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
- ART Options for Drug Resistant HIV
  - NADIA and VISEND Trials
- Other Brief Topics of Interest
  - Third HIV remission 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
- IMPAACT 2010 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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No neural tube defects with periconception dolutegravir in the US

- Tsepamo study in Botswana raised concern about DTG and neural tube defects (NTD)[1]
  - As of 4/2020, the incidence of NTDs was not statistically significant
- Retrospective review of two large databases of pregnant persons in the US, 2008-2019[2]

		Women without HIV	Women with HIV, DTG in early pregnancy		Women with HIV, Other ARV in early pregnancy	
		N (Rate, per 1,000)	N (Rate, per 1,000)	Risk Ratio (95% Confidence Interval)	N (Rate, per 1,000)	Risk Ratio (95% Confidence Interval)
MarketScan (Weighted)	Pregnancies (N)	17,522,140	509		6,892	
	Live births*	12,988,678 (741.3)	316 (620.3)	0.84 (0.78 – 0.90) ‡	4,427 (642.3)	0.87 (0.85 – 0.88) ‡
	NTD**	9,901 (0.8)	0 (0.00)	N/A	4 (0.9)	1.12 (0.41 – 3.07)
	Stillbirths	108,164 (6.2)	8 (15.9)	2.58 (1.30 – 5.11) ‡	83 (12.1)	1.96 (1.58 – 2.42) ‡
	Pregnancy Loss†	4,304,479 (245.7)	185 (363.8)	1.48 (1.32 – 1.66) ‡	2,304 (334.2)	1.36 (1.32 – 1.41) ‡
Medicaid	Pregnancies (N)	18,904,008	2,331		18,437	
	Live births*	15,515,806 (820.8)	1,515 (649.9)	0.79 (0.77–0.82) ‡	13,182 (715.0)	0.87 (0.86–0.88) ‡
	NTD**	12,910 (0.8)	1 (0.7)	0.79 (0.11 – 5.63)	9 (0.7)	0.82 (0.43 – 1.58)
	Stillbirths	104,465 (5.5)	12 (5.1)	0.93 (0.53–1.64)	130 (7.1)	1.28 (1.07–1.51) ‡
	Pregnancy Loss†	3,205,797 (169.6)	795 (341.1)	2.01 (1.90 – 2.13) ‡	4,976 (269.9)	1.59 (1.55 – 1.63) ‡

*: per 1,000 pregnancies; **: per 1,000 livebirths; †: Pregnancy Loss includes spontaneous and induced abortions. ‡: p-value < 0.05;

1- Zash. AIDS 2020. Abstr OAXLB0102. 2-Kourtis AP, CROI 2022 – Abstract 677.

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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]

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.

