I RISULTATI DEGLI STUDI GEMINI: QUALI SONO LE POSSIBILI IMPLICAZIONI?

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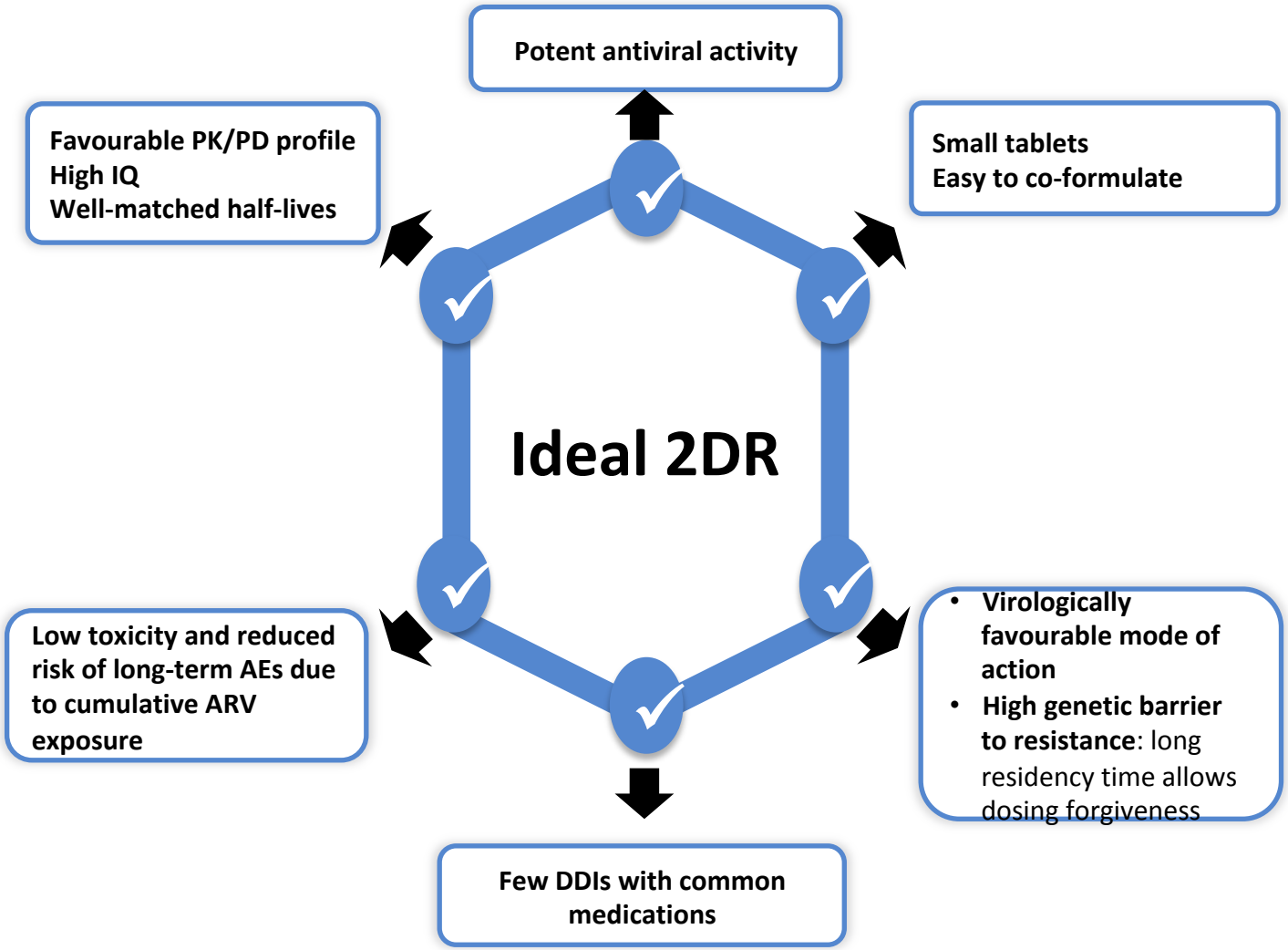
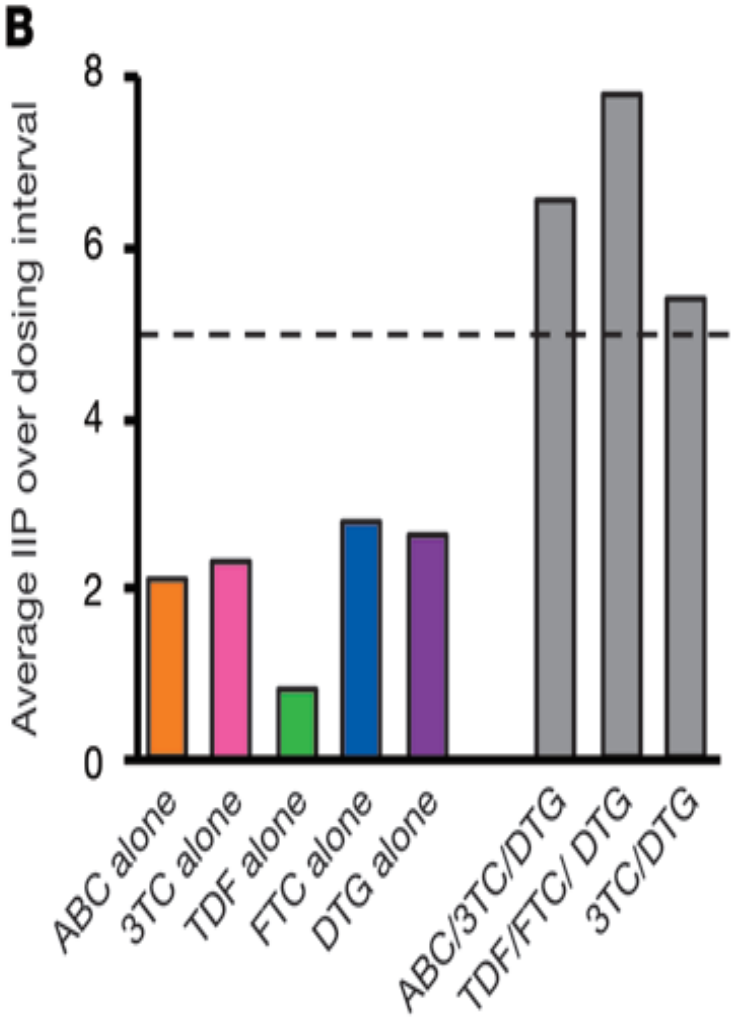
Characteristics of an ideal 2DR



Quantitative evaluation of the antiretroviral efficacy of dolutegravir



Using an in vitro infectivity assay and quantitative analysis, we evaluated critical DTG pharmacodynamic parameters.

Instantaneous inhibitory potential (IIP) is a metric of combined drug efficacy. IIP correlates with the clinical success of antiretroviral regimens.

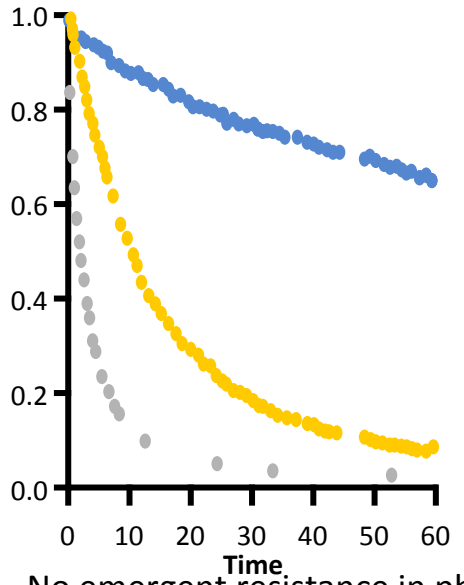
Average instantaneous inhibitory potential (IIP) over a 24-hour dosing period for individual drugs and their combinations.

A dashed line at IIP = 5 shows the minimum IIP for a fully suppressive antiretroviral regimen.

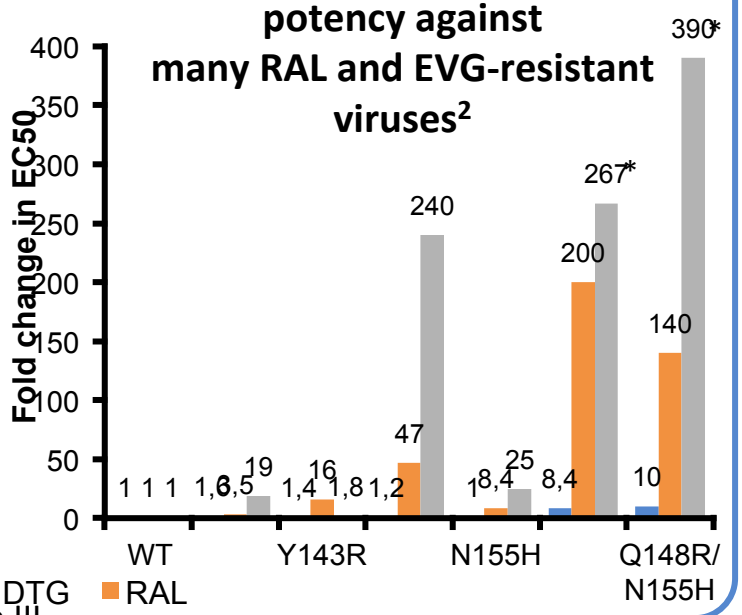
Laskey SB & Siliciano RF. JCI Insight,

Special requirement: high genetic barrier to viral resistance

DTG binds to integrase 8x longer than RAL and 26x longer than EVG[1]



DTG has high intrinsic potency against many RAL and EVG-resistant viruses[2]



- No emergent resistance in phase III, treatment-naïve studies[3-7]
- Low rates of DTG resistance in phase III studies in experienced, INI-naïve[8] and INI-resistant patients
- This supports the high genetic barrier to resistance of DTG

INI	k_{off} (s^{-1})[1]	Dissociation $t_{1/2}$ (h)[1]
DTG	2.7×10^{-6}	71
EVG	71×10^{-6}	2.7
RAL	22×10^{-6}	8.8

*Mean FC from one or two experiments. See slide notes for abbreviations.

1.Adapted from Hightower et al. Antimicrob Agents Chemother 2011;5:4552–9; 2. Kobayashi et al. Antimicrob Agents Chem 2011;55:813–21; 3. Raffi et al. Lancet Infect Dis 2013;13:927–35; 4. Walmsley et al. J Acquir Immune Defic Syndr 2015;70:515–19; 5. Molina et al. Lancet HIV 2015;2:e127–36; 6. Orrell et al. Lancet HIV 2017; Jul 17 [Epub ahead of print]; 7. Clotet et al. Lancet 2014;383:2222–31; 8. Cahn et al. *Lancet* 2013;382(9893):700–708; 9. Castagna et al. J Infect Dis 2014;210:354–62.

