AETC AIDS Education & Training Center Program Mountain West

CROI 2022 Report Back: Treatment Updates

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Disclosures

No conflicts of interest or relationships to disclose.

Data presented in this presentation offer a limited glimpse of health inequities that exist within a larger social context. Racism, not race, creates and perpetuates health disparities.

The MWAETC, in alignment with the American Medical Association, encourages characterizing race as a social construct, rather than an inherent biological trait, and supports ending the practice of using race as a proxy for biology in medical education, research and clinical practice.

https://www.ama-assn.org/press-center/press-releases/new-ama-policies-recognize-race-social-not-biological-construct

January 2022

Outline

- **ART and Pregnancy**
  - IMPAACT 2010, DTG and neural tube defects, and perinatal transmission
- **ART Options for Drug Resistant HIV**
  - NADIA and VISEND Trials
- **Other Brief Topics of Interest**
  - Third HIV cure case, Lenacapavir and Islatravir, ANCHOR results

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ART and Pregnancy

ART and Pregnancy: Background

- ART options in pregnancy remain limited
- IMPAACT 2010 is a global, multicenter, randomized trial of ART-naïve pregnant women with HIV started on the below ART during 14-26 weeks gestation:
  - TAF/FTC + DTG vs
  - TDF/FTC + DTG vs
  - TDF/FTC/EFV
- Results from CROI 2020-2021
  - Arms with DTG had superior virologic efficacy & closer to expected weight gain in pregnancy
  - TAF/FTC + DTG had lowest rate of adverse pregnancy outcomes through 50w post-partum

Chinula L et al, Virtual CROI 2021 - Abstract 177.

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Growth of Infants with Perinatal Exposure to DTG vs EFV and TDF vs TAF

- Length-for-age and weight-for-age Z scores
  - Lower in EFV vs DTG arms
  - Within the DTG arm, similar between TDF vs TAF
- Weight-for-length Z scores no differences in between arms

- Infants born to mothers starting EFV in pregnancy were smaller throughout infancy
- Rates of stunting high across all arms, but higher in the EFV arm
- Infant growth was similar following exposure to maternal TDF or TAF with DTG

Stranix-Chabanda L, CROI 2022 – Oral Abstract 30.

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Other Key Abstracts regarding ART and Pregnancy

- **No neural tube defects (NTDs) with periconception dolutegravir use in US, 2008-2019[1]**
  - Tsepamo study in Botswana raised initial concern about DTG and NTDs, though as of 4/2020, the incidence of NTDs was not statistically significant
  - In a large cohort of pregnant persons in the US (~35 million without HIV, ~3000 with HIV on DTG in early pregnancy, and ~20,000 with HIV on other ARVs in early pregnancy), no increased risk of NTDs of infants exposed to DTG periconception

- **Lack of perinatal transmission in French women with HIV on ART with viral suppression[2]**
  - 17,673 infant & women with HIV pairs in the in the ANRS-EPF registry between 2000-2017 who were on ART before conception
  - Among 5482 women treated at conception, with any ART combination who did not breastfeed, no perinatal transmission was observed if VL < 50 copies/mL near time of delivery

1-Kourtis AP, CROI 2022 – Abstract 677. 2-Sibiude J, CROI 2022 – Abstract 684.

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ART and Pregnancy: Take-Away Points

- New data from IMPAACT 2010 study continues to reassure regarding DTG and TAF use in pregnancy and post-partum[1]
  - DTG containing regimens have superior virologic efficacy at delivery
  - TAF containing regimens have lowest composite frequency of adverse pregnancy outcomes
- DTG was not associated with neural tube defects in US infants exposed periconception[2]
- In a French cohort of women with HIV on ART at conception with VL < 50 copies/mL not breastfeeding, no perinatal transmission occurred[3]

2021 DHHS Perinatal Guidelines recommend DTG and TAF as preferred ART in pregnancy and peri-conception

1-Stranix-Chabanda L, CROI 2022 – Oral Abstract 30. 2-Kourtis AP, CROI 2022 – Abstract 677. 3-Sibiude J, CROI 2022 – Abstract 684.

