Treatment With 3TC + DTG: Any Missing Gaps?

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Barcelona, 29th October 2020

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Presenter Disclosure Information

- Research Support: ViiV, BMS

- Speaker's Bureau: Abbvie, Bristol-Myers Squibb, Merck, Janssen, ViiV Healthcare, Stendhal

- Advisory Panel: Gilead, Janssen, ViiV

Agenda

- Less than 3: nothing new…but something new
- Data supporting DTG/3TC
- Missing gaps…
- Conclusions

Table 1. Summary of Results of Induction–Maintenance Trials

Study	Induction Therapy	Maintenance Therapy	Failure Rate (%)
ACTG 343 (Havlir et al. *N Engl J Med*, 1998)	Zidovudine/lamivudine/ indinavir	Zidovudine/lamivudine/ indinavir	4
		Zidovudine/lamivudine	23
		Indinavir	23
Trilege (Pialoux et al. *N Engl J Med*, 1998)	Zidovudine/lamivudine/ indinavir	Zidovudine/lamivudine/ indinavir	9
		Zidovudine/lamivudine	31
		Zidovudine/indinavir	22
ADAM (Reijers et al. *Lancet*, 1998)	Stavudine/lamivudine/ nelfinavir/ saquinavir	Stavudine/lamivudine/ nelfinavir/saquinavir	9
		Stavudine/nelfinavir	57
		Nelfinavir/saquinavir	71

Lopinavir/Ritonavir as Single-Drug Therapy for Maintenance of HIV-1 Viral Suppression

48-Week Results of a Randomized, Controlled, Open-Label, Proof-of-Concept Pilot Clinical Trial (OK Study)

J Acquir Immune Defic Syndr • Volume 40, Number 3, November 1 2005

Dual Therapy With Darunavir and Ritonavir Plus Lamivudine vs Triple Therapy With Darunavir and Ritonavir Plus Tenofovir Disoproxil Fumarate and Emtricitabine or Abacavir and Lamivudine for Maintenance of Human Immunodeficiency Virus Type 1 Viral Suppression: Randomized, Open-Label, Noninferiority DUAL-GESIDA 8014-RIS-EST45 Trial

CID 2017:65 (15 December) • Pulido et al

JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2020 Recommendations of the International Antiviral Society–USA Panel

Box 2. Recommended Initial Antiretroviral Therapy (ART) Regimens

Recommended for Most People With HIV[a]

- Bictegravir/tenofovir alafenamide/emtricitabine (evidence rating: AIa)
- Dolutegravir plus (all evidence ratings: AIa)
  - Tenofovir alafenamide/emtricitabine
  - Tenofovir disoproxil fumarate/emtricitabine
  - Tenofovir disoproxil fumarate/lamivudine
- Dolutegravir/lamivudine with caveats[b] (evidence rating: AIa)

[b] Not recommended for rapid start because baseline laboratory evaluation results must be reviewed before initiation. Also not recommended for patients with chronic hepatitis B or HIV RNA level above 500 000 copies/mL, and perhaps a CD4 cell count below 200/μL, although the latter is unclear. Close monitoring for adherence and virological response is needed. Not recommended for patients being treated for an active opportunistic infection.

Switching When the Patient Has Achieved Viral Suppression

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

AIDSinfo

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC (**AI**)
- DTG/ABC/3TC (**AI**)—**if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[a] plus (FTC or 3TC) (**AI**)
- RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)

INSTI plus 1 NRTI:

- DTG/3TC (**AI**), except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2020 Recommendations of the International Antiviral Society–USA Panel

Switching When the Patient Has Achieved Viral Suppression

- In the setting of viral suppression, switching from a 3-drug regimen to an oral 2-drug regimen is an appropriate strategy to manage toxic effects, intolerance, adherence, or patient preference provided both agents are fully active (evidence rating: AIa). Recommended regimens include dolutegravir/rilpivirine (evidence rating: AIa), a boosted PI with lamivudine (evidence rating: AIa), dolutegravir/lamivudine (evidence rating: AIa) or a long-acting injectable 2-drug regimen of cabotegravir and rilpivirine dosed every 4 weeks (evidence rating: AIa) or every 8 weeks (evidence rating: BIb)

Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

AIDSinfo

Dolutegravir plus Lamivudine

A switch from three-drug regimens to DTG plus 3TC as maintenance strategy in patients with virologic suppression has been examined in a large randomized clinical trial (TANGO),[30] in two small clinical trials,[31,32] and in observational studies[33,34] with good success. The result of the TANGO trial is discussed below.

The Phase 3 TANGO study enrolled participants who were on their first ARV regimen with HIV RNA <50 copies/mL for ≥6 months. Participants were randomized to switch to open label DTG plus 3TC (n = 369) or to continue their TAF-based triple therapy (n = 372). The participants had no history of virologic failure or evidence of resistance to DTG or 3TC and did not have HBV coinfection. At week 48, switching to DTG plus 3TC was non-inferior to continuing on the current regimen, with 93% of participants in both arms maintaining HIV RNA <50 copies/mL. No unexpected adverse events were identified as related to DTG or 3TC.[30] Switching to a DTG plus 3TC regimen can be a good option for individuals who have no evidence of resistance to either drug and do not have HBV coinfection **(AI)**.

Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment–Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials

