30th CROI 2023

Been There, Did That - Research Reflections from CROI 2023

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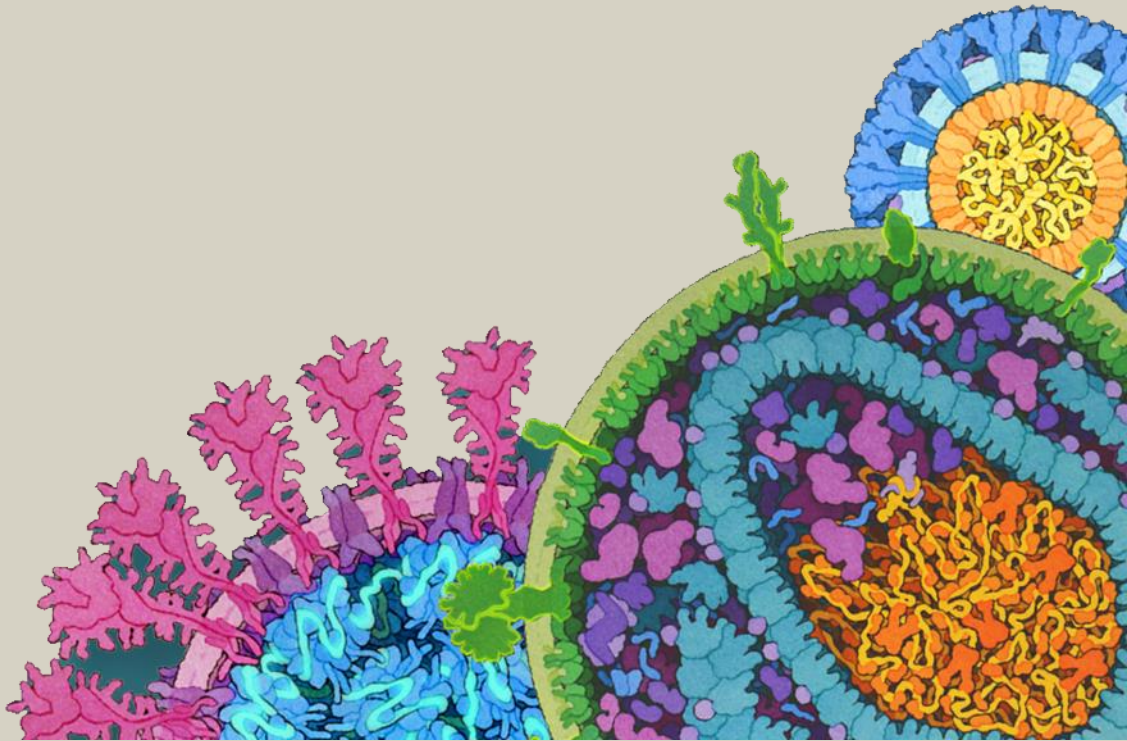
March 23, 2023

Disclosure:



5 major topics

UPDATES IN TREATMENT IN NAÏVE OR SUPPRESSED PATIENTS

UPDATES IN TREATMENT IN PATIENT WITH RESISTANCE

NEW STRATEGIES IN LONG-ACTING ART FOR EXPERIENCED

CO-MORBIDITIES AND OIs

PREVENTION

UPDATES IN TREATMENT IN NAÏVE PATIENTS

Study	Population	Comparator	Outcome	Resistance
BICTEGRAVIR				
1489	Naïve	DTG/ABC/3TC	Non-inferior	0
1490	Naïve	DTG+FTC/TAF	Non-inferior	0
1844	Suppressed		on-inferior	0
1878	Suppressed		on-inferior	0 to INSTI but 1 L74V in PI arm
1961 (women)	Suppressed		on-inferior	0 to INSTI but 1 M184V in ELV/cobi
SINGLE	Naïve		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

Potency and high genetic barrier to resistance of both dolutegravir and bictegravir as first-line integrase-inhibitor regimens undisputed so will focus on LA ART & side effects

LONG ACTING ART IN NAÏVE OR SUPPRESSED

At CROI, added 4th trial to look at LA CAB/RPV in treatment naïve (SOLAR)

Oral Abstract Session-12 ANTIVIRAL STRATEGIES FOR TREATMENT AND PREVENTIONS
Ballroom 1 (Level 5) **10:00 AM - 12:00 PM**

Wednesday

191
10:05

SOLAR 12-MONTH RESULTS: RANDOMIZED SWITCH TRIAL OF CAB+RPV LA VS ORAL B/FTC/TAF

Moti N. Ramgopal, Antonella Castagna, Charles Cazanave, Vicens Diaz-Brito, Robin Dretler, Shinichi Oka, Olayemi Osiyemi, Kenneth Sutton, Denise Sutherland-Phillips, Alessandro Berni, Christine Latham, Feifan Zhang, Ronald D'Amico, Kimberly Smith, Jean Van Wyk

- SOLAR Phase 3b, randomized, open-label, multicenter, noninferiority (study assessing switching virologically suppressed adults to CAB+RPV LA every 8 weeks vs continuing BIC/FTC/TAF)
- Of 670 participants, 447 switched to LA ART and 223 continued B/FTC/TAF
- Trial out to 12 months

FLAIR

- CAB/RPV LA in treatment naïve participants q4 weeks suppressed x 20 weeks on DTG/ABC/3TC

ATLAS

- CAB/RPV LA in treatment experienced participants q4 weeks suppressed on regimen ≥ 6 months

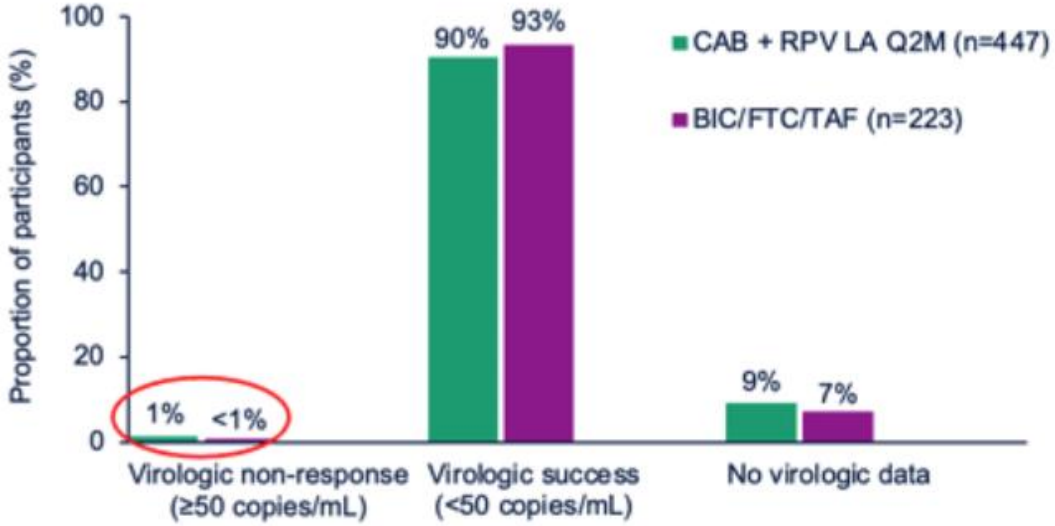
ATLAS 2M

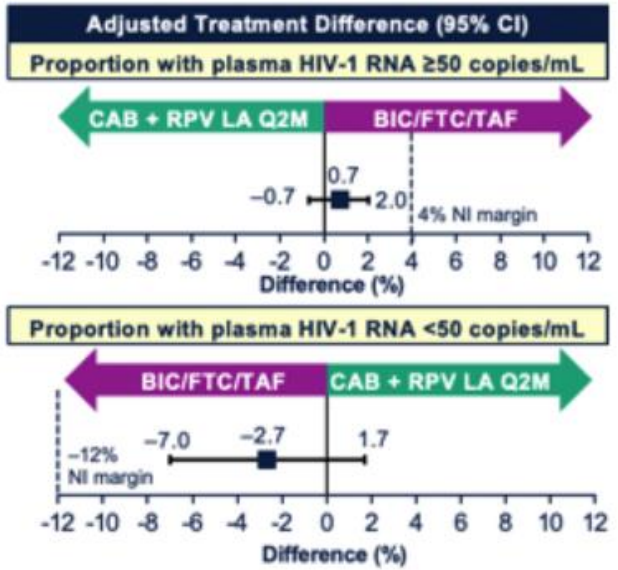
- CAB/RPV LA (higher dose) in treatment experienced participants q8 weeks on suppressed participants

Psychosocial Challenges With Daily Oral BIC/FTC/TAF at Baseline

- At baseline, 47% (n=315/670) of participants who were virologically suppressed on BIC/FTC/TAF "always/often" reported at least one of the following psychosocial challenges with daily oral therapy:
  - *"Worried about people unintentionally discovering their HIV status"*
  - *"Worried about forgetting to take their HIV medication"*
  - *"Felt that taking their HIV medication was an uncomfortable reminder of their HIV status"*

Virologic Outcomes at Month 12 (mITT-E Population)





SOLAR trial

- Many patients expressed desire for long-acting
- 2 patients out of 447 had on-treatment mutations

Bottom line: Participants with higher treatment satisfaction & same outcomes on LA CAB/RPV than BIC/TAF/FTC

LENACAPAVIR FOR TREATMENT NAÏVE POPULATION

THE LANCET
HIV

Lenacapavir administered every 26 weeks or daily in combination with oral daily antiretroviral therapy for initial treatment of HIV: a randomised, open-label, active-controlled, phase 2 trial

Samir K Gupta, Mezgebe Berhe, Gordon Crofoot, Paul Benson, Moti Ramgopal, James Sims, Cheryl McDonald, Peter Ruane, William E Sanchez,

Wednesday

Poster Session-H2 ANTIRETROVIRAL THERAPY: PROSPECTIVE CLINICAL TRIALS
2:30 PM - 4:00 PM

522 **LONG-ACTING LENACAPAVIR IN A COMBINATION REGIMEN FOR TREATMENT-NAIVE PWH: WEEK 80**

Debbie Hagins, Ellen Koenig, Rachel Safran, Lizette Santiago, Michael Wohlfeiler, Chiu-Bin Hsiao, Shan-Yu Liu, Laurie A. Vanderveen, Hadas Dvory-Sobol, Martin S. Rhee, Jared M. Baeten, Samir Gupta

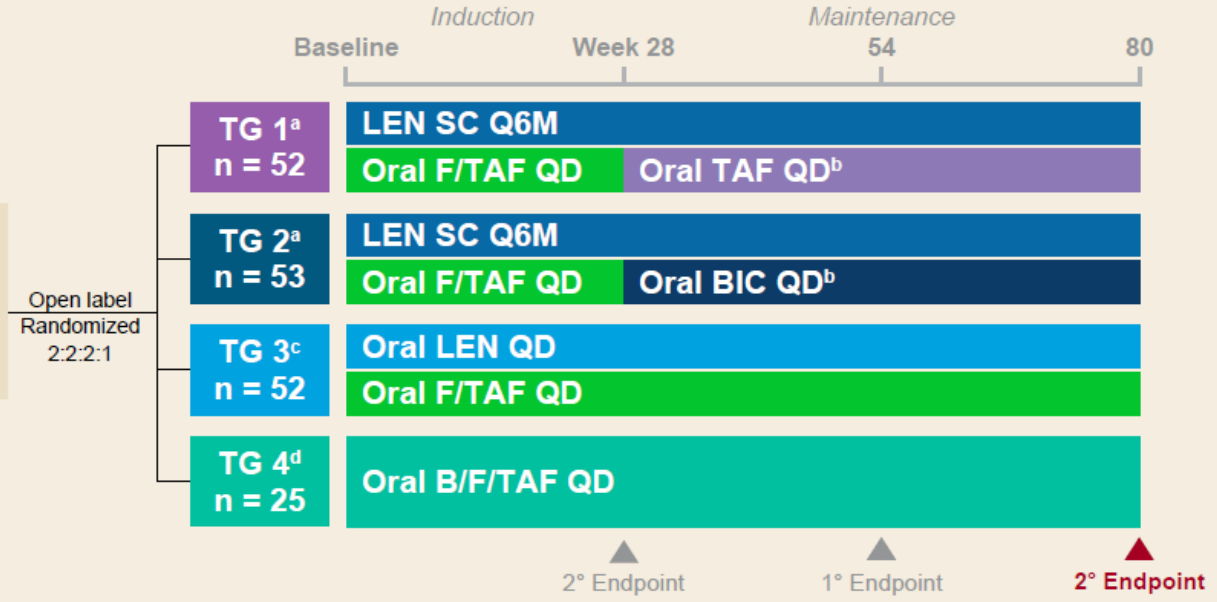
Study Design

Calibrate

Treatment Naïve
N = 182

Key eligibility criteria:
- HIV-1 RNA ≥ 200 copies/mL
- CD4+ cell count ≥ 200 cells/μL

