Use of Dolutegravir In Clinical Care

WINDHOEK

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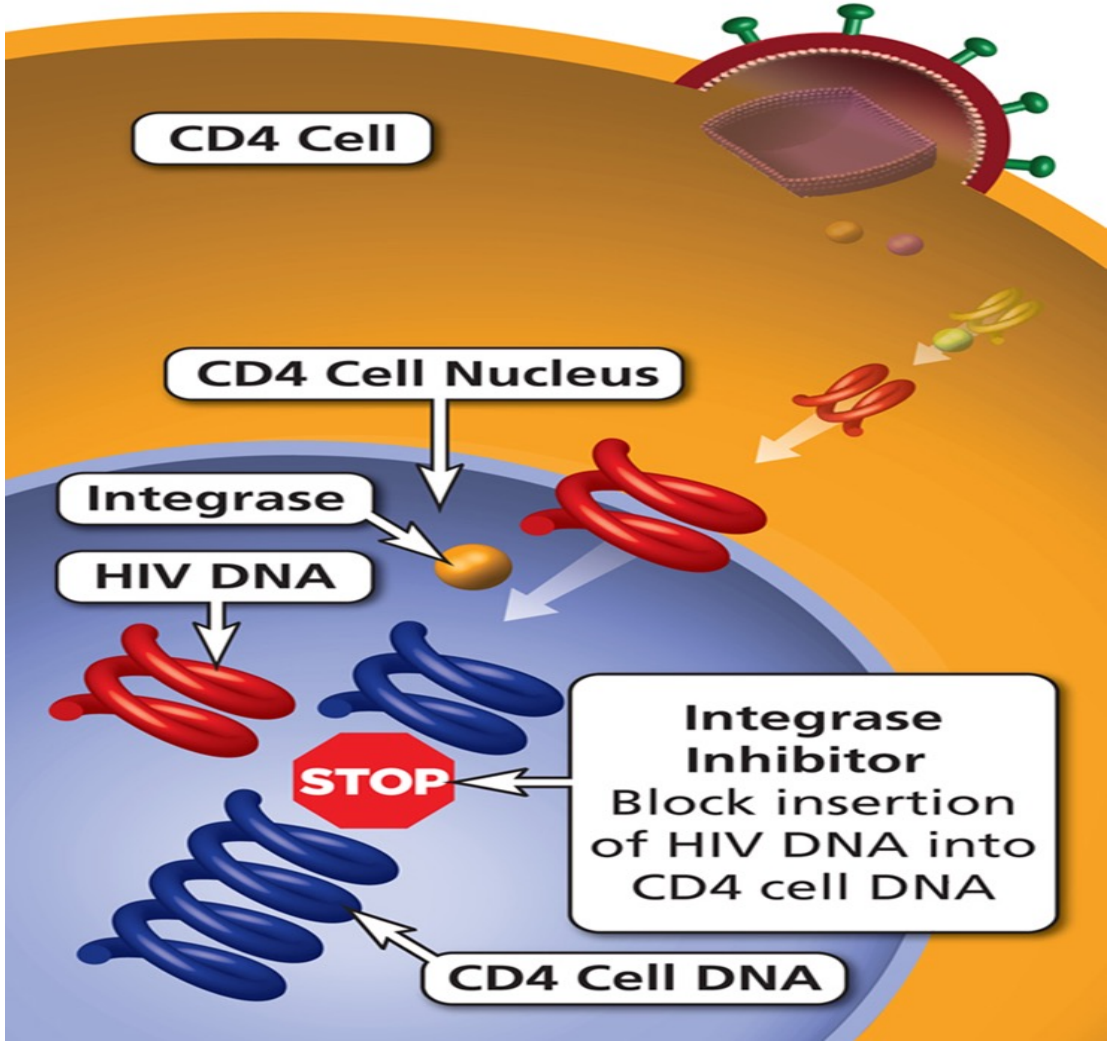
Outline

- Introduction
- Use of DTG in Namibia
- Use in Treatment Experienced Patients
- Common Adverse Events
- Interactions
- Use in Women of Childbearing Potential
- Metabolic Effects and Implications
- DTG as Dual Therapy
- Use in Paeditrics

Integrase Inhibitors (INSTIs)

- The mechanism is to prevent HIV integrase enzyme from incorporating proviral into the host genome.
  - Cabotegravir (CAB)
  - Dolutegravir (DTG)
  - Elvitegravir (EVG)
  - Raltegravir (Isentress®)



Dolutegravir (DTG)

- High genetic barrier to developing drug resistance.
- Advantages compared to most ARVs:
  - lower potential for drug interactions,
  - shorter median time to viral suppression
  - a long half-life
- A potential safety issue related to neural tube defects among infants born to women who were taking DTG at the time of conception
- Weight gain is another adverse effect that has been observed with the use of DTG in some studies.