DTG as a Core Agent to Support 2DRs

The only INSTI developed as an agent of 2DR regimens

Rapid and potent antiviral activity[1], with evidence from clinical trial data[2,7–9]

DTG superior vs

1. **EFV** in tx-naïve subjects
2. **DRV/r** in tx-naïve subjects,
3. **ATV/r** in tx-naïve women,
4. **LPV/r** in 1st failure and
5. **RAL** in tx-experienced subjects

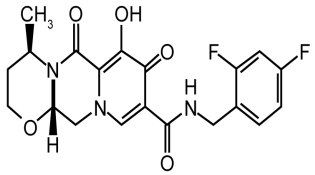
High barrier to resistance[2,3]

- *In vitro* findings supported by Phase III data

Long binding to WT INI[4]

- Dissociation from mutant INI–DNA complexes slower versus RAL or EVG

DTG



Well tolerated

- Few discontinuations due to AEs in INI-naïve clinical trials[2, 7–10]

DDIs

- Booster-free
- Few clinically significant DDIs

Long half-life; low variability in exposure

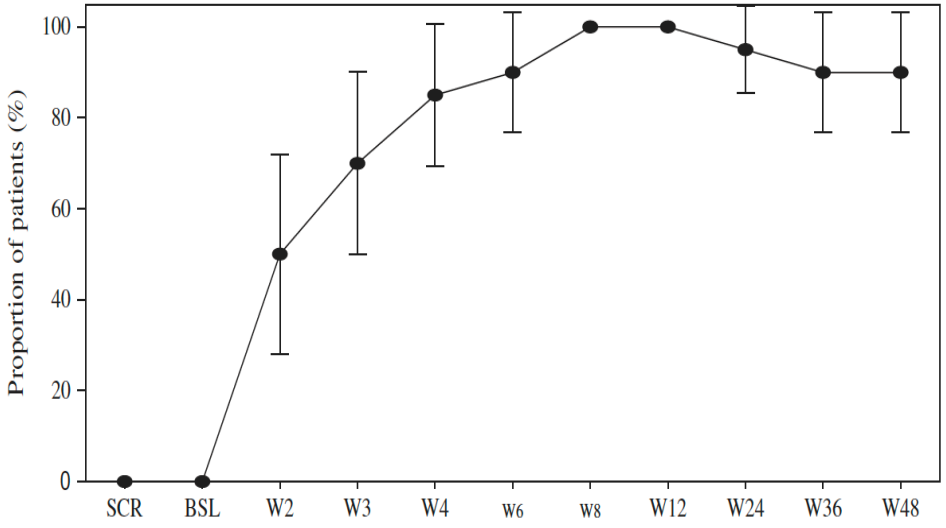
- DTG (50 mg QD) exposures 19-fold above IC_{90}[5]
- Long 'tail' – drug plasma concentrations up to 216 hours post-dose[6]

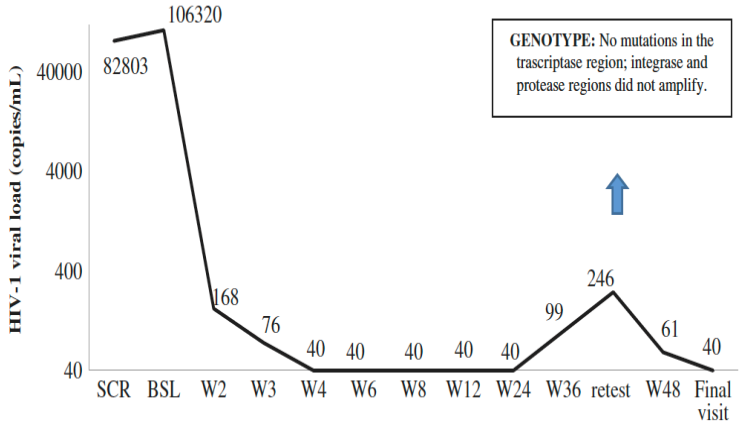
- IC_{50}, half-maximal inhibitory concentration; INI, integrase inhibitor; QD, once daily; TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; tx, treatment; WT, wild-type

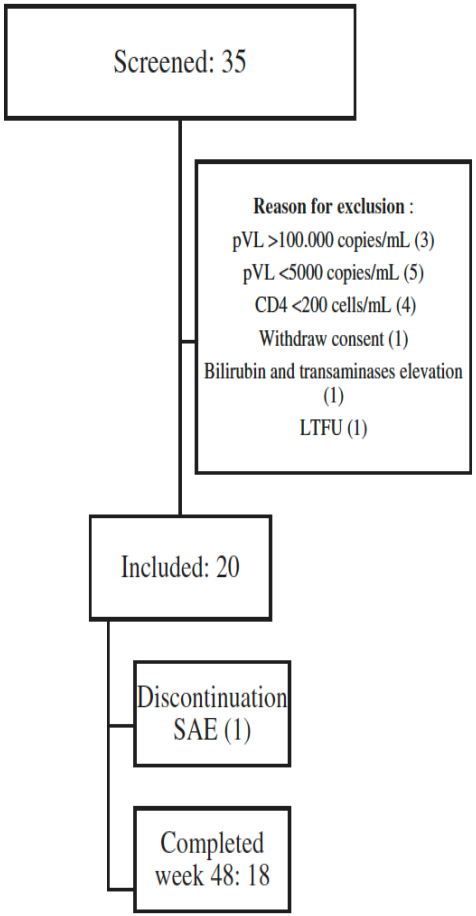
1. Min S, et al. AIDS 2011;25:1737–45; 2. Cahn P, et al. Lancet 2013;382:700–8; 3. Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21; 4. Hightower KE, et al. Antimicrob Agents Chemother 2011;5:4552–9; 5. van Lunzen J, et al. Lancet Infect Dis 2012;12:111–8; 6. Elliot E, et al. IWCPHIV 2015. Abstract 13; 7. Walmsley S, et al. N Engl J Med 2013;369:1807–18; 8. Clotet B, et al. Lancet 2014;383:2222–31; 9. Orrell C, et al. International AIDS Conference 2016. Abstract 10215; 10. Raffi F, et al. Lancet 2013;381:735–43

PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE)

DTG+3TC as initial therapy in HIV-1 infected ARV-naive patients







Cahn P, et al. Journal of the International AIDS Society 2

Comparable viral decay in dual and triple DTG-based antiretroviral therapy

Viral load decay with DTG/3TC was similar to that with DTG-based triple therapy regimens in patients with pVL < 100, 000 copies/mL.

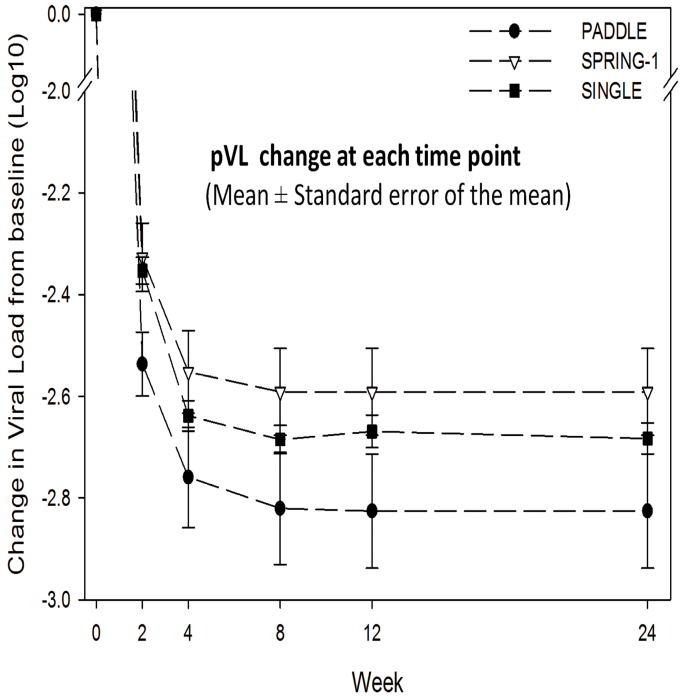


FIGURE 1: pVL change at each timepoint (Mean= standard error of the mean)

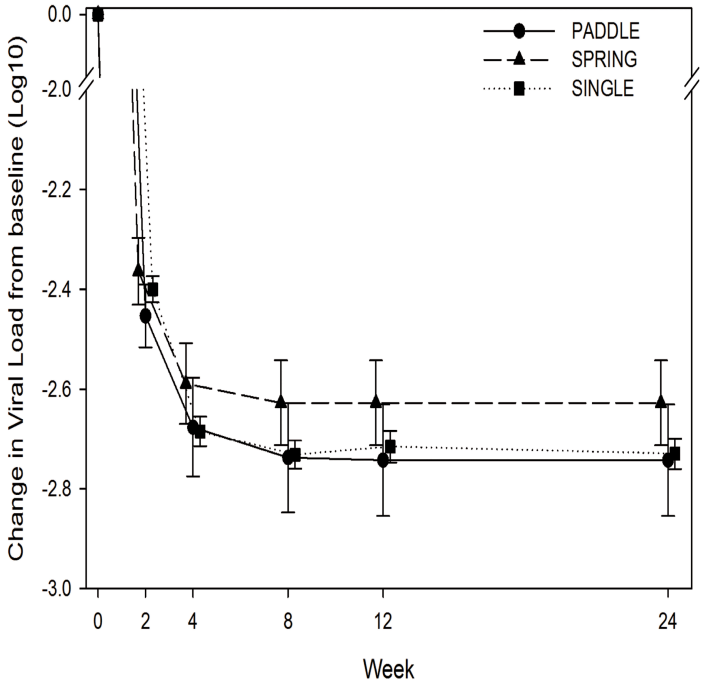


FIGURE 2: pVL change at each timepoint (Mean= standard error of the mean) , normalized per baseline pVL

Sued O, et al. CROI 2017; Abst#947

ACTG 5353
Virologic Outcome by FDA Snapshot at Week 24

	Baseline HIV-1 RNA					
	>100 000 Copies/mL (N = 37)		≤100 000 Copies/mL (N = 83)		Total (N = 120)	
Virologic success, HIV-1 RNA <50 copies/mL, N (%)	33	(89)	75	(90)	108	(90)
[95% confidence interval]		(75, 97)		(82,96)		(83,95)
Virologic nonsuccess	3	(8%)	2	(2%)	5	(4%)
HIV-1 RNA ≥50 copies/mL	3		0		3	
Discontinued study treatment for other reasons[a] while HIV-1 RNA ≥50 copies/mL	0		2		2	
No virologic data in window	1	(3%)	6	(7%)	7	(6%)
Discontinued study treatment for other reasons[b]	1		5		6	
On study but missing data in window	0		1		1	

Abbreviation: HIV, human immunodeficiency virus.