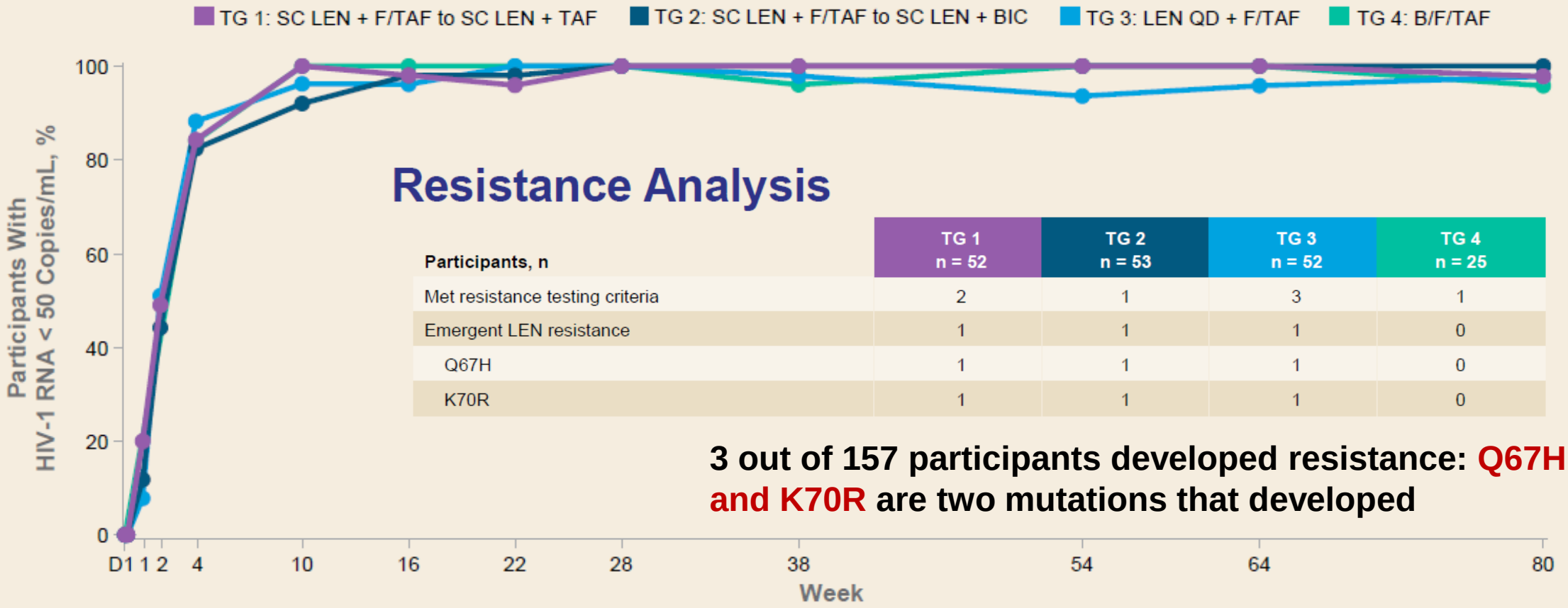
Open label
Randomized
2:2:2:1



[a]LEN PO lead-in (600 mg on Days 1 and 2, 300 mg on Day 8) followed by LEN 927 mg SC on Day 15; F/TAF 200/25 mg; [b]Participants in treatment groups (TGs) 1 and 2 needed to have HIV-1 RNA < 50 copies/mL at Weeks 16 and 22 to initiate TAF 25 mg or BIC 75 mg at Week 28; participants with HIV-1 RNA ≥ 50 copies/mL discontinued study at Week 28; 3 participants (2 in TG 1 and 1 in TG 2) discontinued due to having HIV-1 RNA ≥ 50 copies/mL prior to Week 28; [c]LEN 600 mg on Days 1 and 2, followed by LEN 50 mg from Day 3; F/TAF 200/25 mg; [d]B/F/TAF 50/200/25 mg

Participants With HIV-1 RNA < 50 Copies/mL by Visit

Missing = Excluded (on Treatment)



Resistance Analysis

Participants, n	TG 1 n = 52	TG 2 n = 53	TG 3 n = 52	TG 4 n = 25
Met resistance testing criteria	2	1	3	1
Emergent LEN resistance	1	1	1	0
Q67H	1	1	1	0
K70R	1	1	1	0

3 out of 157 participants developed resistance: Q67H and K70R are two mutations that developed

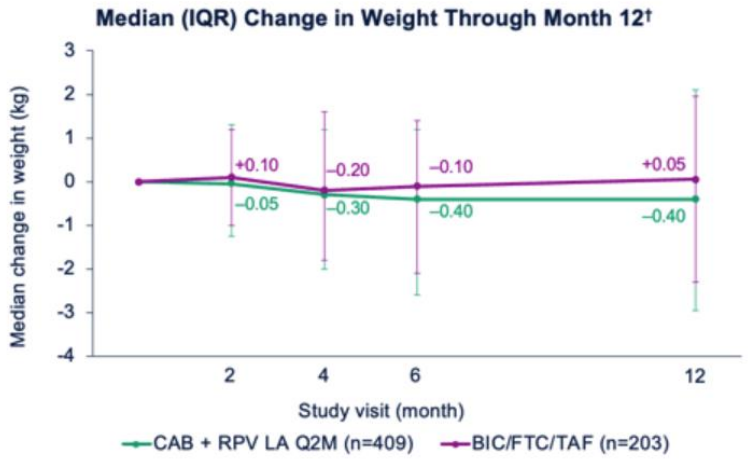
	TG 1 n = 46	TG 2 n = 40	TG 3 n = 46	TG 4 n = 25
Participants with HIV-1 RNA < 50 copies/mL, % (n)	98 (45)	100 (40)	98 (45)	96 (23)

Bottom line: Too small of a study for LEN to get indication in treatment naïve patients so only in resistant HIV

WEIGHT and METABOLIC EFFECTS

Does switching from BIC/TAF/FTC to CAB/RPV help weight (SOLAR trial) and do INSTIs increase MI risk?

Change in Weight Through Month 12 by Treatment Regimen*



- At Month 12, median (IQR) change in weight in the CAB + RPV LA group was -0.40 (-2.95, +2.10) kg and +0.05 (-2.30, +1.95) kg in the BIC/FTC/TAF group

Didn't seem to help to switch from BIC/TAF/FTC to CAB/RPV in SOLAR in terms of weight gain, metabolic syndrome, insulin resistance

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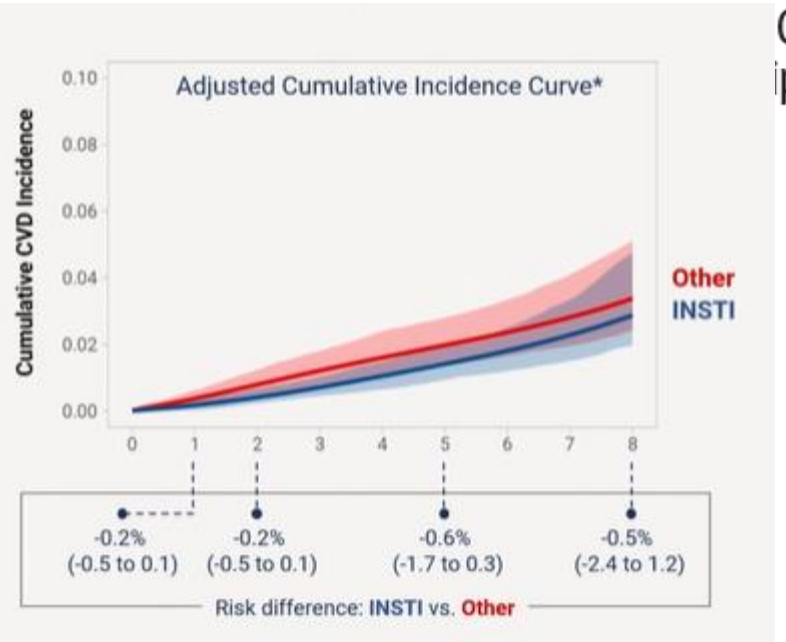
11:08

IMPACT OF INTEGRASE INHIBITORS ON CARDIOVASCULAR EVENTS IN PERSONS STARTING ART

Bernard Surial, David Haerry, Mar… Huldrych F. Günth… Calmy, …p Tarr,



29,340-person study of adults starting INSTI in 17 European and Australian cohorts (RESPOND) linked INSTI use to a higher risk of cardiovascular events in the first 24 months of INSTI therapy but not after that [Lancet 2022, could have prior non-INSTI experience). The new Swiss study in naïve patients did not find increased risk x 24 months (patients naïve)

Bottom line on weight

- ***EFV to DTG:*** Efavirenz seems to be "anorectic" so starting DTG after EFV (IeDEA cohort) associated with more weight gain than after NVP
- **TAF to TDF**: Switching from TAF to TDF associated with more weight loss (both with DTG) in S. Africa women
- **DTG/3TC**: Small single site (Amsterdam) study but improved cholesterol & lean trunk mass to drop TAF

Themed Discussion-11 WEIGHT GAIN: DOES WHAT GOES UP ALWAYS COME DOWN?

Ballroom 1 (Level 5) 1:30 PM - 2:30 PM

• Wednesday

671 *1:35*
WEIGHT LOSS AND METABOLIC CHANGES AFTER SWITCHING FROM TAF/FTC/DTG TO TDF/3TC/DTG
Bronwyn E. Bosch, Godspower Akpomiemie, Nomathemba Chandiwana, Simiso Sokhela, Andrew Hill, Kaitlyn McCann, Ambar Qavi, Manya Mirchandani, Francois Venter

672 *1:40*
FAVORABLE METABOLIC OUTCOMES 48 WEEKS AFTER SWITCH TO DTG/3TC
Sophie Degroote, Sophie Vanherrewege, Els Tobback, Els Caluwe, Lara Vincke, Wim Trypsteen, Mareva Delporte, Evy Blomme, Linos Vandekerckhove, Marie-Angélique De Scheerder
Research Group: the ATHENA national observational cohort

674 *1:45*
WEIGHT GAIN AMONG PARTICIPANTS SWITCHING TO A DOLUTEGRAVIR-BASED HIV REGIMEN IN KENYA
Kassem Bourgi, Susan Ofner, Beverly Musick, Kara Wools-Kaloustian, Lameck Diero, Constantin Yiannoutsos, Samir Gupta

Clinical Infectious Diseases

BRIEF REPORT

Weight and Metabolic Changes After Switching From Tenofovir Alafenamide (TAF)/Emtricitabine (FTC) +Dolutegravir (DTG), Tenofovir Disoproxil Fumarate (TDF)/FTC + DTG, and TDF/FTC/Efavirenz (EFV) to TDF/Lamivudine (3TC)/DTG

Bottom line: TAF associated with more weight gain than TDF and Efavirenz suppressed weight

TREATMENT EXPERIENCED WITH NRTI RESISTANCE

NRTI resistance- Bottom line can use DTG or DRV/r if have NRTI resistance in background

Name of study	Type of study, n	Comparison	Outcome	Emergent resistance
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; none 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 well even if resistance predicted)	9 patients in DTG arm failed with resistance; none in DRV/r arm
VISEND	Open-label study randomized PWH failing NNRTI-based therapy, n=1201	DTG or boosted PI regimens	>80% virologic suppression (<50) on DTG regimens	None reported (abstract CROI 2022)
2SD	Randomized study 2nd line therapy, Kenya, n=795	PI/r + 2 NRTIs randomized switch to DTG + 2 NRTI or continue	>90% virologic suppression each arm	No emergent resistance either arm

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 et al, CROI 2022, Abstract 136

DTG + DRV/r (remember DUALIS study) works here too (superior)

Wednesday

Oral Abstract Session-12 ANTIVIRAL
STRATEGIES FOR TREATMENT AND PREVENTIONS
Ballroom 1 (Level 5) 10:00 AM - 12:00 PM

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11:24
LB

D2EFT: DOLUTEGRAVIR AND DARUNAVIR EVALUATION IN ADULTS FAILING FIRST-LINE HIV THERAPY

Gail Matthews, Margaret Borok, Nnekelu Eriobou, Richard Kaplan, N Kumarasamy, Anchalee Avihingsanon, Marcelo H. Losso, Iskander Shah Azwa, Muhammad Karyana, Sounkalo Dao, Mohamed Cisse, Emmanuelle Papot, Simone Jacoby, Jolie Hutchison, Matthew G. Law, Leo Perelis, Fafa Addo Boateng, Dannae Brown