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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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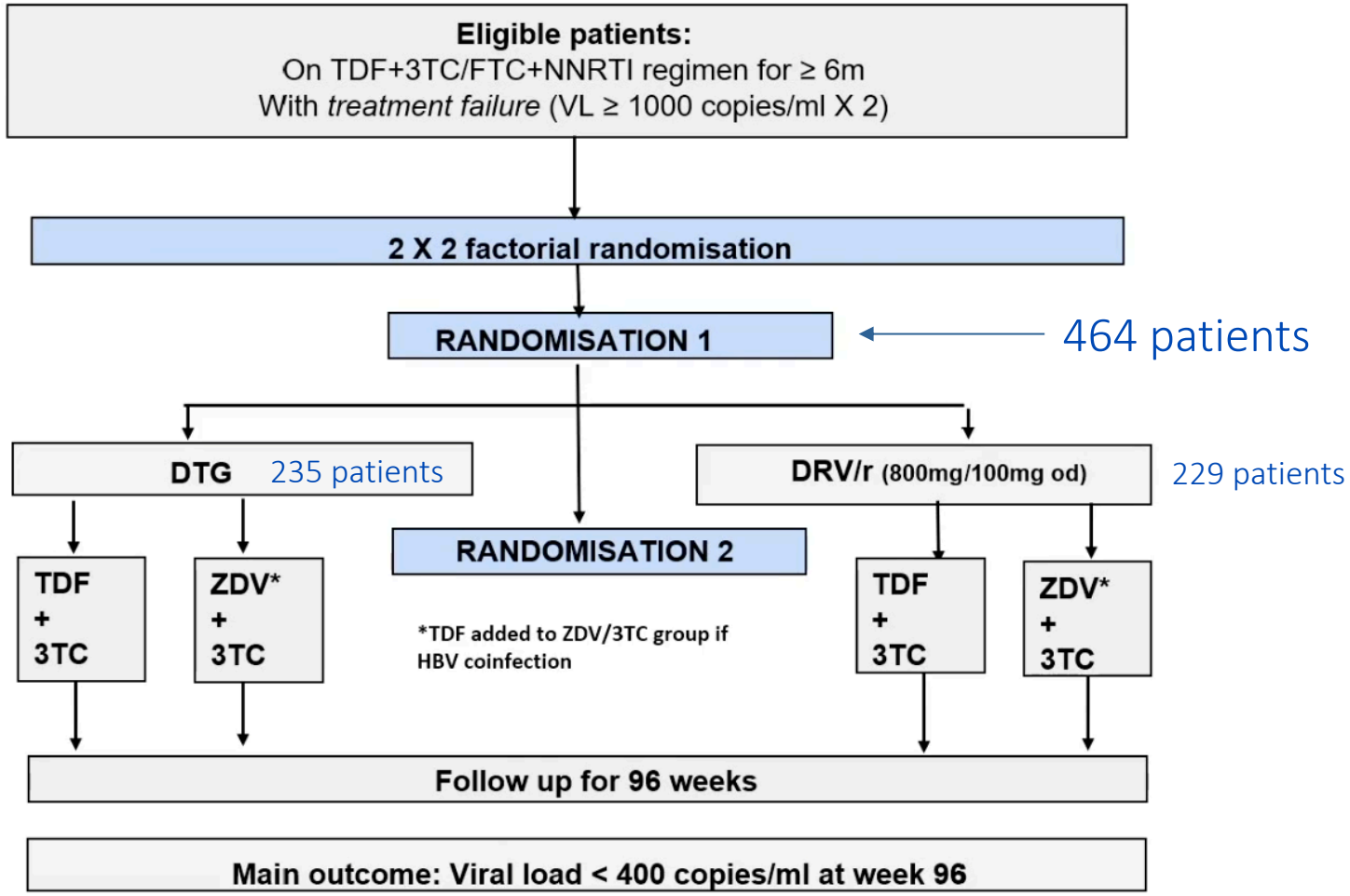
NADIA Trial: Study Design & Baseline Characteristics



