Demonstration project of administering long-acting ART at Ward 86

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Forum for Collaborative Research:
Expanding Inclusion for Long-Acting HIV Treatment Trials Workshop
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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

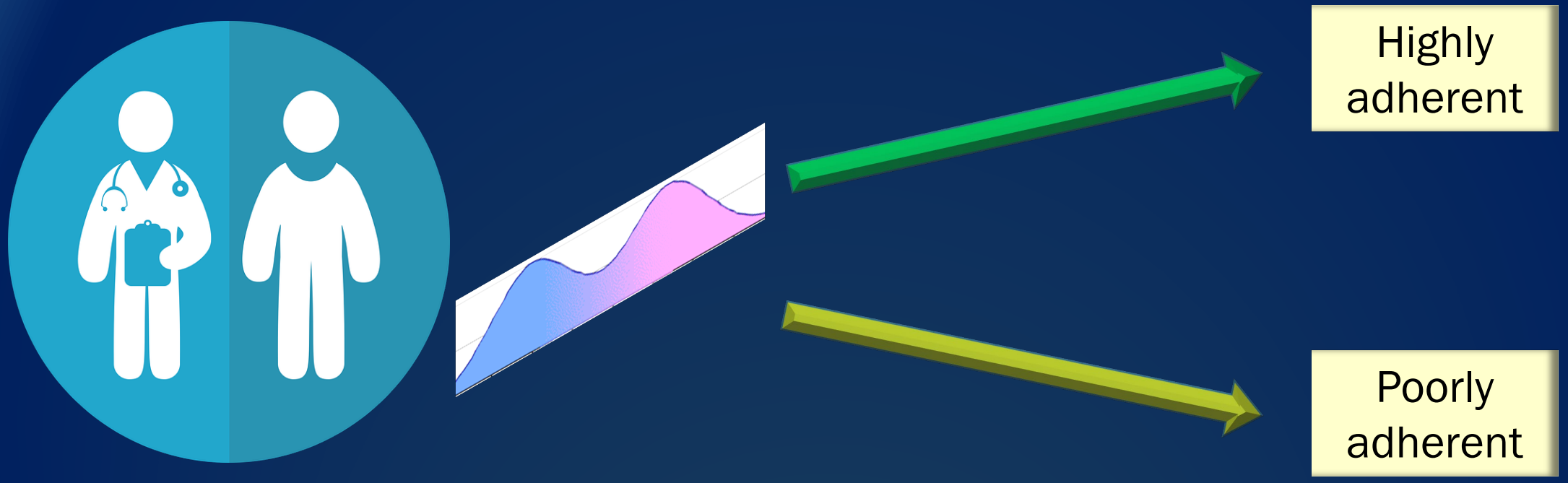
McComsey, G. A., et al. Real-World Adherence to Antiretroviral Therapy Among HIV-1 Patients Across the United States. *Advances in therapy*, *2021*

