HIV Update: Long Term Injectables

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Disclosures

Research support: Gilead, Merck, ViiV
Consultant: Gilead, Merck, ViiV, Theratechnologies

HIV Prevention

Pre-exposure Prophylaxis

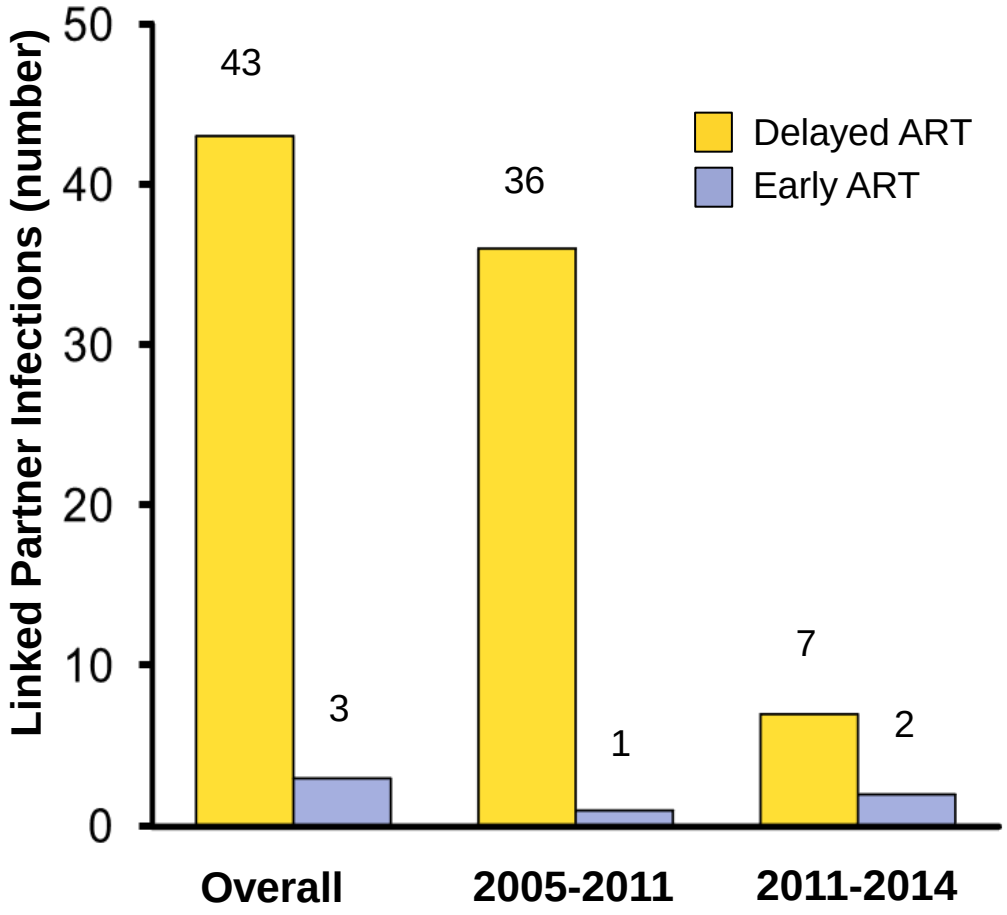
MSM/TGW

Tenofovir disoproxil fumarate/emtricitabine po qd
Tenoffovir disoproxil fumarate/emtricitabine po 2:1:1
Tenofovir alafenamide/emtricitabine po qd
Cabotegravir IM q8 weeks

Cis-Women

Tenofovir disoproxil fumarate/emtricitabine po qd
Cabotegravir IM q8 weeks

HPTN 052: Treatment as Prevention



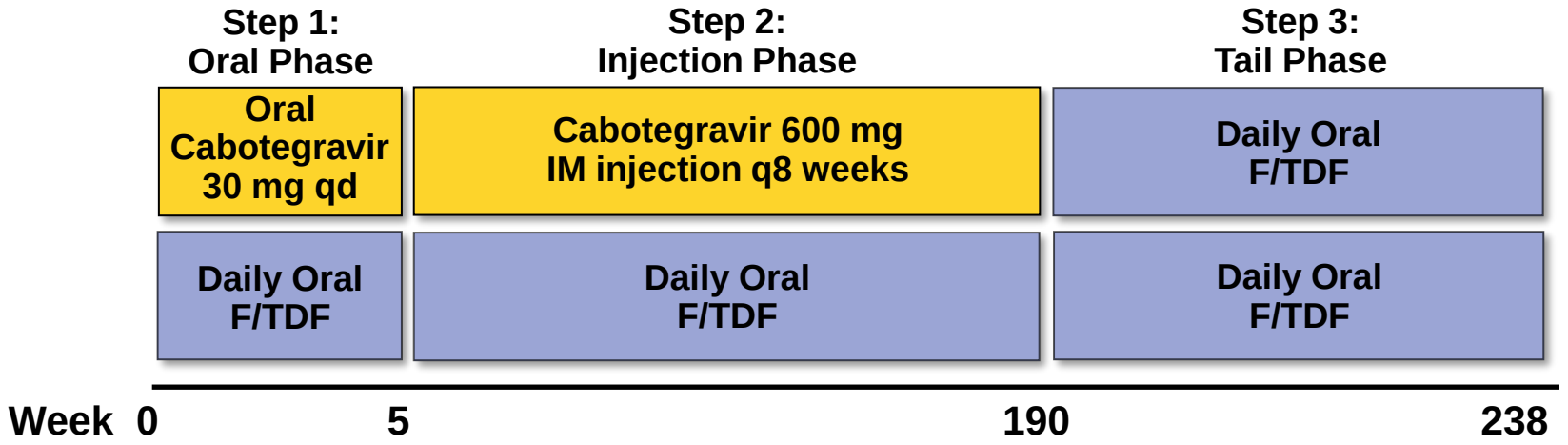
Cohen M ,et al. NEJM 2016; 375:830-839

LA PrEP: HPTN 083 and HPTN 084

Phase 3 studies

Double-blind, double-dummy, active controlled
Persons at high-risk for HIV infection
In general good health
No IDU, HCV, HBV, seizure disorder, CVD, abnormal liver function

HPTN 083: MSM/transgender women
HPTN 084: cisgender women

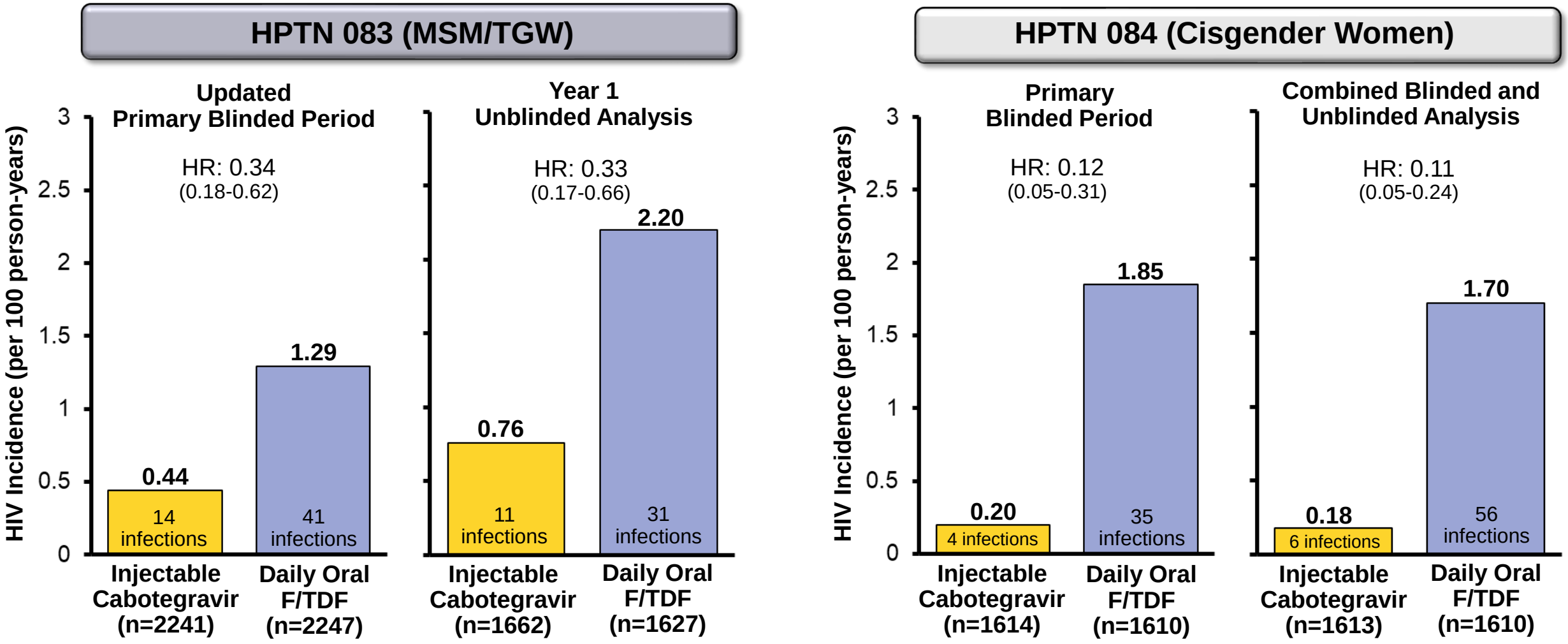


DSMB recommended early termination of blinded phase of both studies

Matching oral and IM placebos included in the oral and injection phase double-blind arms.
HPTN 083 was conducted in US, Brazil, Peru, Argentina, South Africa, Vietnam, and Thailand.
HPTN 084 was conducted in Botswana, Kenya, Malawi, South Africa, Swaziland, Uganda, and Zimbabwe.

Landovitz RJ, et al. *N Engl J Med*. 2021;385:595-608.
Delany-Moretlwe S, et al. *Lancet.* 2022;399:1779-1789.
Delany-Moretlwe S, et al. *J Int AIDS Soc.* 2022;25(suppl 3):227-228. Abstract OALBX0107.

HPTN 083 and HPTN 084 Infection Rate



Landovitz RJ, et al. *N Engl J Med*. 2021;385:595-608.
Delany-Moretlwe S, et al. *Lancet.* 2022;399:1779-1789.
Delany-Moretlwe S, et al. *J Int AIDS Soc.* 2022;25(suppl 3):227-228. Abstract OALBX0107.

Monitoring for Oral vs Injectable PrEP

	Oral PrEP	Injectable PrEP
HIV Ag/Ab and HIV-1 RNA	Every 3 mo	Every 2 mo on IM CAB
Lipid panel	At initiation and then yearly on FTC/TAF	N/A
Serum creatinine	▪ **Every 6 mo** if age ≥50 yr or eCrCl <90 mL/min ▪ **Every 12 mo** if age <50 yr and eCrCl ≥90 mL/min ▪ Persons with CrCl <60 mL/min should not take FTC/TDF for PrEP ▪ Persons with CrCl <30 mL/min should not take FTC/TAF for PrEP	N/A

www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf

Delayed CAB in Cisgender Women (HPTN 084)

- Delayed injections (n=224 in 194 pts)
  - Type 1 (n=19): 2nd injection (week 9) took place 8-14 weeks after the 1st injection
  - Type 2 (n=205): any subsequent injection that took place 12 to 18 weeks after the last injection
- Late injections maintained CAB levels >4x and >8x PC-IC_{90} in 98% and 87% of the time, respectively, following a 6-week delay (12-14 weeks between injections)

Type 1 Delay		
	>8x PA-IC_{90} (%)	**>4-8 PA-IC_{90} (%)**
Weeks between injections		
8 to 10 (n=11)	91	9
10 to 12 (n=4)	50	25
12 to 14 (n=4)	0	25

Type 2 Delay		
	>8x PA-IC_{90} (%)	**>4-8 PA-IC_{90} (%)**
Weeks between injections		
12 to 14 (n=109)	87	11
14 to 16 (n=57)	84	11
16-18 (n=39)	62	28

PA-IC_{90}: protein-adjusted 90% inhibitory concentration.

Marzinke MA, et al. CROI 2023. Abstract 159.

HIV infection diagnosis challenges when using CAB PrEP

- Cabotegravir can suppress virus and delay antigen/antibody production
  - Rapid tests and Ag/Ab assays with delayed detection of HIV infection
  - Supplemental Ab test may be negative/ indeterminate for many months
  - HIV RNA levels often remain low or undetectable for long periods
  - Testing may show reversion from positive to negative and back
- Delayed detection of HIV
  - Impact on personal health
  - Ongoing HIV transmission
  - Emergence of INSTI resistance limiting first-line treatment options and requiring use boosted PIs

Marzinke M, et al. *J Infect Dis*. 2021;224:1581-1592.
Eshleman S, et al. *J Infect Dis.* 2022;225:1741-1749.

