1401 Long-Acting ART in an Adherence Challenged Population Including those with Viremia Results in High Rates of Virologic Suppression

Implementation Strategies for HIV Treatment and Prevention Oral Abstract Session

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Adherence 2023 · June 11-13 · Puerto Rico

Long-acting ARVs

CLINICAL TRIAL DATA ON LONG-ACTING CAB/RPV

LONG-ACTING CAB/RPV AT WARD 86 HIV CLINIC

PRACTICAL/CLINICAL CONSIDERATIONS OF LA CAB/RPV

STUDY OF LONG-ACTING LENACAPAVIR/ CABOTEGRAVIR`

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

FLAIR

- CAB/RPV LA in treatment naïve participants (K103N mutation allowed); First put on DTG/ABC/3TC for 20 weeks then switched to LA ART with virologic suppression; 80% VS 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; 97% VS rate 6 months

ATLAS 2M

- CAB/RPV LA in treatment experienced participants every 8 weeks (higher dose 600mg/900mg) after VS x ≥ 6 months; 97% VS at 152 weeks

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

Summary of resistance mutations across FLAIR/ATLAS/ATLAS 2M (1.4% virologic failure rate)

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

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

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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 "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

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

MMWR

MORBIDITY AND MORTALITY WEEKLY REPORT

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

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%)

METHODS

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

DON'T USE IF HAVE RPV MUTATIONS THAT CAME OUT IN ECHO/THRIVE TRIALS (RPV vs EFV)

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

DON'T USE IF HAVE CAB MUTATIONS THAT CAME OUT IN FINAL ANALYSIS OF HPTN 083 TRIAL/OLE BREAKTHROUGHS

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**

Markzinke M et al. Extended Analysis of HIV Infection in Cisgender Men and Transgender Women Who Have Sex with Men Receiving Injectable Cabotegravir for HIV Prevention: HPTN 083. AAC April 2023

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
- 194 patients have been started on long-acting ART: rigorous protocol – will present first 133 here

Long Acting Injectables - Learning As We Go: An Implementation Science Agenda

Katerina Christopoulos (University of California San Francisco, San Francisco, CA, USA)

9:50 AM - 11:05 AM

TUESDAY, JUNE 13, 2023

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)

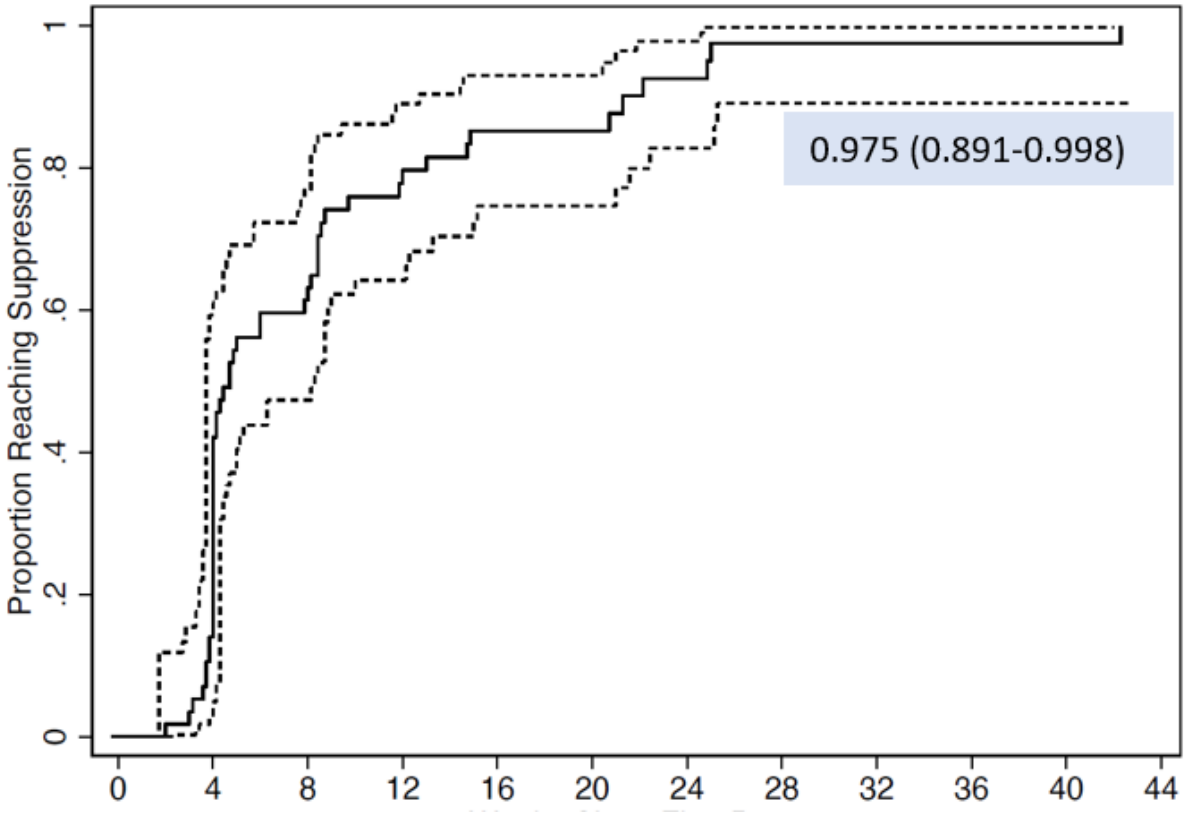
* Note: ADAP is AIDS Drug Assistance Program; Baseline CD4 defined as the CD4 count closest to and including date of first injection. Median time from CD4 count to first injection was 70 (range 0 to 882) days

