AETC AIDS Education & Training Center Program

Southeast Regional Conference 2023

Innovations in HIV Management, Current and Future

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Southeast AETC Regional Conference

August 30, 2023

Objectives of talk

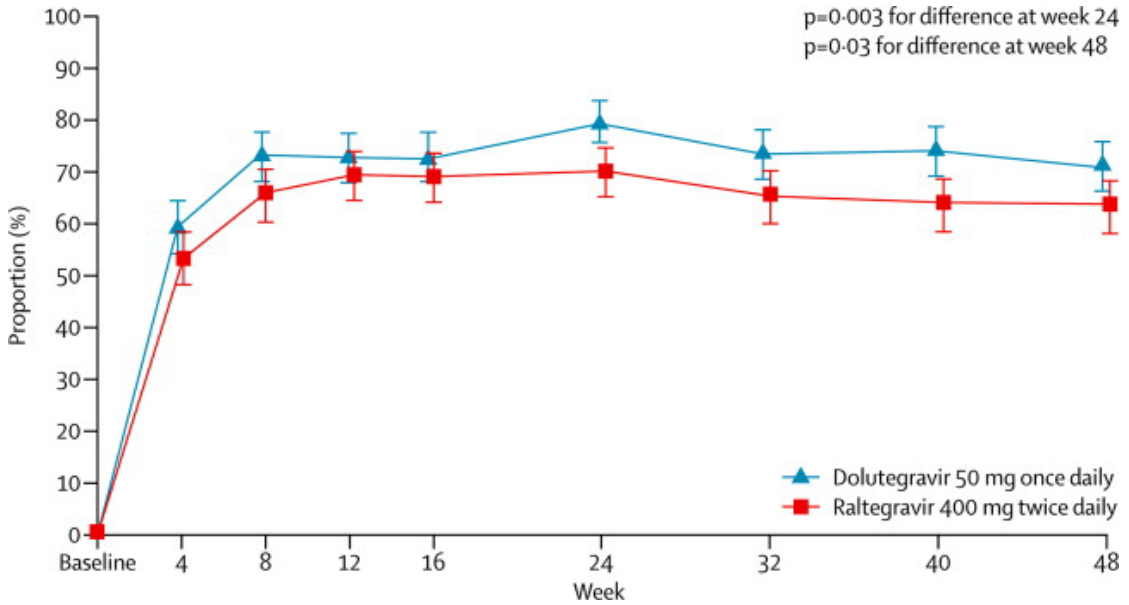
- First line therapy worldwide and why
- Summary of long-acting ART currently available – clinical trial and real world data
- Practical considerations of long-acting ART
- Treatment strategies in the future what is coming?

INSTIs FIRST-LINE AT THIS POINT FROM NAÏVE/SWITCH TRIALS WITHOUT RESISTANCE

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

ACCUMULATING DATA FOR INSTIS AS 2ND LINE IN FACE OF RESISTANCE

- SAILING STUDY –PI, NNRTI AND /OR NNRTI RESISTANCE
- Dolutegravir 50mg po daily vs Raltegravir 400mg po BID in patients with resistance to ≥ 2 classes of antiretrovirals with 1-2 remaining active agents for background therapy
- Investigator chosen background
- DTG was SUPERIOR to RTG in virologic suppression at week 48 and no development of resistance



71%

64%

Cahn P. Lancet 2013. 382(9893):700-8

VIKING STUDY: DTG in setting of NRTI, NNRTI, PI, and INSTI resistance

- Dolutegravir 50mg po **BID** vs placebo in patients with resistance to ≥ 2 classes including INSTIs (resistance to raltegravir or elvitegravir) – should have 1 other active drug
- Investigator chosen background
- DTG resulted in 53% virologic suppression (<400)
- Participants with Q148 with 2 other INSTI mutations don't have activity

Remember to double the dose of dolutegravir to 50mg po BID

Table 2. Comparison of DTG 50 mg twice daily versus PCB for change in BL HIV-1 at day 8 and antiviral efficacy of open-label DTG 50 mg twice daily with OBR at weeks 24 and 48 by BL characteristics[a]

	DTG 50 mg twice daily change from BL[b] at day 8[a] (*n*=14)		PCB 50 mg twice daily change from BL[b] at day 8[a] (*n*=16)		Combined arms, HIV-1 RNA <50 copies/ml[a] (%) (*n*=30)	
Subgroup	*n*	Mean (SD)	*n*	Mean (SD)	Week 24	Week 48
Overall[c]	14[d]	-1.06 (0.17)	16	0.10 (0.18)	14/30 (47)	12/30 (40)
DTG FC						
0–2.5	4	-1.33 (0.82)	7	0.00 (0.34)	6/11 (55)	5/11 (45)
>2.5–4	2	-1.22 (0.65)	3	-0.13 (0.28)	3/5 (60)	3/5 (60)
>4–8	5	-0.89 (0.65)	4	-0.02 (0.22)	2/9 (22)	1/9 (11)
>10–20	1	-0.86	1	-0.06	1/2 (50)	1/2 (50)
>20	1	-0.16	1	0.09	1/2 (50)	1/2 (50)
Missing	1	-1.82	0		1/1 (100)	1/1 (100)
Derived IN mutation group						
No Q148[e]	5	-1.43 (0.745)	9	-0.03 (0.325)	9/14 (64)	8/14 (57)
Q148 +1[f]	6	-0.87 (0.587)	6	-0.05 (0.182)	4/12 (33)	3/12 (25)
Q148 +≥2[f]	3	-0.90 (0.758)	1	0.09	1/4 (25)	1/4 (25)
OSS[g] of background ART						
0	–	–	–	–	2/3 (67)	2/3 (67)
1	–	–	–	–	6/15 (40)	5/15 (33)
2	–	–	–	–	3/8 (38)	3/8 (38)
>2	–	–	–	–	3/4 (75)	2/4 (50)

Bisher A. Antivir Ther. 2015;20(3):343-8

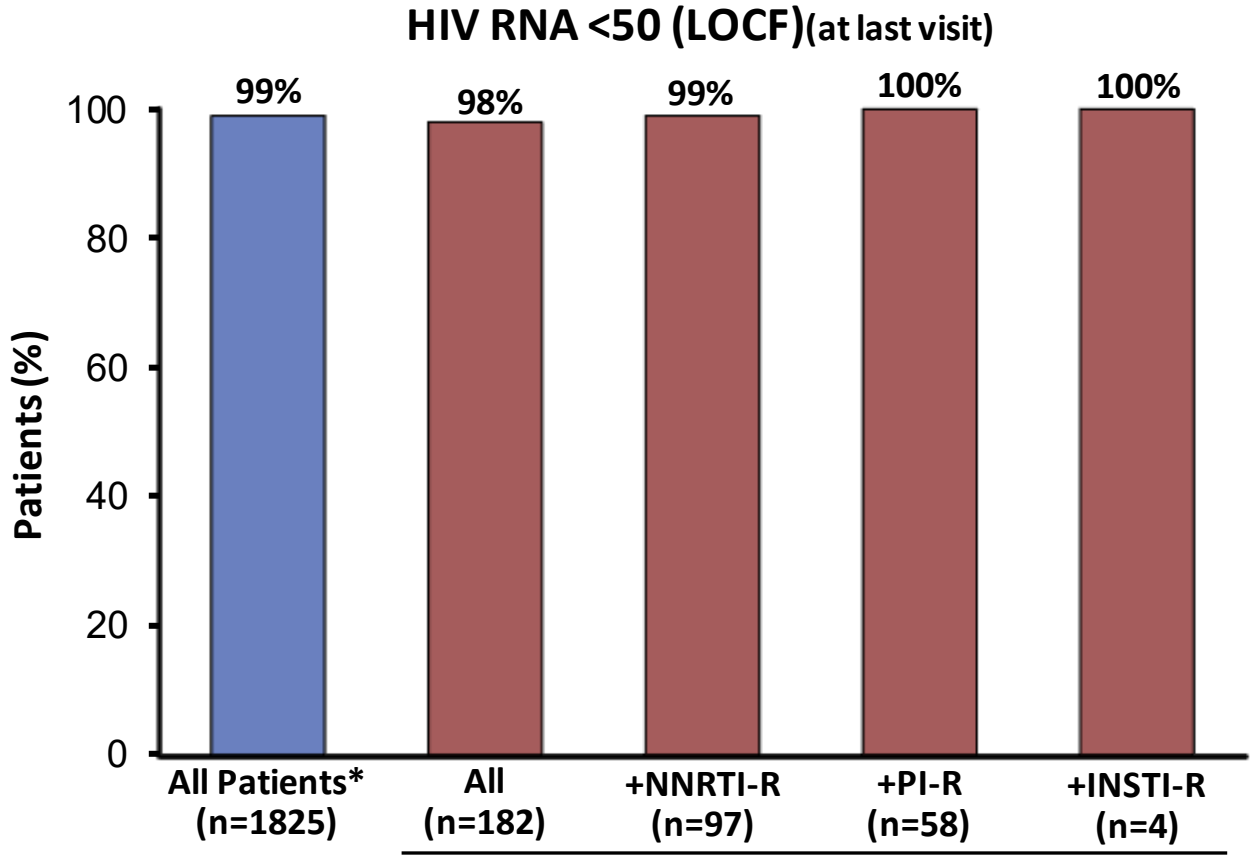
Recent studies of DTG with NRTI resistance

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

Bictegravir/FTC/TAF with Suppressed HIV and pre-existing M184V/I

- Pooled data from 6 trials in which PWH and virologic suppression switched to B/F/TAF (n=1825 with baseline data)
- Preexisting M184V/I identified in 182 participants (10%)
- 98% of participants with pre-existing M184V/I maintained viral suppression



LOCF: last observation carried forward.
*Patients with baseline data.

Sax PE, et al. *AIDS*. 2022

What was the first data suggesting INSTIs are linked with weight gain? (CROI 2019)

Bourgi K et al. *Journal of the International AIDS Society* 2020, **23**:e25484
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25484/full | https://doi.org/10.1002/jia2.25484

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

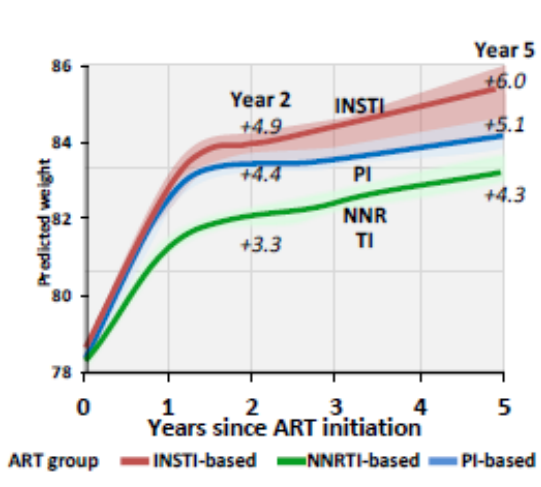
RESEARCH ARTICLE

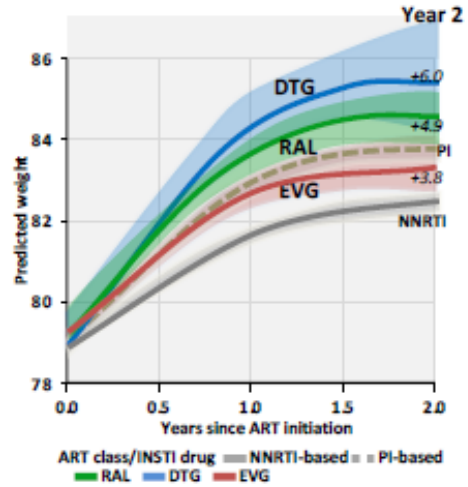
Weight gain among treatment-naïve persons with HIV starting integrase inhibitors compared to non-nucleoside reverse transcriptase inhibitors or protease inhibitors in a large observational cohort in the United States and Canada

Kassem Bourgi[1,2], Cathy A Jenkins[1], Peter F Rebeiro[1], Bryan E. Shepherd[1], Frank Palella[3], Richard D Moore[4],

Weight Gain and Integrase Inhibitors

- NA-ACCORD: observational study of 24,001 participants initiating ART
  - INSTIs, PIs associated with greater weight increase than NNRTI
  - DTG and RAL associated with greater weight gain than EVG

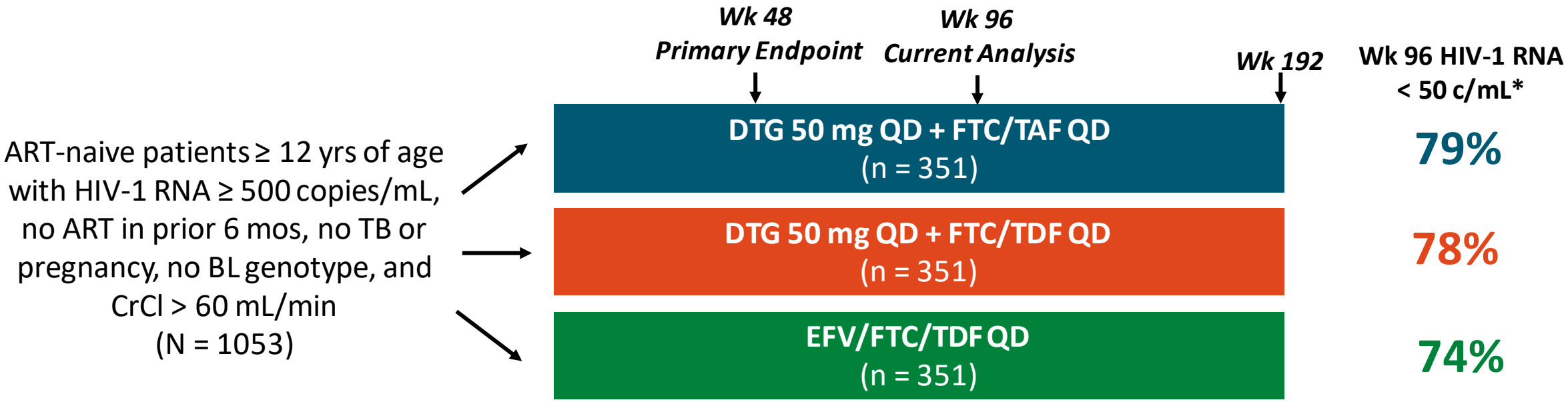




Bourgi K et al, CROI 2019, #670

ADVANCE: Phase III Trial of First-line DTG + FTC/(TAF or TDF) vs EFV/FTC/TDF in South Africa

- Multicenter, randomized, open-label phase III trial conducted in South Africa



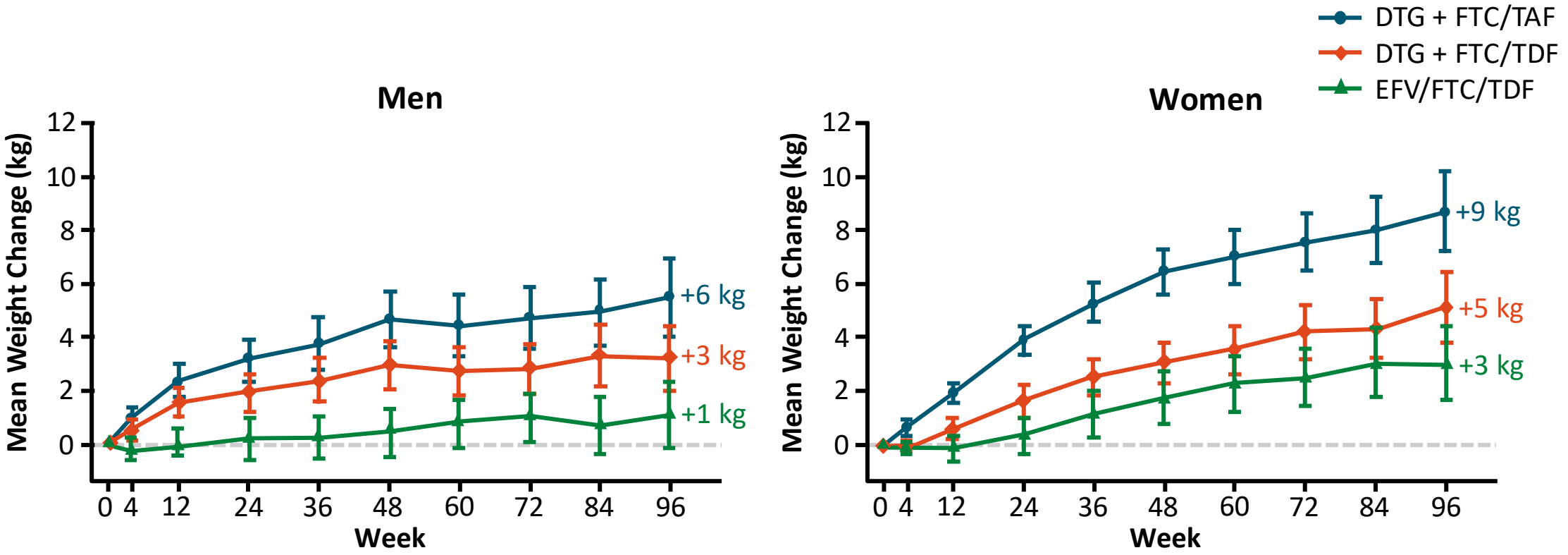
*Differences between arms not statistically significant.