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

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

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

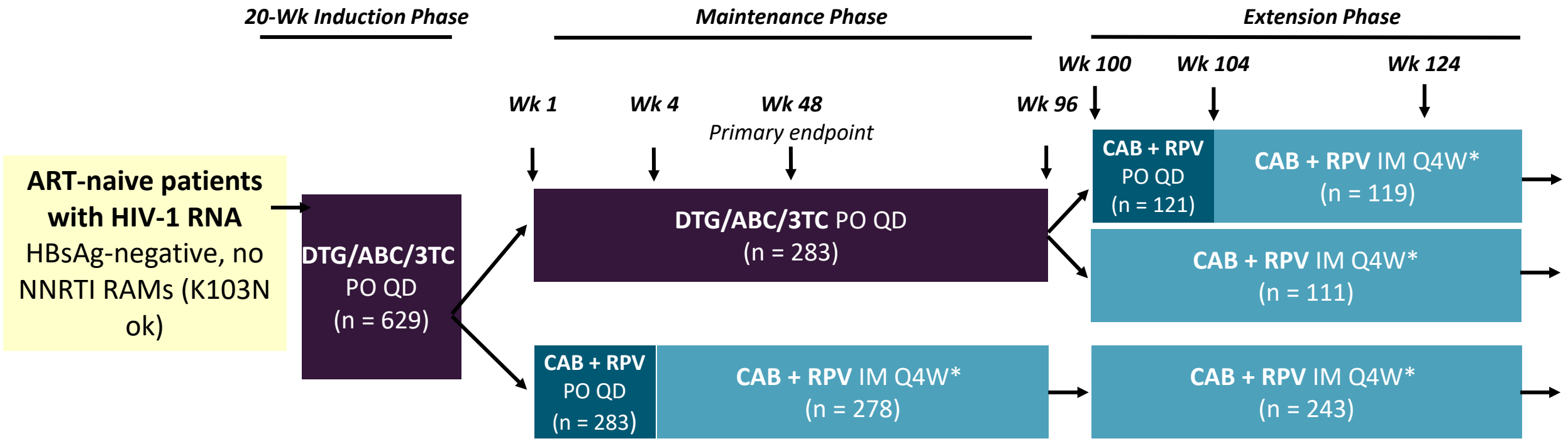
ATLAS 2M

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

FLAIR

Naïve study: “Flair for new things”

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



- 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

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

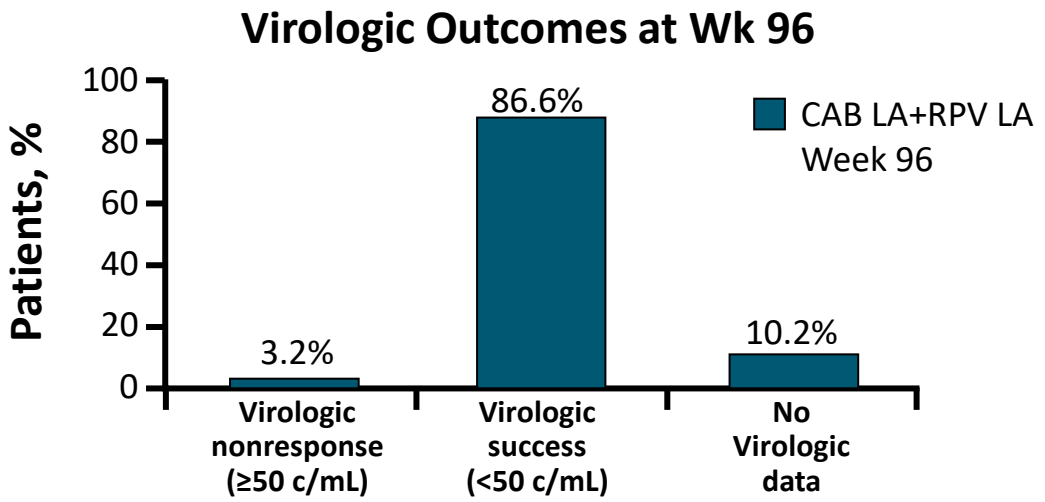
Oral CAB + RPV† (n = 308)

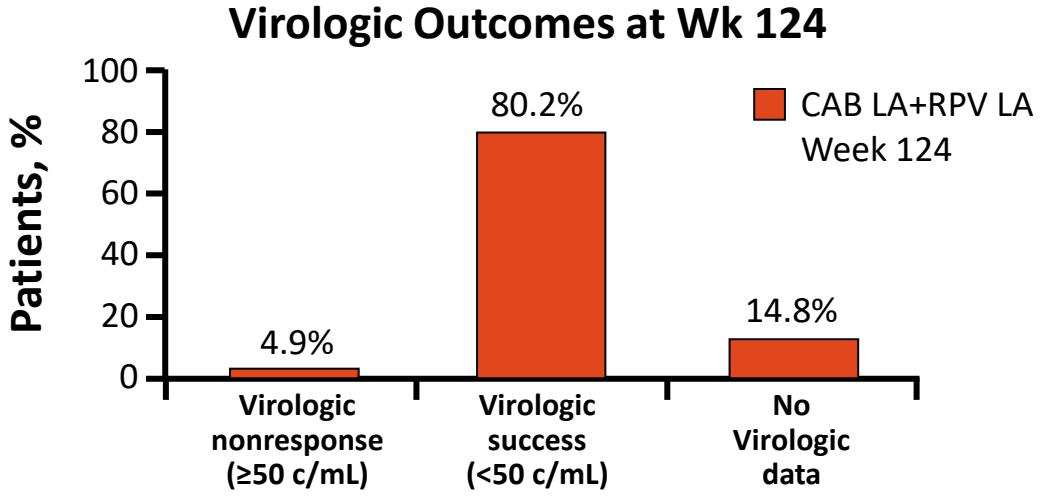
CAB LA 400 mg IM monthly + RPV LA 600 mg IM monthly† (n = 308)

