AMERICAN ACADEMY OF HIV MEDICINE

Long-acting Antiretrovirals for Treatment and Prevention: Promises and Pitfalls

Monica Gandhi MD, MPH

Director, UCSF Center for AIDS Research (CFAR) and Medical Director, Ward 86 HIV Clinic

Professor of Medicine, University of California, San Francisco (UCSF)

This activity is jointly provided by the Partners for Advancing Clinical Education (PACE) and the American Academy of HIV Medicine.

PACE
Partners for Advancing Clinical Education

This activity is supported by an independent educational grant from ViiV.

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Target Audience

This activity has been designed to meet the educational needs of physicians, physician assistants, nurse practitioners, and pharmacists; other healthcare providers, such as nurses, nutritionists, social workers, and case managers are also encouraged to attend.

Statement of Need/Program Overview

Academy-credentialed providers, clinicians, members, and guest participants will gain a broader perspective on the intersection of unintended weight change and HIV, how to prescribe a more individualized, tailored ARV regimen, and a clear understanding of how weight change can affect metabolic syndromes. Metabolic syndromes such as insulin resistance, diabetes mellitus, and dyslipidemia are a significant concern in patients with HIV, and increasingly, clinicians are caring for patients with unintended weight change and associated complications, such as accelerated atherosclerosis and cardiovascular disease. This series will serve as an in-depth discussion on FDA-approved HIV treatment options, therapeutic alternatives, and weight change treatment options. Additionally, how to incorporate diet and nutrition into patient counseling is discussed to emphasize patient quality of life issues and treatment efficacy.

Joint Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by the Partners for Advancing Clinical Education (PACE) and the American Academy of HIV Medicine. PACE is accredited by the American Council for Continuing Medical Education (ACCME), Accreditation Council for Pharmacy Education (ACPE) and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Physician Continuing Medical Education

CREDIT DESIGNATION

- PACE designates this live activity for a maximum of 1 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Pharmacist Continuing Education

CREDIT DESIGNATION

- PACE designates this continuing education activity for 1 contact hour(s) (0.1 CEUs) of the Accrediting Council for Pharmacy Education.
  (Universal Activity Number # JA4008073-9999-24-027-L02-P

- Type of Activity: Knowledge

Upon completion of the online evaluation, your credit will be submitted to CPE Monitor.Pharmacists have up to thirty (30) days to complete the evaluation and claim credit. Please check your NABP account within thirty (30) days to make sure the credit has posted.

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Nursing Continuing Professional Development

CREDIT DESIGNATION

- The maximum number of hours awarded for this Nursing Continuing Professional Development Activity is 1 contact hour.
- Designated for 0.75 contact hours of pharmacotherapy credit for Advanced Practice Registered Nurses.

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Faculty Disclosures:

The ***faculty*** reported the following financial relationships or relationships to products or devices they have with ineligible companies:

Monica Gandhi has no relevant financial disclosures

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Planners and Managers Disclosures

American Academy of HIV Medicine (AAHIVM)

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Partners for Advancing Clinical Education (PACE)

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The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Fee Information

There is no fee for this educational activity.

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Educational Objectives

Upon completion of this activity, participants should be able to:

- Discuss the use of long-acting ART in people with HIV with virologic suppression
- Evaluate emerging data on long-acting ART in people with HIV with adherence challenges
- Compare and contrast long-acting options for pre-exposure prophylaxis (PrEP)
- Describe upcoming options for long-acting ART and PrEP in the future

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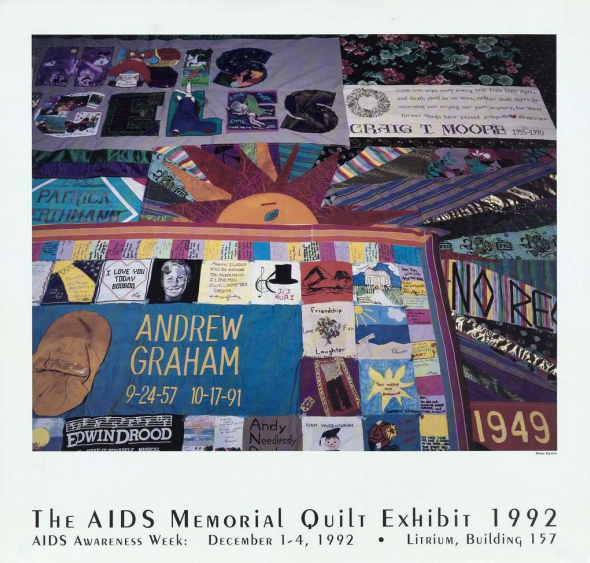
Objectives of talk

- Why long-acting?
- Data on long-acting CAB/RPV for treatment in those starting with virologic suppression (VS), including in LMICs
- Data on LA CAB/RPV in those with adherence challenges
- Data on long-acting CAB for prevention
- Lenacapavir for MDR-HIV (naïve, prevention)
- Pitfalls of LA medications



INTEGRASE INHIBITORS (INSTIs) FIRST LINE IN WORLD- TLD

Study	Population	Comparator	Outcome	Resistance
BICTEGRAVIR				
1489	Naïve	DTG/ABC/3TC	Non-inferior	0
1490	Naïve	DTG+FTC/TAF	Non-inferior	0
1844	Suppressed	DTG/ABC/3TC	Non-inferior	0
1878	Suppressed	Boosted PI + 2 NRTIs	Non-inferior	0 to INSTI but 1 L74V in PI arm
1961 (women)	Suppressed	E/C/F/(TAF or TDF) ATV+RTV + FTC/TDF	Non-inferior	0 to INSTI but 1 M184V in ELV/cobi
DOLUTEGRAVIR				
SINGLE	Naïve	EFV/TDF/FTC	Superior	0 in DTG arm; 7 in EFV
FLAMINGO	Naïve	DRV/r with 2 NRTI backbone	Superior	0 in either
SPRING-2	Naïve	RAL with 2 NRTI backbone	Non-inferior	0 in DTG; 1 INSTI/NRTI in RAL

So, why long-acting?

- Even though rates of virologic suppression high in many settings (>89% in Ryan White Care clinics including Ward 86; >90% in many settings in LMICs including Kenya, Uganda), still barriers to taking ART for some, including pill fatigue

UNAIDS

THE PATH THAT ENDS AIDS

2023 UNAIDS GLOBAL AIDS UPDATE

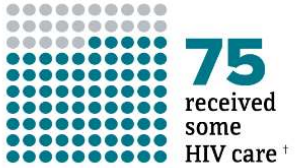
- Among all people living with HIV, 86% [73– >98%] knew their status, 76% [65–89%] were accessing treatment and 71% [60–83%] were virally suppressed in 2022.

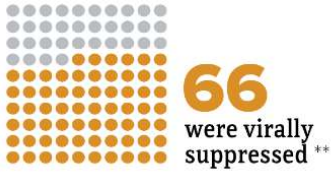
HRSA
Ryan White & Global HIV/AIDS Programs

89.7% of RWHAP clients receiving HIV medical care **reached viral suppression* in 2021**

HIV Care Among People with Diagnosed HIV in 47 States and the District of Columbia, 2021*

More than half of people with diagnosed HIV are virally suppressed. For every **100 people overall with diagnosed HIV:**





DTG 1st line even with NRTI resistance but..

Study	Type of study, n	Comparison	Outcome	Emergent resistance
SAILING	Randomized to DTG vs RAL in face of NRTI, NNRTI and/or PI resistance, n=715	DTG + 2NRTIs vs RAL+ 2 NRTIs	DTG superior to RAL	**4 with INSTI resistance in DTG arm**; 17 in RAL arm
VIKING	Randomized to DTG vs optimized background in MDR HIV (including INSTI)	DTG + OBR vs OBR	DTG superior to optimized regimen with multidrug resistant HIV	**5 emergent INSTI mutations in DTG arm** (n=14)
DAWNING	Open-label noninferiority study in PWH failing 1st line NNRTI + 2 NRTIs, n=624	DTG + 2NRTIs vs LPV/RTV + 2 NRTIs	DTG superior to LPV/RTV in subgroups	**2 patients failed with INSTI resistance; 0 with PI resistance**
NADIA	Switch study in PWH failing NNRTI/TDF/3TC (86% M184V; 50% K65R), n=464	DTG or DRV/r with either TDF/3TC or AZT/3TC	DTG + 2 NRTIs noninferior to DRV/r + 2 NRTIs (TDF/FTC works with K65R)	**9 patients DTG arm failed with resistance; 0 in DRV/r arm**
VISEND	Randomized when failing NNRTI-based therapy, n=1201	DTG or boosted PI regimens	>80% virologic suppression (<50) on DTG regimens	Not yet reported (abstract CROI 2022)
2SD	Randomized study 2nd line therapy, Kenya, n=795	PI/r + 2 NRTIs switch DTG/ 2 NRTI	>90% virologic suppression each arm (48 weeks)	No emergent resistance either arm

SAILING: Cahn Lancet 2013; **VIKING**: Bisher Antiviral Therapy 2015; **DAWNING:** Aboud M, et al. *Lancet Infect Dis*. 2019**;** **NADIA:** Patton N. Lancet HIV 2022; **VISEND**: Mulenga LB, et al. CROI 2022. Abstract 135; **2SD Study**: Ombajo L NEJM 2023

World Health Organization

March 5, 2024

New report documents increase in HIV drug resistance to dolutegravir

5 March 2024 | News release | Reading time: 3 min (817 words)

However, among the four surveys reported, levels of resistance to dolutegravir ranged from 3.9% to 8.6%, and reached 19.6% among people experienced with treatment and transitioned to a DTG-containing ART while having high HIV viral loads. To date, only a few countries have reported survey data to WHO.

South African study confirming ART exposure by LC-MS/MS- 11.9% resistance if taking DTG & high viral load (increased from 2.7% in 2021 to 11.9% in 2022)

XXX INTERNATIONAL WORKSHOP ON HIV DRUG RESISTANCE AND TREATMENT STRATEGIES
20 - 22 September 2023 • Cape Town, South Africa

Comparison with previous surveys in South Africa 2019-2022

	2019	2021	2022
Total number of samples tested	779	621	709
Succesful DLT	779	621	708
Any ARV detected	55.7%	52.0%	58.6%
EFV detected	42.5%	35.8%	22.7%
FTC detected	30.1%	23.5%	8.3%
3TC detected	12.6%	9.6%	8.3%
LPV detected	3.9%	6.9%	5.8%
DTG detected	NA	7.2%	15.0%
Succesful HIVDR	753	538	595
Any resistance	72.1%	67.6%	57.9%
NNRTI resistance	70.5%	66.4%	56.0%
NRTI resistance	49.0%	41.4%	28.5%
PI resistance	2.2%	4.1%	3.1%
INSTI resistance	NA	0.2%	1.6%

Risk factors for dolutegravir resistance:

- Underlying NRTI mutations (tx experience)
- DTG monotherapy, dual therapy
- Children (Kenya, Uganda)
- **Off and on adherence (drug selective pressure)-** ***could long-acting ART address?***

Loosli Lancet HIV 2023; Bello CROI 2024; Kingwara. CROI 2024; Namayanja XXX International Workshop 2023

Long-acting medications in other fields support adherence- so let's turn to HIV

Treatment of psychiatric disorders

Adherence Challenges and Long-Acting Injectable Antipsychotic Treatment in Patients with Schizophrenia

Contraception

Long-Acting Reversible Contraception for Adolescents: A Review of Practices to Support Better Communication, Counseling, and Adherence

Substance use disorder treatment

What is long-acting (XR) buprenorphine injection?

Long-acting buprenorphine injection (XR-buprenorphine, currently available brand name: Sublocade) is an injectable formulation of buprenorphine that is given once a month to assist people in obtaining and sustaining long-term recovery from opioid use disorder (OUD). There may be additional XR-

Long-acting injectable naltrexone for the treatment of alcohol dependence

Objectives of talk

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- Data on long-acting CAB/RPV for treatment in those starting with virologic suppression (VS), including in LMICs
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- Data on long-acting CAB for prevention
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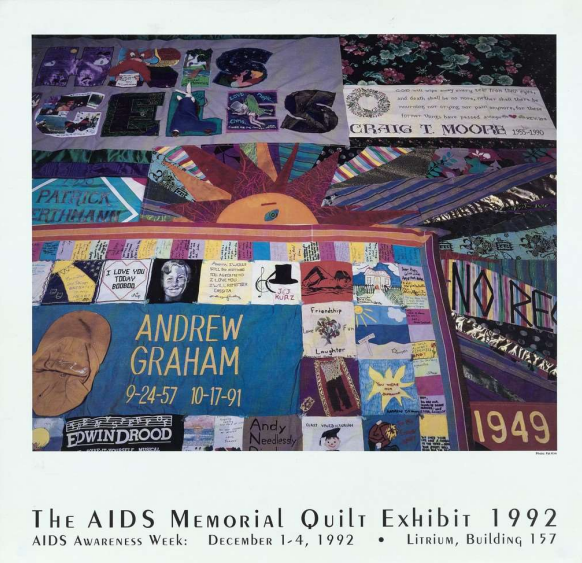


Only combination treatment for LA ART -Cabotegravir (CAB)/ Rilpivirine (RPV)- 3 registrational trials (all with VS)

Virologic suppression rate to date

FLAIR

- CAB/RPV LA in treatment naïve participants (K103N mutation allowed); First put on DTG/ABC/3TC for 20 weeks then LA ART with virologic suppression

80.2% at 124 weeks

ATLAS

- CAB/RPV LA in treatment experienced participants every 4 weeks (K103N okay); on suppressive regimen for 6 months prior to switch

85.9% at 152 weeks

ATLAS 2M

- CAB/RPV LA in treatment experienced participants every 8 weeks (higher dose 600mg/900mg) after VS x ≥ 6 months

87.4% at 152 weeks

Orkin C. Lancet HIV 2021; Swindells S. AIDS 2022; Overton E. CID 2023

An RCT after approval and real-world studies of LA CAB/RPV

Virologic suppression rate to date

SOLAR study

- CAB/RPV LA every 8 weeks in treatment experienced participants (47% expressed internal or external stigma) switched BIC/TAF/FTC when VS (n=670)

↔ 90% at 44-48 weeks

DAT'AIDS Cohort

- Real-world cohort in France among those with VS on oral ART switched to LA CAB/RPV every 8 weeks (n=1134)

↔ 98.8% at median f/u 28 weeks (7.1% d/c rate)

CARISEL cohort

- Real-world study across 5 countries Europe (18 clinics) of switching those on oral ART with VS to LA CAB/RPV every 8 weeks (n=430)

↔ 87% at 52 weeks

Smaller studies (ATHENA, BEYOND, ABOVE, COMBINE-2, Swiss cohort, UCSD Own Clinic, JABS) similar findings among those with VS

CARLOS cohort

- Real-world study in Germany of switching those on oral ART with VS to LA CAB/RPV every 8 weeks (n=230)

↔ 89.5% at 24 weeks

Ramgopal M. Lancet HIV 2023; Allavena. EACS 2023.; de Wit ID week 2022 (OFID 2023); Borch HIV Glasgow 2022

Oral Abstract Session-03

Monday, March 4, 2024

Randomized Trial of Cabotegravir and Rilpivirine Long-Acting in Africa (CARES): Week 48 Results

Nicholas Paton
London School of Hygiene & Tropical Medicine, London, UK

Disclosure: Nicholas Paton received research funding from Janssen

CROI 2024

CARES Trial- CAB/RPV in LMICs

CROI 2024

Study Design

Phase 3b, Randomized (1:1), Open-Label, Active-Controlled, Multi-Centre, Parallel-Group, Noninferiority Study

Main eligibility criteria

- ≥18 years of age
- On stable oral therapy: TDF + 3TC/FTC + DTG/NVP/EFV*
- HIV-1 RNA <50 copies/mL at ≥4-12m prior to and at screening
- No history of Rx failure
- No HBV infection

Study treatment

Oral ART (SOC)
TDF + 3TC/FTC + DTG/NVP/EFV
n=256

Optional Oral CAB + RPV

CAB (600 mg) + RPV (900 mg) LA
IM Q8W
n=256

Study timepoint: Day −28 to −1 (Confirm HIV-1 RNA <50 copies/mL); Day 1 (Randomization (1:1)); Week 4; Week 24; Week 48; Week 72; Week 96