- Primary efficacy endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 by ITT (M = F) analysis
  - DTG + FTC/TAF and DTG + FTC/TDF noninferior to EFV/FTC/TDF at Wk 48: 84% vs 85% vs 79%
- Secondary endpoints: safety, weight gain

Sokhela. AIDS 2020. Abstr OAXLB01. Venter. NEJM. 2019;381:803.

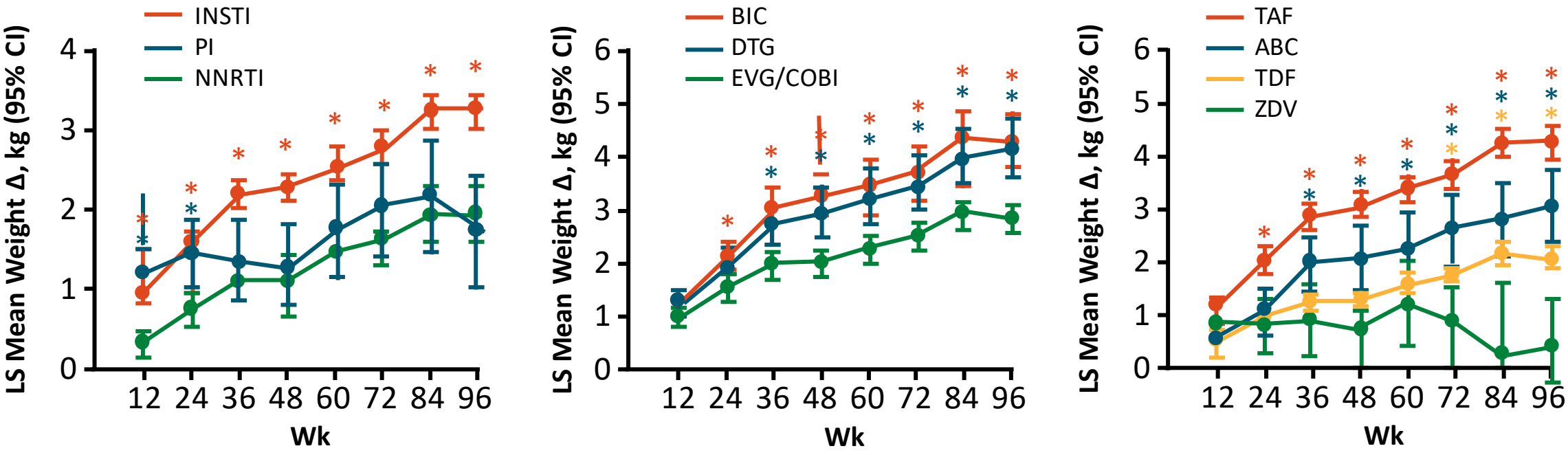
ADVANCE: Mean Weight Change by Sex up to 96 weeks

- Greater weight increase with DTG vs EFV, with TAF vs TDF; plateau in weight gain after Week 48 observed in men but not in women
  - Same patterns observed for percentage change in weight and change in BMI category over time



McCann. EACS 2019. Abstr PS3/3. Venter. NEJM. 2019;381:803.

Weight Gain Following ART Initiation by ARV Class and ARV Drug: BIC, DTG, TAF

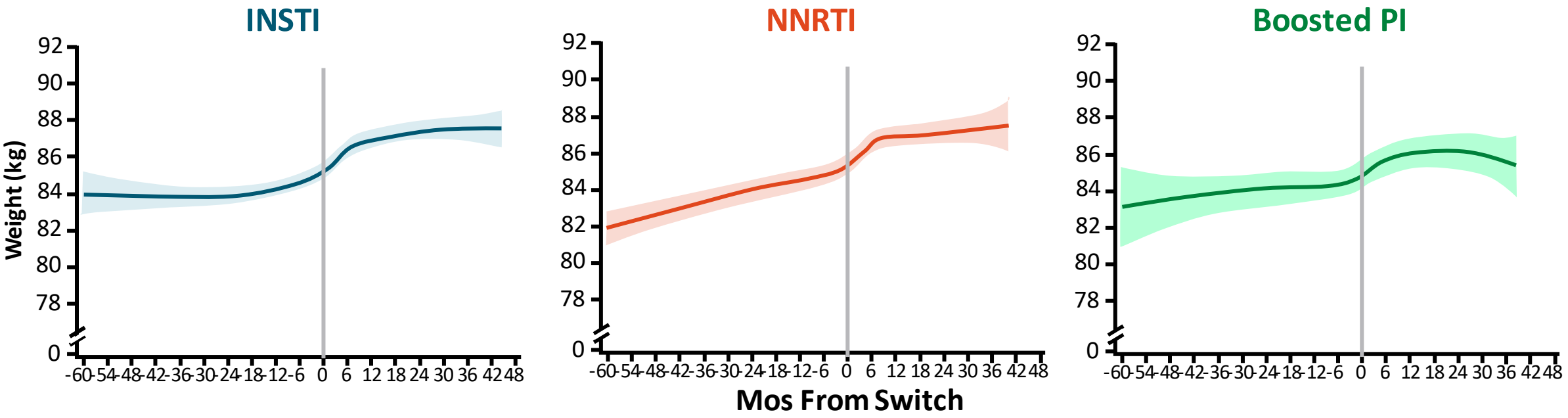


*8 RCTs of PWH treatment-naïve initiating ART between 2003 and 2015, >5000 participants & 10 000 person-years of follow-up

Color-coded to match respective comparators, denoting $P \leq .05$ vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).

Sax. Clin Infect Dis. 2020;71:1379.

OPERA: Weight Change With Switch From TDF to TAF (maintain anchor so this is just about TAF)

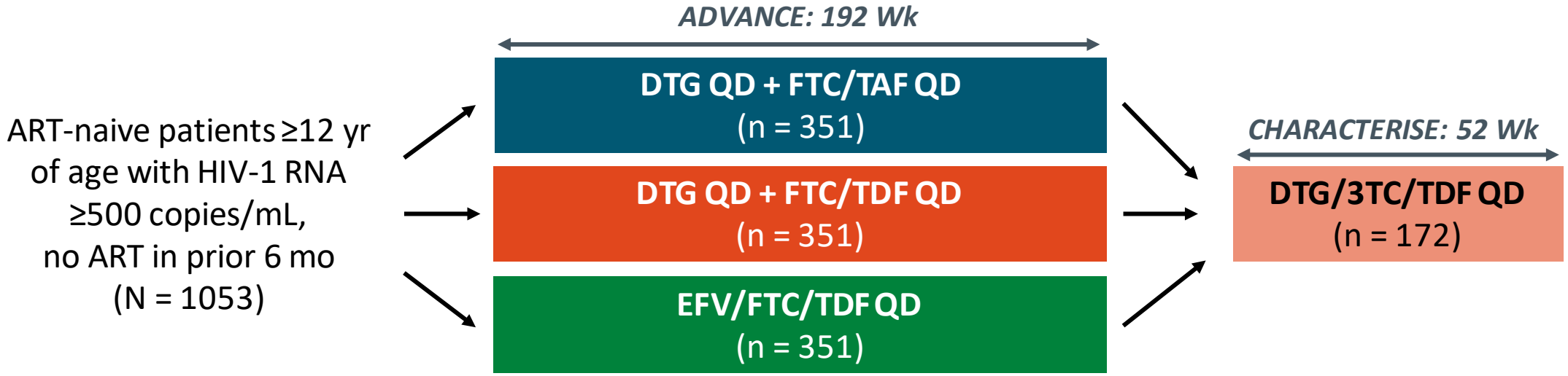


Estimated Weight Δ by Time From TDF to TAF Switch, kg/yr (95% CI)	INSTI (n = 3281)	NNRTI (n = 1452)	Boosted PI (n = 746)
-60 to 0 mos	0.42 (0.26 to 0.59)	0.66 (0.51 to 0.81)	0.31 (-0.02 to 0.64)
0 to 9 mos	2.64 (2.26 to 3.01)	2.25 (1.78 to 2.71)	1.98 (1.13 to 2.83)
9+ mos	0.29 (0.08 to 0.51)	0.20 (-0.14 to 0.54)	-0.11 (-0.57 to -0.35)

Mallon. AIDS 2020. Abstr OAB0604. Mallon JIAS 2021

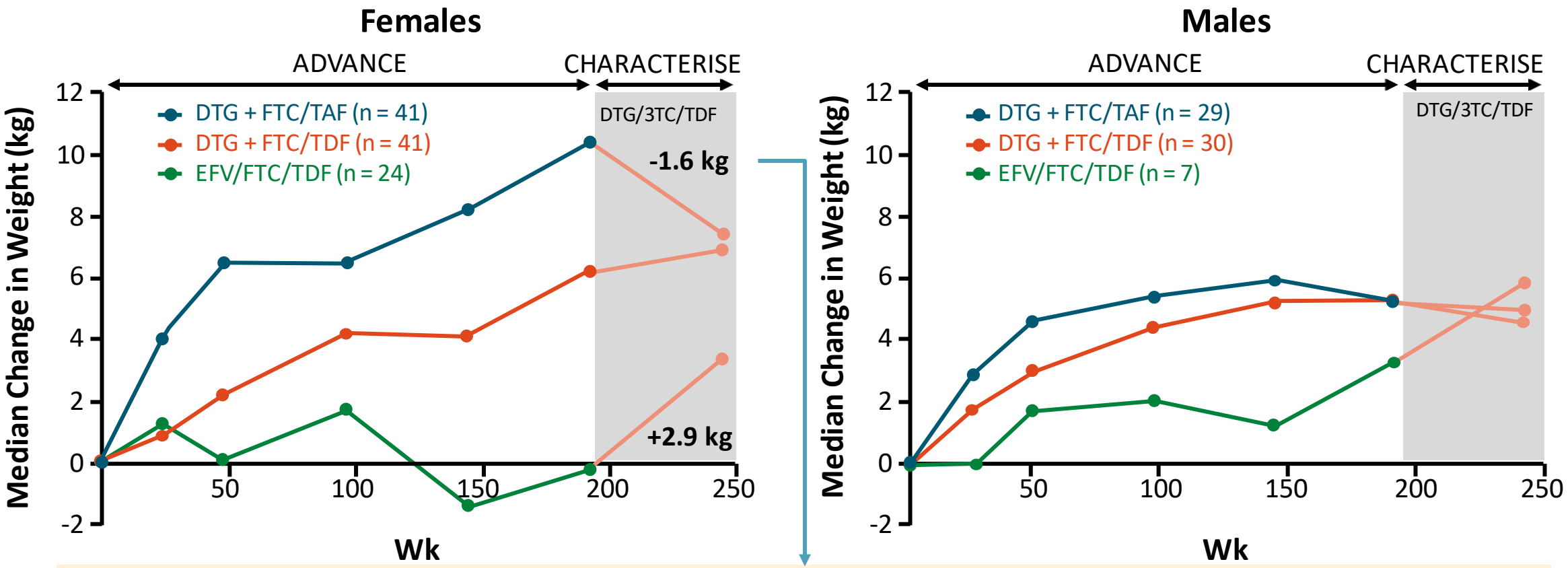
CHARACTERISE: Switch to DTG/3TC/TDF After ADVANCE Trial Participation

- **ADVANCE:** randomized, open-label phase III noninferiority trial in South Africa
  - HIV-1 RNA <50 copies/mL similar across treatment groups at Wk 48 (primary endpoint)[1] and through Wk 192,[2] but weight increases higher with DTG regimens: **+8.9 kg with DTG + FTC/TAF**, **+5.8 kg with DTG + FTC/TDF**, and **+3.3 kg with EFV/FTC/TDF** at Wk 192[2]
- **CHARACTERISE:** evaluation of weight and laboratory changes ≥52 wk after switch from ADVANCE trial to open-label DTG/3TC/TDF[3,4]



1. Venter. NEJM. 2019;381:803. 2. Venter. AIDS 2022. Abstr PELBB01.
3. **Bosch. CROI 2023. Abstr 167. 4**. Bosch. Clin Infect Dis. 2022;ciac949.