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)

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

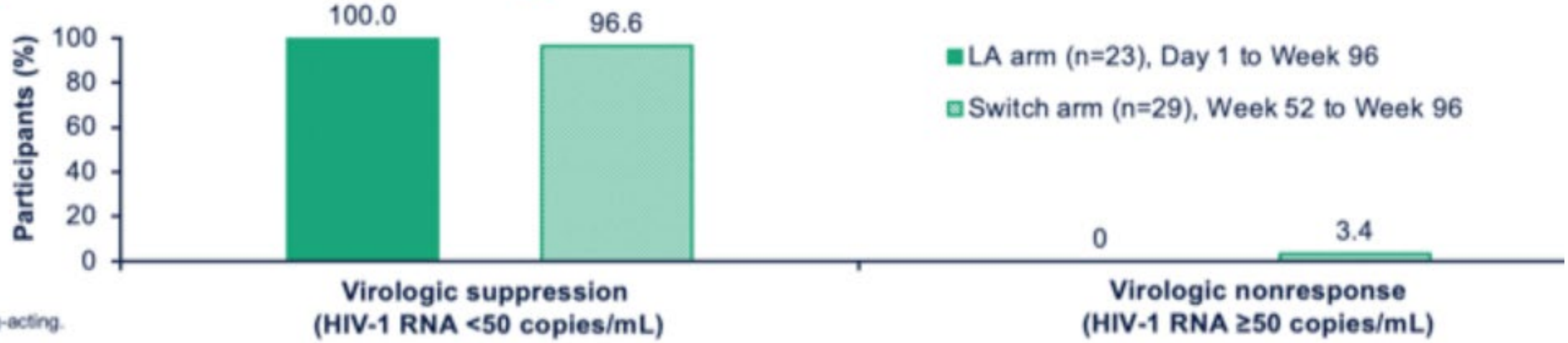
Orkin. IAS 2021. Abstr OAB0302.

