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The following faculty and planning committee members have no financial relationships to disclose:

- Cynthia H. Miller, MD, AAHIVS
- Carl J. Koenigsmann, MD
- Catherine Marra, RN
- Sarah J. Walker, MS
- Jennifer Price
Disclosures

- Speaker
  - AbbVie, BMS, Gilead, Janssen, Merck
- Consultant
  - BMS, Gilead, ViiV

Roadmap

- Prevention
- Current Meds and Trends
- Adverse Events
- New Meds/Strategies
- HCV
Slide Credit/Comments

- Clinical Care Options (noted on select slides)
- Some, scanned from posters on CROI Website
- Others were homemade
- Plenary presentations and all posters available on line

HIV PREVENTION
PrEP Breakthrough

- 50 year old MSM
- Amsterdam, adherence confirmed
- 8 months roughly on PrEP
- Man had had over 50 partners a month with whom he had had condomless sex (averaging 3.7 partners each time he had sex)
- May have had repeated exposures to HIV as well as damage to the lining of the rectum
- Rectal chlamydia and gonorrhea diagnosed as well

Case Report: Wild-Type HIV-1 Infection in MSM Adherent to PrEP

- 50-yr-old MSM using daily oral FTC/TDF PrEP in Amsterdam Pre-Exposure Prophylaxis project
  - Reported drug use during sex, excellent PrEP adherence
  - Median number of condomless anal sex partners per day in each mo following PrEP initiation ranged from 2-5
  - Tested positive for rectal STIs - gonorrhea (2x) and chlamydia
- HIV Ag/Ab results negative at PrEP start and after 1, 3, 6 mos
  - After 8 mos: fever, dysuria, HIV Ab positive, Ag negative, and HIV-1 RNA negative; PrEP discontinued and HIV-1 RNA detectable 3 wks later; no drug resistance detected
  - Dried blood spot TFV-DP levels protective at Mos 6 and 8
- HIV-1 RNA suppressed 1 mo after initiating ART
Wild-Type HIV Infection While Adherent to PrEP

- First reported case of WT HIV infection in person with protective TFV-DP levels
  - Seroconversion pattern atypical: no HIV DNA in bulk PBMCs, no HIV DNA or RNA in 3 sigmoid biopsies at time of seroconversion
  - Hypothetical mechanisms of infection
    - High number of repeated HIV exposures with or without mucosal damage?
    - Decreased TDF and/or FTC levels in rectal mucosa?
- Highlights importance of periodic HIV testing during PrEP use and awareness of potential for atypical seroconversion patterns

STIs and STI PEP in PrEP Users

- IPERGAY: randomized double-blind trial of event-driven oral FTC/TDF vs PBO as on-demand PrEP in high-risk MSM in France and Canada\(^1\)
  - 86% reduction in HIV infection risk with on-demand PrEP (\(P = .002\)); 41% acquired STIs
- Among 220 MSM initiating PrEP at STD clinic in Seattle, WA, from Sept 2014 to June 2016\(^2\):
  - Decreased rate of condom use during receptive anal intercourse with HIV+ partners and increased rates of CT and GC diagnosis following PrEP initiation (vs pre-PrEP baseline)
- Current study enrolled participants from open-label IPERGAY extension\(^3,4\)
  - 232 men randomized 1:1 to on-demand doxycycline (two 100-mg pills within 72 hrs following condomless intercourse; no more than 6 pills/wk) vs no PEP
  - All participants given condoms, risk-reduction counseling, HIV & STI testing every 8 wks

---

On-Demand Doxycycline STI PEP for MSM Using On-Demand Oral FTC/TDF PrEP

- Median follow-up: 8.7 mos
- 73 new STIs: 28 in PEP arm, 45 in no PEP arm
- Rate of GI AEs: 53% in PEP arm vs 41% in no PEP arm ($P = .07$)
- 8 pts (7%) discontinued PEP for AEs

<table>
<thead>
<tr>
<th>STI</th>
<th>HR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any STI</td>
<td>0.53 (0.33-0.85)</td>
<td>.008</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>0.83 (0.47-1.47)</td>
<td>.52</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>0.30 (0.13-0.70)</td>
<td>.006</td>
</tr>
<tr>
<td>Syphilis</td>
<td>0.27 (0.07-0.98)</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

Although effective for reducing chlamydia and syphilis rates in the short term, concerns about antibiotic resistance and long-term safety/efficacy need to be addressed before widespread adoption is considered.