Viral load every 24 weeks

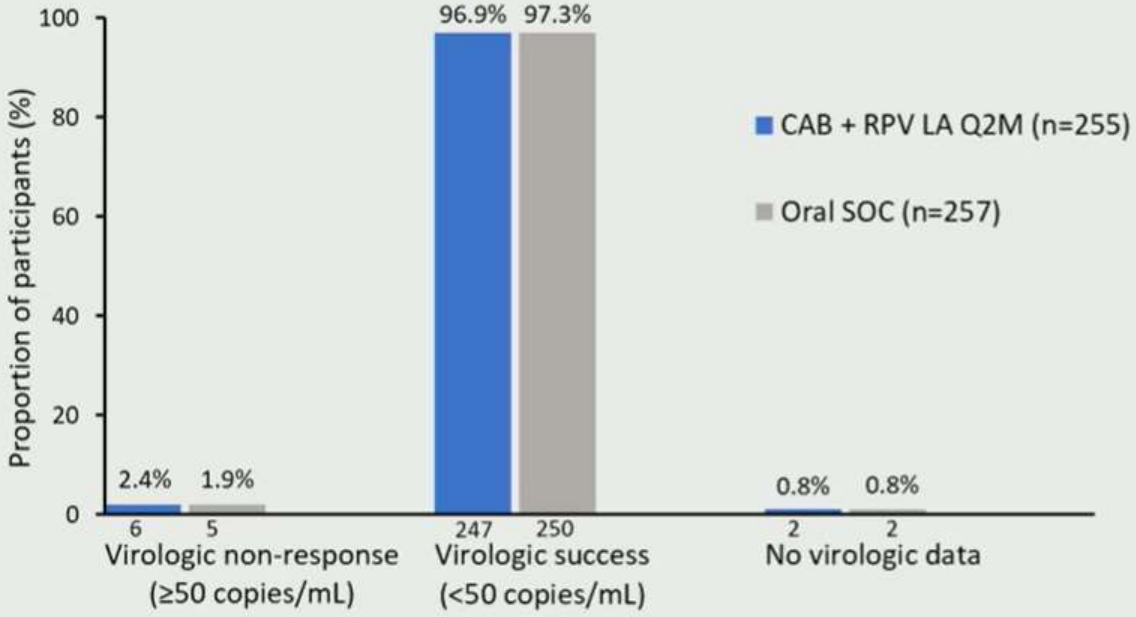
Baseline Characteristics

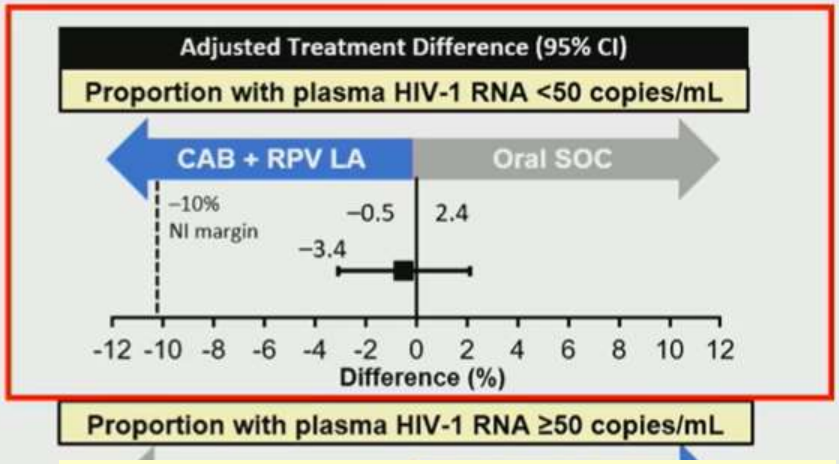
Characteristic	CAB + RPV LA (n=255)	Oral ART (SOC) (n=257)	Overall (N=512)
Female sex, n (%)	146 (57.2)	149 (58.0)	295 (57.6)
Age, median (IQR), years	43 (36-51)	42 (35-49)	42 (35-51)
BMI≥30 kg/m^2, n (%)	57 (22.4)	51 (19.8)	108 (21.1)
Black race, n (%)	254 (99.6)	256 (99.6)	510 (99.6)
Time on first-line ART, median (IQR), years	8 (4-13)	7 (4-13)	8 (4-13)
Prior exposure to NNRTI, n (%)	189 (73.7)	191 (74.3)	380 (74.2)
INSTI regimen at screening	231 (90.6)	240 (93.4)	471 (92.0)
NNRTI regimen at screening	24 (9.4)	17 (6.6)	41 (8.0)
Archived DNA analysis * †			
Viral subtype A1, n/n (%)	119/213 (55.9)	115/201 (57.2)	234/414 (56.5)
RPV resistance mutations, n/n (%)	25/200 (12.5)	26/177 (14.7)	51/377 (13.5)
RPV intermediate/high-level resistance, n/n (%)	17/200 (8.5)	21/177 (11.9)	38/377 (10.1)
CAB resistance mutations, n/n (%)	15/95 (15.8)	14/85 (16.5)	29/180 (16.1)
CAB intermediate/high-level resistance, n/n (%)	10/95 (10.5)	5/85 (5.9)	15/180 (8.3)

Archived DNA run later

- * Retrospective, batched sequencing performed on archived viral DNA extracted from PBMCs stored at baseline
- † Viral subtype, resistance mutations and drug susceptibility were determined using the Los Alamos National Laboratory Panel, and Stanford algorithm respectively

Virologic Outcomes at Week 48 (ITT)





96% injections given within 7-day window; importantly, treatment satisfaction improved; public health approach (VL only every 24 weeks); 2 treatment failures with NNRTI & INSTI resistance

Primary outcome - proportion with plasma HIV-1 RNA <50 copies/ml:

- Main analysis (ITT): adjusted difference -0.5% (95% CI, −3.4 to 2.4), **meeting the non-inferiority criterion**
- Sensitivity analysis (per-protocol): adjusted difference -0.3% (95% CI, -3.0 to 2.3) **confirming non-inferiority**

Note: minor changes in numbers from abstract

Oral Abstract Session-11

Wednesday, March 6, 2024

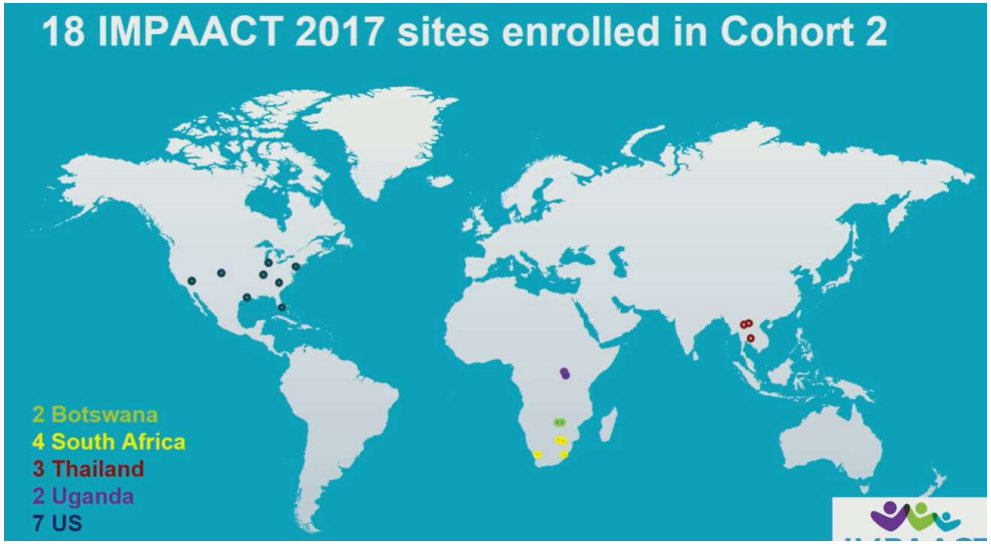
Long-Acting Cabotegravir Plus Rilpivirine In Adolescents With HIV: Week 24 IMPAACT 2017(MOCHA) Study

Aditya Gaur

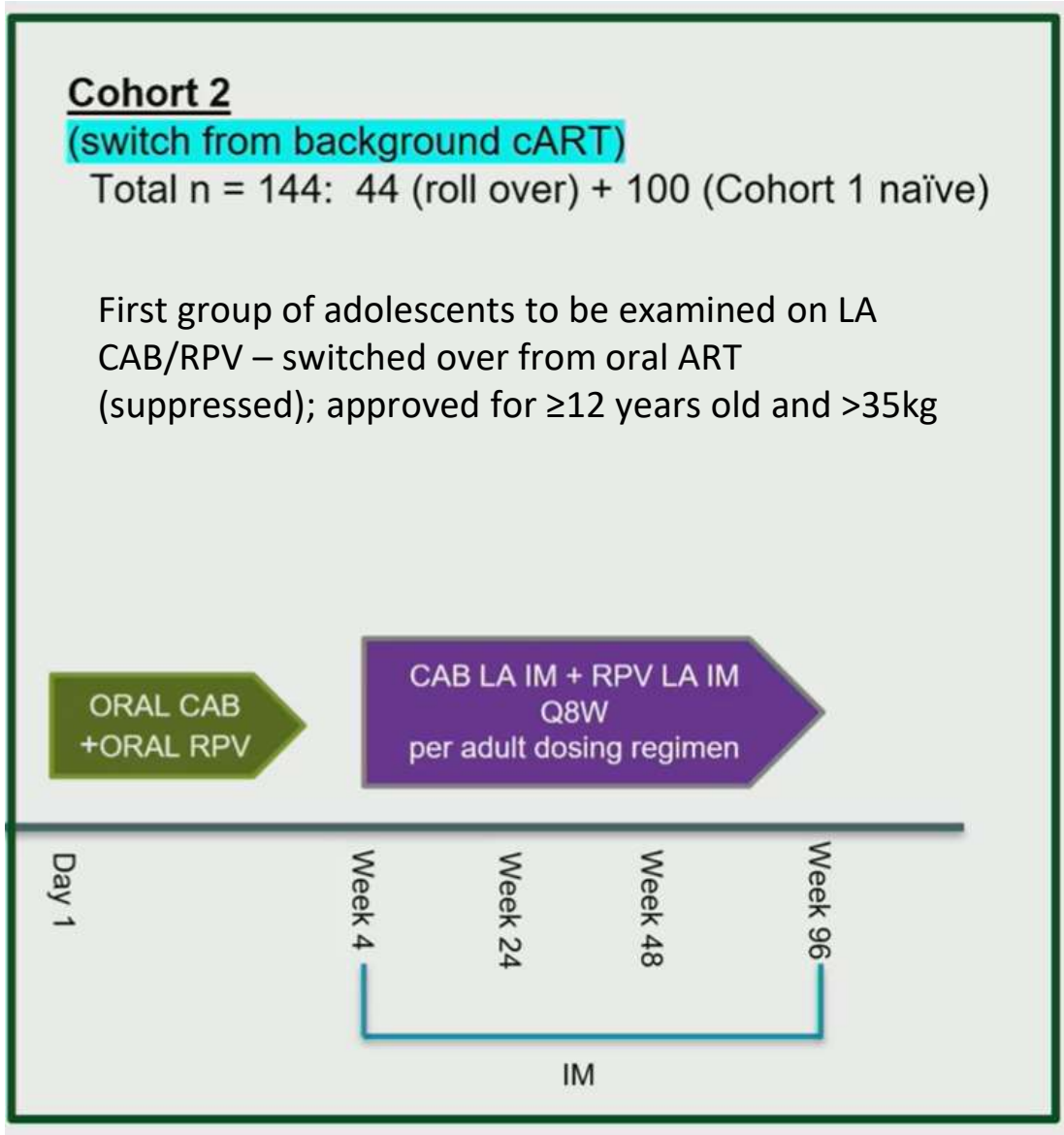
St Jude Children's Research Hospital, Memphis, TN, USA

Disclosure: Dr Gaur reported Institution: Grants/grants (Gilead Sciences, Inc, ViiV Healthcare).

CROI 2024



- IMPAACT study
- 18 sites, 5 countries
- First group of adolescents to be examined on LA CAB/RPV – switched over from oral ART (suppressed); CAB/RPV already approved for ≥12 years old and >35kg
- 144 participants



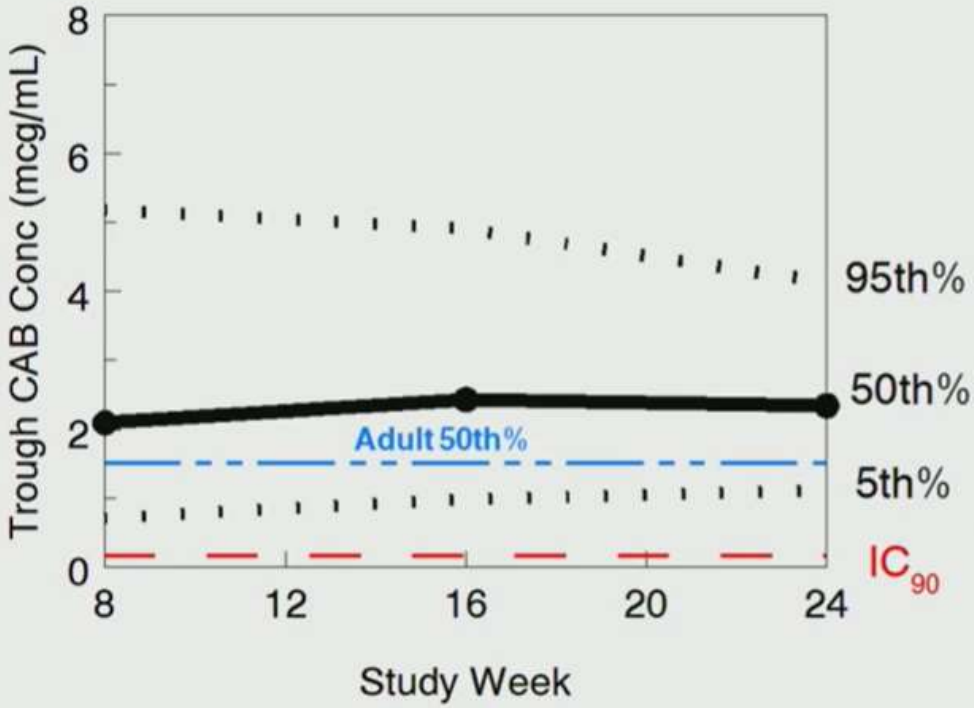
BASELINE (N = 144)

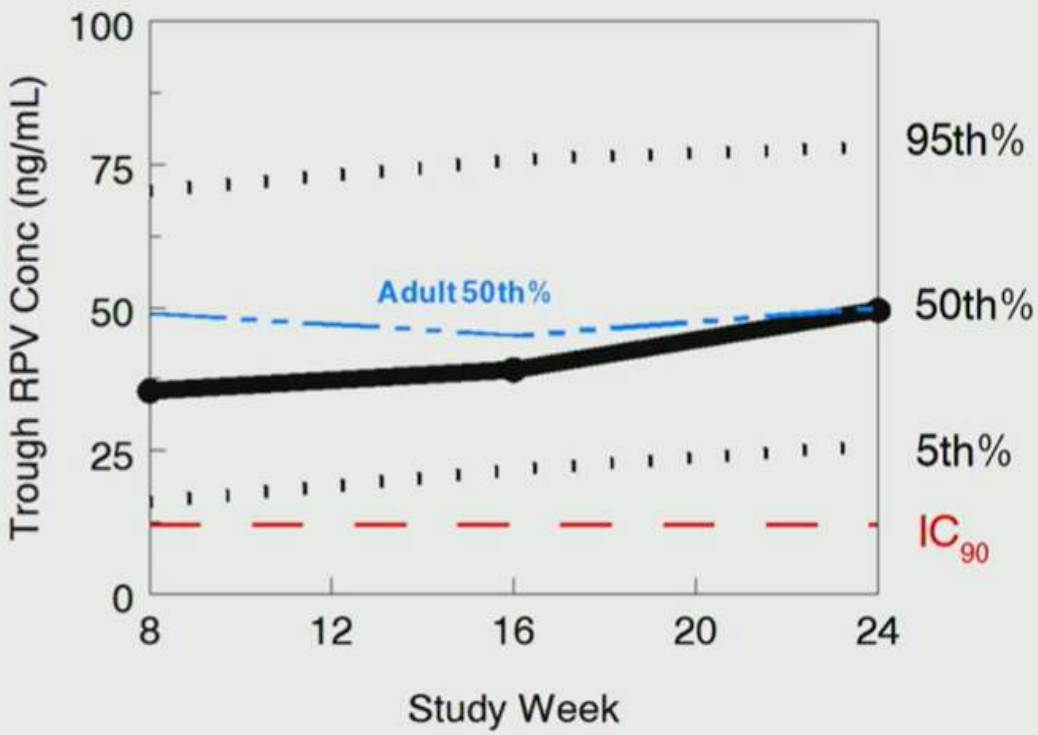
96.5% maintained virologic suppression; no virologic failures (>=200 copies/mL); overwhelming majority preferred IM injections; contributing to regulatory approval