Long-Acting Early Viral Inhibition LEVI With LA CAB PrEP (HPTN 083)

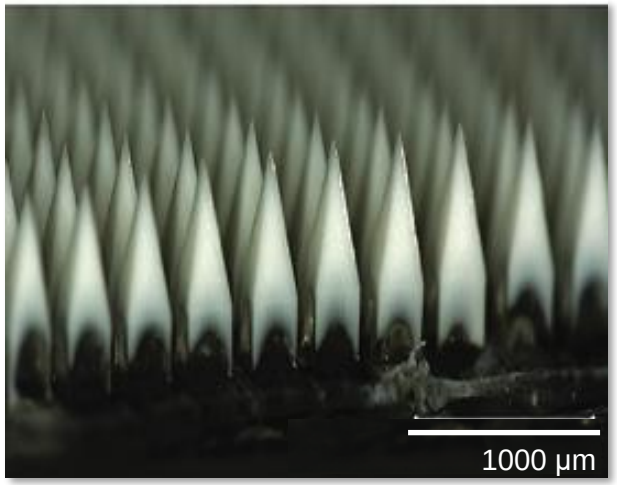
Feature	AHI	LEVI
Cause	Phase of natural HIV infection	LA ARV for PrEP
Onset	New infection	Infection during PrEP; initiation of PrEP during acute/early infection
Viral replication	Explosive	Smoldering
Symptoms	Fever, chills, rash, night sweats, muscle aches, sore throat, fatigue, swollen glands	Minimal, variable, often no symptoms reported
Detection	Ag/Ab, RNA (including point-of-care and pooled tests), DNA, and total nucleic acid assays	Ultrasensitive RNA assay (often low/undetectable HIV-1 RNA and HIV-1 DNA, diminished/delayed Ab production)
Assay reversion	Rare	Common for many test types
Duration	1-2 wk (until Ab detection)	Mo (until viral breakthrough, drug clearance, or ART start); can persist mo after ARV is discontinued
Transmission	Very likely	Unlikely (except possibly via blood transfusion)
Drug resistance	No (unless transmitted)	Yes (can emerge early when HIV-1 RNA is low)

- 6 incident infections despite on-time cabotegravir injections (0.27%)- Detection often delayed
- HIV infections that occurred >6 months from last dose without resistance

Eshleman. CROI 2023. Abstr 160.

Future LA CAB PrEP options

Microarray patch

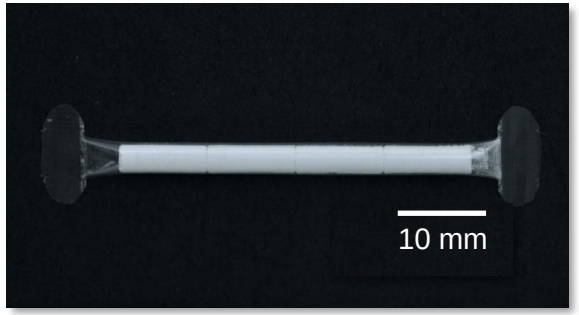


Light microscopic image (x25)

Cabotegravir LA (reformulation)

- Double-strength concentration (400 mg/mL)
- Phase 1 study of safety/ tolerability
  - Subcutaneous (abdominal)
  - Intramuscular (gluteus medius and vastus lateralis)

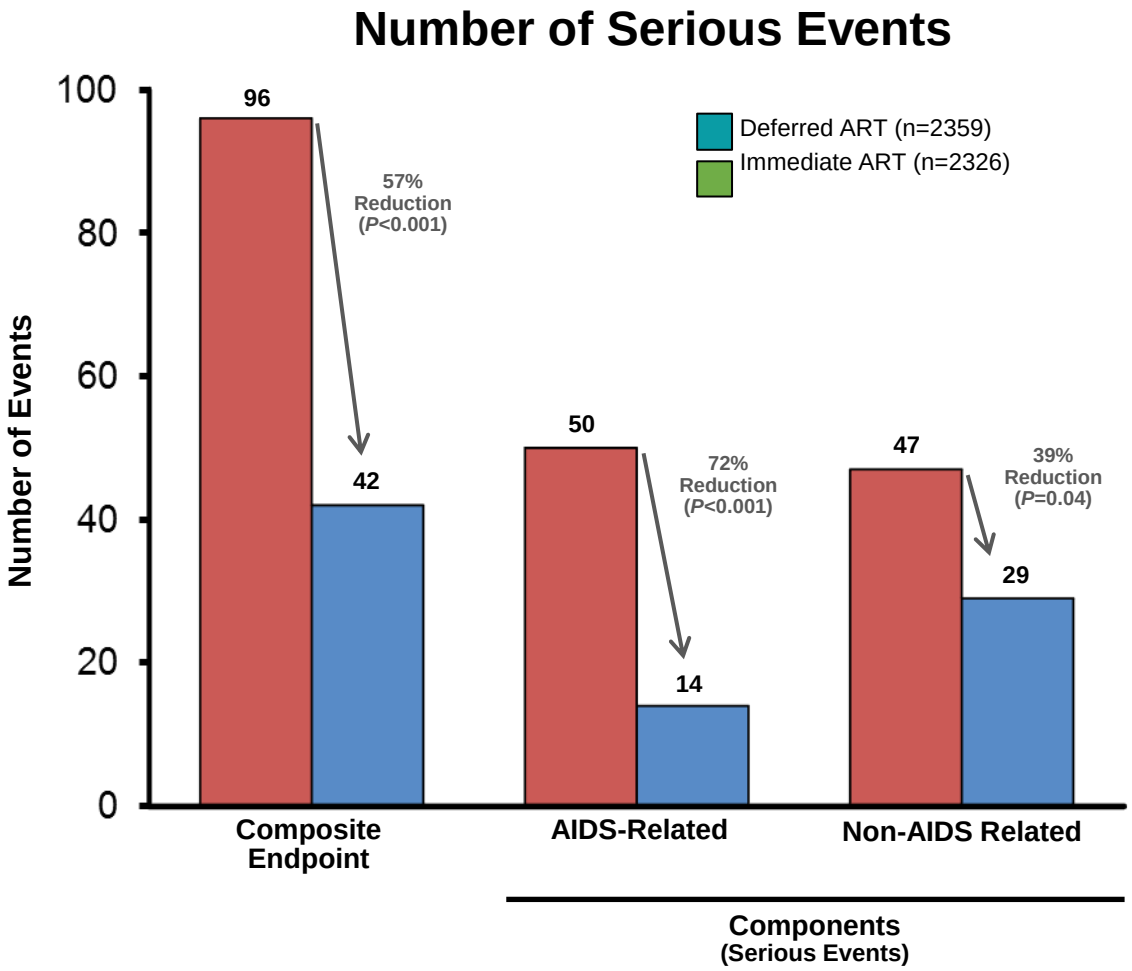
Cabotegravir Implant (non-biodegradable, retrievable)

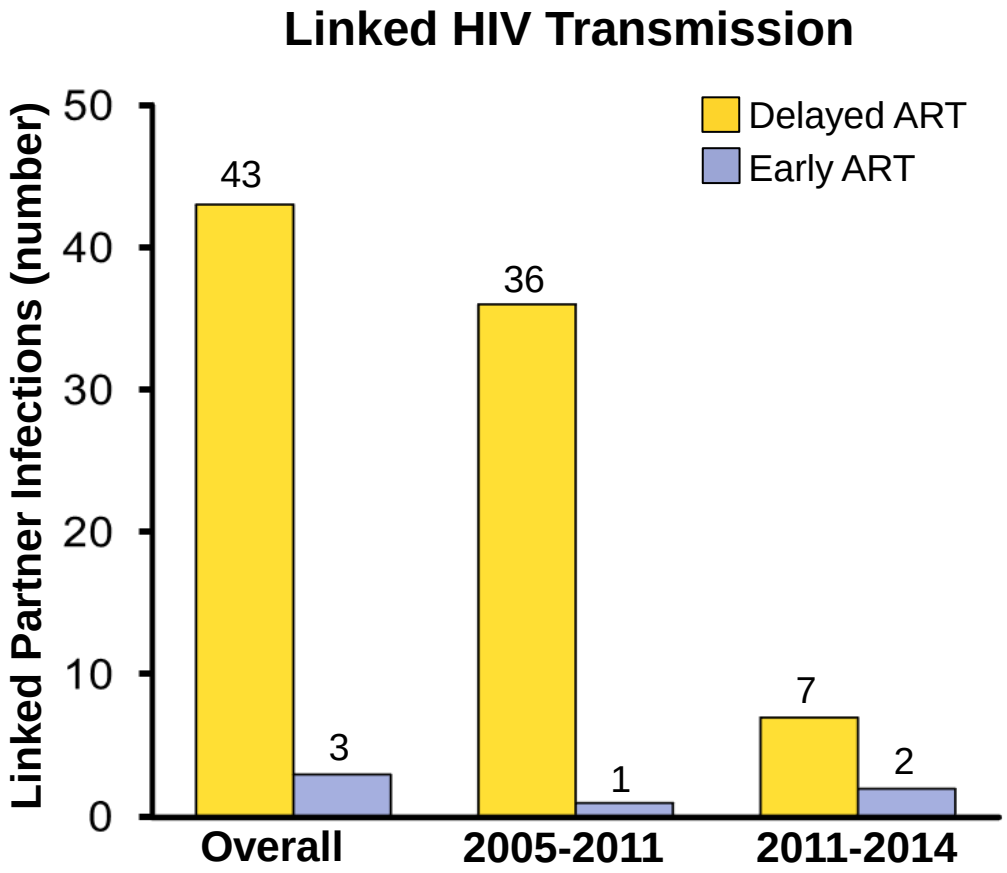


Rein-Weston A, et al. *Open Forum Infect Dis*. 2019;6(suppl 2):S996. Abstract LB 8.
Benn P, et al. *J Int AIDS Soc.* 2022;25(suppl 3):125-126. Abstract PESUB24.
Hope TJ, et al. *J Int AIDS Soc.* 2021;24(suppl 1):12-13. Abstract OA04.04.

ART: When and What to Start

When to Start: START and HPTN 052 Studies





Lundgren JD, et al. NEJM 2015; 373:795-807; Cohen M ,et al. NEJM 2016; 375:830-839

What Do the Guidelines Recommend for Rapid ART?

- **DHHS:** ART should be started immediately or as soon as possible following diagnosis[1]
  - Should not include an NNRTI, ABC, or DTG/3TC
- **IAS-USA:** Recommended for all ambulatory patients committed to starting ART as soon as possible after diagnosis[2]
  - Caveats in setting of possible opportunistic infection
  - Should not include an NNRTI or ABC

Rapid ART, or starting ART immediately or as soon as possible following diagnosis, can be started without labs or resistance testing

1. DHHS. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0-. Accessed April 2023; 2. Gandhi R, et al. *JAMA 2022*

Antiretroviral Guidelines: First-line Therapy

DHHS (1/2023) Recommended for Most People With HIV
Bictegravir/Emtricitabine/Tenofovir alafenamide
Dolutegravir/Abacavir/Lamivudine*
Dolutegravir + Emtricitabine/Tenofovir alafenamide (or disoproxil fumarate)
Dolutegravir/Lamivudine†

*Only for persons HLA-B*5701 negative and without chronic HBV coinfection.
†Not for persons with pre-treatment HIV RNA >500K copies/mL or known to have active HBV coinfection, or no genotype available