Doxy PEP in PrEP Study

- IPERGAY study presented a randomized study of on-demand doxycycline (2x 100 mg tabs) as post-exposure prophylaxis for STIs in 232 high risk MSMs.
- Subjects were screened for STIs every 8 weeks
- After 8.7 months, the incidence of any STI in the PEP and no-PEP arms was 28 and 45, for incidences of 37.7/100 pt yrs vs 69.7/100 pt yrs.
- The hazard ratios for syphilis and chlamydia were 0.30, and 0.27, respectively, and no benefit was seen for GC infection (HR 0.83, CI 0.47-1.47).
- Patients in the PEP arm used an average of 7 pills/month. GI adverse effects occurred in 53% and 41% of PEP and no PEP patients, and led to discontinuations in 7% of PEP patients.
- The investigators called for further studies, and they were careful to note that this practice is not yet ready for widespread use, given the danger of rising drug resistance, in particular with gonorrhea.
Current Status of INSTI Resistance in the United States

- Transmitted INSTI resistance remains rare and rates of on-treatment INSTI resistance continue to be low\(^1\)\(^-\)\(^3\)
- CDC National HIV Surveillance System\(^1\):
  - Prevalence of INSTI resistance for HIV diagnoses through 2014: 65/14,468 (0.4%)
  - Pre-ART prevalence of INSTI resistance (ie, transmitted): 2/4631 (0.04%)
- UNC CFAR HIV Clinical Cohort\(^2\):
  - 2015 INSTI resistance prevalence in 685 pts who began ART in 2007 or later: 1%
- In modeling study assuming 0.1% rate of transmitted INSTI resistance and $250 cost per test: pre-ART INSTI resistance testing correlated with worse outcomes, higher costs vs no test\(^3\)


Slide credit: clinicaloptions.com
INSTI Testing at Baseline, Yes or No

- Modelling Study
- Authors concluded NO
- WHY?
  - Prevalence of transmitted integrase resistance low
  - DTG-based regimens will likely succeed even when resistance to first-generation INSTIs is present
  - Even if virologic failure occurs, it will delay use of a salvage regimen only briefly

Koullias Y, et al CROI 2017, Seattle Abstract #493

Rare, but are we testing?

Two Reported Cases of Only Primary Integrase Inhibitor Drug-Class Resistance Transmission including the First Reported Case of Primary Elvitegravir Resistance Transmission

Ricky Hsu, MD

Open Forum Infect Dis (2016) 3 [suppl._1]: 1506.
DOI: https://doi.org/10.1093/ofid/ofw172.1208
Published: 25 October 2016
### Case Report: Emergence of INSTI Resistance in Acute Infection Treated With DTG + FTC/TDF

- **45-yr-old man, no PMH, presented with *P. jirovecii* and new acute HIV diagnosis**
- Initiated DTG + FTC/TDF and discharged; readmitted to ICU several days later for worsened hypoxia
- HIV-1 RNA increased after readmission despite med adherence (including directly observed therapy in hospital) and no concurrent divalent cation use
  - DRV/RTV added, HIV-1 RNA decreased
  - Pneumonia improved and pt discharged
- HIV-1 RNA remains suppressed; DRV/RTV switched to RPV for diffuse erythroderma
- Rapid INSTI emergence by deep seq: eg, Q148K population increased from 0.0015% at Timepoint 1 to 20.9% at Timepoint 3

### DTG Resistance, Tx Naïve Patient

- Patient was treated with TDF/FTC plus DTG as initial therapy (HIV RNA 1,970,000 copies/ml and CD4 78 cells/mm$^3$)
- Population sequencing showed no clinically significant resistance mutations in reverse transcriptase (RT) or protease (PR).
- Baseline IN genotype was not performed.
- HIV RNA initially decreased to 2,770 copies/ml after two weeks, but then increased to 15,700 copies/ml and plasma samples were collected serially over an eight day period.
- Emergence of Q148K. Population sequencing corresponding to the middle time point showed RT mutations M184V and V118I and confirmed IN mutation G163E.
- First description of potential DTG-resistance in a treatment naive individual.
DTG Monotherapy failures

- Observational, uncontrolled analysis of virologic failure and resistance in 178 patients on DTG monotherapy as maintenance therapy in 3 large European cohorts
- 11 patients (6%) experienced virologic failure, and 7 (4%) had INSTI resistance mutations via one of three pathways, 148 R/H (3 pts), 155H (2 pts), and 118R (2 pts).
- Why was it done? IRB approval? Ethics?

Commentary

Dolutegravir monotherapy: when should clinical practice be clinical research?

Joel Gallant1,*, Jeremy Sugarman2

1Southwest CARE Center, Santa Fe, NM, USA
2Johns Hopkins University School of Medicine, Baltimore, MD, USA
*Corresponding author e-mail: jgallant@southwestcare.org
IRIS and INSTIs

- Does ART with integrase inhibitors increase the risk of immune reconstitution inflammatory syndrome (IRIS)? The answer is yes, based on two studies conducted in non-TB endemic region.

144 week, Studies 104 and 111, Genvoya verus Stribild

- Virologic failure was similar between groups (Genvoya, 4.6 percent; Stribild, 3.9 percent)
- Fewer discontinuations on Genvoya due to adverse events or other reasons not related to efficacy (Genvoya, 11.2 percent; Stribild, 16.0 percent)
- Protein markers of glomerular and tubular function were examined all favored Genvoya
- Statistically significant difference in the median change in estimated glomerular filtration rate (eGFR) from baseline to Week 144 (Genvoya, -1.6 mL/min; Stribild, -7.7 mL/min, p<0.001)
- No cases of renal tubulopathy in the Genvoya arm and four cases in the Stribild arm
- No participants on Genvoya had renal-related discontinuations compared to 12 participants in the Stribild arm (p<0.001).

