2020 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

New Antiretroviral Drugs in Development and Novel ART Regimens

Constance A. Benson, MD
Professor of Medicine and Global Public Health
University of California San Diego
La Jolla, California

Financial Relationships With Commercial Entities

Dr Benson has served on advisory and data safety monitoring boards for GlaxoSmithKline/ViiV Healthcare and received research grants awarded to her institution from Gilead Sciences, Inc. Her spouse has served as a consultant to CytoDyn, AbbVie and Sempra Energy; owns stock options in Antiva Biosciences and CytoDyn; has served on the board for Gilead Sciences, Inc., with payment remitted to his institution; and has served on data and safety monitoring boards for Gilead Sciences, Inc., and VIR. (Updated 07/25/20)

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe new or novel antiretroviral drugs in development for treatment of HIV
- Monitor new findings related to long-acting antiretroviral regimens in development

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Do We Need New Antiretroviral Drugs or Regimens?

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US DHHS & IAS-USA Guidelines: Recommended Regimens for First-Line ART in People Living With HIV

Class	DHHS[1]	IAS-USA[2]
INSTI	▪ BIC/TAF/FTC (AI)* ▪ DTG/ABC/3TC (AI)* ▪ DTG + TAF or TDF/FTC or 3TC (AI) ▪ RAL + TAF or TDF/FTC or 3TC (BI; BII) ▪ DTG/3TC (AI)	▪ BIC/FTC/TAF* ▪ DTG/ABC/3TC* ▪ DTG + FTC/TAF

*Single-tablet regimens.

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, osteoporosis status, and pregnancy status or intent
- No currently recommended first-line regimens contain a pharmacologic-boosting agent
- With FDA approval of 1200-mg RAL,[3] all options now available QD (except in pregnancy)[4]

1. DHHS ART. Guidelines. December 2019; 2. Saag. JAMA. 2018;320:379 (in revision 2020). 3. Raltegravir PI. 4. DHHS Perinatal Guidelines. October 2018.

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Antiretroviral Drug Resistance in the US

- 84,611 de-identified samples from pts in the US from 2012-2018; 33% had reduced susceptibility to at least one ARV
  - Decreasing prevalence of multiclass ARV resistance corresponding to availability of newer, more effective drugs and formulations with favorable cross resistance profiles

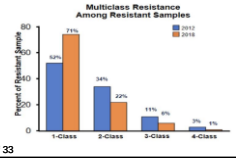


Figure 2. Prevalence of multi-class resistance among samples with resistance, 2012-2018



Unmet need for new ARVs = Populations with limited treatment options due to:
- Resistance
- Intolerance
- Adverse effects

Heneger CE et al. CROI 2020; Abstr. 521

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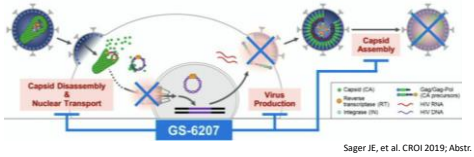
Novel Antiretroviral Drugs in Development

New ARV Classes with Novel Mechanisms of Action

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Lenacapavir (GS-6207): A Novel First in Class Capsid Inhibitor

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

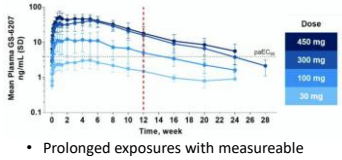


Sager JE, et al. CROI 2019; Abstr. 141

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Lenacapavir Dose Ranging Studies

- Randomized, blinded, placebo-controlled, phase 1 single ascending SQ dose study in healthy volunteers
- 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



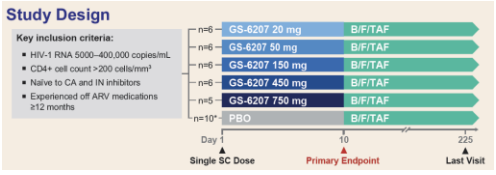
- Prolonged exposures with measureable concentrations for ≥ 24 weeks
- At doses ≥ 100 mg, plasma concentrations are above the $paEC_{95}$ at 12 weeks **supporting Q12 week dosing**

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

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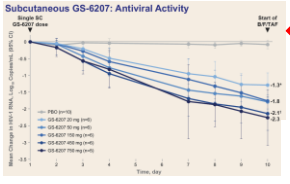
Lenacapavir (GS-6207): Antiviral Activity in PLWH