CHARACTERISE: Weight Change by Sex After Switch From ADVANCE Trial Regimens to DTG/3TC/TDF



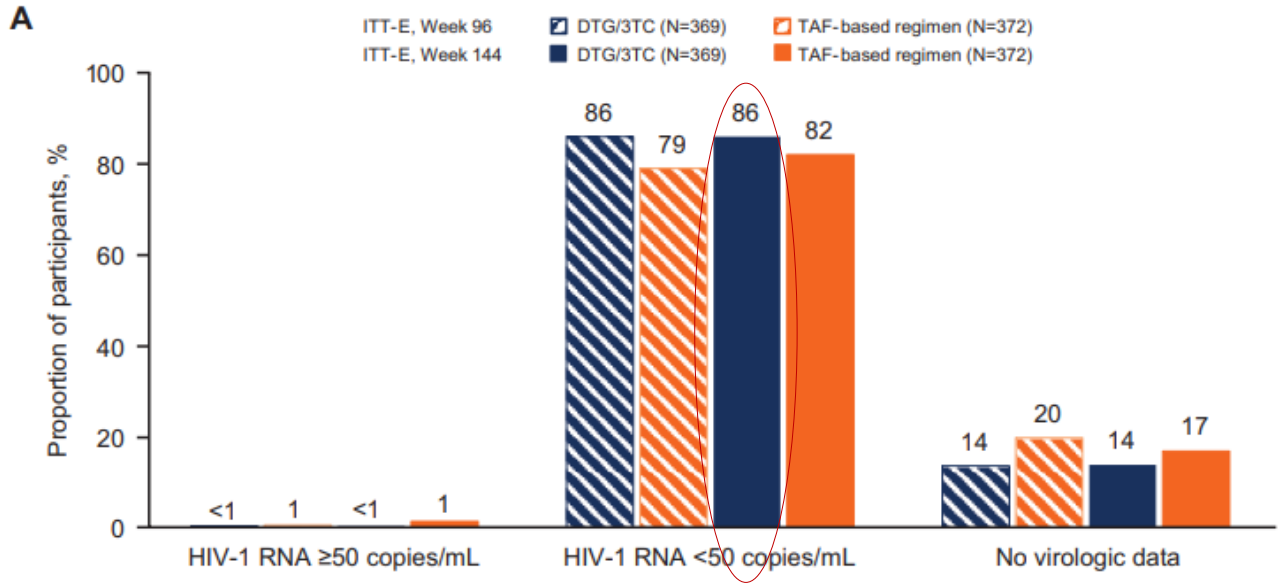
In females, switch from **DTG + FTC/TAF** to **DTG/3TC/TDF** associated with median **1.6 kg weight loss**

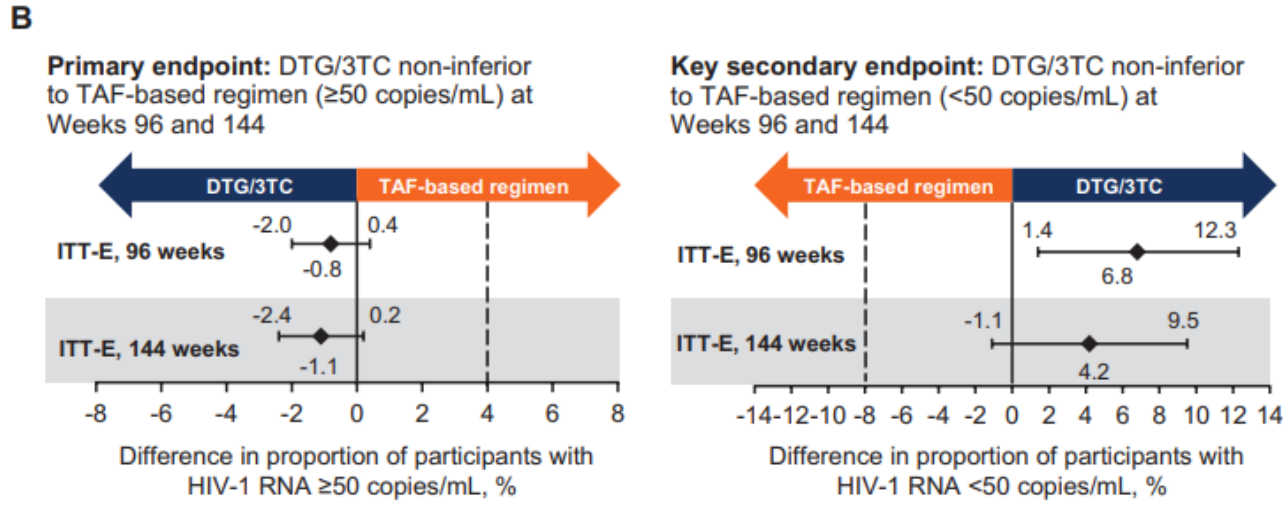
Bosch. CROI 2023. Abstr 167.

If want to simplify to DTG/3TC, know TANGO & SALSA

TANGO:

- Switched from 3-4 drug TAF-containing regimen to DTG/3TC
- Had to be virologically suppressed for 6 months prior to switch
- No h/o NRTI or INSTI mutations
- No prior switch for virologic failure
- Noninferior





Clinical Infectious Diseases
MAJOR ARTICLE

Efficacy and Safety of Switching to Dolutegravir/Lamivudine Versus Continuing a Tenofovir Alafenamide–Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults With Human Immunodeficiency Virus Type 1: Results Through Week 144 From the Phase 3, Noninferiority TANGO Randomized Trial

CID 2022

TANGO study – weight, lipid, inflammatory parameters

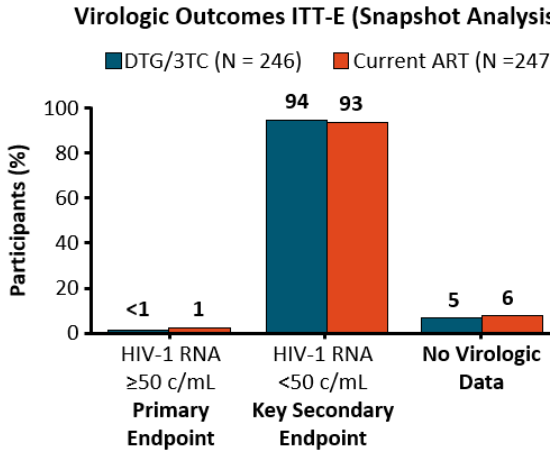
- Bottom line: No difference in weight gain between the two groups (2.2 kg in DTG/3TC vs 1.7 kg in TAF-containing ART by 144 weeks)
  - Among participants with obesity at baseline, higher proportion was referred for dietary counseling/weight management programs in the TAF-based group than in the DTG/3TC group
- Changes from baseline in lipid values generally favored DTG/3TC (especially for total cholesterol, LDL, triglycerides), sustained across 3 years
- No clinical impact on renal function and comparable changes in inflammatory and bone biomarkers across the 2 groups

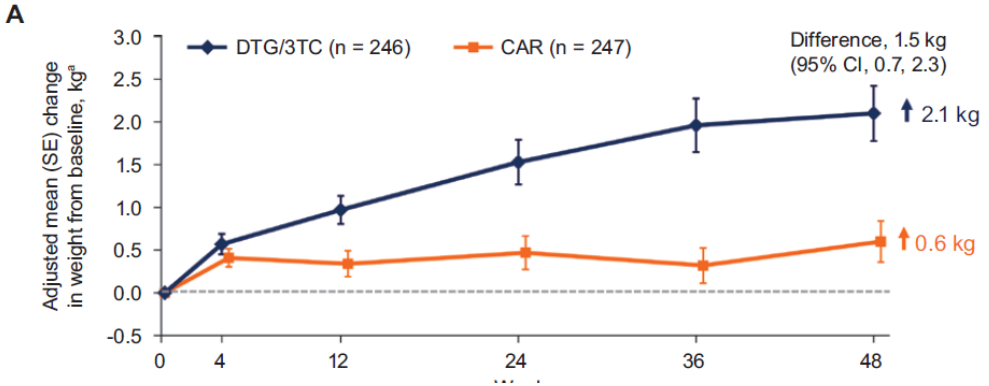
Osiyemi et al. CID 2022

SALSA study: Switched from 3-4 drug regimen to DTG/3TC

SALSA:

- Switched from 3-4 drug regimen to DTG/3TC
- Had to be virologically suppressed for 6 months prior to switch (on 1st or 2nd line ART)
- No h/o NRTI or INSTI mutations
- Noninferior





CID 2023

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Efficacy and Safety of Switching to the 2-Drug Regimen Dolutegravir/Lamivudine Versus Continuing a 3- or 4-Drug Regimen for Maintaining Virologic Suppression in Adults With Human Immunodeficiency Virus 1: Week 48 Results From the Phase 3, Noninferiority SALSA Randomized Trial

Josep M. Llibre,[1] Carlos Brites,[2] Chien-Yu Cheng,[3,4] Olayemi Osiyemi,[5] Carlos Galera,[6] Laurent Hocqueloux,[7] Franco Maggiolo,[8] Olaf Degen,[9] Stephen Taylor,[10,11] Elizabeth Blair,[12] Chey Man,[12] Brian Wynne,[12] James Oyee,[13] Mark Underwood,[12] Lloyd Curtis,[13] Gilda Pantomo,[12] and Jean van Wyk[14]

- Weight gain actually higher in DTG/3TC group but driven by those who switched from TDF and/or EFV
- Both groups minimal changes in lipids and Inflammatory biomarkers
- Better renal (proximal tubular) and bone biomarkers with DTG/3TC

CROI 2023 insights

- ***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

CROI 2023, Seattle, February 2022

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

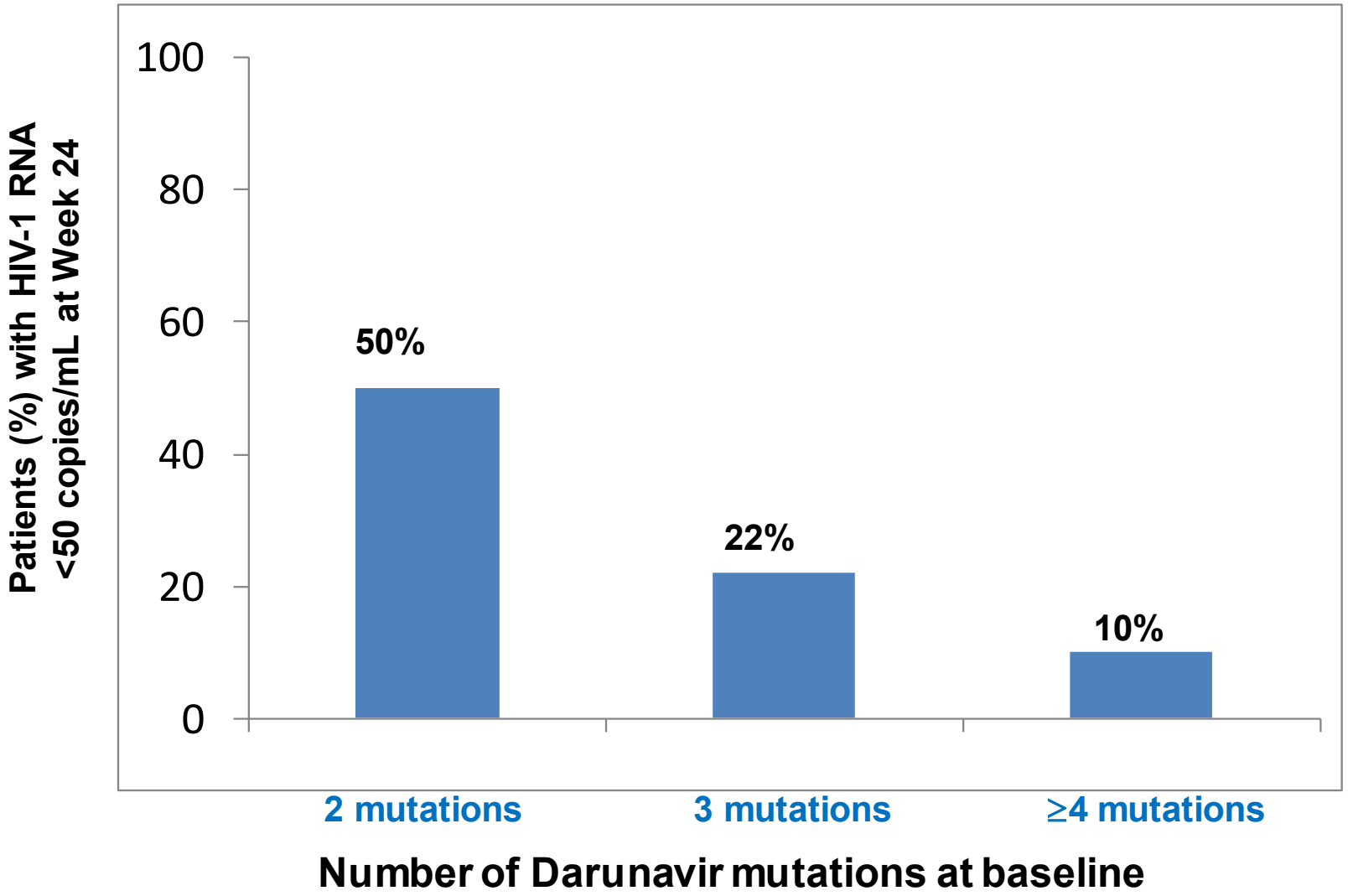
Bosch B. et al. CID April 2023; 76:8: 1492-5

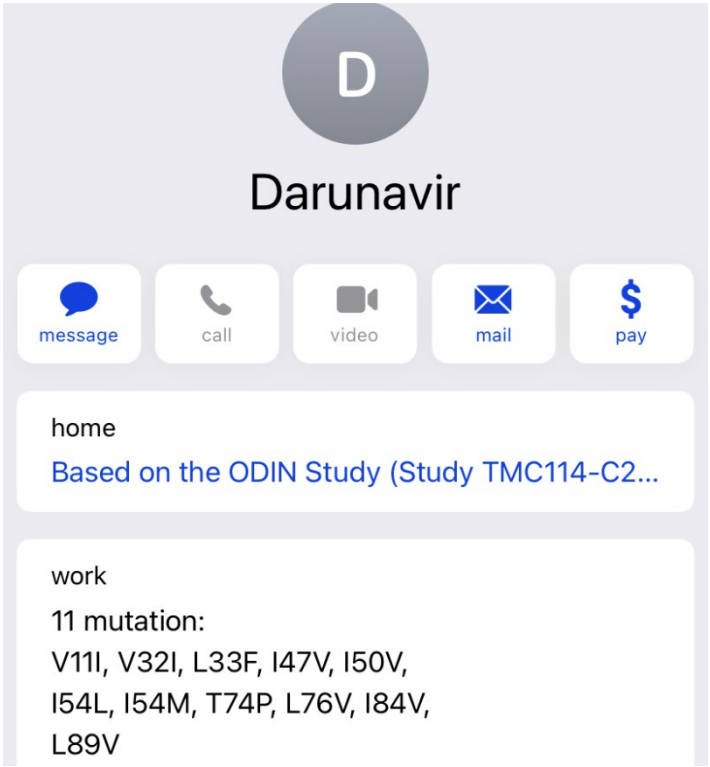
Bottom line: TAF associated with more weight gain than TDF and Efavirenz suppresses weight

What are the four drugs we can use for multidrug resistant HIV?

1. TDF, T20, bNAbs
2. Boosted darunavir, T20, Delavirdine
3. Maraviroc, Fostemsavir, Ibaluzimab, Lenacapavir
4. Boosted lopinavir, boosted tipranavir, TDF

Darunavir response by DRV score





If you text me, I will send you the darunavir contact!

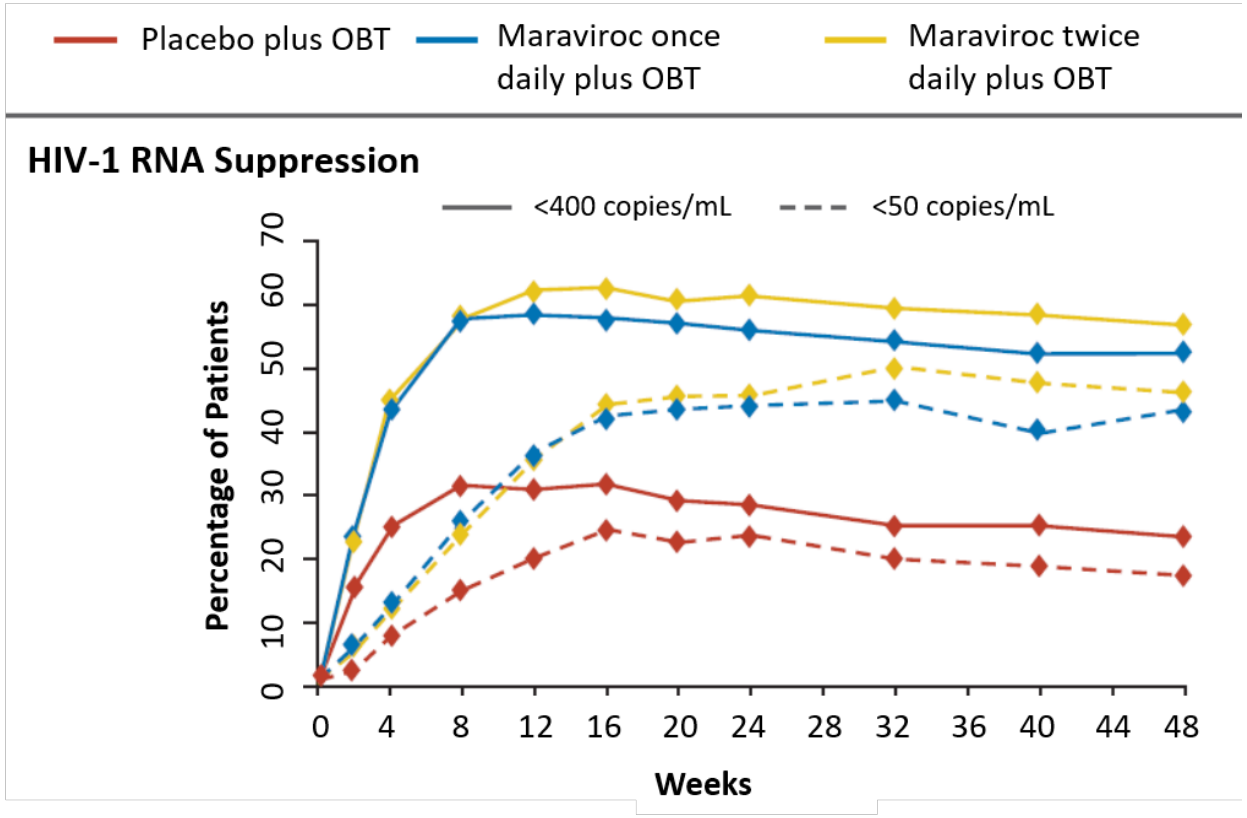
Use BID (twice daily DRV/r) if have 2-3 mutations and efficacy really falls off after 4 or more mutations

De Meyer S, et al. Resistance Workshop 2006. Abstract 73.; Levin J et al, XVIII Intl Drug Resistance Workshop, June 9-13, 2009.

