Investigational Approaches to Antiretroviral Therapy

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe the current status of using available 2-drug regimens in treatment-naive and -experienced patients
- Describe novel 2-drug regimens in development
- List new novel antiretroviral agents in development

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United States Guidelines: First-Line Regimens

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

Bold text identifies single-tablet regimens.
***TDF optional if TAF not available**

- Recommendations may differ based on renal function, hepatitis B and HLA-B*5701 status
- Data is limited for women of child-bearing age not reliably using contraception

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1. DHHS Guidelines. May 2018. 2. Saag MS, et al. JAMA. 2018;320:379-396.

Dual Drug Therapy for Treatment Naïve Individuals

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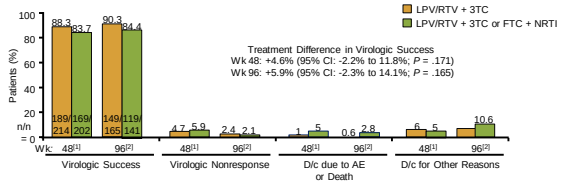
Gardel Study: LPV/r + 3TC or two NRTIs



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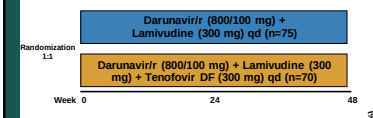
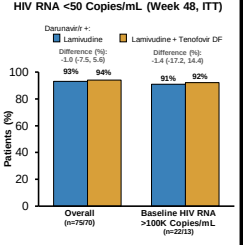
1. Cahn P, et al. Lancet Infect Dis. 2014;14:572-580. 2. Cahn P, et al. EACS 2015. Abstract 961

ANDES Study: DRV/r + 3TC or TDF/3TC



Baseline characteristics:

Age: 30 years.
Male: 91%.
MSM/bisexual: 73%.
CDC stage B: 8%.
HIV RNA: 4.5 $\log_{10}$ copies/mL.
HIV RNA >100K copies/mL: 24%.
Median CD4 count: 383 cells/mm^3.



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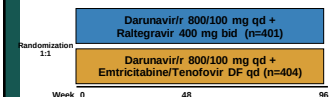
Figueroa MI, et al. 25th CROI. Boston, 2018. Abstract 489.

NEAT 001/ARNS 143: DRV/r + RAL or 2 TDF/FTC



Week 96 Virologic or Clinical Failure

	DRV/r + RAL (n=401)	DRV/r + FTC/TDF (n=404)	Adjusted % Difference (95% CI)
Overall analysis (%)	17.8	13.8	4.0 (-0.8, 8.8)
By baseline CD4 (%)			
<200 cells/mm³	43.2	20.9	22.3 (7.4-37.1)
≥200 cells/mm³	13.7	12.3	1.4 (-3.5, 6.3)
By baseline HIV RNA (%)			
<100K copies/mL	7.4	7.3	0.1 (-3.8, 4.0)
≥100K copies/mL	36.8	27.3	9.6 (-0.1, 20.1)

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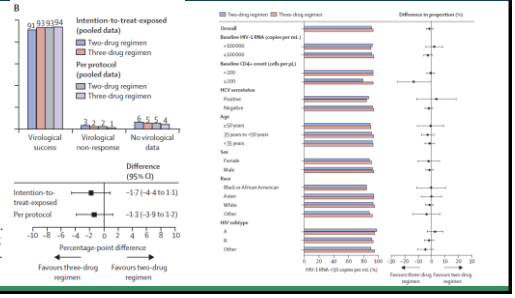
Raffi F, et al. *Lancet*. 2014;384:1942-1951.

Gemini 1 and 2: DTG + 2 NRTIs or 3TC



Cahn P, et al. Lancet 2019; 393:143-155.