Variable	Value
Age (median [min, max])	15 years (12, 17)
Female	51%
Black or African American	74%
Acquired HIV Vertically	92%
Body Mass Index (median [min, max])	19.5 kg/m^2 (16, 34)
Weight (median [min, max])	48 kgs (35, 101)

IMPAACT

PHARMACOKINETICS





IMPAACT 2017 CAB and RPV troughs (Black lines - medians [solid] with 5th%-95th% [dashed]) compared to adults (Blue lines) from LATTE-2 / ATLAS-2M studies and protein adjusted IC_{90}s (Red lines)

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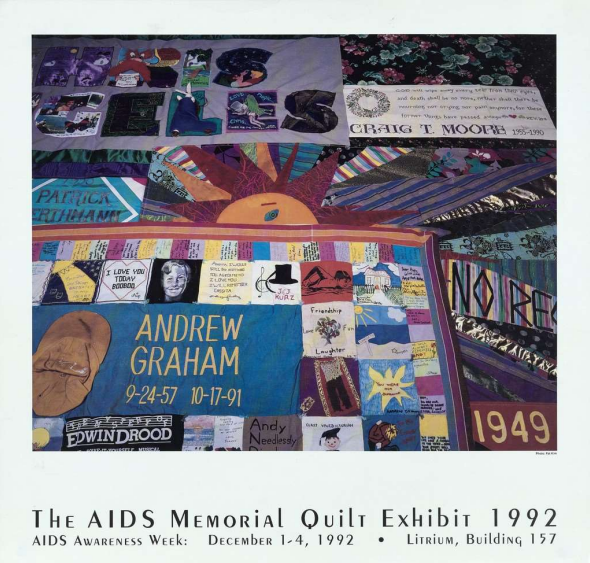

Equity in access to long-acting injectables in the USA

THE LANCET HIV

Cabotegravir, an integrase strand transfer inhibitor, and rilpivirine, a non-nucleoside reverse transcriptase inhibitor, recently received regulatory approval in the Canada, the EU, and the USA as a monthly intramuscular long-acting injectable (LAI) antiretroviral therapy regimen in adults with HIV-1 who are virologically

Published Online February 4, 2022 https://doi.org/10.1016/S2352-3018(22)00031-5

*J Carlo Hojilla, Monica Gandhi, Derek D Satre, Mallory O Johnson, Parya Saberi

Groups have now been trying LA CAB/RPV in viremic patients off ART

- With registrational data, clinicians "flying blind" in how to use LA-ART in nonsuppressed
- Critically important population for Ending the HIV epidemic
- 10% of people living with HIV holding 90% of the virus- concomitant challenges

Long-acting antiretrovirals and HIV treatment adherence

Jean B Nachega*, Kimberly K Scarsi*, Monica Gandhi, Rachel K Scott, Lynne M Mofenson, Moherndran Archary, Sharon Nachman, Eric Decloedt, Elvin H Geng, Lindsay Wilson, Angeli Rawat, John W Mellors

Christopoulos K AIDS 2017

Demonstration project at Ward 86 HIV Clinic

Inclusion criteria of trials:

- Virologically suppressed x at least 16 weeks on oral regimen first
- No history of virologic failure
- Only K103N in NNRTI; no INSTI mutations
- Oral CAB/RPV x 28 days but direct-to-inject approved FDA March ‘22

Inclusion criteria of Ward 86

- Need not be virologically suppressed or take oral ART before injectables
- No RPV or INSTI mutations (strengthened criteria later)
- **Express willingness to come to clinic q4 weeks, contact information, outreach from staff**
- Rigorous protocol, Biweekly review of patients

Descriptive statistics summarized patient characteristics, median/range number of injections received, viral suppression outcomes, stratified by viral load ≥30 copies/mL at LA-ART initiation; Kaplan Meier plot for viremic

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Implementation of program

- Hired pharm tech (Francis!) to help get injectable meds (Janet critical lead)
- Biweekly meetings with Pharm D, pharm tech, clinic leadership, POP-UP program leadership to review each patient on injectables or being considered
- Protocol development with ongoing refinements based on observations in our pilot program
- 261 patients have been started on long-acting ART: rigorous protocol

THE LANCET HIV

CrossMark

Realising long-acting ART as first-line treatment

RESULTS

Table 1: Demographics and clinical characteristics of cohort in Ward 86 LA ART program (n=133)

Characteristic	Distribution, n (%)
Age (median, range)	45 (38-45) years
Gender	
Cis Man	117 (88%)
Cis Woman	11 (8%)
Transgender Woman	5 (4%)
Race/ethnicity	
Black	21 (16%)
Latino/a	50 (38%)
White	43 (32%)
Multiracial	19 (14%)
Housing	
Unstable	77 (58%)
Stable	45 (34%)
Homeless	11 (8%)
Insurance	
Medicare or Medicaid or both	130 (98%)
ADAP	3 (2%)
Current stimulant use	44 (33%)
Major mental illness	51 (38%)
Virologically non-suppressed (>30 copies/ml)	57 (43%) with log10 viral load (mean, STD) 4.21 (1.30)
CD4 count (median with interquartile range)	Virologically suppressed 616 (395–818) Virologically non-suppressed 215 (75–402)

* Note: ADAP is AIDS Drug Assistance Program; Baseline CD4 defined as the CD4 count closest to and including date of first injection. Median time from CD4 count to first injection was 70 (range 0 to 882) days

- Between June 2021-November 2022, 133 PWH started on LA-ART, 76 suppressed on oral ART, 57 (43%) with viremia
- Diverse (68% non-White; 88 (66%) unstably housed; 44 (33%) endorsed substance use)
- Median CD4 count in those with viremia lower than those w/ suppression
- 74% (66-81%) on-time injections
- In those with virologic suppression, 100% (95% CI 94%-100%) remained suppressed (median 26 weeks (2-42) for whole cohort)

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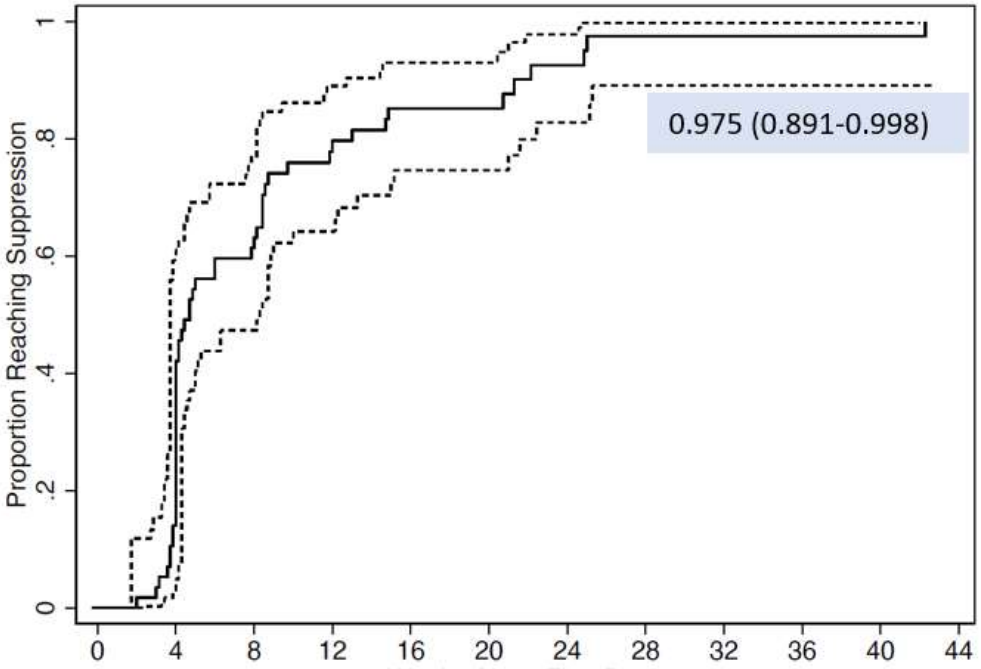
RESULTS (continued)

Figure: KM curve of probability of reaching virologic suppression (VL <30) on LA ART (n=57); dotted lines 95% CI



- Among viremic PWH, at median of 33 days, 55 suppressed, 2 had early virologic failure
- Two failures < 24 weeks, both had minor mutations so protocol tightened; 3rd didn't suppress <100 (182) so added LEN

What is counterfactual? 38% VS rate among those who cannot take oral ART & have incentives, interventions to try to use oral ART

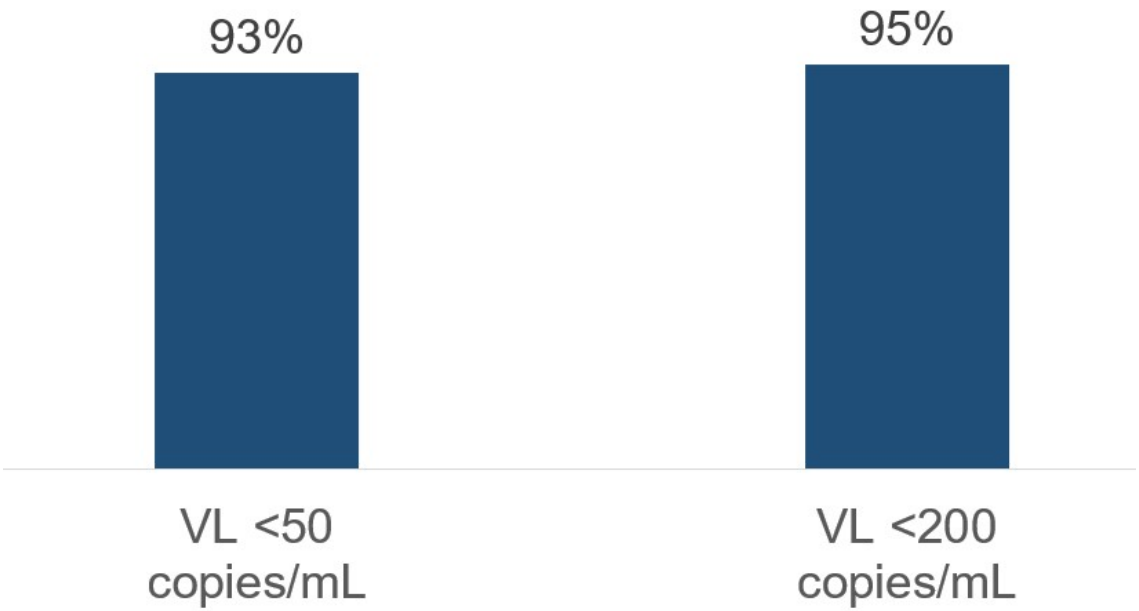
[1]Gandhi Ann Intern Med 2023; [2]Chen W. OFID 2023

48 week follow-up results of our demonstration project

- 286 PWH received ≥1 dose of LA-ART at Ward 86 as of Jan 2024 (101 with baseline VL ≥50 copies/mL)
- **59 started LA-CAB/RPV with VL ≥50 copies/mL by Dec 2022 who had 48 weeks of data**
  - 86% with baseline VL ≥1000; 69% ≥10,000
  - Half with CD4 <200
  - 52% experiencing homelessness/unstable housing
  - 61% using stimulants; 10% using opioids

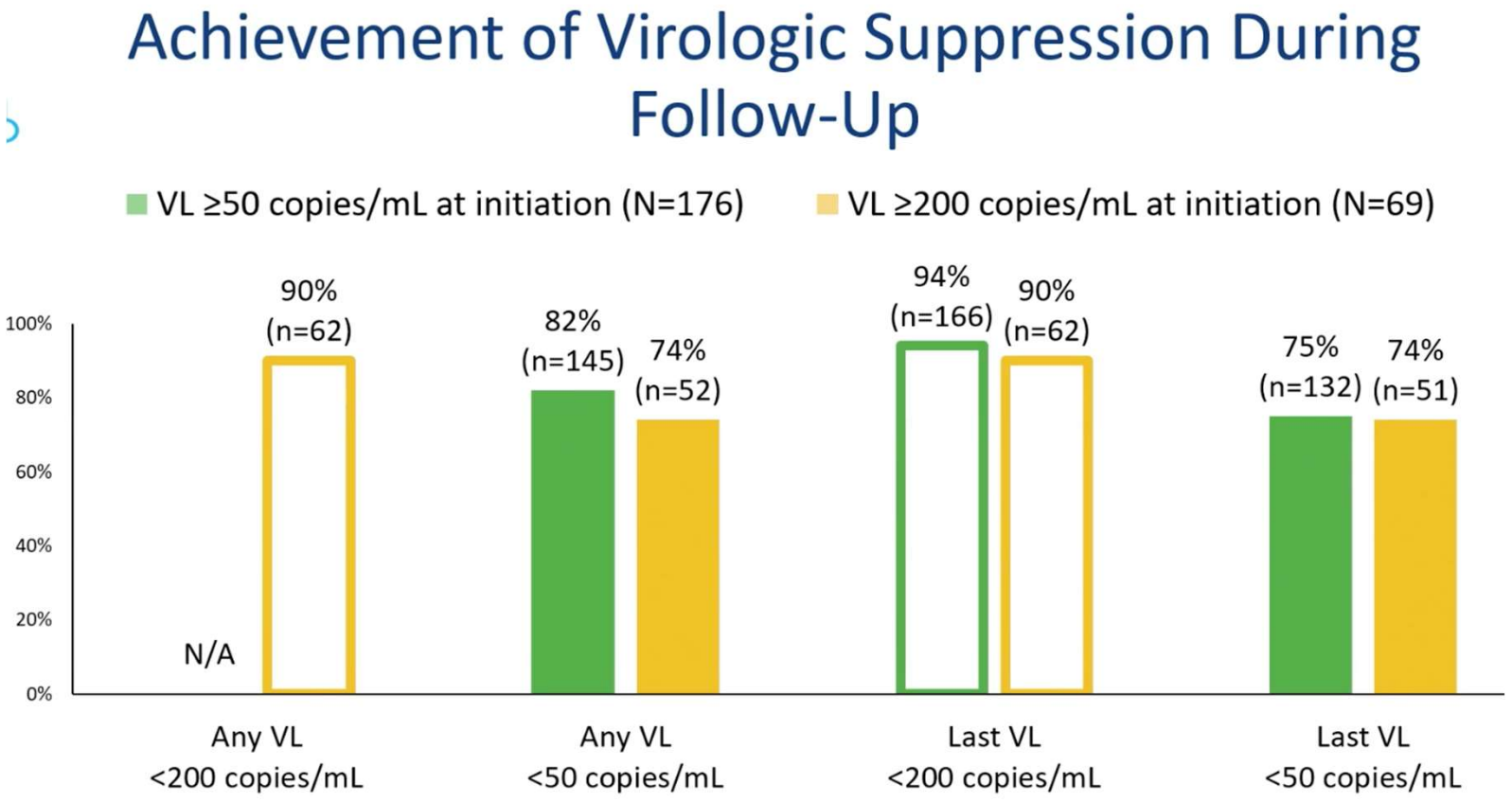
Hickey M et al. CROI 2024

HIV Viral Suppression at 48 weeks following initiation of LA-CAB/RPV with baseline HIV RNA ≥50 copies/mL (n=59)



Hickey M et al. CROI 2024

OPERA COHORT (Represents 14% of PWH in US, EMR) - 176 started LA ART with viremia >50, 82% VS rate <50 (94% <200)



Hsu BK. ID Week 2023 (October 11-15), Boston, MA

LA CAB + RPV in patients with viremia – Small study (n=12)