- 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)

Gandhi Annals of Internal Medicine 2023

RESULTS (continued)

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



Neither patient who didn't have virologic suppression could take oral ART

- Among viremic PWH, at median of 33 days, 55 suppressed, 2 had early virologic failure.
- 97.5% (89.1 to 99.9%) expected to achieve virologic suppression by median 26 weeks
- Current cohort virologic failure rate 1.5% similar to that across clinical trials (1.4%) by 48 weeks (68% by 24 weeks)
- Two failures < 24 weeks, both had minor mutations so protocol tightened; 3rd didn't suppress <100 (182) so added LEN

Virologic failure #1: Started with V179I mutations, didn't show 2 $\log_{10}$ reduction by 1st visit (baseline viral load 214,540 → 39,293 copies/mL); Developed Y181C, L100I

Virologic failure #2: Started with T97A mutation, didn't show 2 $\log_{10}$ reduction by 1st (baseline viral load 137,134 → 4,371 copies/mL); Developed R263K, E138K mutations

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STUDY OF LONG-ACTING LENACAPAVIR/ CABOTEGRAVIR`

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)

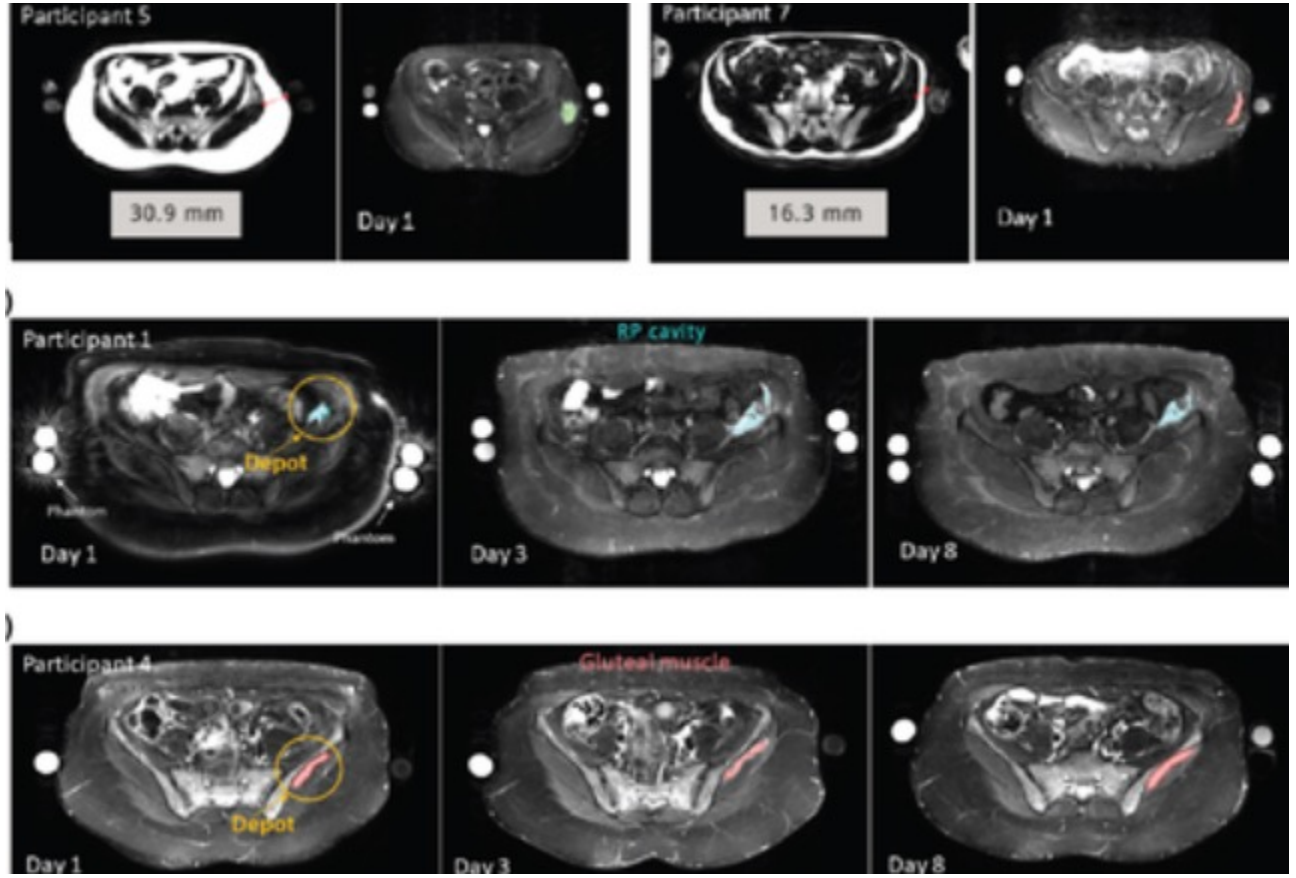
IDWeek

BMI and CAB

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

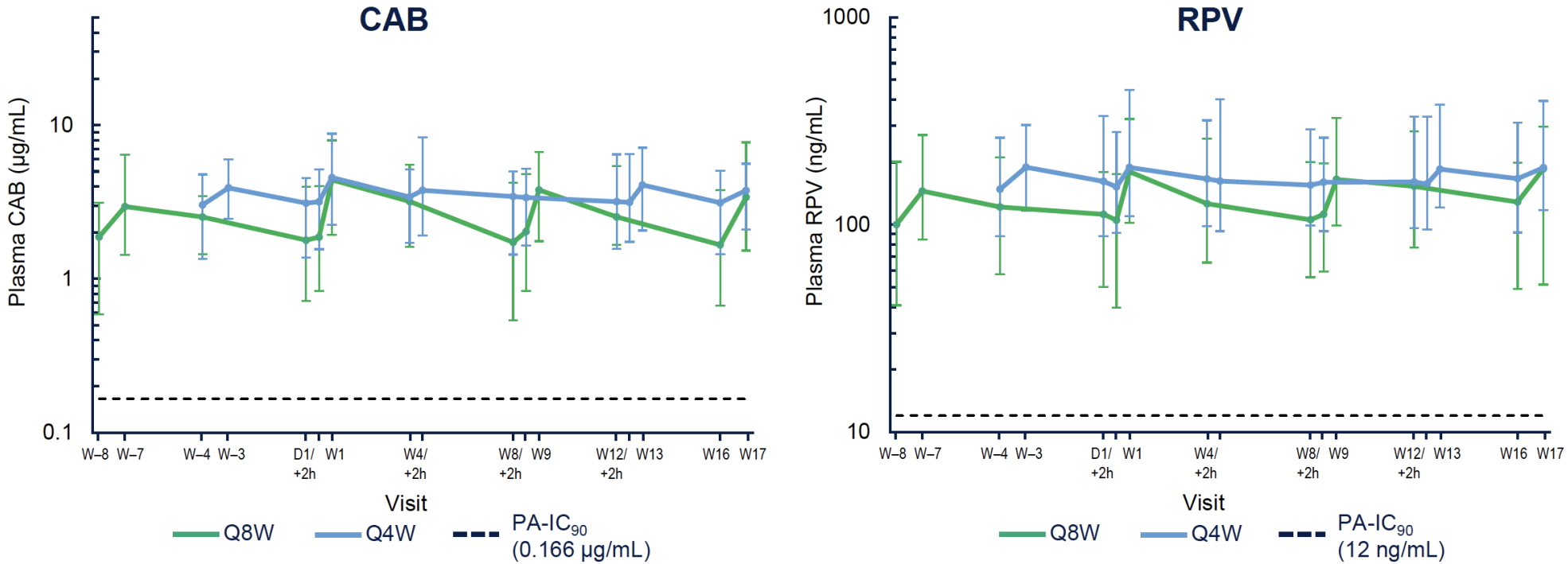
Elliot. EACS 2021. Abstr BPD1/8.