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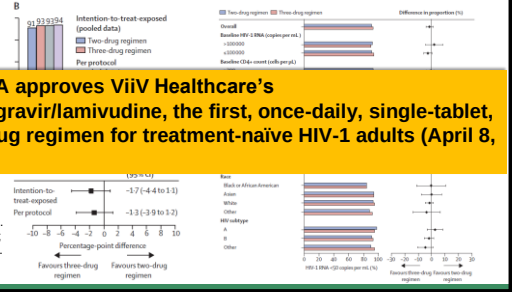
Gemini 1 and 2: DTG + 2 NRTIs or 3TC



US FDA approves ViiV Healthcare's dolutegravir/lamivudine, the first, once-daily, single-tablet, two-drug regimen for treatment-naïve HIV-1 adults (April 8, 2019)

Cahn P, et al. Lancet 2019; 393:143-155.

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Dual Drug Therapy for Virologically Suppressed Individuals

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Switch to Boosted PI + 3TC

	HIV RNA <50 copies/mL (%)	Treatment Difference (95% CI)	Findings of Note
Atazanavir/r + 3TC SALT (n=286)	84 versus 78	6.0% (9.5, 16)	Non-inferior, similar incidence of low-level viral rebounds Treatment-emergent resistance (n=1; triple therapy: M184V)
ATLAS-M (n=266)	90 versus 80	9.8% (1.2, 18.4)	Non-inferior, no emergent resistance in dual therapy virologic failures Improved eGFR (*P*<0.001), slightly increased bilirubin levels (*P*=0.4), and increased total cholesterol (*P*=0.002) and HDL-C (*P*=0.002) with dual therapy
Darunavir/r + 3TC DUAL-GESIDA (n=249)	89 versus 93	-3.8% (-11, 3.4)	Non-inferior No treatment-emergent resistance in dual therapy virologic failures (n=4) Significant increase in total cholesterol, LDL-C, and HDL-C with dual therapy
Lopinavir/r + 3TC OLE (n=253)	88 versus 87	-1.2% (-9.6, 7.3)	Non-inferior, similar virologic failure rates (2%) Treatment-emergent resistance at failure (n=1, dual therapy: K103N + M184V)

Perez-Molina JA, et al. *Lancet Infect Dis*. 2015;15:775-784 Fabbiani M, et al. *J Antimicrob Chemother*. 2018; Pulido F, et al. *Clin Infect Dis*. 2017;65:2112-2118; Arribas JR, et al. *Lancet Infect Dis*. 2015;15:785-792.

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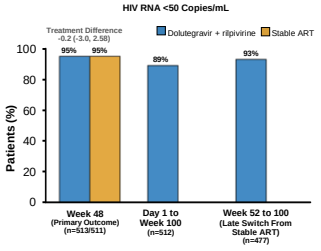
SWORD 1 and 2: Stay or Switch to DTG/RPV

2 Identical Phase 3 Studies
Open-label
On stable ART ≥6 months (INSTI, NNRTI, or PI + 2 NRTIs)
HIV RNA <50 copies/mL for 12 months
HBV negative

Dolutegravir 50 mg qd + rilpivirine 25 mg qd.
Non-inferiority margin:
Pooled data: -8%.
Baseline characteristics (median values):
Age: 43 years.
Male: 78%.
White: 80%.
CD4 count: 611-638 cells/mm³.
CD4 ≤500 cells/mm³: 31%.
ART 3rd agent PI/NNRTI/INI: 26%/54%/20%.
Baseline tenofovir DF use: 72%.
Duration of ART use: 51-53 months.



Aboud M, et al. *J Int AIDS Soc*. 2018;21(suppl 6). Abstract THPEB047.

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ASPIRE Trial: DTG + 3TC or Two NRTIs

Taiwo B, et al. *Clin Infect Dis*. 2018;66:1794-1797

Switch to Dolutegravir 50 mg + Lamivudine 300 mg qd (n=44)

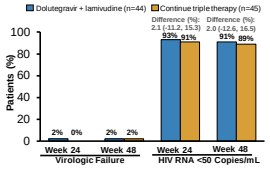
Continue Triple Therapy (n=45)

Week 0 — 24 — 48

Primary Endpoint
Virologic failure, loss to follow-up, or discontinuation/modification

Baseline:
- Male: 88%.
- Age: 47 years.
- White/black/Hispanic: 60%/38%/15%.
- CD4: 680 cells/µL.
- Time on ART: 5.7 years.
- Current ART:
  - NNRTI (30%), PI/r (33%), INSTI (37%).
  - FTC/TDF (86%), ABC/3TC (14%).