Name of study	Type of study, n	Comparison	Outcome	Emergent resistance
D2EFT	international randomized open-label trial in patients failing NNRTI therapy, n=831	DTG + DRV/r vs DTG + 2NRTIs vs DRV/r + 2 NRTIs	DTG + DRV/r **superior** to either regimen	None mentioned; Abstract on Wednesday

History of D²EFT

- Originally conceived as a 2 arm RCT utilising 1 innovative simplified dual ART regimen versus SOC commencing April 2017

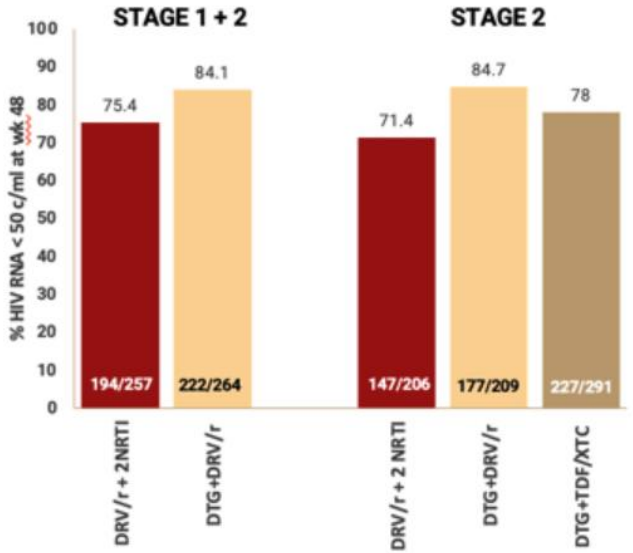
STANDARD OF CARE	INTERVENTION ARM	INTERVENTION ARM
DRV/r+2N	**DRV/r+DTG**	**DTG + XTC/TDF**
Nucleosides **Selected** - Genotyping or WHO Algorithm	No Nucleosides	Recycled Nucleosides
Drug Class But Not Drug Recycled	No Genotyping Required	No Genotyping Required
No Coformulation Possible	No Drug or Drug Class Recycled	Drugs and Class Recycled
	Potential Coformulation	Coformulated
ARM 1	ARM 2	ARM 3

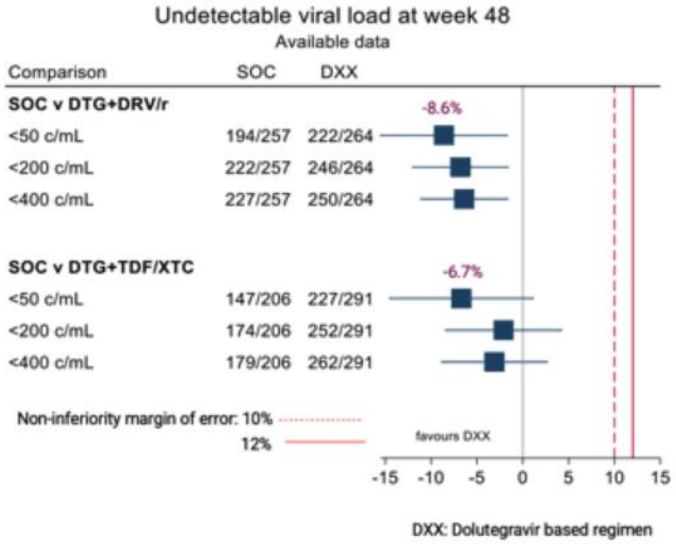
XTC= FTC or 3TC

In response to a changing therapeutic landscape and after extensive stakeholder consultation (and additional funding) a third arm was added in May 2018

DRV/r + DTG added as an afterthought and the superiority seen is unlikely to change clinical practice – save DRV/r for later

Primary outcome





DRUG RESISTANCE IN PEOPLE FAILING DOLUTEGRAVIR-BASED ART: HIV COHORT COLLABORATION

576

Tom Loosli[1,2], Stefanie Hossmann[3], Suzanne M. Ingle[4], Hajra Okhai[5], Ard van Sighem[6], Melanie Stecher[7], Antonella D'Arminio Monforte[8], M. John Gill[9,10], Caroline A. Sabin[5], Gary Maartens[11], Huldrych F. Günthard[1,2], Jonathan A.C. Sterne[4], Richard Lessells[12,13], Matthias Egger[3,4,13], Roger D. Kouyos[1,2]

METHODS

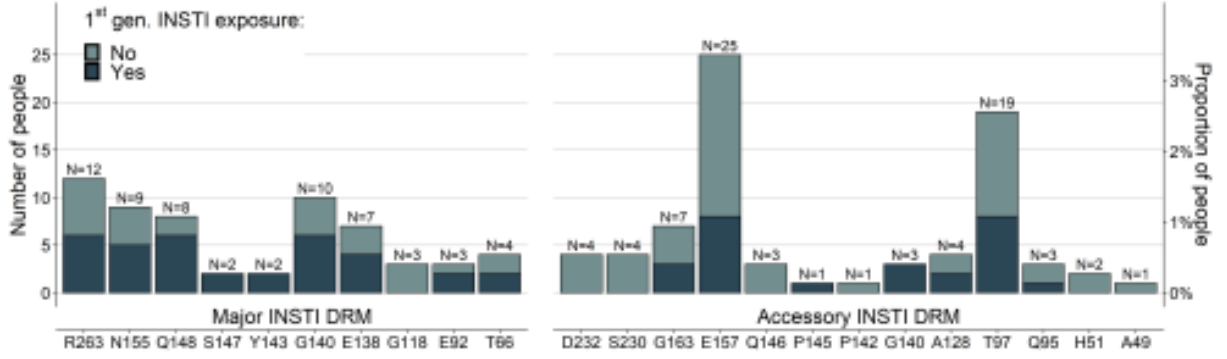
- Cohorts from Canada, Europe, and South Africa contributed clinical data and genotypic resistance tests (GRTs) on people with genotypic resistance testing on DTG-based ART.
- DRMs were identified and resistance levels categorised using the Stanford algorithm.
- We identified risk factors for DTG resistance using mixed-effects ordinal logistic regression models.

Poster showed 13.5% (!) DTG-associated mutations in those failing therapy in Canada, Europe, S. Africa (& associated with DTG monotherapy and NRTI resistance)

In people on failing DTG-based ART, INSTI DRMs were uncommon and DTG resistance was rare. DTG monotherapy and NRTI resistance were associated with a substantially increased risk for DTG resistance which should be of concern, notably in resource-limited settings.

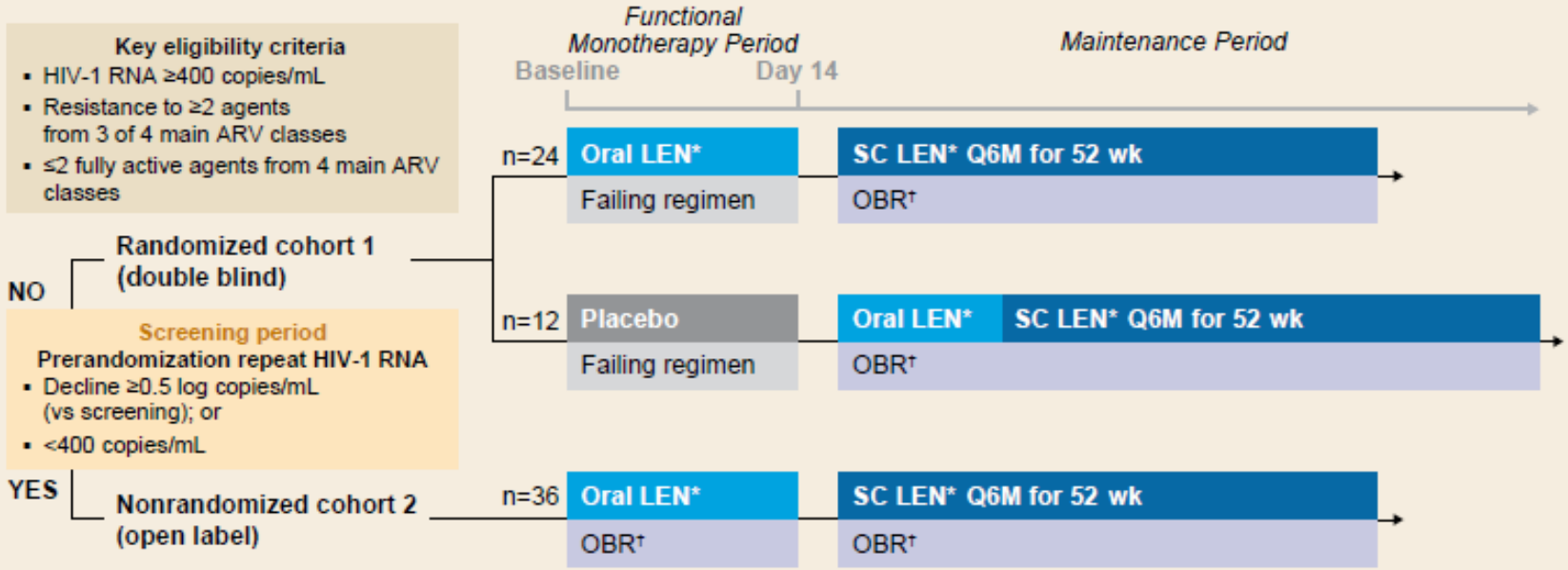
WIDE RANGE OF INSTI DRUG RESISTANCE MUTATIONS

- A wide range of INSTI DRMs were detected in 100/742 (13.5%) individuals.
- T97A was significantly associated with HIV subtype, no association with 1st generation INSTI experience could be detected.

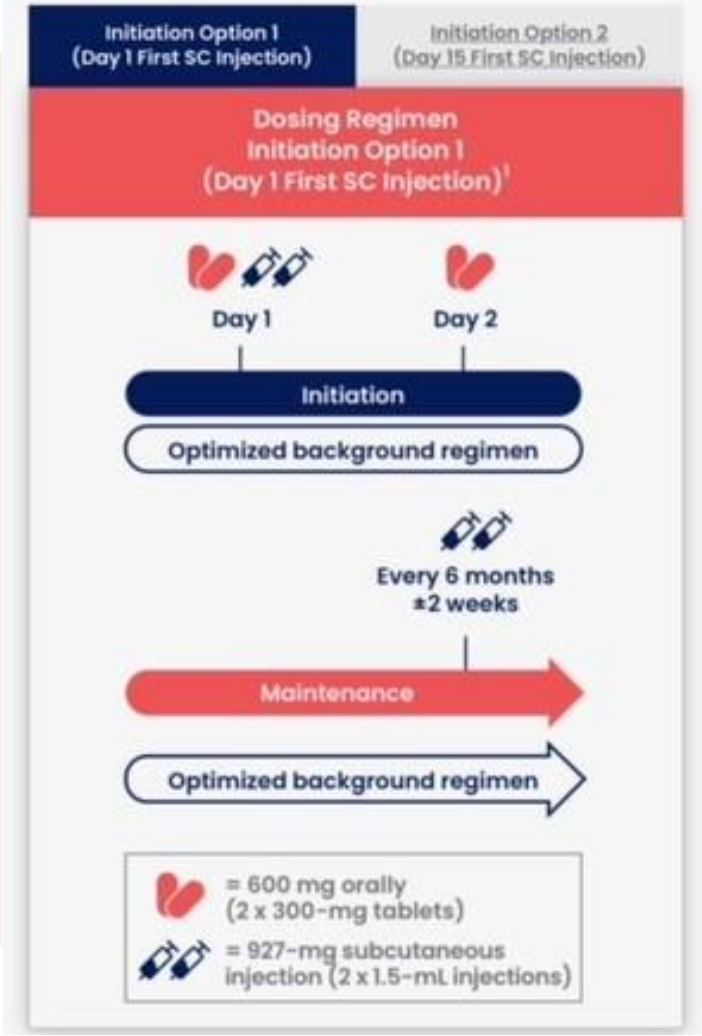


Bottom line: Lenacapavir has a low genetic barrier to resistance so use carefully with resistant HIV

CAPELLA Study Design[9-11]