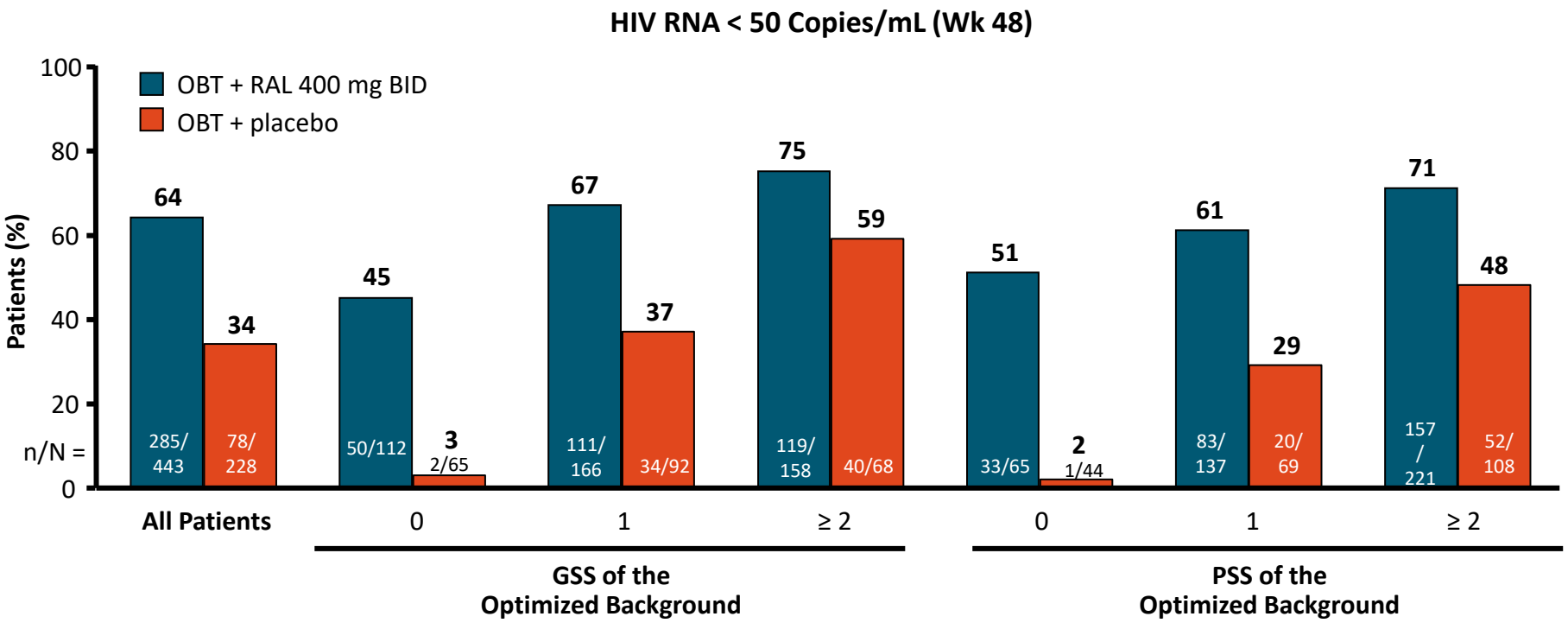
IAS-USA (2022) Recommended Initial Regimens
Bictegravir/Emtricitabine/Tenofovir alafenamide
Dolutegravir + Emtricitabine/Tenofovir alafenamide (or disoproxil fumarate), or Lamivudine + Tenofovir disoproxil fumarate
Dolutegravir/Lamivudine*

*Not recommended for rapid start because baseline laboratory evaluation results must be reviewed before initiation. Also not recommended for patients with chronic HBV or HIV RNA level >500K copies/mL.
Close monitoring for adherence and virological response is needed.
Not recommended for patients being treated for an active opportunistic infection.

DHHS. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Revision January 20, 2022.
Gandhi R, et al. JAMA. 2022.

Managing Virologic Failure

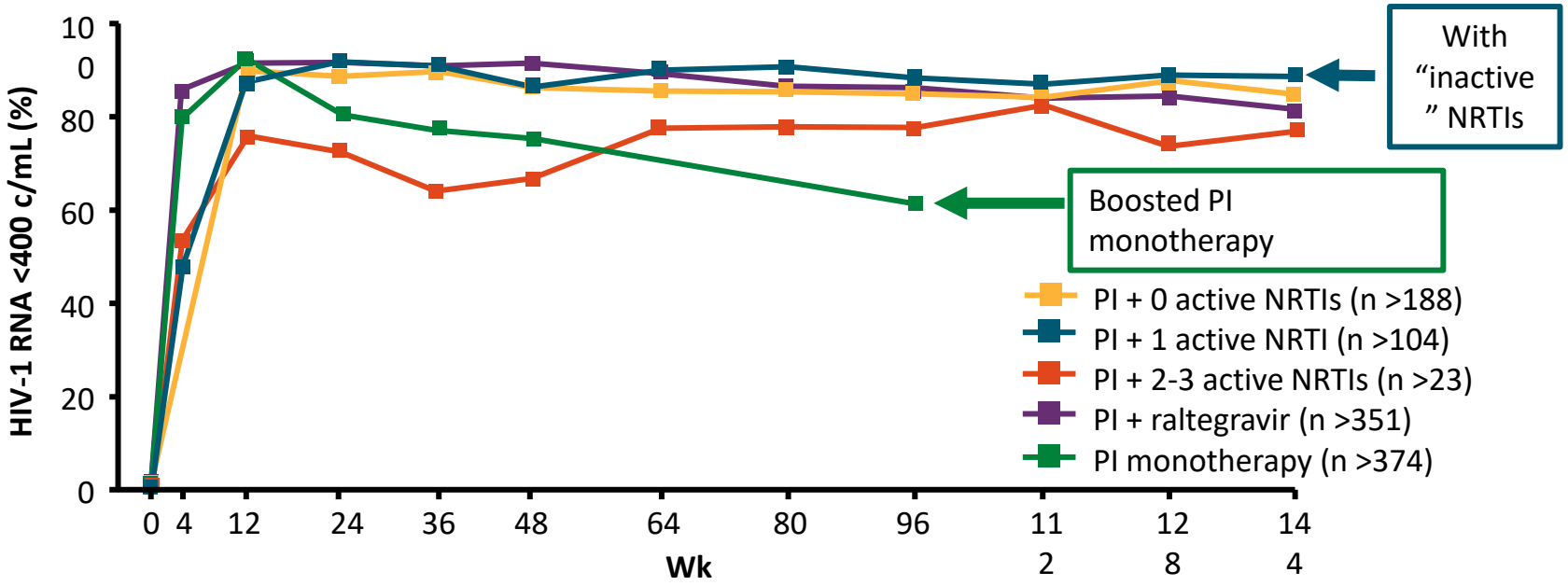
BENCHMRK: Management of Treatment-Experienced



Cooper. NEJM. 2008;359:355.

EARNEST: Activity of Boosted PI with Partially Active NRTIs

- Second-line therapy after failure of 2 NRTIs + NNRTI-based regimen (N = 1277)
- Recycled “inactive” NRTIs + boosted PI more active than boosted PI monotherapy

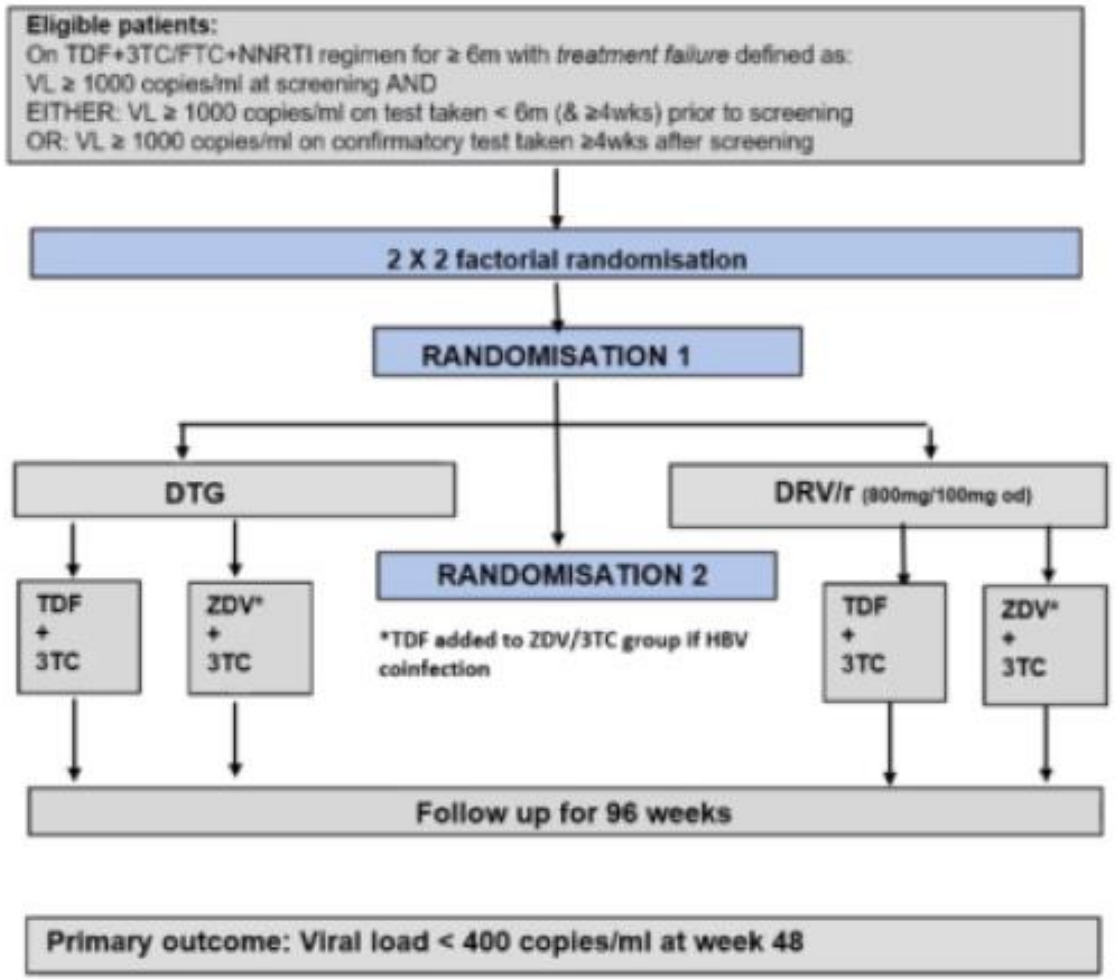


Paton. Lancet HIV. 2017;4:PE341.

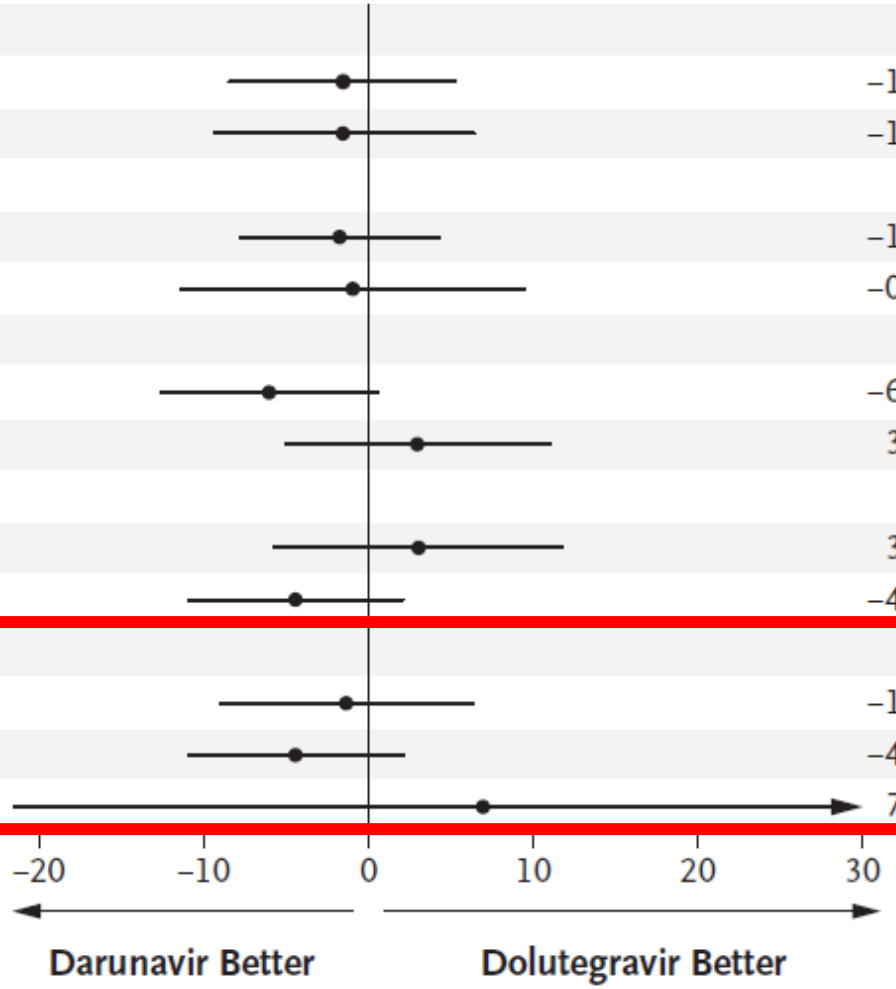
Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV

Nicholas I. Paton, M.D., Joseph Musaazi, M.Sc., Cissy Kityo, Ph.D., Stephen Walimbwa, M.D., Anne Hoppe, Ph.D., Apolo Balyegisawa, M.D., Arvind Kaimal, M.D., Grace Mirembe, M.Med., Phionah Tukamushabe, R.N., Gilbert Ategeka, M.D., James Hakim, F.R.C.P., Henry Mugerwa, M.D., Abraham Siika, M.Med., Jesca Asienzo, B.P.L.M., Barbara Castelnuovo, Ph.D., Agnes Kiragga, Ph.D., and Andrew Kambugu, M.Med., for the NADIA Trial Team*