Virologic Outcomes (FDA Snapshot)



Phase 3 TANGO Study fully enrolled

United States Guidelines: 2-drug regimens

DHHS	IAS-USA
In some situations, it may be necessary to avoid ABC, TAF, and TDF, such as in the case of a patient who is HLA-B*5701–positive or at high risk of cardiovascular disease and with significant renal impairment	Initial 2-drug regimens are under investigation (may offer cost or toxicity advantages over 3-drug regimens, but efficacy needs to be confirmed)
Strategies with good supporting evidence Dolutegravir + lamivudine HIV RNA <500K copies/mL Darunavir/r + lamivudine Darunavir/r + raltegravir HIV RNA <100K copies/mL and CD4 >200 cells/mm^3	Until further data are available: Initial 2-drug regimens are reserved for the rare situation when individuals cannot take ABC, TAF, or TDF
Strategy that is efficacious but has disadvantages Lopinavir/r + lamivudine	Darunavir/ritonavir plus raltegravir If <100 000 HIV RNA copies/mL and CD4 >200/µL Darunavir/ritonavir plus 3TC If there is no 3TC resistance Dolutegravir + 3TC Short-term data from comparative trials may provide support as initial 2-drug therapy Dolutegravir plus rilpivirine Has not yet been assessed for initial therapy

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision October 25, 2018
Saag MS, et al. *JAMA*. 2018;320:379-396

ARS 1: Which dual therapy regimen has been shown to be effective for first-line therapy?

1. Dolutegravir + rilpivirine
2. Atazanavir/ritonavir + lamivudine
3. Dolutegravir + lamivudine
4. Cabotegravir LA + Rilpivirine LA
5. None of the above.

Novel Drugs and Combinations in Development

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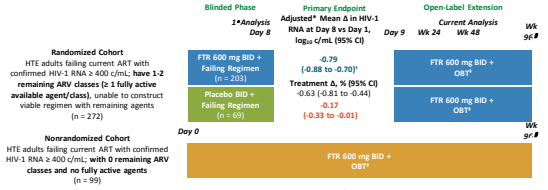
BRIGHTE Study: Fostemsavir in Rx Failure

Multicenter, part-randomized phase III trial



Wks 24-96 counted from start of open-label FTR + OBT. *Mean adjusted by HIV-1 RNA $\log_{10}$ c/mL on Day 1. †Excluded 2 participants for data entry errors. §OBT permitted to include investigational agents. ‡Study to be conducted until another option, rollover study, or marketing approval available.

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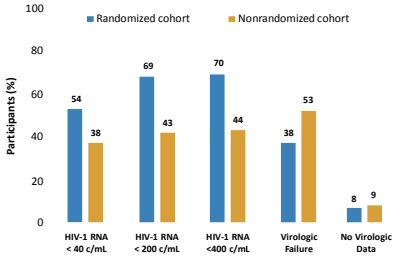
Aberg et al. Glasgow 2018. Abstr O334A.

BRIGHTE Open-Label Extension at Week 48



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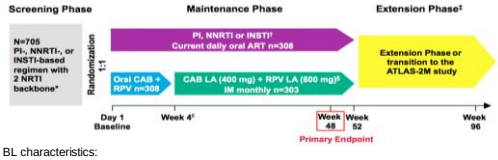
ATLAS: CAB LA + RPV LA in Suppressed Patients

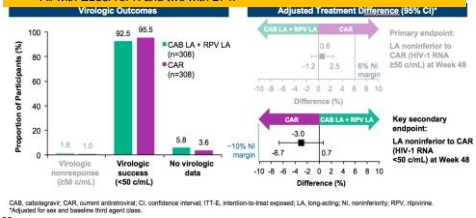


BL characteristics:
- Median age 42 yr
- Female (33%)
- White (68%)
- Median duration ART 4 yrs
- Regimen 50% NNRTI, 33% InSTI, 17% PI