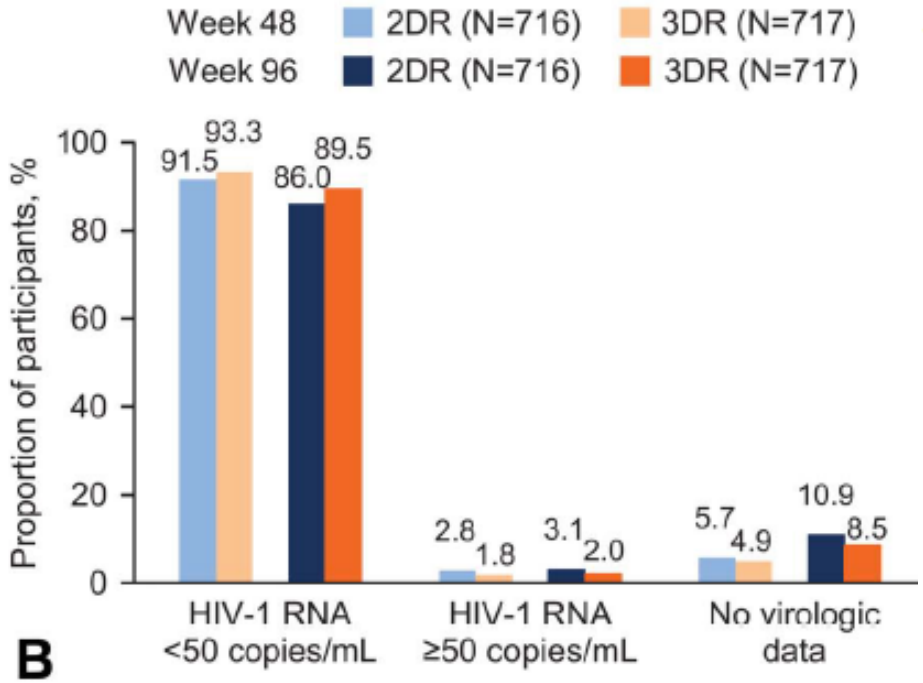
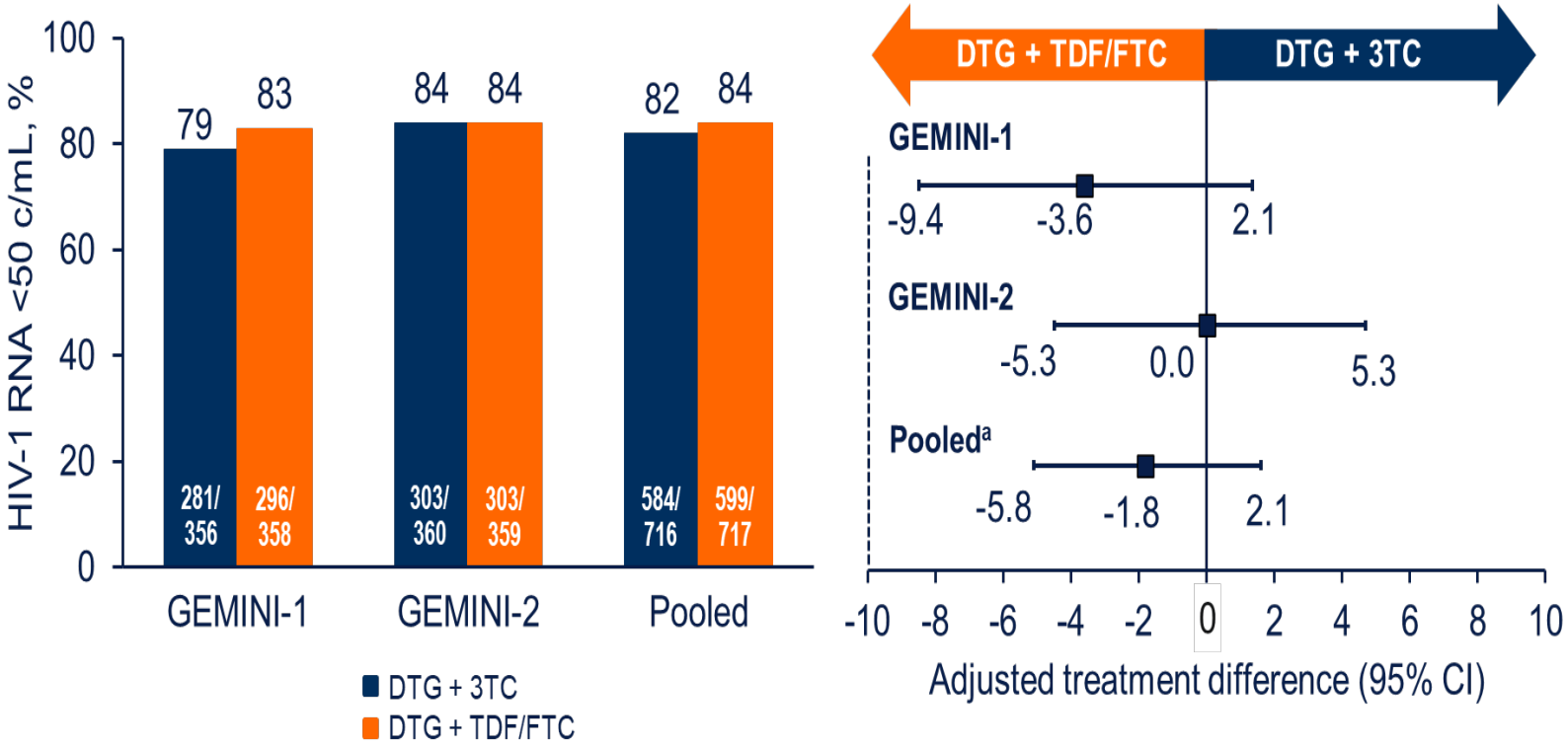


TABLE 2. Summary of AEs in the Pooled Safety Population From GEMINI-1 and GEMINI-2

n (%)	2DR (N = 716)	3DR (N = 717)
Drug-related AEs	140 (19.6)	179 (25.0)
Grade 2–5 AEs occurring in ≥1% of participants	50 (7.0)	57 (7.9)
Headache	8 (1.1)	8 (1.1)
Serious AEs	64 (8.9)	67 (9.3)
AEs leading to withdrawal from treatment and study	24 (3.4)	23 (3.2)
AEs of interest leading to withdrawal from the study		
Neuropsychiatric	10 (1.4)	5 (0.7)
Renal-related	2 (0.3)	7 (1.0)
Osteoporosis	0	2 (0.3)

2DR, 2-drug regimen (dolutegravir + lamivudine); 3DR, 3-drug regimen (dolutegravir + tenofovir disoproxil fumarate/emtricitabine).

Snapshot Analysis of the Proportion of Participants With Plasma HIV-1 RNA <50 c/mL Through Week 144 in the GEMINI-1, GEMINI-2, and Pooled ITT-E Populations



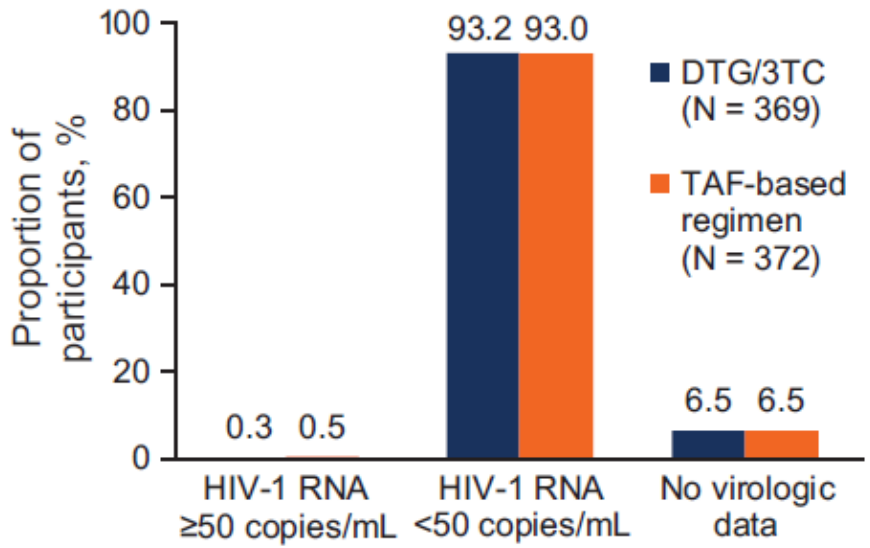
[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL), baseline CD4+ cell count (≤200 vs >200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2).

