Long-Acting Cabotegravir / Rilpivirine for Individuals With Detectable Viral Loads

Monica Gandhi MD, MPH
Medical Director, Ward 86 HIV Clinic
Division of HIV, Infectious Diseases, and Global Medicine
University of California, San Francisco

Last Updated: January 12, 2023

Disclosures

No conflicts of interest or relationships to disclose.

Disclaimer

Funding for this presentation was made possible by U1OHA29296 from the Human Resources and Services Administration HIV/AIDS Bureau. The views expressed do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. *Any trade/brand names for products mentioned during this presentation are for training and identification purposes only.*

AETC AIDS Education & Training Center Program Mountain West

ARS question: As an HIV clinician, have you yet started anyone on long-acting ART?

1. **Yes**
2. **No**

Case

- 38 yo gay man with HIV diagnosed two years ago, lives with brother
- Comes from family with whom he is not comfortable coming out as either gay nor living with HIV- brother does not know his status
- Genotype on diagnosis was wild type
- Pt not comfortable taking oral ART as does not want family to know & has not been on meds steadily since diagnosis
- You discuss long-acting ART with him

MWAETC

Adherence Challenges with ARTs

Overall adherence to ART in US

- Among 206,474 adults with HIV treated with ART, majority had suboptimal adherence:
  - 60% had adherence < 90% and 40% had adherence < 80% (McComsey. Adv Ther. 2021)

Rates of virologic suppression worldwide:

- **In adults on ART, 79% suppression at 1 year, 65% by 3 years**
- In children/adolescents on ART, 36% suppression at 1 year, 24% at 3 years (Han. Lancet HIV 2021)

Barriers to ART adherence:

- Systematic review of 125 studies identified main barriers to ART adherence
  - Forgetting
  - Being away from home
  - Change to daily routine
  - Depression
  - Alcohol/substance misuse
  - Secrecy/stigma
  - Feeling sick
  - Far distance to clinic
  - Stock outs

McComsey, G. A., et al. Real-World Adherence to Antiretroviral Therapy Among HIV-1 Patients Across the United States. *Advances in therapy*, *2021*

Min Han W et al. Global estimates of viral suppression in children and adolescents and adults on antiretroviral therapy adjusted for missing viral load measurements: a multiregional, retrospective cohort study in 31 countries. Lancet HIV 2021.

Shubber, Z., et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. *PLoS medicine, 2016.* 13(11), e1002183.

Altice, F., et al. . Adherence to HIV treatment regimens: systematic literature review and meta-analysis. *Patient preference and adherence*, 2019

MWAETC

Discontinuation, suboptimal adherence, and reinitiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis

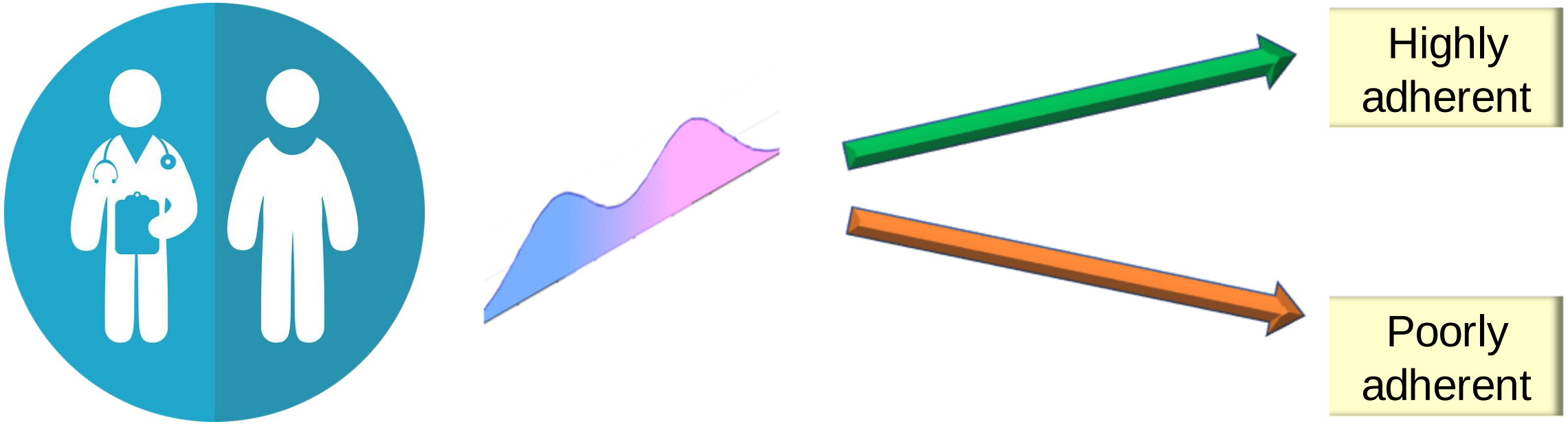
Jing Zhang, Chunyan Li*, Junjie Xu*, Zhili Hu, Sarah E Rutstein, Joseph D Tucker, Jason J Ong, Yongjun Jiang, Wenqing Geng, Sarah T Wright, Myron S Cohen, Hong Shang†, Weiming Tang†*

- Systematic review, 41·0% of those on PrEP discontinued within 6 months; suboptimal adherence for those who stayed 37·7%
- Discontinuation rate higher in sub-Saharan Africa 47·5% than other regions
- Discontinuation rates lower in studies with adherence interventions than in those without (24·7% *vs* 36·7%, p=0·015). \
- Men who have sex with men and transgender women offered daily or non-daily dosing options had lower discontinuation rates than those offered daily dosing alone (21·6% *vs* 31·5%; p<0·001).
- **Though oral PrEP important, we need other options**

ARTICLES | VOLUME 9, ISSUE 4, E254-E268, APRIL 01, 2022

MWAETC

Patient with challenges to ART adherence could benefit from long-acting ART



Would then KNOW date of “medication consumption” (not adherence, but coming in), pharmacies or mobile vans administering the shots, home health

MWAETC

Original registrational trials of LA CAB/RPV- FLAIR, ATLAS and ATLAS 2M

FLAIR

- CAB/RPV LA in treatment naïve participants -data out to 124 weeks

ATLAS

- CAB/RPV LA in treatment experienced participants every 4 weeks- data out to 96 weeks