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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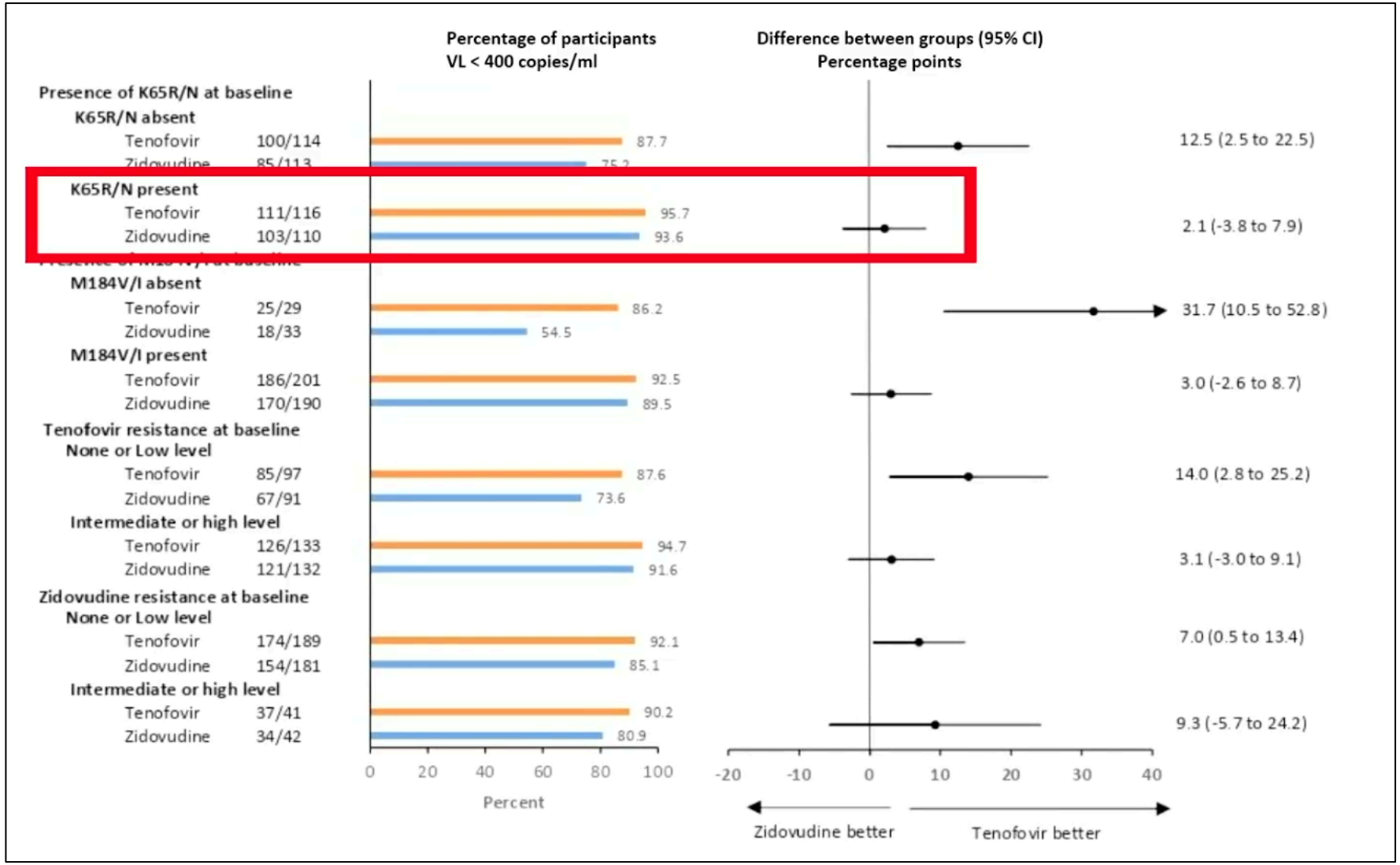
NADIA Trial 96w Results: Subgroup Analysis



Paton NI, CROI 2022 – Oral Abstract 137.

NADIA Trial 96w Results: Info on Dolutegravir RAMs

Regimen in Trial	DTG-R level (Stanford)	DTG mutations
ZDV-3TC-DTG	High	T66TA, G118R, E138K, G149GA, G163GR
ZDV-3TC-DTG	High	T66TAIV, T97A, G118R, E138K
ZDV-3TC-DTG	High	T66I, G118R, E138K, G149GA
ZDV-3TC-DTG	High	T66A, G118R, E138K
ZDV-3TC-DTG	High	E138K, G140A, Q148R
ZDV-3TC-DTG	Intermediate	R263RK
TDF-3TC-DTG	Intermediate	M50I, R263K
TDF-3TC-DTG	Intermediate	M50I, R263K
TDF-3TC-DTG	Intermediate	M50I, R263K

Most DTG-RAMs occurred with AZT

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

Other less frequent RAMs:
Q148R, G140A, G149A, G163R

Paton NI, CROI 2022 – Oral Abstract 137.