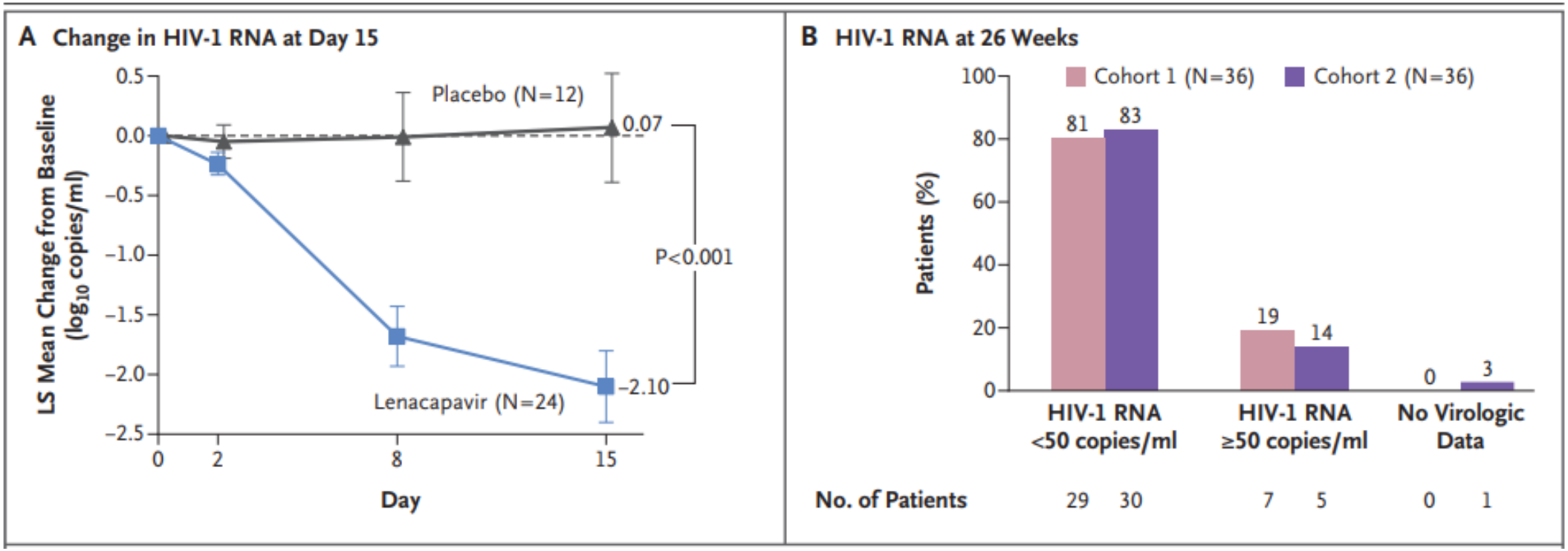
*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8 (600 mg on Days 15 and 16, and 300 mg on Day 22 for placebo participants); SC LEN administered as 927 mg (2 x 1.5 mL) in abdomen on Day 15; †Investigational agents, such as fostemsavir (FTR), were allowed; atazanavir (ATV), ATV/cobicistat (c), ATV/ritonavir (r), efavirenz, entecavir, nevirapine, and tipranavir were not allowed.



Oral loading dose given days 1, 2 and 8 in CAPELLA but further PK study showed only 600mg (300mg x 2) on days 1 and 2 needed (package insert); then 927mg sq injection (two 1.5ml) q26 weeks (Jogiraju. PK study. AIDS 2022)

CAPELLA STUDY- Lenacapavir in MDR HIV

Approved for MDR HIV now in Europe and in the US since December 2022



Segal Maurer NEJM 2022

Bottom line on LEN resistance in MDR study

Phase 2/3: LEN in HTE PLWH

LEN in HTE ‡

Capella

Postbaseline Resistance Analysis at Week 52

Resistance category, n (%)	Randomized cohort n = 36	Nonrandomized cohort n = 36	Total N = 72
Resistance analysis population	11 (31)	11 (31)	22 (31)
With data	11 (31)	10 (28)	21 (29)
With LEN resistance	4 (11)	5 (14)	9 (13)
M66I, n	4	2	6
Q67H/K/N, n	1	3	4
K70H/N/R/S, n	1	3	4
N74D, n	3	0	3
A105S/T, n	3	1	4
T107A/C/N, n*	1	3	4

- Since Week 26, one additional participant had emergent LEN resistance at Week 52 (*Q67H*)
- All 9 participants with emergent LEN resistance were at high risk for resistance development
  - 4 had no fully active drugs in OBR
  - 5 had inadequate adherence to OBR
- All 9 remained on LEN
  - 4 participants resuppressed at a later visit (2 without OBR change and 2 with OBR change)
- The most common pattern was *M66I* ± other mutations (median LEN fold change was 234)

All nine cases of emergent LEN resistance occurred in the setting of functional monotherapy. More than half of participants who met criteria for resistance testing did not develop LEN resistance

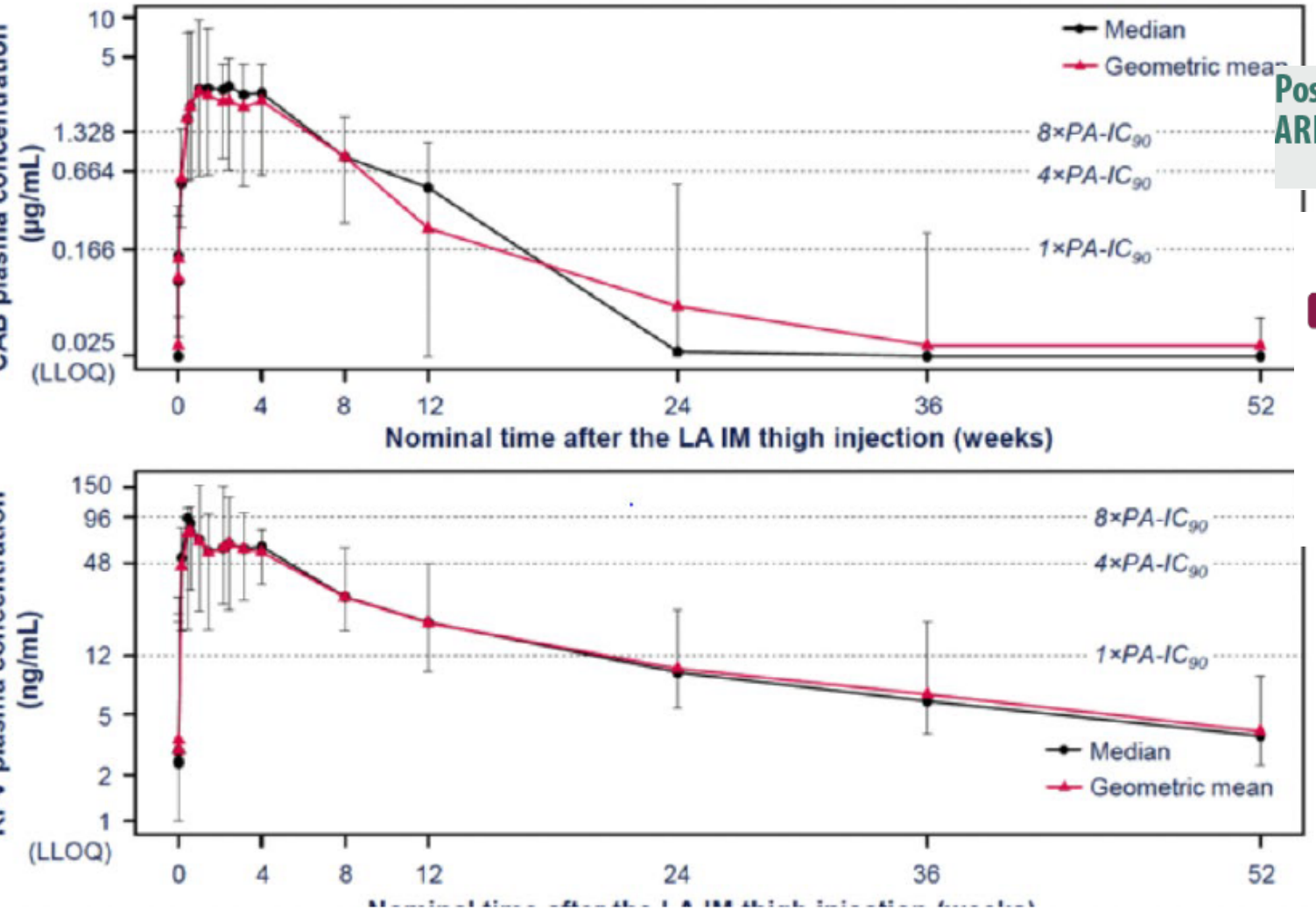
*1 participant had emergent *T107A* mutation in capsid, with no loss in LEN susceptibility before achieving HIV -1 RNA suppression; the participant was not categorized as having emergent capsid resistance. HTE, heavily treatment-experienced; OBR, optimized background regimen

Ogbuagu O, et al. IDWeek 2022, Oral 1585

- Mutations emerging with LEN: M66I, K70S, T107A, N74D, A105T, K70S, Q67H
- All 9 out of 72 occurred during "functional" monotherapy – not having support of other agents in regimen

armacokinetics (PK) and tolerability of cabotegravir (CAB) and rilpivirine (RPV) g-acting (LA) intramuscular (IM) injections to the vastus lateralis (lateral thigh) scles 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

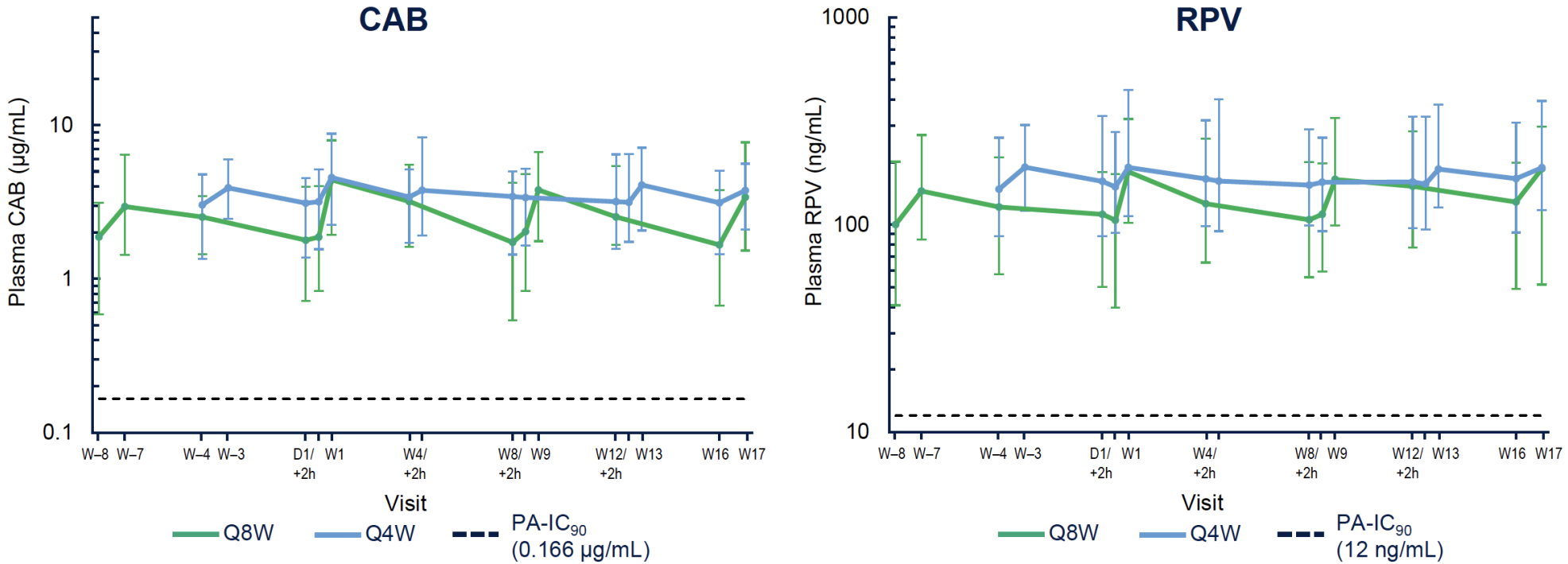
519 LB

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

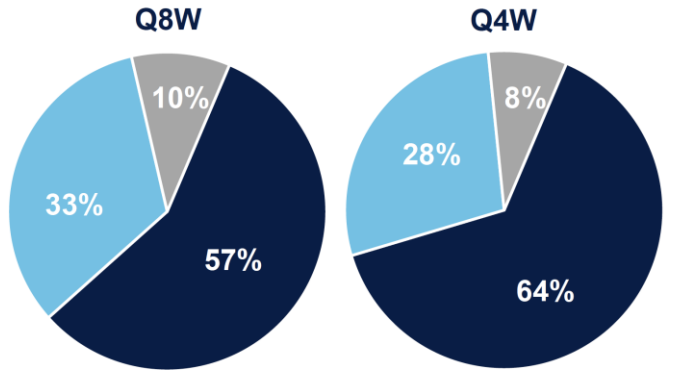
Franco Felizarta, Ronald D'Amico, Kehui Wang, Herta Crauwels, Mar Masiá, Miguel Garcia Deltoro, Olaf Degen, Jonathan Angel, Chiu-Bin Hsiao, Vasiliki Chounta, Kelong Han, Conn Harrington, Kelly Rimler, William R. Spreen, Susan Ford

Poster Sessions • Tuesday

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.