Formulations

- Single formulation
  - 50mg tablet
  - 10mg tablet
- Fixed Dose formulation
  - Tenofovir | Lamivudine | Dolutegravir
  - Tenofovir | Emitricitabine | Dolutegravir
  - Abacavir | Lamivudine | Dolutegravir

Use In Namibia

Populations	Preferred first-line regimen	Alternative first-line regimen
Adults and Adolescents weighing at least 30 kg	TDF + 3TC (or FTC) + $DTG_{a,b}$ (TLD_1)*	TDF + 3TC + EFV 400mg TAF + 3TC + DTG**
Adolescents 25kg to < 30kg	TAF + 3TC + DTG	ABC + 3TC + DTG ABC + 3TC + ATV/r_c
Adolescents 20kg to < 25kg	ABC + 3TC + DTG	ABC + 3TC + ATV/r_c
Children from 4 weeks weighing at least 3kg	ABC + 3TC + $_pDTG$	ABC + 3TC + ATV/r_c ABC + 3TC + LPV/r_d
Neonates	AZT (or ABC) + 3TC + RAL_e	AZT + 3TC + NVP_e

Use In Namibia 2

Populations	Failing first-line regimen	Preferred Second-line regimen
Adults and Adolescents from 25kg	TDF + 3TC (or FTC) + DTG (TLD_1)* TAF + 3TC + DTG ABC + 3TC + DTG	AZT/3TC/(ATV/r or LPV/r)
	TDF + 3TC + EFV 400mg TDF + 3TC + ATV/r ABC + 3TC + LPV/r	AZT/3TC/DTG
Children from 4 weeks weighing at least 3kg up to 25kg	ABC + 3TC + LPV/r ABC + 3TC + ATV/r	AZT/3TC/$_p$DTG
	ABC + 3TC + $_p$DTG	AZT/3TC/(LPV/r or ATV/r)

Use in TB

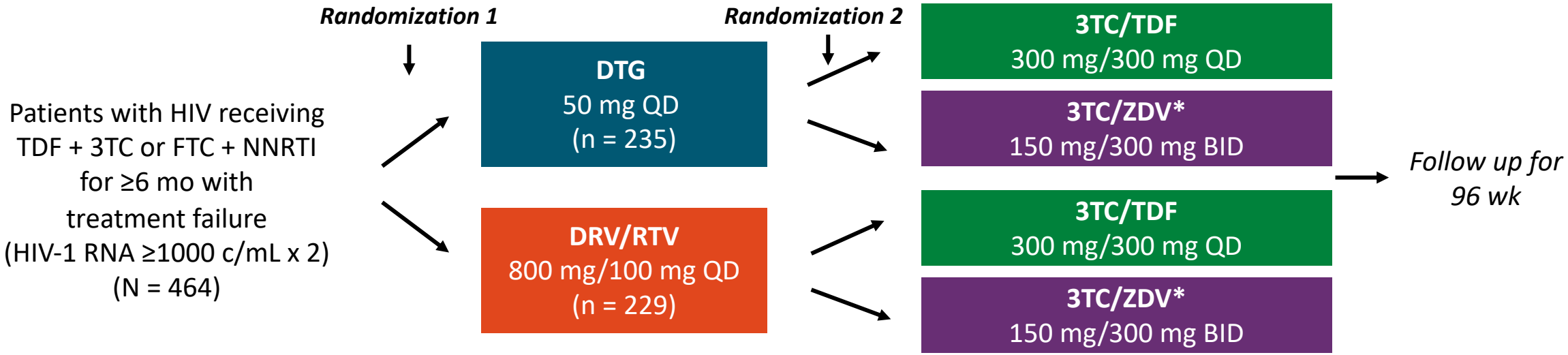
Preferred 1st line ART regimen	TDF + FTC (or 3TC) + DTG (at 50mg twice daily)
Alternate 1st line ART regimen	TDF + FTC (or 3TC) + EFV (at **400mg once daily**)
For PLHIV on a boosted PI regimen	***Option 1:*** Substitute rifampicin in the TB treatment with rifabutin ***Option 2:*** If Rifabutin is unavailable or contraindicated, maintain rifampicin in TB treatment and use PI based regimen super boosted with ritonavir. * TDF or AZT + 3TC with LPV/r 400mg+ritonavir 400 mg BD (LPV/RTV) or **(LPV/r 800 +ritonavir 200mg BD)** Note: ATV/r is contraindicated in patients with TB/HIV co-infection

Use in Treatment Experienced

- DTG also used in second and third line treatment
- Patients exposed to multiple drug classes
  - NRTIs and NNRTIs
  - PIs
  - Raltegravir
- Resistance testing is required for second line treatment failures
- If DTG is recycled need to be given twice daily