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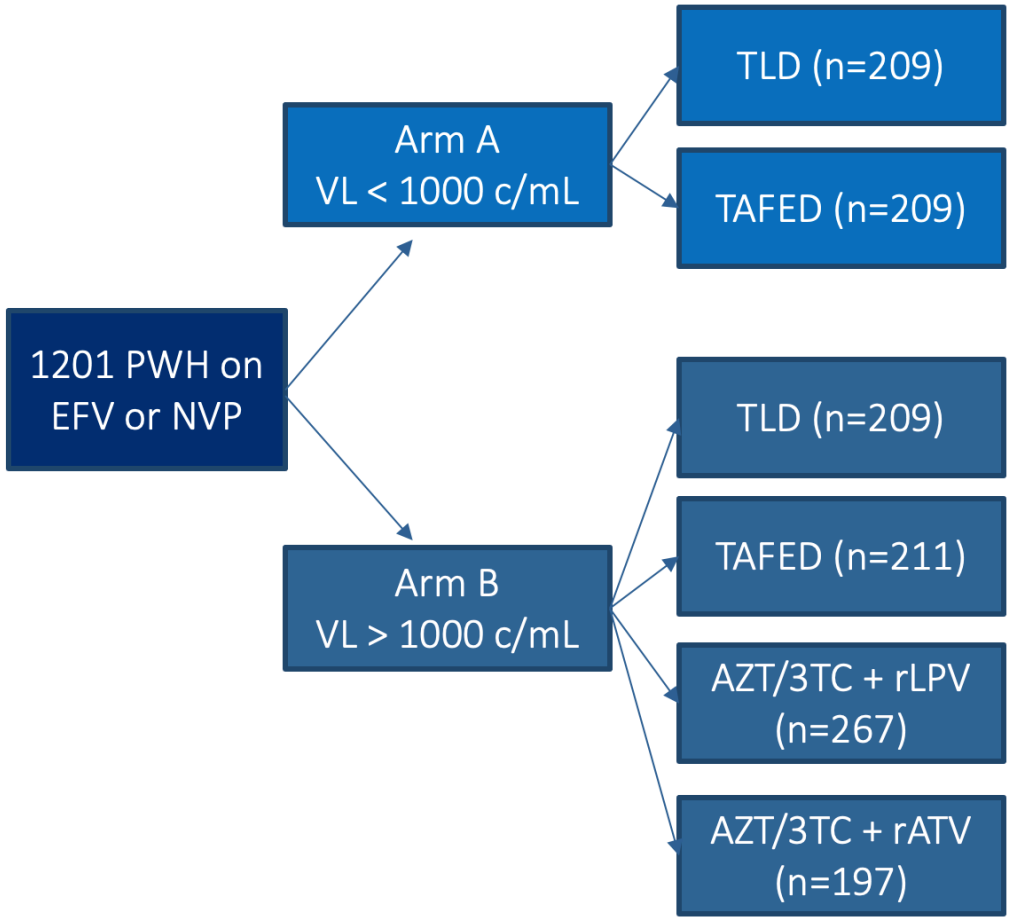
VISEND Trial: Study Design & Results

- 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.

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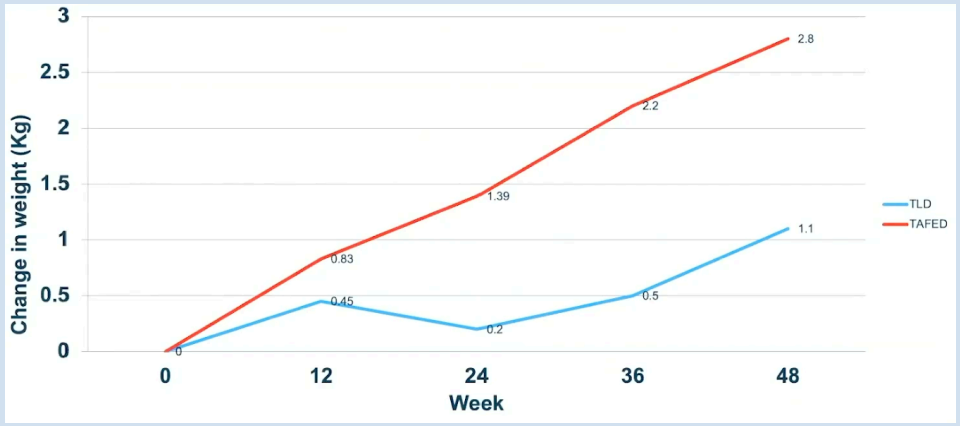
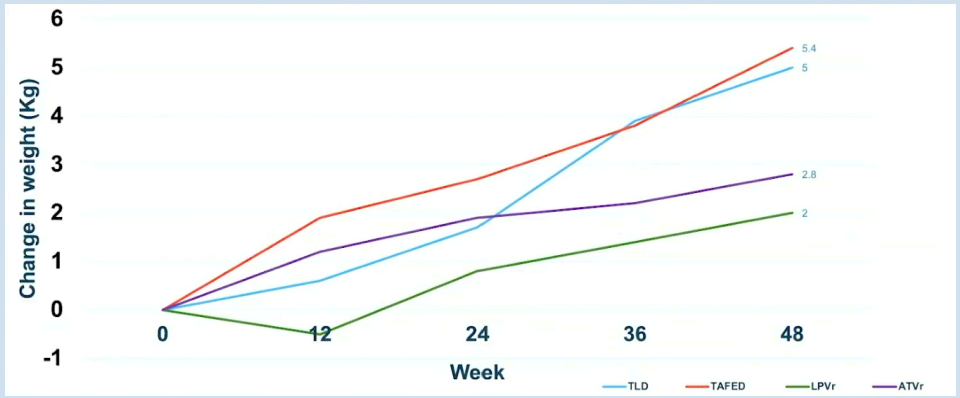
VISEND Trial: Impact on Weight Gain