- Phase 1b randomized, double-blind, placebo-controlled dose ranging study in PLWH
  - Overall, median age 33, 10% women, 54% white, 31% black, HIV-1 RNA 4.5 copies/ml, CD4 463 cells/mm3, 82% ART naïve, median duration of F/U 225d

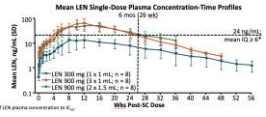


Daar E, et al. CROI 2020; Abstr. 469

10-Day Antiviral Activity of GS-6207 in PLWH



- HIV-1 RNA decline over 10d 1.4 to 2.3 log_{10} copies/mL
- Generally safe and well tolerated
  - Most common AEs were ISRs
  - Gr 3-4 AEs→ CPK and amylase increases

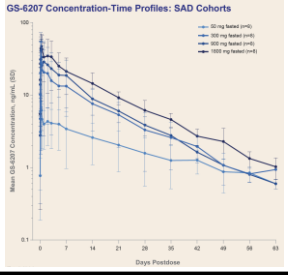


- Per antiviral activity, mean lenacapavir target plasma concentration is 24 ng/mL, corresponding to mean inhibitory quotient ≥ 6 (range: 6.2-20.3)

Daar E, et al. CROI 2020; Abstr. 469; Begley R, et al. IAS 2020; Abst PEB0265

PK of Oral GS-6207 in Healthy Volunteers

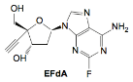
- Single doses of up to 1800 mg of GS-6207 oral tablets were generally safe and well tolerated
- The t1/2 was 11-13d, supporting less frequent dosing
  - Exposure increases were less than dose proportional
- No substantive food effect
- Development of oral and SC GS-6207 continuing

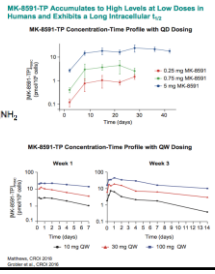


Begley R, et al. CROI 2020; Abstr. 470

Islatravir (MK-8591): A Novel Nucleoside Reverse Transcriptase Translocation Inhibitor

- NRTTI with unique mechanisms of action (translocation inhibition and chain termination)
- 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

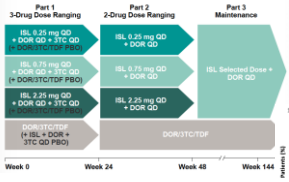




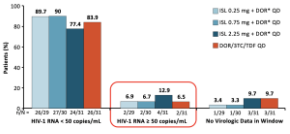
Grobler JA, et al. CROI 2019; Abstr. 481

Islatravir (MK-8591) Phase 2b Trial in PLWH

Figure 3. Phase 2b Dose-Ranging Trial



- Islatravir plus doravirine – potent, simple, 2-drug regimen with activity similar to DOR/3TC/TDF but with long IC half-life; well-tolerated



Orkin C, et al. AIDS 2020. Abstr OAB0302; DeJesus E, et al. AIDS 2020; Abstr OAB0305.

Islatravir (MK-8591) Metabolic Outcomes in PLWH

Figure 4. Mean % Change in Weight at Week 48

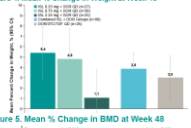


Figure 5. Mean % Change in BMD at Week 48

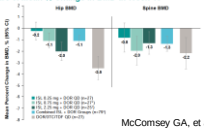
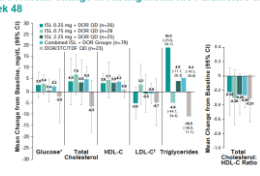


Figure 7. Mean Change in Fasting Metabolic Parameters at Week 48



- Minimal effect on body composition and metabolic parameters demonstrated; support ongoing development of ISL+DOR in phase 3

McComsey GA, et al. CROI 2020; Abstr. 686

Allosteric HIV-1 Integrase Inhibitor STP0404

- ALLINI: New class of ARVs that target LEDGF/p75 binding site of the viral integrase; interferes with IN-viral RNA interaction→vRNA mislocalization
- Significant activity against RAL-resistant strains
- Suppresses HIV-1 rebound from latently infected primary T cell reservoir
- No toxicity issues identified in cellular and animal testing
- Development as long-acting ARV (oral or IM/SQ)
- Phase 1 clinical trials Q2 2020