*Return to gluteal injection phase.
Q4W, every 4 weeks; Q8W, every 8 weeks.

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

Long-acting ART in treatment naïve patients (Ward 86 data)

- 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%)

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

Tuesday

Themed Discussion-08 LAI CAB/RPV: WHERE ARE WE NOW AND WHERE ARE WE GOING?
Flex C (Level 2) **1:30 PM - 2:30 PM**

518 *1:45*

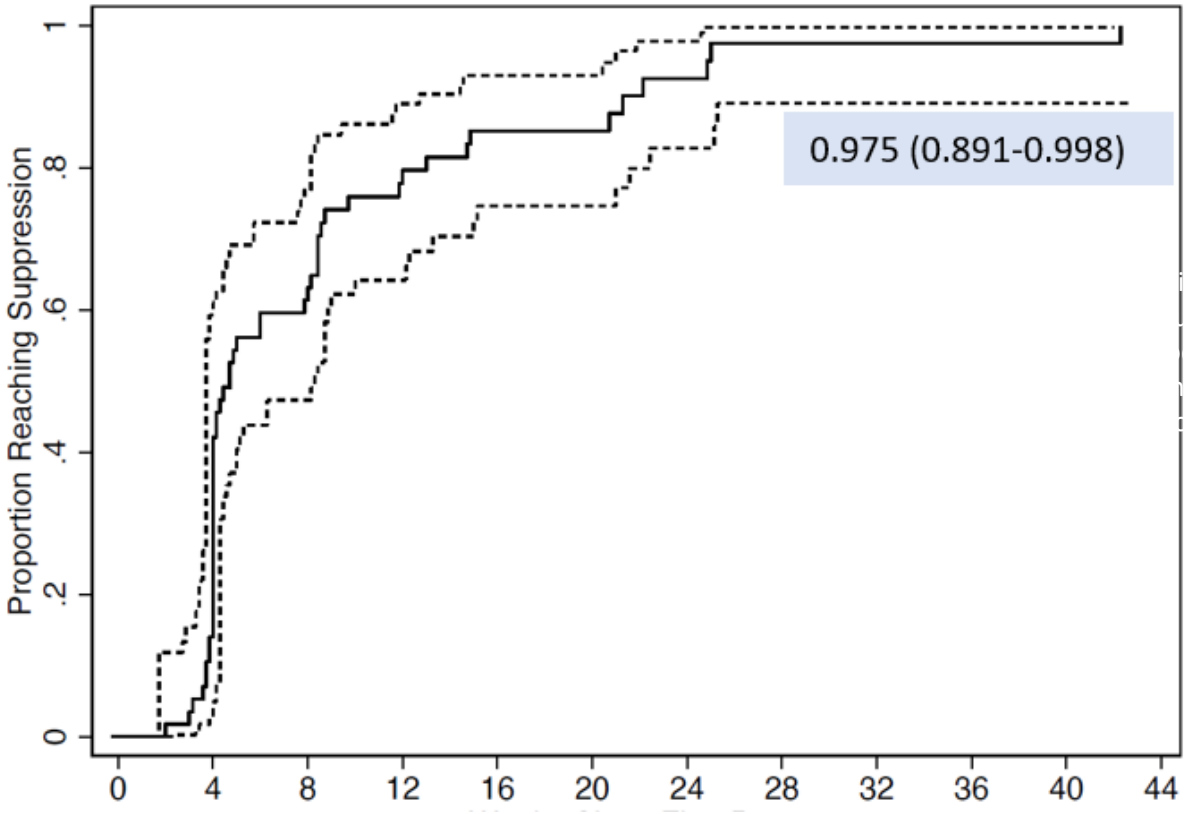
HIGH VIROLOGIC SUPPRESSION RATES ON LONG-ACTING ART IN A SAFETY-NET CLINIC POPULATION

Monica Gandhi, Jorge Salazar, Matthew D. Hickey, Katerina Christopoulos, Jon Oskarsson, Mary Shiels, John Szumowski, Janet Grochowski, Francis Munoz-Mayorga, John Sauceda, Elizabeth Imbert, Janet Nguyen, David V. Glidden, Diane V. Havlir

- Between June 2021-November 2022, 133 PWH started on LA-ART, 76 suppressed on oral ART, 57 (43%) with viremia
- Diverse in race/ethnicity, substance use, housing, mental illness
- 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.

RESULTS (continued)

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



Neither patient could take nor has started oral ART since (methamphetamine use)

- 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,

Patient #1 without suppression: 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

Patient #2 without suppression: 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

PREVENTION- One study in women showed CAB levels high even after missed doses; a study mainly in men showed low CAB/RPV levels in “real world”

ORAL AND INJECTABLE PrEP USE IN THE UNITED STATES, 2013 TO 2022

CROI 2023 Feb 20-23

Weiming Zhu, Ya-Lin A. Huang, Athena P. Kourtis, Karen W. Hoover
Division of HIV Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention,
Centers for Disease Control and Prevention, Atlanta, GA

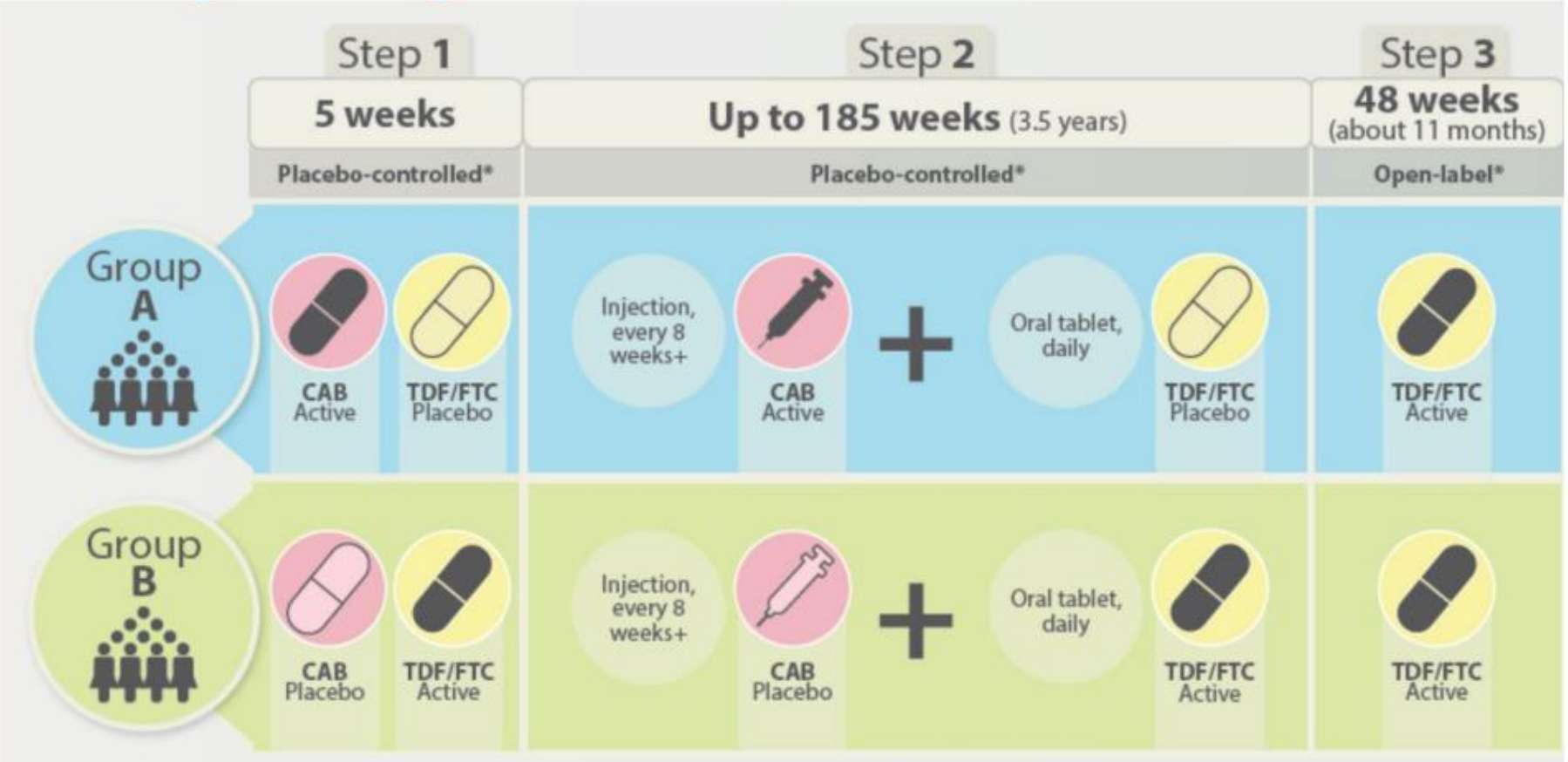
Results

- In September 2022, 186,367 persons were prescribed PrEP
  - Generic FTC/TDF: 93,808 (50.3%)
  - FTC/TAF: 84,141 (45.1%)
  - Brand FTC/TDF: 7,065 (3.8%)
  - CAB-LA: 1,353 (0.5%)
- From January 2022 through August 2022
  - 1,951 persons picked up CAB-LA prescription
  - 1,638 (84.0%) received a prescription for a second dose within one month of the first prescription

Bottom line: US system – not a lot of cabotegravir PrEP use yet

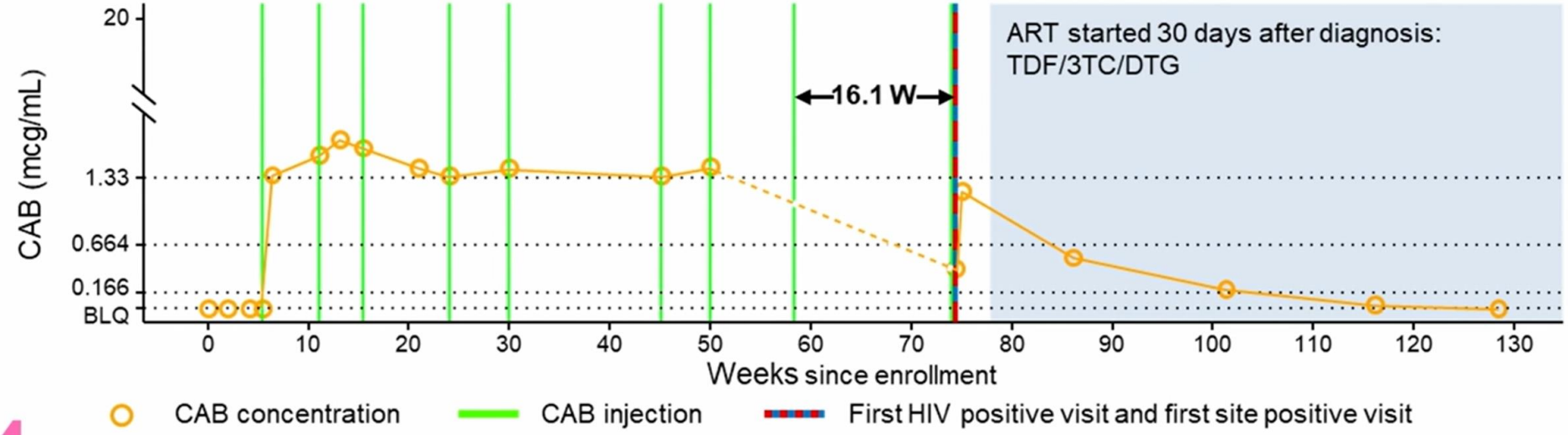
What happens with drug levels if injection is delayed?