NADIA: DTG vs DRV/RTV and TDF vs ZDV for Second-line Therapy

- Multicenter, 2 x 2 randomized, open-label, noninferiority phase III trial



- Study aims: Evaluate noninferiority of DTG to DRV/RTV and of 3TC/TDF to 3TC/ZDV in second line
- Primary outcome: HIV-1 RNA <400 c/mL at Wk 96 by FDA snapshot
- Wk 48 results: DTG was noninferior to DRV/RTV (but 4 cases of DTG resistance); 3TC/TDF was noninferior to 3TC/ZDV

Paton. CROI 2022. Abstr 137. Paton. NEJM. 2021;385:330. NCT03988452.

Implications of Nadia Study

- If patient fails on:
  - TDF/3TC/EFV (first line)
  - Can switch to either:
    - AZT/3TC/DTG – current Namibia guidelines
    - TDF/3TC/DTG – Nadia Study

  } Non - inferior
- User cases:
  - Patients with chronic Hep B
  - Challenges with adherence
  - Adolescents
  - Low HB
- Caution – close monitoring of patients

Common Adverse Events Noted

- Rash
  - Transient rash
  - Responds to antihistamines
  - Use of topical steroids can be considered
- Abdominal Pain
  - Upper quadrant pain
  - Mimick reflux
  - Associated with increased liver enzymes
  - Monitor LFTs and discontinue if rapid increase

IRIS

- No increase of IRIS noted or reported
  - Cutaneous manifestations
  - TB
  - Rebound Hepatitis B – flare up

Interactions

Table 1. Important pharmacokinetic drug-drug interactions with dolutegravir

Interacting drug	Effect of co-administration*	Recommendation
Metformin	↑ metformin	Maximum metformin dose 500 mg 12-hourly
Polyvalent cations (magnesium, iron, calcium, aluminium, zinc), e.g. antacids, sucralfate, supplements	↓ dolutegravir	Take dolutegravir either 2 hours before or 6 hours after Calcium and iron can be co-administered with a meal
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ dolutegravir	Avoid co-administration if possible (lamotrigine, valproate, levetiracetam and topiramate can be used) or double dolutegravir dose to 50 mg 12-hourly
Rifampicin	↓ dolutegravir	Double dolutegravir dose to 50 mg 12-hourly, or switch rifampicin to rifabutin 300 mg daily
Efavirenz	↓ dolutegravir	Avoid co-administration if possible (rilpivirine can be used) or double dolutegravir dose to 50 mg 12-hourly
Nevirapine	↓ dolutegravir	Avoid co-administration if possible (rilpivirine can be used) or double dolutegravir dose to 50 mg 12-hourly

*Arrows indicate the effect of the interaction in the concentration of the drug.