Clinical Infectious Diseases

MAJOR ARTICLE

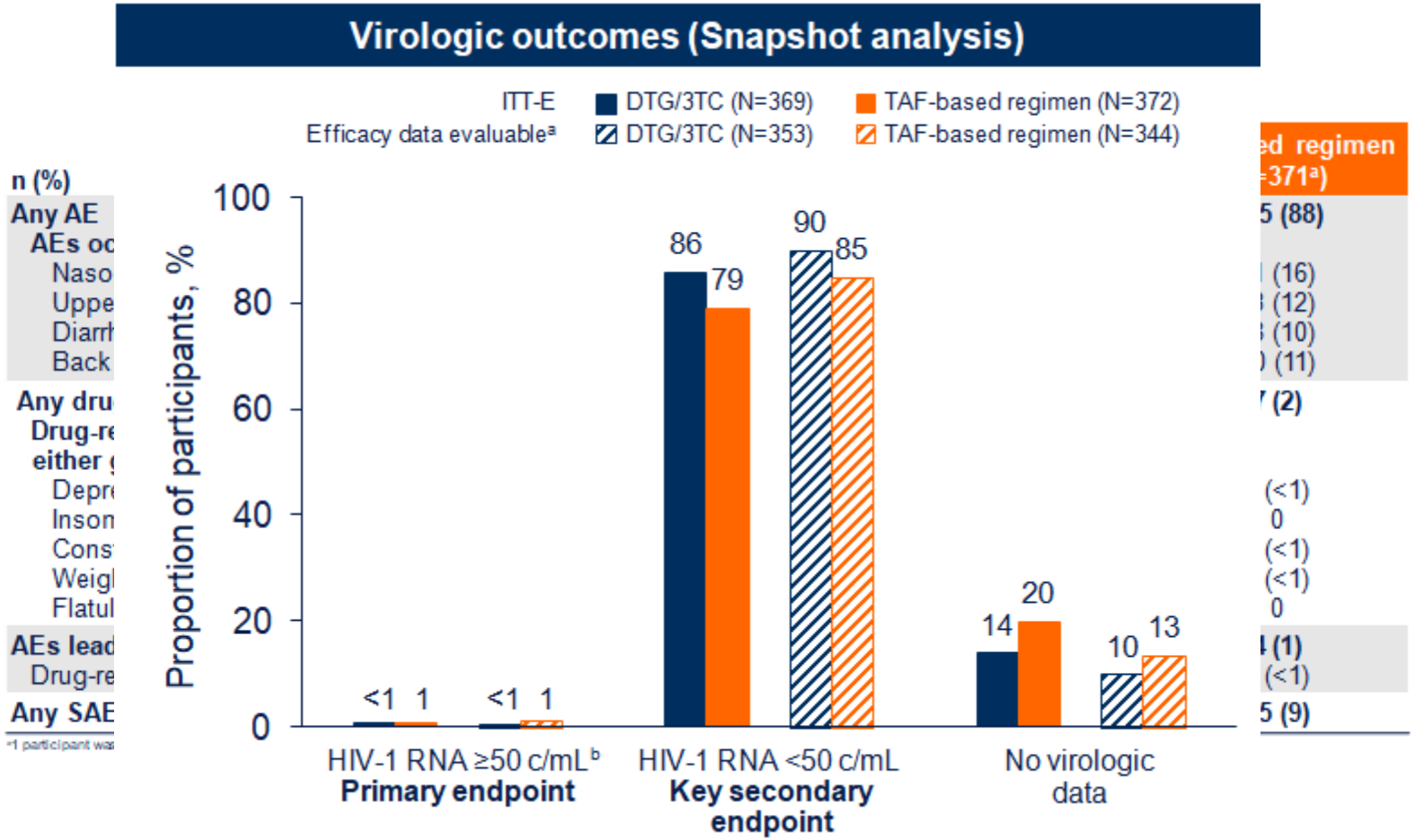
Efficacy and Safety of Switching to Dolutegravir/ Lamivudine Fixed-Dose 2-Drug Regimen vs Continuing a Tenofovir Alafenamide–Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults Living With Human Immunodeficiency Virus Type 1: Phase 3, Randomized, Noninferiority TANGO Study

A



Snapshot outcome, n (%)	DTG/3TC (N = 369)	TAF-based regimen (N = 372)
HIV-1 RNA <50 copies/mL	**344 (93.2)**	**346 (93.0)**
HIV-1 RNA ≥50 copies/mL	**1 (0.3)**	**2 (0.5)**
Discontinued for lack of efficacy	0	2 (0.5)
Discontinued for other reason and HIV-1 RNA ≥50 copies/mL	1 (0.3)	0
No virologic data	**24 (6.5)**	**24 (6.5)**
Discontinued due to AE/death[a]	12 (3.3)	1 (0.3)
Discontinued for other reasons	12 (3.3)	22 (5.9)
Missing data during window	0	1 (0.3)