Arribas J, et al. CROI 2017, Seattle Abstract #453
144 week, Studies 104 and 111, Genvoya versus Stribild

- Decreases in bone mineral density (BMD) were significantly less in the Genvoya group versus the Stribild group for both lumbar spine and total hip (spine: Genvoya, -0.92 percent; Stribild, -2.95 percent, p<0.001; hip: Genvoya, -0.75 percent; Stribild, -3.36 percent, p<0.001).

- Patients on Genvoya had statistically higher increases in total, LDL and HDL cholesterol from baseline to Week 144 compared to patients on Stribild. There was no significant difference in the total cholesterol-to-HDL ratio at Week 144, nor any difference in the rate of initiation of lipid-modifying agents.
Resistance, through 144 weeks

- 24 patients developed virologic resistance
  - 12 patients in each arm
- Genotypic resistance data
  - NRTI and EVG resistance (n=8), NRTI resistance only (n=4) in the TAF group
  - NRTI and EVG resistance (n=7), NRTI resistance only (n=4), and EVG resistance only (n=1) in the TDF group

DTG exposure with RTV or Cobicistat

- 10 patients on dolutegravir and darunavir + ritonavir who switched to co-formulated darunavir/cobicistat
- Mean DTG trough concentrations increased 100% following the switch in 9 of 10 patients, with no effect on darunavir levels.
- No effect on serum creatinine levels were seen following the change.
- The authors speculated that the greater effect of COB on intestinal efflux transporters may have led to higher trough concentrations of DTG
Miscellaneous

- Rilpivirine in pregnancy
  - Abstract 754, 16 patients
  - 50% lower levels in pregnancy during 3rd trimester
  - No cases of virologic failure
  - PANNA European network, ? Food effect
- Similar with Stribild as well, 44% reduction in EVG levels in 3rd trimester abstract 755

ADVERSE EVENTS
NA-ACCORD: Smoking, HTN, and Cholesterol Contribute to MI Risk in HIV Infection

- Retrospective meta-analysis of pts with validated MI events from 7 clinical cohorts within NA-ACCORD from 1/2000 to 12/2013 (N = 29,515)[1]
- Population attributable fraction: proportion of MIs avoidable by prevention of modifiable HIV-related and traditional MI risk factors
- 347 pts (1.2%) had type 1 MI due to plaque rupture
- Sensitivity analysis added for 16,687 pts (57%) with BMI data, 227 had type 1 MI
- ~ 40% MI reduction achievable through prevention of smoking, elevated TC, or HTN, regardless of BMI

D:A:D: Exposure to ATV/RTV or DRV/RTV and Risk of CVD

- Prospective analysis of pts followed from 1/1/2009 (BL) to earliest CVD, last visit + 6 mos, or 2/1/2016 (N = 35,711)
  - 1157 pts (3.2%) developed CVD (MI, stroke, sudden cardiac death, invasive CV procedure)
- Cumulative expos. to DRV/RTV, but not ATV/RTV, assoc. with increased CVD risk in multivariate analysis: 59% risk increase per 5-year of DRV/RTV
  - Assoc. does not appear to be mediated through dyslipidemia, in contrast with first-generation PIs
- Limitations: potential for unmeasured confounding; observational study; unable to distinguish between DRV/RTV 800/100 mg QD vs DRV/RTV 600/100 mg BID

<table>
<thead>
<tr>
<th>CVD Risk per 5 Yrs of ARV Exposure, IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
</tr>
<tr>
<td>Univariate</td>
</tr>
<tr>
<td>Multivariate</td>
</tr>
</tbody>
</table>
| *Adjusted for: BMI, CKD, DM, CD4, dyslipidemia.

---

DAD Database, CVD with DRV or ATV

- Additional adjustment for time-updated dyslipidemia, and other factors potentially on the causal pathway to CVD, did not affect the association (DRV/r 1.53 [1.28-1.84] and ATV/r 1.01 [0.88-1.16]/5 years).
- Associations remained consistent after adjustment for bilirubin levels (associated with ATV/r use and potentially protective of CVD); when stratifying for whether DRV/r was used as the first ever PI/r containing regimen or not (p=0.29 for interaction); whether DRV/r was used with a non-nucleoside reverse transcriptase inhibitor or not (p=0.43 for interaction); and in those at high vs. low estimated 5 year CVD risk (p=0.12 for interaction).