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ART Options for Drug Resistant HIV

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ART Options for Resistant HIV: Background

- DAWNING study showed DTG > r/LPV as salvage therapy and sub-analysis showed that DTG + 2 NRTIs, regardless of pre-existing RAMs to one of the NRTIs, maintained VS[1]
  - In DAWNING, DTG can fail with INSTI-R but b/PI generally do not fail with PI-R

- NADIA (**N**ucleosides **a**nd **D**arunavir/**D**olutegravir **i**n **A**frica) Trial
  - Multicenter, non-inferiority randomized trial of PWH failing TDF+3TC/FTC + NNRTI then comparing DTG vs rDRV and TDF vs ZDV[2]
  - 48w data (CROI 2021) showed that DTG was non-inferior to DRV and TDF non-inferior to ZDV
  - Those with viral rebound developed INSTI-R while on DTG (4 cases) but no PI-R while on DRV

1-Aboud M, Lancet Infect Dis, 2019. 2-Paton NI, NEJM, 2021.

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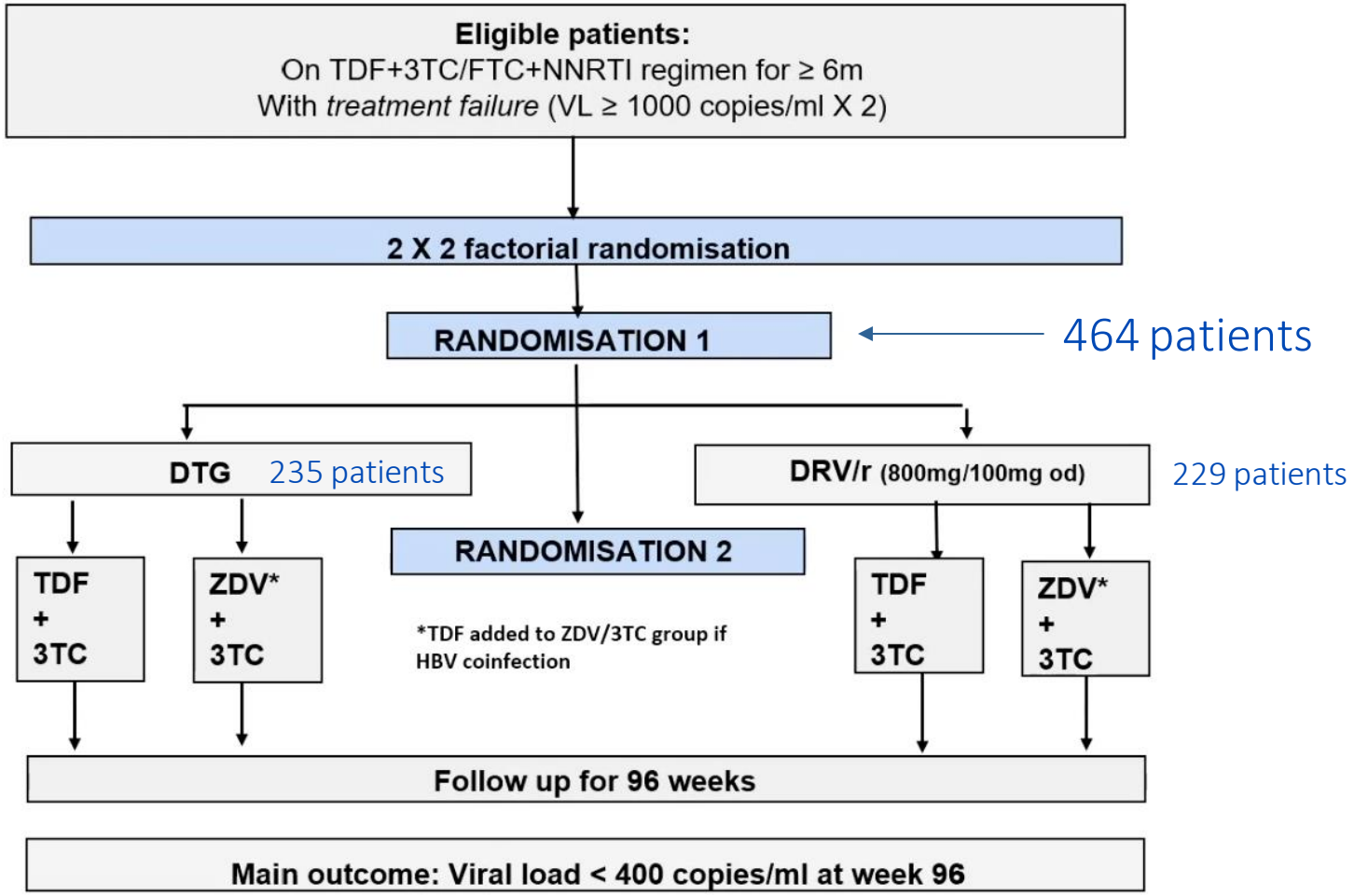
NADIA Trial: Study Design & Baseline Characteristics