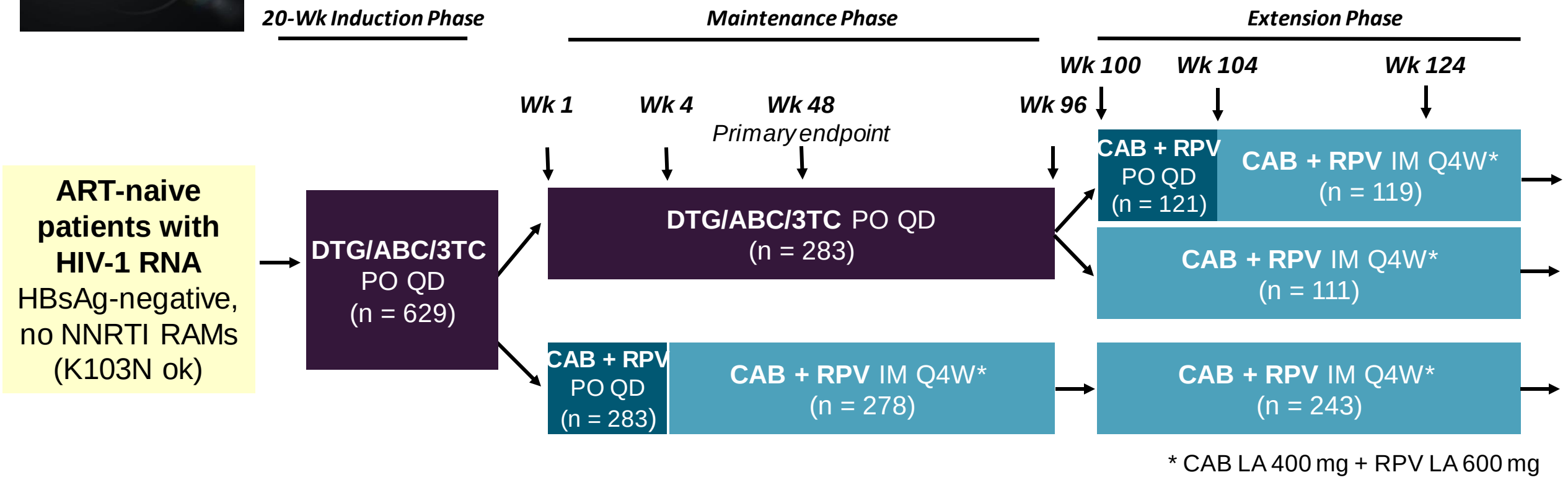
ATLAS 2M

- CAB/RPV LA in treatment experienced participants every 8 weeks- data out to 152 weeks

MWAETC

FLAIR Naïve study: "Flair for new things"

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



* CAB LA 400 mg + RPV LA 600 mg

- Naïve patients, only K103N okay, suppressed on DTG/ABC/3TC x 20 weeks
- Then oral "lead in" of CAB 30mg/RPV 25mg x 28 days (111 went straight to LA)
- Then CAB 600mg IM/RPV 900mg IM x 1 (load), then CAB 400mg/RPV 600mg every 4 weeks

MWAETC

ATLAS Switch study: "Ah, you have traveled before"

- Multicenter, randomized, open-label phase III noninferiority trial

Adults on stable ART* (either first or second regimen) with **HIV-1 RNA < 50 copies/mL for ≥ 6 mos** with no previous VF
(N = 616)

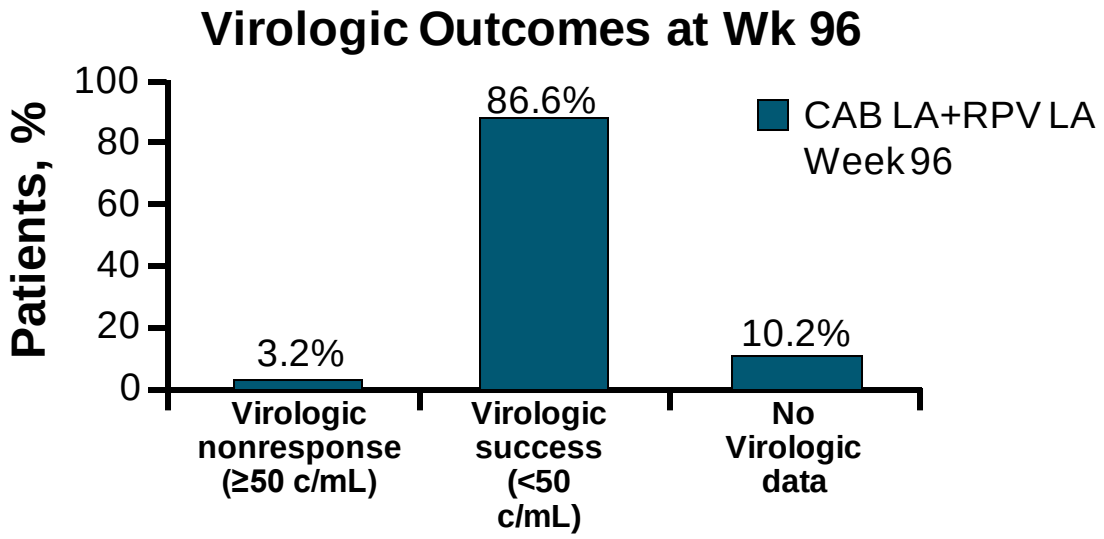
Wk 4

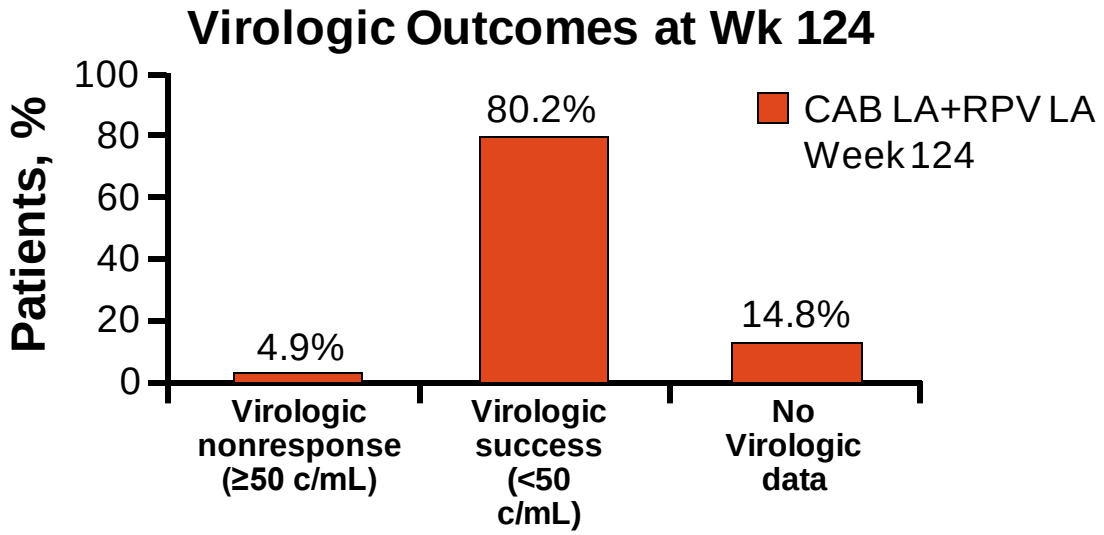
Oral CAB + RPV† (n = 308)	CAB LA 400 mg IM monthly + RPV LA 600 mg IM monthly† (n = 308)
Continue Baseline ART (n = 308)	

- 1st or 2nd regimen, no VF in past, no known INSTI or NNRTI mutations (K103N okay), suppressed x 6 months <50 copies/mL
- Then oral "lead in" of CAB 30mg/RPV 25mg x 28 days then initiation dose (CAB 600mg IM/RPV 900mg IM), then maintenance every 4 weeks (400/600)

MWAETC

FLAIR: Viral Suppression Through Week 124





THE LANCET

Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study

- 4 failures up to week 96; 1 additional failure between 96-124 weeks (at 108 weeks – male, BMI 24.7, ended up being treated with EFV/TDF/FTC after and suppressed)
- Of the 14.8% "without virologic data", most discontinued with AEs

IAS 2021
18 –21 July

Orkin. IAS 2021. Abstr OAB0302.