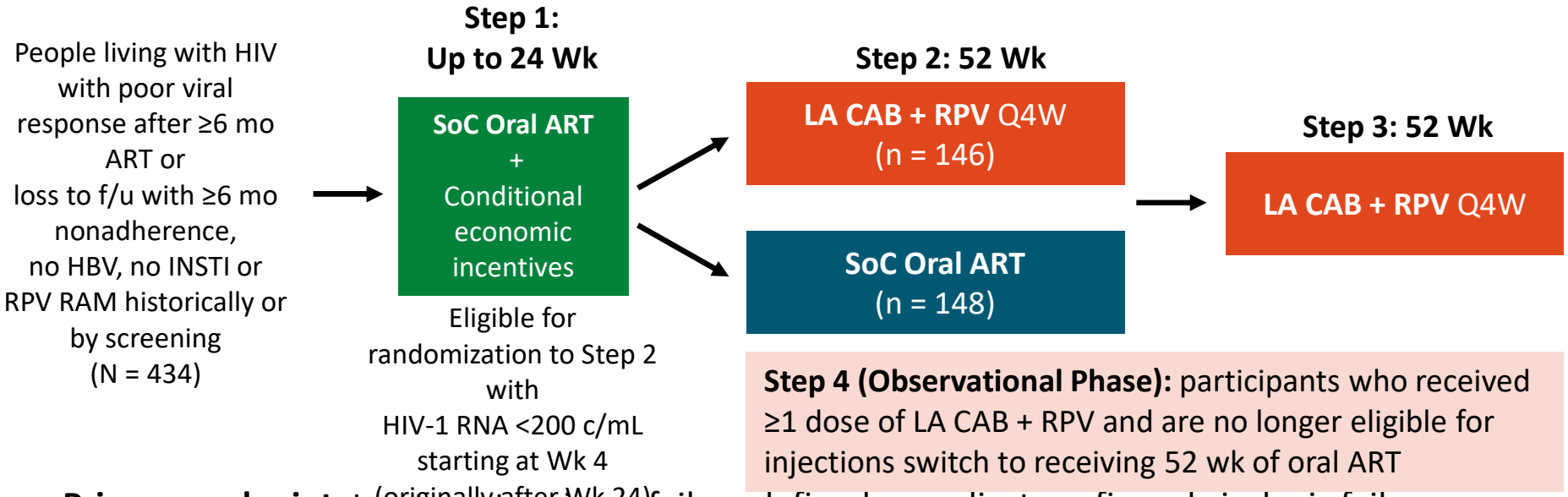
University of Mississippi Network[1]

- Adult Special Care Clinic, a Ryan White–funded HIV clinic at the University of Mississippi
- CAB/RPV LA offered as a salvage option for patients with viremia despite ART optimization and intensive case management strategies
- **12 patients;** Follow-up : 1 to 17 months
- Despite historical poor adherence to oral therapy, adherence to injection visits was very good with 94% on-time injections
- HIV RNA < 50 c/mL : all patients, within 3 months, no discontinuations

[1]Brock JB. Clin Infect Dis 2023

ACTG A5359 LATITUDE: Study Design

- Prospective, randomized, open-label, phase III trial



- **Primary endpoint:** treatment regimen failure defined as earliest confirmed virologic failure or discontinuation during step 2
- **Key secondary endpoints:** virologic failure, treatment-related failure, permanent treatment discontinuation

Rana. CROI 2024. Abstr 212.

Courtesy of CCO

ACTG A5359 LATITUDE: Baseline Characteristic, Safety, and Injection Timing

Characteristic	Step 1 Total (N = 434)
Median age, yr (Q1, Q3) ▪ ≤30, n (%) ▪ 31-50, n (%) ▪ ≥51, n (%)	40 (32, 51) 88 (20) 232 (53) 114 (26)
Female at birth, n (%)	129 (30)
Transgender spectrum, n (%)	21 (5)
Race, n (%) ▪ Black ▪ White ▪ Other/multiple/unknown	 277 (64) 117 (27) 40 (9)
Hispanic or Latino/a, n (%)	75 (17)
Current or previous injection drug use, n (%)	61 (14)
Nonadherence criteria, n (%) ▪ Lost to f/u ▪ Poor response ▪ Both	 87 (20) 283 (65) 64 (15)
Median time since HIV diagnosis, yr (Q1, Q3)	13 (7, 21)

Rana. CROI 2024. Abstr 212.

Step 2

Characteristic	LA CAB + RPV (n = 146)	SoC (n = 148)
BL HIV-1 RNA >200 c/mL, n (%)	24* (17)	10 (7)
Median BL CD4 count, cells/mm^3 (Q1, Q3)	417 (198, 688)	374 (198, 605)

*Includes 8 participants with HIV-1 RNA >10,000 c/mL.

- Safety on LA CAB + RPV
  - ≥ 1 ISR: 77 (57%)
  - Grade 3/4 ISR: 3 (2.2%)
- Timing of LA CAB + RPV Injections
  - On time: 1092 (93%)
  - Missed: 36 (3%)

Courtesy of CCO

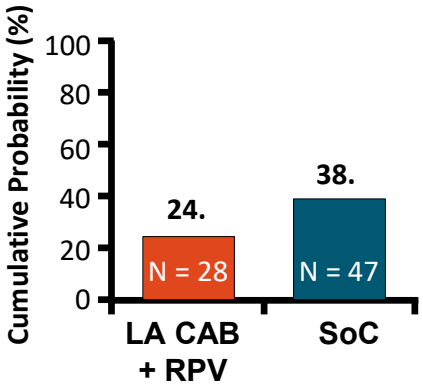
ACTG A5359 LATITUDE: Efficacy Outcomes

Primary Outcome

Regimen Failure

Difference -14.5%

Nominal 98.75% CI (-29.8% to 0.8%)

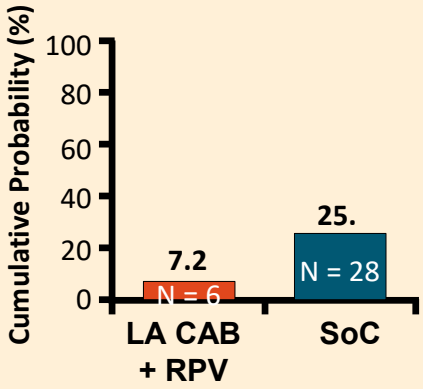


Secondary Outcomes

Virologic Failure

Difference -18.2%

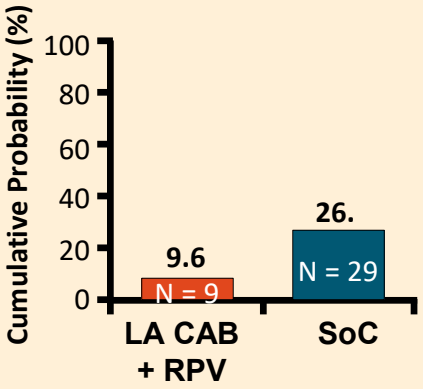
Nominal 98.75% CI (-31.1% to -5.4%)



Treatment-Related Failure

Difference -16.6%

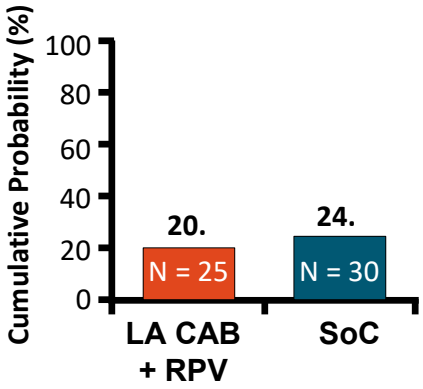
Nominal 98.75% CI (-29.9% to -3.3%)



Permanent Treatment Discontinuation

Difference -4.1%

Nominal 98.75% CI (-18.0% to 9.8%)



1 additional virologic failure after Wk 24 included in secondary endpoints, but not primary

Rana. CROI 2024. Abstr 212.

Courtesy of CCO

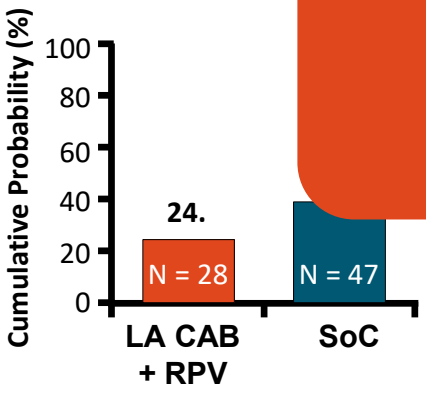
ACTG A5359 LATITUDE: Efficacy Outcomes

Primary Outcome

Regimen Failure

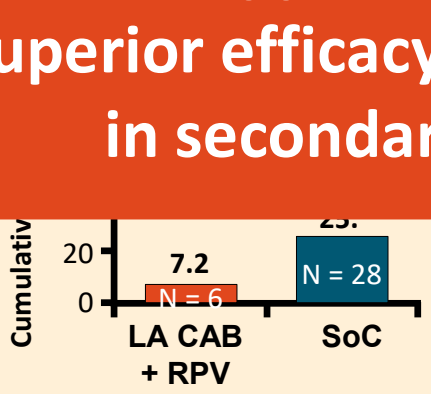
Difference -14.5%

Nominal (-29.8%

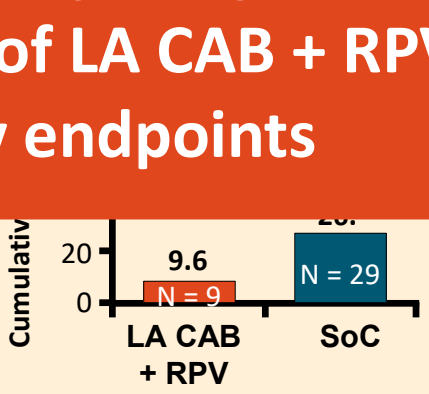


Secondary Outcomes

Virologic Failure

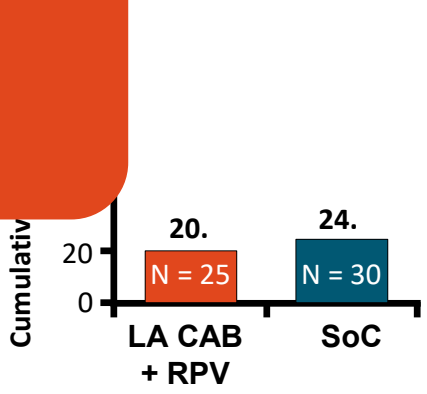


Treatment-Related Failure



Permanent Treatment Discontinuation

Nominal 98.75% CI (-18.0% to 9.8%)



DSMB stopped study early due to superior efficacy of LA CAB + RPV in secondary endpoints

1 additional virologic failure after Wk 24 included in secondary endpoints, but not primary

Rana. CROI 2024. Abstr 212.

Courtesy of CCO

Updated IAS-USA Recommendations for LA CAB + RPV March 1, 2024

- *When supported by **intensive follow-up** and **case management services**, injectable LA CAB + RPV may be **considered for people with viremia** who meet the criteria below when **no other treatment options are effective** due to a patient's persistent inability to take oral ART:*
  - ***Unable to take oral ART** consistently despite extensive efforts and clinical support*
  - ***High risk of HIV disease progression** (CD4 cell count <200/µL or history of AIDS-defining complications)*
  - ***Virus susceptible to both CAB and RPV***
- *If applicable, patients should also be referred for treatment of substance use disorder and/or mental illness.*

2024

Sax. JAMA. 2024;[Epub].

Courtesy of CCO

Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis

AIDS: July 15, 2021 - Volume 35 - Issue 9 - p 1333-1342

Conclusion: CVF is an infrequent multifactorial event, with a rate of approximately 1% in the long-acting CAB+RPV arms across Phase 3 studies (FLAIR, ATLAS and ATLAS-2M) through Week 48. Presence of at least two of proviral RPV RAMs, HIV-1 subtype A6/A1 and/or BMI at least 30 kg/m^2 was associated with increased CVF risk. These findings support the use of long-acting CAB+RPV in routine clinical practice.

BMI, low rilpivirine troughs, **presence of two proviral RPV RAMS**, HIV-1 subtype A6/A1 associated with increased risk of failure (updated CID 2023)

Clinical Infectious Diseases

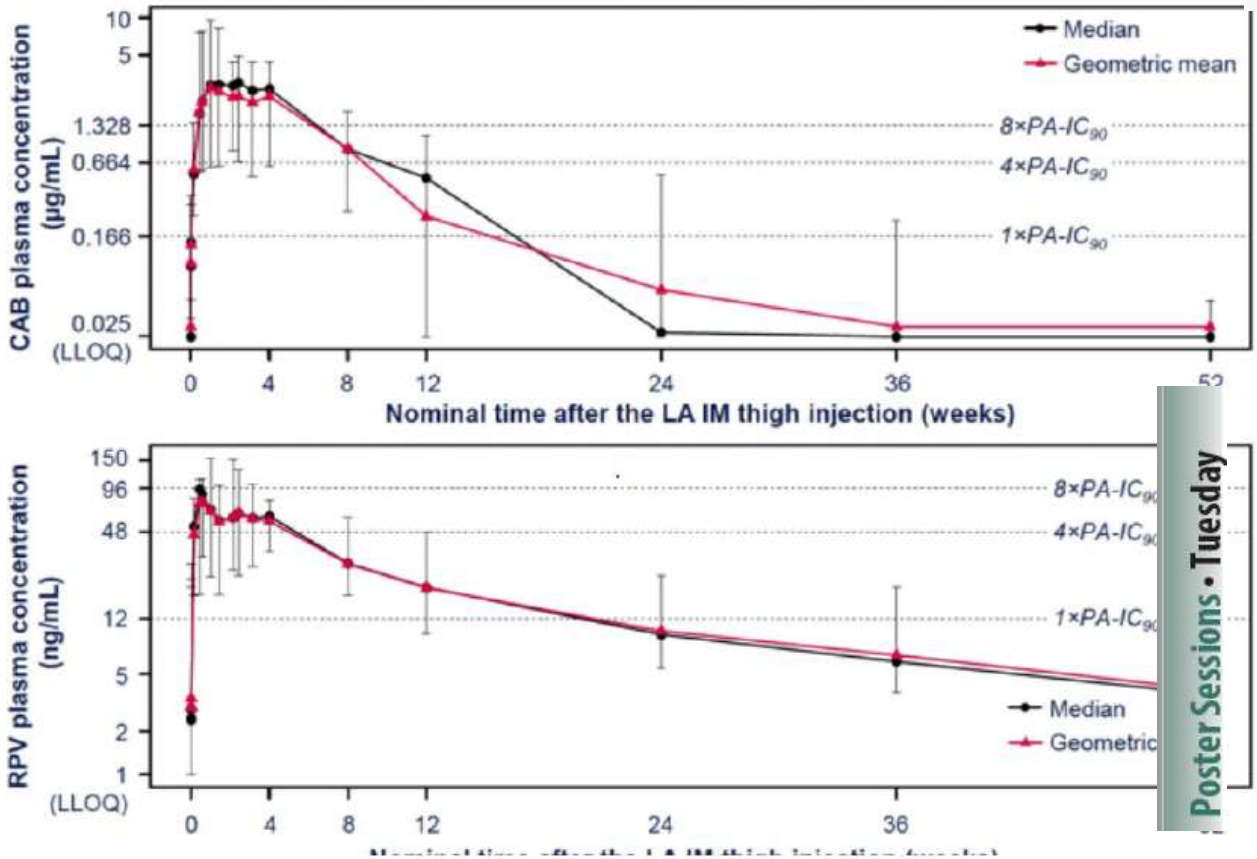
MAJOR ARTICLE

Expanded Multivariable Models to Assist Patient Selection for Long-Acting Cabotegravir + Rilpivirine Treatment: Clinical Utility of a Combination of Patient, Drug Concentration, and Viral Factors Associated With Virologic Failure

Chloe Orkin,[1,*] Jonathan M. Schapiro,[2] Carlo F. Perno,[3] Daniel R. Kuritzkes,[4] Parul Patel,[5] Rebecca DeMoor,[6] David Dorey,[7] Yongwei Wang,[5] Kelong Han,[6]

Pharmacokinetics (PK) and tolerability of cabotegravir (CAB) and rilpivirine (RPV) long-acting (LA) intramuscular (IM) injections to the vastus lateralis (lateral thigh) muscles of healthy adult participants

Figure 2. Plasma Concentration–Time Profiles of CAB and RPV



AIDS 2022
29 July – 2 August

Poster Session-H1 LAI CAB/RPV: WHERE ARE WE NOW AND WHERE ARE WE GOING?