- 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

Figure 2. Median (5th, 95th Percentiles) Plasma CAB and RPV Concentration–Time Plots



CAB, cabotegravir; Cτ, concentration at dosing interval; D, day; Q4W, every 4 weeks; Q8W, every 8 weeks; $PA\text{-}IC_{90}$, protein-adjusted 90% inhibitory concentration; PO, oral therapy; RPV, rilpivirine; W, week.

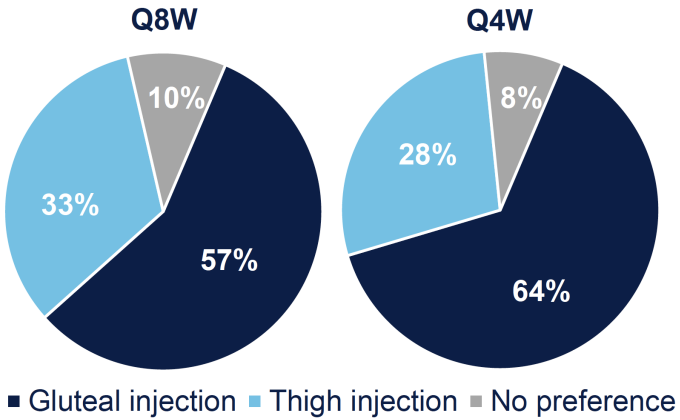
Poster Session-H1 LAI CAB/RPV: WHERE ARE WE NOW AND WHERE ARE WE GOING?