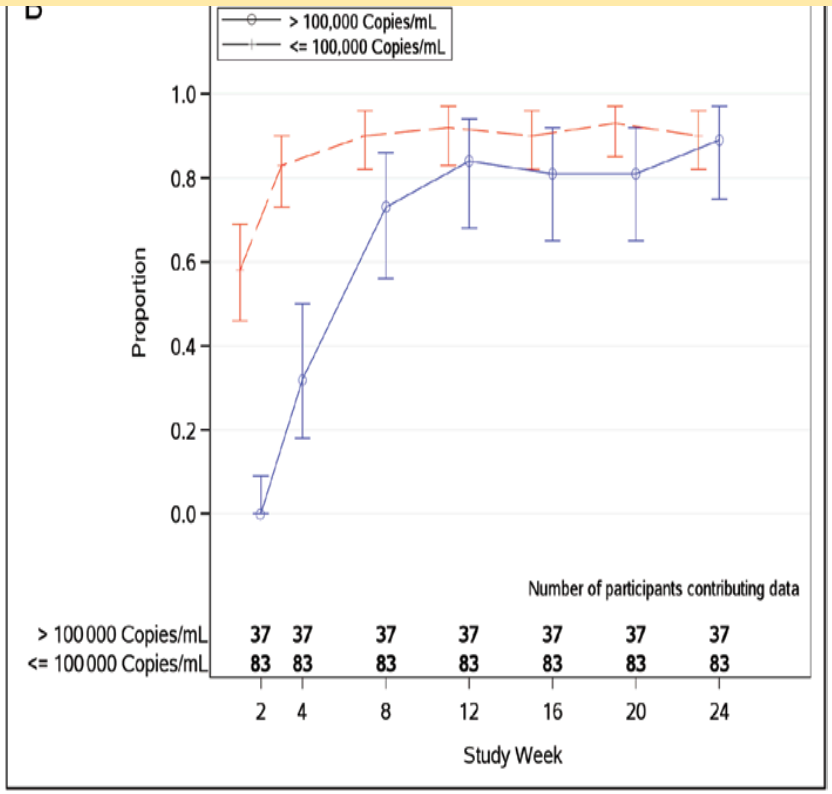
[a]Poor adherence.

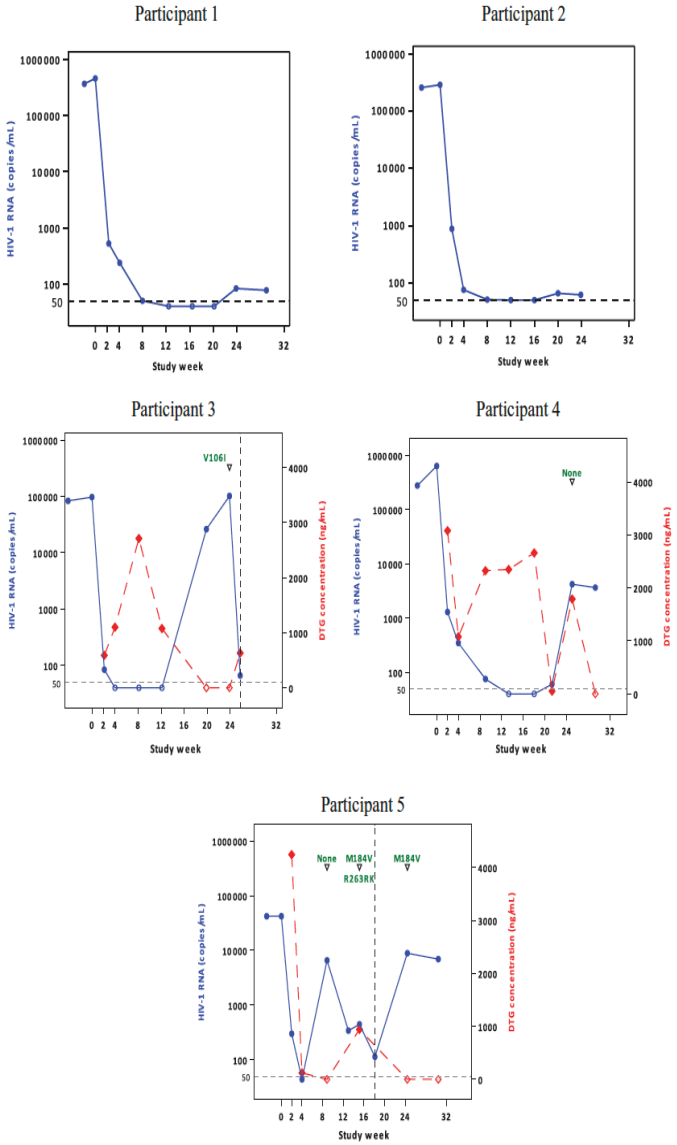
[b]Lost to follow-up, pregnancy

Taiwo B, et al. Clin Infect Dis, 2018

ACTG 5353
Virologic response by baseline 100K and 5 cases with virologic unsu

Proportion (95% CI) of participants with HIV-1 RNA levels <50 copies/mL by week (intention-to-treat/ missing/off treatment = ignored).

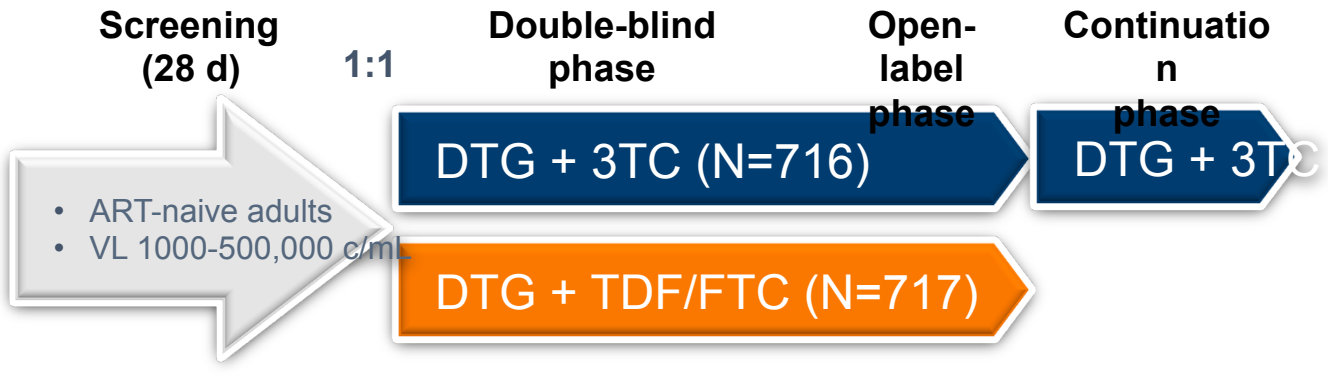




Taiwo B, et al. Clin Infect Dis, 2018

GEMINI-1 and -2 Phase III Study Design

Identically designed, randomized, double-blind, parallel-group, multicenter, noninferiority studies



Primary endpoint at Week 48: participants with HIV-1 RNA <50 c/mL (ITT-E snapshot)[a]

Eligibility criteria
- ≤10 days of prior ART
- No evidence of pre-existing viral resistance based on presence of any major resistance-associated mutation
- No HBV infection or need for HCV therapy

Countries

Argentina, Australia, Belgium, Canada, France, Germany, Italy, Republic of Korea, Mexico, Netherlands, Peru, Poland, Portugal, Romania, Russian Federation, South Africa, Spain, Switzerland, Taiwan, United Kingdom, United States

Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3).

[a]–10% noninferiority margin for individual studies.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

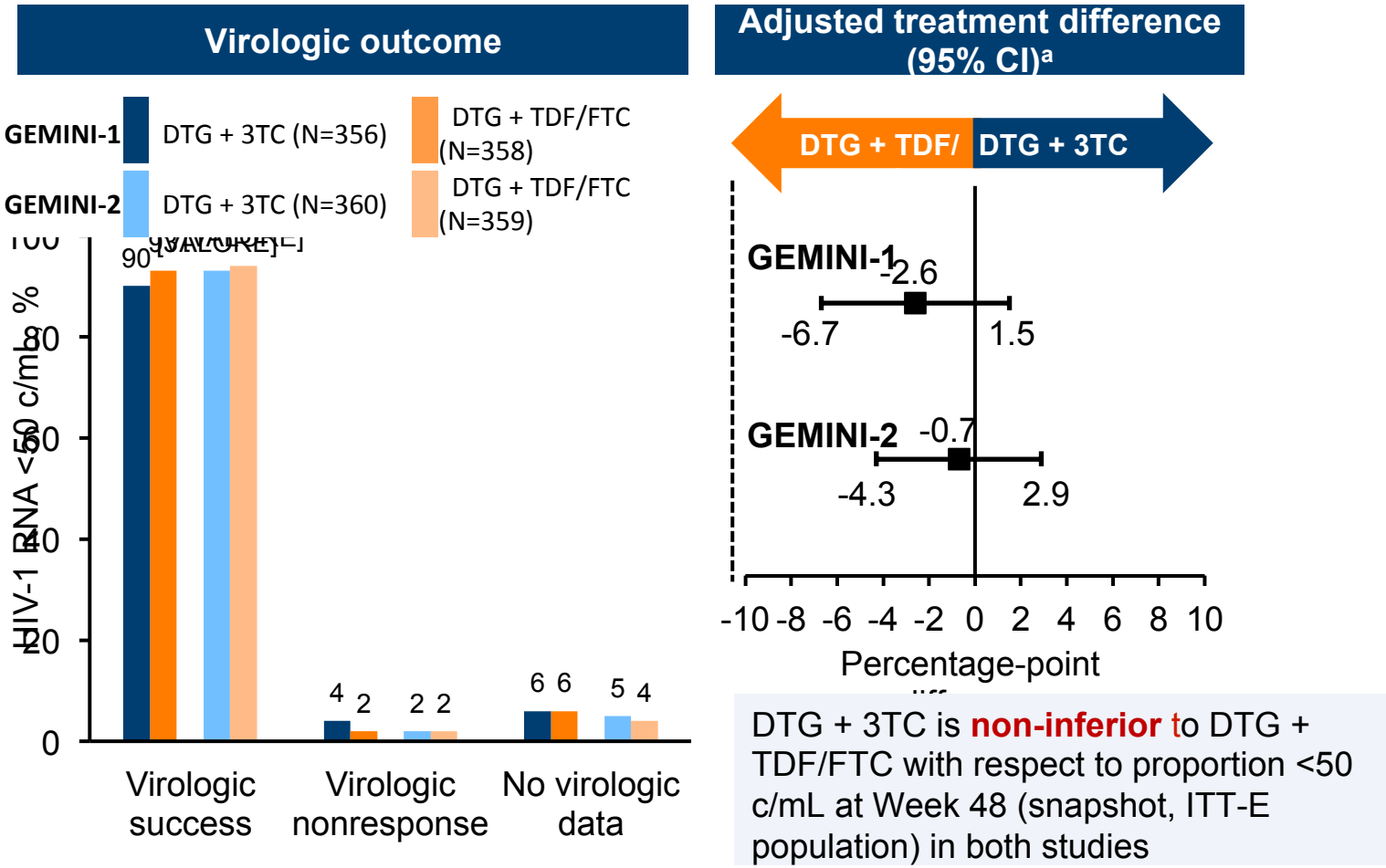
Demographic and Baseline Characteristics for the Pooled GEMINI-1 and -2 Population

Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
Other	66 (9)	72 (10)
Ethnicity, n (%)		
Hispanic or Latino	215 (30)	232 (32)
Not Hispanic or Latino	501 (70)	485 (68)
HIV-1 RNA, median (range), log_{10} c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
≤100,000	576 (80)	564 (79)
>100,000[a]	**140 (20)**	**153 (21)**
CD4+ cell count, median (range), cells/ mm^3	427.0 (19-1399)	438.0 (19-1497)
>200	653 (91)	662 (92)
≤200	**63 (9)**	**55 (8)**

[a]2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Snapshot Outcomes at Week 48 for GEMINI-1 and -2

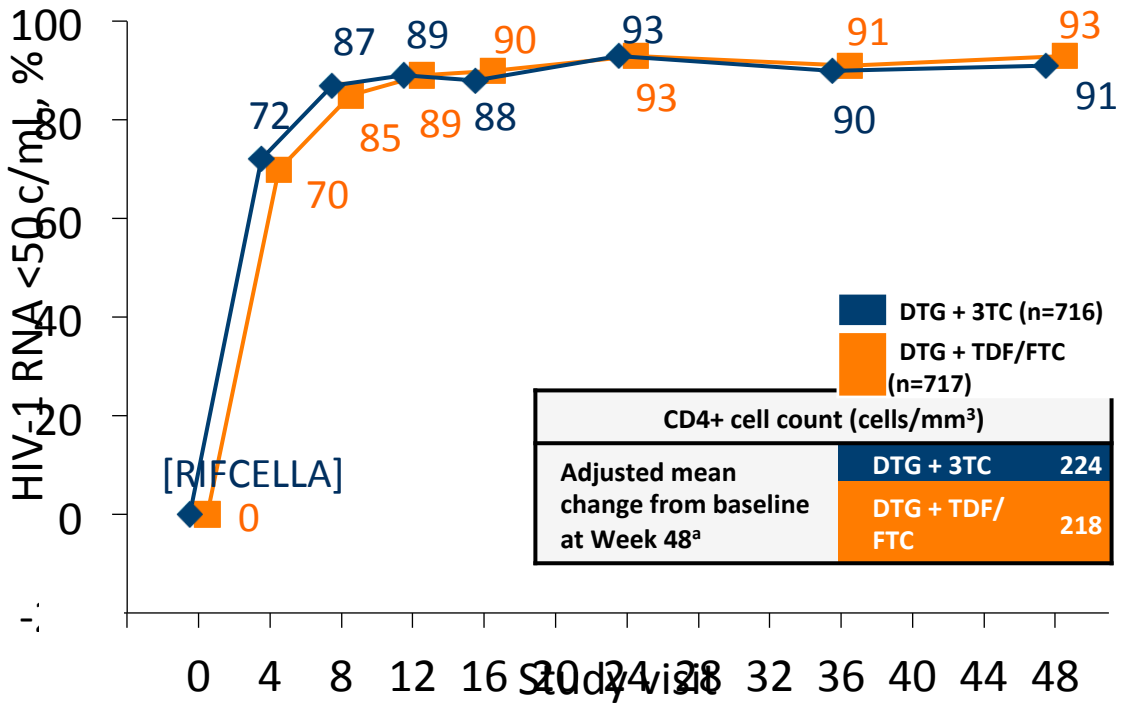


DTG + 3TC is **non-inferior** to DTG + TDF/FTC with respect to proportion <50 c/mL at Week 48 (snapshot, ITT-E population) in both studies

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

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

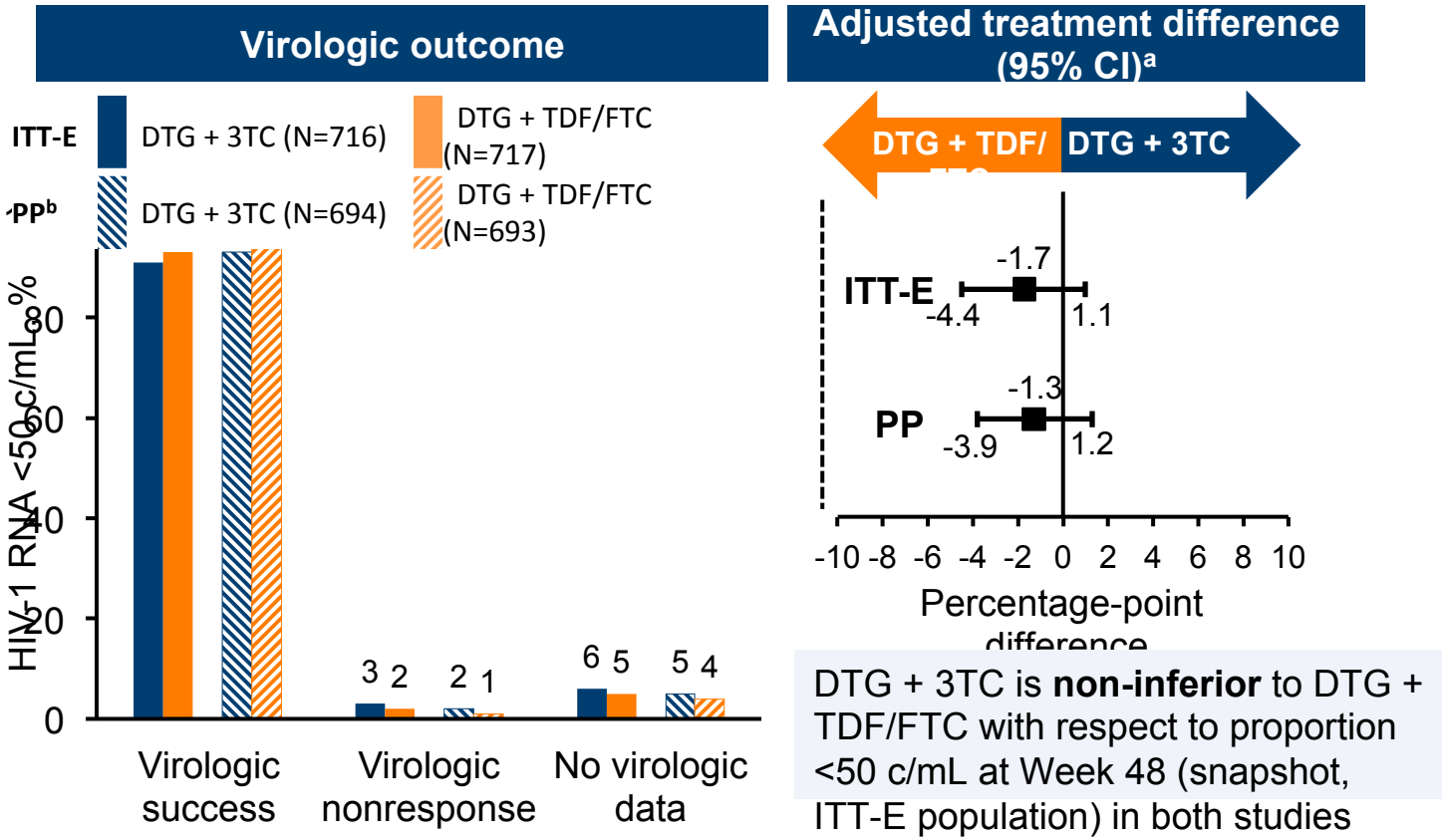
Snapshot Analysis by Visit: Pooled ITT-E Population



[a]Calculated from a repeated measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Pooled Snapshot Outcomes at Week 48: ITT-E and Per Protocol Populations



DTG + 3TC is **non-inferior** to DTG + TDF/FTC with respect to proportion <50 c/mL at Week 48 (snapshot, ITT-E population) in both studies

[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL), CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2). [b]PP, per protocol: population consisted of participants in the ITT-E population except for significant protocol violators, which could potentially affect efficacy outcomes as determined by the medical monitor prior to database lock.

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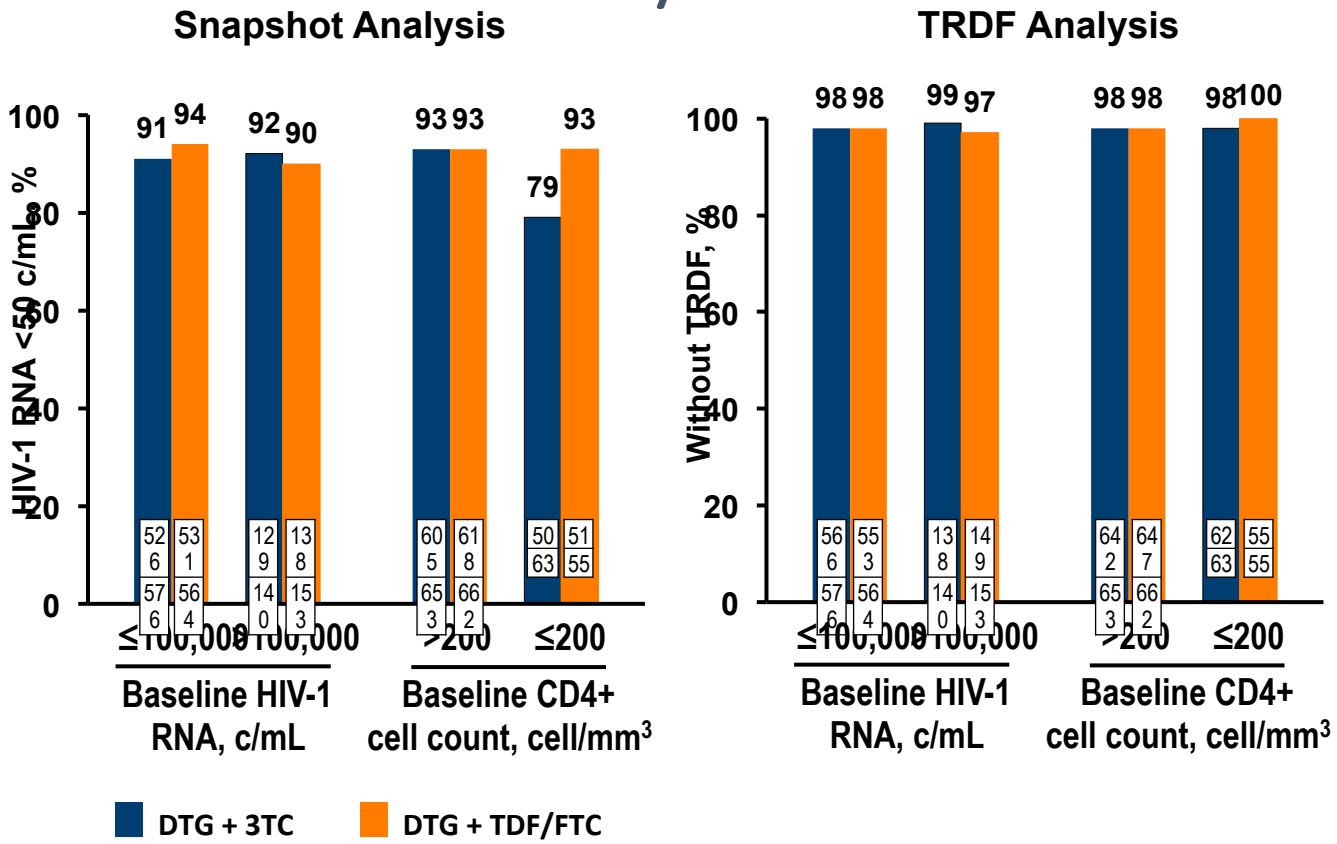
Pooled Outcomes at Week 48 Stratified by Baseline HIV-1 RNA and CD4+ Cell Count: Snapshot and TRDF Analysis