Discontinuation of INSTI, prospective cohort

- 2,096 patients in a prospective multicenter cohort in Spain.
- 430 patients stopped an INSTI an INSTI,
  - 74 (17%) were attributed to an AE
  - DTG/ABC/3TC (2.9%), DTG + TDF/FTC (2.5%), RAL/ABC/3TC (5.8%), RAL + TDF/FTC (4.7%), and ELV/COB/TDF/FTC (3.4%),
  - For the same regimens, D/Cs due to CNS toxicities were 2.1%, 0%, 0.9%, 2.1%, and 0.7%.
  - The adjusted hazard ratios for CNS toxicity for DTG compared to RAL and to ELV were 3.18 and 4.93, respectively.
  - These data support other studies showing a high level of tolerability for all INSTIs, and a higher level of discontinuations for CNS toxicity in DTG compared to RAL and ELV.
NEW STRATEGIES, NEW DRUGS

SWORD 1 & 2: Switch to DTG + RPV, 48 week Study

Identically designed, randomized, multicenter, open-label, parallel-group, non-inferiority studies

Screening

Early switch phase

Late switch phase

Continuation phase

Day 1

Week 52

Week 148

Inclusion criteria

- On stable CART 6 months before screening
- 1st or 2nd ART with no change in prior
- regimen due to VI
- Confirmed HIV RNA <50 c/mL during the 12 months before screening
- HIV negative

Primary endpoint at 48 weeks: subjects with VL <50 c/mL [ITT-E snapshot]

Countries

- Argentina
- Australia
- France
- Germany
- Italy
- Russia
- Spain
- Taiwan
- United States
- United Kingdom

Libre J, et al. CROI 2017, Seattle Abstract #44LB
SWORD 1 & 2: BL Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DTG + RPV (n=513)</th>
<th>CAR (n=511)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) ≤50 years</td>
<td>43 (11.1)</td>
<td>43 (10.2)</td>
</tr>
<tr>
<td></td>
<td>147 (28)</td>
<td>142 (28)</td>
</tr>
<tr>
<td>Female</td>
<td>120 (23)</td>
<td>108 (21)</td>
</tr>
<tr>
<td>Race, non-white</td>
<td>92 (18)</td>
<td>111 (22)</td>
</tr>
<tr>
<td>CD4+ cell count, cells/mm³ (median) ≤500</td>
<td>61 (32)</td>
<td>149 (29)</td>
</tr>
<tr>
<td></td>
<td>185 (32)</td>
<td>149 (29)</td>
</tr>
<tr>
<td></td>
<td>346 (56)</td>
<td>362 (71)</td>
</tr>
<tr>
<td>Baseline 3rd-agent class</td>
<td>Pi</td>
<td>133 (26)</td>
</tr>
<tr>
<td></td>
<td>NNRTI</td>
<td>276 (54)</td>
</tr>
<tr>
<td></td>
<td>INI</td>
<td>106 (20)</td>
</tr>
<tr>
<td>Baseline TDF use</td>
<td>474 (73)</td>
<td>395 (70)</td>
</tr>
<tr>
<td>Duration of ART prior to Day 1, median, months</td>
<td>51</td>
<td>53</td>
</tr>
</tbody>
</table>

FDA Snapshot Analysis, 48 Weeks

Virologic outcomes

<table>
<thead>
<tr>
<th>Virologic success</th>
<th>Virologic non-response</th>
<th>No virologic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>95</td>
<td>96</td>
<td>94</td>
</tr>
</tbody>
</table>
**SWORD 1 and 2, Miscellaneous**

- The most commonly reported (>5%) adverse events in the dolutegravir and rilpivirine arm were nasopharyngitis, headache, diarrhea and upper respiratory tract infection.
- For the CAR arm, the most commonly reported adverse events were nasopharyngitis, upper respiratory tract infection, back pain, headache and diarrhea.
- Virologic failure rates were <1% in the dolutegravir and rilpivirine arm and 1% in the three- or four- antiretroviral-drug arm. **No INSTI resistance-associated mutations were reported.**

**LAMIDOL Study**

- DTG+3TC alone, deintensification strategy
- 110 patients with no history of failure and who tolerated 8-weeks of DTG + 2NRTIs prior to switch
- One virologic failure one low-level viremia.
- Comparative clinical studies ongoing
LATTE: Efficacy, Safety of Dual Oral Cabotegravir + RPV Maintenance Thru Wk 144

- Dose-ranging, randomized phase IIb study

Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48

At Wk 96: 76% of pts receiving CAB + RPV had HIV-1 RNA < 50 copies/mL

- Induction Phase**
  - CAB 10 mg QD + 2 NRTIs* (n = 60)
  - CAB 30 mg QD + 2 NRTIs* (n = 60)
  - CAB 60 mg QD + 2 NRTIs* (n = 60)
  - EFV 600 mg QD + 2 NRTIs QD (n = 62)

Wk 24: Primary Endpoint

Wk 48: Maintenance Phase

Wk 96: Ad Hoc

- Open-Label Phase
  - CAB 30 mg QD + RPV 25 mg QD

ART-naive pts, HIV-1 RNA ≥ 1000 c/mL (N = 243)

- Pts with HIV-1 RNA < 50 c/mL at Wk 24 continued to maintenance phase.
- TDF/FTC or ABC/3TC.