2:30 PM - 4:00 PM

519 LB

THIGH INJECTIONS OF CABOTEGRAVIR+RILPIVIRINE IN VIRALL SUPPRESSED ADULTS WITH HIV-1

Franco Felizarta, Ronald D'Amico, Kehui Wang, Herta Crauwels, Mar Masiá, Miguel Garcia Deltoro, Olaf Degen, Jonathan Angel, Chiu-Bin Hsiao, Vasiliki Chounta, Kelong Han, Conn Harrington, Kelly Rimler, William R. Spreen, Susan Ford

- **Bottom line**: Can use thigh injections for cabotegravir and rilpivirine (same PK) but hurt more; ID week 2023 abstract 33 patients given option of home injection (by home health nurse, Meissner ID week 2023)

We don't RPV in anyone who has these mutations on historical genotypes (signature mutations in Echo/Thrive)

Antiviral Therapy 2013; 18:967–977 (doi: 10.3851/IMP2636)

Original article

96-Week resistance analyses of rilpivirine in treatment-naive, HIV-1-infected adults from the ECHO and THRIVE Phase III trials

Laurence Rimsky[1], Veerle Van Eygen[1], Annemie Hoogstoel[1], Marita Stevens[1], Katia Boven[2], Gaston Picchio[2], Johan Vingerhoets[1]*

[1]Janssen Infectious Diseases BVBA, Beerse, Belgium

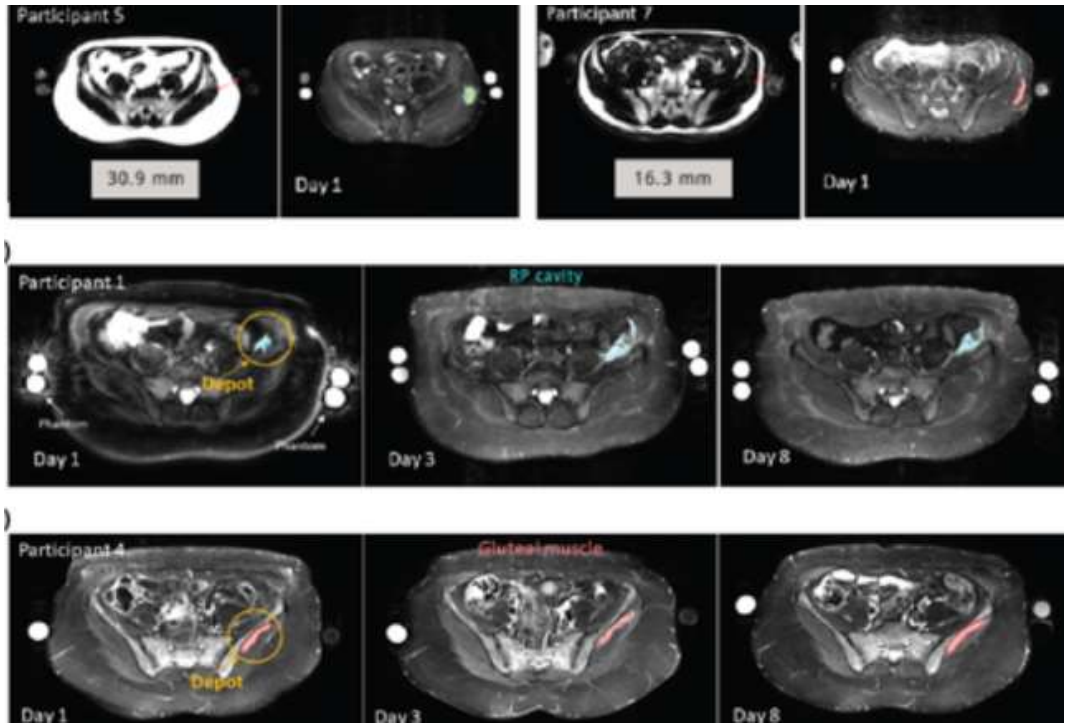
- V90I
- L100I
- K101E
- E138K/Q
- V179I
- Y181C
- V189I
- H221Y
- F227C

We use longer needles in those with high BMI

Combined Analysis of ATLAS, FLAIR, ATLAS-2M: Efficacy and Safety of Switch to LA CAB + RPV by BMI Class

Elliot. EACS 2021. Abstr BPD1/8.

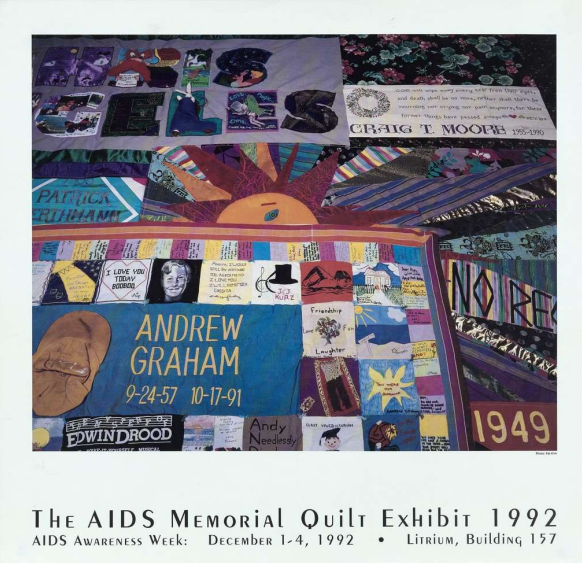
- In this EACS study, use of longer 2-inch needles resulted in higher median CAB trough concentrations in all BMI
- Pharmacology study showed deeper injections with more adipose tissue lead to more spread
- Longer 2-inch needles recommended in participants with BMI ≥30 kg/m^2



Jucker B. Br J of Pharm 2021

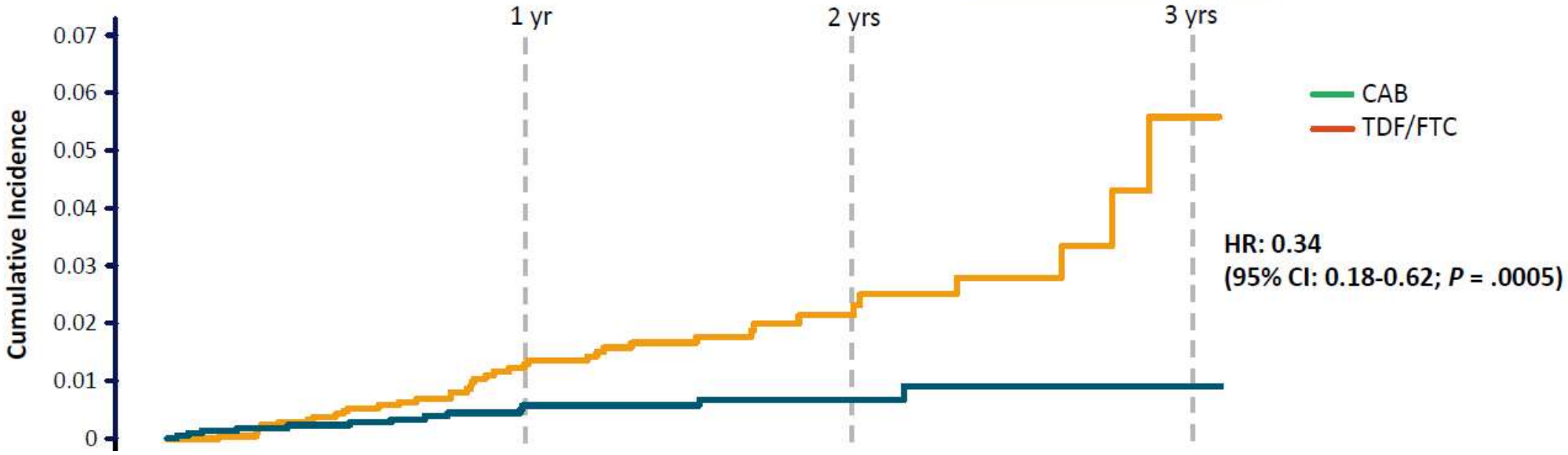
Objectives of talk

- Why long-acting?
- Data on long-acting CAB/RPV for treatment in those starting with virologic suppression (VS), including in LMICs
- Data on LA CAB/RPV in those with adherence challenges
- Data on long-acting CAB for prevention
- Lenacapavir for MDR-HIV (naïve, prevention)
- Pitfalls of LA medications
- New long-acting formulations coming



HPTN 083: HIV Incidence (ITT) With LA Injectable CAB vs Daily Oral TDF/FTC PrEP

66% reduction over daily TDF/FTC



66% superiority maintained into the year of unblinding

Landovitz. NEJM 2021; Landovitz Lancet HIV 2023

Summary of resistance mutations across HPTN083 (Phase 3 plus 1-year open label extension phase)

The table shows all INSTI resistance associated mutations (RAMs) detected in cases in the cabotegravir arm of HPTN 083. The mutations shown were detected at one or more study visits. Major INSTI RAMs are bolded.

ID Code	HIV Subtype	INSTI RAMs detected
A2	C	M50I, **E138K, Q148K**
A3	B	T97A
B3	AE	V151I
B6	B	M50I
B8	B	L74I
B9	B	L74I
B11	B	L74I
B15	B	M50M/I
C1	B	L74I, Q146Q/R, **E138E/K**, **G140G/S**, **Q148R**, E157Q
C3	B	**E138A**, **Q148R**
D1	Likely B	Q146L, **Q148R**, **N155H, R263K**
D2	Likely B	**N155H**, S230R
D3	BF	**R263K**
D4	C	M50I, **E138K**, **G140A**, **Q148R**
D5	F	M50I, **R263K**
D6	AE	L74I, **Q148R**
DX2	BF	V151I
BR1	BC	**Q148R**

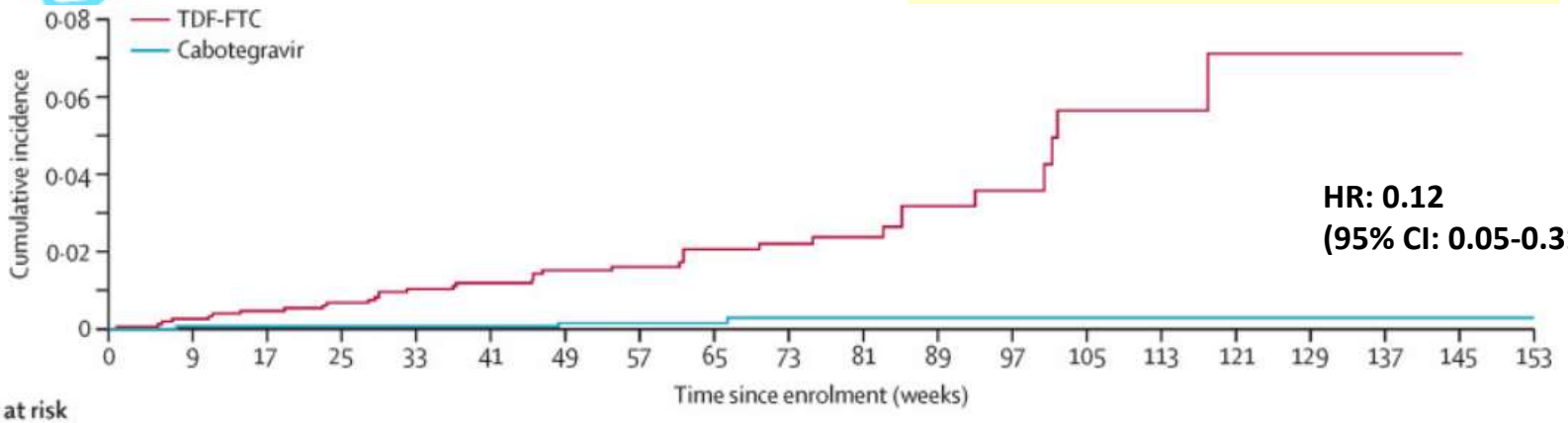
18 out of 34 CAB failures developed 1 or more INSTI mutations (n=2244 in combined study)

Markzinke M et al: HPTN 083. AAC April 2023

HPTN 084

Long-acting Injectable For the Epidemic

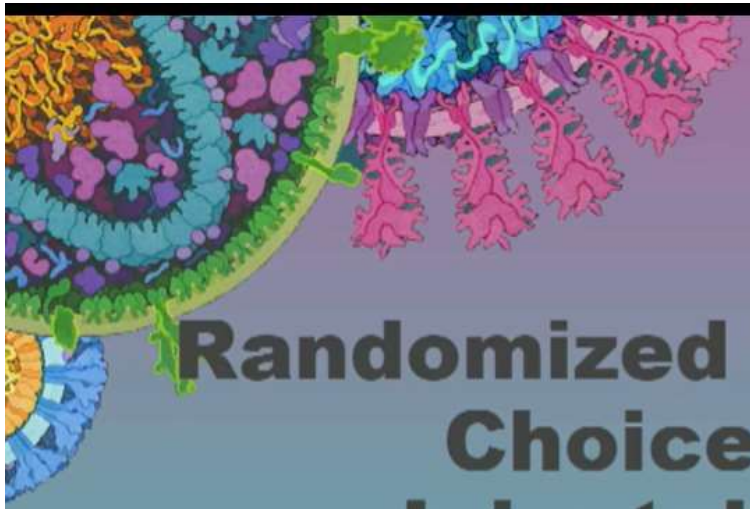
88% reduction over daily TDF/FTC- few failures and none with INSTI resistance



HR: 0.12
(95% CI: 0.05-0.31; *P* = .0001

Number at risk																				
TDF-FTC	1610	1490	1429	1410	1353	1260	1160	984	800	656	485	306	201	115	70	63	52	22	3	0
Cabotegravir	1614	1488	1441	1429	1371	1279	1181	988	801	647	482	304	204	116	67	58	50	23	3	2
Cumulative number of events																				
TDF-FTC	0	4	7	10	15	17	21	22	26	27	28	31	32	35	35	36	36	36	36	36
Cabotegravir	0	1	1	1	2	2	3	3	3	4	4	4	4	4	4	4	4	4	4	4

S Delany-Moretlwe. Lancet 2022



Oral Abstract Session-09

Tuesday, March 5, 2024

Randomized Trial of SEARCH Dynamic Choice HIV Prevention Including Injectable Cabotegravir (CAB-LA)

Moses R. Kamya
Makerere University, Kampala, Uganda

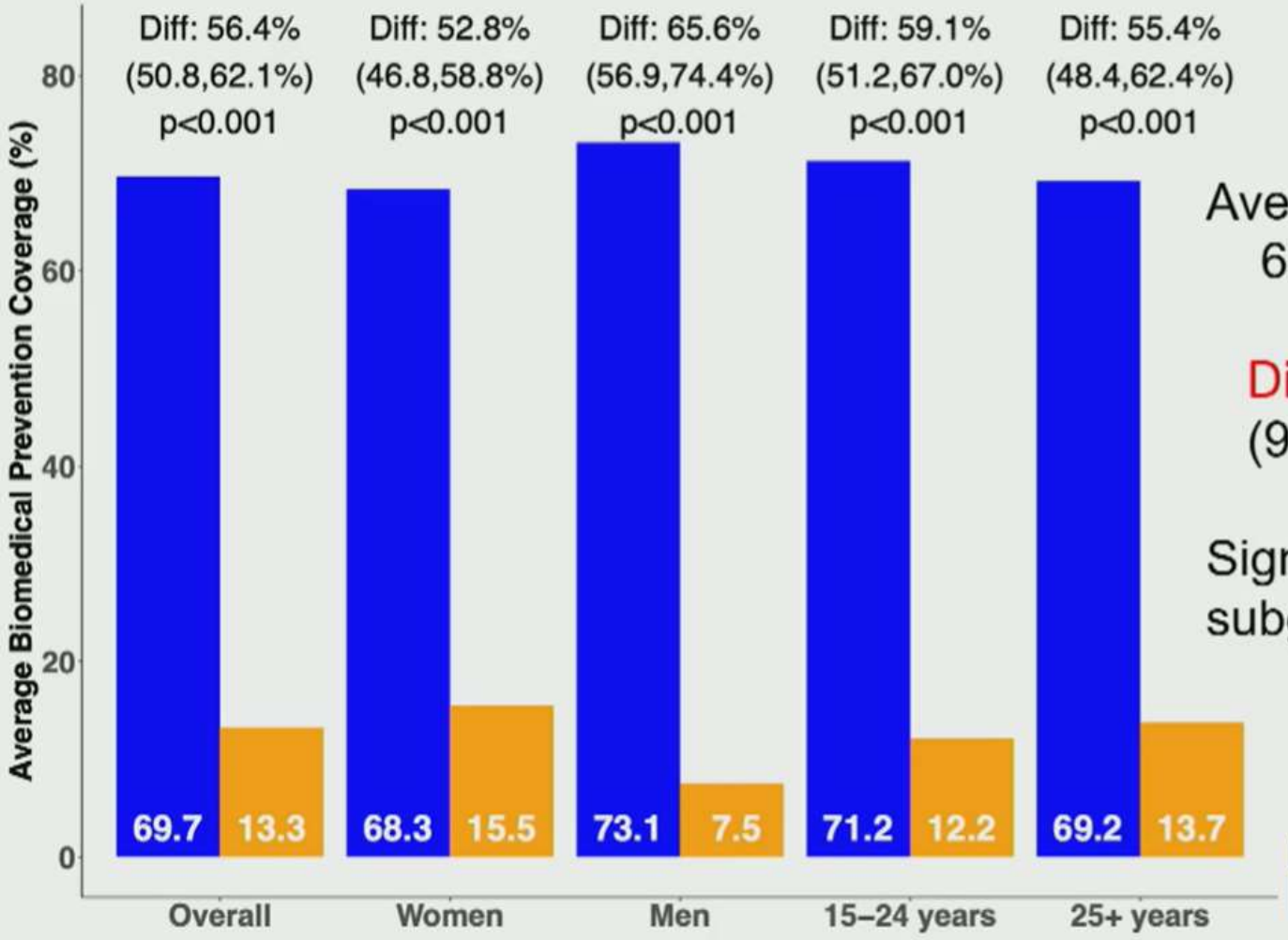
Disclosure: Dr Kamya reported no relevant financial relationships with ineligible companies.