Table 3. Antiviral activity in Raltegravir-resistant strains

Compounds	Average IC_{50} (range, nM)	
	PBMC	MT-4
STP0404	0.08 (0.02–0.22)	2.49 (0.95–3.48)
Zidovudine	7.96 (0.22–20.7)	37.94 (29.7–57.6)
Raltegravir	1,227.70 (12.5–3,036)	2525 (351–4,322)
Elvitegravir	-	2751.5 (276–10,000)
Dolutegravir	-	4.57 (3.07–8.54)

RAL-resistant strains: 4736_2, 4736_4, 4670_1, 4670_2, 1588_1

Table 4. Pharmacokinetic parameters

Parameters	Cyno-Monkey		Beagle Dog		SD Rat	
	1 mpk (p.o)	1 mpk (i.v)	2 mpk (p.o)	2 mpk (i.v)	10 mpk (p.o)	5 mpk (i.v)
$T_{1/2}$ (hr)	5.25	8.02	6.90	6.11	4.56	3.83
AUC (hr·nM)	950	3,601	4,683	9,260	78,047	42,676
C_{max} (nM)	193	-	3,983	-	21,380	-
F_1 (%)	26.9	-	50.6	-	92.8	-

Ahn S, et al. CROI 2020; Abstr. 504

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VPU Inhibitor BIT225

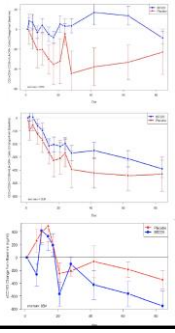
- Vpu → HIV-1 encoded membrane protein with regulatory functions that enhance HIV replication fitness and promote innate immune evasion in multiple cell types
- BIT225 is a Vpu inhibitor → inhibits HIV-1 replication *in vitro*
- Randomized clinical trial comparing BIT225 100mg, 200mg vs placebo added to ART in 36 ART-naïve PLHV starting therapy
  - At the end of a 12-week treatment period markers of viral replication and immune function endpoints were evaluated

Avihingsanon A, et al. CROI 2020; Abstr. 508

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VPU Inhibitor BIT225

- Plasma HIV-1 RNA levels declined similarly in all cohorts
- Significant changes in multiple immune markers observed with BIT225 vs placebo
- Activated macrophages (sCD163 markers) were significantly reduced in the 200 mg BIT225 cohort vs ART alone
- Significant increase in activated CD8+, CD4+, and NK cells in BIT225 cohort vs placebo
  - Enhanced NK cell recruitment and activation suggested elimination of HIV-infected cells mediated via Vpu cell signaling



Avihingsanon A, et al. CROI 2020; Abstr. 508

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Conclusions: Addition of BIT225 to ART

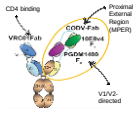
- Unique stimulation of multiple components of the innate immune system
- T cell, NK cell, sCD163, and IL-21 data together suggest the addition of BIT225 to ART stimulates antigen presentation and T cell and NK cell priming.
- May induce changes to the immune system similar to that of long-term non-progressors
- BIT225 immune modulating effects may improve HIV-1 induced immune activation and its outcomes

Avihingsanon A, et al. CROI 2020; Abstr. 508

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Broadly Neutralizing Antibodies (bNAbs) for Treatment of HIV

- Naturally occurring bNAbs have a half-life of 2-3 wks and alone can lower VL by 1.5 $\log_{10}$
- In combination, bNAbs maintain viral suppression
- May be able to trigger immune function to clear latently infected cells
- Combinations of multispecific bNAbs may be a promising new ART approach
- SAR441236 trispecific bNAb combines 3 HIV-1 *env* specificities in one antibody.
- Demonstrated potent broad HIV-1 neutralization *in vitro* and protection from challenge in primates



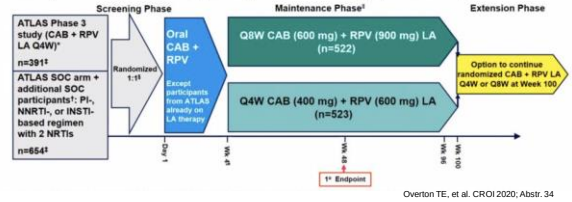
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New Long-Acting Injectable ARV Regimens and Novel Long-Acting Injectable ARV Drugs in Development