HPTN 084 Study Design



HIV Infections in Participant with Delayed Injections

- During blinded phase of HPTN 084, one participant acquired HIV in the background of late injections
  - 3/9 injections occurred late (8.5, 15.1, 16.1 weeks)
  - CAB concentration at first HIV positive visit: 0.416 mcg/mL (<4x PA-IC_{90})



CAB concentrations were above target (PA-IC90) in 98%, 95% and 90% of persons receiving injections 4-6, 6-8, and 8-10 late – lots of “pharmacokinetic forgiveness”- could go 3 months?- cisgender female but also African-based study

Low trough concentrations of cabotegravir and rilpivirine in patients infected with HIV switching to long-acting treatment

CROI 2023 Feb 20-23

What about delays on injections on treatment if given every 8 weeks?
Two French University clinics; 88% male

Baseline characteristics

Characteristics	n=58
Median age, years (IQR)	30 (27 – 34)
Male, n (%)	51 (88)
Median BMI, kg/m² (IQR)	24 (22 – 26)
Geographical origin, n (%)	
Europe	40 (69)
Other	18 (31)
Population groups (%)	
MSM	43 (74)
Heterosexual	13 (22)
IV drug user	2 (3)
Median time since HIV RNA < 50 copies/mL, years (IQR)	8 (3 – 10)
Median CD4 T-cell count, /mm³ (IQR)	694 (529 – 830)
HIV subtype, n (%)	
A (A1)	2 (3)
B	35 (60)
Other	21 (36)
Cumulative RNA/DNA genotype: major NNRTI RAM (K103N), n (%)	3 (5)
Treatment before switch to CAB/RPV combination, n (%)	
INSTI	30 (52)
NNRTI	28 (48)
PI	3 (5)
Oral lead-in with CAB/RPV, n (%)	16 (28)

Unexpectedly low CAB concentrations

- **Cohort study of patients initiating q8 week CAB/RPV in France, (900mg/600 at day 0, M1, M3)**
  - 1 virologic failure (2%)
- **RPV levels as expected**
- **CAB concentrations one month and three months after dosing initiation**

Trough concentrations

Drug trough concentrations		At 1 month (n=58)	At 3 months (n=56)
CAB	**Trough < 1120 ng/mL**, n (%)	**35 (60)**	**43 (77)**
	Median trough, ng/mL (IQR)	**976 (706 – 1434)**	**701 (440 – 1087)**
	No lead-in (n=42)	*951 (681 – 1196)*	*625 (397 – 880)*
	Lead-in (n=16)	*1213 (908 – 1479)*	*1103 (689 – 1246)*

*Abstract 519 Showed PK of thigh injections

ACTG AIDS CLINICAL TRIALS GROUP

Risk factors for low trough levels

- **Cabotegravir:**

Characteristics	M1 cabotegravir trough level				M3 cabotegravir trough level		
	< 1120 ng/mL (n=35)	≥ 1120 ng/mL (n=23)	p	p*	< 1120 ng/mL (n=43)	≥ 1120 ng/mL (n=13)	p
Median age, years (IQR)	29 (26 – 34)	31 (28 – 34)	0.7		29 (26 – 34)	31 (30 – 36)	0.1
Male, n (%)	29 (83)	22 (96)	0.2		38 (88)	11 (85)	0.7
European origin, n (%)	25 (71)	15 (65)	0.8		32 (74)	8 (62)	0.5
Median BMI, kg/m² (IQR)	24 (22 – 27)	22 (20 – 25)	**0.01**	**0.009**	24 (22 – 26)	24 (22 – 27)	0.5
No lead-in, n (%)	29 (83)	13 (57)	**0.04**	**0.02**	35 (81)	6 (46)	**0.03**

* Multivariate analysis

Bottom line: Can have lower levels if treatment given every 8 weeks and have high BMI and didn't give oral loading dose

Conclusions

- **Low cabotegravir trough concentrations at 1 month and 3 months**
  - 60% (M1) / 77% (M3) < first quartile
  - In patients without lead-in, M3 median trough level < 4x$PAIC_{90}$
  - **No lead-in** and **high BMI** associated with low trough concentrations
- **High intra- and inter-individual variability**
- **Only one patient with virologic failure, without resistance mutation**
  - Low cabotegravir and rilpivirine trough concentrations at 1 month
  - No lead-in and high BMI

8+ Year Pooled Analysis: Adherence and HIV Incidence in >6000 Women on F/TDF for PrEP

Jeanne Marrazzo,[1] Marissa Becker,[2] Linda-Gail Bekker,[3] Connie Celum,[4] Michael Kiragu,[5] Ashley A. Leech,[6] Allan Taylor,[7] Faith Ussery,[7] Juan Yang,[8] Melanie de Boer,[8] Christoph Carter,[8] Moupali Das,[8] Jared Baeten,[8] Li Tao[8]

[1]University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA; [2]University of Manitoba, Winnipeg, Manitoba, Canada; [3]The Desmond Tutu HIV Centre, Cape Town, South Africa; [4]University of Washington, Seattle, WA, USA; [5]LVCT Health, Nairobi, Kenya; [6]Vanderbilt University School of Medicine, Nashville, TN, USA; [7]Centers for Disease Control and Prevention, Atlanta, GA, USA; [8]Gilead Sciences, Inc., Foster City, CA, USA

Presenting author disclosure: Merck (consulting or advisor fee)

Oral #163

Eleven Demonstration Projects of F/TDF for PrEP in Cisgender Women (N = 6296)

PrEPception[1]
Sullivan
n / N = 16 / 24

CRUSH–PrEP for Women[2]
Myers
n / N = 7 / 25

Ashodaya PrEP (India)[3]
Moses
n / N = 646 / 647

Durbar Mahila Samanwaya Committee[4]
Jana
n / N = 678 / 678

Study
Lead investigator
n/N: available adherence/ Total

Kenya IPCP[5]
Kiragu
n / N = 507 / 1347

MPYA (Kenya)[6,7]
Baeten
n / N = 348 / 348

SCIP Kenya[8]
Baeten
n / N = 40 / 40

Partners PrEP (Kenya, Uganda)[9]
Baeten
n / N = 330 / 334

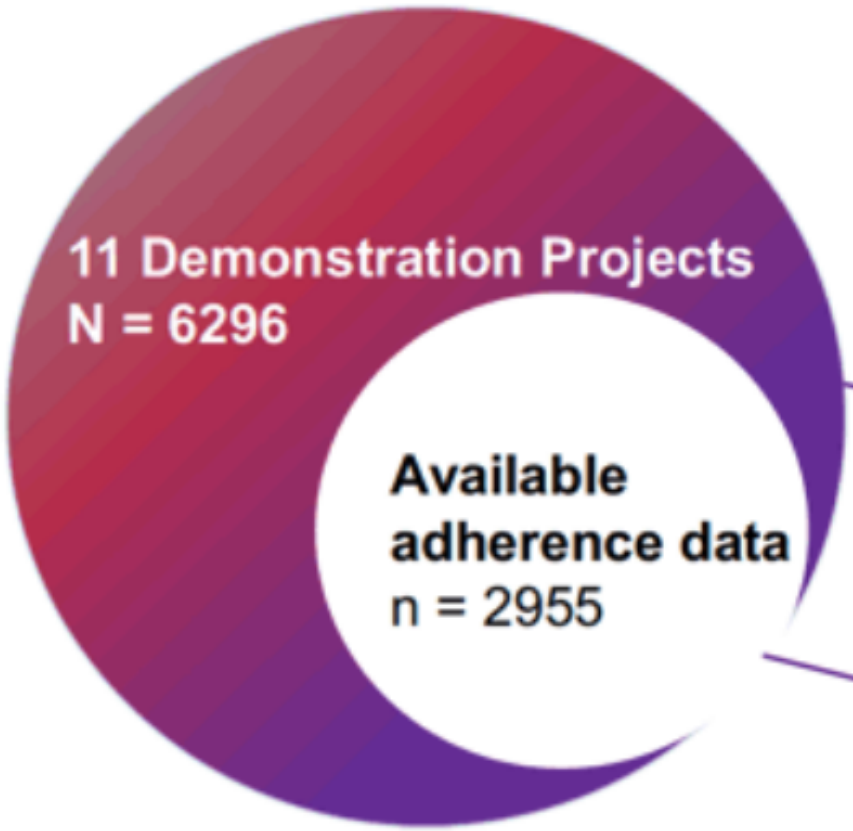
CDC Botswana PrEP OLE[10]
Taylor, Ussery
n / N = 45 /102

Power (Kenya, South Africa)[11]
Celum
n / N = 152 / 2551

3P (South Africa)[12]
Bekker
n / N = 186 / 200

1. Leech AIDS Patient Care STDS 2020; 2. Koester IAPAC 2019; 3. Reza-Paul Glob Public Health 2020; 4. Jana Int J STD AIDS 2021;32:638-47; 5. Masyuko Sex Health 2018; 6. Haberer Lancet HIV 2021 (MPYA); 7. Haberer J Acquir Immune Defic Syndr 2022; 8. Heffron Gates Open Res 2018; 9. Baeten PLOS Medicine 2016; 10Henderson FL, et al. IAS 2015; https://www.natap.org/2015/IAS/IAS_92.htm; 11. Celum J Int AIDS Soc. 2022; 12.Celum J Int AIDS Soc 2020.

Methods: Incidence and Adherence

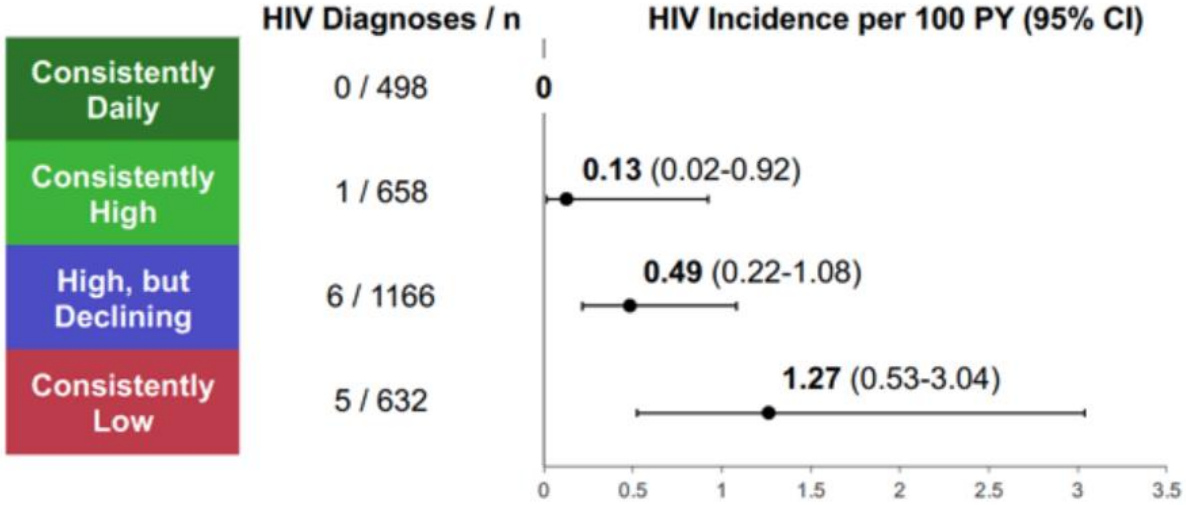


Between November 2012 and December 2020, 6,296 cisgender women initiated F/TDF for PrEP*

We calculated overall efficacy (HIV incidence per 100 PY) by Poisson regression

We evaluated adherence in a subset (n=2955) who had either objective or self-reported data

HIV Incidence Rates Among Women with Available Adherence Data (n = 2955)



- Even with low incidence overall, higher patterns of adherence were directly associated with lower risk of HIV acquisition

Calculated by Poisson regression.