Maraviroc for MDR Patients with Viremia: *MOTIVATE-1 and -2 Studies*

CCR5 receptor antagonist approved in 2007 for patients with CCR5-tropic, multidrug-resistant HIV

Parallel phase studies of viremic MDR patients (N = 1,049) on optimized background therapy (OBT) per treatment history and resistance testing, randomized to additionally receive maraviroc daily, maraviroc BID, or placebo

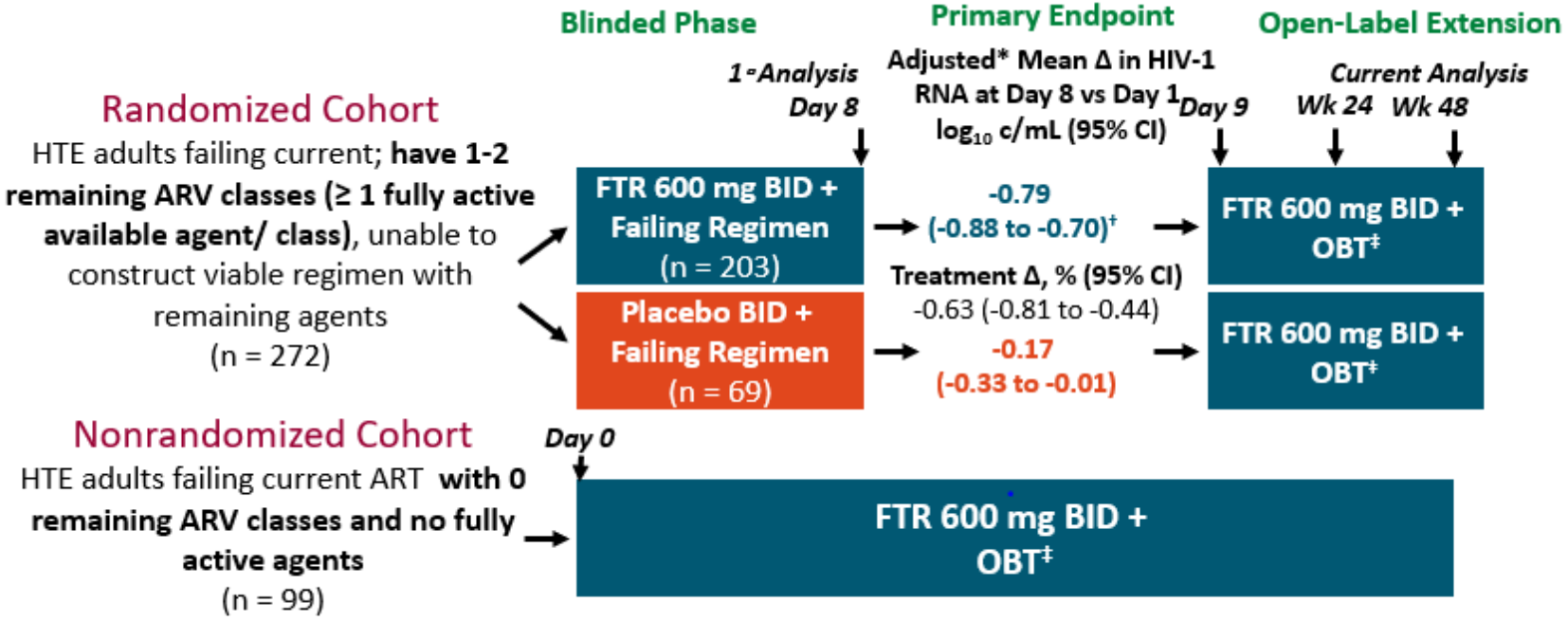


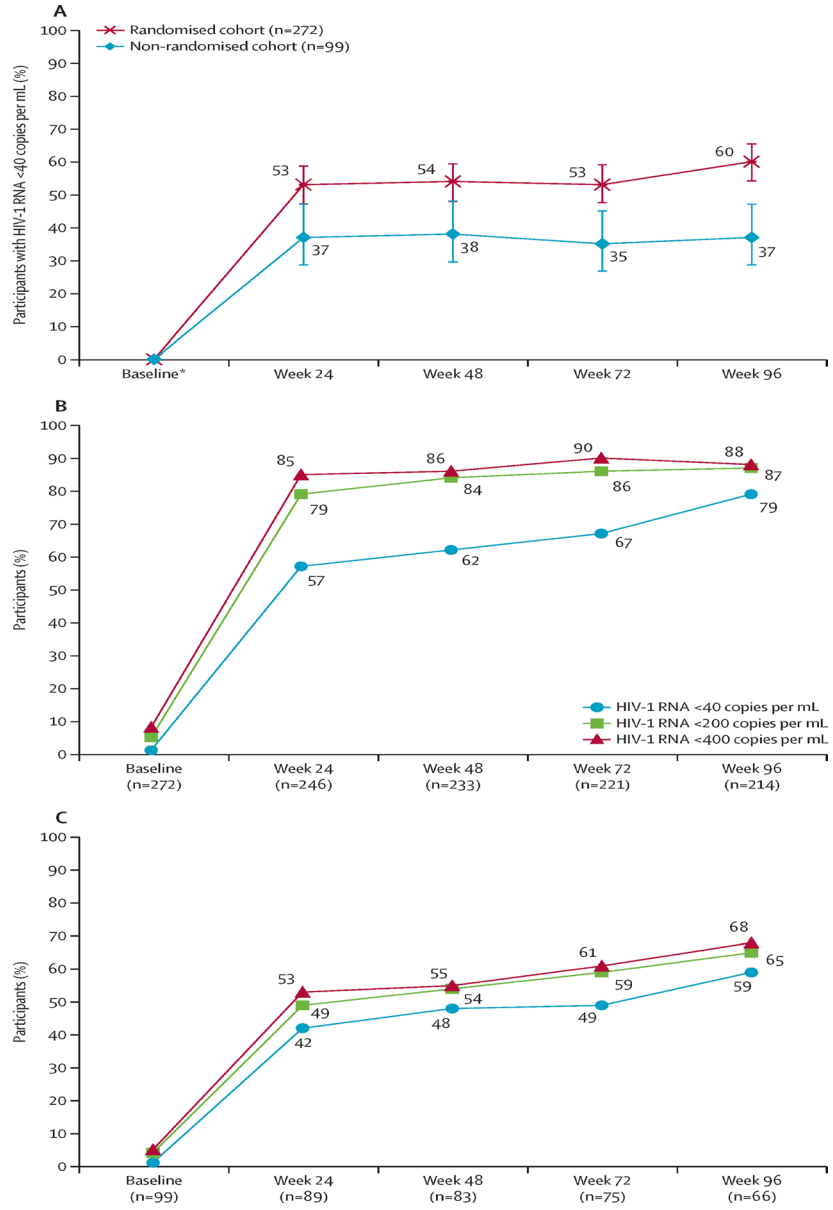
- **Must assess CCR5 tropism prior to using this medication**

Adding maraviroc to OBT was associated with improved viral suppression

OBT = Optimized Background Regimen; MVC = Maraviroc; BID = Twice Daily; **Gulick RM, et al. *N Engl J Med*. 2008;359(14): 1429-1441.**

BRIGHTE: Fostemsavir in Heavily Treatment–Experienced Adults at Wk 96





Metabolized into temsavir which binds to viral glycoprotein 120, preventing binding to CD4 (600mg po BID, no major ddIs)

Latallaide Lancet HIV 2020.

Ibalizumab: IV (now 30 second push) Option for MDR HIV

Guernica –
Pablo Picasso

Given every 2 weeks in addition to optimized background regimen in MDR HIV failing ART
Administered via intravenous infusion or 30-second IV push (IV push approved Oct 2022)

Phase 3 TMB-301 Efficacy Results:

% of participants with HIV RNA < 50 c/mL

- **Week 24: 43%**
- **Week 48: 59%**

Efficacy Results from TMB-311 Expanded Access Protocol (N = 38):

% of participants with HIV RNA < 50 c/mL

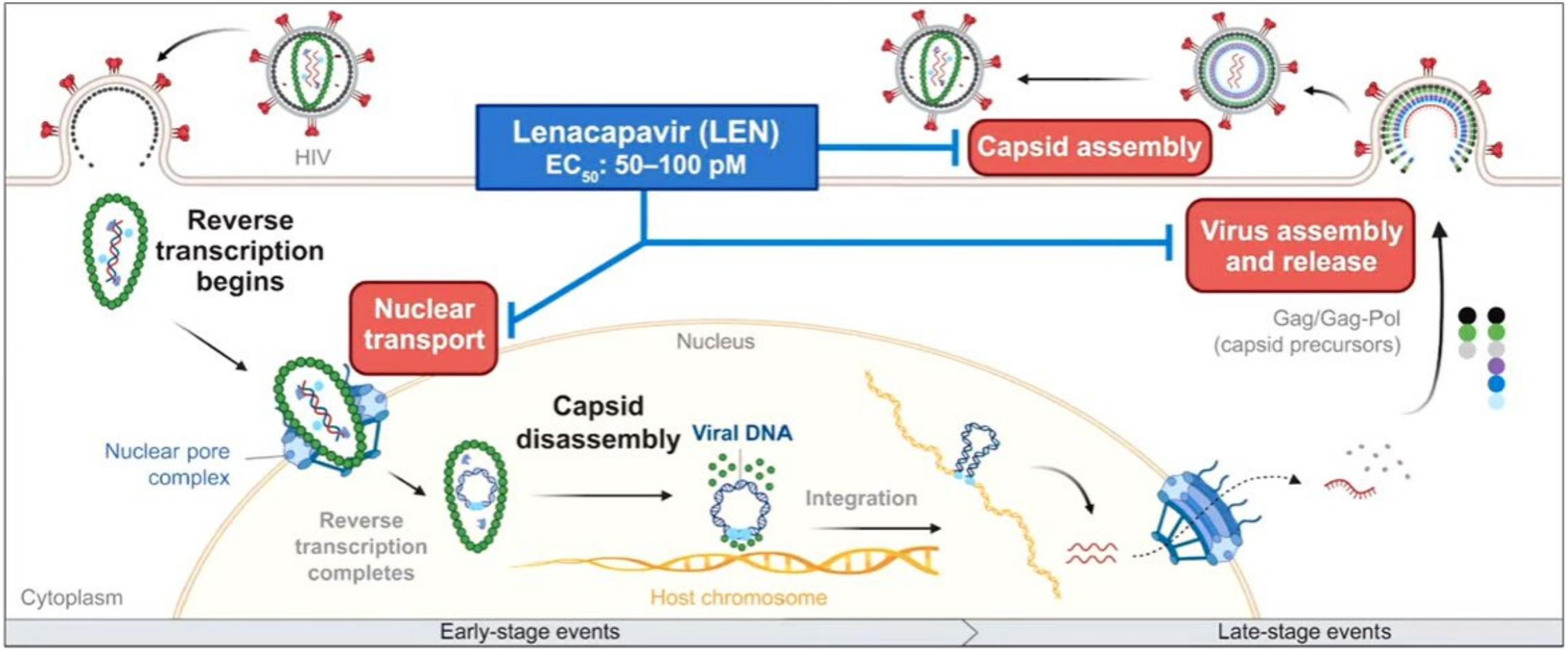
- **Week 24: 46%**
- **Week 48: 47%**
- **Week 96: 55%**

CD4-directed (gp120) post-attachment inhibitor approved in 2018

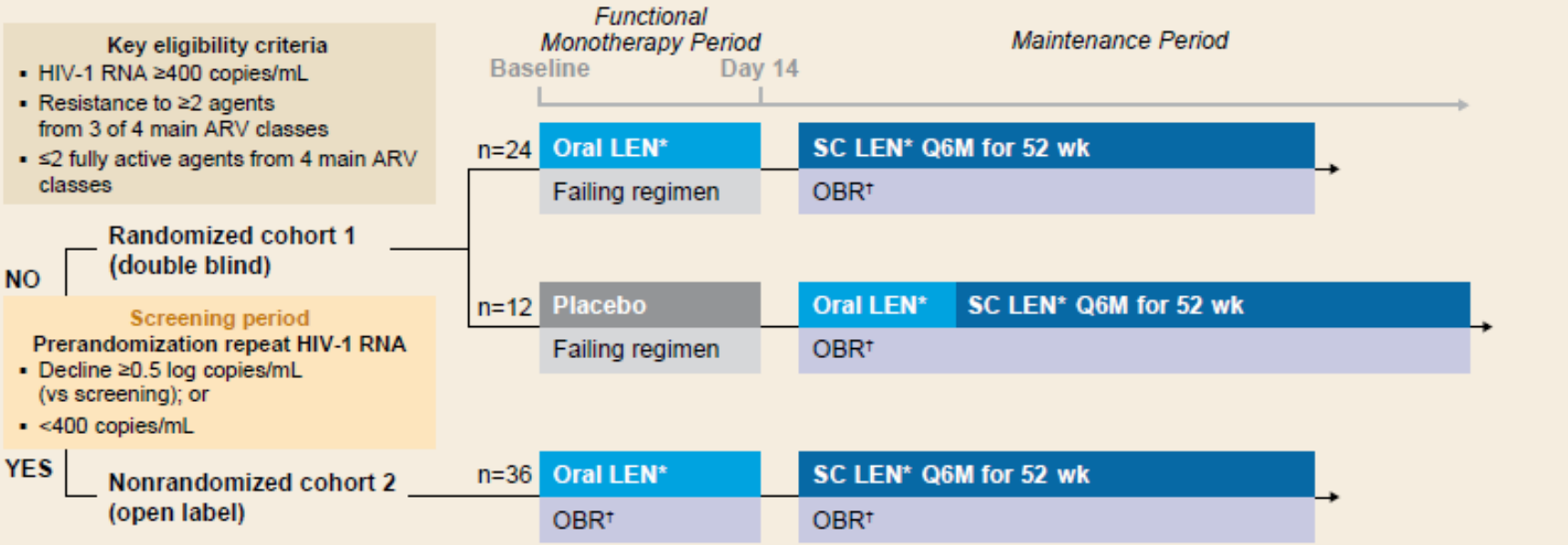
HTE = Heavily Treatment-Experienced; MDR = Multidrug-Resistant; ART = Antiretroviral Therapy

Emu B, et al. *New Engl J Med*. 2018;379(7):645–654; Emu B, et al. IDWeek 2019. Washington, DC. Abstract 661; Emu B, et al. CROI 2019. Seattle, WA. Abstract 485; Towner W, et al. IDWeek 2020. Abstract 1027.