CAB 10 mg QD + CAB 30 mg QD + CAB 60 mg QD

CAB 10 mg QD + 2 NRTIs

CAB 30 mg QD + 2 NRTIs

CAB 60 mg QD + 2 NRTIs

EFV 600 mg QD + 2 NRTIs QD

Wk 96:

Primary Endpoint

Wk 24:

Induction Phase**

Maintenance Phase

Ad Hoc

Open-Label Phase

LATTE: Viral Suppression Continues Through Wk 144 With Dual Oral CAB + RPV Maintenance

- Ad hoc analysis through Wk 144 of open-label phase
- Serious AEs: 9%; d/c for AEs: 3%
- PDVF in 9 pts (ITT-E)
  - 6 during induction/maintenance
  - 3 during open-label (Wks 96-144)
    - 2 of 3 had emergent mutations: n = 1 with V151I/V (IN); n = 1 with K101E + M230L (NNRTI)
    - 1 pt without PDVF developed E138K + V108I (NNRTI)
- 1 pt without PDVF developed E138K + V108I (NNRTI)

<table>
<thead>
<tr>
<th>Treatment Outcomes at Wk 144 (Snapshot), n (%)</th>
<th>CAB Subtotal* (ITT-E) (n = 181)</th>
<th>CAB Subtotal* (ITT-ME) (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA &lt; 50 c/mL</td>
<td>122 (67)</td>
<td>122 (76)</td>
</tr>
<tr>
<td>HIV-1 RNA ≥ 50 c/mL</td>
<td>18 (10)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>Previous change in ART</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>No virologic data in window</td>
<td>41 (23)</td>
<td>25 (16)</td>
</tr>
<tr>
<td>D/c for AE or death</td>
<td>8 (4)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>D/c for other reasons</td>
<td>27 (15)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>On study with missing data in window</td>
<td>6 (3)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>PDVF</td>
<td>9 (5)</td>
<td>6 (4)</td>
</tr>
</tbody>
</table>

*CAB 10 mg + CAB 30 mg + CAB 60 mg.
Bictegravir/TAF/FTC versus DTG + TAF/FTC

- Bictegravir, new INSTI – metabolized via CYP3A4, UGT1A, low DDI potential
- Phase 2 compared dolutegravir plus FTC/TAF enrolled 98 treatment-naive people with a viral load at or above 1000 copies, a CD4 count above 200
- 65 patients received Bictegravir + TAF/FTC, 33 received DTG + TAF/FTC
  - Median ages of 30 and 36, 90% were men, 57% white.
  - After 24 weeks 97% people randomized to bictegravir and 95% randomized to dolutegravir had a viral load below 50 copies
  - After 48 weeks of treatment, 97% assigned to bictegravir and 91% assigned to dolutegravir still had a viral load below 50 copies
  - Average CD4 gains were 258 with bictegravir and 192 with dolutegravir
  - 75mg in this study, 50mg going forward in STR with TAF/FTC

Sax PE, et al. CROI 2017, Seattle Abstract #41
Bictegravir metabolism

- Low potential as a victim of DDIs
  - INSTIs are affected by cation-containing antacids
    - BIC administration with antacids should be staggered (± 2 hours)
    - Fasted administration 2 hours before or 2 hours after antacid resulted in a decrease in BIC exposures of 13% and 52%, respectively
  - BIC is a substrate of CYP3A4 and UGT1A1
    - Inhibition of both CYP3A4 and UGT1A1 needed for substantial increase in exposure
    - Potent induction reduces exposure to a clinically significant extent

Bictegravir, DDI Profile

- Dual metabolism through UGT1A and CYP3A

Effect of BIC on the PK of Coadministered Drugs

<table>
<thead>
<tr>
<th>CYP3A4 Probe Substrate</th>
<th>Change in AUC</th>
<th>Effect on other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>++</td>
<td>Not an inhibitor or inducer of CYP3A4 or UGT1A1</td>
</tr>
<tr>
<td>Oral Contraceptive</td>
<td>++</td>
<td>No interaction with a representative oral contraceptive</td>
</tr>
<tr>
<td>Ethinyl Estradiol</td>
<td>++</td>
<td>No effect on midazolam</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>++</td>
<td>No effect on norgestimate/ethinyl estradiol</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>++</td>
<td>No interaction with a representative HCV DAA</td>
</tr>
<tr>
<td>Metformin†</td>
<td>↑ 39%</td>
<td>Limited liability for inhibition of renal transporters (OCT2 and MATE1)</td>
</tr>
</tbody>
</table>

*Norgestimate is circulating pharmacologically active progesin from norgestimate.
90% CI of GMR were within † or extended above↑ The predetermined protocol defined equivalence boundaries of 75–143%.
Long acting ARV in Development

- Phase 3
  - Cabotegravir
  - Rilpivirine
- Phase 2
  - Idaluzimab
  - PRO 140
  - Neutralizing antibodies
  - Albuvirtide
- Phase 1
  - MK8591
  - GSCA1

http://www.croiwebcasts.org/console/player/33659?mediaType=audio&

Doravirine, background

- Doravirine, novel next generation non-nucleoside RTI
  - Unique resistance profile, activity against most prevalent NNRTI mutations (K103N, Y181C, G190A, K103N/Y181C, E138K)
  - Minimal drug interactions
  - Once daily, without regard for food
  - Being developed as an STR with TDF ad 3TC
  - Comparable efficacy, better neuropsychiatric profile compared to efavirenz in previous Phase 2b study, CROI 2017 Abstract# 470
DRIVE-FORWARD Study