DTG/3TC Is Non-Inferior to TAF-Based Regimen at Week 96



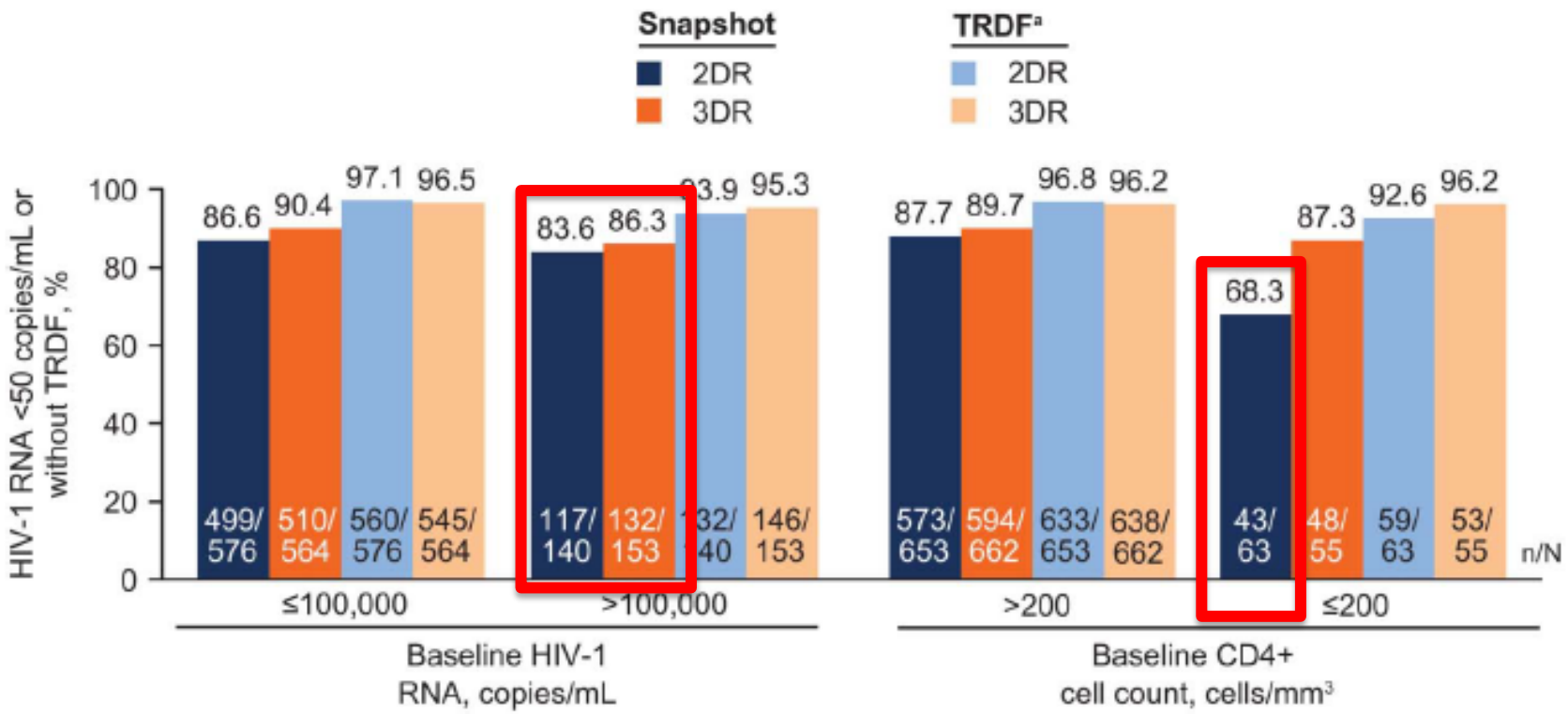
- In the per-protocol population,[d] superiority was demonstrated with 0/348 participants in the DTG/3TC group and 4/351 (1%) in the TAF-based regimen group with HIV-1 RNA ≥50 c/mL at Week 96 (adjusted difference, −1.1%; 95% CI, −2.3% to −0.0%)

[a]Sensitivity analysis excluding 16 and 28 participants in the DTG/3TC and TAF-based regimen groups, respectively, because of no Week 96 HIV-1 RNA data due to effects of the COVID-19 pandemic. [b]Primary endpoint (Snapshot virologic non-response, ITT-E). [c]Based on Cochran-Mantel-Haenszel stratified analysis (DTG/3TC − TAF-based regimen) adjusting for baseline third agent class. [d]Sensitivity analysis.

Missing gaps

- Efficacy in in extreme situations
- Efficacy in special scenarios
- Reservoir & Inflammation
- What if bad adherence

Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment–Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials



Only 2% VL>500.000 cop/mL

J Acquir Immune Defic Syndr • Volume 83, Number 3, March 1, 2020

FEASIBILITY, EFFICACY, AND SAFETY OF USING DOLUTEGRAVIR/LAMIVUDINE (DTG/3TC) AS A FIRST-LINE REGIMEN IN A TEST-AND-TREAT SETTING FOR NEWLY DIAGNOSED PEOPLE LIVING WITH HIV (PLWH): THE STAT STUDY

Charlotte-Paige Rolle,[1] Mezgebe Berhe,[2] Tulika Singh,[3] Roberto Ortiz,[4] Anson Wurapa,[5] Moti Ramgopal,[6] Peter A. Leone,[7] Jessica E. Matthews,[7] Marybeth Dalessandro,[8] Mark R. Underwood,[7] Konstantinos Angelis,[9] Brian R. Wynne,[7] Deanna Merrill,[7] Christopher Nguyen,[7] Jean van Wyk[10]

[1]Orlando Immunology Center, Orlando, FL, USA; [2]Baylor University Medical Center, Dallas, TX, USA; [3]Desert AIDS Project, Palm Springs, CA, USA; [4]Bliss Healthcare Services, Orlando, FL, USA; [5]Infectious Disease Specialists of Atlanta, Decatur, GA, USA; [6]Midway Immunology and Research Center, Fort Pierce, FL, USA; [7]ViiV Healthcare, Research Triangle Park, NC, USA; [8]GlaxoSmithKline, Upper Providence, PA, USA; [9]GlaxoSmithKline, Uxbridge, UK; [10]ViiV Healthcare, Brentford, UK