2:30 PM - 4:00 PM

519 LB

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

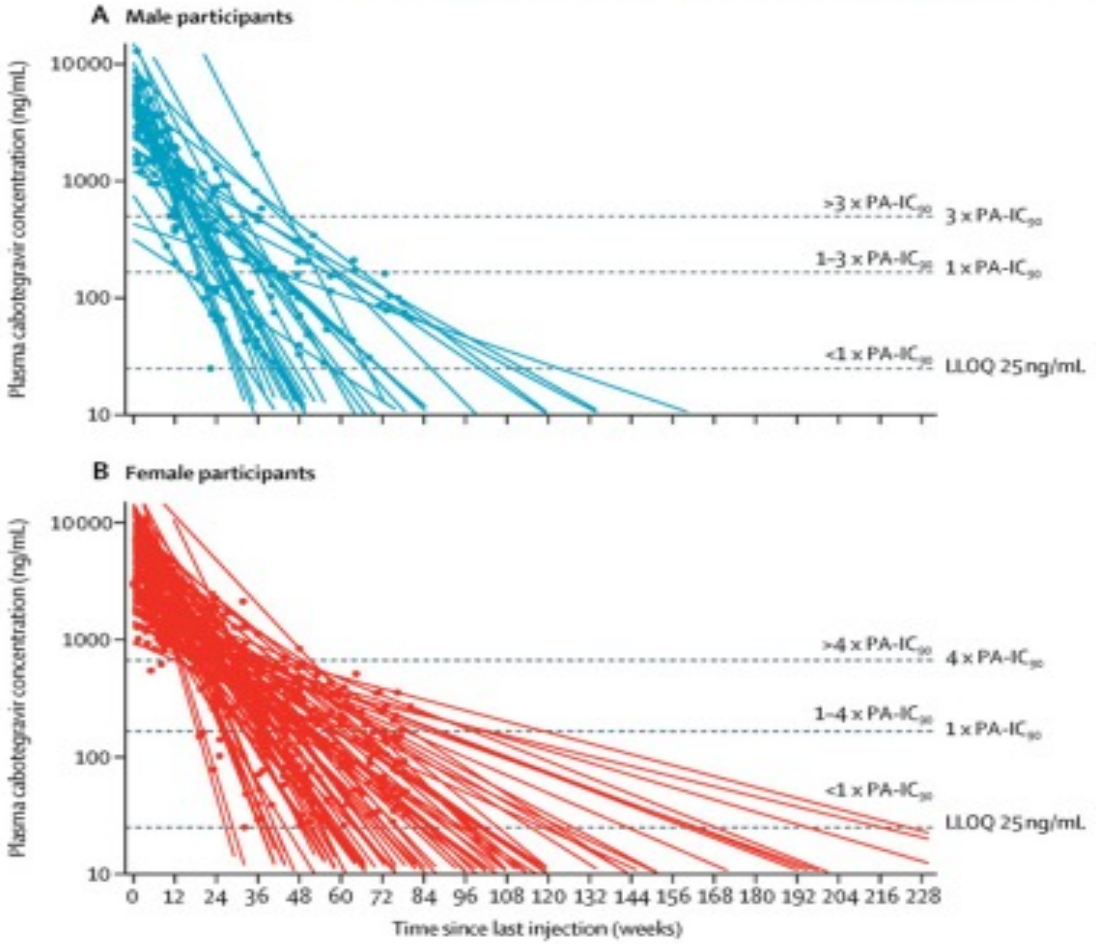
Franco Felizarta, Ronald D'Amico, Kehui Wang, Herta Crauwels, Mar Masiá, Miguel Garcia Deltoro, Olaf Degen, Jonathan Angel, Chiu-Bin Hsiao, Vasiliki Chounta, Kelong Han, Conn Harrington, Kelly Rimler, William R. Spreen, Susan Ford



*Return to gluteal injection phase.

- **Bottom line**: Can use thigh injections for cabotegravir and rilpivirine (same PK) but hurt more

CAB LA TAIL IS LONGER IN WOMEN THAN MEN



- Median time to undetectable cabotegravir is longer in women at 66.3 weeks (range 17.7 to 182) when compared to 42.7 weeks (range 20.4 to 134) in men