Use In Women of Childbearing Potential

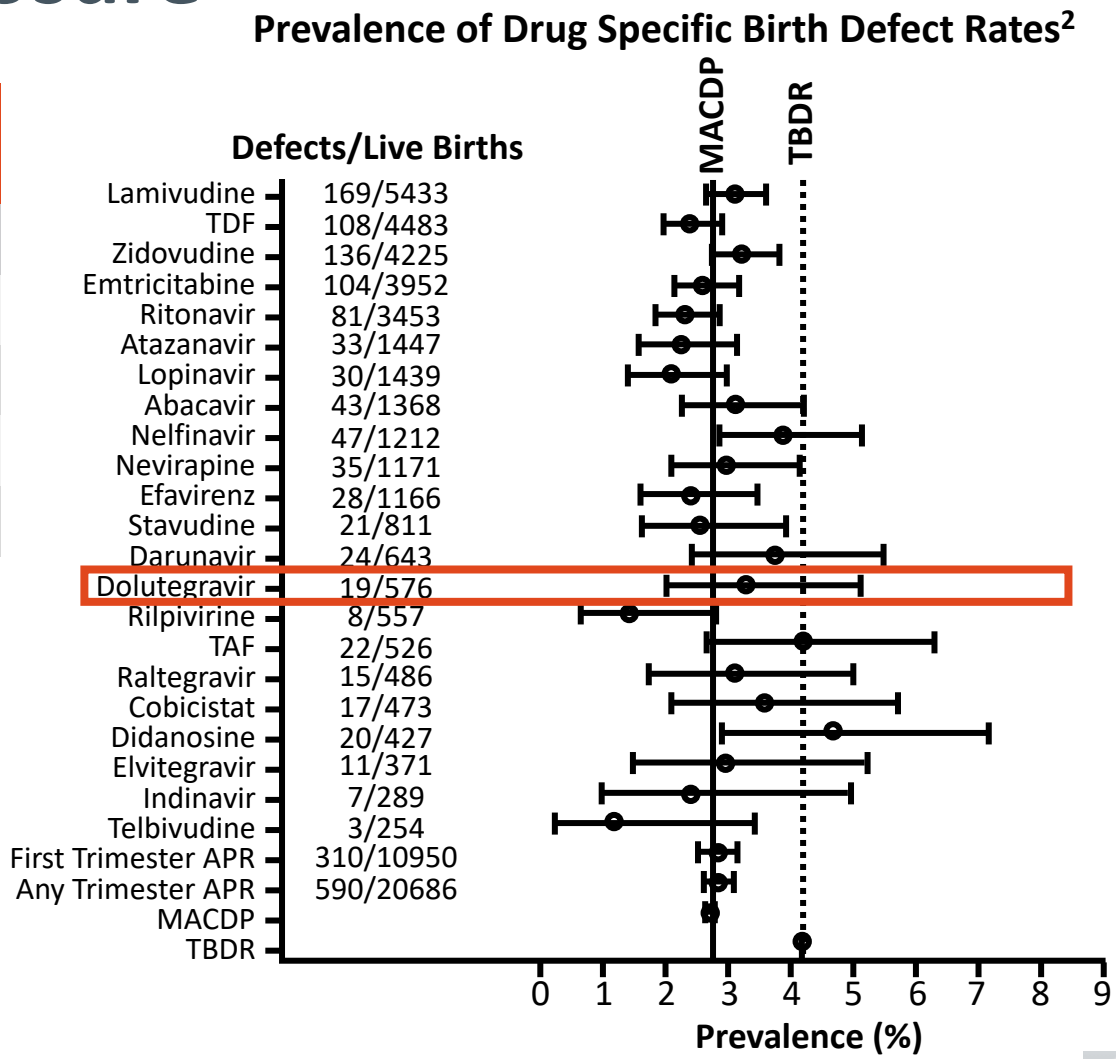
- In May 2018, an unplanned analysis of the Tsepamo study observed increased NTD prevalence among infants born to women receiving DTG at conception1
  - NTD prevalence with DTG vs non-DTG ART at conception: 0.94% vs 0.12%
- Updated 2021 analysis of Tsepamo reported lower prevalence of NTDs with maternal use of DTG at conception
  - NTD prevalence with DTG vs non-DTG ART at conception: 0.15% vs 0.10%
    - Prevalence difference: 0.06% (95% CI: -0.03% to 0.20%)

Antiretroviral Pregnancy Registry: Birth Defects After DTG Exposure

Birth Defects by Timing of DTG Exposure, n (%)[1]	Number per live births, n/N	Prevalence, % (95% CI)*
Overall	39/956	4.1 (2.92-5.53)
First trimester	19/576	3.3 (2.00-5.10)
Periconception	16†/475	3.4 (1.94-5.41)
Later first trimester	3/101	3.0 (0.62-8.44)
Second/third trimester	20/380	5.3 (3.24-8.01)

*Based on Clopper-Pearson exact method. †Includes 1 NTD.

- Birth defect prevalence in any trimester with prenatal DTG consistent with general population[1]
  - Prevalence in MACDP: 2.72 (95% CI: 2.68-2.76)
  - Prevalence in TBDR: 4.17 (4.15-4.19)
- Birth defect prevalence with any prenatal ARV exposure: 2.85 (95% CI: 2.63-3.09)



1. Vannappagari. IDWeek 2021. Abstr 74. 2. apregistry.com/forms/interim_report.pdf.

Slide credit: clinicaloptions.com

Use In Women of Childbearing Potential: Conclusion

- Analysis of data from the Antiretroviral Pregnancy Registry through January 2021 shows that prevalence of birth defects with prenatal DTG is comparable with that seen in the general population
- Prevalence of NTD with periconception DTG exposure was 1/475 exposures (0.21%)
- DTG can safely be initiated in Women of Childbearing potential