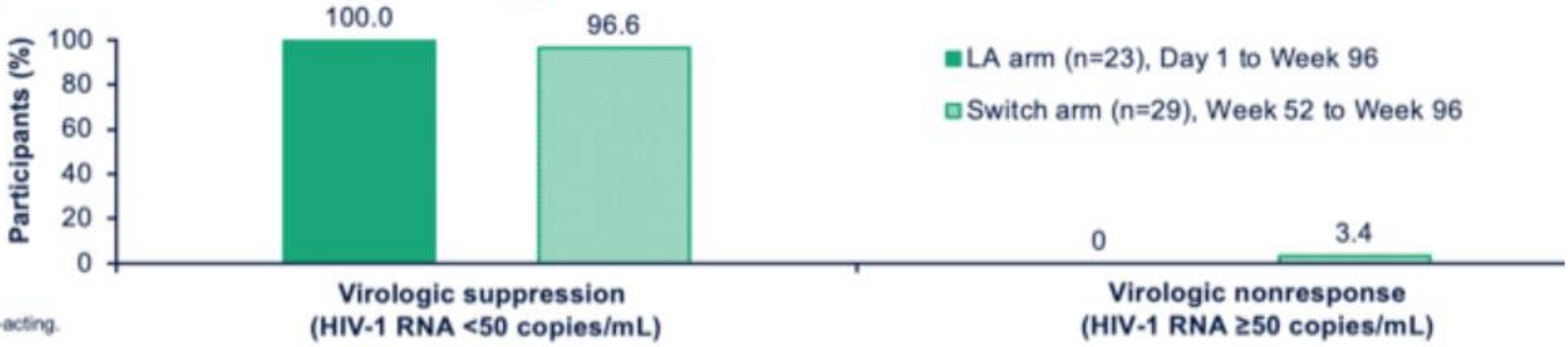
MWAETC

ATLAS: 96 week data

- CAB LA + RPV LA was non-inferior to continuing 3 drug ART
- In CAB + RPV arm, 3 failures (2 of 3 had baseline NNRTI RAMs)

HIV Drug Therapy GLASGOW 2020

Figure 2. ATLAS Week 96 Virologic Outcomes



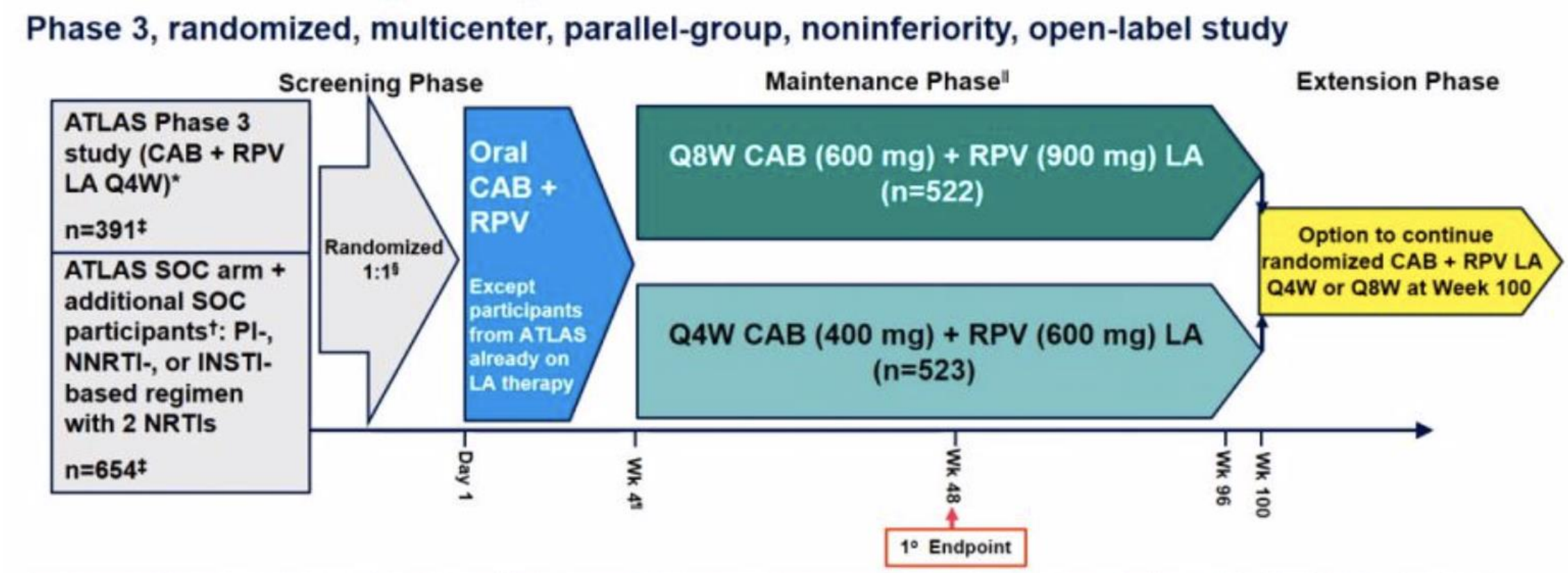
LA, long-acting.

MWAETC

ATLAS 2M: Cabotegravir and Rilpivirine LA every 8 weeks

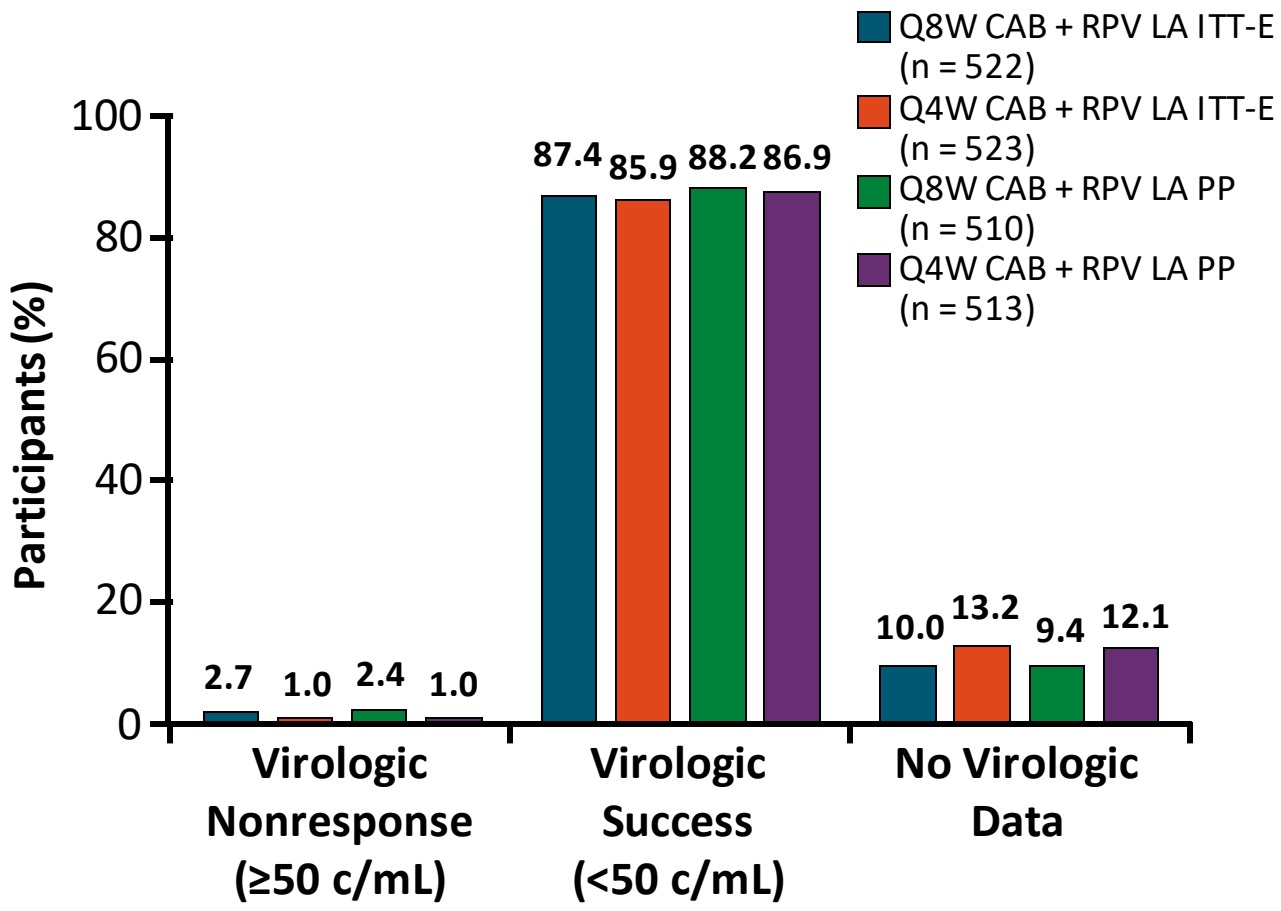
- ATLAS 2M – after q4 weeks, tried q8 weeks vs q4 weeks (ATLAS 2M)

Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study



Overton TE. Lancet 2020

ATLAS-2M: Wk 152 Virologic Outcomes



- 2 additional participants (both male at birth, BMI <30 kg/m^2) in Q8W arm met CVF criteria between Wk 96 and 152 (Wk 112, 120)
  - At BL, neither had RAMs; participant with A6 subtype had L74I integrase polymorphism

Country	Baseline	At Failure		
	HIV-1 Subtype	HIV-1 RNA (c/mL)	RPV RAMs	INI RAMs
Germany	B	24,221	**E138A+ M230M/L**	**Q148R**
Russia	A6*	59,467	**E138A+ Y181Y/C**	**Q148R**

*Originally classified as A1; later reclassified as A6 upon reanalysis

- Through Wk 152, 13 participants had CVF: Q8W, n = 11 (2%); Q4W, n = 2 (<1%)
  - None with injection >7 days late

Overton. CROI 2022. Abstr 479.

ARS question: In the updated pooled analysis presented at HIV Glasgow, what was the 152-week virologic failures rate on LA CAB/RPV in FLAIR, ATLAS and ATLAS 2M?

1. 0.5%
2. 1%
3. 1.4%
4. 2.8%
5. 4.5%

Summary of resistance mutations across FLAIR/ATLAS/ATLAS 2M (1%-5% rate of failure)

Study	INSTI mutations(n)	NNRTI mutation(s) some baseline	Time of virologic failure
FLAIR (4 failures)	N155H, R263K, G140R, Q148R	L74I	Weeks 20, 28, 48, 108
ATLAS (3 failures)	N155H	L74I, E183E/A, V108V/I, E138K	Weeks 8, 12, 30
ATLAS 2M (8wk) 13 failures	Q148R,N155H	K101E, E138E/K, E138A, Y188L, Y181C, M230L	7: before week 24 3: week 24-48 1: week 88 2: weeks 88-152
ATLAS 2M (4wk) 2 failures	N155N/H,E138E/K+ Q148R	K101E, M230L	Before week 24

HIV GLASGOW 2022
Drug Therapy
Hybrid meeting | 23-26 October

Updated analysis at Glasgow: 1.4% risk of failure 1224 participants across trials

MWAETC

ARS question: Of the below risk factors for virologic failures across trials, which one can you circumvent by different ways of administering the injections?

1. Low rilpivirine trough concentrations
2. HIV subtype A1/A6
3. High BMI
4. History of rilpivirine mutations
5. Low BMI

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 all associated with increased risk of failure (updated ID week 2022)