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Cabotegravir and Rilpivirine LA: ATLAS-2M Study Design

Phase 3, randomized, multicenter, parallel-group, noninferiority, open-label study



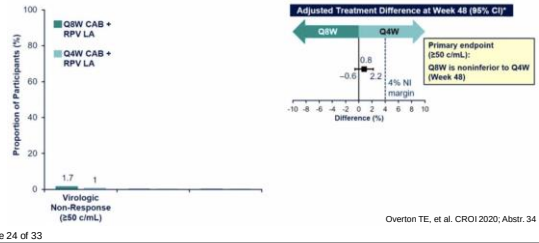
Overton TE, et al. CROI 2020; Abstr. 34

ATLAS-2M Baseline Characteristics (ITT-E)

Parameter	Q8W n=522	Q4W n=523	Total N=1045*
Prior exposure to CAB + RPV, n (%)			
None	327 (63)	327 (63)	654 (63)
1–24 weeks	69 (13)	68 (13)	137 (13)
>24 weeks	126 (24)	128 (24)	254 (24)
Median age (range), years	42 (20–83)	42 (19–75)	42 (19–83)
Age ≥50 years, n (%)	143 (27)	139 (27)	282 (27)
Female (sex at birth), n (%)	137 (26)	143 (27)	280 (27)
Female (participant-reported gender), n (%)	142 (27)	146 (28)	288 (28)
Race, n (%)			
White	370 (71)	393 (75)	763 (73)
Black or African American	101 (19)	90 (17)	191 (18)
Other	51 (10)	40 (8)	91 (9)
Median body mass index (IQR), kg/m^2	26 (23–29)	26 (23–29)	26 (23–29)
≥30, n (%)	113 (22)	98 (19)	211 (20)
Median CD4 count (IQR)	642 (499–827)	688 (523–878)	661 (508–849)

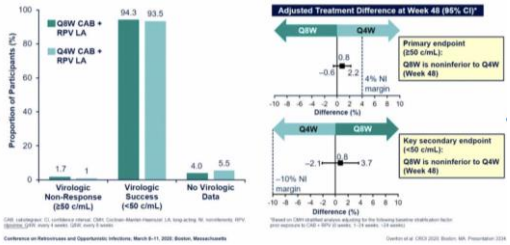
Overton TE, et al. CROI 2020; Abstr. 34

ATLAS-2M Week 48 Virologic Outcomes Snapshot: Non-Inferiority for 1^0 and 2^0 Endpoints (ITT-E)



Overton TE, et al. CROI 2020; Abstr. 34

ATLAS-2M Week 48 Virologic Outcomes Snapshot: Non-Inferiority for 1^0 and 2^0 Endpoints (ITT-E)



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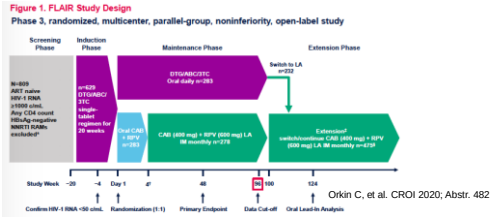
ATLAS-2M Week 48 Conclusions

- Q8W dosing of CAB + RPV LA was highly effective and non-inferior to Q4W dosing
  - Virologic non-response infrequent and confirmed virologic failure low overall (1%); similar in both arms
  - Virologic suppression maintained (94.3% Q8W and 93.5% Q4W)
- CAB + RPV LA was well-tolerated; comparable safety profile in both arms
  - ISRs mostly Grade 1-2 (98%); median duration 3d
- Q8W dosing preferred over oral (98%) and over Q4W (94%)
- CAB + RPV LA, dosed Q8W, is an effective and well-tolerated approach to maintenance of virologic suppression in PLWH

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LA CAB + RPV: FLAIR Week 96 Results

- Phase 3 RCT comparing antiviral activity of IM CAB + RPV LA vs continuing DTG/ABC/3TC in previously ART-naïve pts.