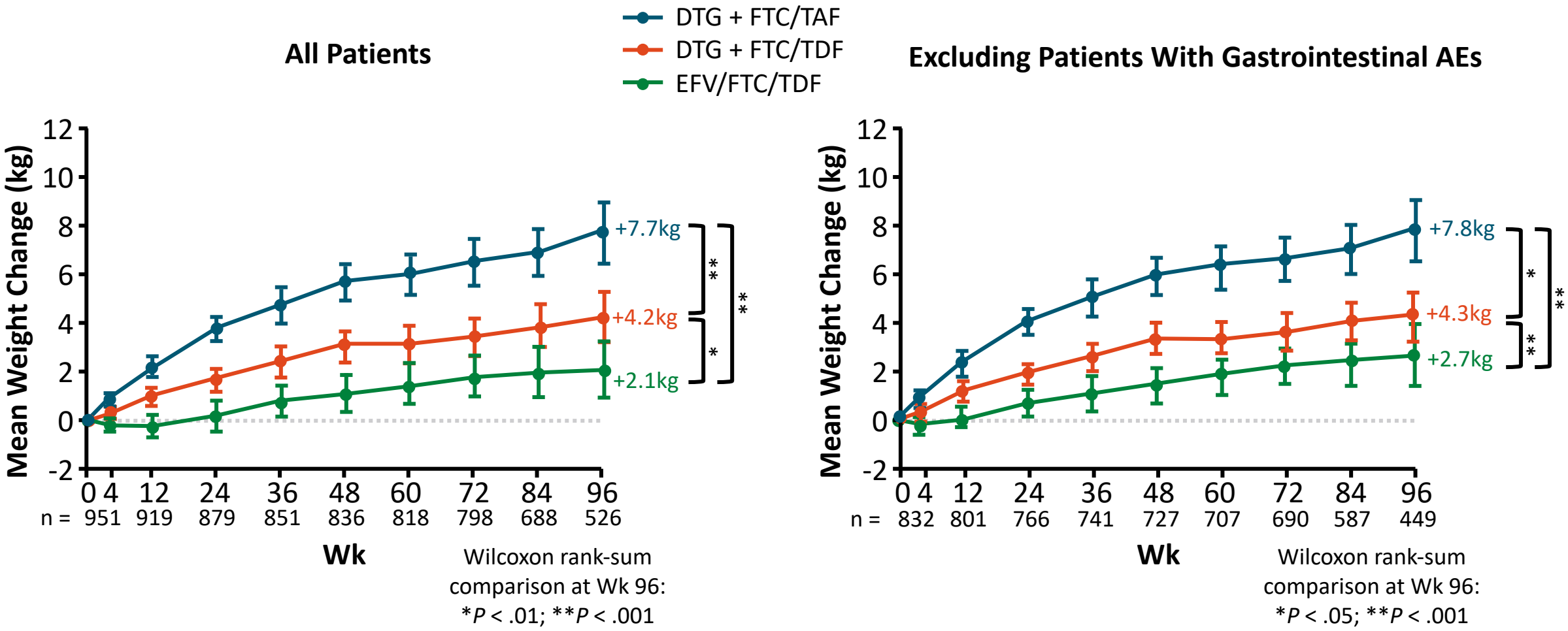
Vannappagari. IDWeek 2021. Abstr 74.

DTG and Weight Gain

- Obesity (BMI > 30) is associated with multiple comorbidities, including T2DM, CVD, MI, Alzheimer, cancer, and negative birth outcomes[1-3]
- In the phase III ADVANCE trial in South Africa, increased weight gain was observed in ART-naive patients initiating DTG-based ART vs EFV/FTC/TDF[4,5]
  - Weight gain higher with TAF vs TDF and in women vs men
- Current analysis compared the risk of metabolic syndrome, CVD, and T2DM in ART-naive patients initiating DTG + FTC/TAF vs DTG + FTC/TDF vs EFV/FTC/TDF in the ADVANCE trial using standard risk equations[6]

1. Pi-Sunyer. Postgrad Med. 2009;121:21. 2. Naderali. Am J Alzheimers Dis Other Demen. 2009;24:445. 3. Ahmed. Int J Health Sci. 2009;3:203. 4. Venter. NEJM. 2019;381:803. 5. McCann. EACS 2019. Abstr PS3/3. 6. Hill. CROI 2020. Abstr 81.

ADVANCE: Mean Weight Change Overall, in Subset Without Gastrointestinal AEs



McCann. EACS 2019. Abstr PS3/3.

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ADVANCE: Factors Associated With Obesity and Weight Gain

- Factors independently associated with treatment-emergent obesity in multivariate analysis
  - DTG + FTC/TAF, baseline CD4+ cell count, baseline HIV-1 RNA, baseline BMI
  - Additional significant factors when baseline BMI excluded: Female sex, South African nationality, employment status
- Factors independently associated with ≥ 10% increase in body weight in multivariate analysis
  - DTG + FTC/TAF, baseline CD4+ cell count, baseline HIV-1 RNA, female sex, age, baseline weight

McCann. EACS 2019. Abstr PS3/3.

Conclusions

- Among treatment-naive patients initiating ART in the ADVANCE trial, DTG + FTC/TAF resulted in significantly greater increases in VAT/SAT and predicted 10-yr risk of diabetes vs DTG + FTC/TDF and EFV/FTC/TDF at Wk 96
  - DTG + FTC/TAF associated with significantly increased risk of metabolic syndrome (P = .031) and heart attack or stroke (P = .027) vs EFV/FTC/TDF at Wk 96
  - No differences between arms in risk of MI or coronary death
- Limitations of current study include:
  - Median age of study population was 31 yrs, when risk of MI or diabetes is low
  - Weight gain among women did not plateau and models do not account for weight gain after Wk 96

Hill. CROI 2020. Abstr 81.