Swindells S, et al. CROI 2019, Abst. 139

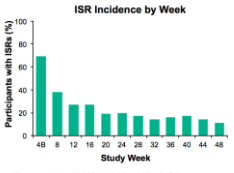
Virologic Snapshot Outcomes (Week 48)

HIV RNA ≥50 copies/mL: CAB/RPV 5 (1.6%); CAR 3 (1.0%)
Confirmed VF CAB/RPV (n=3):
- Russia (2) both A/A1 subtype; France (1) AG subtype
- All with E138A or K and two with L74I



CAB, cabotegravir; CAR, current antiretroviral; CI, confidence interval; ITT-E, intention-to-treat exposed; LA, long-acting; NI, noninferiority; RPV, rilpivirine.
*Adjusted for sex and baseline third agent class.

Injection Site Reactions

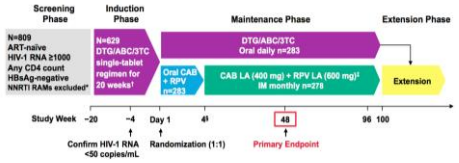


Event	CAB LA + RPV LA N=308
Participants receiving injections, n	303
Injections given, n	6978
ISR events, n (%)	1460 (20.9)
Pain	1208 (82.7)
Nodule	54 (3.7)
Induration	54 (3.7)
Swelling	48 (3.3)
Grade 3 ISR pain	20 (1.7)
Median duration of ISRs, days	3
Participants with ISR leading to withdrawal, n (%)	4 (1.3)

- The majority (99%,1439/1460) of ISRs were grade 1–2 and most (88%) resolved within ≤7 days

CAB, cabotegravir; IM, intramuscular; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine.
Bars represent incidence of onset ISRs relative to the most recent IM injection visit.

FLAIR: CAB LA + RPV LA after Patient Suppressed



BL characteristics:

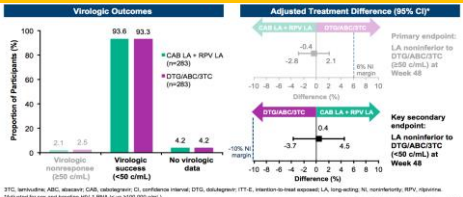
- Median age 34 yr
- Female (22%)
- White (74%)
- BL RNA <100,000 c/mL (80%)
- Median CD4 <200 cells/uL (7%)

Orkin C, et al. CROI 2019, Abst. 140

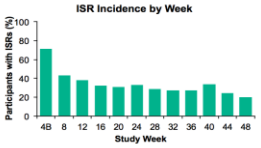
Virologic Snapshot Outcomes (Week 48)

HIV RNA ≥50 copies/mL: CAB/RPV 6 (2.1%); CAR 7 (2.5%)
Confirmed VF CAB/RPV (n=3):

- Russia (3) all A1 subtype from Russia
- Two with E138K and all three with L74I, two with Q148R, one Q140R and all with increased CAB resistance



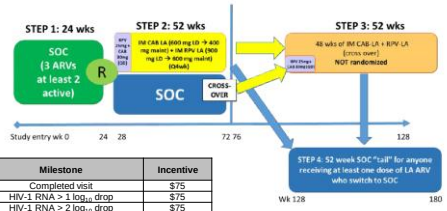
Injection Site Reactions



- The majority (99%, 2189/2203) of ISRs were grade 1–2 and most (88%) resolved within ≤7 days

Event	CAB LA + RPV LA N=283*
Participants receiving injections, n	278
Injections given, n	7704
ISR events, n (%)	2203 (28.6)
Pain	1879 (85.3)
Nodule	86 (3.9)
Induration	82 (3.7)
Swelling	38 (1.7)
Warmth	38 (1.7)
Grade 3 ISR pain	12 (<1)†
Median duration of ISRs, days	3
Participants with ISR leading to withdrawal, n (%)	2 (<1)‡