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

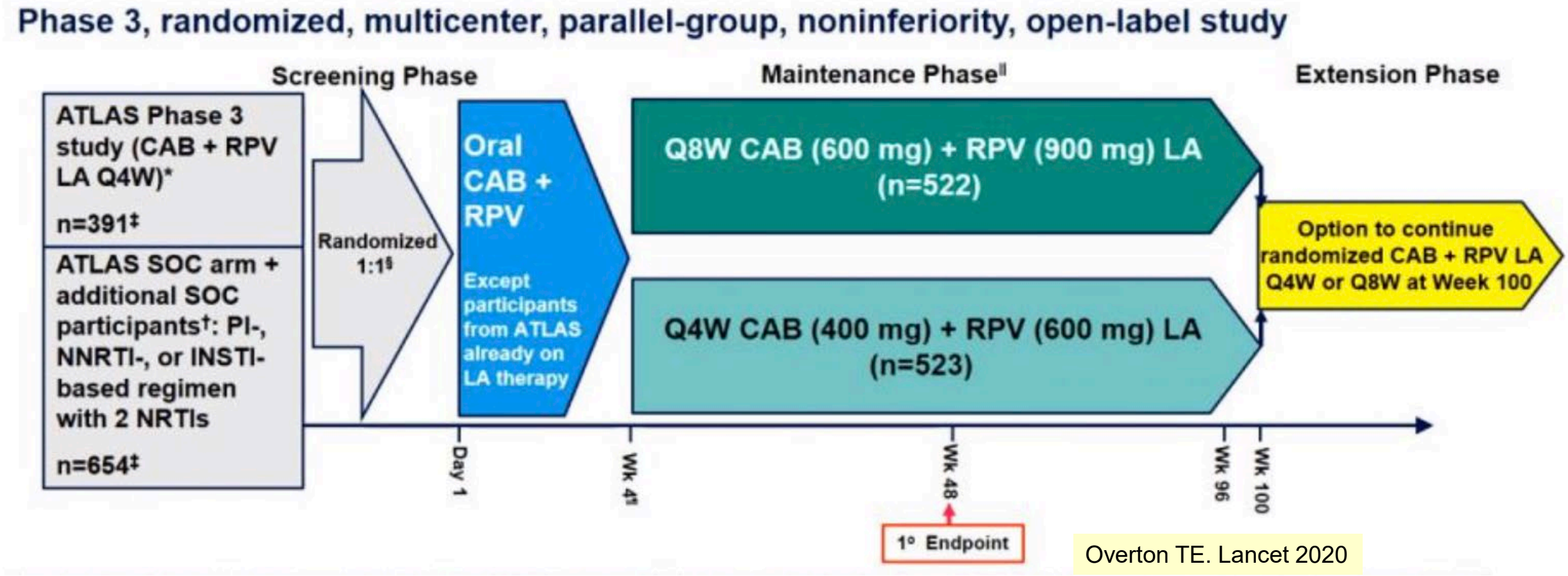


LA, long-acting.

ATLAS 2M: Cabotegravir and Rilpivirine LA every 8 weeks

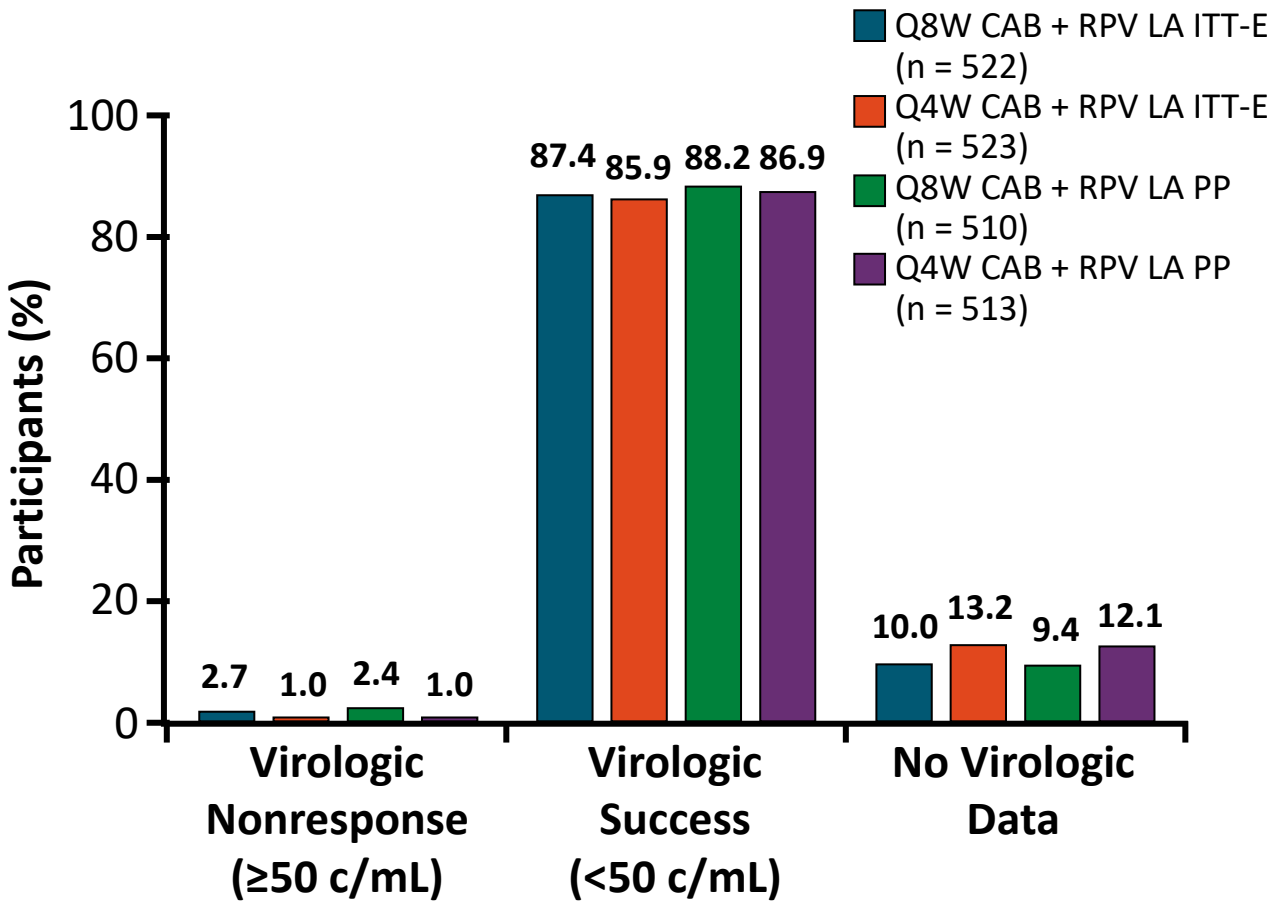
- ATLAS 2M – after q4 weeks, tried q8 weeks vs q4 weeks (ATLAS 2M)