HIV Drug Therapy Glasgow 2020; October 5-8, 2020; Virtual

SE-ES-HVX-PPT-200010

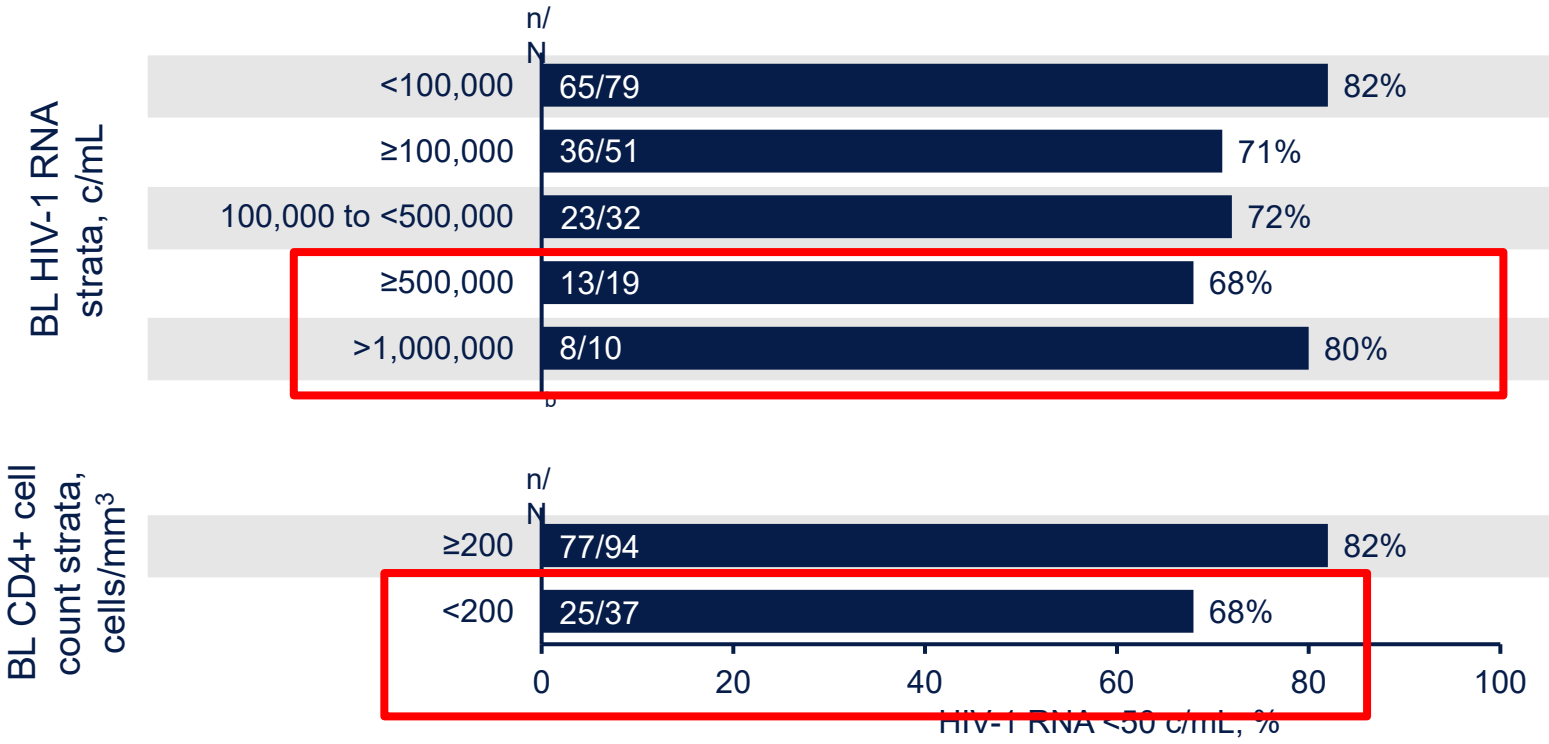
Selected Baseline Demographics and Participant Characteristics (ITT-E Population)

Characteristic	DTG/3TC (N=131)
Age, median (range), years	31 (18-63)
≥50 years, n (%)	20 (15)
Cisgender female, n (%)	10 (8)
Transgender female, n (%)	1 (<1)
Ethnicity, n (%)	
Hispanic/Latino	38 (29)
Not Hispanic/Latino	93 (71)
Race, n (%)	
Black/African American	61 (47)
White	65 (50)
Other	5 (4)
Time to enrollment since diagnosis, median (range), days	5 (0-15)
HIV-1 RNA, median (range), c/mL, n (%)[a,b]	63,056 (<40 to 68,706,840)[c]
<100,000	79 (60)
100,000 to <500,000	32 (24)
500,000 to <1,000,000	9 (7)
≥1,000,000	10 (8)
CD4+ cell count, median (range), cells/mm^3[b]	389.0 (<20 to 1466)[d]
<200, n (%)	37 (28)
HBV co-infection, n (%)[b,e]	7 (5)
M184V resistance mutation, n (%)[b]	1 (<1)

[a]1 (<1%) participant had missing plasma HIV-1 RNA results at BL. [b]BL resistance was identified at Week 4, and HIV-1 viral load, CD4+ cell count, and HBV co-infection were identified at Week 1 from samples taken at BL. [c]Lower limit of quantification is <40. [d]Lower limit of quantification is <20. [e]2 participants with HBV co-infection remained on DTG/3TC.

Rolle et al. HIV Glasgow 2020; Poster P020.

Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 24 by BL HIV-1 RNA[a] and CD4+ Cell Count (ITT-E Missing = Failure Analysis)



[a]1 (<1%) participant had missing plasma HIV-1 RNA results at BL. [b]Of the 19 participants with BL viral load ≥500,000 c/mL, 13 (68%) were suppressed to <50 c/mL, 4 remain on study with viral load >50 c/mL (3 <200 c/mL), and 2 discontinued.

Rolle et al. HIV Glasgow 2020; Poster P020.

Participants Who Switched From DTG/3TC at Any Time Point by Week 24

- All participants with available data who had an ART adjustment and remained on study at Week 24 had HIV-1 RNA <50 c/mL

Reason for switch	Visit window	Modified ART	Plasma HIV-1 RNA at Week 24
BL HBV	Week 1	DTG/3TC + TAF	<40 c/mL
BL HBV	Week 1	BIC/FTC/TAF	NA[a]
BL HBV	Week 4	DTG + TDF/FTC	<40 c/mL
BL HBV	Week 4	BIC/FTC/TAF or DTG + TDF/FTC[b]	49 c/mL
Decision by participant or proxy	Week 4	BIC/FTC/TAF	NA[c]
BL HBV	Week 8	DTG/3TC + TAF	<40 c/mL
BL M184V	Week 8	DTG/RPV	NA[d]
AE (rash)	Week 12; Week 12	COBI/DRV/FTC/TAF; BIC/FTC/TAF[e]	<40 c/mL

[a]Participant on study but missing data in window. Participant had HIV-1 RNA <40 c/mL at Week 36. [b]Participant participates in another double-blind clinical trial with a tenofovir-based regimen; switched to either Biktarvy or Truvada + Tivicay. [c]Participant withdrew consent after switch from DTG/3TC. [d]Participant had HIV-1 RNA 18,752 c/mL at baseline, <40 c/mL on Day 47, switched to DTG/RPV on Day 49, and had last HIV-1 RNA 54 c/mL on Day 57; participant withdrew consent (due to relocation) on Day 106 (Week 12). [e]Participant switched ART twice.

Rolle et al. HIV Glasgow 2020; Poster P020.