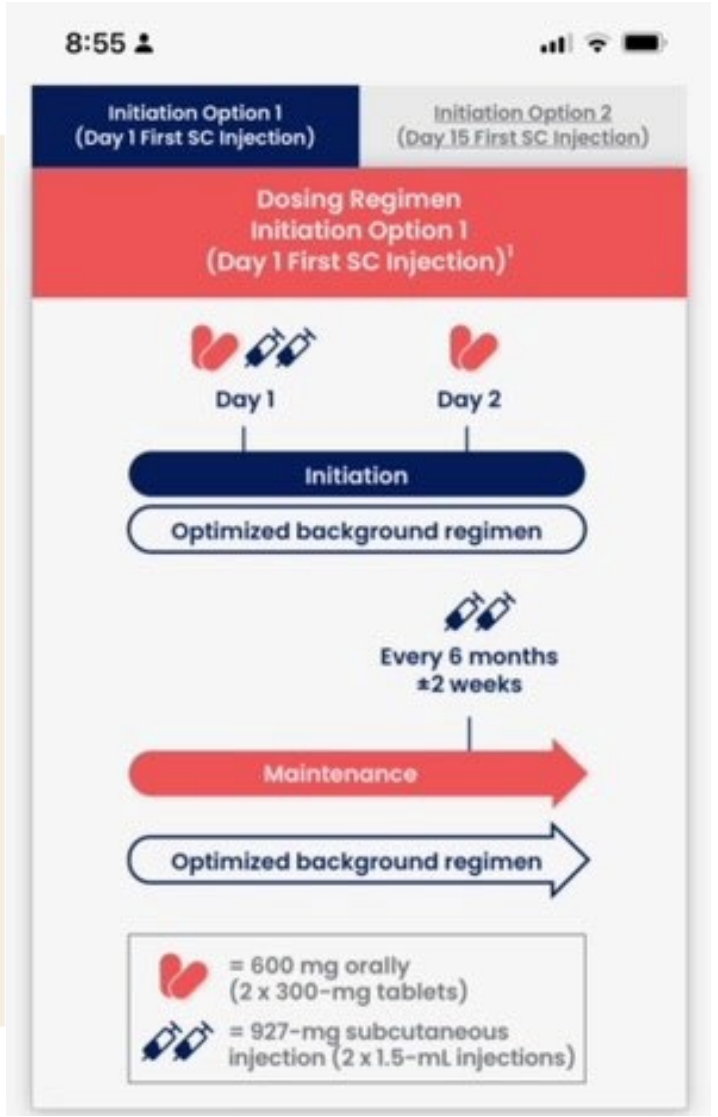
LEN Targets Multiple Stages of HIV Replication Cycle



CAPELLA Study Design[9-11]



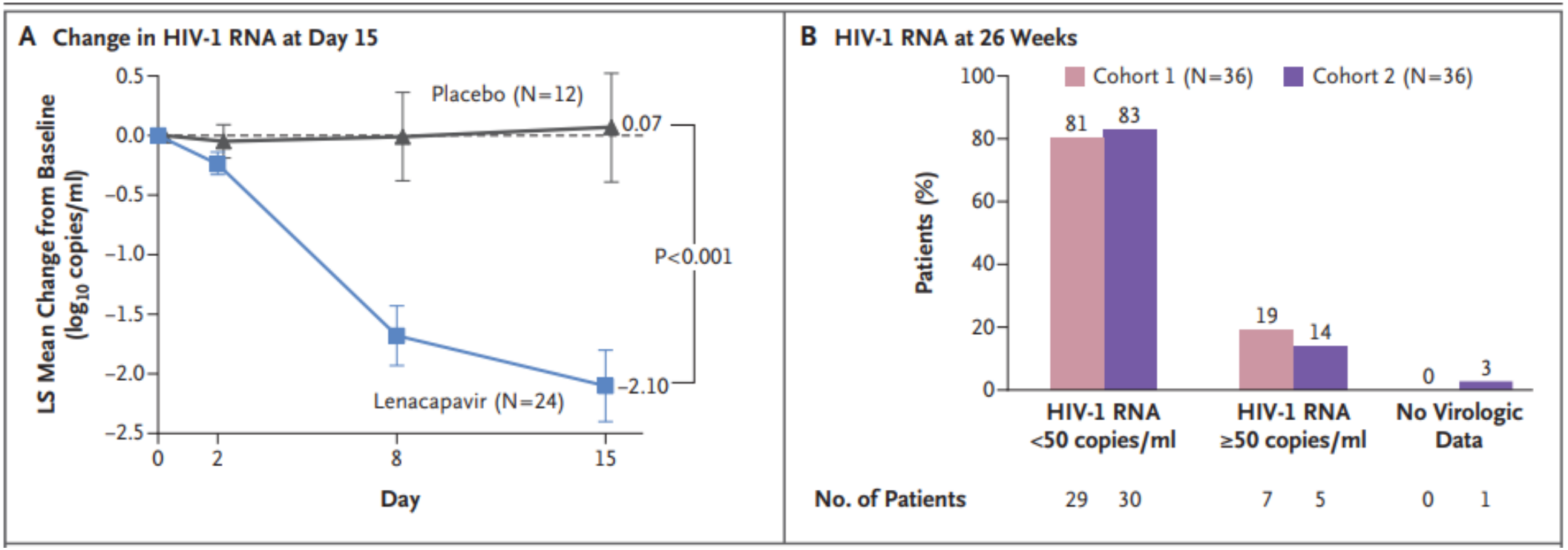
*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8 (600 mg on Days 15 and 16, and 300 mg on Day 22 for placebo participants); SC LEN administered as 927 mg (2 x 1.5 mL) in abdomen on Day 15; †Investigational agents, such as fostemsavir (FTR), were allowed; atazanavir (ATV), ATV/cobicistat (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

Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial

Published: July 11, 2023

THE LANCET HIV

Phase 2/3: LEN in HTE PLWH

Postbaseline Resistance Analysis at Week 52

Capella

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 to put into your phone contact: M66I, K70S, T107A, N74D, A105T, K70S, Q67H
- All 9 out of 72 occurred during “functional” monotherapy – not having support of OBR

Objectives of talk

- First line therapy worldwide and why
- **Summary of long -acting ART currently available – clinical trial and real world data**
- Practical considerations of long-acting ART
- Treatment strategies in the future what is coming?

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

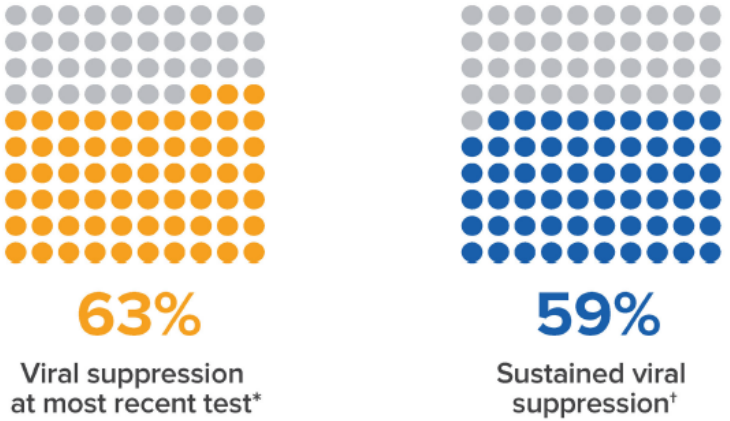
ATLAS 2M

- 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

Adherence Challenges with ARTs

Figure 4. Percentage of adults with diagnosed HIV who were virally suppressed during the 12 months befo interview—Medical Monitoring Project, United States, 2020



Overall rates of VS in US 59% sustained (CDC HIV Special Surveillance Report 8/23)

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, retrospectiv 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

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

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

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)

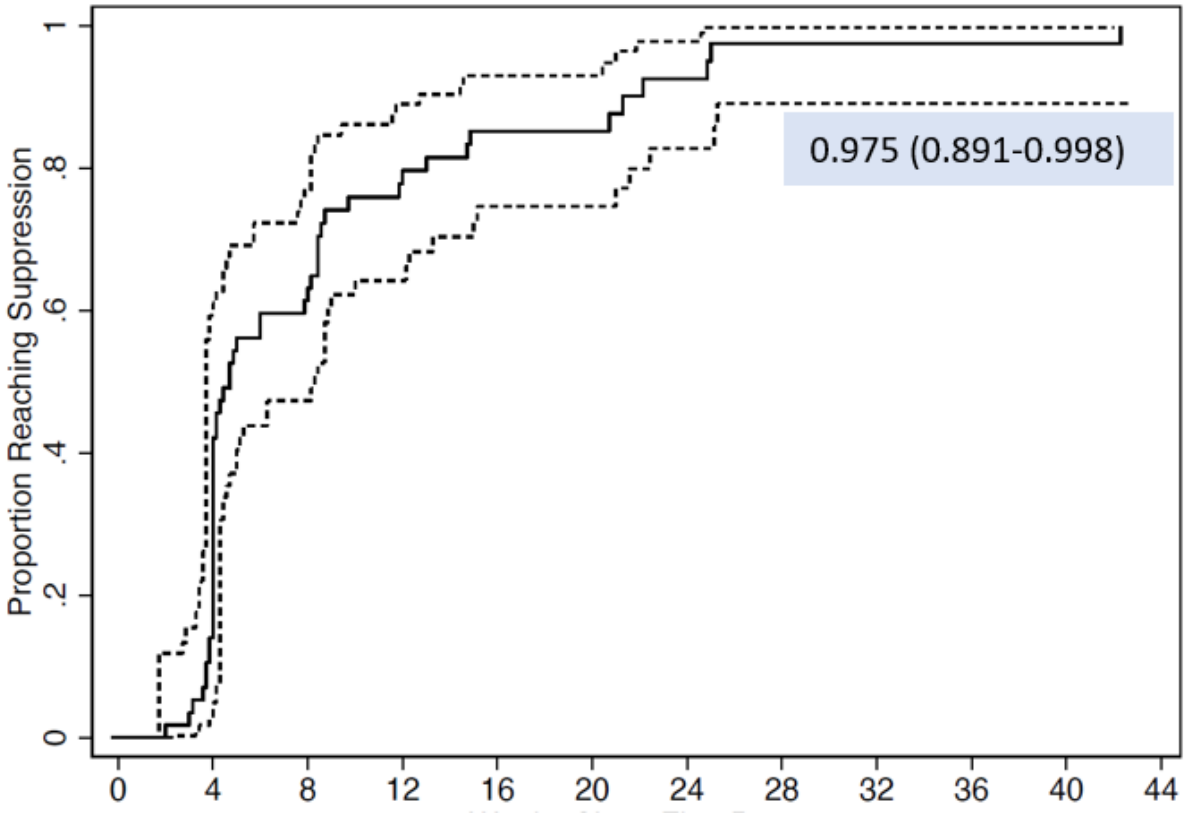
* Note: ADAP is AIDS Drug Assistance Program; Baseline CD4 defined as the CD4 count closest to and including date of first injection. Median time from CD4 count to first injection was 70 (range 0 to 882) days

- 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

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- WHO resistance report Nov '21)

TECHNICAL REPORT

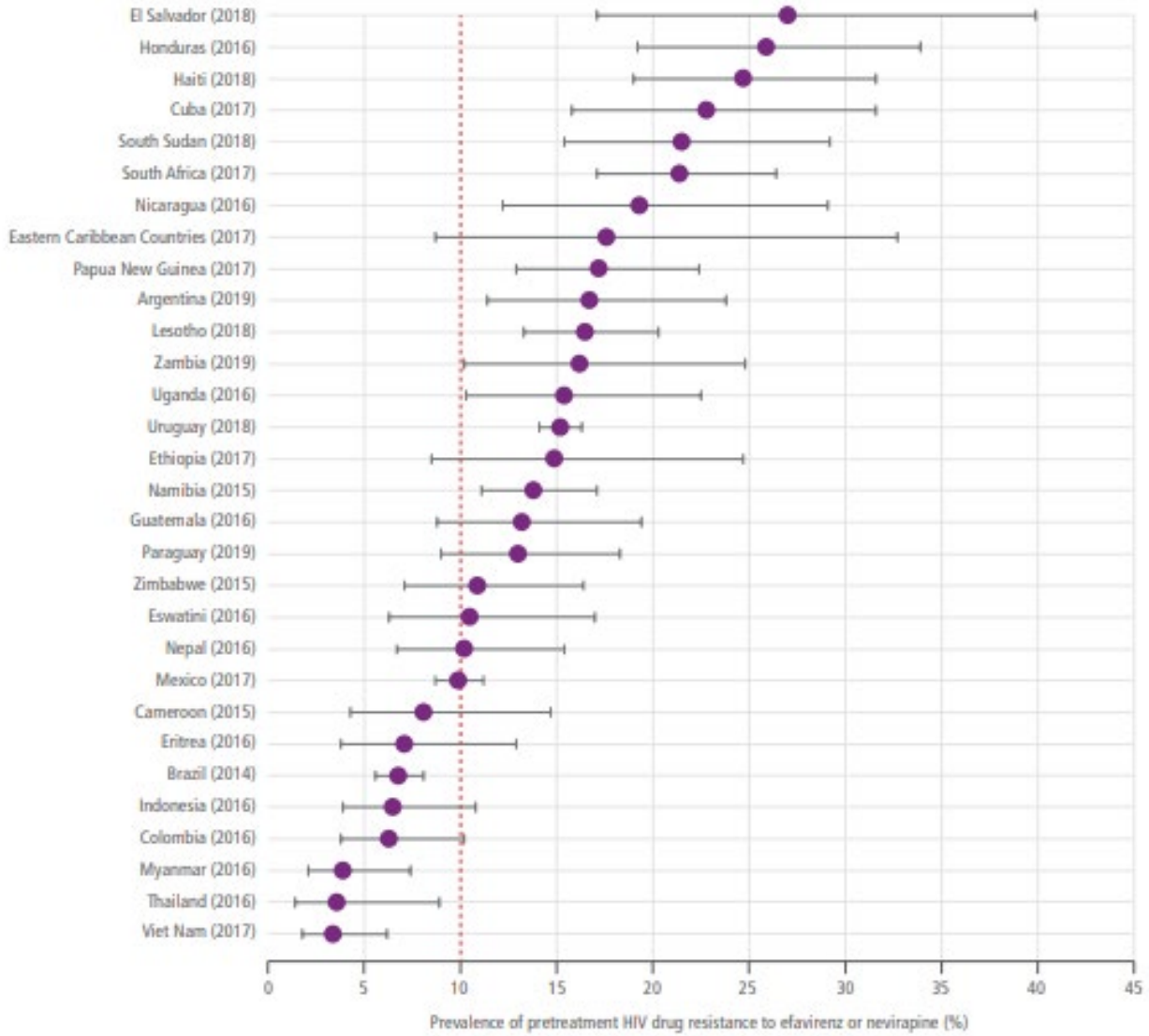
HIV DRUG RESISTANCE REPORT 2021

NOVEMBER 2021

HIV DRUG RESISTANCE

World Health Organization

Fig. 1.3. Prevalence of pretreatment HIV drug resistance to efavirenz or nevirapine among adults initiating antiretroviral therapy, 2014–2020



Objectives of talk

- First line therapy worldwide and why
- Summary of long-acting ART currently available – clinical trial and real world data
- **Practical considerations of longacting ART**
- Treatment strategies in the future what is coming?