Implications

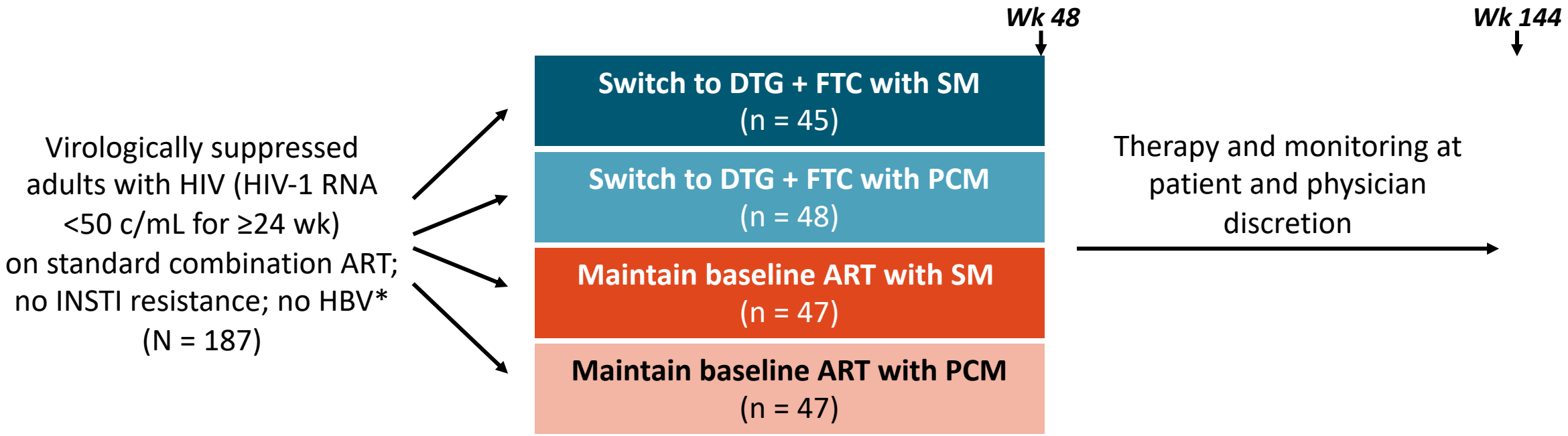
- Monitoring required
  - Baseline BMI and monitoring
  - Baseline Lipogram for at high risk patients
  - Glycated Hemoglobin HBAIc baseline for at high risk patients

DTG as Dual Therapy

- Dual therapies of DTG + XTC supported by large randomized clinical trials or meta-analyses:
  - In clinical trials, no association with more virological rebounds than triple therapy.
- Patient should have VL < 50 copies/mL for the past 6 month plus
  - No historical resistance **and**
  - HBV immunity or if non-immune concomitant HBV Vaccination
- Use case:
  - Renal impairment
  - Other use cases – please consult

SIMPL'HIV: Study Design

- Randomized, open-label, multicenter phase III trial



*Excluded if previous ART change due to suboptimal virologic response (M184V accepted); CrCl <50 mL/min; transaminase elevation >2.5 ULN.

- Post study endpoints: HIV-1 RNA <100 c/mL throughout Wk 144 and HIV-1 RNA <50 c/mL at Wk 144
- Other endpoints: change in lipids, weight, renal biomarkers, and QoL from baseline

Marinosci. AIDS 2022. Abstr OAB0302.