7 Sites
Uganda, Kenya, Zimbabwe

61% female
Median age 34 (IQR 28-41)
Median CD4 189 (IQR 68-347)
51% CD4 < 200
28% VL ≥ 100,000 copies/mL

Median time on 1st line ART 3.7y
86% with baseline M184V/I
50% with baseline K65R/N

Paton NI, CROI 2022 – Oral Abstract 137.

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NADIA Trial 96w Results: DTG is non-inferior to rDRV

Outcome	DTG group (n=235)	DRV group (n=229)	*p*
HIV-1 RNA level, intention-to-treat population – no (%)			
< 400 copies/mL	211 (89.8)	199 (86.9)	0.332
Secondary and other efficacy outcomes – no (%)			
VL rebound > 1000 c/mL	20 (8.5)	26 (11.3)	0.306
VL rebound > 1000 c/mL, ≥ 1 major RAM to DTG or DRV	7	0	

Paton NI, CROI 2022 – Oral Abstract 137.

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NADIA Trial 96w Results: TDF is superior to AZT

Outcome	TDF group (n=233)	AZT group (n=231)	*p*
HIV-1 RNA level, intention-to-treat population – no (%)			
< 400 copies/mL	214 (91.8)	196 (84.8)	0.019
Secondary and other efficacy outcomes – no (%)			
VL rebound > 1000 c/mL	13 (5.6)	33 (14.3)	0.002
VL rebound > 1000 c/mL, ≥ 1 major RAM to DTG	2	5	
VL rebound > 1000 c/mL, ≥ 1 major RAM to DRV	0	0	

Paton NI, CROI 2022 – Oral Abstract 137.