Bottom line: We used to think women needed higher adherence than 4 doses a week but 4 doses per week fine (just like with MSM)

Conclusions

- This pooled analysis of >6000 cisgender women is the largest assessment of effectiveness and adherence of F/TDF in diverse, global, real-world settings
- Effectiveness of F/TDF was similar in cisgender women who demonstrated consistently high (>4 tablets/week) or high (7 tablets/week) adherence
  - Comparable to the adherence-efficacy relationship for cisgender MSM
- However, over half of all participants did not use F/TDF consistently, highlighting the urgent need for additional prevention options such as long-acting modalities

30th CROI 2023

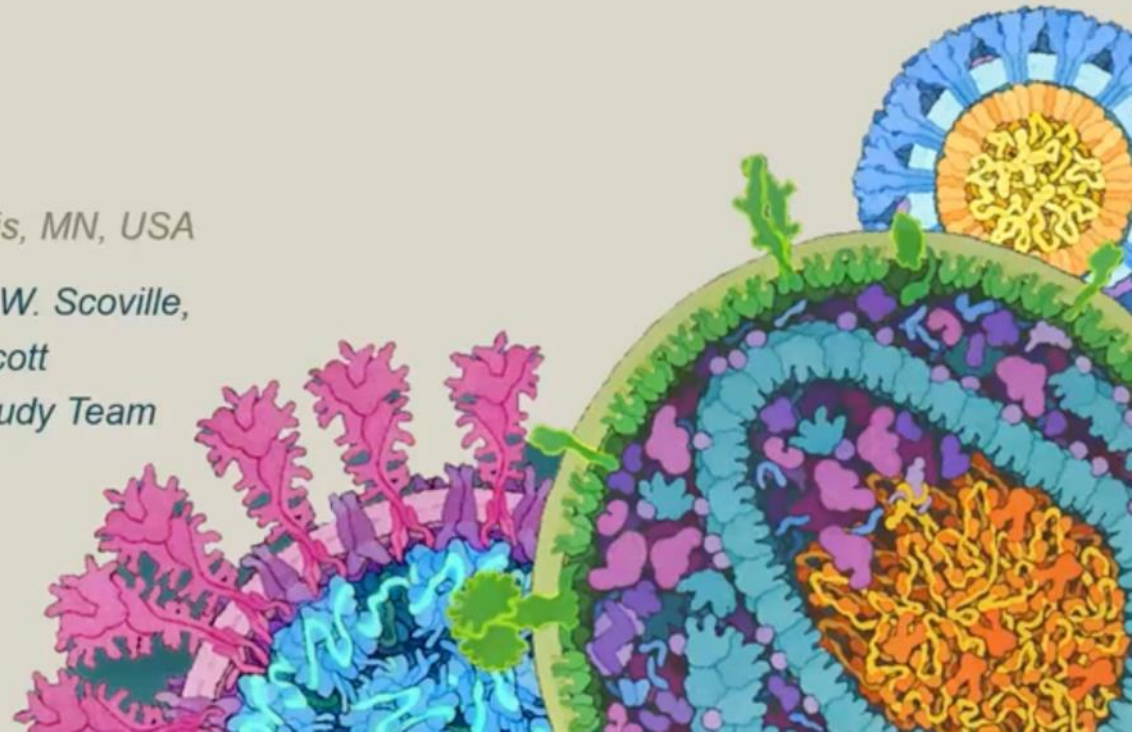
DOXYCYCLINE POSTEXPOSURE PROPHYLAXIS FOR PREVENTION OF STIs AMONG CISGENDER WOMEN

Jenell Stewart, DO, MPH

Hennepin Healthcare Research Institute / University of Minnesota, Minneapolis, MN, USA

Kevin Oware, Deborah Donnell, Lauren R. Violette, Josephine Odoyo, Caitlin W. Scoville, Olusegun O. Soge, Victor Omollo, Felix O. Mogaka, Fredricka A. Sesay, R. Scott McClelland, Elizabeth A. Bukusi and Jared M. Baeten, for the dPEP Kenya Study Team

Disclosure: Presenting author has none.



Background: Doxy PEP for cisgender women

- Globally, cisgender women bear the highest burden of morbidity and mortality from bacterial STIs (chlamydia, gonorrhea, syphilis).[1,2]
- In cisgender men and transgender women taking HIV PrEP with high STI rates, doxy PEP significantly reduced incident STIs.[3-6] (Annie's abstract doesn't show increase in AMR)
- ***This study conducted first ever trial of doxy PEP among cisgender women***

STI sequalae

- PID
- chronic pain
- infertility
- pregnancy complications
- HIV acquisition

1. WHO, 2022; 2. Perslev et al, 2019; 3. Bolan et al, 2017; 4. Molina et al, 2019; 5. Luetkemeyer et al, 2022; 6. Molina et al, 2023.

Results: Baseline characteristics – 449 women Kenya, lots of STIs

	Doxycycline PEP (N=224)	Standard of Care (N = 225)
Age, Median [IQR], years	24 [22-27]	24 [22-27]
Months on HIV PrEP, Median [IQR]	7.5 [4.1-14.9]	7.2 [3.7-13.8]
	% (n)	% (n)
Bacterial STI at baseline	18% (40)	18% (40)
Chlamydia trachomatis	13% (30)	15% (33)
Neisseria gonorrhoeae	5% (10)	3% (7)
Treponema pallidum	0% (0)	1% (2)

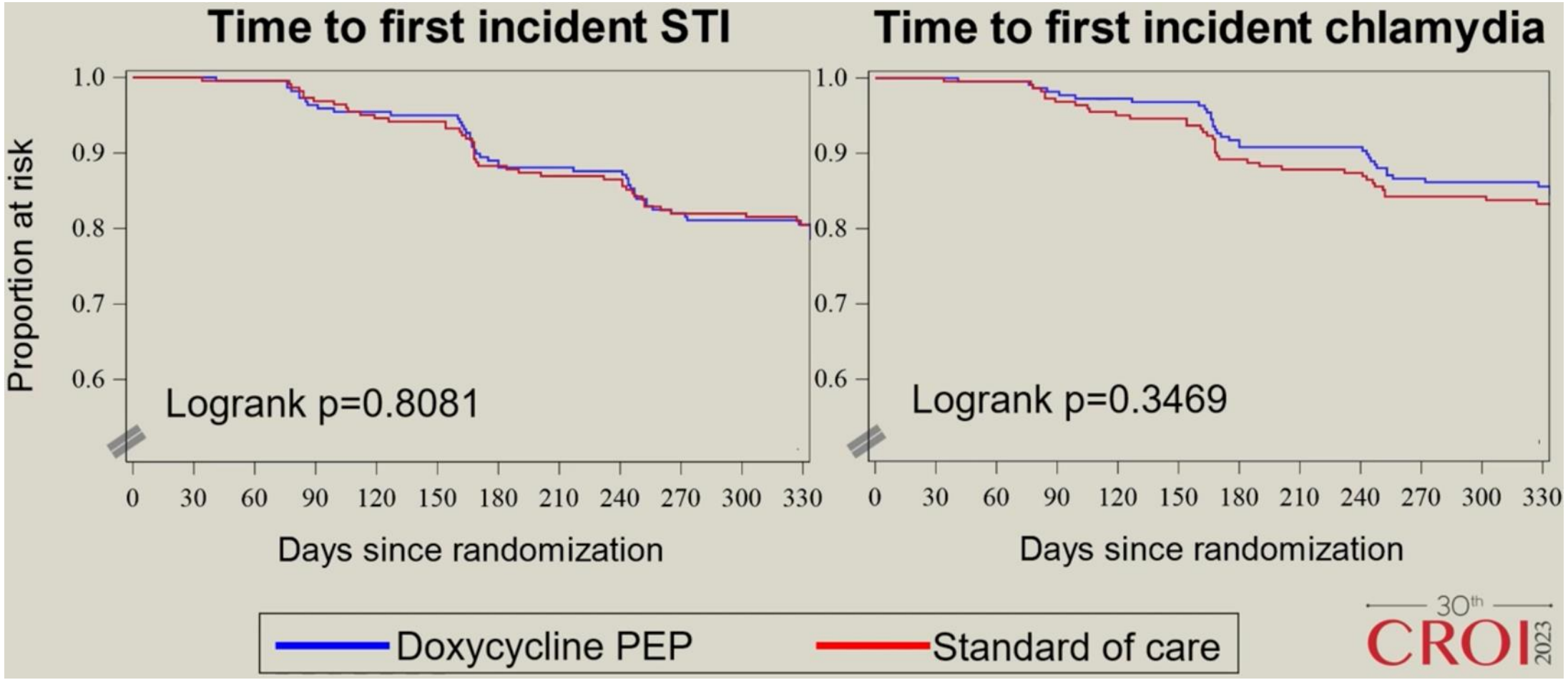
Results: Incident STIs

Analysis	Endpoint	Total	PEP (N=224)	SOC (N=225)	RR	95% CI	P-value
Intention to Treat	All STIs	109	50	59	0.88	0.60-1.29	0.51
	Chlamydia	85	35	50	0.73	0.47-1.13	0.16
	Gonorrhea	31	19	12	1.64	0.78-3.47	0.19
Censoring Pregnancy Time	All STIs	105	48	57	0.91	0.62-1.35	0.65
	Chlamydia	82	33	49	0.73	0.46-1.15	0.18

*****Subgroups analyses of STI incidence by age, hormonal contraception use, transactional sex, and STI detected at baseline found similar results*****

Bottom line: DoxyPEP did not decrease the incidence of STIs in Kenyan women

Results: Time to first incident infection



Results: follow-up and adherence

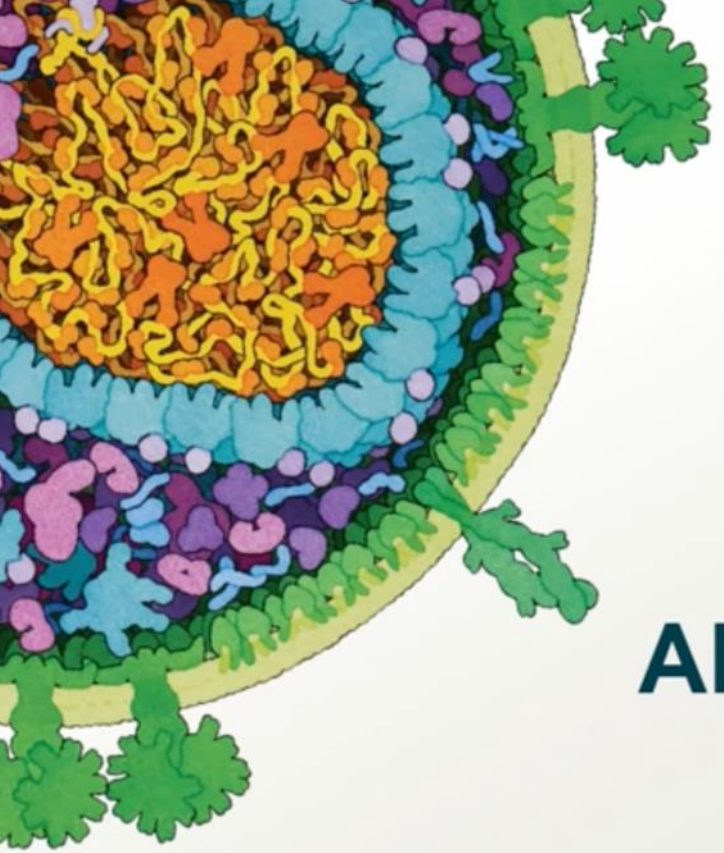
- **Follow-up:** 97% of all follow-visits were completed (95% PEP and 98% SOC)

- **Adherence:** 81% weekly response rate to SMS adherence survey

  →**Women in Doxy PEP arm reported 78% event-driven dosing coverage**

  →**Need an objective adherence metric**

Disappointing lack of efficacy in cisgender women
Could be mucosal pharmacology although earlier abstract in same session didn't show differences in doxy levels by site
Could be adherence (no chlamydia resistance) and must be ascertained