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 CID 2023)

Clinical Infectious Diseases

MAJOR ARTICLE

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

ECHO/THRIVE TRIALS (RPV vs EFV) SHOWED US MOST IMPORTANT RPV EMERGENT MUTATIONS

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

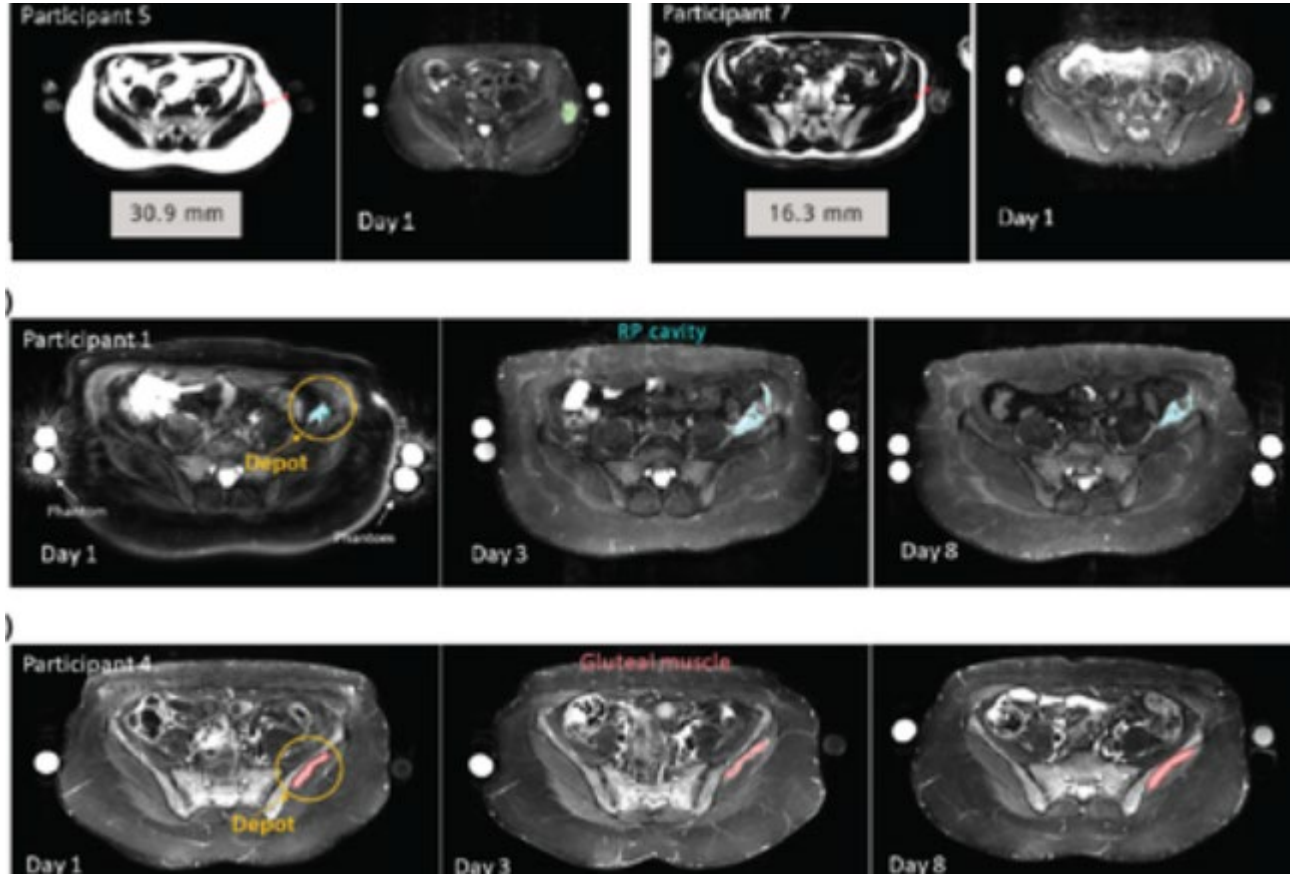
- V90I
- L100I
- K101E
- E138K/Q
- V179I
- Y181C
- V189I
- H221Y
- F227C

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

At CROI 2023, added 4th trial to look at LA CAB/RPV in treatment naïve (SOLAR, now published)

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

THE LANCET
HIV

Efficacy, safety, and tolerability of switching to long-acting cabotegravir plus rilpivirine versus continuing fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV, 12-month results (SOLAR): a randomised, open-label, phase 3b, non-inferiority trial

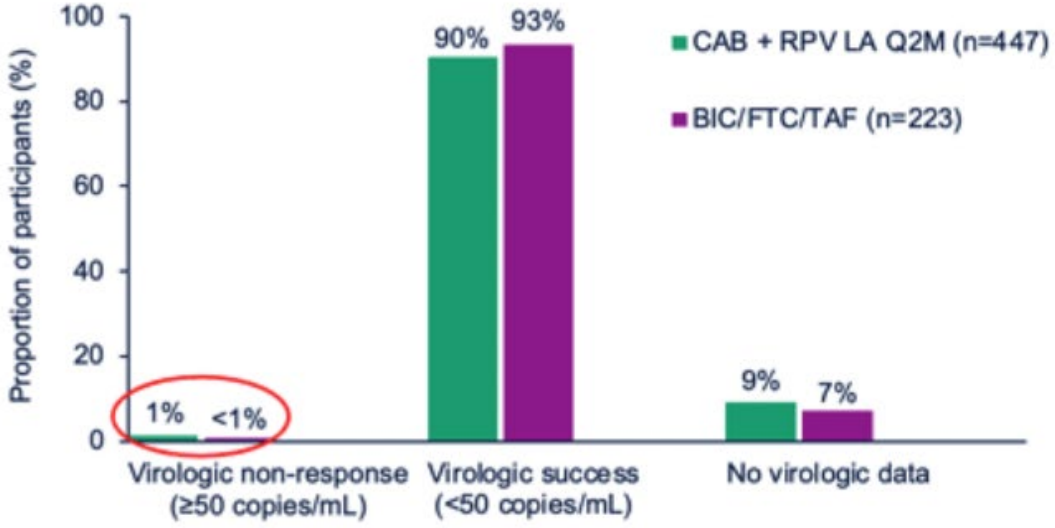
Published: August 08, 2023

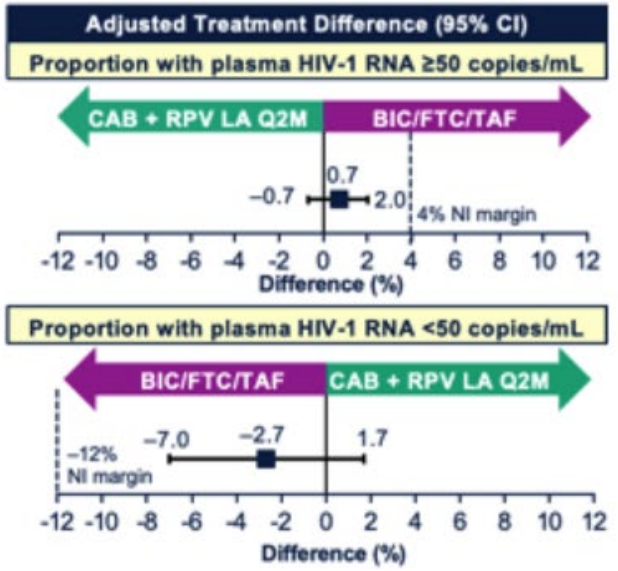
- SOLAR Phase 3b, randomized, open-label, multicenter, noninferiority (study assessing switching virologically suppressed adults to CAB+RPV LA every 8 weeks vs continuing BIC/FTC/TAF)
- Of 670 participants, 447 switched to LA ART and 223 continued B/FTC/TAF
- Trial out to 12 months

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

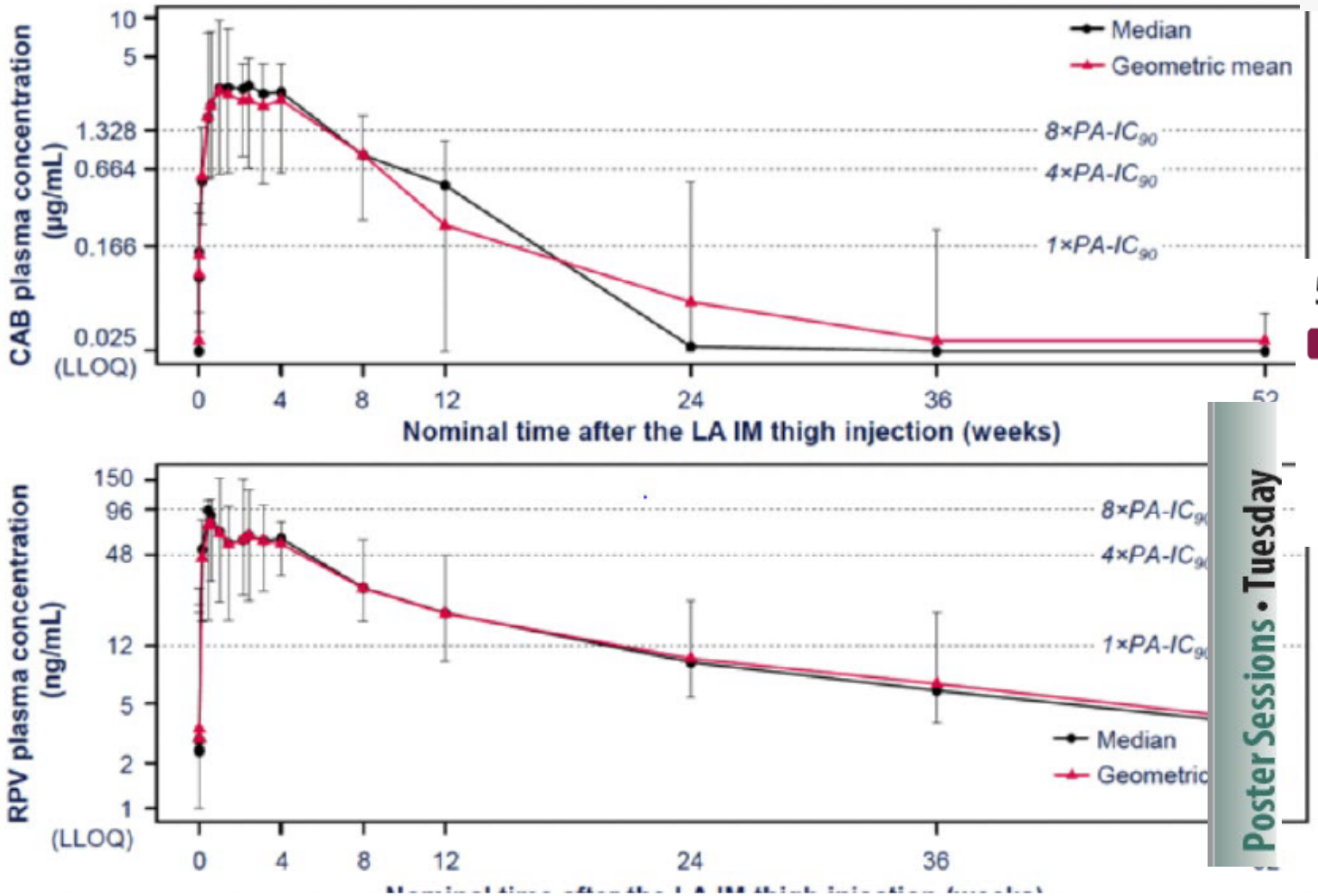
- Many patients expressed desire for long-acting
- 2 patients out of 447 had on-treatment mutations

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

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

AIDS 2022
29 July – 2 August

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



Poster Session-H1 LAI CAB/RPV: WHERE ARE WE NOW AND WHERE ARE WE GOING?
2:30 PM - 4:00 PM

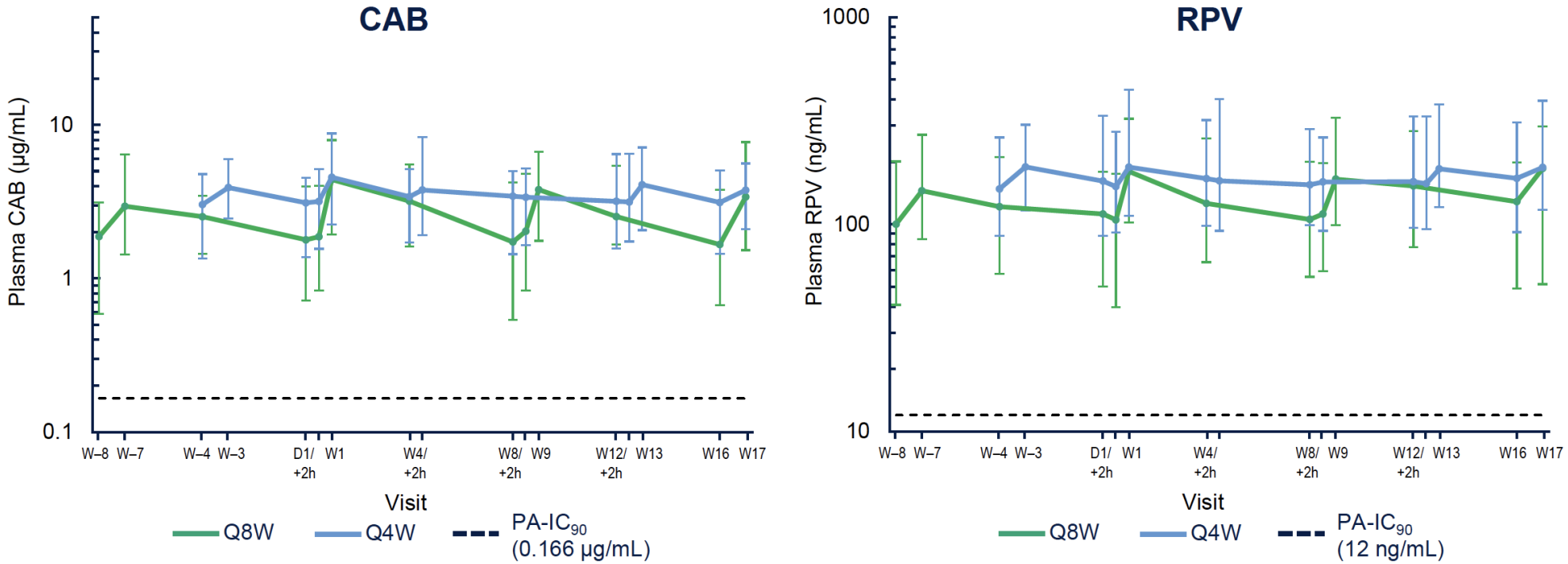
519 LB

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

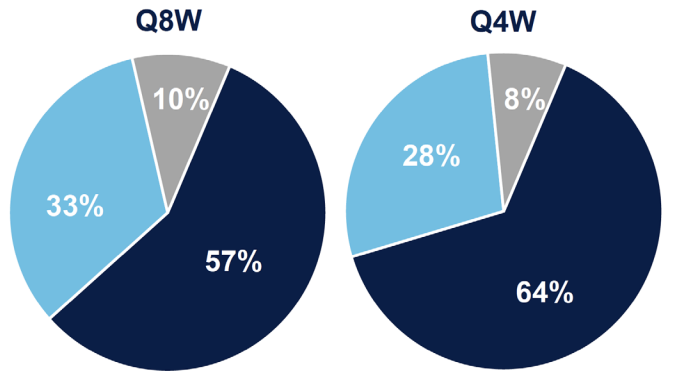
Franco Felizarta, Ronald D'Amico, Kehui Wang, Herta Crauwels, Mar Masiá, Miguel Garcia Deltoro, Olaf Degen, Jonathan Angel, Chiu-Bin Hsiao, Vasiliki Chounta, Kelong Han, Conn Harrington, Kelly Rimler, William R. Spreen, Susan Ford