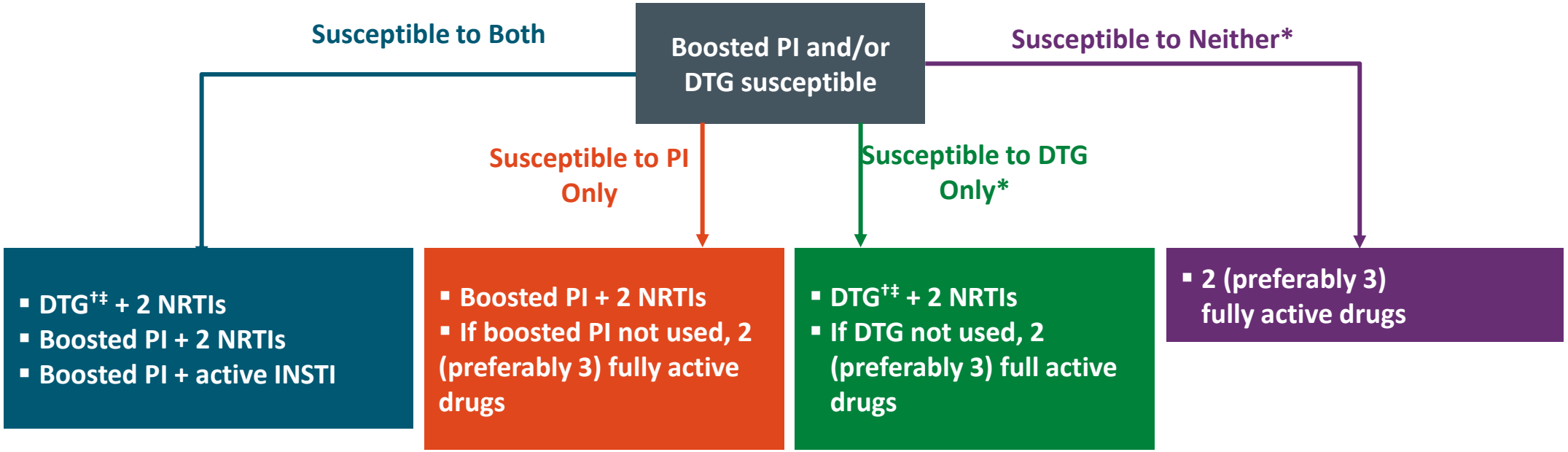
NADIA



Subgroup	Dolutegravir	Darunavir	Difference in Percentage Points (95% CI)
	no. of patients/total no. (%)		
NRTI randomization group			
Tenofovir	108/118 (91.5)	107/115 (93.0)	−1.5 (−8.4 to 5.3)
Zidovudine	104/117 (88.9)	103/114 (90.4)	−1.5 (−9.3 to 6.4)
Viral load at baseline			
<100,000 copies/ml	153/169 (90.5)	154/167 (92.2)	−1.7 (−7.7 to 4.3)
≥100,000 copies/ml	59/66 (89.4)	56/62 (90.3)	−0.9 (−11.4 to 9.5)
CD4+ cell count at baseline			
<200 cell/mm^3	112/125 (89.6)	108/113 (95.6)	−6.0 (−12.5 to 0.6)
≥200 cell/mm^3	100/110 (90.9)	102/116 (87.9)	3.0 (−5.0 to 11.0)
Sex			
Male	87/95 (91.6)	77/87 (88.5)	3.1 (−5.7 to 11.8)
Female	125/140 (89.3)	133/142 (93.8)	−4.4 (−10.9 to 2.1)
No. of predicted active NRTIs			
0	85/92 (92.4)	75/80 (93.8)	−1.3 (−8.9 to 6.2)
1	107/118 (90.7)	116/122 (95.1)	−4.4 (−10.9 to 2.1)
≥2	13/18 (72.2)	15/23 (65.2)	7.0 (−21.4 to 35.4)



Management of ARV Failure: Second Line and Beyond

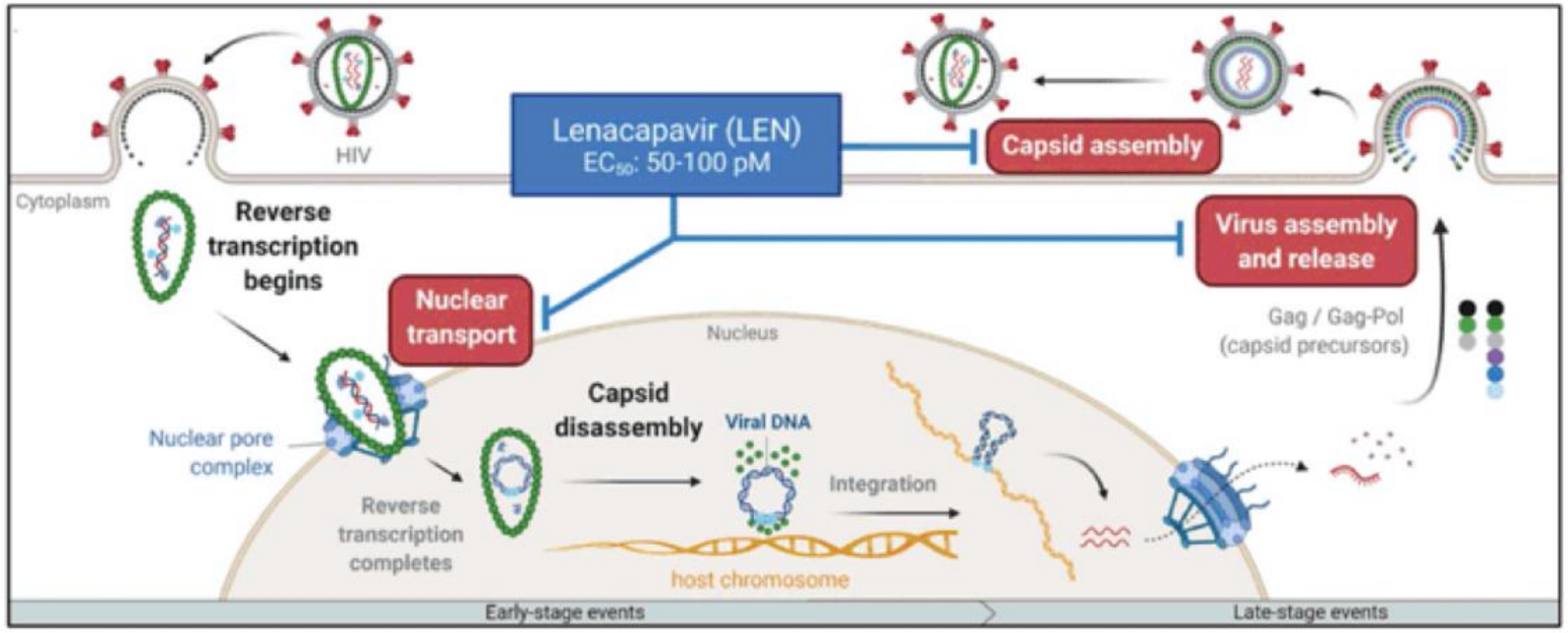


*Rare in patients never exposed to unboosted PIs (eg, NFV, DHHS alternative since 2003 and not recommended since 2008).

†If INSTI naive or experienced with no resistance (limited data in patients with resistance to RAL or EVG but susceptibility to DTG).

‡Data limited to DTG, but similar results might be seen with BIC.

Adapted from DHHS ART Guidelines. January 2023.



Link JO, et al. Nature 2020;584:614-8; Bester SM, et al. Science 2020;370:360-4.

Lenacapavir
Dec 2022
approved for
Q6M SC

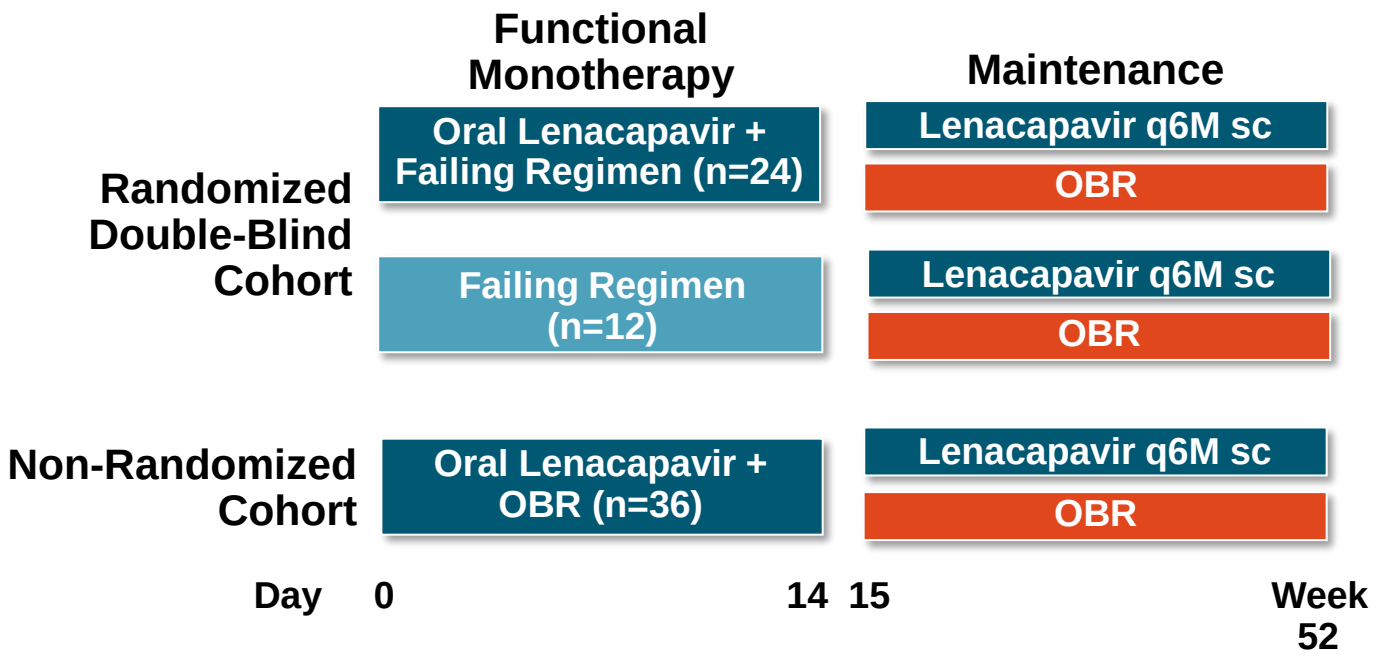
- Two 22 g, 0.5 inch SC injections q6 months by health care provider
- SC abdominal injection with each 2 inches from navel (rotate injection sites)
- Contraindicated with strong CYP3A inducers
- Insufficient human data for use during pregnancy

fda.gov/news-events/press-announcements/fda-approves-new-hiv-drug-adults-limited-treatment-options.
Lenacapavir extended-release injectable solution PI. Updated December 2022.