IDWeek™

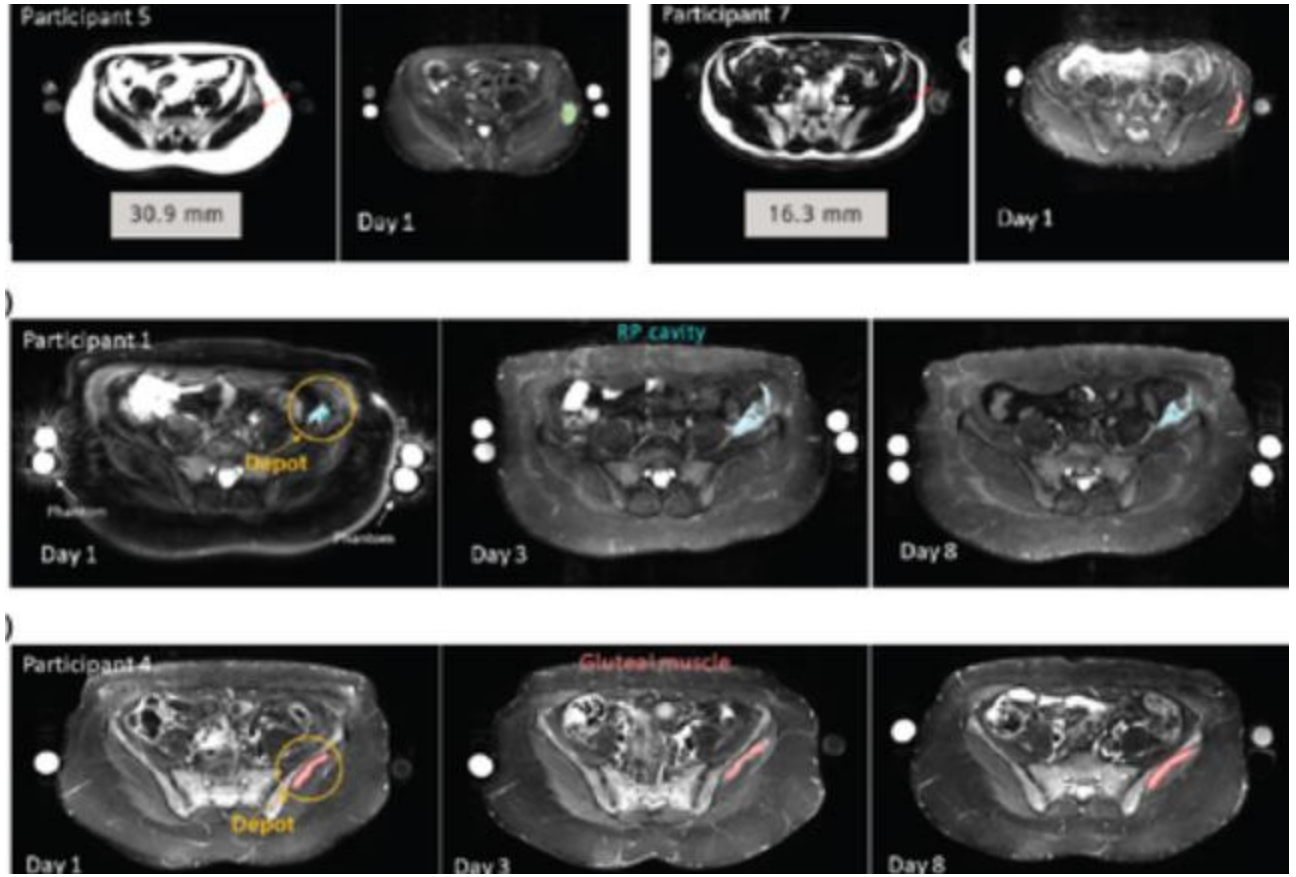
MWAETC

BMI and CAB

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

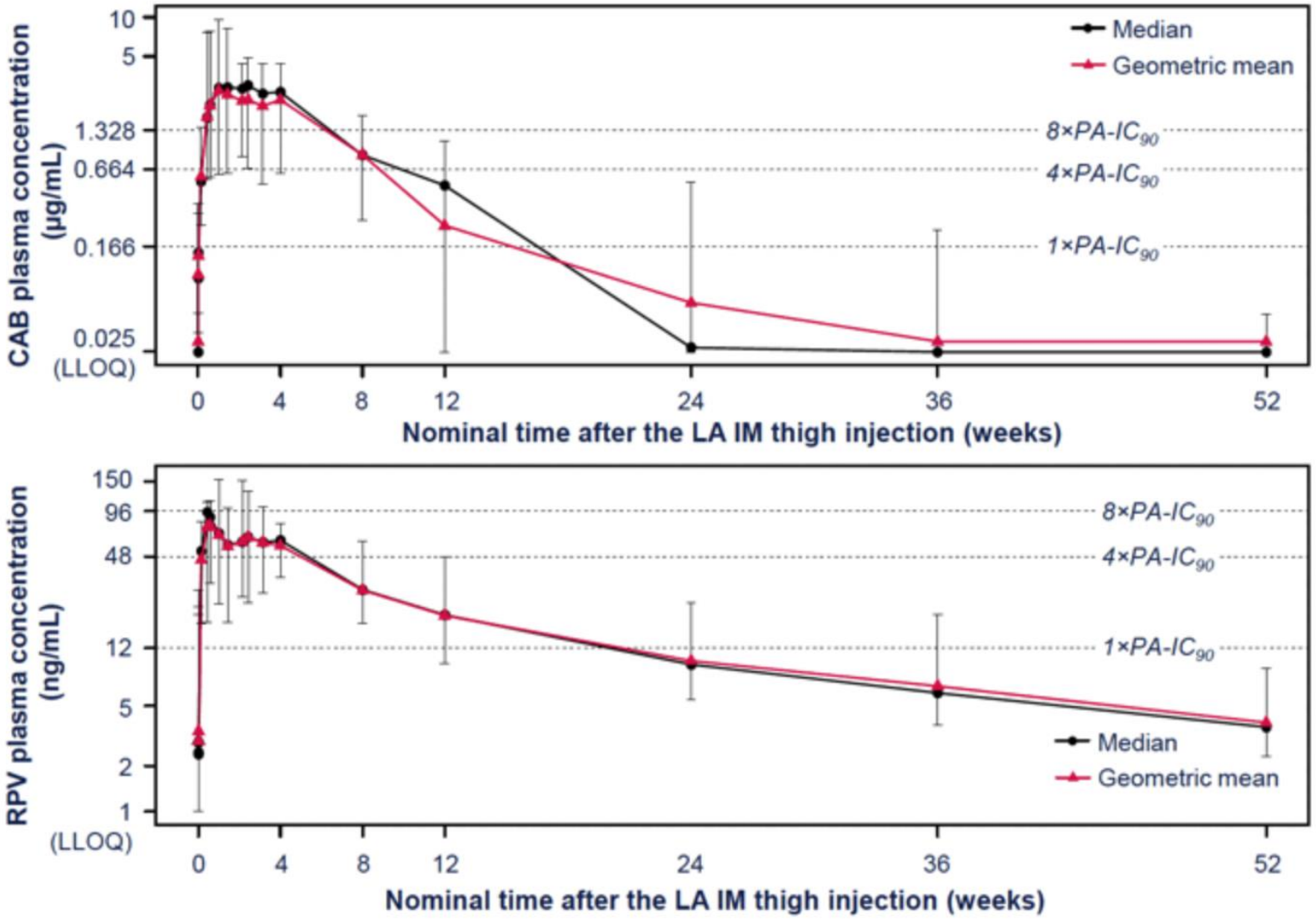


Jucker B. Br J of Pharm 2021

MWAETC

Pharmacokinetics and Tolerability of Cabotegravir and Rilpivirine Long-Acting Intramuscular Injections to the Vastus Lateralis (Lateral Thigh) Muscles of Healthy Adult Participants

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



Implications for self-injection

AIDS 2022
29 July – 2 August

MWAETC

Equity in access to long-acting injectables in the USA

THE LANCET
HIV

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

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

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

Why do we have to study this in "hardly reached" populations?

- If wait until drug approved or not studied at outset, 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 in these patients

MWAETC

REAL WORLD STUDIES OF LA CAB/RPV

ARS question: How many real-world studies of LA CAB/RPV implementation have been performed?

1. 1 of course, just the cool and awesome Ward 86 program
2. 2
3. 3
4. 4
5. 5
6. 6

HIV MEDICINE | BHIVA British HIV Association

ORIGINAL ARTICLE | Open Access

Compassionate use of long-acting cabotegravir plus rilpivirine for people living with HIV-1 in need of parenteral antiretroviral therapy

Ronald D'Amico, Santiago Cenoz Gomis, Riya Moodley, Rodica Van Solingen-Ristea, Bryan Baugh,

- 35 patients in compassionate use program for LA-CAB/RPV
- 28 not virologically suppressed on entry; 15 (43%) due to oral ART adherence difficulties (difficulty swallowing, pill fatigue, stigma)
- After a median of 10 months (range 1-47) of follow-up, 22 of 35 (63%) participants were virologically suppressed
- Of the 13 people not suppressed, 3 (23%) not enrolled in program long enough to achieve suppression, but 10 (29%) did fail
- No report on % on-time injections

MWAETC

Study population

People with HIV (PWH) in OPERA
N = 145,398

PWH in care 1/21/21 to 2/28/22
N = 105,833

Adult PWH who ever received CAB+RPV injections
N = 421

1st CAB+RPV injections between 1/21/21 and 2/28/22
N = 383

ART experience and baseline viral load* at first CAB+RPV LA injections

	n (%)
Treatment-naïve	0 (0%)
Treatment-experienced, VL <50 copies/mL	321 (84%)
Treatment-experienced, VL ≥50 to <200 copies/mL	27 (7%)
Treatment-experienced VL ≥200 copies/mL	28 (7%)
No baseline VL	7 (2%)
Total	**383 (100%)**

IDWeek

OPERA The Longitudinal Cohort

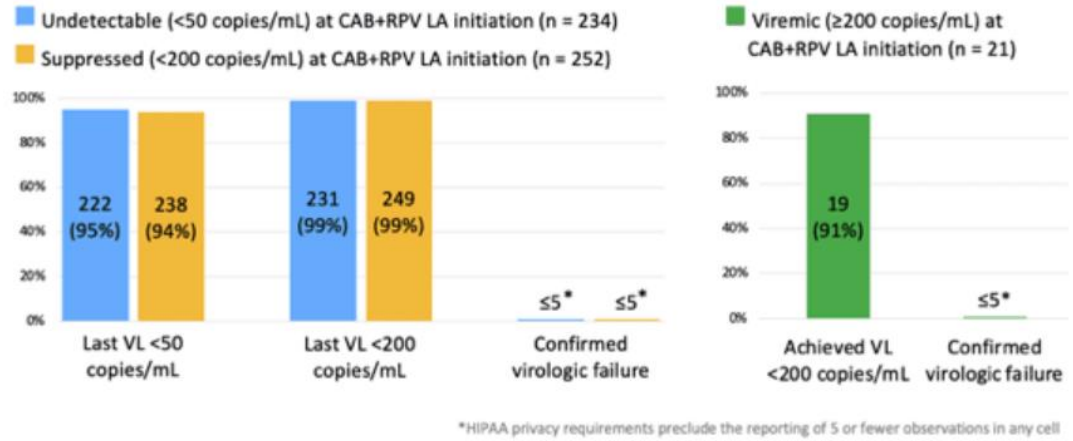
Real-World Use of Long-Acting Cabotegravir + Rilpivirine in the US:

Effectiveness in the First Year

Of 21 viremic patients started, 91% (19) suppressed

Virologic outcomes

Among those with ≥1 VL after first injections



*HIPAA privacy requirements preclude the reporting of 5 or fewer observations in any cell

MWAETC

Open Forum Infectious Diseases

Open Forum Infect Dis. 2022 Sep; 9(9): ofac455.
Published online 2022 Sep 2. doi: 10.1093/ofid/ofac455

PMCID: PMC9487705
PMID: 36147599

Early Experience Implementing Long-Acting Injectable Cabotegravir/Rilpivirine for Human Immunodeficiency Virus-1 Treatment at a Ryan White-Funded Clinic in the US South

Lauren F Collins, Della Corbin-Johnson, Meron Asrat, Zoey P Morton, Kaylin Dance, Alton Condra, Kimberly Jenkins,

- First 15 patients assessed in Ryan White Care program in Atlanta, all suppressed
- 13 remained virologically suppressed 6 months after LA initiation
- 1 (with severe malabsorption) stayed at HIV RNA level of ~700 copies/mL, despite no missed or delayed injections, & switched back to oral ART (BMI 21)
- Another suppressed at 3 months and then rebounded to 750 copies/mL by 6 months (although VL two weeks later was <40) with a K103N and L00I not on prior genotype, BMI 27.7kg

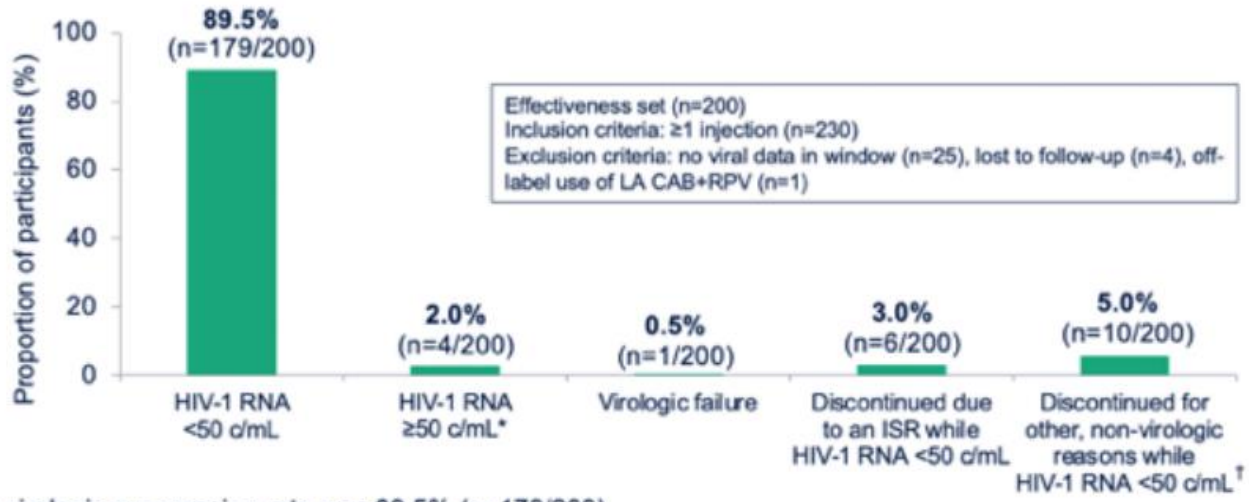
CARLOS COHORT

HIV Drug Therapy 30 YEARS
GLASGOW 2022 | HYBRID

- 3 year observational cohort study of LA CAB/RPV given every 2 months after oral ART in conjunction with label/ATLAS 2M, Germany
- Among 200 patients included 89.5% virologically suppressed after 6 months
- Of 633 injection visits, 18 (2.8%) occurred late (>7 days after scheduled injection).

6-Month Outcomes of Every 2 Months Long-Acting Cabotegravir and Rilpivirine in a Real-World Setting – Effectiveness, Adherence to Injections, and Patient-Reported Outcomes of People Living With HIV in the German CARLOS Cohort

Effectiveness: Virologic Outcomes at M6



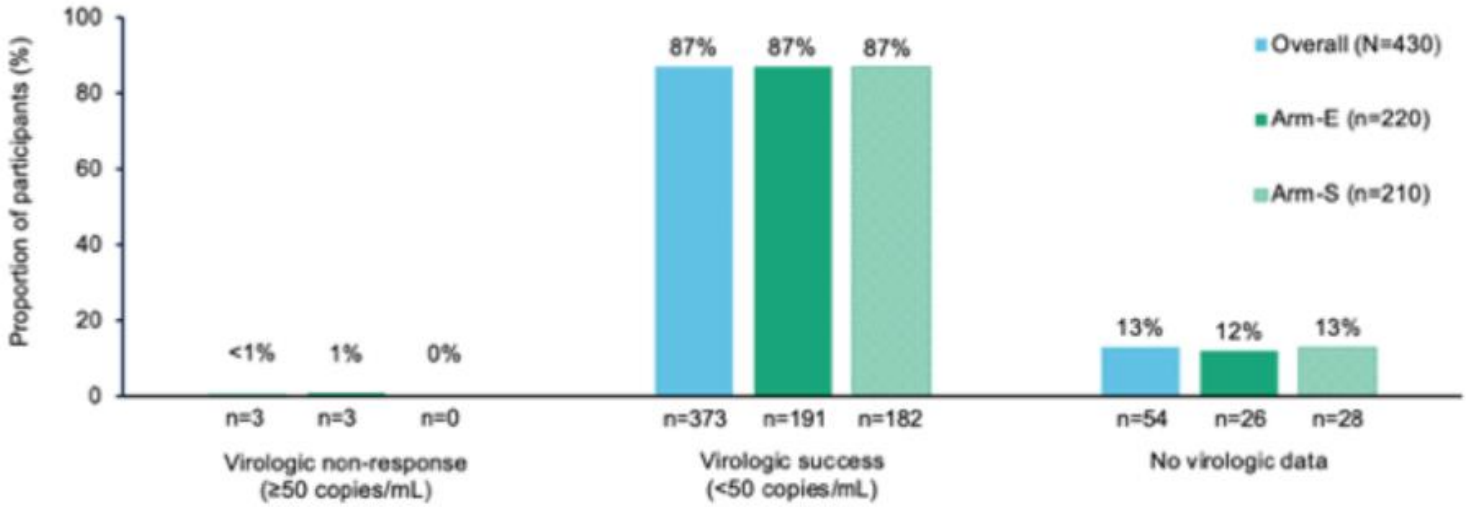
- At M6, the virologic suppression rate was 89.5% (n=179/200)

MWAETC

CARISEL COHORT

- CAB and RPV Implementation Study in European Locations (CARISEL) – 5 countries, 18 centers
- Among 430 participants, 87% maintained virologic suppression, 0.7% experienced virologic failure (>50 cps/mL) and 13% had no virologic data through month 12
- Of 2,376 injections, most (99%) occurred before or within the 7-day dosing window, 1% after or missed