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.

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

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

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.

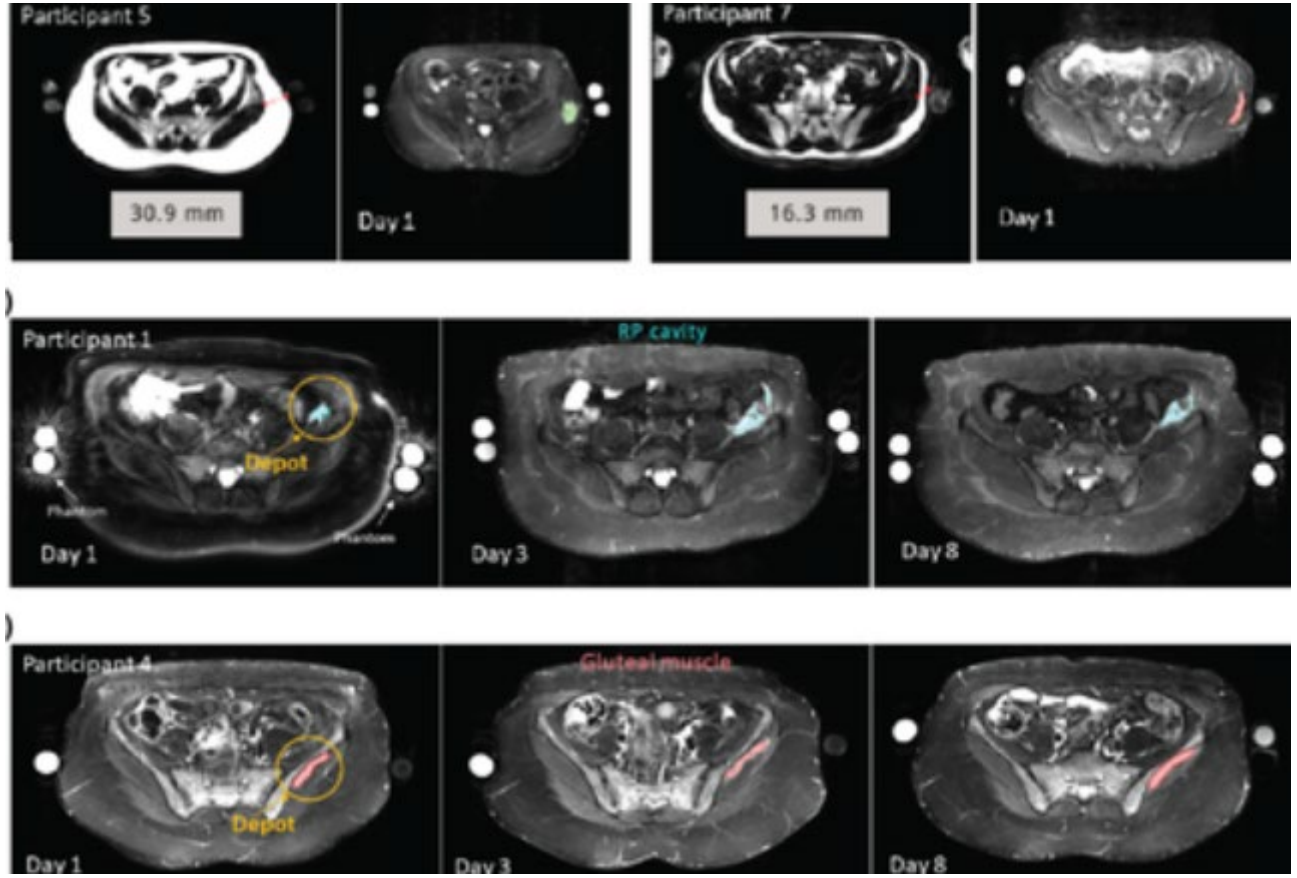
BMI, low rilpivirine troughs, presence of two proviral RPV RAMS, HIV-1 subtype A6/A1 all associated with increased risk of failure (updated ID week)