- 2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL
- Treatment related discontinuation = failure (TRDF) population accounts for confirmed virologic withdrawal (CVW), withdrawal due to lack of efficacy, withdrawal due to treatment-related AE, and participants who met protocol-defined stopping criteria
- DTG + 3TC CD4 <200 Snapshot non-response (n=13): **1 CVW**, 3 with VL >50 in window **(2 of 3 re-suppressed)**, 2 discontinued due to AE (TB, Chagas disease), 2 protocol violations, 2 lost to follow-up, 1 withdrew consent, 1 withdrew to start HCV treatment, 1 change in ART (incarcerated)
- DTG + TDF/FTC < 200 Snapshot non-response (n=4):1 investigator discretion, 1 withdrew consent, 1 lost to follow-up, 1 VL >50 (re-suppressed)

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Confirmed Virologic Withdrawals Through Week 48: ITT-E Population

- Low rates of virologic withdrawals were observed at Week 48

	GEMINI 1		GEMINI 2		Pooled	
Variable, n (%)	**DTG + 3TC (N=356)**	**DTG + TDF/ FTC (N=358)**	**DTG + 3TC (N=360)**	**DTG + TDF/ FTC (N=359)**	**DTG + 3TC (N=716)**	**DTG + TDF/ FTC (N=717)**
CVW	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)
Treatment-emergent resistance	**0**	**0**	**0**	**0**	**0**	**0**

- No treatment-emergent INSTI mutations or NRTI mutations were observed among participants who met CVW (confirmed virologic failure) criteria

CVW criteria defined as a second and consecutive HIV-1 RNA value meeting virologic non-response or rebound.

- **Virologic non-response:**
  - a decrease in plasma HIV-1 RNA of less than 1 log10 c/mL by Wk 12 with subsequent confirmation unless plasma HIV-1 RNA is <200 c/mL, or
  - confirmed plasma HIV-1 RNA levels ≥200 c/mL on or after Week 24.
- **Virologic rebound**
  - confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Adverse Events: Pooled ITT-E Population

n (%)	DTG + 3TC (N=716)	DTG + TDF/ FTC (N=717)
Any AE	543 (76)	579 (81)
AE occurring in ≥5% of participants in either group		
Headache	71 (10)	75 (10)
Diarrhea	68 (9)	77 (11)
Nasopharyngitis	55 (8)	78 (11)
Upper respiratory tract infection	56 (8)	44 (6)
Nausea	27 (4)	53 (7)
Insomnia	27 (4)	45 (6)
Pharyngitis	36 (5)	32 (4)
Back pain	35 (5)	31 (4)
Drug-related AE	126 (18)	169 (24)
Grade 2-4 AE occurring in ≥1% of participants	42 (6)	47 (7)
Headache	8 (1)	8 (1)
AE leading to withdrawal from the study	15 (2)	16 (2)
Neuropsychiatric AEs leading to withdrawal	6 (<1)	4 (<1)
Any serious AE[a]	50 (7)	55 (8)

[a]2 deaths (acute myocardial infarction, n=1; Burkitt's lymphoma, n=1) in the GEMINI-2 study; both were in the DTG + 3TC group and were considered unrelated to the study drug regimen.

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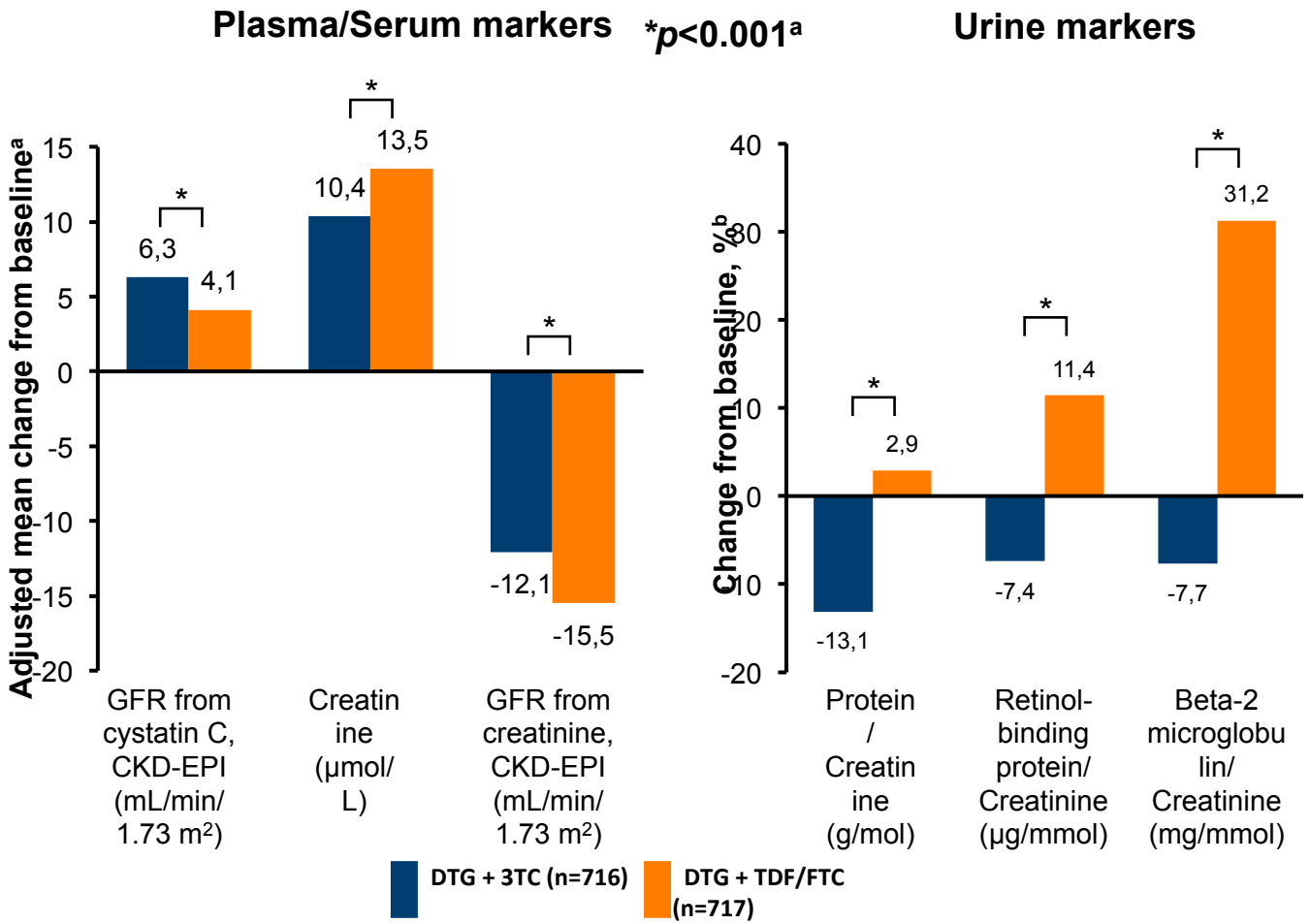
Change in Renal Biomarkers at Week 48: Pooled ITT-E Population



[a]Estimated mean change from baseline at Week 48 in each arm calculated from ANCOVA model adjusting for: study, treatment, baseline plasma HIV-1 RNA, baseline CD4+ cell count, age, sex, race, presence of diabetes mellitus, presence of hypertension, and baseline biomarker value. Multiple imputed dataset (missing at random). [b]Estimated from geometric mean ratio for baseline and Week 48.

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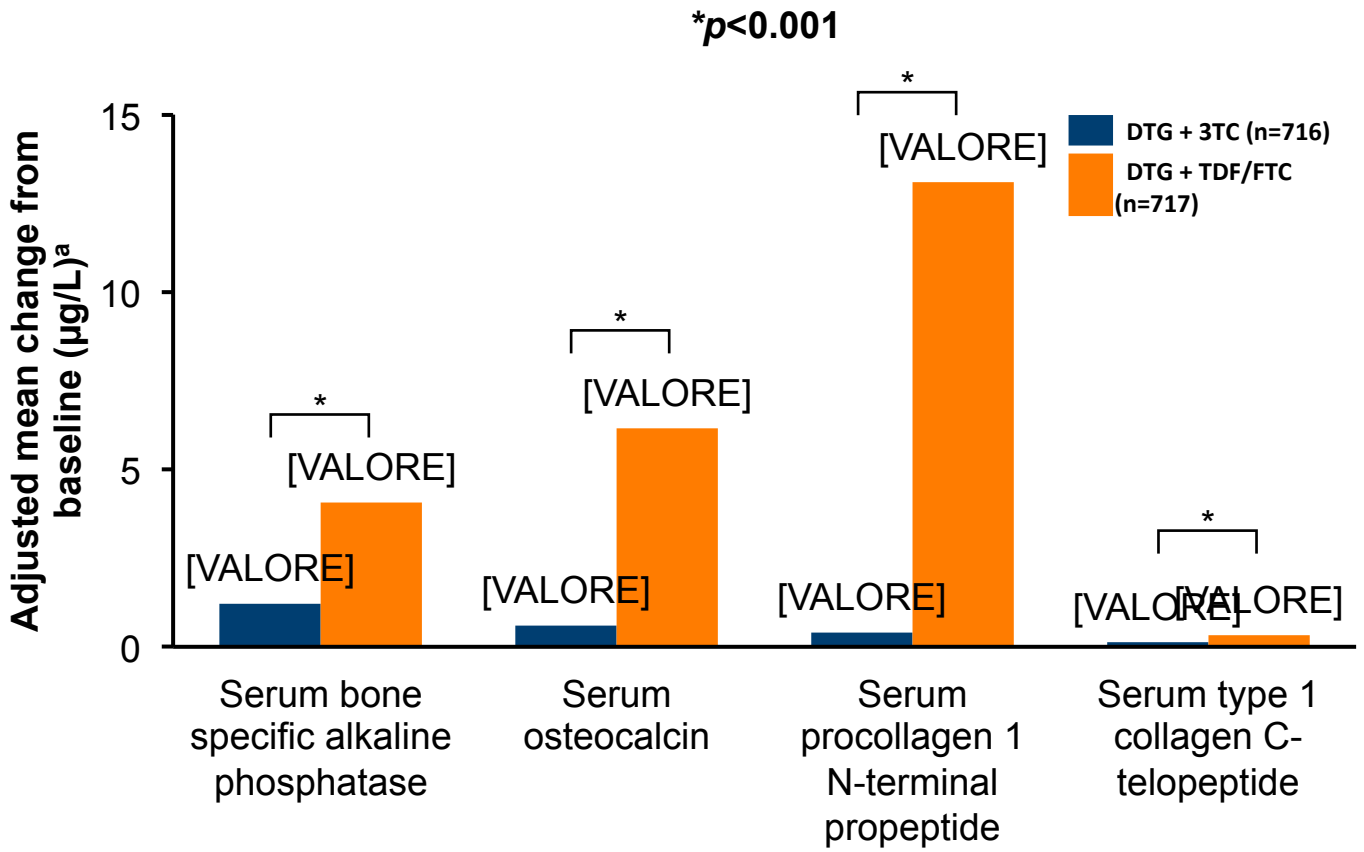
Change in Bone Markers at Week 48: Pooled ITT-E Population



[a]Estimated mean change from baseline at Week 48 in each arm calculated from ANCOVA model adjusting for study, treatment, baseline plasma HIV-1 RNA, baseline CD4+ cell count, age, sex, race, BMI, smoking status, current vitamin D use, and baseline biomarker value. Multiple imputed dataset (missing at random).