CROI 2024

Primary outcome results: Prevention coverage

SEARCH
SUSTAINABLE EAST AFRICA RESEARCH IN COMMUNITY HEALTH

Intervention group – SEARCH trial-communities in Kenya/Uganda- given LA CAB choice



Average coverage was
69.7% in the intervention
vs. 13.3% in the SoC;
Difference of 56.4%
(95%CI: 50.8-62.1%); p<0.001

Significant increases across all subgroups (p<0.001)

Dynamic Choice HIV Prevention
Standard-of-Care

Secondary outcome: HIV incident infection

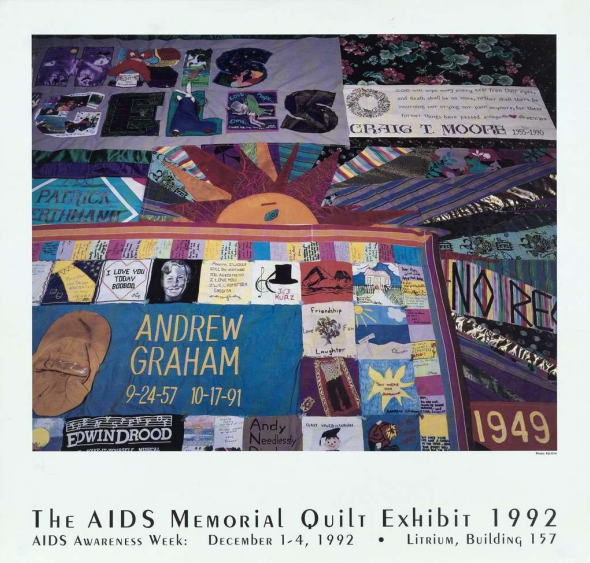
	Dynamic Choice HIV Prevention intervention	Standard of Care
Overall	0/400 PY	7/390 PY
Women	0/293 PY	5/283 PY
Men	0/107 PY	2/106 PY
15-24 years	0/113 PY	1/122 PY
25+ years	0/287 PY	6/268 PY

- 7 participants in the SoC and 0 in intervention had incident HIV infection
- Incidence rate was
  0% in the intervention vs.
  1.8% in the SoC
- Difference of -1.8% (p=0.01)

- In addition, 1 infant born to participant in SoC was infected
  - Not included in incidence

Objectives of talk

- Why long-acting?
- Data on long-acting CAB/RPV for treatment in those starting with virologic suppression (VS)
- Data on LA CAB/RPV in those with viremia
- Data on long-acting CAB for prevention
- Lenacapavir for MDR-HIV (prevention)
- Pitfalls of LA medications



LEN Targets Multiple Stages of HIV Replication Cycle

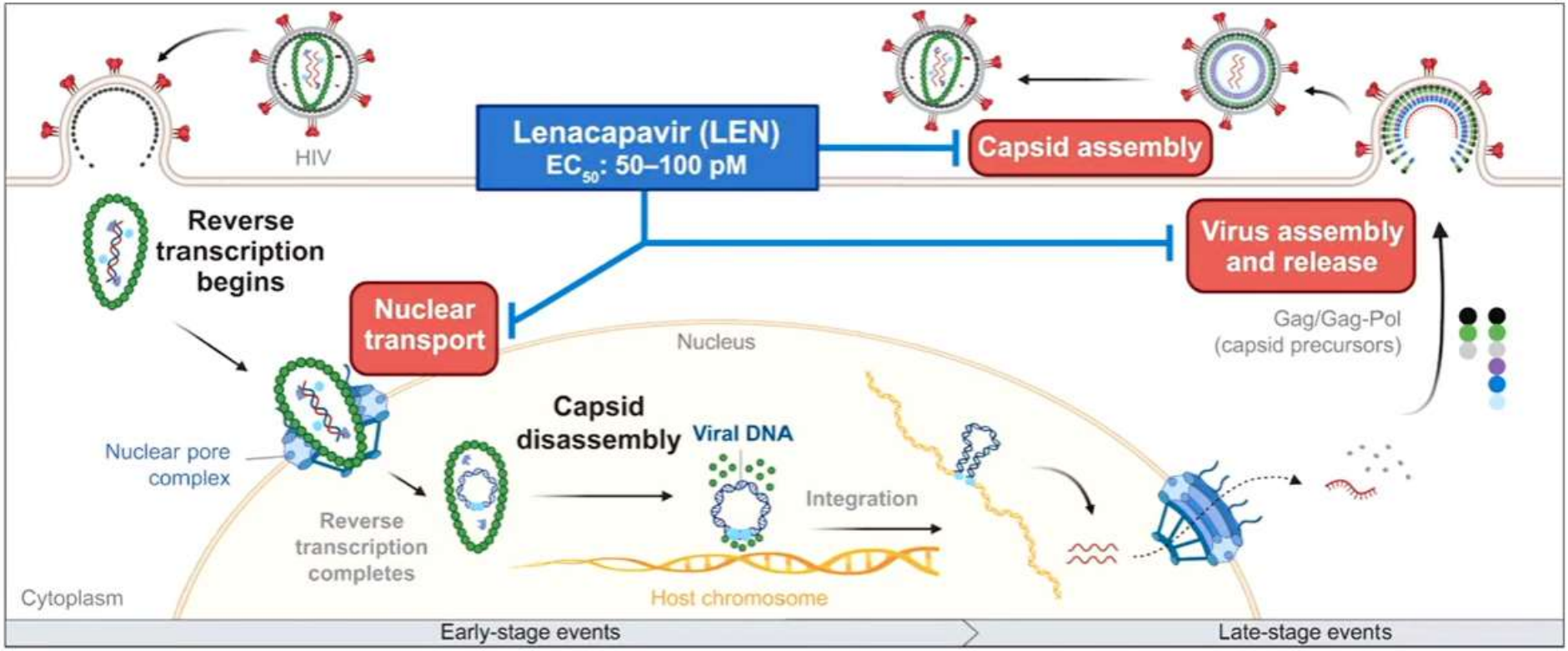
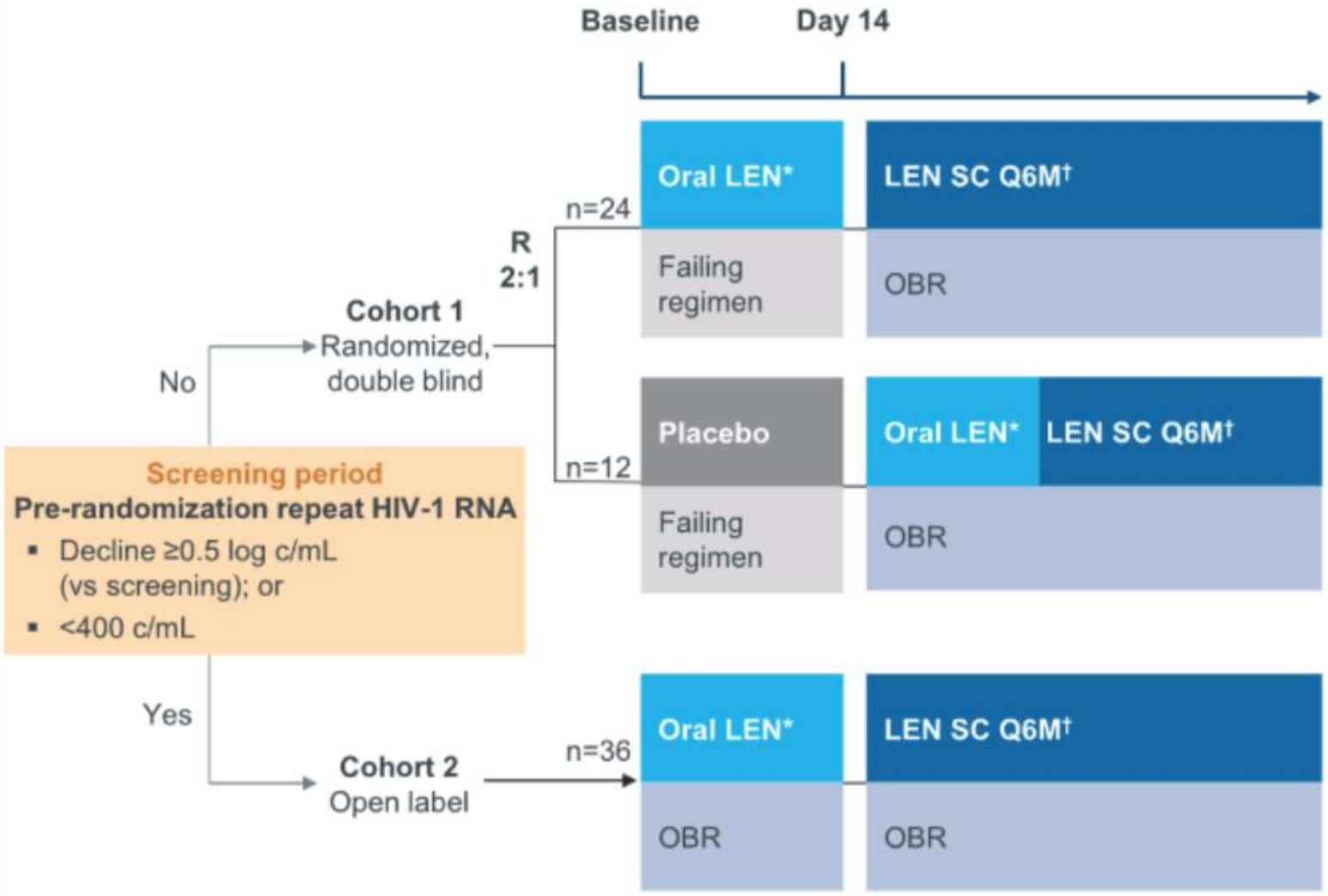
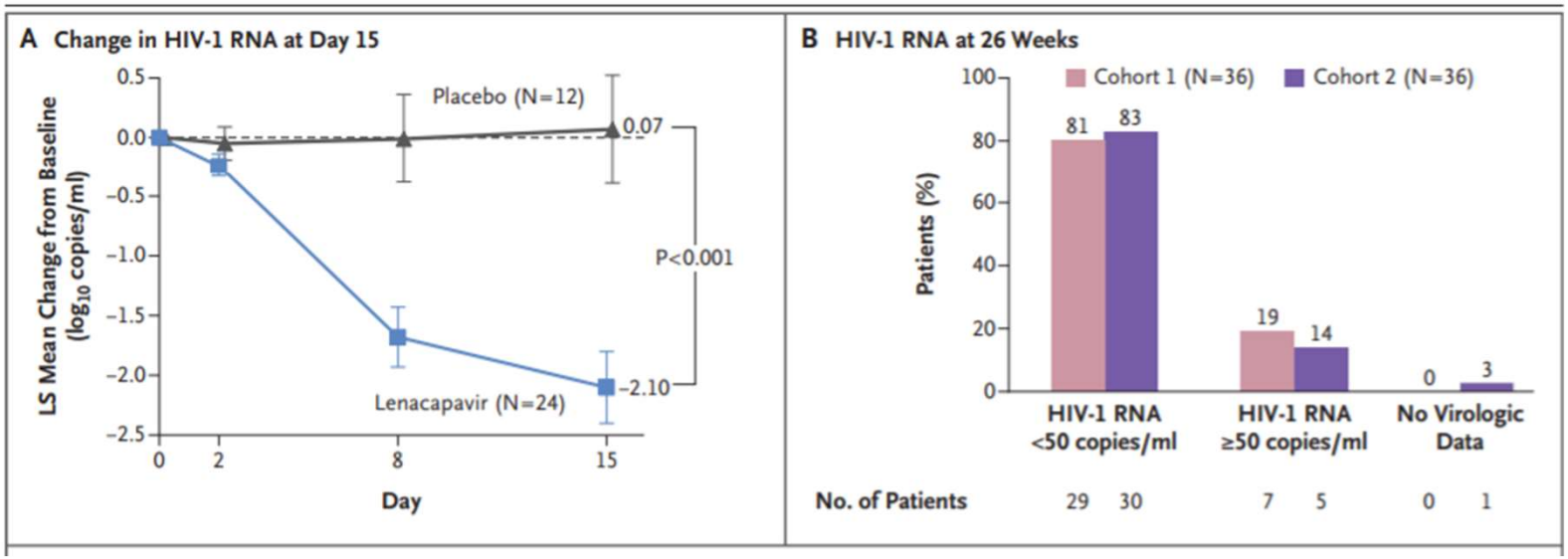


Figure 1: CAPELLA study design



Patients with multidrug resistance to NRTIs, NNRTIs, Pis, INSTIs

CAPELLA Secondary Endpoints: Wk 26 Efficacy in Randomized Cohort



- **Mean change in CD4+ cell count: +81 cells/mm^3**
- Proportion of participants with very low CD4+ cell count (< 50 cells/mm^3) **decreased from 22% (8 of 36) at baseline** to **0% (0 of 34) at Wk 26**

Segal-Maurer NEJM 2022

Now have data on CAPELLA out to 104 weeks

Conclusions

- In heavily treatment-experienced (HTE) people with HIV-1 (PWH) with multidrug resistance, lenacapavir (LEN) combined with an optimized background regimen (OBR) led to sustained virologic suppression through Week 104 for most participants with no fully active antiretrovirals (ARVs) in their OBR
- A clinically meaningful increase in mean CD4 cell count was observed through Week 104
- Three participants had emergent LEN resistance, two of whom had virologic suppression at Week 104. No participants experienced treatment-emergent resistance to OBR through Week 104
  - A previous analysis demonstrated that emergence of LEN resistance is associated with inadequate OBR adherence, as well as OBRs lacking fully active agents[5,6]
- These data further support the role of LEN as an important treatment option for HTE PWH with limited treatment options due to multidrug resistance