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

Why study in “difficult to suppress”

TARGET POPULATIONS: Two cohorts to consider (viremic and aviremic)

Patients with persistent or intermittent viremia despite oral ART; patients viremic and out of care

Patients at high-risk for viral rebound (*e.g.* substance users, adolescents, those with mental illness, marginally housed individuals)

REAL WORLD STUDIES

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

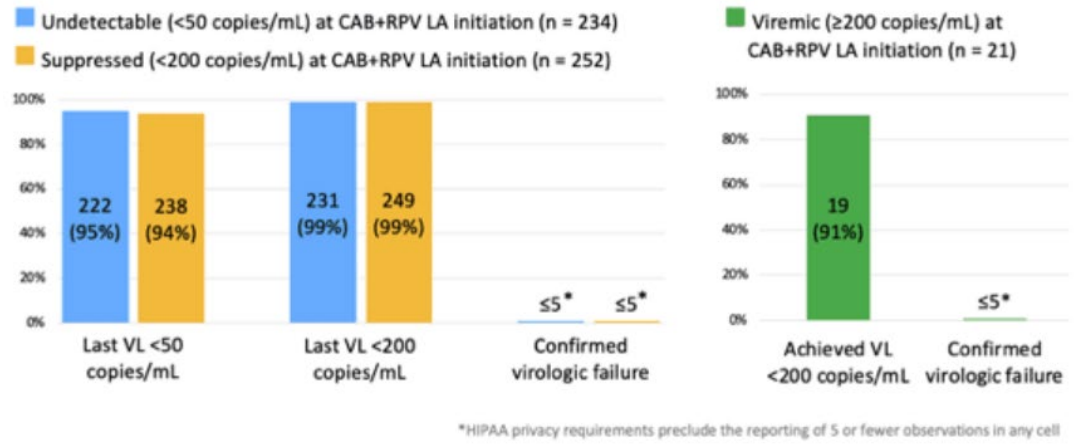
Real-World Use of Long-Acting Cabotegravir + Rilpivirine in the US:

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

THE LANCET
HIV

Equity in access to long-acting injectables in the USA

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

Why do we have to study this in hard to reach 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

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**

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.

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.