CAPELLA Study: Phase 3, LEN in Highly Treatment Experienced Patients

Treatment-experienced on failing regimen
Resistance to ≥2 agents from
3 of 4 main ARV classes
≤2 fully active agents available

Non-randomized cohort
Pre-randomization repeat HIV RNA
Decline of ≥0.5 $\log_{10}$ copies/mL or <400 c/mL



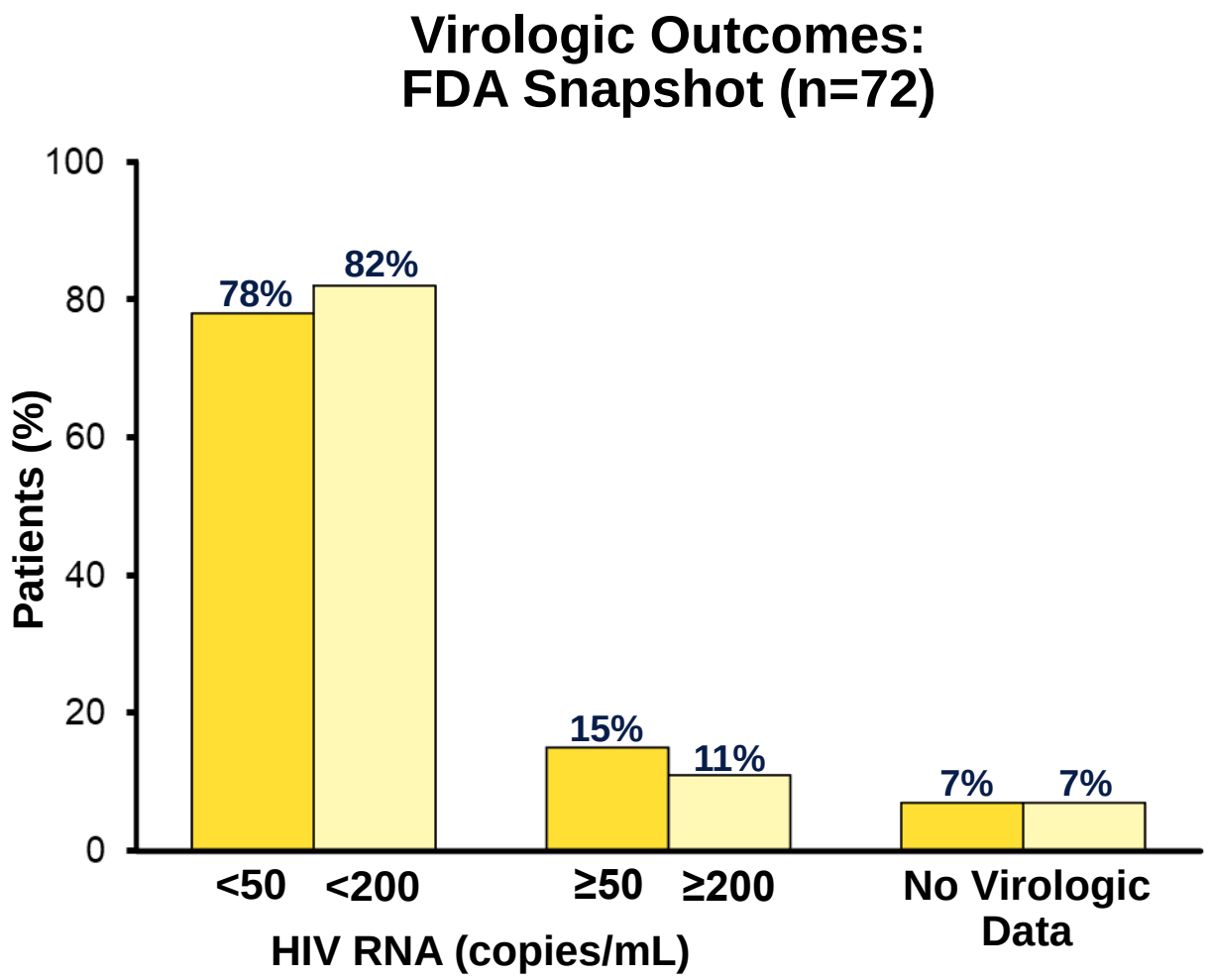
Baseline resistance:
NRTI: 99%.
NNRTI: 97%.
PI: 81%.
INSTI: 69%.
All 4 major drug classes: 46%.

- Oral LEN 600 mg day 1 and 2, 300 mg on day 8.
- SC LEN 927 mg (2 x 1.5 mL) day 15 and q6 months.
- Primary outcome (randomized cohort):
  ≥0.5 $\log_{10}$ copies/mL decline after 14 days.

Ogbuagu O, et al. CROI 2023. Abstract 523.

CAPELLA Study: Outcomes Week 52

- HIV RNA <50 copies by number of active agents in OBR
  - 0 (n=12): 75%; 1 (n=26): 77%; ≥2 (n=34): 79%
- CD4 increase: 84 cells/μL
- LEN resistance (n=9)
  - Resuppressed during receipt of LEN (4/9)
- Tolerability
  - Discontinuations due to injection site reaction (n=1)
  - No serious drug-related adverse events



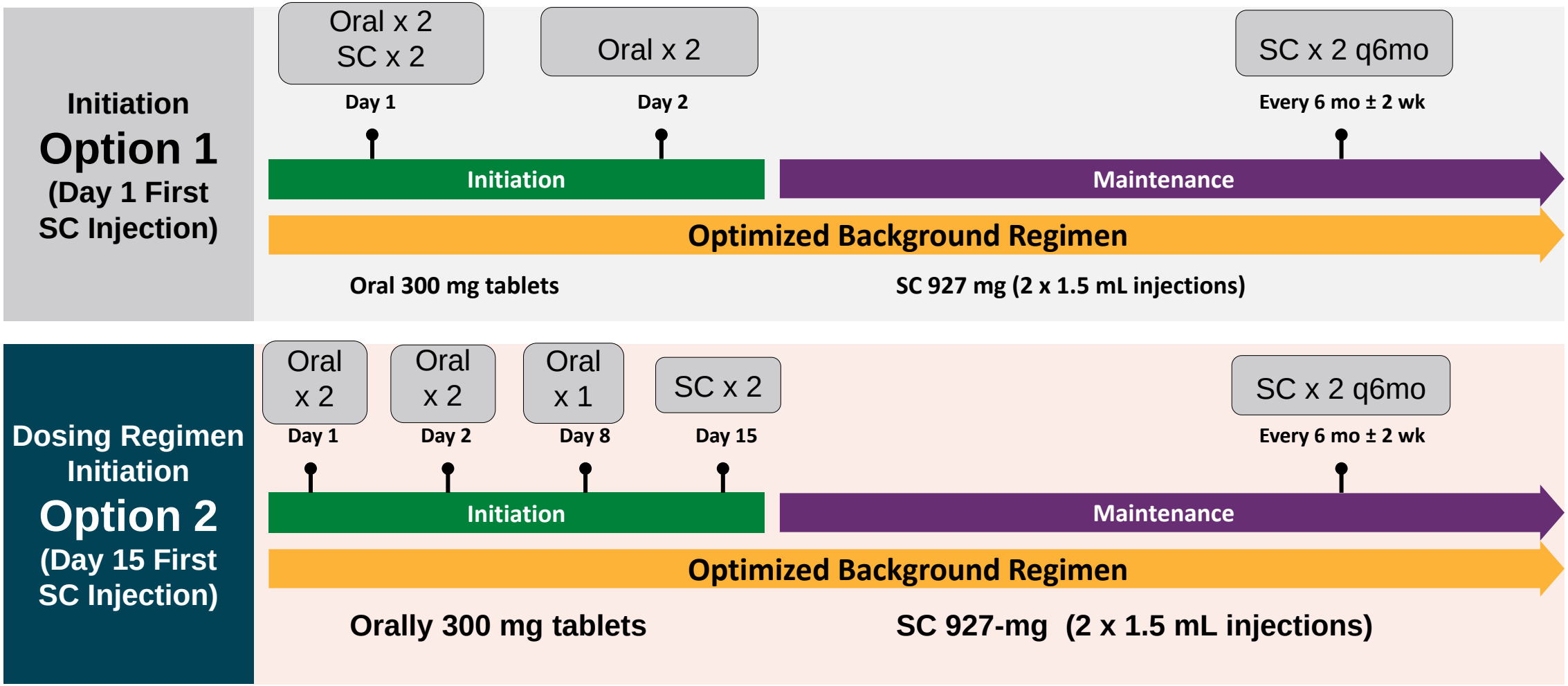
Ogbuagu O, et al. CROI 2023. Abstract 523.

CAPELLA: Emergent Resistance (Week 52)

Participants	Randomized (n = 36)	Nonrandomized (n = 36)	Total (N = 72)
Meeting criteria for resistance testing, n (%)	11 (31)	11 (31)	22 (31)
▪ With data	11 (31)	10 (28)	21 (29)
Emergent LEN resistance, n (%)	4 (11)	5 (14)	9 (13)
▪ M66I	4	2	6
▪ Q67H/K/N	1	3	4
▪ K70H/N/R/S	1	3	4
▪ N74D	3	0	3
▪ A105S/T	3	1	4
▪ T107A/C/N	1	3	4

Ogbu

Lenacapavir Initiation and Maintenance Schedule



Lenacapavir extended-release injectable solution PI. Updated December 2022.

ARV Switch: The Why and How in Clinical Practice

Why

- Simplify regimen (# and frequency)
- Tolerability
- Co-morbidity
- Drug-drug, drug-food interactions
- Pregnancy
- Cost

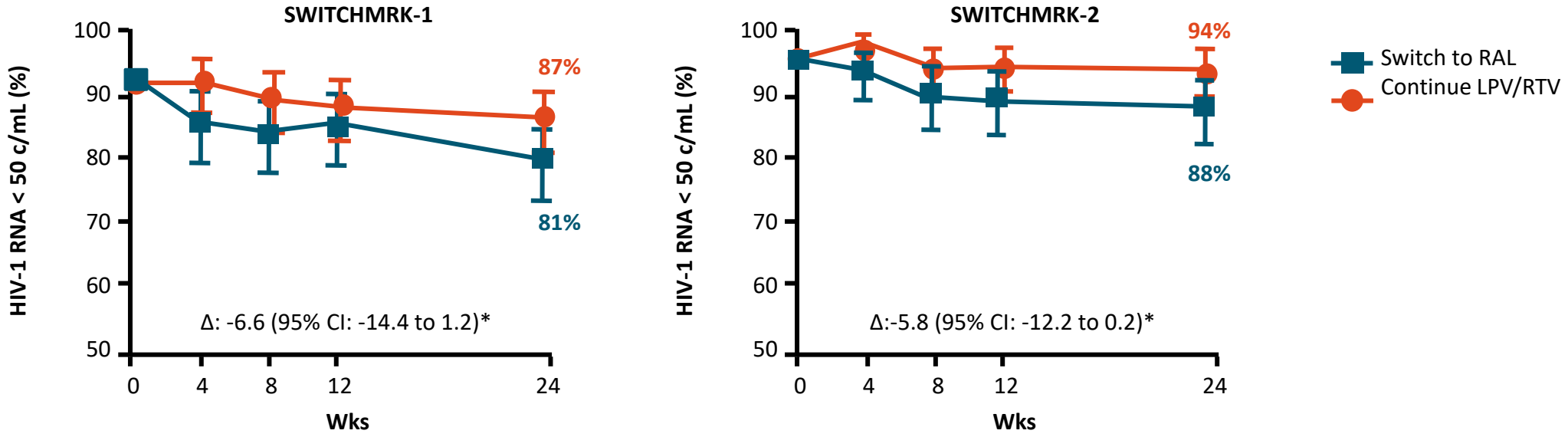
How

- Maintain viral suppression to avoid resistance
- Need to consider
  - Previous ART
  - Previous resistance
  - Likelihood of adherence
  - Drug-drug or drug-food
  - Comorbid conditions

DHHS. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision 2022.

SWITCHMRK: A Cautionary Tale if Underlying Resistance

- Randomized, double-blind trials in which virologically suppressed patients continued LPV/RTV-based regimen or switched to RAL-based regimen (N = 702)



*Prespecified noninferiority margin: -12%.

Underlying Resistance Matters

% with HIV-1 RNA < 50 c/mL for RAL vs LPV/RTV by investigator report of previous virologic failure: NO- 89% vs 90%; YES- 77% vs 92%

Eron. Lancet. 2010;375:396.