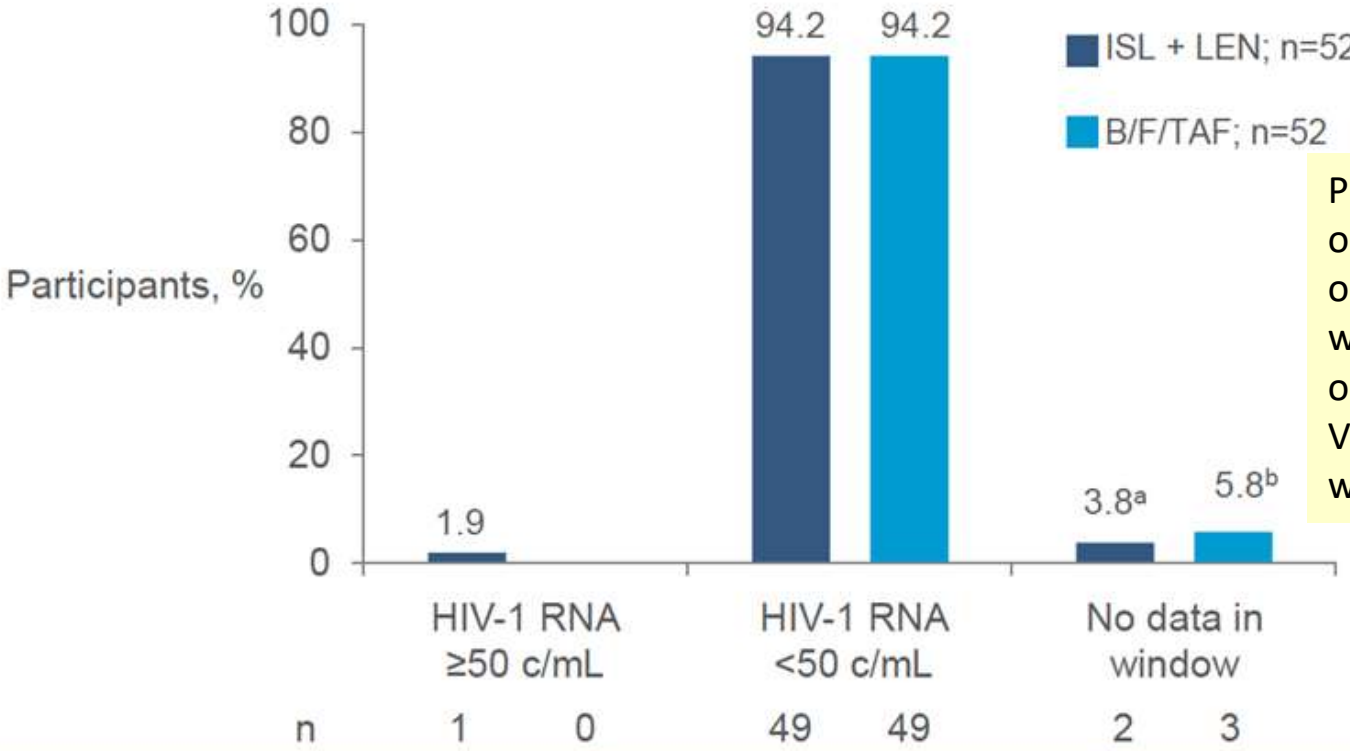
CROI 2024

104 week data CROI 2024 – 14/72 failures at ID week but all on "functional" monotherapy – not having support of OBR (all but 2 participants suppressed)

Ogbuagu et al. CROI 2024

Efficacy at Week 24 Islatravir + Lenacapavir once weekly

Colson A CROI 2024



Phase II study of LEN 300mg orally + Islatravir 2mg orally once a week in participants with virologic suppression on oral ART – 94.2% maintained VS – no significant toxicities- will move forward in phase 3

Participants in both treatment groups maintained high rates of virologic suppression

Segal-Maurer NEJM 2022

Summary of LA agents for treatment

IM q4 or q8 weeks; ULA formulation in development (q4 months)

CAB/RPV

Cold chain only with RPV

Trials in naïve or suppressed (switch)	Trials in those with adherence challenges
FLAIR ATLAS ATLAS 2M SOLAR CARES IMPAACT 2017 (MOCHA) - adolescents	A5359 (17% viremic) (Demonstration projects- U Mississippi; OPERA cohort- real world; Ward 86)

LEN

Likely has higher genetic barrier than RPV

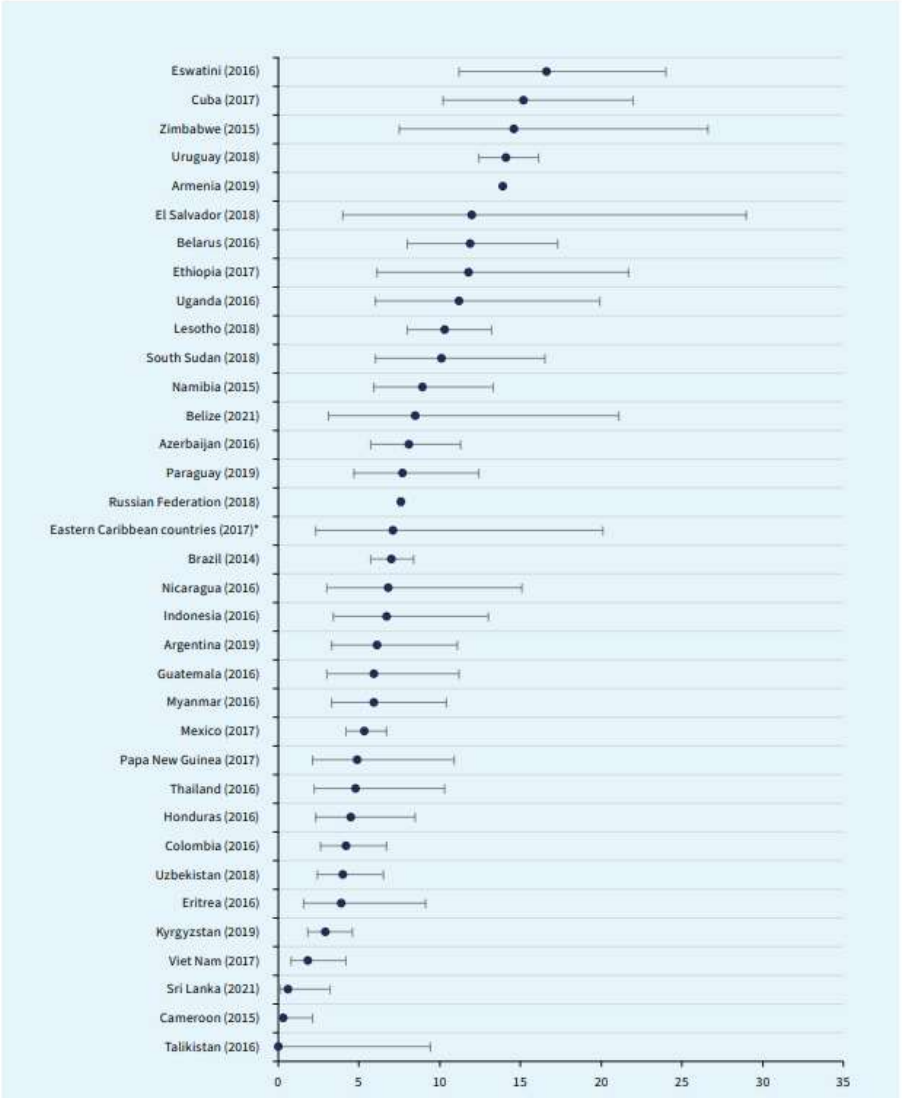
Capsid inhibitor – first in class; 927mg sq q26 weeks or 300mg po qwk

Trial in those with MDR HIV	Naïve or suppressed trials
CAPELLLA study – Only 72 participants but 104 week data from CROI 2024 (Ogbuagu et al) shows all but 2 suppressed even with no oral agents	CALIBRATE (had LEN/BIC arm) and ARTISTRY (Phase II study, LEN/BIC oral daily) – good VS

World Health Organization

- From March 5 report, rilpivirine resistance ranges from 0% to 16.6% across countries (should fade but not yet)- can't use CAB/RPV ff present
- **Lenacapavir (capsid inhibitor) + cabotegravir (INSTI)** needs trial for those with NNRTI resistance (and can't take oral ART)

Fig. A4. Prevalence of pretreatment HIV drug resistance to RPV among adults initiating ART without previous exposure to ARV drugs, 2014–2021



CROI 2024

Case Series Examining the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

Monica Gandhi;[1] Lucas Hill;[2] Janet Grochowski;[1] Alexander Nelson;[3] Katerina Christopoulos;[1] Diane Havlir;[1] Catherine A. Koss;[1] Francis Mayorga-Munoz;[1] Jon Oskarsson;[1] John Szumowski;[1] Ann Avery;[3] Laura Bamford;[2] Jillian Baron;[4] William R. Short;[4] Corrilynn O. Hileman[3]

[1]University of California, San Francisco (UCSF), SF, CA; [2]University of California, San Diego (UCSD), San Diego, CA; [3]Metrohealth Medical Center and Case Western University, Cleveland, OH; [4]University of Pennsylvania (UPenn), Philadelphia, PA

629

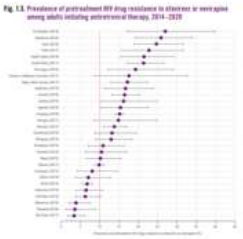
Background

- Injectable cabotegravir (CAB)/rilpivirine (RPV) is the only combination long-acting (LA) antiretroviral treatment (ART) regimen approved for HIV
- RPV is not effective among individuals with nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance (when the mutations are RPV resistance associated mutations, RAMs), which has >10% prevalence in many countries (Figure)
- Lenacapavir (LEN) is a LA capsid inhibitor given every six months but has not been studied in combination with other LA agents

Methods

- Four clinics where providers are using either LA CAB/RPV or LA CAB paired with LA LEN for selected patients with adherence challenges off-label were identified (UCSF Ward 86, UCSD Owen Clinic, MetroHealth's HIV Clinic, UPenn Clinic) and a case series assembled
- All patients in this series experienced challenges to taking oral ART which is why LA ART was prescribed
- Variables, including sex; gender; age; race; ethnicity; current housing status; substance use; viral load (VL) prior to starting LEN/CAB; duration between CAB doses (every 4 or 8 weeks); whether injectable RPV was also given; viral mutations in the NNRTI or INSTI class; BMI; time on the regimen; and LEN injection site reaction garnered from medical record
- IRB approval in clinics to present data if no patient identifiers

Figure: Rates of NNRTI resistance across countries as of WHO report 2021 (RPV 2.7-18.7%)



HIV DRUG RESISTANCE REPORT 2021

World Health Organization

In this case series of 34 patients on LEN/CAB from four U.S. academic medical centers, high rates of virologic suppression (94%) were seen (up from 47% at baseline). Clinicians used LEN/CAB for adherence challenges and NNRTI resistance. These data support a clinical trial of LEN/CAB as CAB/RPV cannot be used in LMICs with high rates of NNRTI resistance

Table: Details of patients (n=34) of LEN/CAB in this case series

Reason for LEN	Patient number	Age/Sex/ Gender/ Race-ethnicity/ substance use and/or housing insecurity/BMI (kg/m²)/ viral subtype	VL prior to LEN/CAB, copies/mL	NNRTI or minor INSTI mutations for patients 28-32	Regimen prior to LEN/CAB	Weeks between CAB doses/ RPV included/ ISR*	VS <75 after LEN/CAB start/ time to VS
NNRTI mutations-virologically suppressed when started LEN	1	55/M/M/Latino/yes/29.1	UD	A98G, K103N, V179E, G190A	DRV/c/FTC/TAF	4 weeks/ no/ no	Yes/ NA
	2	32/M/M/Latino/no/33.8	UD	K103N, G190A	DRV/c/FTC/TAF + DTG	8 weeks/ yes/ no	Yes/ NA
	3	28/M/M/Latino/no	UD	K103R, V179D	DRV/c + DTG	4 weeks/ yes/ grade 1	Yes/ NA
	4	47/F/F/Latina/no/28.1	UD	L100I, K103N	DRV/c + DTG	8 weeks/ no/ no	Yes/ NA
	5	75/F/F/Black/no/23.1/B	UD	L100I, K103N, V179I, Y181C	DTG + 3TC + DRV/r	8 weeks/ no/ no	Yes/ NA
	6	41/M/M/Black/yes/23.57/B	UD	V108I, V179D	EVG/c/FTC/TAF + DRV	8 weeks/ no/ grade 1	Yes/ NA
	7	55/M/M/White/no/21.7/B	UD	V90I, E138G	BIC/TAF/FTC	8 weeks/ yes/ no	Yes/ NA
	8	29/F/F/Black/no/30.9/AG	UD	Y181C	DTG/ABC/3TC	8 weeks/ yes/ grade 1	Yes/ NA
NNRTI mutations - viremic when started LEN	9	58/F/F/Latina/yes/29.2/B	329	K101K/Q, K103R, V179I	BIC/TAF/FTC+ DOR	4 weeks/ yes/ grade 2	Yes/ 4 wks
	10	48/M/F/Black/yes/26.7/B	815	V90I, V106I, Y181C, H221Y	DTG + TAF/FTC	4 weeks/ no/ grade 1	Yes/ 12 wks
	11	41/M/M/Black/no/46.22/B	5,280	Y181C, Y188L K103V	DRV/c/FTC/TAF + DTG	8 weeks/ yes/ grade 1	Yes/ 4 wks
	12	54/M/M/Black/yes/22.1/B	9,760	L100I, K103N, Y181Y/C, H221H/Y	EVG/c/FTC/TAF + DRV	8 weeks/ yes/ grade 1	Yes/ 16 wks
	13	50/M/M/Latino/yes/23/B	36,342	L100I, V179I, Y181I	DRV/c/FTC/TAF	4 weeks/ no/ grade 2	Yes/ 4 wks
	14	51/M/M/White/yes/28.2/B	239,000	L100I, K103N	DRV/c/FTC/TAF+DTG	4 weeks/ no/ grade 1	Yes/ 4 wks
	15	59/M/M/Latino/no/19.9/B	1,271,051	V106I, G190S, V179T, F227L	DRV/c/FTC/TAF + DTG	4 weeks/ no/ no	Yes/ 8 wks
Suspected archived NNRTI mutations	16	31/M/M/Black/no/25.18/B	7,240	None	BIC/TAF/FTC + DRV/c	8 weeks/ yes/ no	Yes/ 8 wks
	17	54/M/M/Black/yes/21.8/B	229,000	None	DRV/r/TAF/FTC	8 weeks/ yes/ no	Yes/ 16 wks
High VL within 3 months prior to starting LA ART (+/- NNRTI mutations)	18	57/M/M/Black/yes/22.0	UD	K103N, V108I, P225H	LA CAB/RPV	8 weeks/ yes/ no	Yes/ NA
	19	43/M/M/Black/no/24.9/B	UD	K103N, V108I, P225H	DRV/c/FTC/ TAF+DTG	8 weeks/ yes/ no	Yes/ NA
	20	42/M/M/White/yes/19.4/B	UD	None	LA CAB/RPV	8 weeks/ no/ grade 2	Yes/ NA
	21	28/M/M/Latino/no/30.5	UD	None	LA CAB/RPV	8 weeks/ no/ no	Yes/ NA
	22	60/M/M/White/yes/28.2/B	190	None	BIC/TAF/FTC	8 weeks/ yes/ no	Yes/ 12 wks
	23	39/M/M/Latino/yes/21.2/B	194,000	None	BIC/TAF/FTC	8 weeks/ yes/ no	Yes/ 5 wks
Low level viremia on CAB/RPV (+/- NNRTI mutations)	24	39/M/M/Latino/no/36.0/B	UD	K103R	LA CAB/RPV	8 weeks/ yes/ no	Yes/ NA
	25	35/M/M/Black/yes/34.7/B	95	None	LA CAB/RPV	8 weeks/ yes/ no	Yes/ 3 wks
	26	38/M/M/Latino/yes/23/B	145	None	LA CAB/RPV	4 weeks/ yes/ grade 2	No/ no VS
	27	42/M/M/White/yes/26.5/B	165	K103N, V106I	LA CAB/RPV	8 weeks/ yes/ no	Yes/ 16 wks
INSTI mutations	28	34/M/M/Latino/yes/22/B	UD	V90I, T66T/I	BIC/TAF/FTC	4 weeks/ yes/ grade 1	Yes/ NA
	29	52/M/M/White/yes/22.2/B	105	E92Q	DTG/RPV + DRV/c	8 weeks/ yes/ no	Yes/ 16 wks
	30	44/F/F/Black/no/25.5/B	228	T97A	BIC/TAF/FTC	8 weeks/ yes/ no	No/ no VS
	31	40/F/F/Latina/no/24.8/B	290	E92Q	DRV/c/FTC/TAF + DOR	8 weeks/ yes/ grade 1	Yes/ 9 wks
	32	72/M/M/Black/yes/17.7/B	50,900	T97A	BIC/TAF/FTC + DRV/c	8 weeks/ yes/ no	Yes/5 wks
Other	33[1]	47/F/F/Black/no/41.2/B	UD	None	BIC/TAF/FTC	8 weeks/ yes/ grade 1	Yes/ NA
	34[2]	57/M/M/White/yes/22.7/B	UD	None	LA CAB/RPV	4 weeks/ no/ grade 1	Yes/ NA

M-male; F-female; UD-undetectable; DRV/c-darunavir/cobicistat; BIC-bictegravir; TAF-tenofovir alafenamide; FTC-emtricitabine; DTG-dolutegravir; 3TC-lamivudine; EVG-elvitegravir; DOR-doravirine; [1]High BMI > 40 kg/m²; [2]Intolerance to LA-RPV; *ISR injection site reaction; K103(X) mutations not counted as RPV associated mutations

Results

- All patients (n=34: 76% male; 24% cis/trans female; 41% Black; 38% Latino/a; median age 47 [range 28-75] years; 29% and 71% on CAB every 4 or 8 weeks) reported challenges adhering to oral ART (**Table**)
- Reason(s) for using LEN/CAB with or without RPV were: either documented or suspected NNRTI mutations (n= 21, 59%), integrase mutations (n=5, 15%), high VL (n=6, 18%), or continued viremia on CAB/RPV alone (n=4, 12%)
- Injection site reactions on LA-LEN were reported in 44% (32% grade I, 12% grade 2).
- All patients but two (32/34; 94%) suppressed (VL< 75 copies/mL) after starting LEN at a median of 8 (4-16) weeks, with 16/34 (47%) suppressed at baseline.