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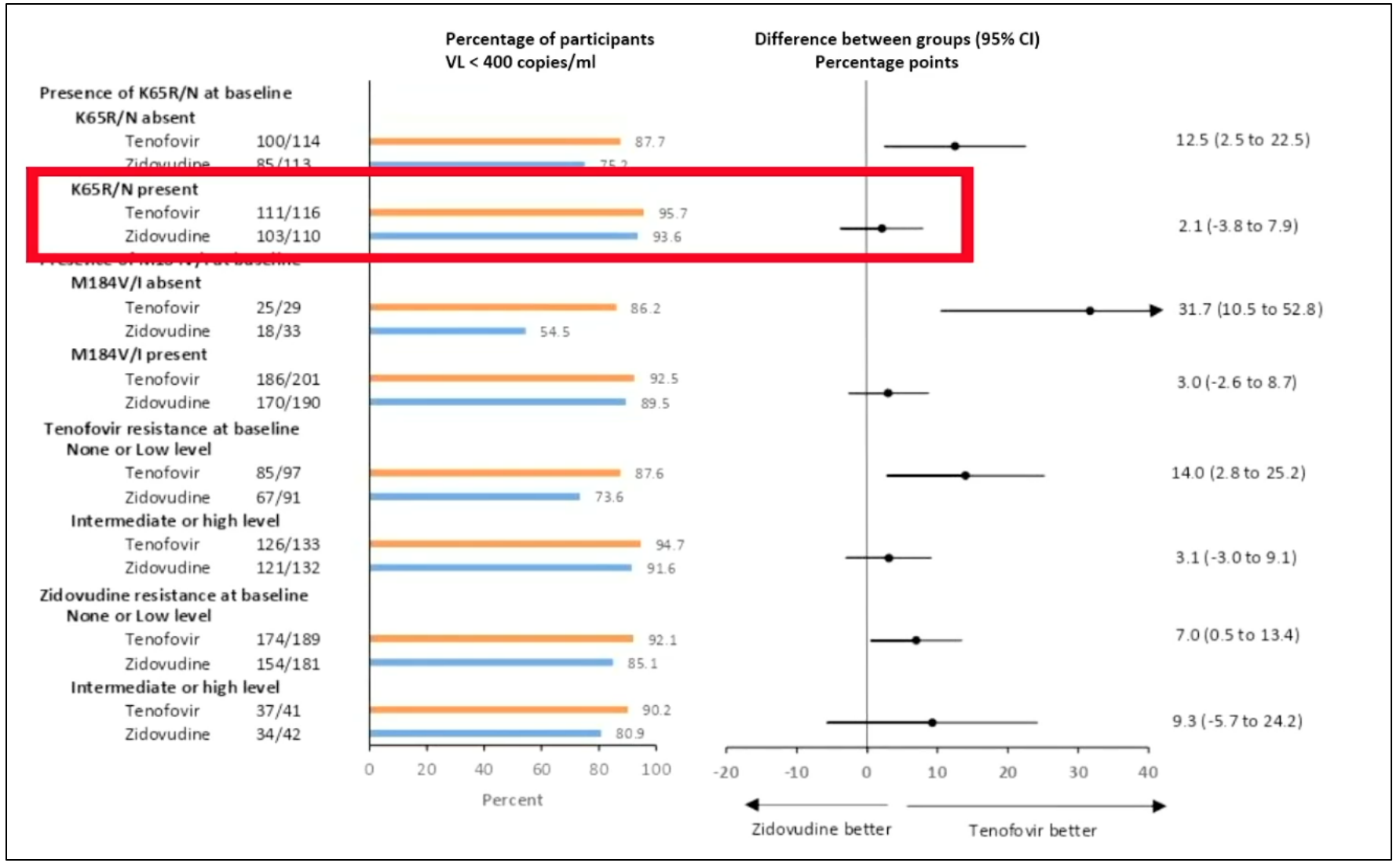
NADIA Trial 96w Results: Subgroup Analysis



Paton NI, CROI 2022 – Oral Abstract 137.

NADIA Trial 96w Results: Info on Dolutegravir RAMs

Dolutegravir resistance mutations

Regimen in trial	VL rebound (c/ml)	DTG resistance level (Stanford)	DTG mutations
ZDV, 3TC, DTG	≥1000	High	T66TA, G118R, E138K, G149GA, G163GR
ZDV, 3TC, DTG	≥400	High	T66TAIV, T97A, G118R, E138K
ZDV, 3TC, DTG	≥1000	High	T66I, G118R, E138K, G149GA
ZDV, 3TC, DTG	≥1000	High	T66A, G118R, E138K
ZDV, 3TC, DTG	≥1000	High	E138K, G140A, Q148R
ZDV, 3TC, DTG	≥1000	Intermediate	R263RK
TDF, 3TC, DTG	≥1000	Intermediate	M50I, R263K
TDF, 3TC, DTG	≥1000	Intermediate	M50I, R263RK
TDF, 3TC, DTG	≥400	Intermediate	M50I, R263RK

Most DTG-RAMs occurred with AZT

Key DTG-RAMs:
T66TAIV (4)
R263K (4)
M50I (3)
E138K (5)
G118R (4)

Other RAMs that occurred once:
Q148R, G140A, G149A, G163R

Paton NI, CROI 2022 – Oral Abstract 137.