Considerations When Switching Regimens in Virologically Suppressed Patients

Drug Resistance

- Review ART history
- Review all resistance test results (old and new)
- Consider switch only if new regimen is likely to maintain suppression
- Within-class switches usually maintain virologic suppression if no resistance to drugs in that class
- Caution when switching from high barrier regimen (e.g., boosted PI) to low barrier regimen (e.g., NNRTI) if any underlying resistance
- Consider expert consultant if underlying resistance

Safety

- Review ART history for intolerance
- Must be HLA-B*5701 negative if considering ABC
- Consider drug–drug interactions with comedications

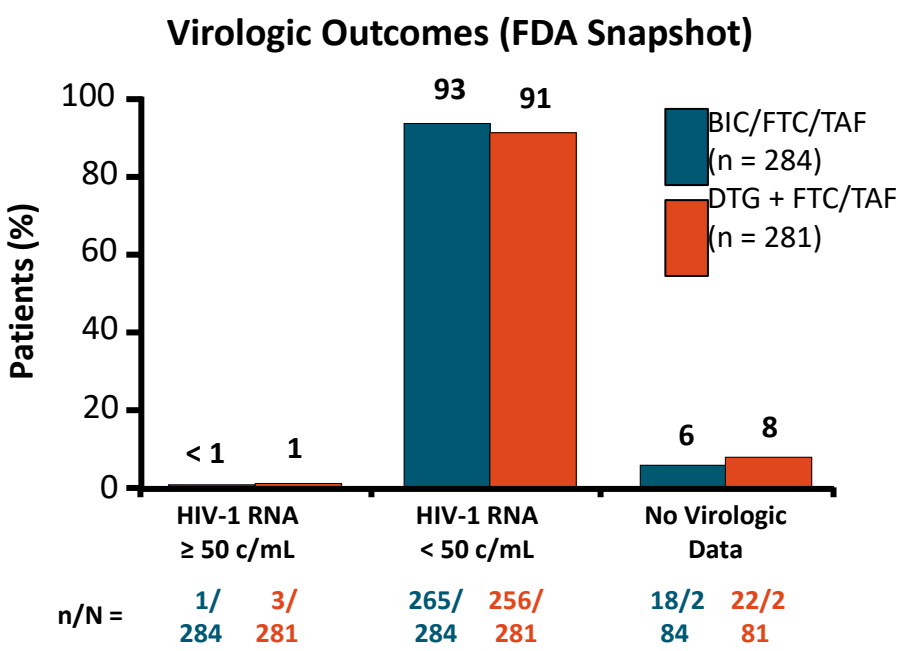
Comorbidity

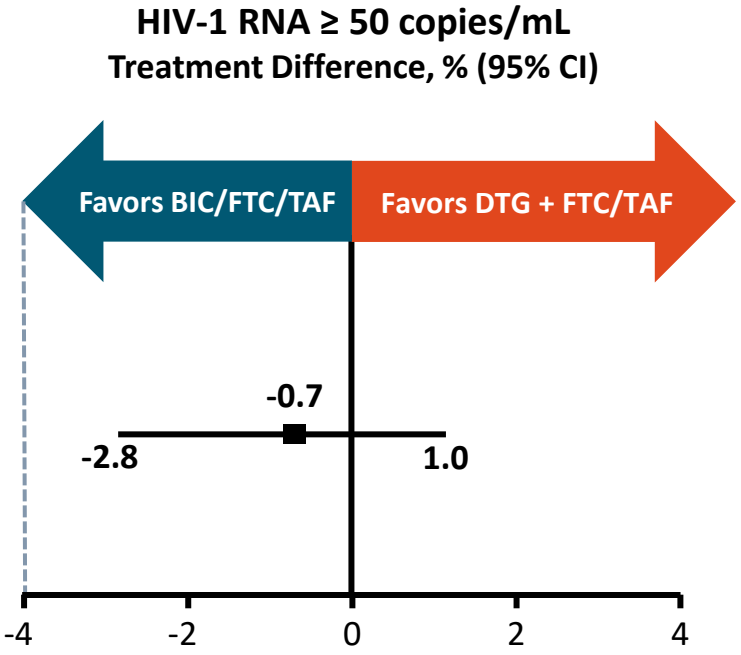
- HBV coinfection
- Cardiovascular disease or risk
- Renal function
- Bone mineral density
- Pregnancy
- Other coinfections

DHHS ART Guidelines. September 2022.

Study 380-4030: Switch to BIC/FTC/TAF from DTG + FTC/TAF (or TDF)

- Patients with viral suppression on stable triple DTG-based ART switched to BIC/FTC/TAF or continued DTG-based ART; documented or suspected NRTI, NNRTI, or PI resistance permitted
  - Preexisting NRTI resistance: 25% in BIC/FTC/TAF arm and 24% in DTG-based ART arm

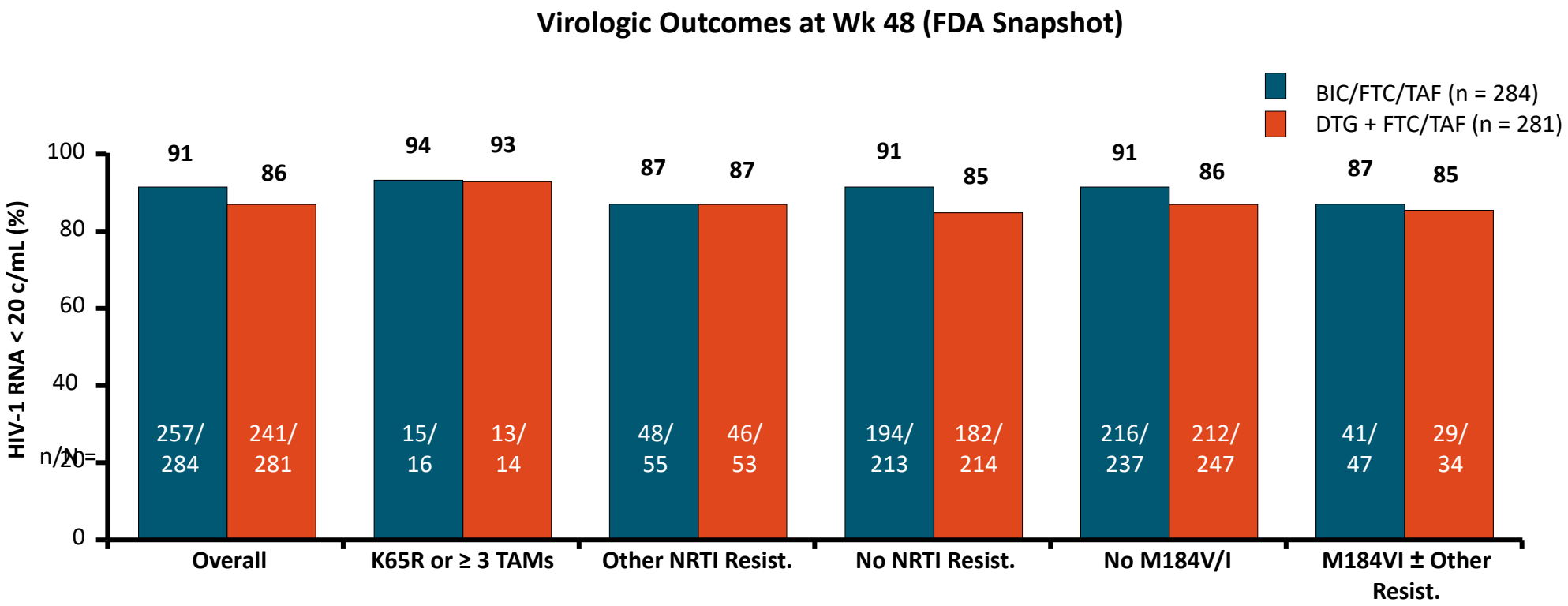




Sax. Clin Infect Dis. 2020;

Study 380-4030: Switch to BIC/FTC/TAF from DTG + FTC/TAF (or TDF)

HIV-1 RNA ≥ 50 c/mL not observed in any patient with preexisting NRTI resistance



Sax. Clin Infect Dis. 2020

Can we extrapolate from treatment failure studies to switch with no fully active NRTIs?

Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV

Nicholas I. Paton, M.D., Joseph Musaazi, M.Sc., Cissy Kityo, Ph.D., Stephen Walimbwa, M.D., Anne Hoppe, Ph.D., Apolo Balyegisawa, M.D., Arvind Kaimal, M.D., Grace Mirembe, M.Med., Phionah Tukamushabe, R.N., Gilbert Ategeka, M.D., James Hakim, F.R.C.P., Henry Mugerwa, M.D., Abraham Siika, M.Med., Jesca Asienzo, B.P.L.M., Barbara Castelnuovo, Ph.D., Agnes Kiragga, Ph.D., and Andrew Kambugu, M.Med., for the NADIA Trial Team*

NADIA

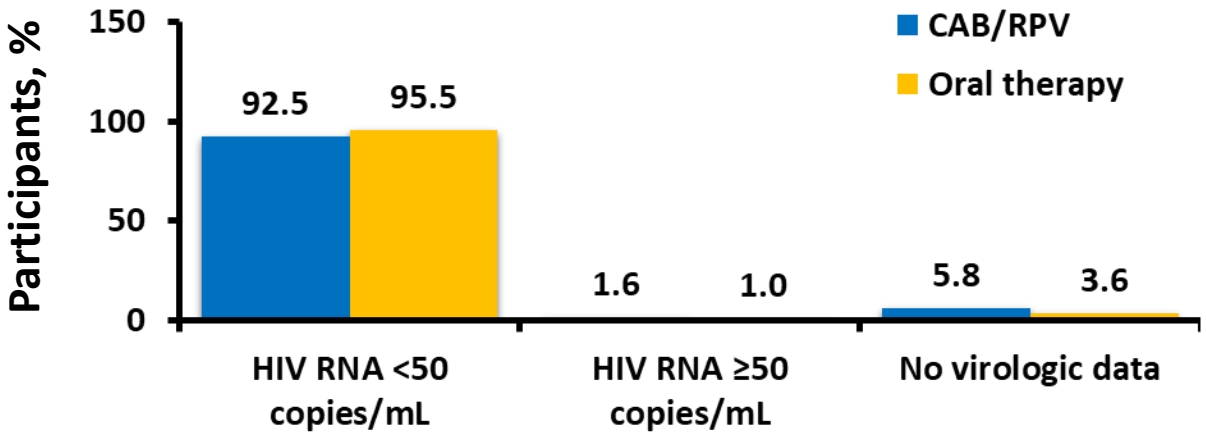
Long Acting Cabotegravir + Rilpivirine

- Approved as Q1 month (1/21) and Q2 months (2/22)
- Virologically suppressed, engaged patients
- No INSTI or NNRTI resistance (except K103N)
- No chronic HBV
- Challenges
  - Administration in clinic
  - Operationalizing for clinic

DHHS Guidelines. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.

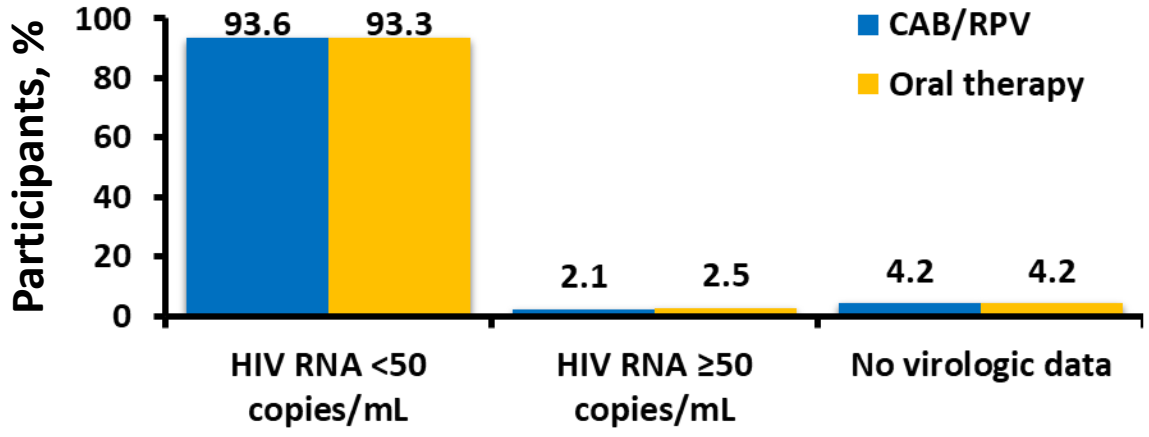
Long-Acting CAB/RPV vs Oral ART in Treatment-Experienced and Treatment-Naïve Patients

ATLAS: LA CAB/RPV is noninferior to oral ART at 48 weeks in treatment-experienced patients[1]



Injection site reactions were seen in 81% of CAB/RPV group and decreased to 11% at week 48

FLAIR: LA CAB/RPV is noninferior to oral ART at 48 weeks in treatment-naïve patients[2]

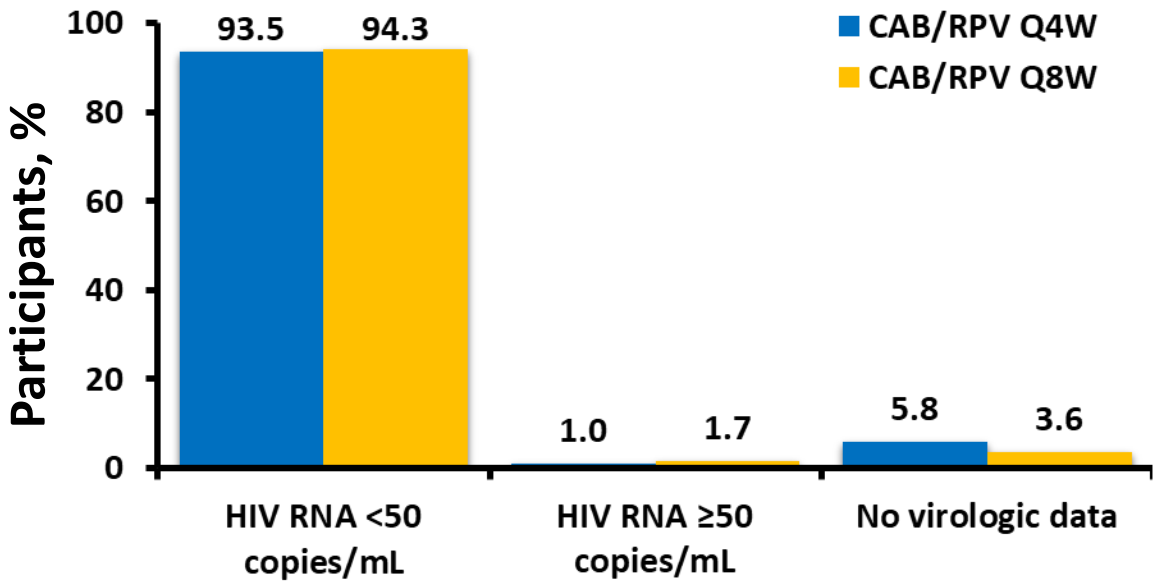


Injection site reactions were seen in 86% of CAB/RPV group and decreased to 20% at week 48

1. Swindells S, et al. *N Engl J Med*. 2020;382(12):1112-1123; 2. Orkin C, et al. *N Engl J Med*. 2020;382(12):1124-1135.