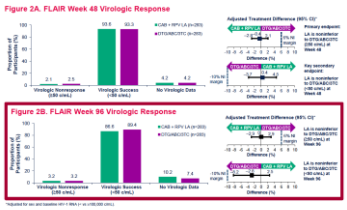


Orkin C, et al. CROI 2020; Abstr. 482

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LA CAB + RPV: FLAIR Week 96 Results

- Plasma concentrations after IM CAB + RPV were comparable to those during oral Rx
- No virologic failures in the LA arm
- Majority of ISRs Grade 1-2 and 89% resolved by ≤ 7d
- Treatment satisfaction was high

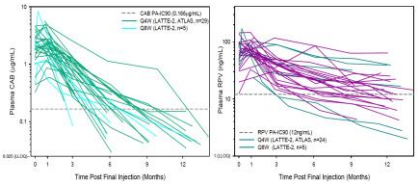


+ At Week 96, 9 (3.2%) participants in each arm had HIV-1 RNA ≥50 c/mL, confirming the noninferiority established at Week 48 (**Figure 2A** and **2B**).

Orkin C, et al. CROI 2020; Abstr. 482

PK After Stopping LA Cabotegravir + Rilpivirine

- PK sampling 1, 3, 6, 9, and 12 mos after final LA CAB + RPV IM inj in LATTE-2 and ATLAS
- Following LA treatment d/c, CAB and RPV LA may be detectable in plasma for ≥ 1 year



Alternative ART regimen selection after stopping LA CAB + RPV:

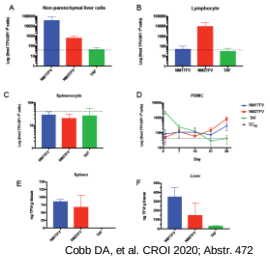
No PK related limitation

While use of UGT1A1 and/or CYP3A inhibitors or inducers could decrease or increase CAB an/or RPV clearance, other regimens are unlikely to be affected.

Ford SL, et al. CROI 2020; Abstr. 466

Long-Acting Nanoformulation of Tenofovir

- TDF modified and formulated into long-acting lipid nanocrystals by high pressure homogenization
  - NM1TFV, NM2TFV and M1, M2 prodrugs
- Sprague Dawley rats used for PK; TFV-DP levels measured in plasma, blood, multiple cell types, & PBMCs
- Formulation modifications extended half-life, improved potency → sustained prodrug and TFV-DP conc for 28d at half the TAF dose.



Cobb DA, et al. CROI 2020; Abstr. 472

VM-1500-LAI: A Novel Long-Acting Injectable

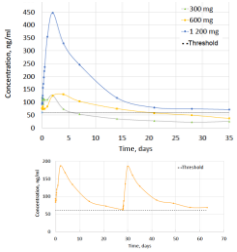
- VM1500A is a novel, potent NNRTI with broad spectrum anti-HIV-1 activity
- An oral prodrug of VM1500A, elsulfavirine, is approved in Russia
- A long acting injectable (LAI) formulation has been developed to expand dosing options
- A Phase 1, open-label, safety, tolerability, PK, ascending dose study in healthy volunteers enrolled:
  - 27 men, mean age 26 y.o., BMI 23.9 kg/m2
- Single, multiple doses ranging from 150 to 1200 mg were administered IM once/month after a 2-week lead-in of daily dosing of elsulfavirine

Murphy R, et al. CROI 2020; Abstr. 473LB

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VM-1500-LAI: PK Results

- Single monthly injection with 600 mg of VM-1500A-LAI achieved a median C_{trough} above target threshold for > 21 days
- Single monthly injection with 1200 mg achieved median plasma C_{trough} for 35 days
- Two consecutive monthly injections of 300 mg twice daily
  - Achieved target levels for 4 weeks after the 1st injection and for 5 weeks after the 2nd injection with drug accumulation in plasma
- VM1500A LAI well tolerated with acceptable PK in healthy volunteers



Murphy R, et al. CROI 2020; Abstr. 473LB

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Summary

- The pipeline for development of novel investigational ARVs continues to evolve
  - There may be less need for new ARVs based on availability of multiple well-tolerated and convenient regimens and decreasing rates of drug resistance
  - With a few exceptions most new agents in development are targeting novel mechanisms of action and long-acting formulations
- The promise of novel long-acting injectable formulations for maintenance of virologic suppression is closer to reality
  - Fewer drugs, fewer pills but costs (monetary and resistance) remain to be established

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Question-and-Answer Session