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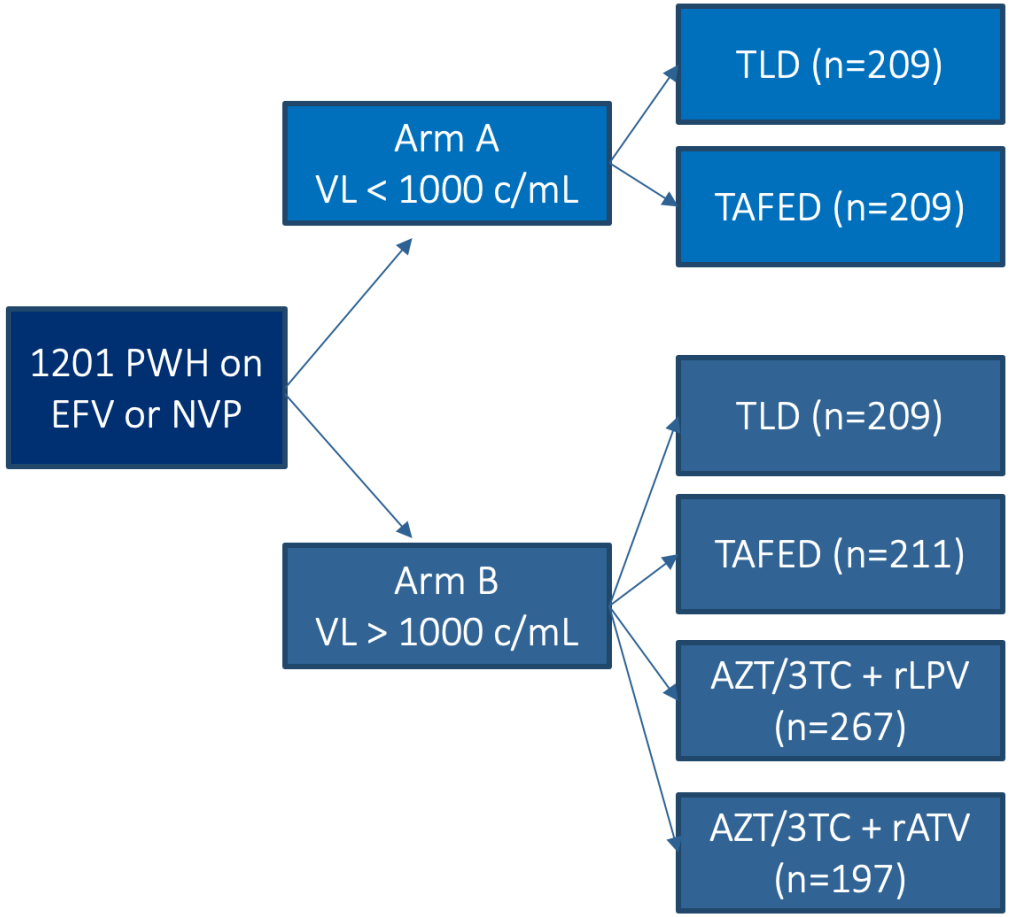
VISEND Trial: Study Design & Results

- Design
  - 144-week randomized open label non-inferiority study in Zambia of 1201 PWH with and without viral suppression
  - Mostly comparing TLD (TDF/3TC + DTG) to TAFED (TAF/FTC + DTG)