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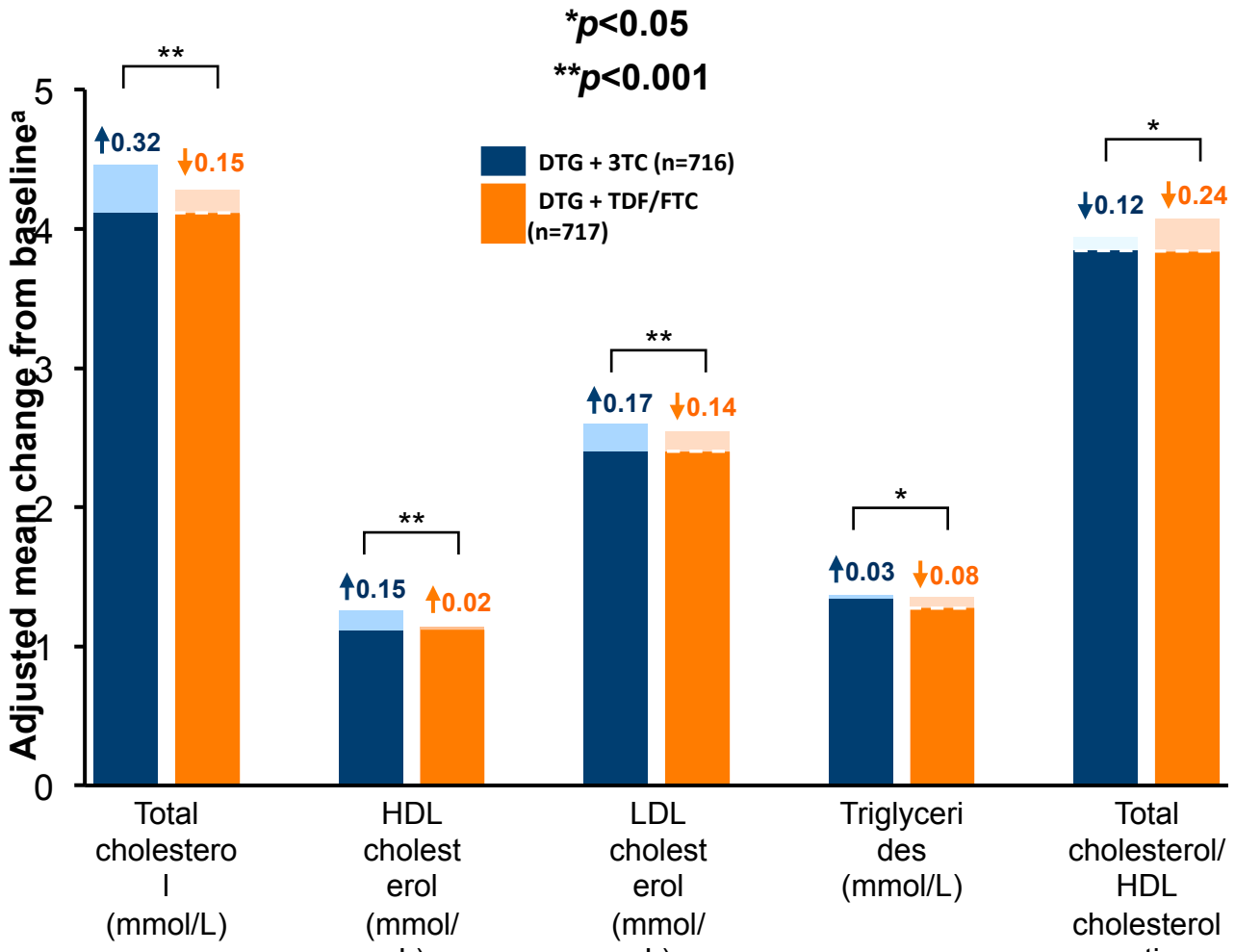
Change in Serum Lipids at Week 48: Pooled ITT-E Population



[a]The adjusted mean is the estimated mean change from baseline in each fasting lipid at Week 48 in each arm calculated from an ANCOVA model adjusting for the following covariates/ factors: study treatment, baseline plasma HIV-1 RNA, baseline CD4+ cell count, age and fasting lipids at baseline. Multiple imputed dataset (missing at random). Absolute values based on summaries. Baseline values are represented by the main legend colors, with changes at Week 48 represented by shaded areas (increases) or dashed lines (decreases).

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Conclusions

- GEMINI-1 and-2 results demonstrate noninferior virologic efficacy for the 2DR DTG + 3TC vs the 3DR DTG + TDF/FTC at Week 48
- Both DTG + 3TC and DTG + TDF/FTC were associated with low rates of confirmed virologic withdrawals through Week 48
  - No treatment-emergent INSTI or NRTI mutations were observed among participants who met CVW criteria
- Overall safety and tolerability profile at Week 48 was comparable between the 2 regimens
  - Fewer drug-related AEs with DTG + 3TC
  - Change in renal and bone biomarkers significantly favors DTG + 3TC
- These data support DTG + 3TC as an effective option for the treatment of HIV-1 infection

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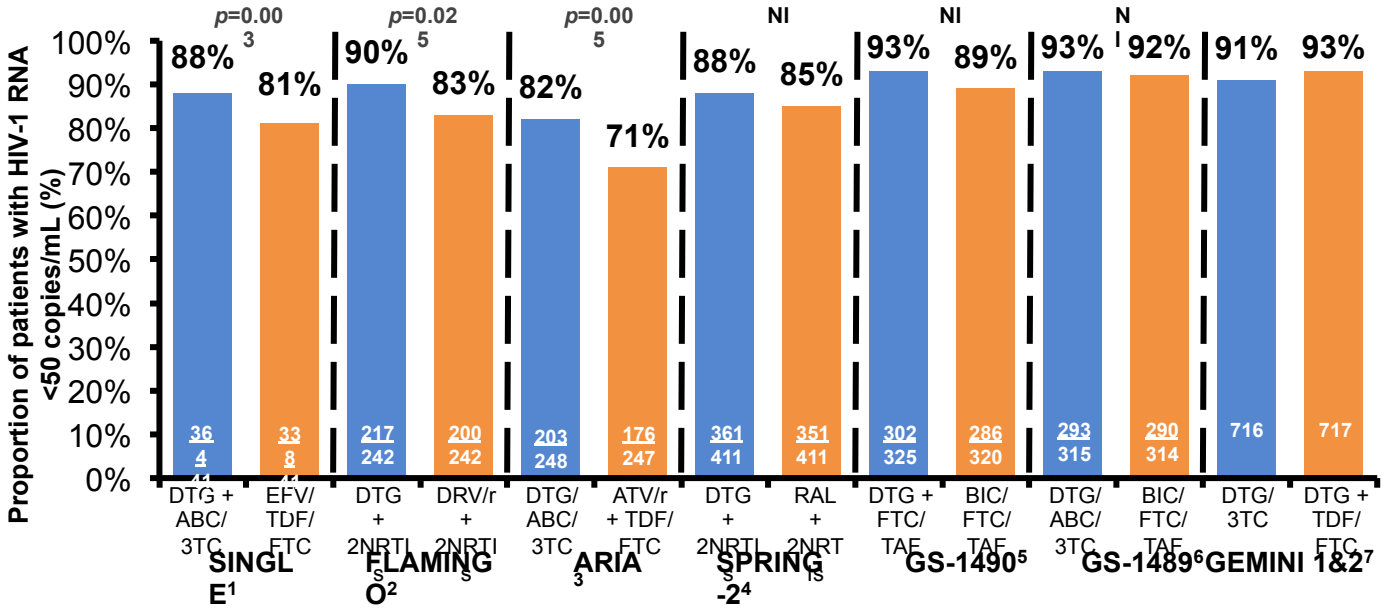
Overall Results for Dolutegravir-based Regimens in Studies of Treatment-Naïve Patients