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%)

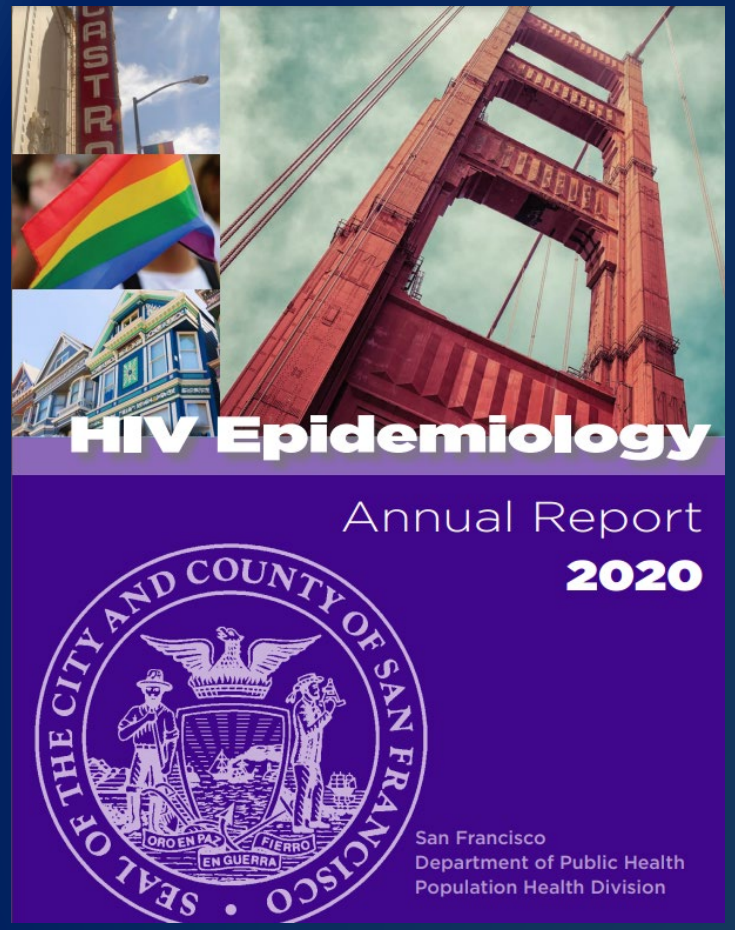
WARD 86 LONG-ACTING INJECTABLE ANTIRETROVIRAL PROTOCOL

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)

GETTING TO ZERO SAN FRANCISCO

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

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

POP-UP program

1. Homeless or Unstably housed
2. Viral load non-suppressed or off ART
3. Poor primary care visit adherence
4. Comes into Urgent Care at Ward 86 regularly

Referred from Ward 86 Urgent Care, LINCS program, reach-out to patients who qualify

Components of POP-UP Clinic

Medical services

-ART: Onsite start DOT 5 days a week & counseling
-Health maintenance car
(vaccines, STI screening,
cancer screening)
-On-site mental health services & buprenorphin
initiation

Five days a week
Welcoming environment
MD every day; RN; Social worker

Life services

-Food resources
ervices (SSI,
, ADAP, case
ment referral)
ncy housing and
t program referrals

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

Implementation of program

- 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)

Clinical Infectious Diseases
MAJOR ARTICLE

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

Demographics of 1st 100 patients at Ward 86

Characteristic (n=100)		Distribution, n (%)	
Age, Median (range)		45 (37-54)	
Gender	**Race/ethnicity**	**Gender**	**Race/ethnicity**
Cis Man	Black	87 (89%)	16 (16%)
Cis Woman	Latino/a	7 (7%)	32 (32%)
Transgender Woman	White	5 (5%)	37 (37%)
Non-binary	Multiracial	1 (1%)	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%)	
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)