- Phase 3, multicenter, double-blind, non-inferiority trial in antiretroviral treatment-naïve adults
- HIV-1 infection, pre-treatment HIV-1 RNA ≥1,000 c/mL
- Participants stratified by screening HIV-1 RNA (≤ or >100,000 c/mL) and investigator-selected NRTI backbone therapy (TDF/FTC or ABC/3TC)
- Randomized 1:1 ratio to receive doravirine 100 mg QD or darunavir 800 mg with ritonavir 100 mg (DRV/r) QD, in combination with the selected NRTI, for up to 96 weeks
- Primary endpoint, % of participants achieving HIV-1 RNA <50 c/mL at Week 48 (NC=F, FDA Snapshot approach) with predefined non-inferiority margin of 10%

48 Week, FDA Snapshot Analysis
Treatment Emergent Resistance

<table>
<thead>
<tr>
<th></th>
<th>DOR (N=383)</th>
<th>DRV+r (N=383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants discontinued without PDVF, n (%)</td>
<td>40 (10%)</td>
<td>53 (14%)</td>
</tr>
<tr>
<td>Genotype test successfully performed, n</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Primary NNRTI resistance</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Primary NRTI resistance</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Primary PI resistance</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Phenotype test successfully performed, n</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>With any phenotypic drug resistance</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

- One participant discontinued due to noncompliance at Week 24 and developed DOR resistance (RT V106I, H221Y, and F227C; >90-fold increased IC₅₀) and FTC resistance (RT M184V).
- One participant discontinued due to rash at Week 2 and had DOR IC₅₀ 2.8-fold WT at discontinuation (assay DOR resistance cutoff 2.5-fold WT). Baseline DOR IC₅₀ was 2.2-fold WT. There were no genotypic resistance mutations nor changes in RT from baseline to discontinuation.

Conclusions

In HIV-1 infected treatment-naïve participants, doravirine in combination therapy demonstrated:
- Potency with non-inferior efficacy to darunavir 800 mg + ritonavir 100 mg regardless of baseline HIV-1 RNA
- Low rate of resistance with only 1/383 participants on doravirine developing genotypic and phenotypic resistance to any study drug through Week 48

Doravirine was generally well tolerated and safe
- Superior lipid profile for fasting LDL-C and non-HDL-C compared to darunavir 800 mg + ritonavir 100 mg
- Low rate of discontinuations due to rash or neuropsychiatric adverse events

Doravirine is a novel once-daily NNRTI for first-line treatment with consistent efficacy regardless of baseline viral load and very good tolerability
Long-acting Ibalizumab In Patients With Multi-drug Resistant HIV-1: A 24-week Study

Background

Ibalizumab (IBA) is a long-acting humanized immunoglobulin G4 monoclonal antibody that blocks HIV to enter the CD4+ T cells. Unlike other antiretroviral agents, IBA binds to a conformational epitope on the second extracellular domain of the CD4 receptor, away from Major Histocompatibility Complex II molecule (MHC II) binding sites. It prevents HIV virus from infecting CD4+ immune cells while preserving normal immunological function. IBA has been shown to have potent activity against a broad spectrum of primary clinical isolates with no evidence of cross-resistance with existing antiretroviral (ARV) agents or drug-drug interactions. IBA was tested in a Phase 3 registration study in patients with multi-drug resistant (MDR) HIV-1 infection (TMB-301). We previously reported significant viral load reductions 7 days after an initial dose of IBA when added to a failing ARV regimen. Here, we describe the sustained efficacy, safety and tolerability of IBA through Week 24 of treatment.

Inclusion Criteria

- VL>1000 copies/ml
- 6 months on ARV therapy
- Documented resistance to at least 1 ARV from 3 classes
- Sensitivity to at least 1 ARV for OBR
- Stable ARV therapy for 8 weeks prior to screening
- N=40, mean age 51, 85% male,
- Mean duration of HIV infection 21 years
- Mean CD4 150 cells/mm3
- 43% required fostemsavir in OBR
Resistance and Background at Baseline

- Mean viral load decrease 1.6 log from baseline
- 55% at least one log reduction
- 48% at least 2 log reduction
- 43% <50 copies/ml at 24 weeks

24 Week Results

- Mean viral load decrease 1.6 log from baseline
- 55% at least one log reduction
- 48% at least 2 log reduction
- 43% <50 copies/ml at 24 weeks
Long-term, Maintenance PRO 140 Monotherapy Following Initial ART