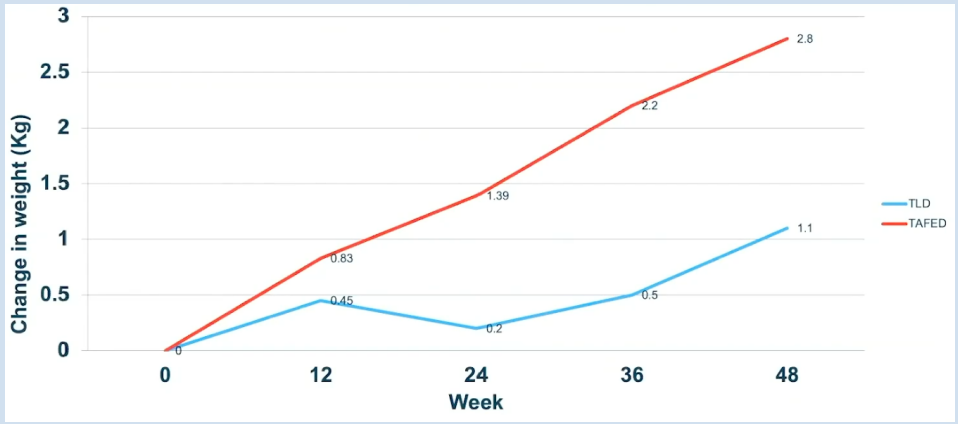
- Results
  - VL < 1000 c/mL: TAFED non-inferior to TLD
  - VL > 1000 c/mL: TAFED non-inferior to TLD and both superior to combined PI arm (though PI + ZDV/3TC)



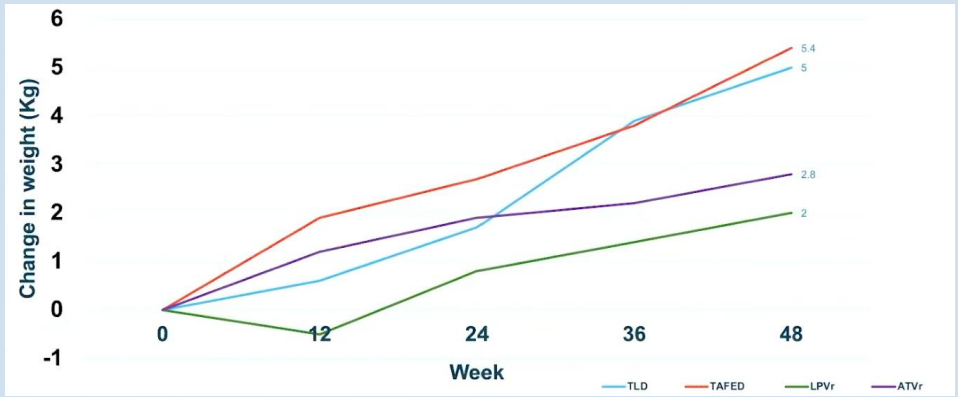
Mulenga LB, CROI 2022- Oral Abstract 135.