Long-Acting CAB/RPV Q4W vs Q8W
ATLAS-2M (at 48 wks)

CAB/RPV Q8W noninferior to Q4W



- Injection site reactions were rated as mild-to-moderate by 98% of participants experiencing them
  - Median duration of 3 days

LA CAB/RPV only indicated for those virologically suppressed: Limited data in those with concern for or actual poor adherence with visits or therapy

Overton ET, et al. *Infect Chemother.* 2020;52(suppl):S378-S379.

Risk Factors for Virologic Failure With LA CAB + RPV

- Post hoc analysis of **Wk 48 phase III data** (ATLAS, FLAIR, ATLAS 2M)
- 13/1039 (1.25%) participants had CVF

Factors Associated With CVF	OR
RPV RAS(s) at baseline	40.36
Wk 8 RPV trough concentration	5.00
Baseline HIV-1 subtype A6/A1	5.92
BMI (kg/m^2) at baseline	1.13

- Among 96.7% with 0 or 1 risk factor for CVF, 0.4% had CVF
- Q8W dosing not associated with CVF

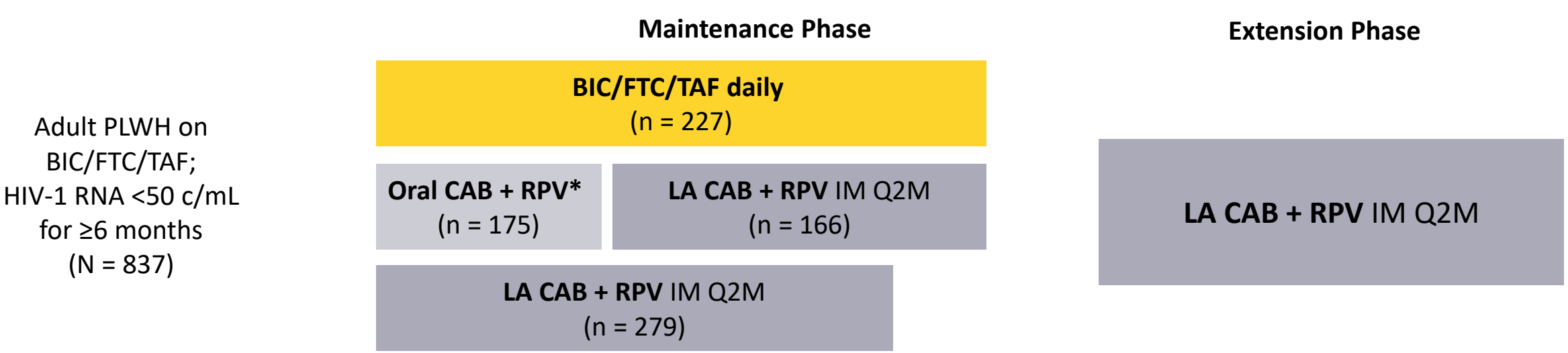
No. of Baseline Factors Associated With CVF	CVF, %	HIV-1 RNA <50 c/mL, %
None	0.4	95
1	0.4	96
≥2	26	71
Total	**1.3**	**94**

- Expanded multivariate analysis of CVF from FLAIR through Wk 124, ATLAS through Wk 96, and ATLAS-2M through Wk 152
  - Baseline RPV RAMs and HIV-1 subtype A6/A1 most significant risk for CVF CVF
  - Patients with 0/1 baseline factors had low risk of failure

1. Cutrell. AIDS. 2021;35:1333. 2. Orkin. HIV Glasgow 2022. Abstr O44.

SOLAR: Randomized Switch to LA CAB + RPV From BIC/FTC/TAF

- Multicenter, randomized, open-label, noninferiority phase IIIb study

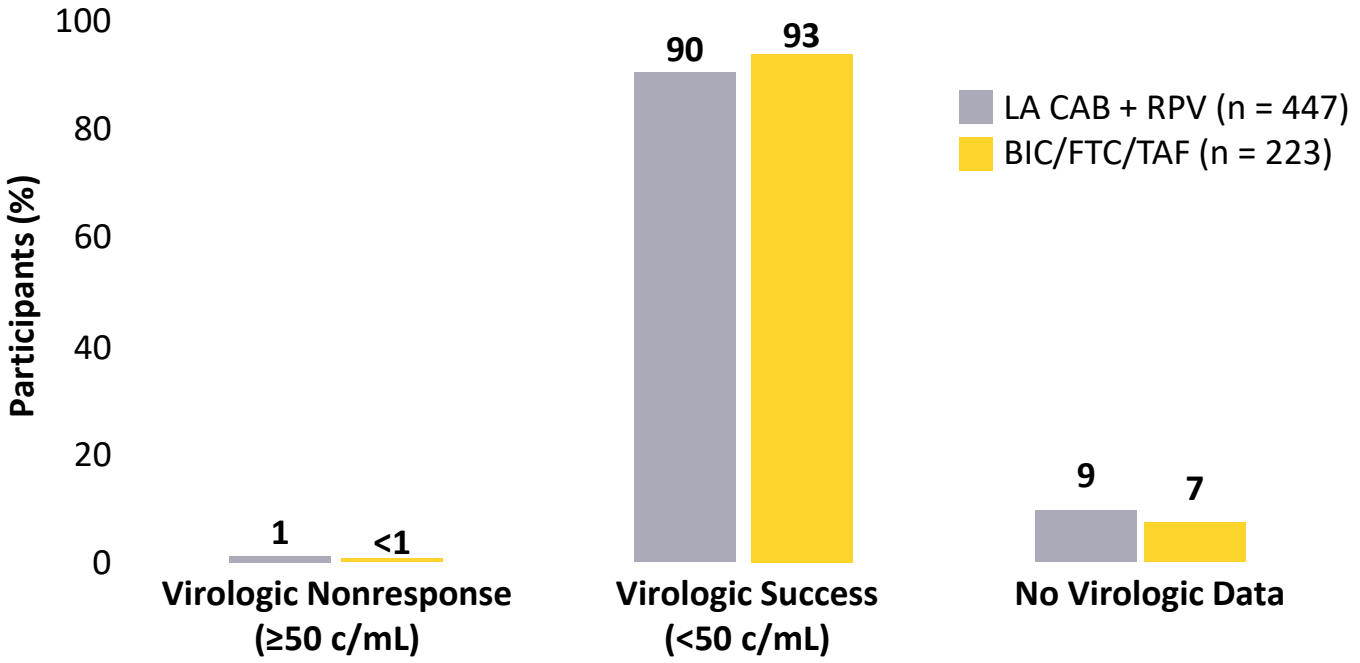


*Patients randomized to LA arm chose between 1 mo OLI or starting with injections.

- Endpoints assessed at 12 months (11 for those without oral lead in)
  - plasma HIV-1 RNA ≥50 c/mL (primary endpoint) and <50 c/mL (secondary endpoint)
  - CVF (2 consecutive HIV-1 RNA ≥200 c/mL)
  - Safety and tolerability
  - Treatment satisfaction (HIVTSQs) and patient preference for therapy

Ramgopal, et al. CROI 2023. Abstr 191.

SOLAR: Virologic Outcomes at 12 Months (mITT-E)



- LA CAB + RPV noninferior virologic efficacy to BIC/FTC/TAF at 12 mo (RNA≥50 c/mL difference 0.7 (95% CI -0.7, 2.0)
- 2 (0.4%) people receiving LA CAB + RPV in mITT-E population met CVF criterion
  - Associated with development of RPV and INSTI RAMs on treatment

Ramgopal, et al. CROI 2023. Abstr 191.

SOLAR: Safety and Treatment Satisfaction

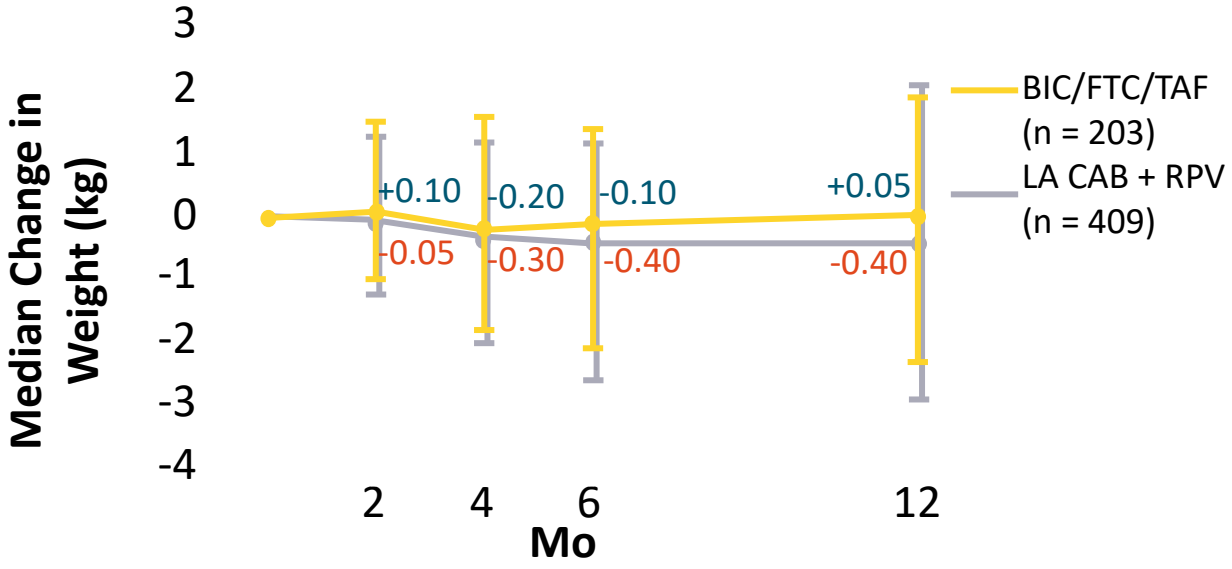
Adverse Events, n (%)	LA CAB + RPV (n = 454)	BIC/FTC/TAF (n = 227)
Any AE	349 (77)	172 (76)
Grade ≥3 AEs	42 (9)	26 (11)
Treatment withdrawal due to AEs	16 (4)	2 (<1)

- 98% of ISRs were grade 1 or 2 and lasted for median of 3 days
- 90% preferred LA CAB/RPV
- Adjusted mean change in total HIVTSQs at 12 months favored LA CAB/RPV (difference 4.95 (95% CI 3.59, 6.31, p<0.001)

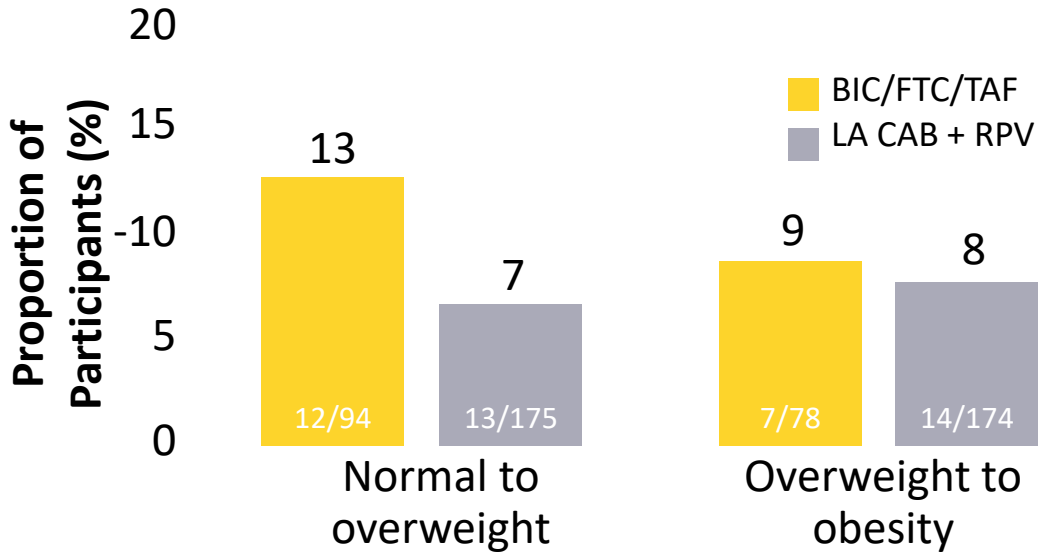
Ramgopal, et al. CROI 2023. Abstr 191.