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

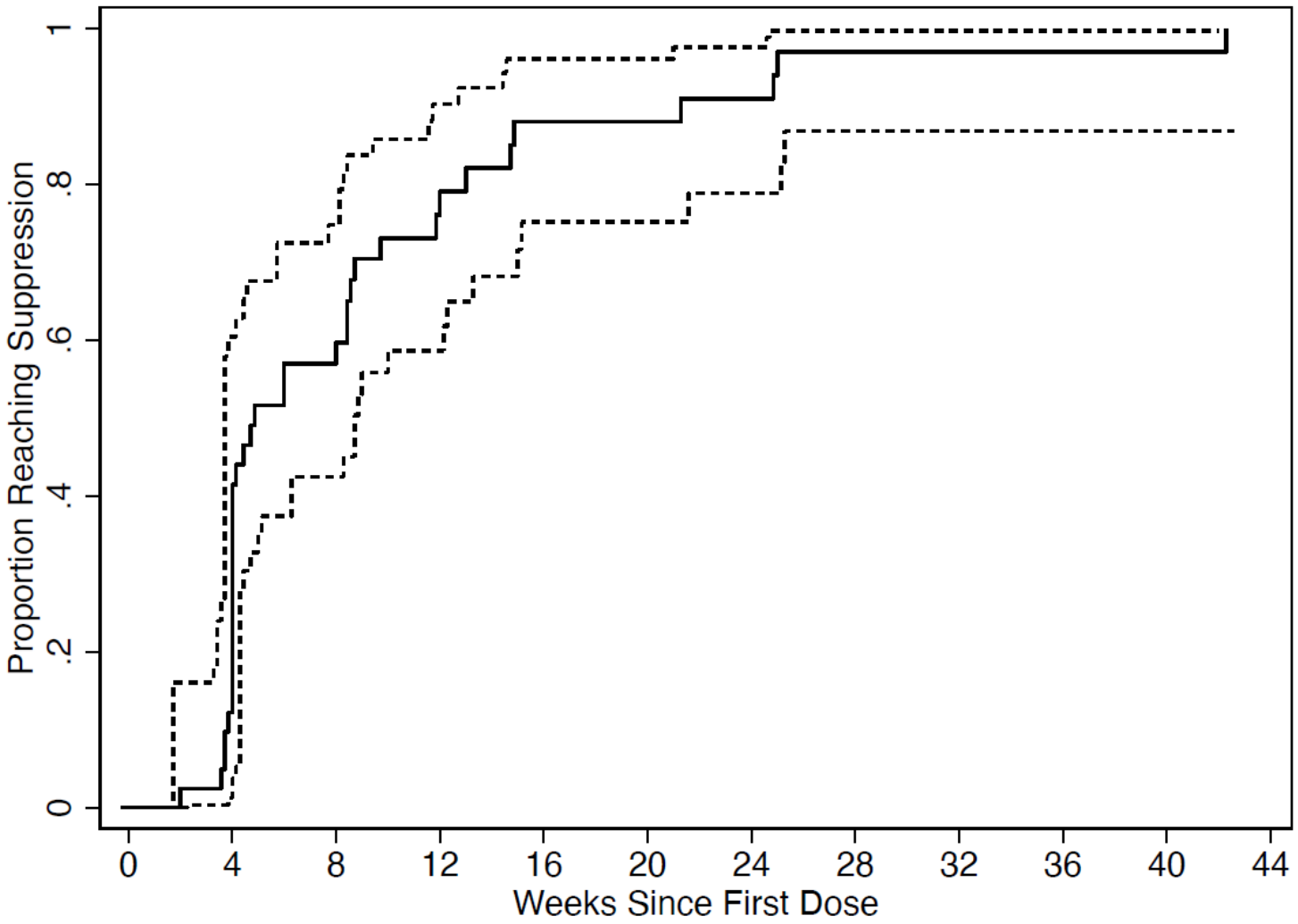
All remain suppressed

41 baseline unsuppressed

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

UCSF IRB approved

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)

Conclusions

- Long-acting ART is here!
- Studied in virologically suppressed patients in the registrational trials
- Clinicians will want to use in those with adherence challenged
- Pilot program at Ward 86 with early success to date – 122 patients enrolled, 100 patients with results