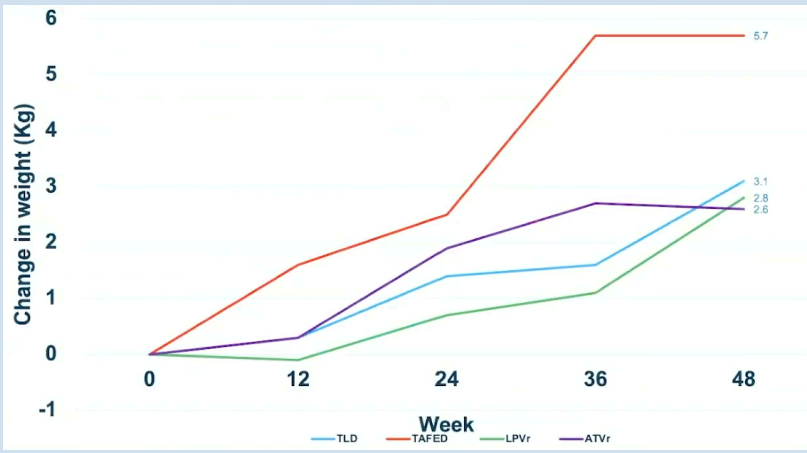
VL < 1000 c/mL



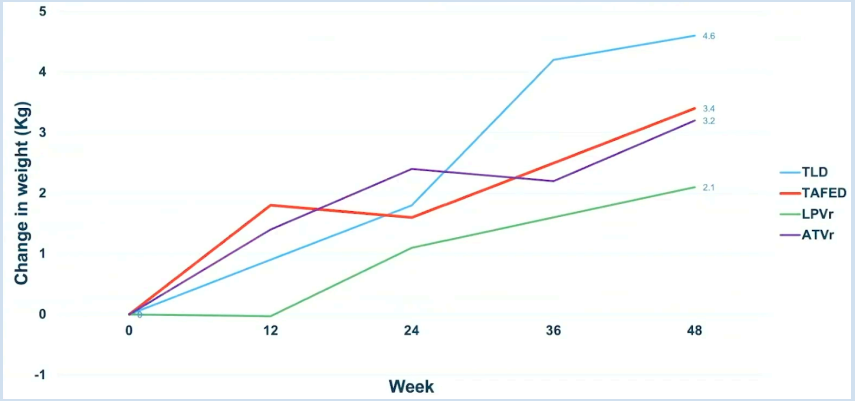
VL > 1000 c/mL



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 we might consider tenofovir (with DTG) in the presence of a K65R
  - Reaffirms that DTG does fail with INSTI-R but that PIs generally do not

- VISEND Trial[2]
  - 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 Remission Case: Background