VISEND Trial: Impact on Weight Gain

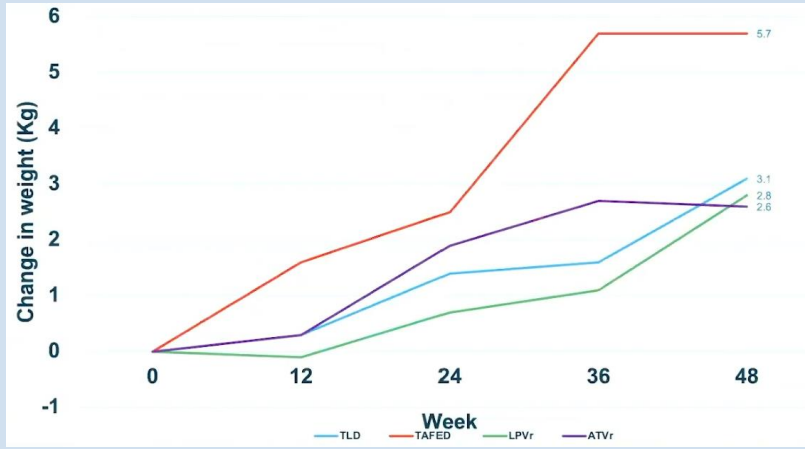
VL < 1000 c/mL



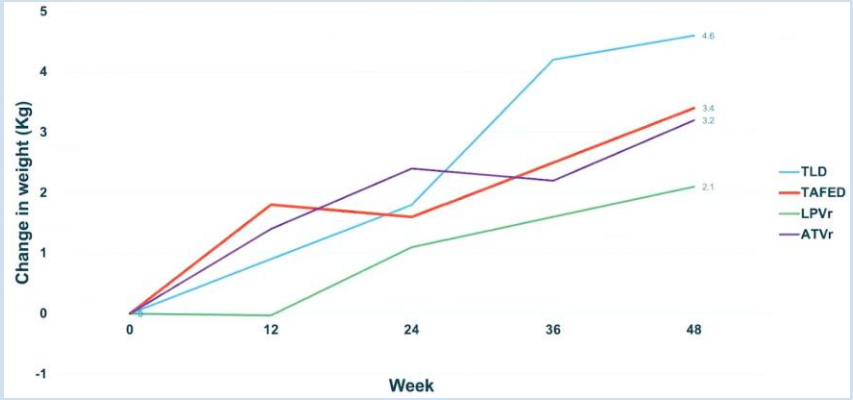
VL > 1000 c/mL



VL > 1000 c/mL in WOMEN



VL > 1000 c/mL in MEN



Mulenga LB, CROI 2022- Oral Abstract 135.

ART Options for Resistant HIV: Take-Away Points

- NADIA Trial[1]
  - Affirms the practice of using DTG with < 2 active NRTIs in the setting of NRTI-R
  - Changes how active I consider tenofovir in the presence of a K65R when paired with DTG
  - Reaffirms that DTG does fail with INSTI-R but that PIs generally do not

- VISEND Trial[2]
  - Again affirms that we can use either DTG or 2nd line PIs as 2nd line therapy
  - In VL < 1000 c/mL, TAFED was associated with more weight gain than TLD
  - If not virally suppressed, TAFED associated with more weight gain than TLD in women and TLD associated with more weight gain than TAFED in men

1-Paton NI, CROI 2022 – Oral Abstract 137. 2-Mulenga LB, CROI 2022- Oral Abstract 135.

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Other Brief Topics of Interest

Third HIV Cure Patient: Background

- Both the Berlin Patient and London Patient underwent HSCTs from donors homozygous for CCR5-△32 mutation[1,2]
- Although the London Patient signified that this approach may be replicated after the Berlin Patient, using this approach to achieve remission is both high risk and high cost
- At IAS 2020, São Paulo patient was thought to achieve remission using DTG + MVC + nicotinamide in addition to 3DR, but had virologic rebound at 72 weeks[3]
- Both the Berlin and London Patient used stem cell transplantation, but umbilical cord blood cells had not been previously used to achieve HIV remission

1-Hutter, NEJM, 2009. 2-Gupta, CROI 2019 #29LB. 3-Diaz R. AIDS 2020. OAXLB0105.