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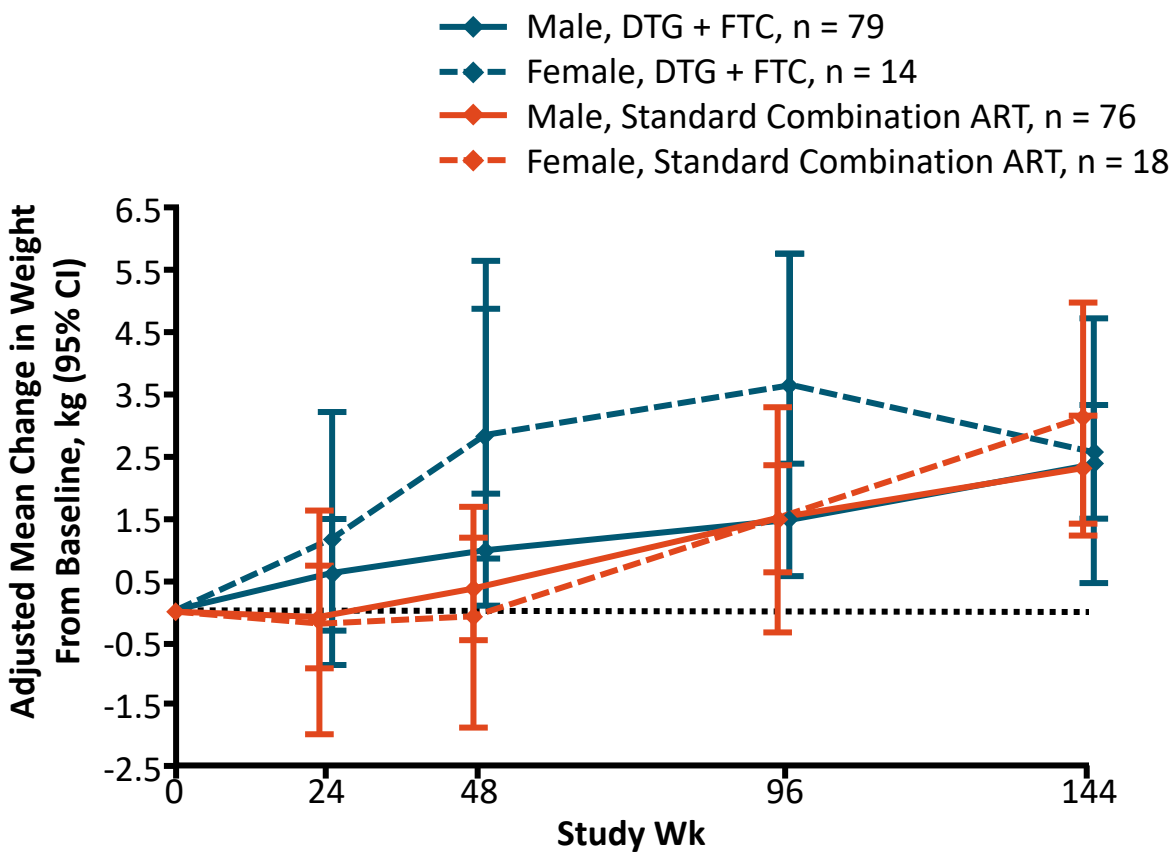
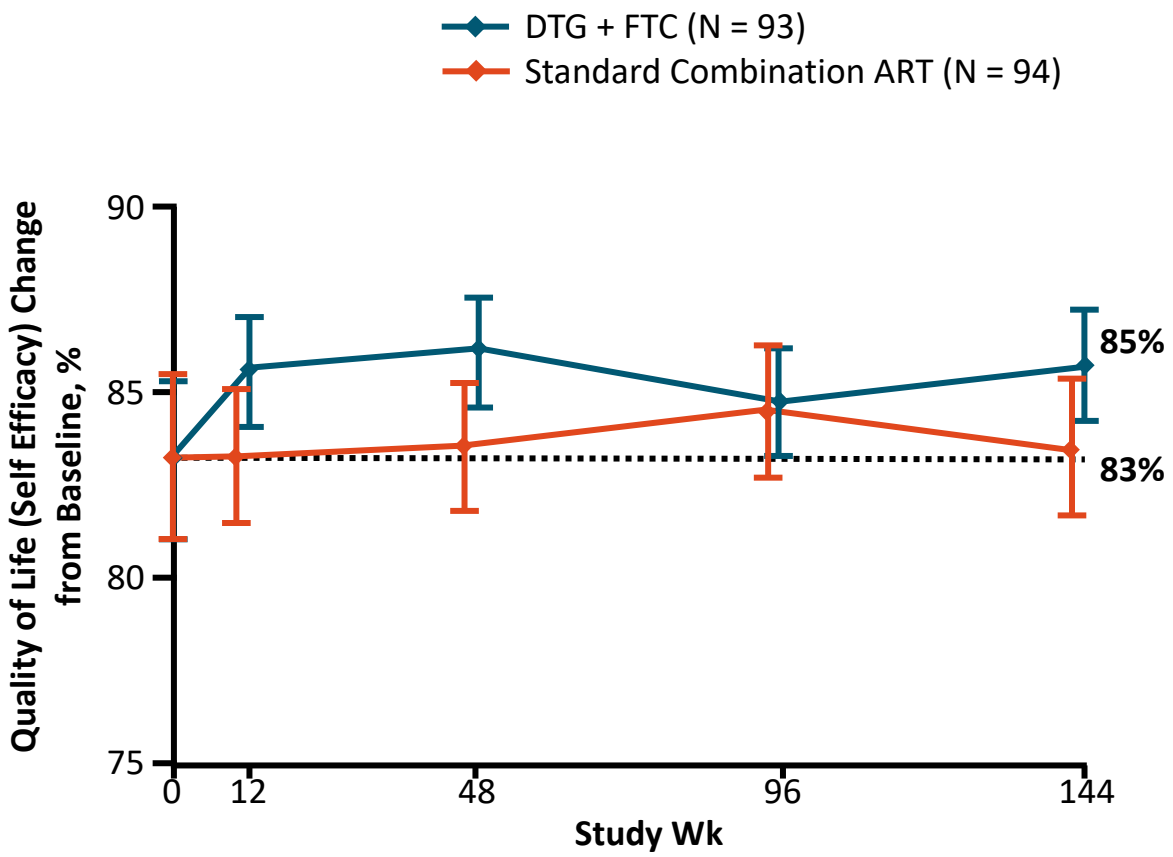
SIMPL'HIV: Change in Weight and Quality of Life