Poster Sessions • Tuesday

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



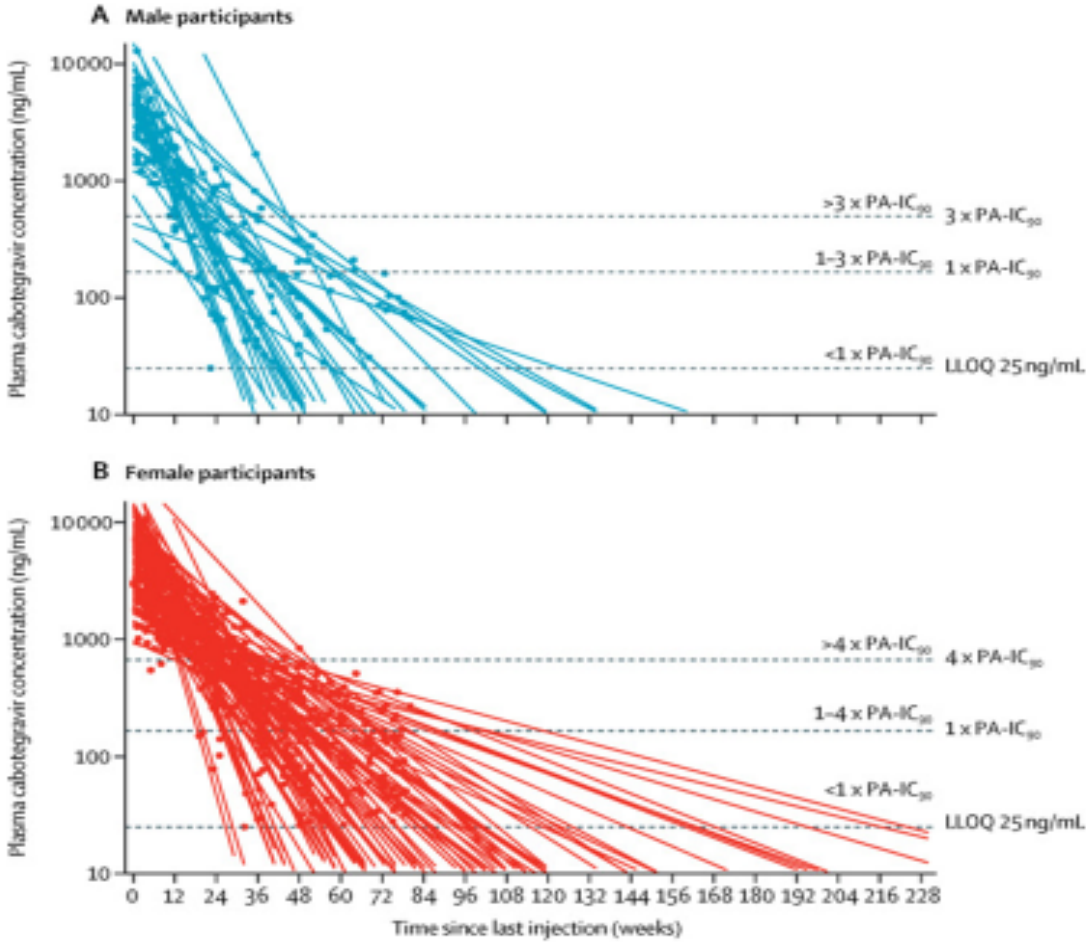
CAB, cabotegravir; Cτ, concentration at dosing interval; D, day; Q4W, every 4 weeks; Q8W, every 8 weeks; $PA\text{-}IC_{90}$, protein-adjusted 90% inhibitory concentration; PO, oral therapy; RPV, rilpivirine; W, week.



*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

CAB LA TAIL IS LONGER IN WOMEN THAN MEN

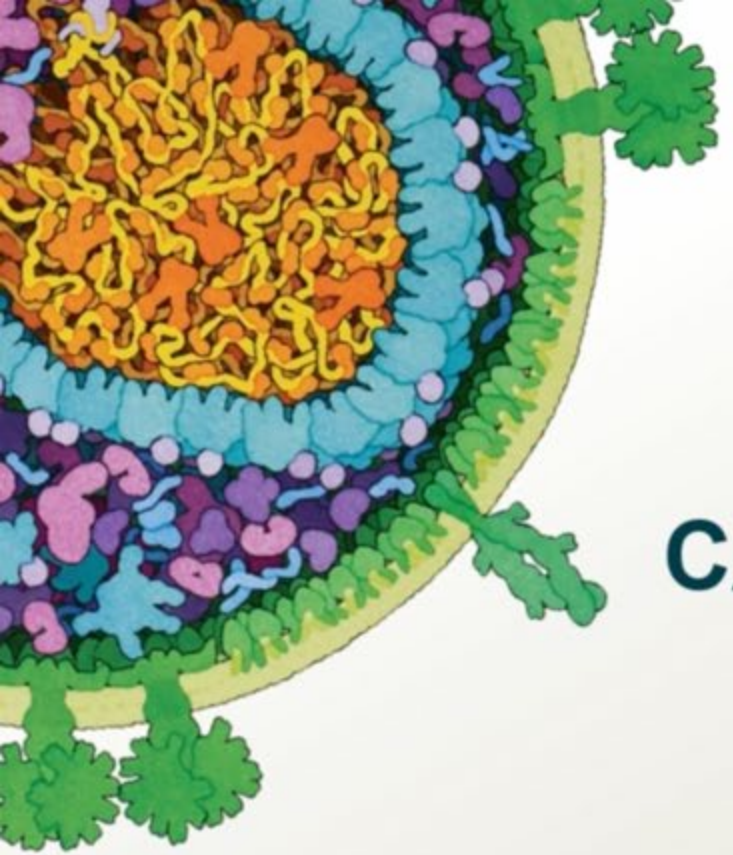


- Median time to undetectable cabotegravir is longer in women at 66.3 weeks (range 17.7 to 182) when compared to 42.7 weeks (range 20.4 to 134) in men

HPTN
HIV Prevention Trials Network

HPTN 077

Landovitz R. Lancet HIV. June 2020



ORAL ABSTRACT: OA-8

Tuesday, February 21, 2023

CABOTEGRAVIR PHARMACOLOGY IN THE BACKGROUND OF DELAYED INJECTIONS IN HPTN 084

Mark A. Marzinke

The Johns Hopkins University School of Medicine, Baltimore, MD, United States

30th CROI 2023

Summary/Conclusions: 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
- May want to study q3 month injections in women (can time with injectable progesterone contraception)

1.

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

CROI 2023 Feb 20-23

Two French University clinics; 88% male

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

Trough concentrations

Drug trough concentrations		At 1 month (n=58)
CAB	**Trough < 1120 ng/mL**, n (%)	**35 (60)**
	Median trough, ng/mL (IQR)	**976 (706 – 1434)**
	No lead-in (n=42)	*951 (681 – 1196)*
	Lead-in (n=16)	*1213 (908 – 1479)*

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

Summary of resistance mutations across HPTN083 (CAB alone, look at bolded mutations)

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**

Yes, N155H came out in CAB breakthroughs in treatment and prevention trials

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

Objectives of talk

- First line therapy worldwide and why
- Summary of long-acting ART currently available – clinical trial and real world data
- Practical considerations of long-acting ART
- **Treatment strategies in the future - what is coming?**

Lenacapavir PrEP studies (in progress) will tell us more about how to use LEN in treatment (injection site reactions, resistance mutations, acceptability)

PrEP Studies Overview

About PURPOSE 1

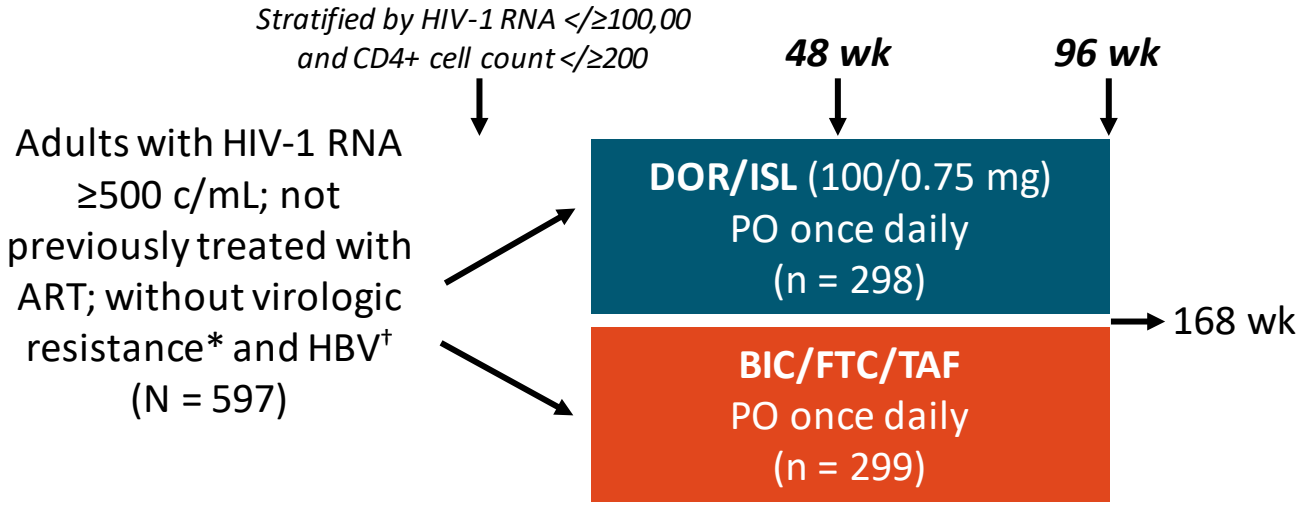
- Phase 3 study of an investigational drug, lenacapavir, for PrEP and emtricitabine/tenofovir alafenamide (F/TAF) for **PrEP in Adolescent Girls and Young Women**
- This study will be conducted in South Africa and Uganda

About PURPOSE 2

- Phase 3 study of an investigational drug, lenacapavir, **for PrEP for Cisgender Men, Transgender Women, Transgender Men, and Gender Non-Binary individuals Who Have Sex With Partners Assigned Male at Birth**
- This study will be conducted in the United States, South Africa, Peru, and Brazil

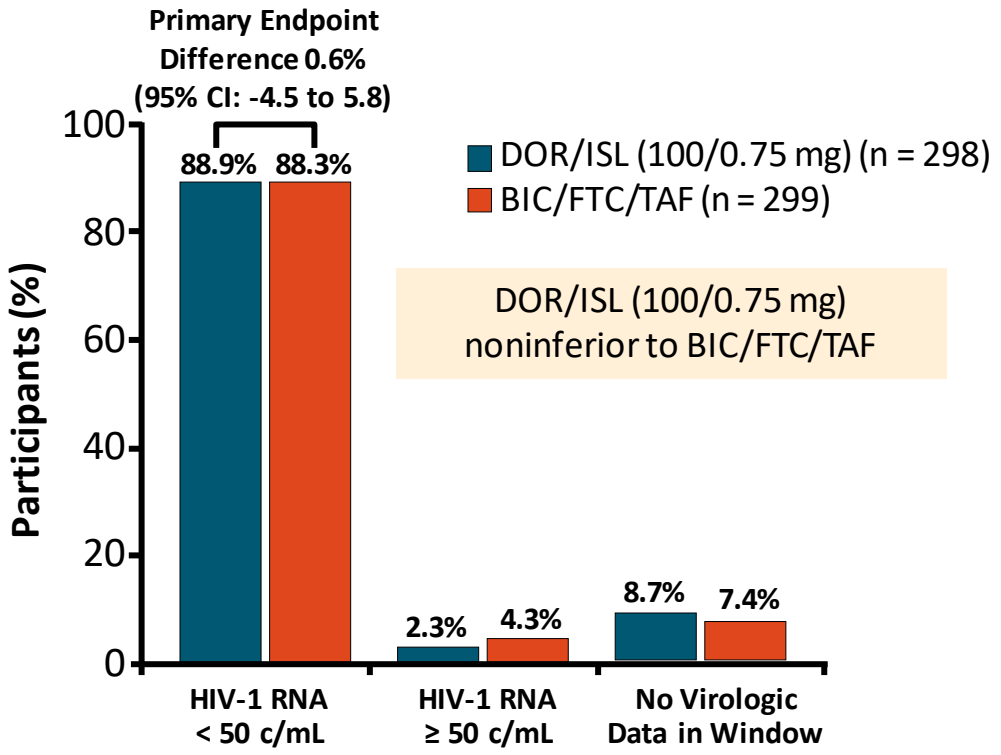
Islatravir: DOR/ISL (100/0.75 mg) vs BIC/TAF/FTC as First-line Treatment of HIV: Study Design and Results

- Double-blind, randomized phase III trial



*V106A/M, V108I, Y188I, H221Y, P225H, F227C/L, M230I/L, L234I, P236L, Y318F, K65R/E/N, M184I/V, K70E, T69insert, Q151M, or ≥3 of M41L, D67N, K70R, L210W, T215F/Y, K219E/Q.
†HCV without synthetic hepatic dysfunction allowed.

Virologic Outcomes Wk 48, FDA Snapshot Approach



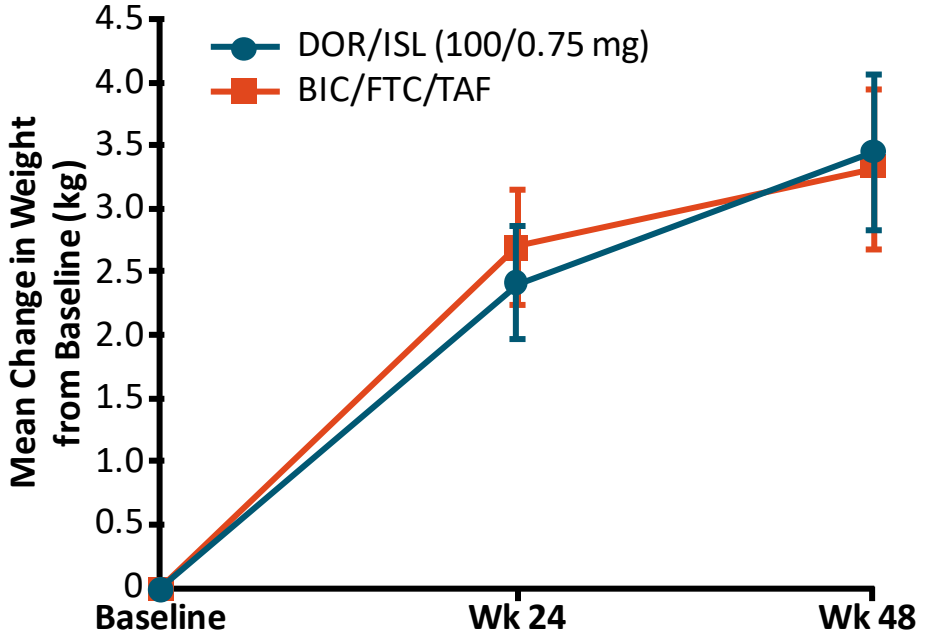
- Primary endpoint: HIV-1 RNA <50 c/mL at Wk 48 by FDA snapshot analysis
- BL characteristics: 25% female, 20% CD4 count <200 cells/mm^3, 19% HIV-1 RNA >100,000 c/mL

Rockstroh. IAS 2023. Abstr OALBX0102.