- PRO 140: humanized IgG4 CCR5 mAb
- Single-arm, open-label phase IIb extension study\(^1\)
  - Maintenance PRO 140 given at 350 mg SC/wk for ≤ 3 yrs in pts stable on initial ART from CD01 study (N = 16)
- Wkly PRO 140 maintenance SC injection generally well tolerated
  - No drug-related severe AEs or d/c for AEs
  - Infrequent, mild, transient administration-site reactions in < 10% of pts
- HIV-1 RNA < 40 copies/mL maintained in majority of pts
  - > 40 wks: 13/16 pts (81.3%)
  - > 2 yrs: 10/16 pts (62.5%)
  - 1 pt d/c due to relocation; 5 pts had VF
- CD4+ cell counts stable through study
- No anti-PRO 140 antibodies detected
- Ongoing phase IIb/III studies of PRO 140 monotherapy\(^2\) and in combination with ART\(^3\)

---

HIV Capsid Inhibitors with Long-Acting Potential

- GS-CA1:
  - First-in-class picomolar inhibitor of HIV capsid function
  - Inhibition of multiple steps in HIV replication cycle
  - High potency against all major HIV subtypes & mutants resistant to current ARVs
  - Resistance maps to conserved inhibitor binding site in p24

- A compound has been selected for clinical development
  - High potency
  - Low metabolic clearance
  - Slow release kinetics from injection

---

\(^2\) ClinicalTrials.gov. NCT02483078.
\(^3\) Tse WC, et al. CROI 2017, Seattle Abstract #O4
### Capsid Inhibitors

![Diagram of Capsid Inhibitors](https://clinicaloptions.com)

### Investigational Agents Reported at CROI 2017: Preclinical and Phase I

<table>
<thead>
<tr>
<th>Agent</th>
<th>MoA or Formulation</th>
<th>Phase</th>
<th>Dosing/Administration</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-CA1&lt;sup&gt;[1]&lt;/sup&gt;</td>
<td>HIV capsid inhibitor</td>
<td>Pre-clinical</td>
<td>Extended release, suitable for SC of solid depot formulation</td>
<td>• Potent ART with orthogonal resistance profile to existing ART; potential for long-acting formulation due to low aqueous solubility, high stability</td>
</tr>
<tr>
<td>GS-9131&lt;sup&gt;[2]&lt;/sup&gt;</td>
<td>NRTI</td>
<td>Pre-clinical</td>
<td>Potential for once daily dosing</td>
<td>• Potent ART active against NRTI RAMs K65R, L74V, M184V alone or in combination; minimal loss of susceptibility with 4 or more TAMs</td>
</tr>
<tr>
<td>MK-8591&lt;sup&gt;[3]&lt;/sup&gt;</td>
<td>Nucleoside Reverse Transcriptase Inhibitor (NRTTI)</td>
<td>Pre-clinical</td>
<td>10 mg QW PO; potential for extended duration</td>
<td>• Comparable MK-8591 levels in animal rectal, vaginal tissue to TDF levels in tissues of human subjects highlights potential prophylaxis utility</td>
</tr>
<tr>
<td>GS-PI&lt;sup&gt;[4]&lt;/sup&gt;</td>
<td>PI</td>
<td>Pre-clinical</td>
<td>Potential for unboosted, once daily dosing</td>
<td>• Potent ART with high barrier to resistance, including &lt; 2-fold loss in potency against major PI RAMs, and 10- to 40-fold longer in vivo half life vs ATV or DRV</td>
</tr>
<tr>
<td>NANO-EFV, NANO-LPV&lt;sup&gt;[5]&lt;/sup&gt;</td>
<td>Oral, lower dose SDN</td>
<td>I</td>
<td>nEFV: 50 mg QD, 21 d nLPV/RTV: 200/100 mg BID, 7 d</td>
<td>• Enhanced oral bioavailability suggests can reduce EFV, LPV dose by ~ 50% while maintaining PK</td>
</tr>
</tbody>
</table>

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## Investigational Agents Reported at CROI 2017: Phase II

<table>
<thead>
<tr>
<th>Agent</th>
<th>MoA or Formulation</th>
<th>Phase</th>
<th>Dosing/Administration</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMC278 LA[1]</td>
<td>LA injectable RPV (IM)</td>
<td>II</td>
<td>1200 mg IM Q8W</td>
<td>- Potential as injectable, long-acting PrEP</td>
</tr>
<tr>
<td>Elsulfavirine[2]</td>
<td>Prodrug of new NNRTI VM1500A</td>
<td>IIb</td>
<td>Combined therapy: 20 mg elsulfavirine + FTC/TDF PO QD</td>
<td>- Less toxic alternative to EFV for initial ART</td>
</tr>
<tr>
<td>UB-421[3]</td>
<td>Anti-CD4 receptor mAb</td>
<td>II</td>
<td>10 mg/kg QW IV or 25 mg/kg Q2W IV</td>
<td>- Possible ART alternative for maintenance therapy in virologically suppressed pts</td>
</tr>
</tbody>
</table>

---

HCV, Gone by 2030?