- Both the Berlin Patient and London Patient underwent HSCTs from donors homozygous for CCR5-Δ32 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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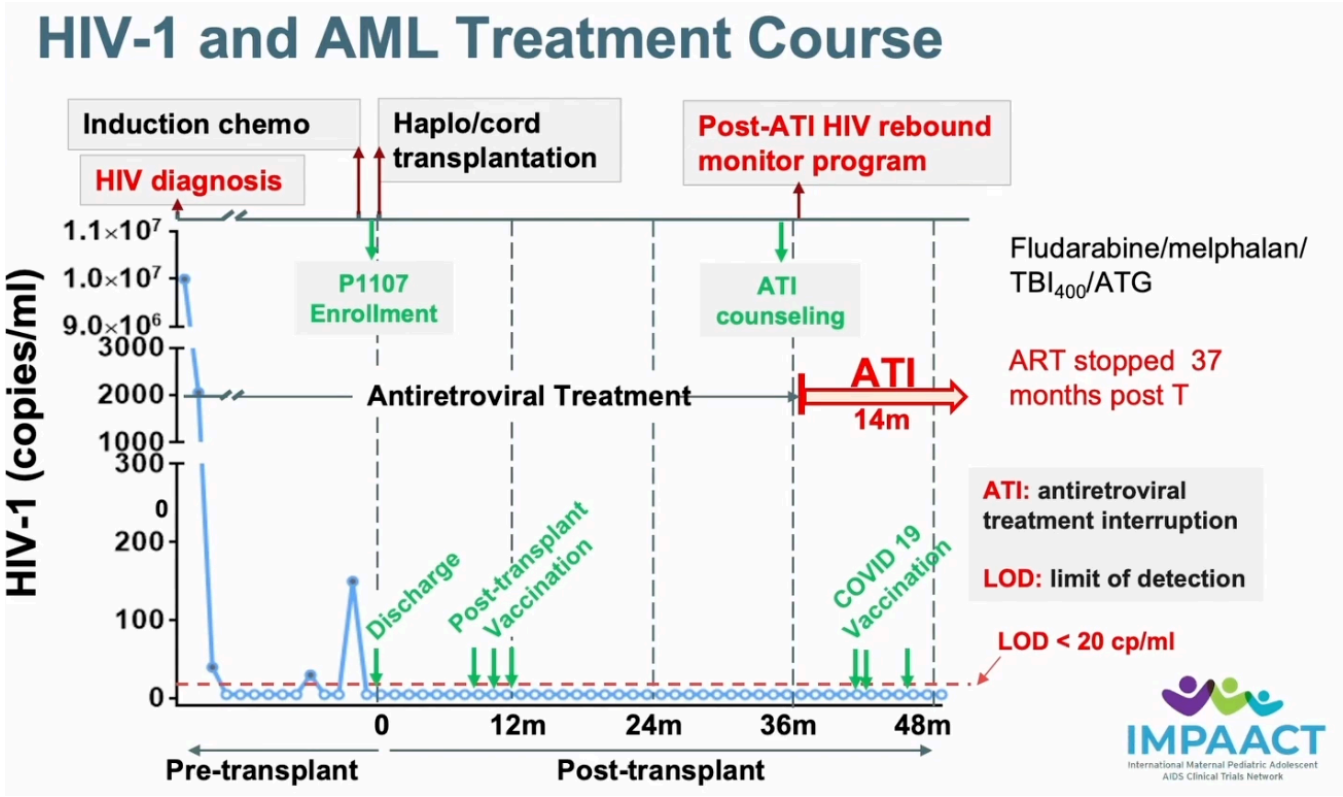
HIV Remission Achieved Using Haplo-Cord SCT

- "Middle-aged US woman of mixed race" with HIV and high-risk AML
- Underwent haplo-cord SCT
  - Cord blood donor homozygous for CCR5-Δ32 mutation and
  - CD34-selected haploidentical stem cell
- 100% chimerism with a donor homozygous for CCR5-Δ32 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[1]

- 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**[2]
  - **CAPELLA** Study: With OBR, q6m LEN led to viral suppression at week 52 in 83% of individuals with **MDR HIV**[3]

1-Orkin C, CROI 2022 – Plenary. 2-Gupta S, CROI 2022 – Oral Abstract 138. 3-Ogbuagu O, CROI 2022 – Abstract 491.