Star of DTG+3TC after PreP

Antiretroviral resistance and management after pre-exposure prophylaxis

*Victoria Tittle, Marta Boffito, Alan McOwan, Gary Whitlock, on behalf of Dean Street Collaborative Group

	Previous PrEP use (n=22)	No previous PrEP use (n=917)	p value
Age (years)	31 (23–52)	32 (18–74)	0·97
Gender and sexual behaviour			
Men who have sex with men	22 (100%)	878 (96%)	0·38
Men who don't have sex with men	0 (0%)	26 (3%)	..
Women	0 (0%)	13 (1%)	..
Baseline viral load (copies per mL)	7700 (<20–320 000)	58 000 (<20–1 000 000)	0·0004
Presence of Met184Val or Met184Ile	5 (23%)	5 (1%)	<0·0001
Unable to amplify genotypic resistance test	4 (18%)	20 (2%)	0·002

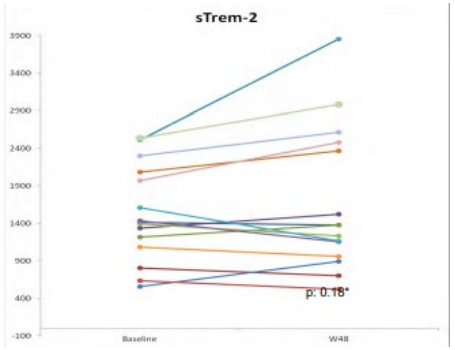
Data are median (range) and n (%). Data represent documented PrEP use in the 12 months before HIV diagnosis.

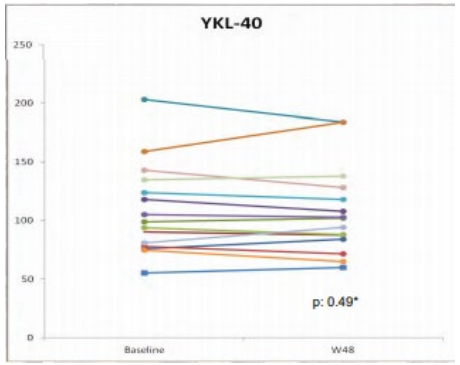
Table: Demographics and genotypic resistance test results of patients with HIV

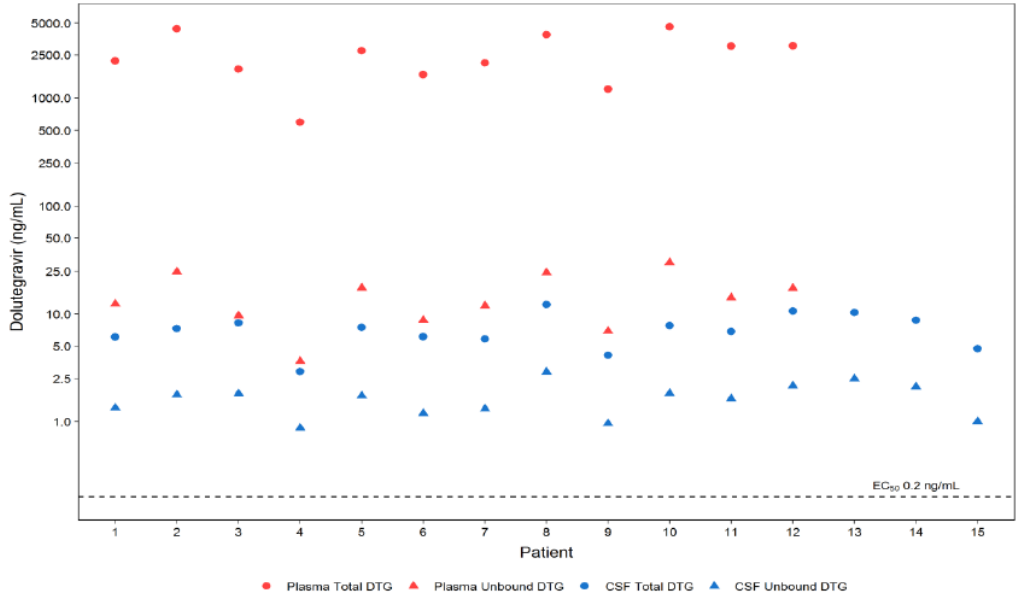
No changes in HIV suppression and inflammatory markers in CSF in patients randomly switched to DTG + 3TC

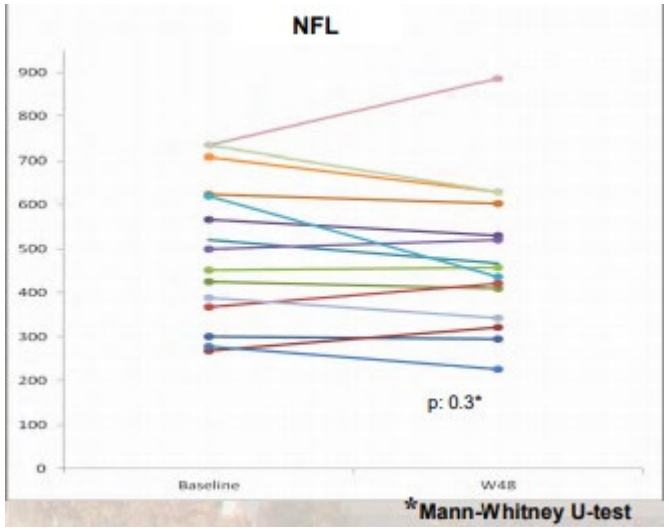
(Spanish HIV/AIDS Research Network, PreEC/RIS 62)