ORAL ABSTRACT: OA-3

Monday, February 20, 2023

ANRS 174 DOXYVAC: AN OPEN-LABEL RANDOMIZED TRIAL TO PREVENT STIs IN MSM ON PrEP

Jean-Michel Molina

University of Paris Cité, Paris, France

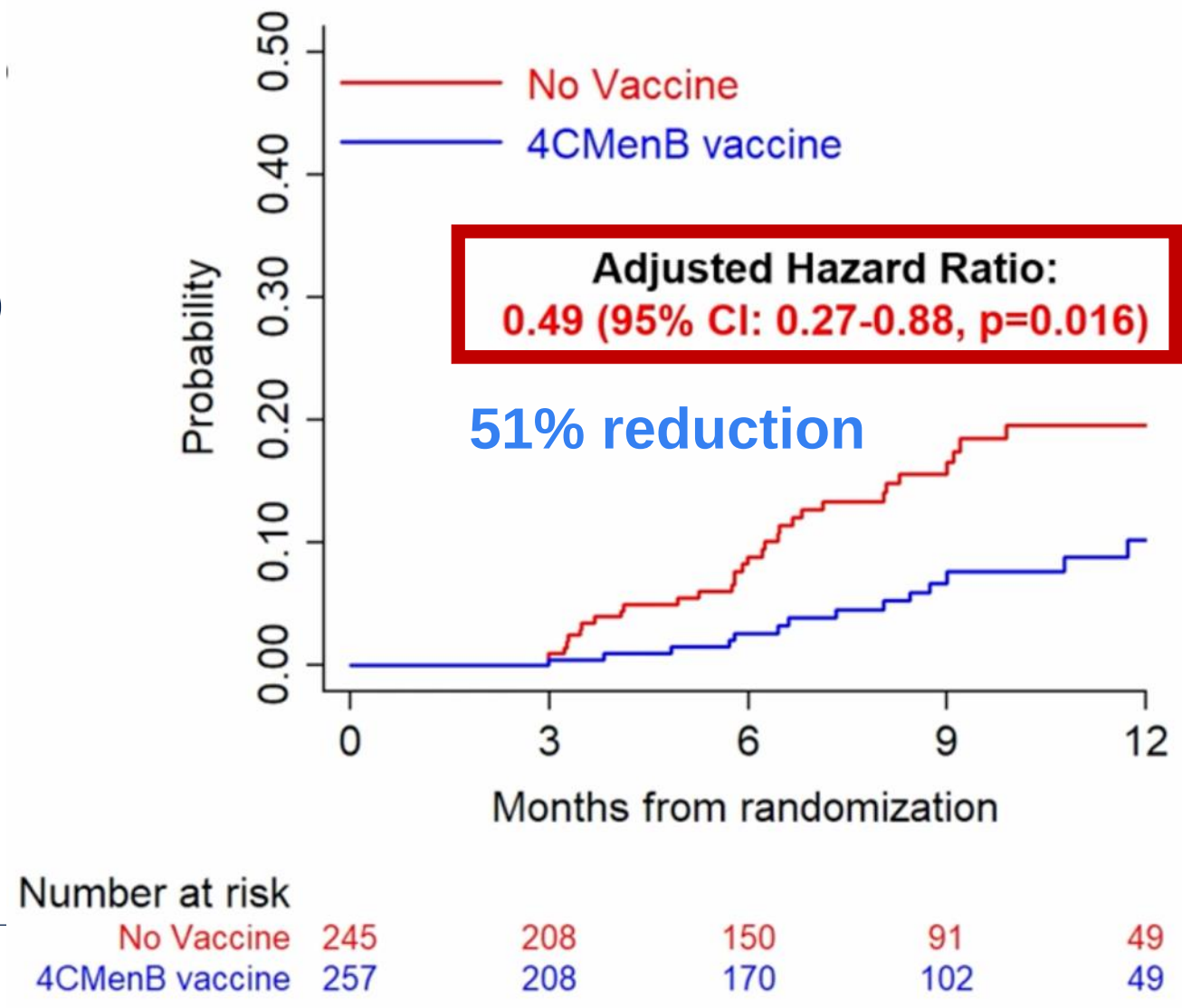
30th CROI 2023

4CMenB Vaccine: Time to first gonorrhea infection

- Median follow-up: 9 months (IQR 6-12)
- 49 participants infected
  - No vaccine arm: 32 infections (19.7/100 PY)
  - Vaccine arm: 17 infections (9.8/100 PY)

- No interaction between DoxyPEP and 4CMenB vaccine (i.e., no additional synergistic benefit, p=0.41)

Gonorrhea infections evaluated from 3-month visit (i.e., 1 month after second visit)



Summary/Conclusions:

- **3rd large, randomized trial to demonstrate doxy-PEP prevents STIs in MSM on PrEP.**
- **In the study, doxy-PEP significantly reduced incidence of several bacterial STIs:**
  - Chlamydia by 89%; Syphilis by 79%; Gonorrhea by 51%; Mycoplasma by 45%
- **Meningococcal B vaccine also significant reduced gonorrhea infections by 51%**
- **No evidence that doxy-PEP and 4CMenB vaccine more effective when used together.**
- **Both interventions were safe and well-tolerated.**

Bottom line: Doxy-PEP is highly efficacious for the prevention of bacterial STIs among MSM – strategies needed to increase access and uptake. Meningococcal B vaccine is a promising tool for gonorrhea prevention and may be appropriate for persons at risk for recurrent STIs.

Islatravir

- **Review of ISL effects on lymphocytes [192]**
  - Dose dependent, greatest effects in monthly and weekly dosing
  - No associated AEs
  - Lymphocytes returned to normal on discontinuation
  - Weekly dosing moving forward; not available yet for ACTG concepts

Bottom line: Islatravir is new medication (NRTTI) but paused due to lymphopenia now back to being studied at lower doses

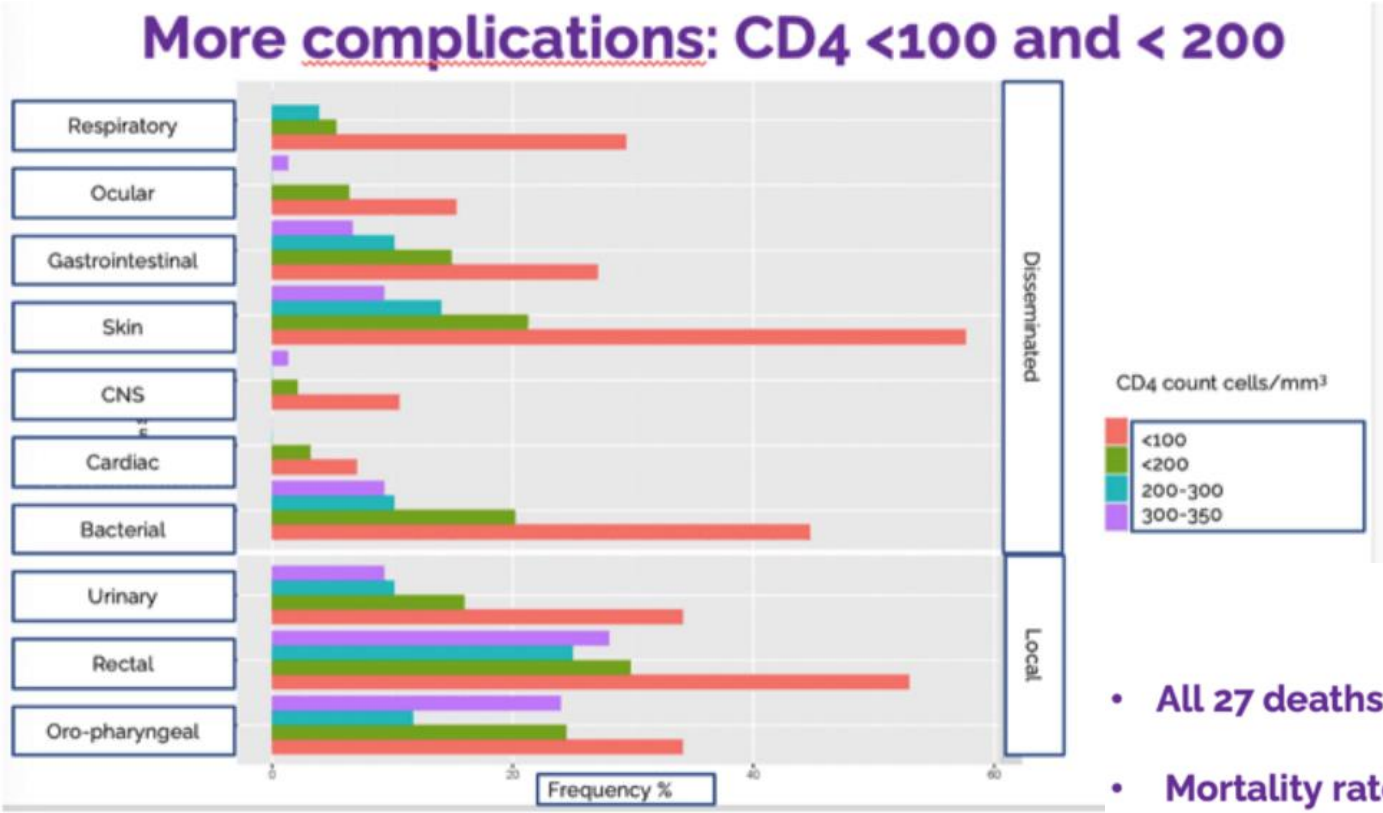
OPPORTUNISTIC INFECTIONS

Mpox in people with advanced HIV infection: a global case series

Oriol Mitjà, Andrea Alemany*, Michael Marks*, Jezer I Lezama Mora, Juan Carlos Rodríguez-Aldama, Mayara Secco Torres Silva, Ever Arturo Corral Herrera, Brenda Crabtree-Ramirez, José Luis Blanco, Nicolo Girometti, Valentina Mazzotta, Aniruddha Hazra, Macarena Silv Juan José Montenegro-Idrogo, Kelly Gebo, Jade Ghosn, María Fernanda Peña Vázquez, Eduardo Matos Prado, Uche Unigwe, Judit Villar-García,*

THE LANCET

More complications: CD4 <100 and < 200



Mpox can be defined as an opportunistic infection
Most severe disease with low CD4 counts

Conclusions

- **All 27 deaths occured in CD4 count <200 cells/mm³**
- **Mortality rate : 15% in CD4 <200; 27% CD4 <100**
- **Severe necrotising, disseminated form of mpox described**:
  - Massive necrotising skin, genital and non-genital cutaneous and mucosal lesions
  - Lung involvement with multifocal opacities (perivascular nodules 5-20mm)
  - Severe cutaneous and bloodstream secondary bacterial infections.
- **Severity of complications and deaths correlate to CD4 and VL strata**
- **Mpox IRIS** - clinical deterioration after initiation of ARV - 57% mortality rate

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 9, 2023 VOL. 388 NO. 10

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc., Erlina Burhan, M.D., Ka Lip Chew, F.R.C.P.A., Victoria B. Dalay, M.D., Qingshu Lu, Ph.D., Tutik Kusmiati, M.D., Vincent M. Balanag, M.D., Shu Ling Lee, B.Sc., Rovina Ruslami, Ph.D., Yogesh Pokharkar, M.Sc., Irawaty Djaharuddin, M.D., Jani J.R. Sugiri, M.D., Rholine S. Veto, M.D., Christine Sekaggya-Wiltshire, Ph.D., Anchalee Avihingsanon, M.D., Rohit Sarin, M.D., Padmasayee Papineni, F.R.C.P., Andrew J. Nunn, M.Sc., and Angela M. Crook, Ph.D., for the TRUNCATE-TB Trial Team*

ABSTRACT

Trial Regimens

Standard Treatment	24w	Rifampicin 10mg/kg	Isoniazid	Pyrazinamide (first 8w)	Ethambutol (first 8w)	
hRIF-LZD	8w	↑ Rifampicin 20-35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg
hRIF-CFZ	8w	↑ Rifampicin 35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Clofazimine 200mg
RPT-LZD	8w	Rifapentine 1200mg	Isoniazid	Pyrazinamide	Levofloxacin 1000mg	Linezolid 600mg
BDQ-LZD	8w	Bedaquiline 400/200mg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg

Table 2. Primary Efficacy Outcome.*

Outcome	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Linezolid vs. Standard Treatment	Strategy with Bedaquiline–Linezolid (N=189)	Strategy with Bedaquiline–Linezolid vs. Standard Treatment
			Adjusted Difference (97.5% CI)†		Adjusted Difference (97.5% CI)†
Intention-to-treat population‡					
Primary outcome: composite of death, ongoing treatment, or active disease at wk 96 — no. (%)§	7 (3.9)	21 (11.4)	7.4 (1.7 to 13.2)	11 (5.8)	0.8 (–3.4 to 5.1)
Death before wk 96	2 (1.1)	5 (2.7)	—	1 (0.5)	—
Ongoing treatment at wk 96	2 (1.1)	8 (4.3)	—	5 (2.6)	—
Active disease at wk 96¶	1 (0.6)	4 (2.2)	—	3 (1.6)	—
Evaluation by telephone at wk 96 with no evidence of active disease but insufficient evidence of disease clearance when last seen	2 (1.1)	3 (1.6)	—	1 (0.5)	—
No evaluation at wk 96 and insufficient evidence of disease clearance when last seen	0	1 (0.5)	—	1 (0.5)	—
Outcomes classified as unassessable — no. (%)	1 (0.6)	1 (0.5)	—	2 (1.1)	—
Single positive culture at wk 96 but no other evidence of active disease‖	0	1 (0.5)	—	0	—
Death from a cause that was definitively unrelated to tuberculosis**	1 (0.6)	0	—	0	—
No evaluation at wk 96 and sufficient evidence of disease clearance when last seen	0	0	—	2 (1.1)	—
No primary outcome or outcome classified as unassessable — no. (%)	173 (95.6)	162 (88.0)	—	176 (93.1)	—
Assessable population††					
Primary outcome — no./total no. (%)	7/180 (3.9)	21/183 (11.5)	7.5 (1.7 to 13.2)	11/187 (5.9)	0.8 (–3.4 to 5.1)
Per-protocol population‡‡					
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

CONCLUSIONS

A strategy involving initial treatment with an 8-week bedaquiline–linezolid regimen was noninferior to standard treatment for tuberculosis with respect to clinical outcomes. The strategy was associated with a shorter total duration of treatment and with no evident safety concerns. (Funded by the Singapore National Medical Research Council and others; TRUNCATE-TB ClinicalTrials.gov number, NCT03474198.)

Bottom line: Can use a shorter course of TB medications (5 meds!) for 8 weeks