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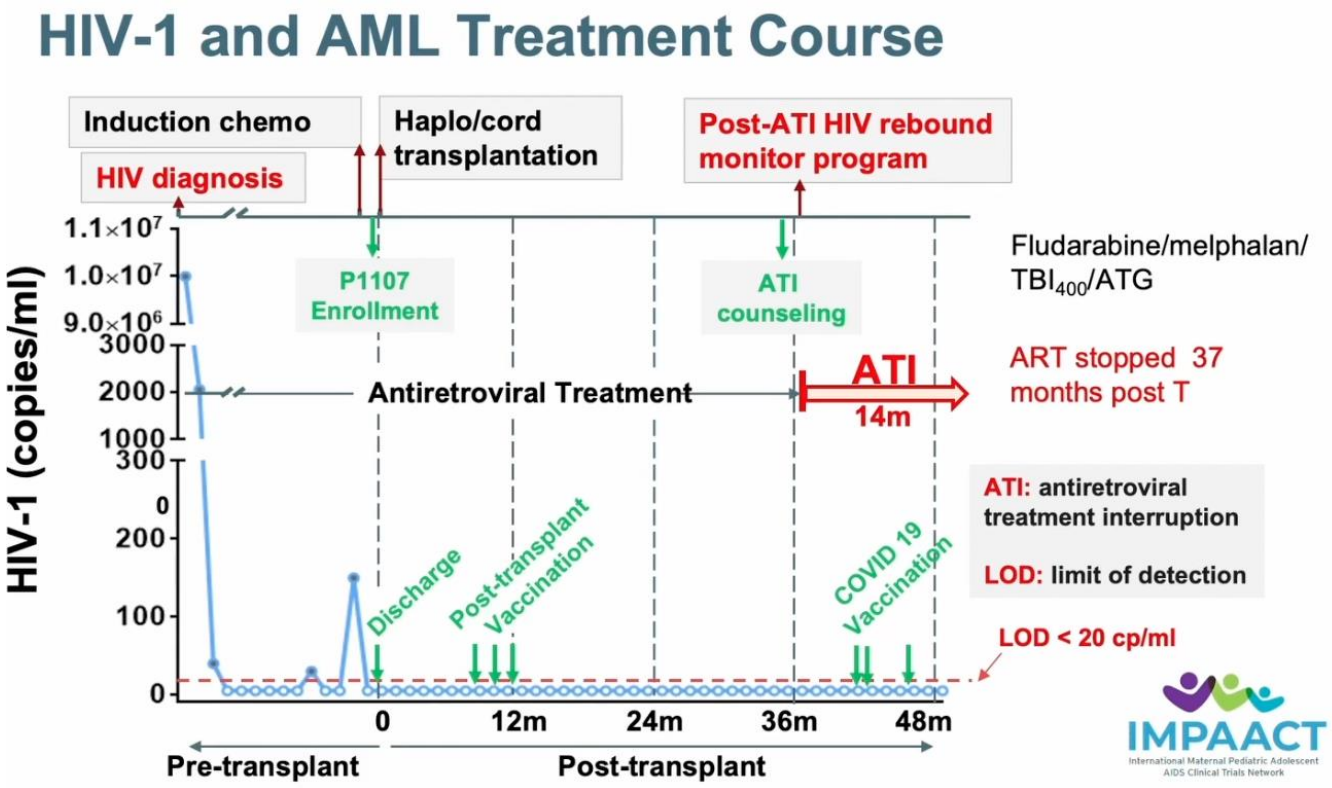
HIV Remission Achieved Using Haplo-Cord SCT

- "Middle-aged US woman of mixed race" with HIV and high-risk AML
- Underwent haplo-cord SCT
  - Cord blood donor homozygous for CCR5-△32 mutation and
  - CD34-selected haploidentical stem cell
- 100% chimerism with a donor homozygous for CCR5-△32 mutation
- First time using cord blood cells or haplo-cord to achieve HIV remission



Hsu JM, CROI 2022 – Oral Abstract 65.

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Novel Agents: Islatravir and Lenacapavir

- Islatravir (NRTTI)
  - Most studies at CROI 2022 regarding ISL were for PrEP
  - Currently on FDA hold due to 30-50% mean drop in CD4 cell count in treatment studies

- Lenacapavir (HIV-1 capsid inhibitor)
  - Currently on partial FDA hold because of issues with glass vials
  - **CALIBRATE** Study: After LEN + 2DR for induction, q6m LEN + TAF or BIC led to viral suppression at week 54 in 85-90% of **ART-naïve PWH**[1]
  - **CAPELLA** Study: With OBR, q6m LEN led to viral suppression at week 52 in 83% of individuals with **MDR HIV**[2]

1-Gupta S, CROI 2022 – Oral Abstract 138. 2-Ogbuagu O, CROI 2022 – Abstract 491.

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ANCHOR Results Introduction

- ANCHOR Study of PWH ≥ age 35 had the following 4 aims:
  1. Whether treating anal HSIL is effective at reducing incidence of anal CA
  2. Determine safety of treatments they use
  3. Develop an instrument to measure an impact on quality of life
  4. Collect clinical specimens and data to do correlative science for predictors and biomarkers
- Aim 1 with ~4500 people randomized to HRA vs active monitoring, 9/2014-8/2021
  - 32 cancers diagnosed (9 in treatment arm, 21 in active monitoring arm)
  - 57% reduction in anal cancer in treatment arm, DSMB stopped the study early

On 3/24 and 3/31, Drs. Stankiewicz Karita and Schouten will be giving ANCHOR updates

Palefsky J, CROI 2022 – Oral Abstract 106.

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Acknowledgment

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