15 individuals from DOLAM







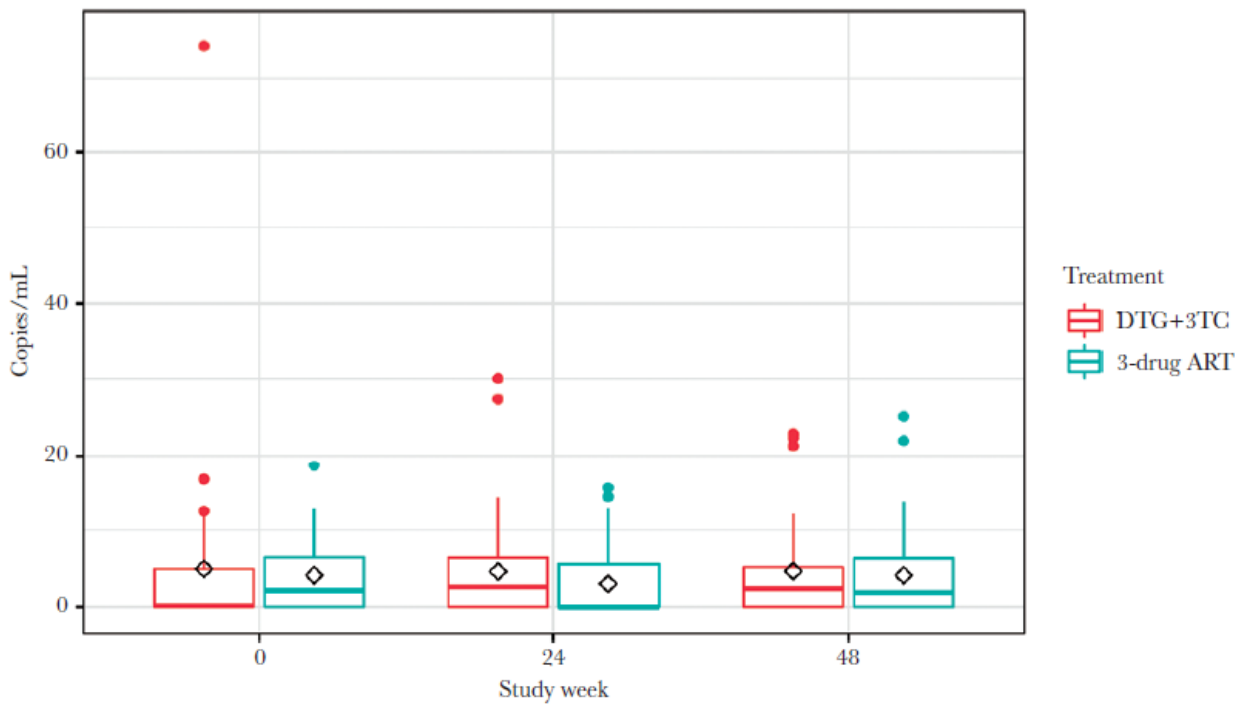


Tiraboschi J, et al . JID 2020, accepted

No Significant Changes to Residual Viremia After Switch to Dolutegravir and Lamivudine in a Randomized Trial

Jonathan Z. Li,[1] Paul E. Sax,[1] Vincent C. Marconi,[2] Jesse Fajnzylber,[1] Baiba Berzins,[3] Amesika N. Nyaku,[4] Carl J. Fichtenbaum,[5] Timothy Wilkin,[6] Constance A. Benson,[7] Susan L. Koletar,[8] Ramon Lorenzo-Redondo,[3] and Babafemi O. Taiwo[3]

Characteristic	DTG+3TC (n = 36)	3-Drug ART (n = 36)	*P*
Age, median, y	45.5	50.5	.67
Male sex, %	92	86	.71
Ethnicity, %			.33
White	58	72	
Black	39	28	
Asian	3	0	
CD4+ cell count, median, cells/mm^3	677	637	.09
Duration of viral suppression, median, y	5.37	6.04	.82



Changes in Inflammatory biomarkers in TANGO study

Switch to DTG+3TC vs 3DR (Week 48)

Table 3. Change From Baseline to Week 48 in Inflammation Biomarkers

Parameter	Treatment	n/N	Visit to baseline ratio (95% CI)[a]	Treatment ratio (95% CI)[b]	*P* value[c]
Blood D-dimer, nmol/L FEU	DTG/3TC	334/369	0.968 (0.920, 1.019)	0.973 (0.907, 1.044)	0.440
	TAF-based regimen	334/371	0.995 (0.948, 1.044)		
Serum hs-CRP, mg/L	DTG/3TC	342/369	1.012 (0.911, 1.124)	0.934 (0.811, 1.075)	0.341
	TAF-based regimen	342/371	1.083 (0.986, 1.190)		
Serum IL-6, ng/L	DTG/3TC	343/369	0.990 (0.909, 1.078)	1.163 (1.045, 1.293)	0.006
	TAF-based regimen	340/371	0.852 (0.800, 0.907)		
Serum sCD14, ng/L	DTG/3TC	343/369	0.953 (0.933, 0.973)	0.971 (0.942, 1.000)	0.048
	TAF-based regimen	343/371	0.982 (0.962, 1.002)		
Serum sCD163, µg/L	DTG/3TC	342/369	0.916 (0.889, 0.943)	1.013 (0.974, 1.054)	0.508
	TAF-based regimen	342/371	0.904 (0.881, 0.927)		

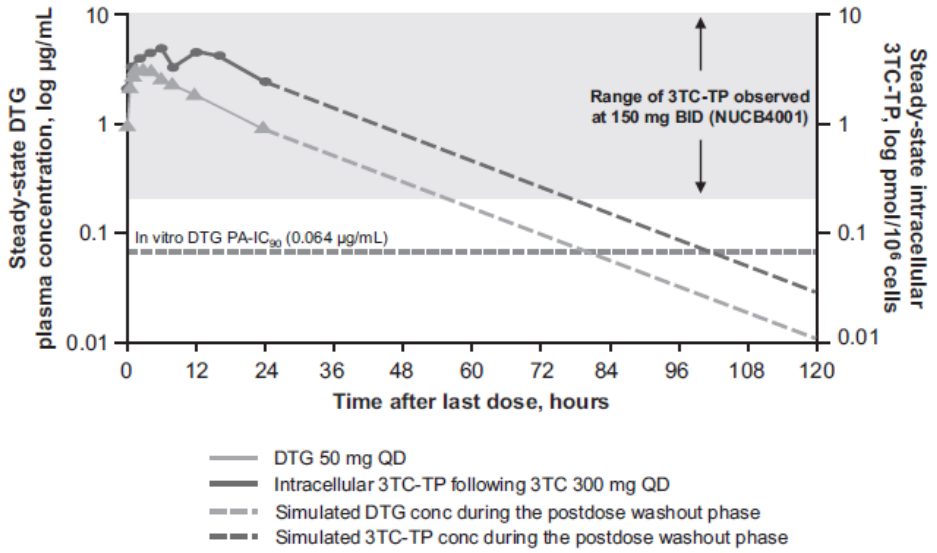
- **Increase of IL-6 x1.16 (p=0.006)**
- **Reduction of sCD14 x0.97 (p=0.048)**
- **No changes in CRP, D-dimers, sCD163**

"Effects on inflammation biomarkers were small and inconclusive, with significant differences observed in differing directions for DTG/3TC and TAF-based regimens."