Overall Week 48 snapshot analysis

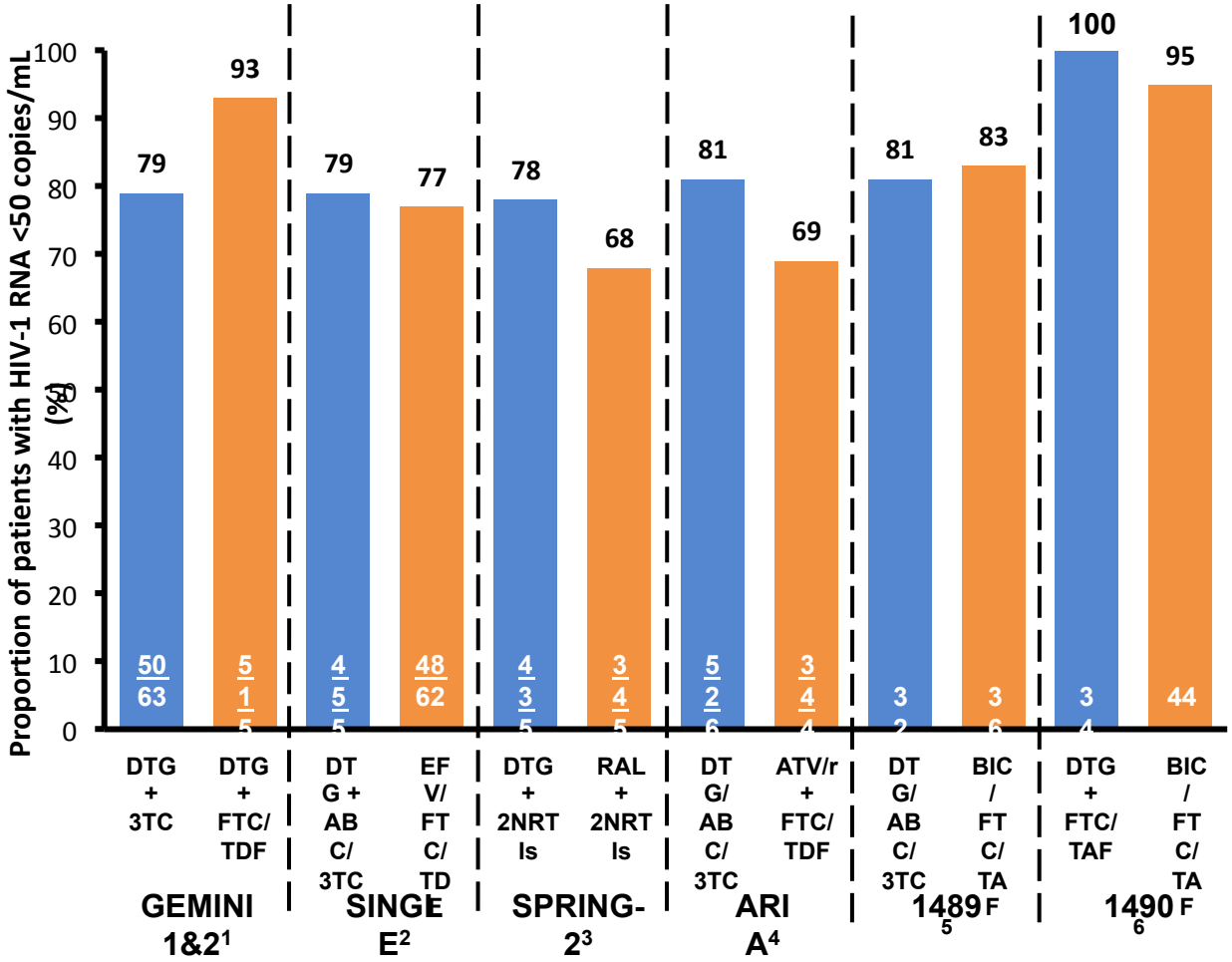


3TC=lamivudine; ABC=abacavir; ATV=atazanavir; BIC=bictegravir; DTG=dolutegravir; EFV=efavirenz; FTC=emtricitabine; NI=noninferior treatment difference; NRTI=nucleos(t)ide reverse transcriptase inhibitor (either ABC/3TC or TDF/FTC in FLAMINGO and SPRING-2); RAL=raltegravir; r=ritonavir; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate

1. Walmsley et al. N Engl J Med 2013; 369:1807–18.
2. Clotet et al. Lancet 2014;383:2222–31.
3. Orrell C, et al. Lancet HIV 2017;4:e536–46.
4. Raffi et al. Lancet 2013;381:735–43.
5. Sax PE, et al. Lancet 2017, Epub http://dx.doi.org/10.1016/S0140-6736(17)32340-1.
6. Gallant J, et al. Lancet 2017, Epub http://dx.doi.org/10.1016/S0140-6736(17)32299-7.
7. Cahn P. et al., AIDS 2018, Oral Abstract TUAB0106LB.

DTG phase III treatment-naïve RCT

Week 48 Snapshot Analysis in patients with baseline CD4+ count ≤200 cells/mm3

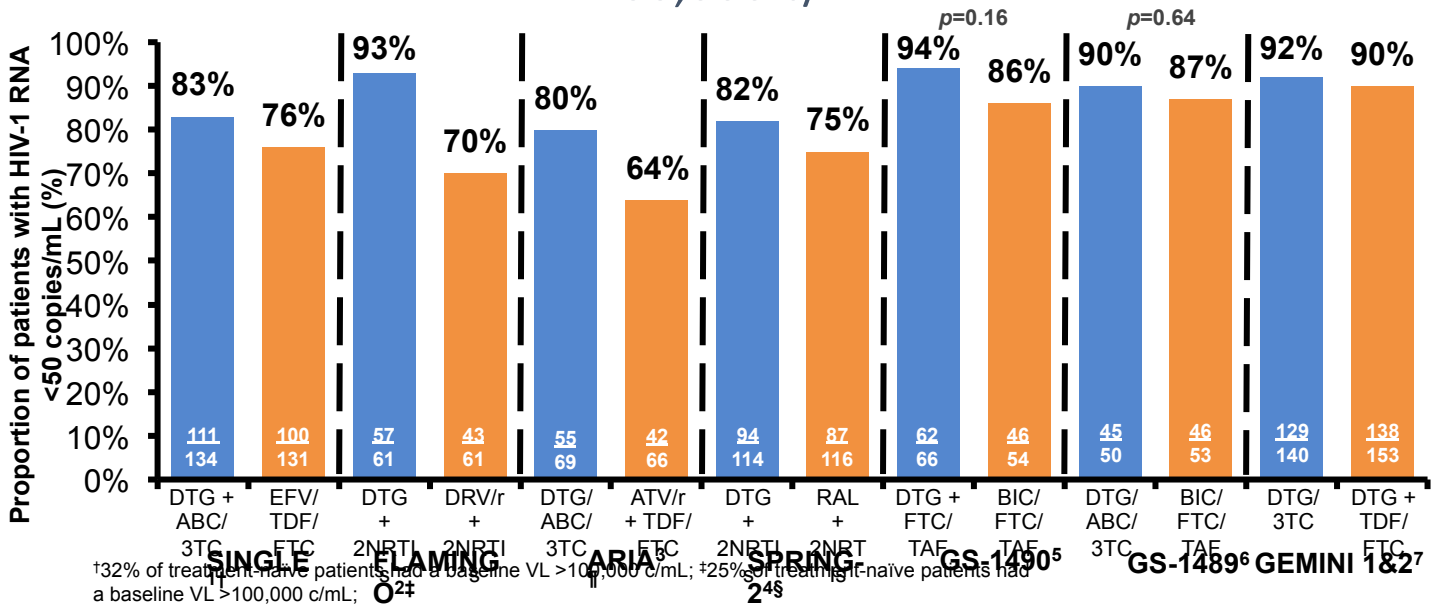


1. Cahn P. et al., AIDS 2018, Oral Abstract TUAB0106LB; 2. Walmsley et al. N Engl J Med 2013;369:1807–18;
3. Raffi et al. Lancet 2013;381:735–43; 4. Orrell et al. Lancet 2017;4:e536–e546;
5. Gallant J, et al. Lancet 2017;390:2063–72; 6. Sax PE, et al. Lancet 2017;390:2073–82

DTG phase III treatment-naïve RCT

Week 48 Snapshot Analysis in patients with baseline VL >100,000 c/mL

Week 48 snapshot analysis for patients with baseline VL > 100,000 c/mL



†32% of treatment-naïve patients had a baseline VL >100,000 c/mL; ‡25% of treatment-naïve patients had a baseline VL >100,000 c/mL;

¶27% of treatment-naïve patients had a baseline VL >100,000 c/mL; §28% of treatment-naïve patients had a baseline VL >100,000 c/mL.

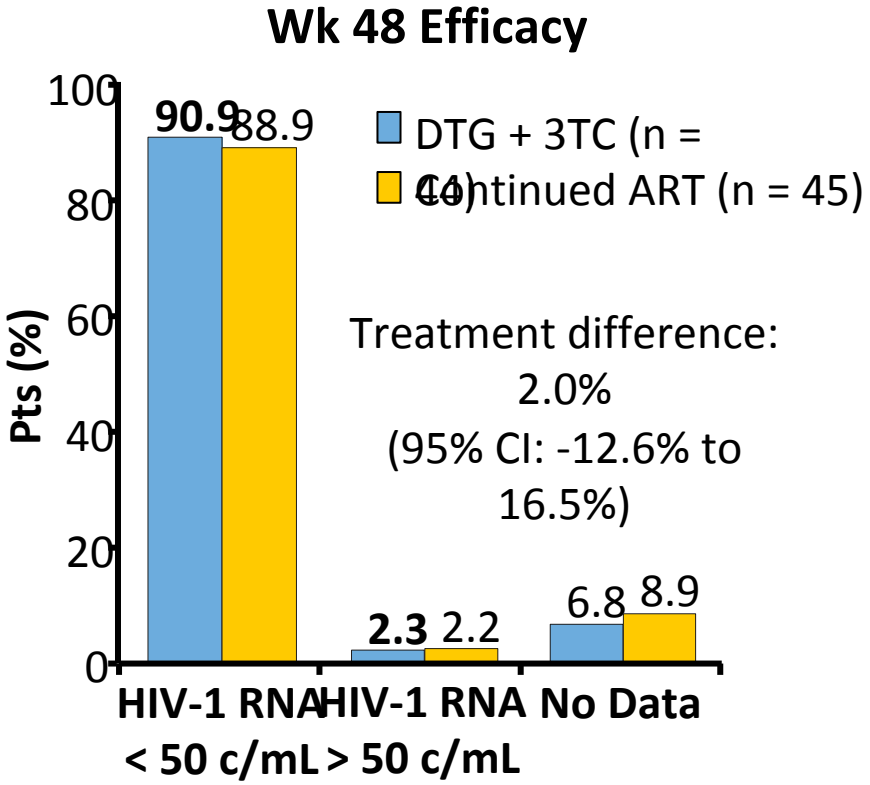
3TC=lamivudine; ABC=abacavir; ATV=atazanavir; BIC=bictegravir; DTG=dolutegravir; EFV=efavirenz; FTC=emtricitabine; NI=noninferior treatment difference; NRTI=nucleos(t)ide reverse transcriptase inhibitor (either ABC/3TC or TDF/FTC in FLAMINGO and SPRING-2); RAL=raltegravir; r=ritonavir; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate

1. Walmsley et al. N Engl J Med 2013; 369:1807–18.
2. Clotet et al. Lancet 2014;383:2222–31. Supplemental Appendix.
3. Hagins et al. IDWeek 2016. Abstract 56539.
4. Raffi et al. Lancet 2013;381:735–43.
5. Sax PE, et al. Lancet 2017, Epub http://dx.doi.org/10.1016/S0140-6736(17)32340-1. Supplementary Appendix.
6. Gallant J, et al. Lancet 2017, Epub http://dx.doi.org/10.1016/S0140-6736(17)32299-7. Supplementary Appendix.
7. Cahn P. et al., AIDS 2018, Oral Abstract TUAB0106LB.