- John Ward, MD CDC

- http://www.croiwebcasts.org/console/player/33550?mediaType=audio&

HIV/HCV Co-infected with cirrhosis, Spanish Cohort

- Prospective cohort study of 170 people with HIV/HCV co-infection with cirrhosis who started DAA therapy at 13 Spanish centers during 2015
- 75% had compensated cirrhosis
  - 12% were Child-Pugh class B and 17% had a history of prior decompensation.
- 89% had undetectable HIV viral load and the median CD4 T-cell count was approximately 500 cells/mm³
- About half were starting hepatitis C treatment for the first time, 38% had been treated before with pegylated interferon plus ribavirin and about 14% had tried early HCV protease inhibitors with pegylated interferon/ribavirin
- Most cohort participants were treated with interferon-free DAA regimens for 12 or 24 weeks, most commonly sofosbuvir/ledipasvir plus ribavirin (25%), sofosbuvir/ledipasvir alone (15%), sofosbuvir and simeprevir plus ribavirin (20%), or sofosbuvir and daclatasvir plus ribavirin (15%)
- Overall, 98% of previously untreated and 89% of treatment-experienced participants achieved sustained virological response, or continued undetectable HCV RNA at 12 weeks post-treatment (SVR12).
- Previously treated people with HCV genotype 1a or 4 had somewhat lower response rates (87% and 83%). Cure rates were 95% or higher for all regimens except sofosbuvir and simeprevir without ribavirin for 12 weeks (63%)
Madrid CORE Cohort

- Madrid CORE Cohort, Abstract 534
  - 146 patients all co-infected
  - All CP B/C or decompensated or with HCC
  - Regimens mostly SOF/LED, but also SOF/DAC, SOF/RIBA, PROD, SMV/DCV, SIM/SOF

Conclusions
- The SVR12 rate with all-oral DAAs in coinfected patients with decompensated cirrhosis was **80.8%**
- Male sex and Child-Turcotte-Pugh stage C were the only variables associated with treatment failure patients with decompensated cirrhosis

RESCUE, ACTG 5348

- Abstract 568 LB, RESCUE, ACTG 5348
  - From Canada, Boston, NY
  - SOF experienced patients, prior SIM/SOF or P/r SIM/SOF, all NS5a naives
  - 8 patients
  - SOF/LED RIBA for 12 weeks or SOF/LED for 24 weeks
  - 7/8 people with BL NS5A ravs achieved SVR12
Glecaprevir/pibrentasvir DDIs

Figure 1. EVG/COBI/FTC/TAF Study Design

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Period 1 (Days 1 – 7)</th>
<th>Period 2 (Days 1-14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>GLE 300 mg + PIB 120 mg QD</td>
<td>EVG/COBI/FTC/TAF 150/300/10 mg QD</td>
</tr>
<tr>
<td>N=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intensive PK sampling for DAA: Cohort 1 - Period 1/Day 7 and Period 2/Day 14
Intensive PK sampling for EVG/COBI/FTC/TAF: Cohort II - Period 1/Day 14 and Period 2/Day 7

Figure 2. ABC/DTG/3TC Study Design

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Period 1 (Days 1 – 7)</th>
<th>Period 2 (Days 1-7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>GLE 300 mg + PIB 120 mg QD</td>
<td>ABC/DTG/3TC 600/50/300 mg QD</td>
</tr>
<tr>
<td>N=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Intensive PK sampling for DAA: Cohort I - Period 2/Day 7 and Period 2/Day 7
Intensive PK sampling for ABC/DTG/3TC: Cohort II - Period 1/Day 7 and Period 2/Day 7

Glecaprevir/pibrentasvir DDIs

- No dosage adjustment needed if used with
  - ELV/c TAF/FTC
  - DTG
  - ABC
  - 3TC
Roadmap

- Prevention
- Current Meds and Trends
- Adverse Events
- New Meds/Strategies
- HCV

HELPFUL RESOURCES
Web Resources of Interest

- DHHS Guideline Tables
  - http://www.aidsinfo.nih.gov/guidelines/
- NY/NJ AIDS Education and Training Center
  - http://www.nynjaetc.org/
- University of Liverpool
  - www.hiv-druginteractions.org
- Toronto HIV Clinic
  - http://www.hivclinic.ca/main/home

HIV Rx DDI Check

- AETC produced DDI App
- Based off of DHHS Guidelines Tables
- Contraindicated Meds
- Primary Care Meds
- Combining ARVs
- Resource Tabs
- Launching SOON!
### Drugs to be Avoided with Select ARVs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>HCV Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV Agent</td>
<td>EFV</td>
</tr>
<tr>
<td></td>
<td>Dasabuvir Elbasvir/Grazoprevir</td>
</tr>
<tr>
<td></td>
<td>Ombitasvir Paritaprevir/Simeprevir</td>
</tr>
</tbody>
</table>

### DDIs with Primary Care Meds and ARV Therapy

- **DDI**
  - Pls and Other Drugs

- **Concomitant Class**
  - Antidepressants, Anxiolytics, and Antipsychotics (Also see Sedative/Hypnotics section below)

- **Concomitant Drug**
  - Quetiapine

- **Pls**
  - All Pls

↑ quetiapine expected

Starting quetiapine in a patient