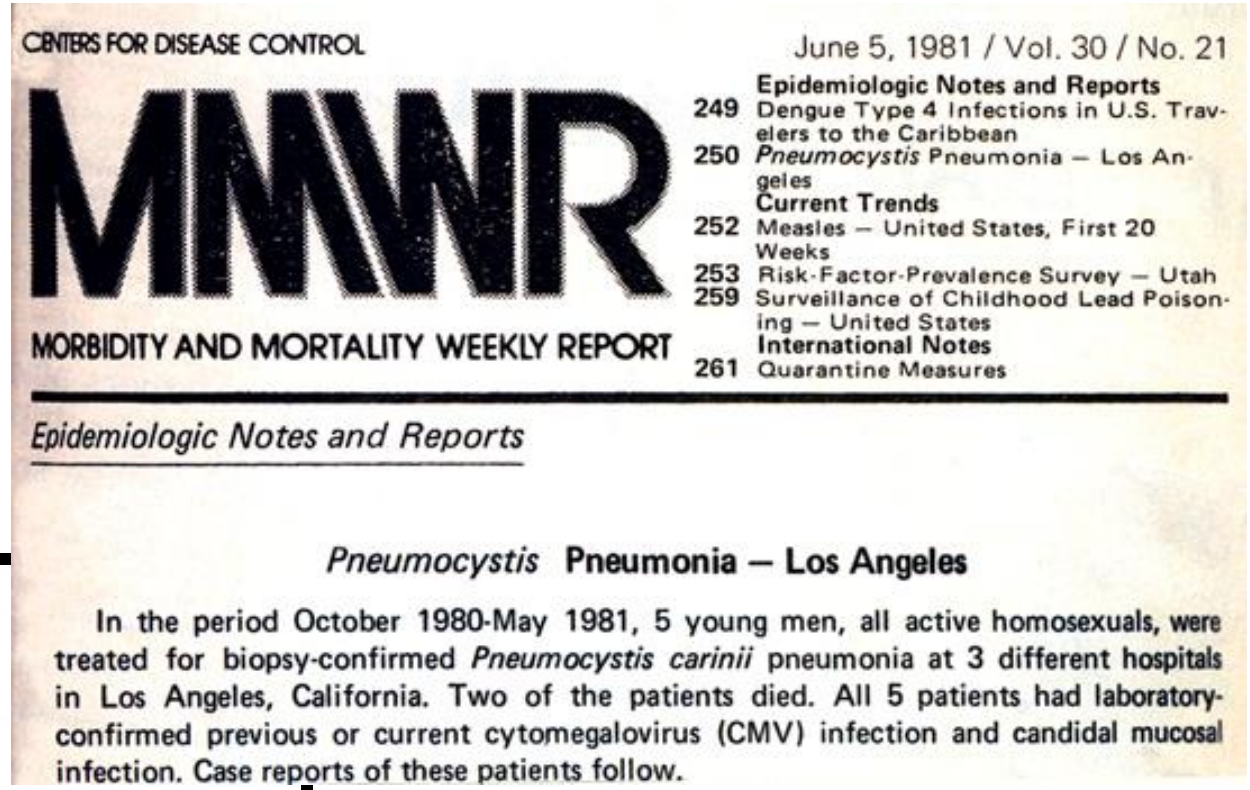
CAB + RPV LA Maintained High Levels of Virologic Suppression at Month 12 (Snapshot, ITT-E)



- At Month 12, 87% (95% CI 83.2–89.8) of participants maintained virologic suppression, with 0.7% (95% CI 0.1–2.0) having virologic non-response

Ward 86: Opened January 1983 at San Francisco General Hospital

- **Ward 86 opens January 1,1983 as the first outpatient HIV clinic in the US**



CENTERS FOR DISEASE CONTROL

June 5, 1981 / Vol. 30 / No. 21

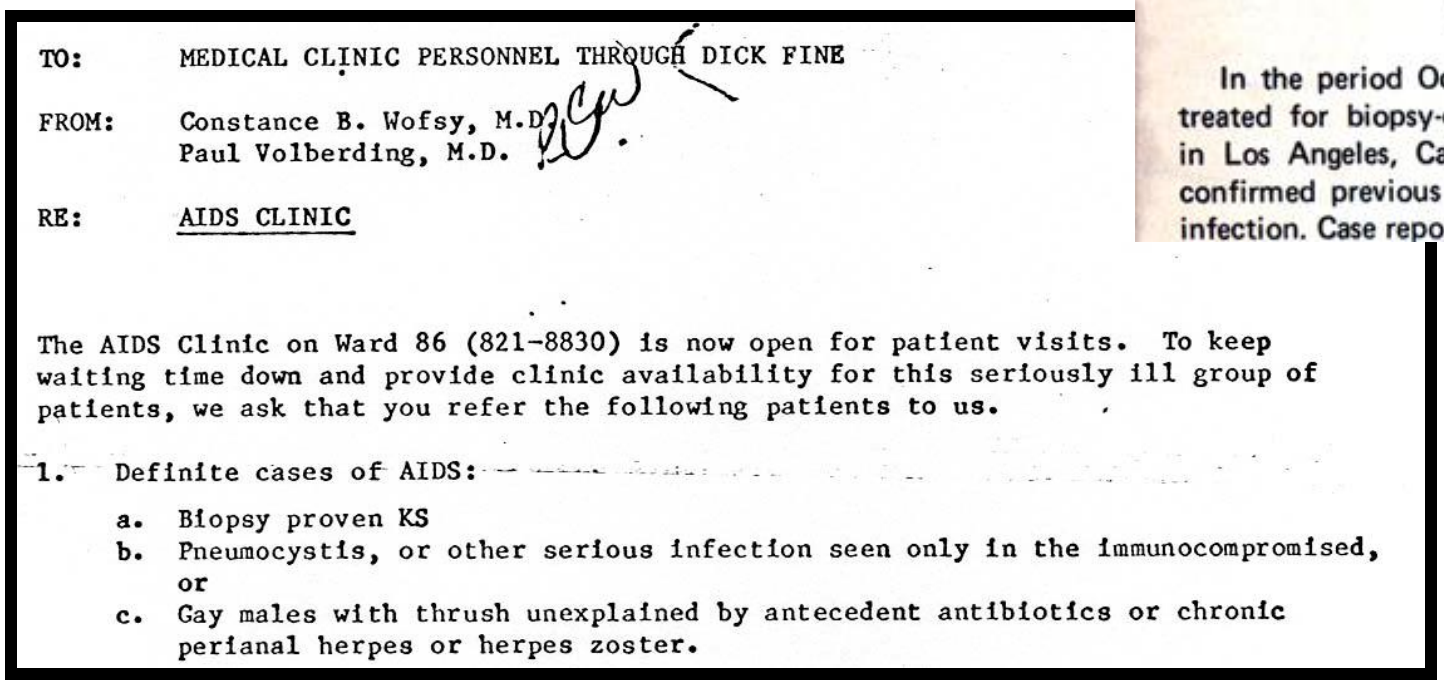
MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

Pneumocystis Pneumonia — Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.



TO: MEDICAL CLINIC PERSONNEL THROUGH DICK FINE

FROM: Constance B. Wofsy, M.D.
Paul Volberding, M.D.

RE: AIDS CLINIC

The AIDS Clinic on Ward 86 (821-8830) is now open for patient visits. To keep waiting time down and provide clinic availability for this seriously ill group of patients, we ask that you refer the following patients to us.

1. Definite cases of AIDS:
   a. Biopsy proven KS
   b. Pneumocystis, or other serious infection seen only in the immunocompromised, or
   c. Gay males with thrush unexplained by antecedent antibiotics or chronic perianal herpes or herpes zoster.

MWAETC

Who are our patients at Ward 86?

- 96% on Medicaid or Medicare
- 4% on municipal health insurance program or uninsured
- Vulnerable population:
    - Mental Illness (now up to 45%)
    - Poverty
    - Addiction (Alcohol, heroin, cocaine methamphetamine) (35%)
    - Marginal Housing (34%)

WARD 86 LONG-ACTING INJECTABLE ANTIRETROVIRAL PROTOCOL

GETTING TO ZERO SAN FRANCISCO

We started a pilot demonstration project February 2022, with protocol (happy to share with anyone!)