SOLAR: Weight and Metabolic Changes (12 months)

Median (IQR) Change in Weight Through Mo 12



Proportion of Participants With an Upward BMI Shift Resulting in Overweight or Obesity at Mo 12



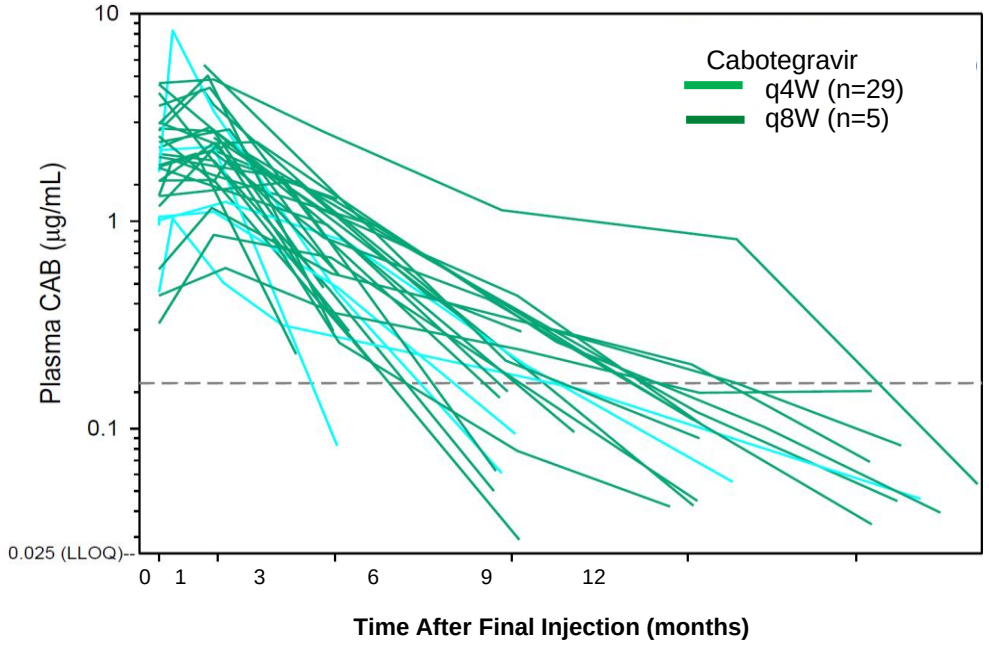
- No clinically relevant changes in hip or waist circumference or frequency of metabolic syndrome and insulin resistance between baseline and Mo 12 in either arm

Tan. CROI 2023. Abstr 146.

CAB + RPV LA Pharmacokinetics Following Discontinuation

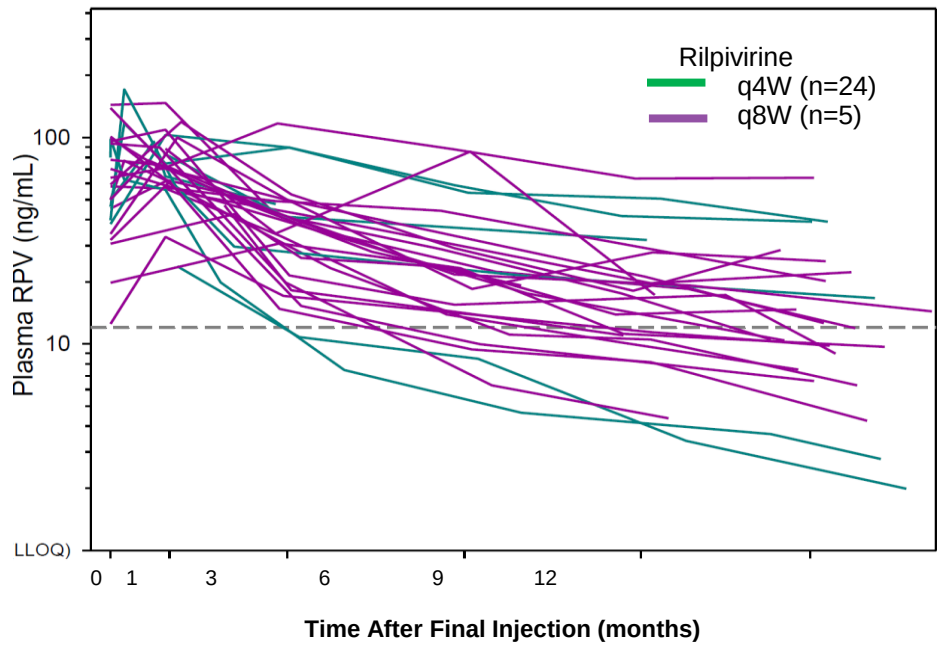
Concentration-Time Profile Following Discontinuation

Cabotegravir



Dotted line: cabotegravir PA-IC_{90} (0.166 µg/mL)

Rilpivirine



Dotted line: rilpivirine PA-IC_{90} (12 ng/mL)

CAB half life: 6.4 weeks

RPV half life: 29.6 weeks

Ford S, et al. CROI 2020. Boston, MA. Abstract 466.

LA CAB + RPV: Getting Started and Follow-up

Once-Monthly Dosing Schedule

Initiation		Continuation	
Mo 1	Administer first injections (1 LA CAB **600 mg/3 mL** and 1 LA RPV **900 mg/3 mL**)	**Mo 2 and Beyond**	For duration of treatment, administer injections monthly (1 LA CAB **400 mg/2 mL** and 1 LA RPV **600 mg/2 mL**)

2 IM injections at separate gluteal sites (opposite sides or 2 cm apart) during same visit

Every-2-Mo Dosing Schedule

Initiation			Continuation			
Mo 1	**Mo 2**	**Mo 3**	**Mo 4**	**Mo 5**	**Mo 6, 8, and Beyond**	
Administer first injections (1 LA CAB **600 mg/3 mL** and 1 LA rilpivirine **900 mg/3 mL**) Administer second set of initiation injections 1 mo later			For duration of treatment, administer injections (1 LA CAB **600 mg/3 mL** and 1 LA RPV **900 mg/3 mL**) every 2 mo			

2 IM injections at separate gluteal sites (opposite sides or 2 cm apart) during same visit

Practical Considerations for LA CAB + RPV

- Administered only by HCP
- Oral CAB + RPV lead-in dosing for ~1 mo to assess tolerability is now optional
- Initiate **Q1M** injections with loading dose (CAB 600 mg/3 mL + RPV 900 mg/3 mL) followed by monthly continuation doses (CAB 400 mg/2 mL + RPV 600 mg/2 mL)
- For **Q2M** dosing schedule: Initiate injections of CAB 600 mg and RPV 900 mg monthly for first 2 mo and then every 2 mo thereafter
- 23-gauge, 1.5-inch intramuscular needle recommended (use 2-inch needle if BMI ≥30 kg/m^2)
- Give ventrogluteal IM injections on opposite sides when possible or ≥2 cm apart if on same side

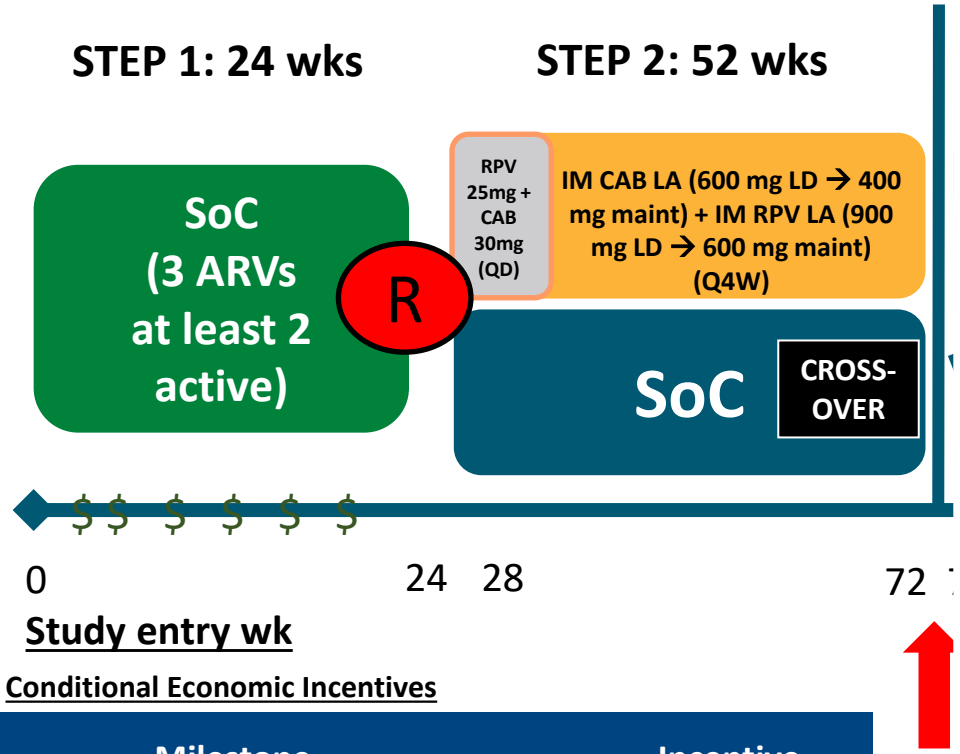
DHHS Guidelines. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents, Accessed 2022

Practical Considerations for LA CAB + RPV: Monitoring and missed doses

- HIV-1 RNA: 4-8 wk after switch to LA CAB + RPV or missed dose
- If viremic, test for resistance (including INSTI resistance)
- Oral bridging for planned missed doses
- *Missed dose:*
  - *If Q4 weeks:* ***≤2 mo*** *since last injection*, resume prior schedule; *If* ***>2 mo*** *give* loading dose, followed by monthly dosing
  - If Q8 weeks:
    - *If* ***injection 2*** *missed* ≤2 mo since first injection, resume prior dosing schedule; if >3 mo since last injection, dose and redoes 1 mo later, then Q2M
    - *If* ***injection 3 or later*** *missed; i*f ≤3 mo since last injection, resume prior dosing schedule; if >3 mo **dose, followed by another 1 mo later, then resume Q2M**
- If stop: oral regimen within 4-8 wk of last IM dose (depending if on Q4 or 8 wk dose)
- Switching to Q8 wk: CAB 600 mg/RPV 900 mg 1 mo after last dose, F/B Q8 wk

DHHS Guidelines. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents, Accessed 2022

ACTG 5359: Long-acting Cabotegravir + Rilpivirine in Persons With HIV Nonadherent to Current ART



Conditional Economic Incentives

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

LA CAB + RPV: SF Ward 86

- LA CAB + RPV using protocol with biweekly patient review and extensive wrap around services
- LA CAB + RPV inclusion criteria:
  - Viral suppression **not required**
  - No RPV or INSTI mutations
  - Agree to Q4 week clinic visits and to provide contact information for outreach from staff
- 133 PWH initiated LA CAB + RPV June 2021 - November 2022

Characteristic, n (%)	LA CAB + RPV (N = 133)
Race/ethnicity	
▪ Black	21 (16)
▪ Latinx	50 (38)
▪ Multiracial	19 (14)
Unstable housing	77 (58)
Homeless	11 (8)
Medicare/Medicaid	130 (98)
Current stimulant use	44 (33)
Major mental illness	51 (38)
Viremic (HIV-1 RNA >30 c/mL)	**57 (43)**

Of those viremic, mean HIV-1 RNA: 4.21 $\log_{10}$, median CD4 cell count: 215 cells/mm^3

Gandhi. CROI 2023. Abstr 518.

War 86 Virologic Outcomes With LA CAB + RPV

- On-time injections: 74%
- Suppressed at entry (n=76)
  - 100% (95% CI: 94, 100) without viral rebound
- Viremic at entry (n=57)
  - 55 achieved suppression at median of 33 days
  - 2 with virologic failure, both in <24 weeks, both with minor resistance mutations pre-entry and <2 log decline at first visit
    - Patient 1: V179I BL and developed Y181C, L100I
    - Patient 2: T97A BL and developed R263K, E138K
  - Subsequently protocol excluded those with any resistance at BL

Gandhi. CROI 2023. Abstr 518.

Thank You!!