ASPIRE

Switch to DTG+3TC in Virologically Suppressed Pts on Triple ART

- Randomized, open-label, multicenter phase III trial in which pts who were virologically suppressed on 3-drug ART regimen with no history of VF were randomized to **DTG + 3TC QD** or **continued 3-drug ART** (N = 90)

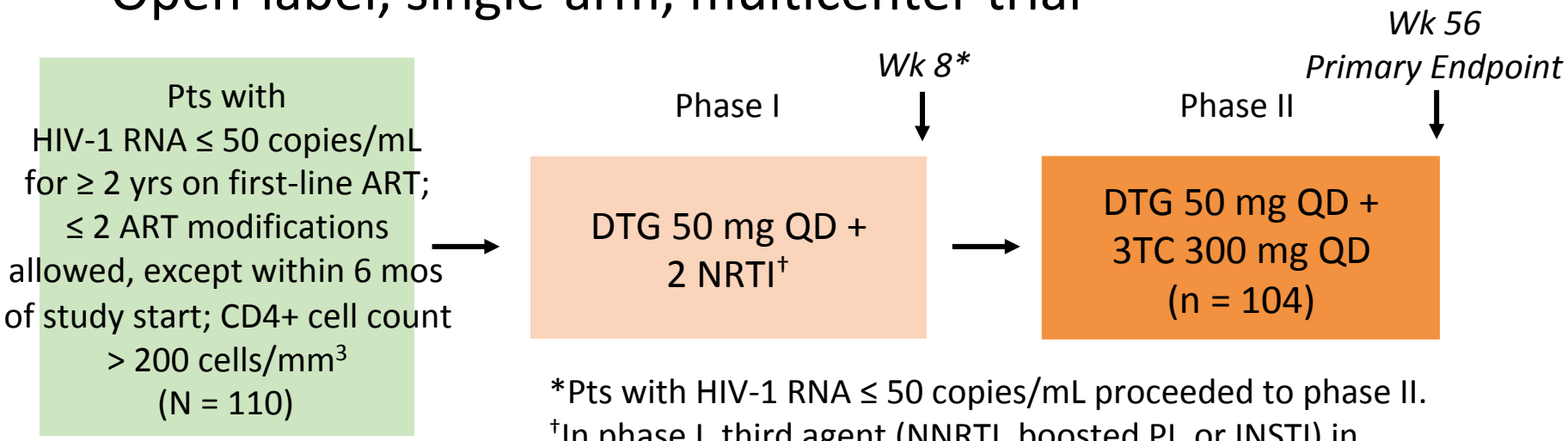


- Similar lipid changes between regimens
- CrCl changes from baseline, DTG + 3TC vs continued ART:
  - Wk 24: –6 vs 3.6 ($P < .001$)
  - Wk 48: –3.8 vs 0 ($P = .07$)
- Similar rates of SAEs; 1 d/c for AEs (DTG + 3TC arm, grade 2 constipation)

Taiwo BO, et al. EACS 2017. Abstract PE8/5, Taiwo BO, et al. Clin Infect Dis, 2017

ANRS 167 LAMIDOL: Switch to DTG + 3TC in Virologically Suppressed Pts on Triple ART

- Open-label, single-arm, multicenter trial



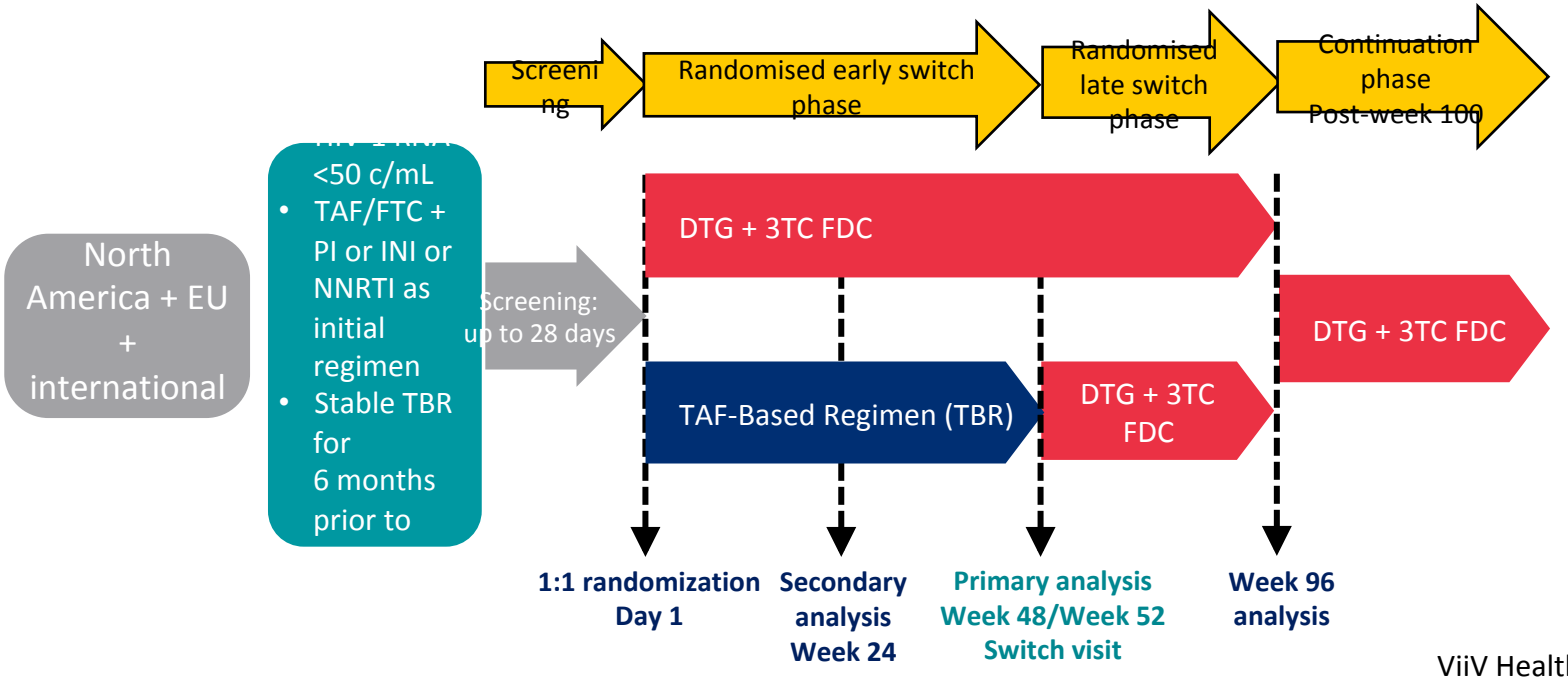
*Pts with HIV-1 RNA ≤ 50 copies/mL proceeded to phase II.
†In phase I, third agent (NNRTI, boosted PI, or INSTI) in regimen replaced with DTG; baseline NRTI backbone maintained.

- 97% (n/N = 101/104) of pts maintained therapeutic success through 40 wks (study Wk 48)
- 7 serious AEs, only 2 related to dual therapy

Joly V, et al. CROI 2017. Abstract 458.

Maintenance Dolutegravir +3TC (TANGO)

- **Design :** Phase III, randomised, multicentre, parallel-group, non-inferiority study
- **Objective:** To demonstrate the non-inferior antiviral activity of switching to DTG/3TC QD compared with continuation of current ARV regimen over 48 weeks in HIV-1-infected ART-experienced patients
- **Primary endpoint:** The proportion of participants who meet the snapshot virological failure criteria at Week 48 using the ITT-E population
  - Non-inferiority margin = 4%; week 48 primary endpoint

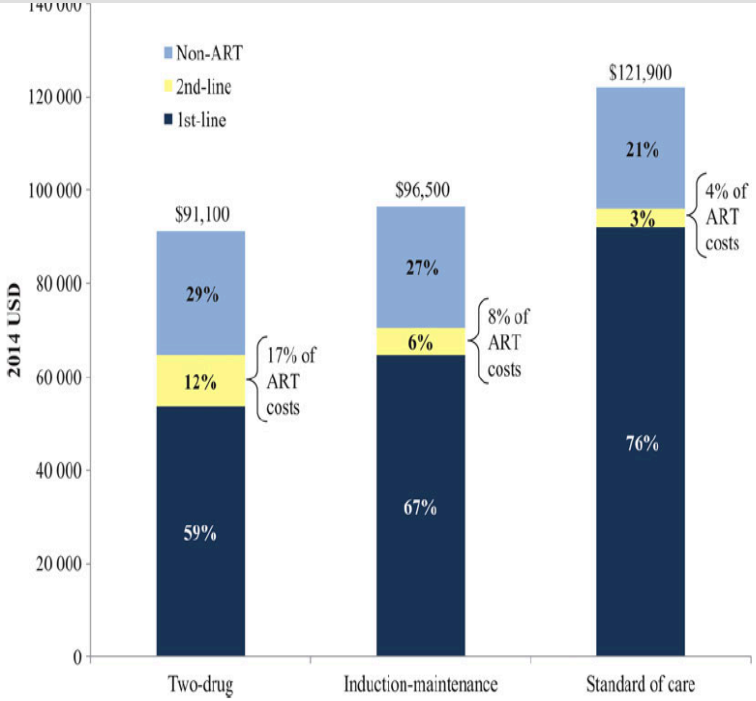


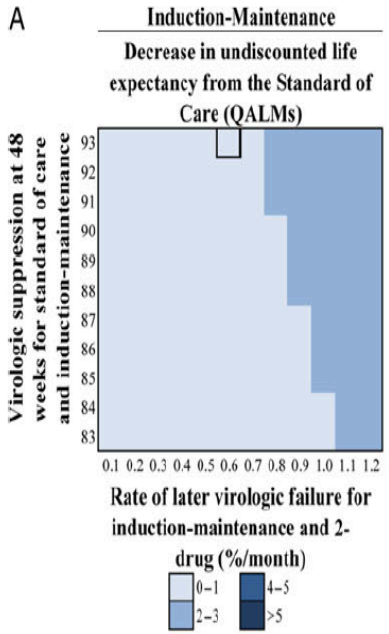
ViiV Healthcare, data on file.

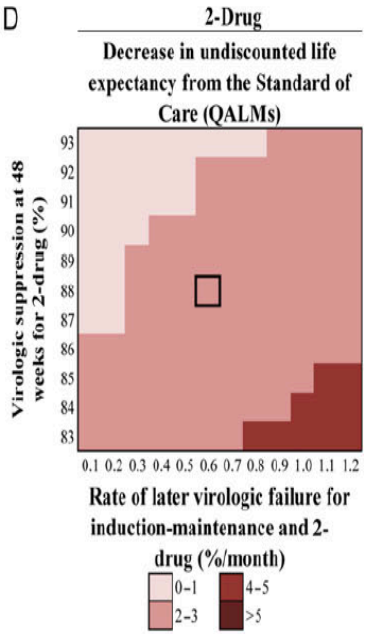
Cost-effectiveness and Budget Impact of DTG+3TC 2DR for the Treatment of HIV Infection in the US

The 3 ART strategies had the **same 5-year survival rates (90%).** The ICER was $22 500/QALY for induction-maintenance and >$500 000/QALY for standard of care. **Two-drug was the preferred strategy only when DTG + 3TC 48-week virologic suppression rate exceeded 90%**. With 50% uptake of either induction-maintenance or **2-drug for ART-naive patients**, cost savings totaled $550 million and **$800 million**, respectively, within 5 years; **savings reached >$3 billion if 25% of currently suppressed patients were switched to DTG + 3TC maintenance.**

Should DTG + 3TC demonstrate high rates of virologic suppression, this regimen will be cost-effective and would save >$500 million in ART costs in the United States over 5 years.







Girouard MP, et al. Clin Infect D