Weight Change Over 144 Wk



Quality of Life Change Over 144 Wk



Marinosci. AIDS 2022. Abstr OAB0302. Reproduced with permission.

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PAEDIATRIC USE OF DTG

Paediatric DTG 10 mg dispersible tablet (DT)

- Paediatric dolutegravir 10 mg dispersible, scored tablets (pDTG) is a new generic formulation of DTG suitable for infants and CLHIV who are
  - ≥ 4 weeks of age and,
  - Weigh at least 3 kg up to less than 20 kg
- Paediatric DTG 10 mg exist as a simpler formulations much easier to administer
- > 90% of CALHIV in Namibia on a DTG based regimen

Differences between the DTG 50 mg film-coated tablets and Paediatric DTG 10 mg DT

DTG 50 mg Film-Coated Tablets

- **Administration:** The adult 50 mg tablet is a small, film coated tablet (FCT) that should be swallowed whole
  - While 50 mg is the adult dose, it can also be used for children who weigh 20kg or more

DTG 10 mg Dispersible Tablets

- **Administration:** The Paediatric DTG 10 mg scored, dispersible tablet (DT) can be swallowed whole, but is meant to be dissolved in water

Paediatric DTG 10 mg DT is a priority commodity and should not be used in children/adults weighing ≥ 20kg as a replacement for DTG 50 mg FCT!

Clinicians and Pharmacist **should not** switch between 50 mg DTG FCT and 10 mg DTG DT
- the product dosing is not 1:1 (i.e. 5 x 10 mg DT is *not* equivalent to 1 x 50 mg FCT).

DTG in CALHIV: Outcomes

Outcome, n (%)	Total Cohort (N = 9419)
Patients remaining in active care	9107 (96.7)
Patients who died or were lost to follow-up	299 (3.2)
▪ Died	72 (0.8)
▪ Lost to follow-up	227 (2.4)
Severe drug toxicity	27 (0.3)

- Virologic suppression, overall
  - Pre-DTG: 92.7% (n/N = 8273/8921)
  - Post-DTG: 93.4% (n/N = 7378/7898)
- Previously unsuppressed who became suppressed: 80% (n/N = 426/534)
- Previously suppressed who remained suppressed: 95% (n/N = 6645/7026)

Bacha. IAS 2021. OAB0504.

Slide credit: clinicaloptions.com

DTG in CALHIV: Achievement of Virologic Suppression Among Those Previously Unsuppressed

Site, Age Category, or Sex	Virologic Suppression (HIV-1 RNA <1000 copies/mL) Post-DTG Switch, %
Site	
▪ Uganda (n = 111)	91.0
▪ Tanzania (n = 175)	85.7
▪ Malawi (n = 57)	68.4
▪ Eswatini (n = 78)	70.5
▪ Lesotho (n = 46)	87.0
▪ Botswana (n = 67)	61.2
Age	
▪ 0-4.99 yr (n = 3)	33.3
▪ 5-9.99 yr (n = 55)	89.1
▪ 10-14.99 yr (n = 199)	82.9
▪ 15-19.99 yr (n = 277)	76.2
Sex	
▪ Female (n = 265)	77.0
▪ Male (n = 269)	82.5

Note: n reflects patients with both pre-and post-DTG HIV-1 RNA measurements.

Bacha. IAS 2021. OAB0504.

DTG in CALHIV: Conclusions

- DTG-based regimens were both effective and well tolerated in this large cohort of CALHIV in sub-Saharan Africa
  - DTG-based regimens maintained virologic suppression in patients previously suppressed
  - DTG-based regimens produced virologic suppression for a sizable proportion of patients previously unsuppressed
  - No difference in rate of virologic suppression based on pill burden of DTG regimen (1 tablet daily vs multiple tablets daily)
- Investigators conclude these results encourage continued and expanded use of DTG-based regimens among eligible CALHIV

Bacha. IAS 2021. OAB0504.

Implications

- Strong recommendation: Switch CALHIV to DTG based regimens

THANK YOU