ACTG 5359: LA Therapy in Non-adherent Patients



Step 1, Wk	Milestone	Incentive
2	Completed visit	$75
4	HIV-1 RNA > 1 $\log_{10}$ drop	$75
8	HIV-1 RNA > 2 $\log_{10}$ drop	$75
12	HIV-1 RNA < 200 copies/mL	$150
16	HIV-1 RNA < 200 copies/mL	$150
20	HIV-1 RNA < 50 copies/mL	$150

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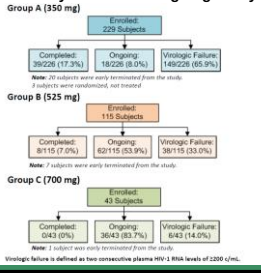
PRO 140 (leronlimab) SC as Maintenance Therapy

- Suppressed patients with R5-only virus by ARCHIVE Assay switched to weekly PRO 140 SC
  - First ~150 to 350 mg
  - Next ~150 randomized 1:1 to 350 or 525 mg
  - Additional ~200 randomized 1:1 to 525 or 700 mg

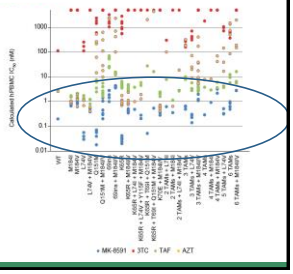
Preliminary Results of Ongoing Study



Slide 27 of 33 Dhody K et al. CROI 2019, Abst. 486

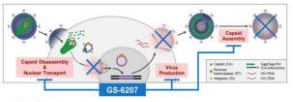
MK-8591: Nucleoside RT Translocation Inhibitor

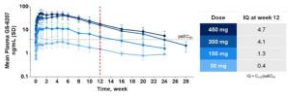
- Potent against most NRTI-resistant strains (Figure)
- Long half-life for daily to once-weekly dosing
- In development for dual therapy with Doravirine



Slide 28 of 33 Grobler JA, et al. CROI 2019, Abst. 481.

GS-6207: Phase 1, Single-Dose SC Capsid Inhibitor





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Sager JE, et al. 26th CROI. 2019. Abstract 141.

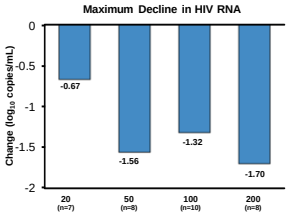
GSK2838232: Maturation Inhibitor

Phase 2a study (n=33)

- GSK2838232 at 20 to 200 mg + cobicistat for 10 days
- HIV RNA 34,000 to 99,000 copies/mL
- CD4 416-620 cells/uL

Outcomes

- Maximum VL reduction (Figure)
- No treatment-emergent resistance
- Headache, somnolence and rash in 4 patients (all mild)
- No serious AEs or discontinuation for AE



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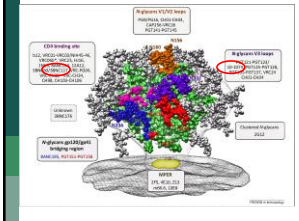
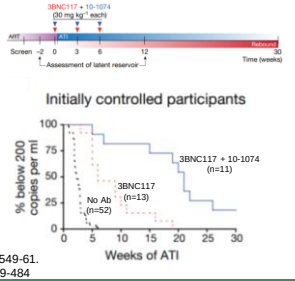
DeJesus E, et al. 26th CROI. Seattle, 2019. Abstract 142.

Combination bNAbs in Suppressed Patients





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Mouquet H. Trends Immunol 2014; 35:549-61.
Mendoza P, et al. Nature 2018; 561:479-484

ARS 2: Which drug maintains inhibitory levels for 12 weeks after subcutaneous injection?

1. PRO 140 (CCR5 mAb)
2. MK-8591 (RTI and translocation inhibitor)
3. GS-6207 (Capsid inhibitor)
4. GSK2838232 (Maturation inhibitor)

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Question-and-Answer

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