Conclusion

- First case series of patients on a novel combination of long-acting ART with LEN (subcutaneous every 6 months) and CAB (intramuscular every 4-8 weeks) with or without RPV
- All experienced adherence challenges with oral ART
- Most common reason for use of this off-label combination was NNRTI mutations
- Overall, viral suppression doubled from 47% at baseline to 94% on LEN/CAB
- Patients with documented or suspected NNRTI mutations all achieved suppression on LEN/CAB
- Due to prevalence of NNRTI mutations worldwide (**Figure**), CAB/RPV not approved as LA ART by WHO in low-and-middle-income countries (LMICs)
- Therefore, in 2024, disparities exist in availability of LA ART between high and LMICs
- Trial needed to study LEN/CAB in patients with NNRTI resistance worldwide given this disparity; this case series serves as a call for this trial

Acknowledgements: Funded by NIAID/NIH 5R37AI098472

UCSF Penn Case Western Reserve University

UC San Diego MetroHealth Devoted to Hope, Health, and Humanity

Trial (small) of LEN/CAB finally approved

- These pharmaceutical companies have not historically worked together before
- After much advocacy (two years), small trial (n=20) finally approved from the pharmaceutical companies of LEN/CAB in the ACTG
- Inclusion criteria:
  - NNRTI resistance
  - Viremic
  - Experiencing adherence challenges with oral ART
- ANRS proposed LEN/CAB trial in virologically suppressed but not yet approved
- Hoping ACTG study will open door to larger trial in LMICs

Lenacapavir is being studied for PrEP across diverse populations

NIH U.S. National Library of Medicine
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Study to Assess Safety and Efficacy of Lenacapavir and Emtricitabine/Tenofovir Alafenamide for Pre-Exposure Prophylaxis in Adolescent Girls and Young Women at Risk of HIV Infection (PURPOSE 1)

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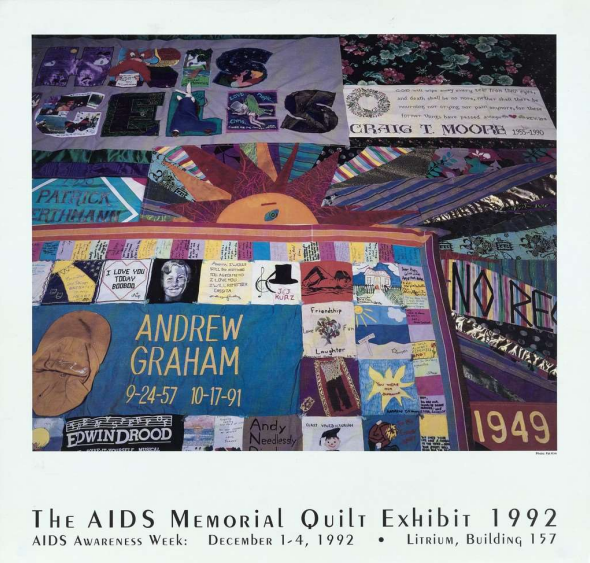
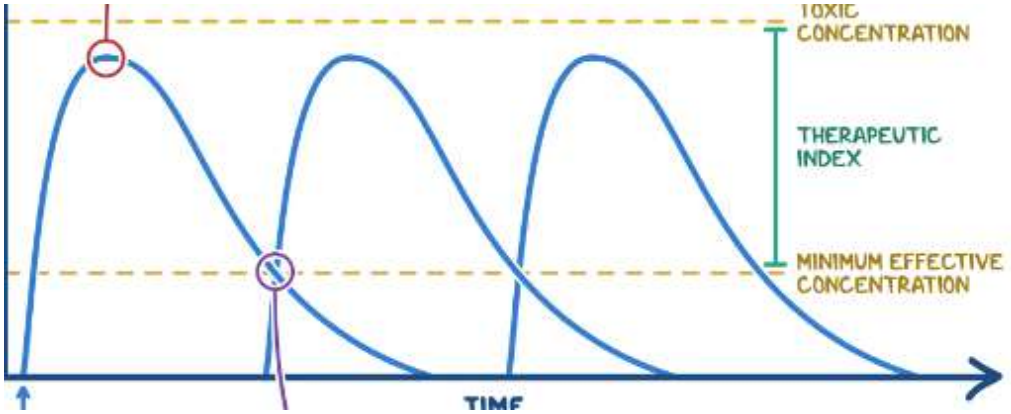
Study to Assess the Effectiveness and Safety of Lenacapavir for Human Immunodeficiency Virus (HIV) Pre-Exposure Prophylaxis (PURPOSE 2)

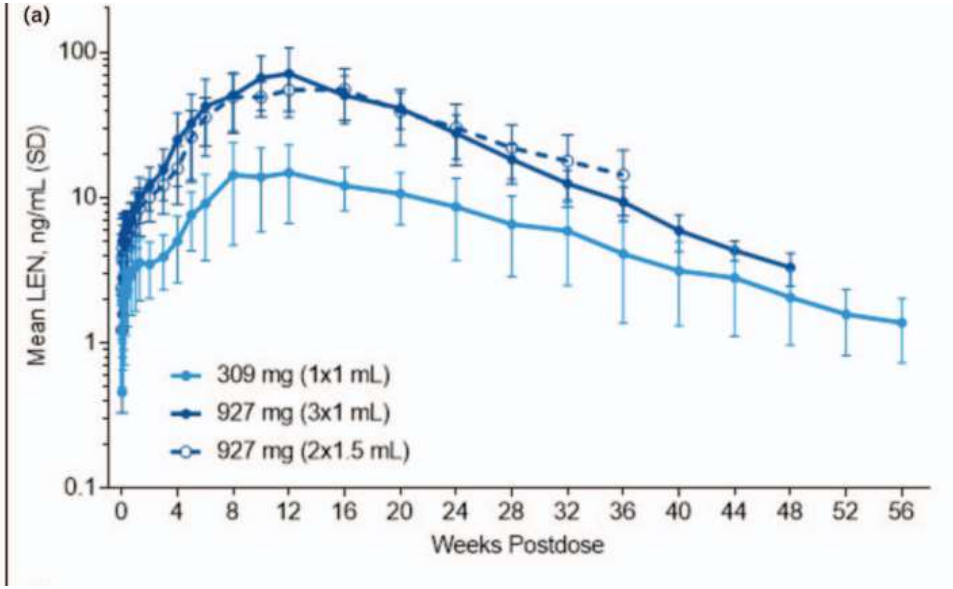
Objectives of talk

- Why long-acting?
- Data on long-acting CAB/RPV for treatment in those starting with virologic suppression (VS), including in LMICs
- Data on LA CAB/RPV in those with adherence challenges
- Data on long-acting CAB for prevention
- Lenacapavir for MDR-HIV (naïve, prevention)
- Pitfalls of LA medications



Daily pill gives high Cmax every day; LA drug has slow decline- does a virus need to see Cmax daily to be totally suppressed? (VS rates with LA are higher when VL cut-off is <200 rather than <50)





Hill L. JAIDS 2024

3 had low RPV levels; 3 had low CAB levels; 1 had both

Long-Acting CAB + RPV Fails With Resistance in 5 After Long Control on Oral Regimens

EACS 2023, October 18-21, 2023, Warsaw

pharmaceutics

MDPI

91 samples from 46 PWH

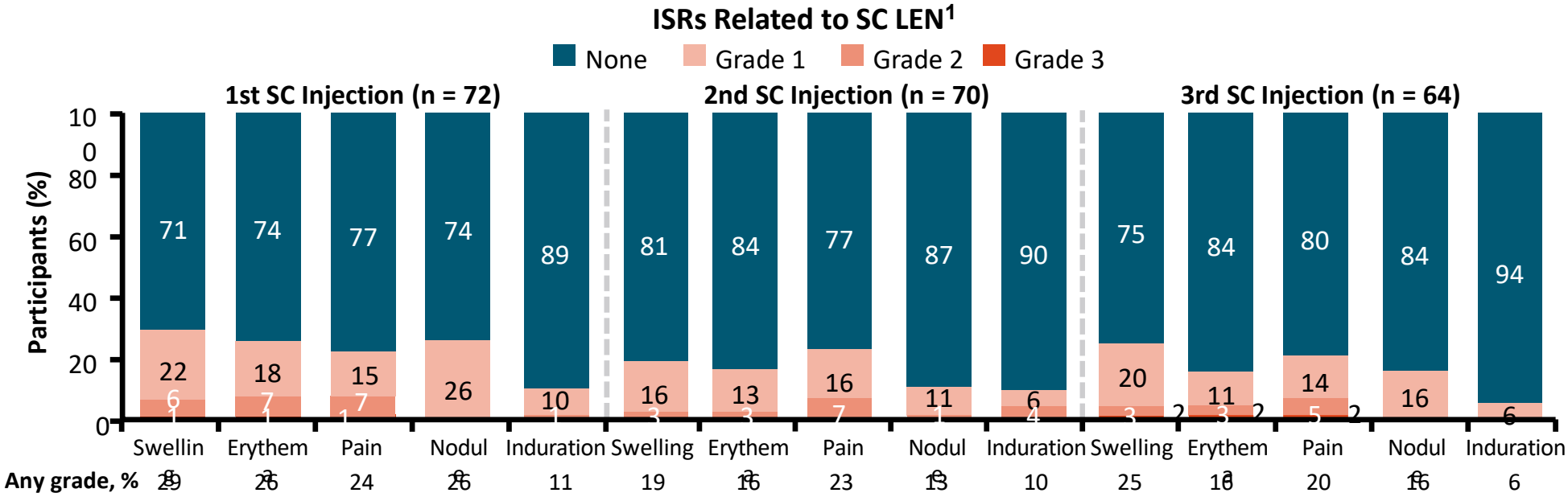
Article

Real-Life Therapeutic Concentration Monitoring of Long-Acting Cabotegravir and Rilpivirine: Preliminary Results of an Ongoing Prospective Observational Study in Switzerland

Paul Thoueille [1], Susana Alves Saldanha [1], Fabian Schaller [1], Aline Munting [2], Matthias Cavassini [2], Dominique Braun [3,4], Huldrych F. Günthard [3,4], Katharina Kusejko [3,4], Bernard Surial [5], Hansjakob Furrer [5], Andri Rauch [5], Pilar Ustero [6], Alexandra Calmy [6,7], Marcel Stoeckle [8], Manuel Battegay [8,9], Catia Marzolini [8,9,10], Pascal Andre [1], Monia Guidi [1,11,12], Thierry Buclin [1], Laurent A. Decosterd [1,*]

Don't have large population PK studies of LA CAB/RPV. Know influenced by BMI but what else? This small study shows a lot of variability in RPV levels – depends on technique of placement among other factors- need more data (large population PK studies in real-world of patients on CAB/RPV)

CAPELLA: Injection-Site Reactions Through Wk 104



- In pooled analysis of ISRs from CAPELLA and CALIBRATE, median resolution of ISRs: swelling, erythema, pain: 10, 5, 3 days, respectively; **nodules, 252 days; induration, 202 days**[2]

Nodules and induration almost the entire injection interval – this is a feature not a bug meaning drug deposits in its depot form under skin and elutes over time – can cut down on acceptability

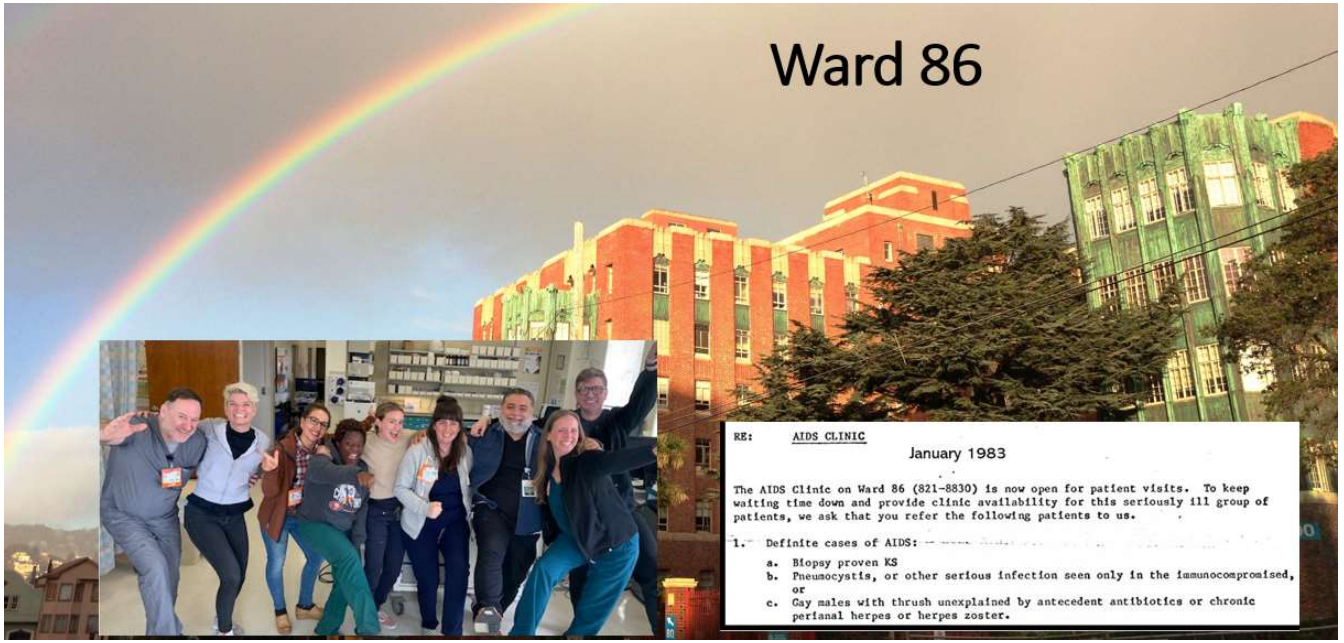
Ogbuagu. IDWeek 2023. Abstr 1596. Castagna. EACS 2023. Abstr eP.A.104.

Conclusions

- Long-acting formulations of HIV medications latest advance
- LA drugs have precedent for increasing adherence in other states
- Much data now in those with virologic suppression of high rates of continuing VS on LA CAB/RPV (80% to over 95%)
- Emerging data on LA CAB/RPV in adherence-challenged and being used by clinicians in patients with viremia
- Lenacapavir for MDR-HIV & should be studied with CAB in NNRTI-resistant patients
- Pitfalls include not knowing enough about PK, nodules with LEN, do we tolerate VL 200 as our cut-off?

stop aids. make the promise

Thank you to AAHIVM, Division of HIV, ID and Global Medicine at UCSF, the HIV movement, and Ward 86!



Method to Obtain CME/CE

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https://www.paceducation.com/LAAlive

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