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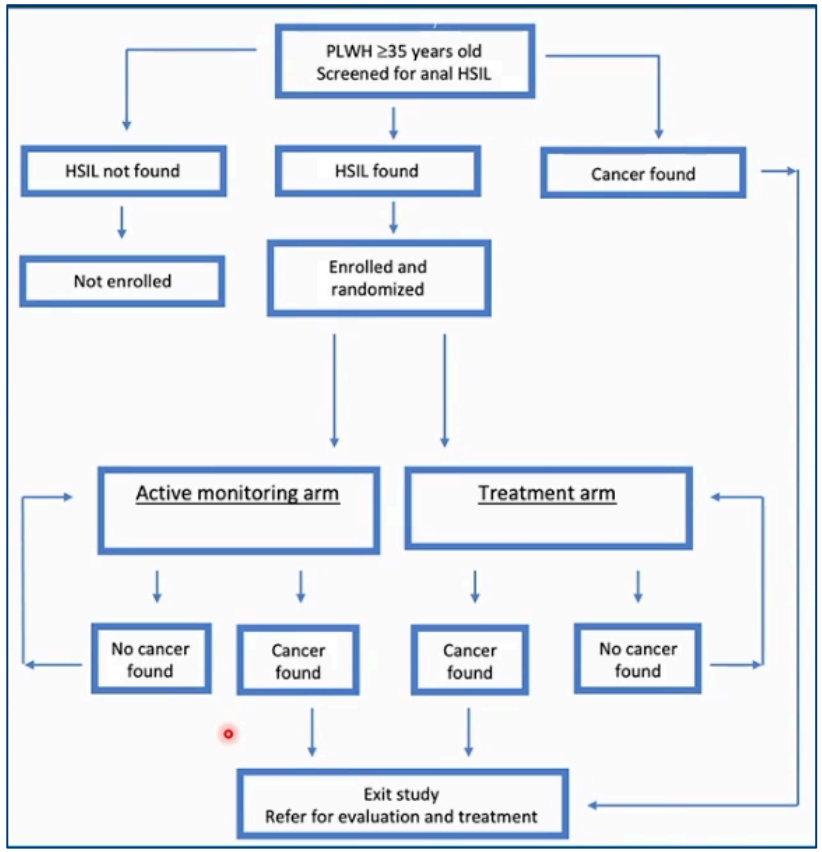
ANCHOR Study: Background

- Why is this important?
  - PWH tend to have larger and multifocal lesions
  - High resolution anoscopy (HRA) requires significant practice
  - Clinicians may inadequately treat lesions
  - New lesions may arise

- Four Aims
  1. Whether treating anal HSIL reduces incidence of anal CA in PWH
  2. Determine safety of treatments for anal HSIL
  3. Develop an instrument to measure impact of ANCHOR on QOL
  4. Collect clinical specimens and data to create a bank of specimens to identify predictors and biomarkers of progression of HSIL to cancer



Palefsky J, CROI 2022 – Oral Abstract 106.

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ANCHOR Study: Results

- Study ran 9/2014-8/2021, ~4500 PWH ≥ age 35 randomized to HRA vs active monitoring
  - Median age 51, 80% male, 1/3 of whom smoked
  - >80% with undetectable HIV-1 RNA
  - Median CD4 ~600 cells/mm^3
- 32 cancers diagnosed (9 in treatment arm, 21 in active monitoring arm)
  - 57% reduction in anal cancer in treatment arm (95% CI 6-80%), DSMB stopped the study early
- Treatment of anal HSIL is effective in reducing the incidence of anal CA
  - Recommendation to optimize screening algorithms for HSIL and scale up HRA training programs. But how do we implement this?

Palefsky J, CROI 2022 – Oral Abstract 106.

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Acknowledgment

The Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of an award totaling $2,911,844 and as part of another award totaling $400,000 with 0% financed with non-governmental sources.

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