”, Rx & prevention
  - VRC01 (CD4-binding site Ab):
    - Randomized, double-blind study vs saline
    - 2 IV doses 3 wks apart
    - 40 HIV-infected persons on ART with HIV RNA <40
    - Safe. Didn’t impact low-level viremia or HIV DNA in PBMCs
  - Multiple ongoing phase II studies; LA versions in development
Cabotegravir-LA + Rilpivirine-LA for Treatment

• Novel integrase inhibitor similar to DTG & new form of NNRTI
• 2016 Phase II study (LATTE-2): q4 wk and q 8 wk injections comparable to oral therapy as maintenance ART
• Cabotegravir-LA detectable in plasma in pts. 52 wks after last injection
• Open-label, extension of original oral LATTE study to 144 wks
  - 138 of 181 original CAB + RIL pts.
  - At 144 wks, 76% HIV RNA <50 copies/mL & 8% VF
  - 4% had drug related AEs (3% d/c); No drug-related SAEs
  - Conclusion: oral CAB & RIL safe and well tolerated
• 2 multi-national randomized phase III studies underway comparing LA parenteral combination of CAB & RIL to oral ART

C Flexner. CROI 2017.
Google Images.
CROI 2017 Implications for ART Treatment

- ARV drug development is continuing
- ART in use likely to continue to change over time
- Less companies with active R & D programs?
- High interest in FDCs
- Increasing interest in long-acting formulations, including injectable forms and implants
- Continued potential for overlapping uses of ART (treatment & prevention)
- Room for agents/regimens that address specific needs or patient populations
THANK YOU

Questions?