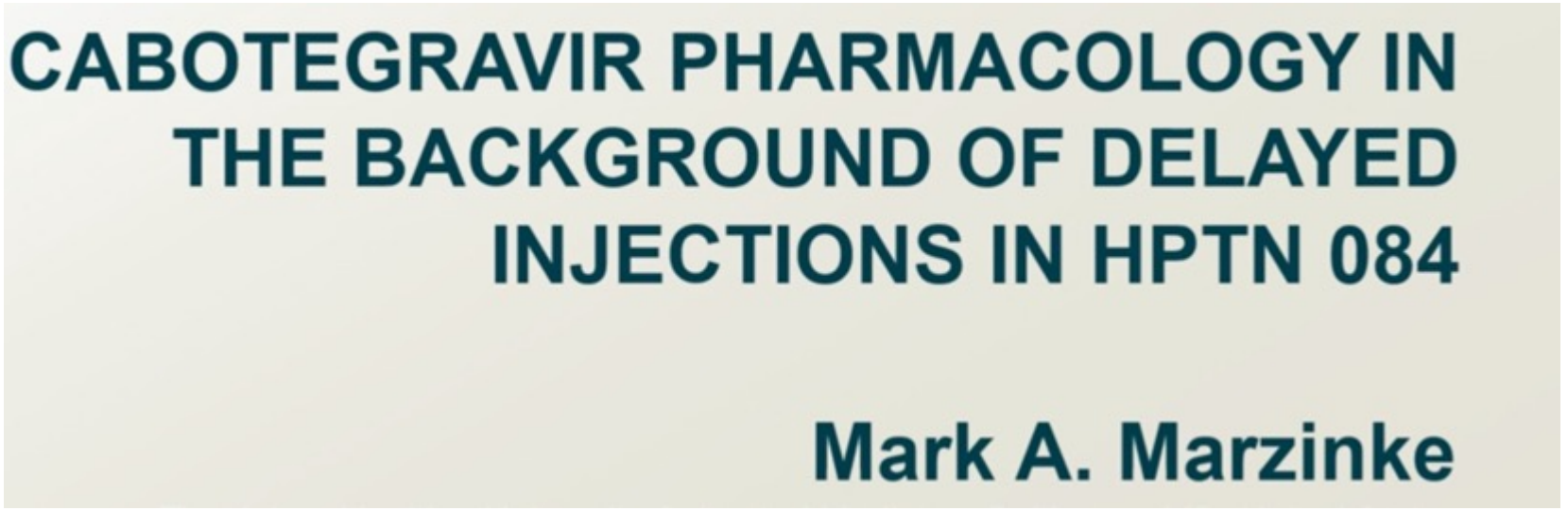
HPTN
HIV Prevention Trials Network

HPTN 077

Landovitz R. Lancet HIV. June 2020

CROI 2023 OA-8: CAB PK in delayed PrEP injections

- In HPTN084, delayed CAB-LA Q8W injections were common (12%).
- CAB concentrations were above target (PA-IC90) in **98%, 95% and 90%** of persons receiving injections **4-6, 6-8**, and **8-10** weeks late, respectively.
- Suggests PK forgiveness perhaps in women



HPTN 084
Long-acting Injectable For the Epidemic

- **Bottom line**: Lot of PK variability and low RPV levels

pharmaceutics

MDPI

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,*]

Long-acting ARVs

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Case

57 yo man with HIV dx'd 1998, CD4 nadir <50, thrush in past

ART history

- AZT monotherapy x 6 months then dual NRTI therapy
- In mid '90's, ddI/d4T/indinavir/ritonavir as well as nelfinavir and saquinavir/RTV
- In 2001, TDF/FTC/EFV for many years with drug holidays but then viremia, NNRTI mutations
- Switched to ATV/r + RAL + TDF/FTC and eventually DRV/cobi + DTG + TAF/FTC. Suppressed but pill fatigue precludes ongoing use

Cumulative mutation history on genotypes:

- NRTI: K67N, K219Q, T215I, M184V,
- PI: M46L
- NNRTI: G190S, V106I, F227L, V179T
- INSTI: none
- Not CCR5 tropic (10/2019)

Case continued

- Despite adherence counseling, viral load now >1.5 million, CD4 142 cells/mm^3
- Patient cannot take oral ART anymore
- ……
- Started patient on lenacapavir 600mg (300mg oral dose x 2) on day 0 and 1 with lenacapavir 927mg sq on day 0
- Added cabotegravir 600mg IM that day and 450mg every month
- Viral load dropped 2-log HIV RNA within 1 week and undetectable by 2 months after starting this regimen

- **Bottom line**: STUDY PROPOSED IN THE ACTG OF LONG-ACTING LEN + LONG-ACTING CABOTEGRAVIR IN PARTICIPANTS WITH NNRTI RESISTANCE (~10% WORLDWIDE)

stop aids. make the promise

Thank you to European HIV Clinical Forum 2023, Division of HIV, ID and Global Medicine, the HIV movement, and Ward 86!