Clinic leadership team: Monica Gandhi MD, MPH (medical director), Janet Grochowski Pharm D (lead pharmacist), John Szumowski MD (associate medical director), Mary Shiels RN (associate nurse manager), Jon Oskarsson RN (clinic nurse manager)

MWAETC

Ward 86 LA-ART Program serves our POP-UP population as well

75%

Housed persons with HIV in San Francisco are Virally Suppressed

27%

Homeless People with HIV in San Francisco are Virally Suppressed (50-60% in POP-UP)

MWAETC

Ward 86 pilot program for long-acting ART for patients with adherence challenges to oral ART

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 data (approved FDA March ‘22)

Inclusion criteria of Ward 86

- Does not need to be virologically suppressed or take orals before
- Can go direct to inject
- No RPV or INSTI mutations (except minor)
- **Must require STRICT demonstration of every 4 week coming to clinic**
- Biweekly review of all patients

MWAETC

Clinical Infectious Diseases
MAJOR ARTICLE

Implementation of Program

First Demonstration Project of Long-Acting Injectable Antiretroviral Therapy for Persons With and Without Detectable Human Immunodeficiency Virus (HIV) Viremia in an Urban HIV Clinic

- Hired pharm tech to help get injectable meds
- 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
- 122 patients have been started on long-acting ART: rigorous protocol – will present first 100 (first 51 published)

Table 1: Demographics of first 100 patients in Ward 86 LA-ART program

Characteristic	Distribution, n (%)
Age, Median (range)	45 (37-54)
Gender	
Cis Man	87 (89%)
Cis Woman	7 (7%)
Transgender Woman	5 (5%)
Non-binary	1 (1%)
Race/ethnicity	
Black	16 (16%)
Latino/a	32 (32%)
White	37 (37%)
Multiracial	15 (15%)
Housing	
Unstable	48 (54%)
Stable	33 (33%)
Homeless	8 (9%)
Insurance	
Medicare or Medicaid or both	98 (98%)
ADAP	2 (2%)
Current Methamphetamine use	35 (39%)
Proportion of on-time injections	73% (95% CI 63%-81%)
Virologically non-suppressed (>30 cp/ml)	41 (41%) with log10 viral load (mean, STD) 4.22 (1.33)
CD4 count (mean)	Virologically suppressed 676 (415–906) Virologically non-suppressed 158 (56–383)

MWAETC

Results

- Between 6/8/21 – 8/5/2022, 100 patients were started on CAB/RPV-LA, of whom 59 were suppressed prior to starting injections & 41 unsuppressed

59 baseline suppressed

All remain suppressed

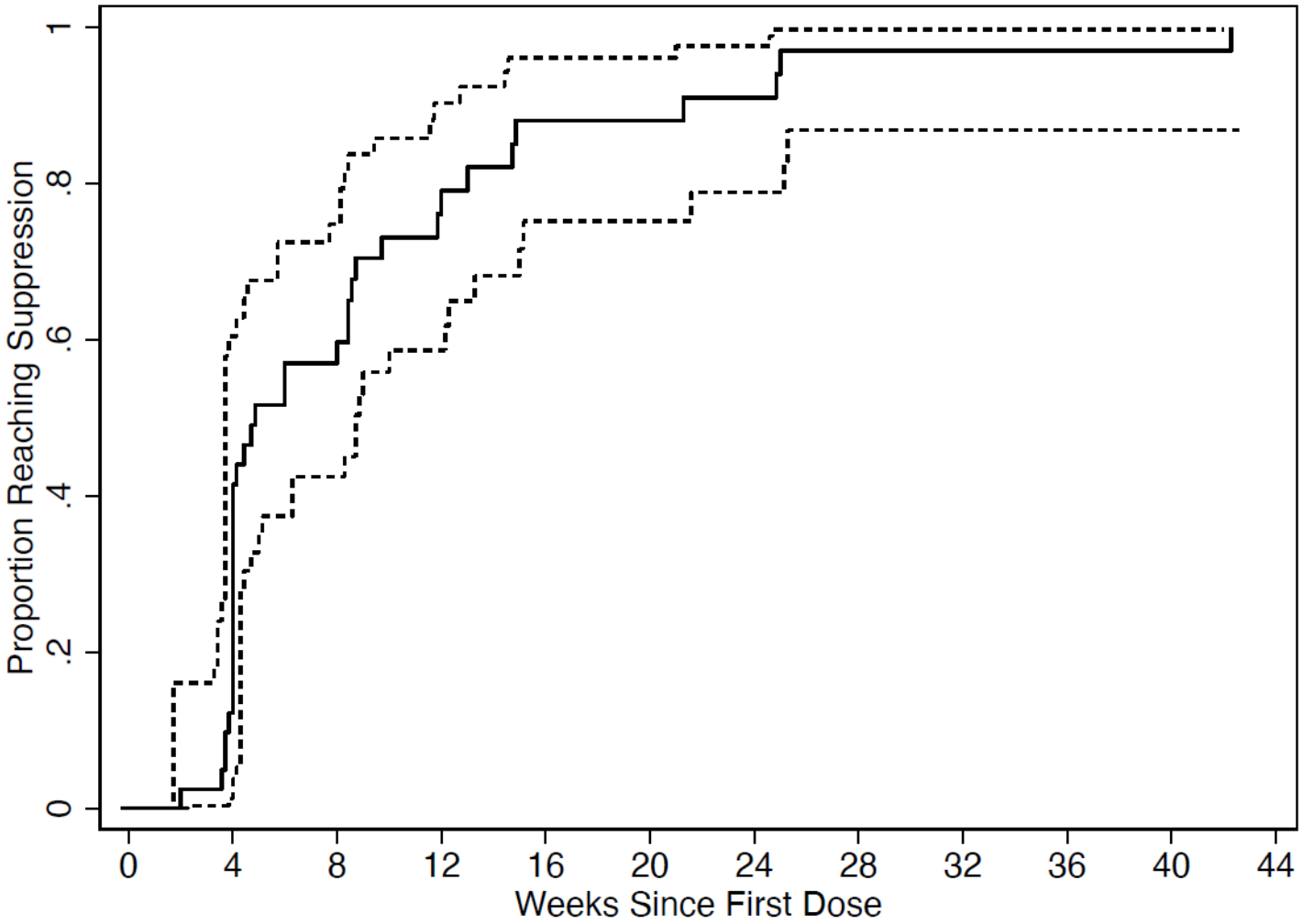
41 baseline unsuppressed

98% suppressed- other 2 two-log drop by 41 days

UCSF IRB approved

MWAETC

Those started without virologic suppression (n=41)



At 12 weeks, 80% of people are suppressed

KM plot projects 100% suppression by 42 weeks (296 days)

Median time to suppression is 34 days, 95% CI (28 to 59 days)

Update from this analysis: 138 patients started on LA ART at Ward 86 – 2 failures now with resistance, 1.4% virologic failure rate

MWAETC

Unveiling the name

- **SPLASH!**
- **Special Programs on Long-Acting Antiretrovirals to Stop HIV**
- **Thanks to members of SPLASH group:** Jon, Janet G and Janet Q, Francis, Anthonia, Mary, John, Liz, Matt H, Matt S, Sarah, Kat, Christy

MWAETC

Acknowledgment

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $3,098,654 with 0% financed with non-governmental sources.

The content in this presentation are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, HRSA, HHS, or the U.S. Government.

AETC AIDS Education & Training Center Program
Mountain West