Slide credit: clinicaloptions.com

DOR/ISL (100/0.75 mg) vs BIC/FTC/TAF as First-line Treatment of HIV: Virologic Failure and AEs

Protocol-Defined Virologic Failure				
Arm	**Wk**	**VF**	**Treatment-Emergent RASs**	**Phenotype**
DOR/ISL	24	Incomplete response	**NNRTI: V106A, P225H NRTI: M184I**	**R: DOR**
BIC/FTC/TAF	8	Rebound	None	S: FTC/TAF
BIC/FTC/TAF	36	Rebound	No result	Unavailable
BIC/FTC/TAF	24	Incomplete response	None	S: BIC/FTC/TAF
BIC/FTC/TAF	36	Incomplete response	None	S: BIC/FTC/TAF



- Similar rates of AEs and serious AEs
  - DOR/ISL associated with numerically higher rates of lymphocyte count decrease, including requiring treatment discontinuation; similar rates of infection-related AEs
- **No difference in mean change in weight**
  - DOR/ISL: +3.45 kg (95% CI 2.83-4.06)
  - BIC/FTC/TAF: +3.32 kg (95% CI 2.86-3.96)

DOR/ISL (100/0.25 mg) moving forward in development

Rockstroh. IAS 2023. Abstr OALBX0102.

Slide credit: clinicaloptions.com

Islatravir: *Clinical Trial Updates*

- ***Trials held Dec 2021 – Sept 2022 - decreases in total lymphocyte and CD4 T-cells***
- ***In Sept 2022, FDA granted permission for resumed testing with a lower dose of islatravir***

Indication	Current status *(October 2022)*	
PrEP *(all patients)*	**All studies discontinued**	
Treatment *treatment-naïve patients*	**Doravirine/ islatravir**	• Once-daily oral combination • New Phase 3 study with 0.25mg po daily of islatravir
Treatment *virally suppressed patients*	**Doravirine/ islatravir**	• Once-daily oral combination • Two new Phase 3 studies 0.25mg po daily of islatravir
	Islatravir + lenacapavir	• Once-weekly oral treatment • Phase 2 study to resume with a lower dose of islatravir

NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor; NRTTI = Nucleoside Reverse Transcriptase Translocation Inhibitor.

Pharmacy Times. Revised Clinical Trial Program to Evaluate Daily Oral Islatravir Plus Doravirine Combo for HIV. Sept 20, 2022. https://www.pharmacytimes.com/view/revised-clinical-trial-program-to-evaluate-daily-oral-islatravir-plus-doravirine-combo-for-hiv-1. Accessed 10/7/2022; ClinicalTrials.gov. Switch to Doravirine/Islatravir (DOR/ISL) in Human Immunodeficiency Virus 1 (HIV-1) Participants Treated With Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/FTC/TAF) (MK-8591A-018). Accessed 10/7/2022; ClinicalTrials.gov. Study Evaluating the Safety and Efficacy of Islatravir in Combination With Lenacapavir in Virologically Suppressed People With HIV. https://clinicaltrials.gov/ct2/show/NCT05052996. Accessed 10/7/2022;

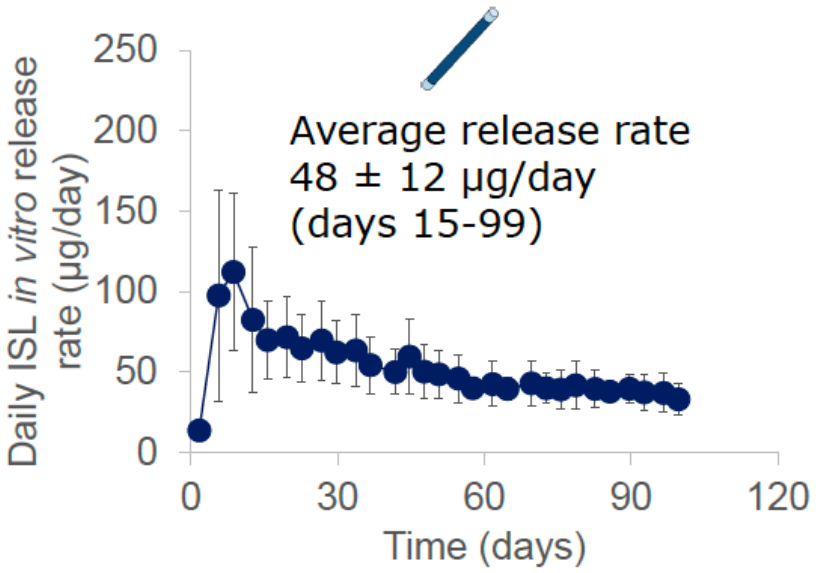
IAS 2023- Islatravir implants

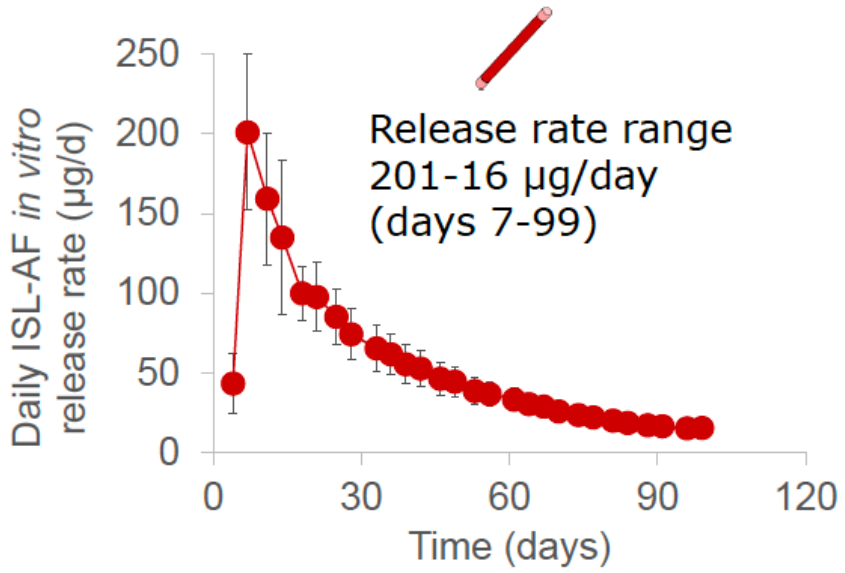
Pharmacokinetics and safety of long-acting islatravir and its novel prodrug islatravir alafenamide implants for HIV prevention

In vitro release profiles of ISL and ISL-AF

- Sustained *in vitro* release observed from a single ISL or ISL-AF implant over 98 days

a F. Cruz,1 Chasity Norton,1 Ellen H.





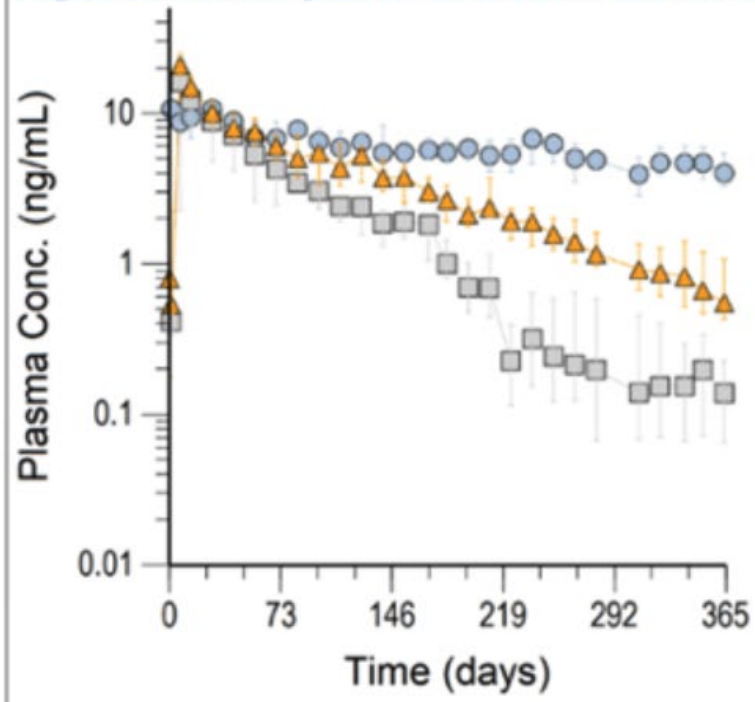
Animal model (rat) but Islatravir implant (not islatravir alafenamide) looks promising for sustained release

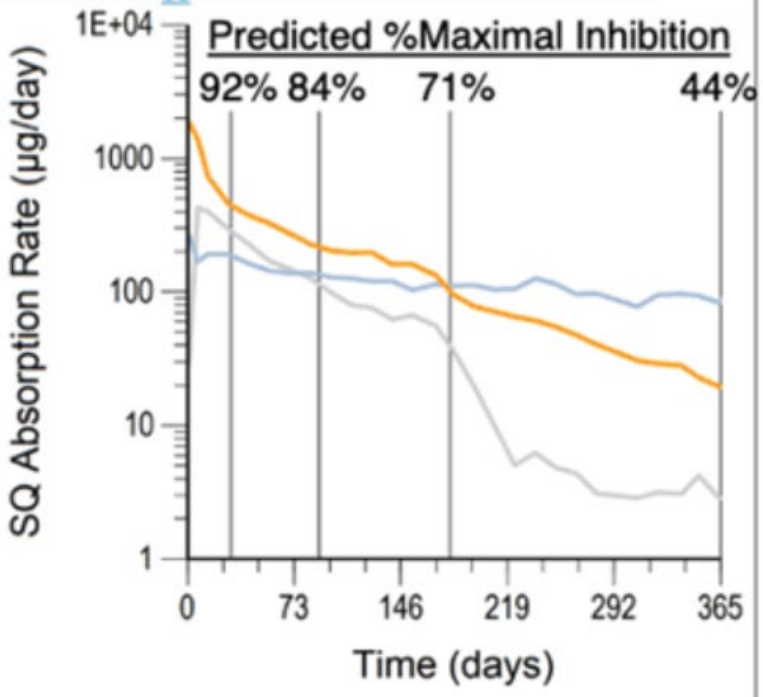
IAS 2023- Subcutaneous formulations for babies/children

A biodegradable, subcutaneous implant delivery platform to treat HIV for up to 6 months in young children

...rne[1], G. Dobek[3], X. Wang[4], R. Veazey[3],

Figure 3. SQ Implants Predicted to Sustain PK >IC_{50} for 6 Months in Children





Left Panel: Median (IQR) plasma concentrations for BIC (blue), ISL (gray), and FTC (orange) observed in rabbits over 1 year following SQ implantation. **Right Panel:** Mean SQ absorption rates estimated by deconvolution for BIC (blue), ISL (gray), and FTC (orange) over 1 year. Model predicted PD response is overlaid for the predicted PK of the mean SQ absorption rates at 1, 3, 6 and 12 months in a 2-year-old child.

Models (animal) showing bictegravir, islatravir and emtricitabine can be given as subcutaneous injections in young children every 6 months

Open access Protocol

BMJ Open

CAPRISA 018: a phase I/II clinical trial study protocol to assess the safety, acceptability, tolerability and pharmacokinetics of a sustained-release tenofovir alafenamide subdermal implant for HIV prevention in women

Tanuja Narayansamy Gengiah ,[1] Quarraisha Abdool Karim,[1,2] Isha
Leila Mansoor,[1] Nonhlanhla Yende Zuma,[1] Precious Radebe,[1]

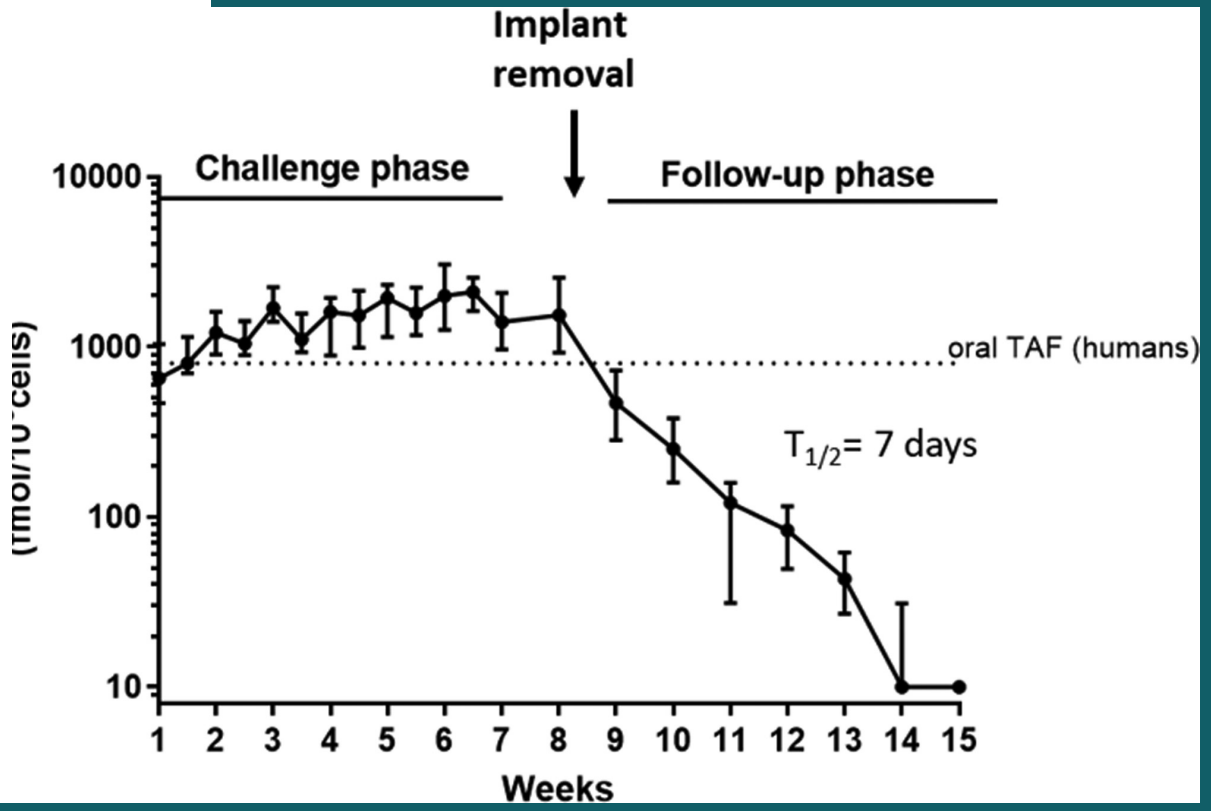
TAF implant shows promise; starting out in looking at a phase I/II study in humans after macaque data below

J Antimicrob Chemother 2022; **77**: 2964–2971
https://doi.org/10.1093/jac/dkac252 Advance Access publication 1 August 2022

Journal of Antimicrobial Chemotherapy

Safety and efficacy of a biodegradable implant releasing tenofovir alafenamide for vaginal protection in a macaque model

I. Massud[1], A. Krovi[2], K. Nishiura[1], S. Ruone[1], L. Li[2], A. Holder[1], J. Gary[3]†, P. Mills[4]‡, J. Mitchell[1], G. Khalil[1], Y. Pan[1],



Conclusion

- First line therapy worldwide is INSTI based but increasing attention to weight and the interaction between INSTIs and TAF
- Long-acting ART with CAB/RPV in exciting phase
- For NNRTI resistant patients, have to consider LEN/CAB as long - acting (hoping for study)
- Subcutaneous formulations (long -acting) and implants in development

stop aids. make the promise

Thank you to Southeast AETC, Division of HIV, ID and Global Medicine, the HIV movement, and Ward 86!