Van Wyk. CID 2020

Perspectives on the Barrier to Resistance for Dolutegravir + Lamivudine, a Two-Drug Antiretroviral Therapy for HIV-1 Infection

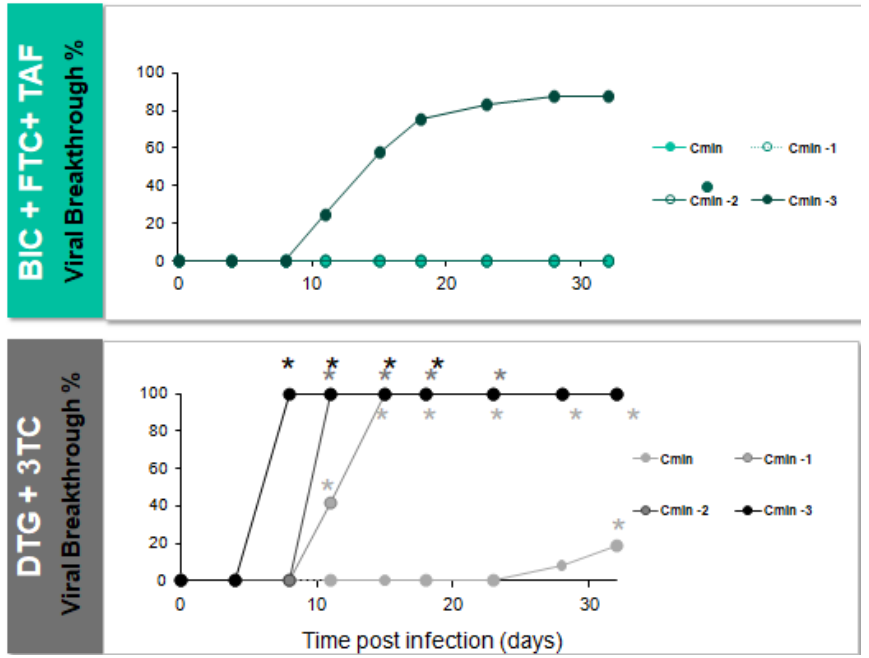
Boffito M, et al. AIRHR 2019



In Vitro "Forgiveness" Studies: BIC+FTC+TAF vs DTG+3TC

Mulato A, et al. IAS 2019. Mexico City, Mexico. TUPEA103

	Mechanisms	BIC+FTC+TAF	DTG+3TC
Drug Levels	**Plasma or intracellular $t_{1/2}$**		
	BIC or DTG[2,3]	17 hr	14 hr
	FTC-TP and 3TC-TP[4-6]	37 hr	17.5 hr
	TFV-DP[6]	116 hr	n/a
	IN/DNA dissociation $t_{1/2}$, BIC or DTG[7,8]	132 hr* 38 hr†	71-78 hr* 16 hr†
Synergy and Mechanisms of Synergy	**Combination antiviral activity**		
	INSTI + FTC or 3TC[9-11]	Synergy	Synergy
	INSTI + TAF[9]	Synergy	n/a
	TFV + FTC[10-11]	Synergy	n/a
	TFV-chain-termination stabilized by dead-end complex with FTC-TP[12]	Decreased TFV excision	n/a



Confirmed Virologic Withdrawal

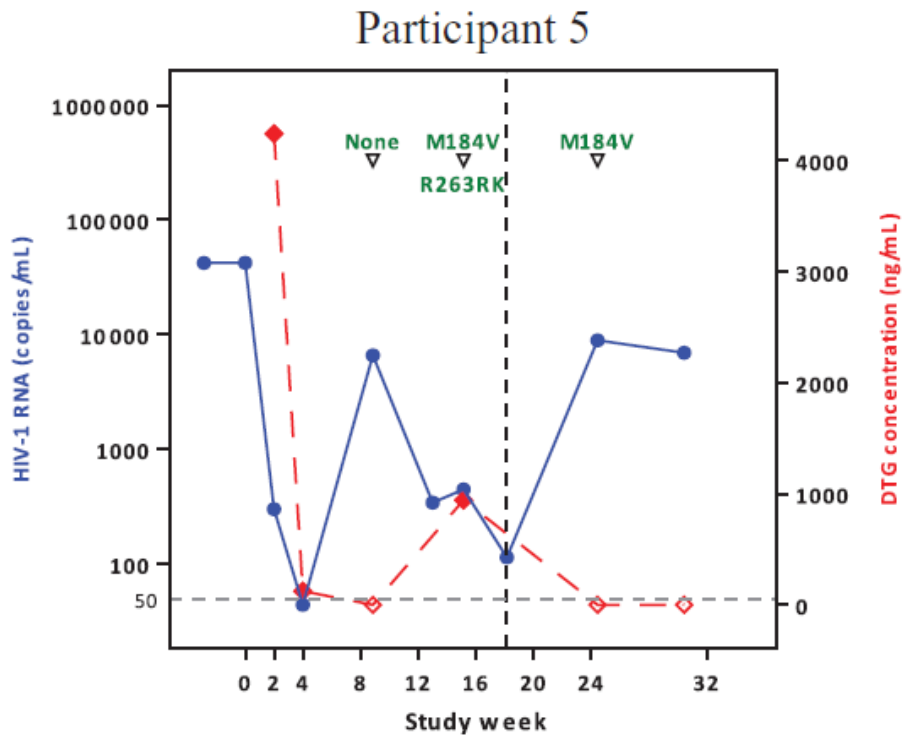
- Across both studies, 12 participants (2%) in the DTG + 3TC group (1 since Week 96) and 9 participants (1%) in the DTG + TDF/FTC group (2 since Week 96) met protocol-defined CVW criteria[1] through Week 144
  - None of these participants had treatment-emergent INSTI or NRTI resistance mutations
- 1 non-CVW participant with reported non-adherence in the DTG + 3TC group developed M184V at Week 132 (HIV-1 RNA 61,927 c/mL) and R263R/K at Week 144 (HIV-1 RNA 135 c/mL), conferring a 1.8-fold change in susceptibility to DTG
  - Baseline HIV-1 RNA: 93,515 c/mL; CD4+ cell count: 393 cells/mm^3
  - Suppressed to HIV-1 RNA <50 c/mL from Week 4 through Week 120; HIV-1 RNA 61,927 c/mL detected at
    Week 132, with successive HIV-1 RNA of <50, 135, and 61 c/mL after Week 132
  - Withdrawn due to lack of efficacy after Week 144, switched to DTG once daily + DRV/COBI, and regained virologic suppression

1. Cahn et al. *Lancet.* 2019;393:143-155.

Clinical Infectious Diseases

MAJOR ARTICLE

ACTG A5353: A Pilot Study of Dolutegravir Plus Lamivudine for Initial Treatment of Human Immunodeficiency Virus-1 (HIV-1)–infected Participants With HIV-1 RNA <500 000 Copies/mL



Conclusions

- DTG+3TC is an excellent option of ART in naïve as well as in therapy optimisation in selected individuals
- DTG+3TC is not recommended in naïve individuals with > 500.000 copies/mL and probably if CD4 cels counts < 200 µL
- DTG+3TC should not be used as a Test&Treat Strategy and if prior use of PreP
- DTG+3TC has not shown to have a worse impact on reservoir and inflammation markers than 3DR
- DTG+3TC selection should be used in patients with good adherence to ART