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Focus su HIV ed epatiti

COI Disclosure Information

Anna Maria Cattelan has served as a paid consultant to Gilead Sciences, Angelini, Abbvie, Janssen, MSD, ViiV Healthcare and received research fundings from Gilead Sciences, Janssen, MSD and ViiV Healthcare

Dual-therapy versus triple-therapy: dai dati della letteratura alla pratica clinica

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Which are the main differences between 2DRs and 3DRs?

1. The lack of TAF (TDF) in the 2DRS → INI + 3TC, PI + 3TC

2. The lack of NRTIs backbone in the 2DRs → NNRTI + INI, PI + INI

First-line Initial ART Regimens for Most Adults and Adolescents With HIV

DHHS[1]	IAS-USA[2]	EACS[3]	WHO[4]
▪ BIC/FTC/TAF ▪ DTG/3TC/ABC* ▪ DTG + (FTC or 3TC) + (TAF or TDF) ▪ DTG/3TC[†]	▪ BIC/FTC/TAF ▪ DTG + FTC/TAF ▪ DTG + FTC/TDF ▪ DTG + 3TC/TDF ▪ DTG/3TC[†‡]	▪ DTG/3TC/ABC* or DTG + 3TC/ABC ▪ BIC/FTC/TAF ▪ DTG + FTC/TAF or (FTC or 3TC)/TDF ▪ RAL QD or BID + FTC/TAF or (FTC or 3TC)/TDF ▪ DTG/3TC or DTG + (FTC or 3TC) ▪ DOR/3TC/TDF or DOR + FTC/TAF or (FTC or 3TC)/TDF	▪ DTG + 3TC (or FTC) + TDF

*If HLA-B*5701 negative and without chronic HBV. [†]Except for individuals with baseline HIV-1 RNA > 500,000 copies/mL, with HBV, or for whom results of HIV genotypic resistance testing or HBV testing are not yet available. [‡]Possibly not suitable for individuals with baseline CD4+ cell count <200 cells/mm^3.

1. DHHS ART Guidelines. 2022. 2. Saag. JAMA. 2020;324:1651. 3. EACS Guidelines v 11.0.
4. WHO. July 2021. www.who.int/publications/i/item/9789240031593.

Initial ART With BIC/FTC/TAF: Newest Oral INSTI Now With Data Through 5 Yr

- Studies 1489 and 1490: BIC/FTC/TAF noninferior to DTG-based ART for HIV-1 RNA <50 c/mL[1]
  - Randomized through Wk 144
  - OLE Wk 145-240
- Pooled BIC/FTC/TAF population[2]
  - N = 634 in randomized phase; n = 506 in OLE
  - Wk 240 HIV-1 RNA <50 c/mL (missing = excluded): 99% (426/432)
  - Wk 240 median CD4+ cell count increase from baseline: 317 cells/mm^3

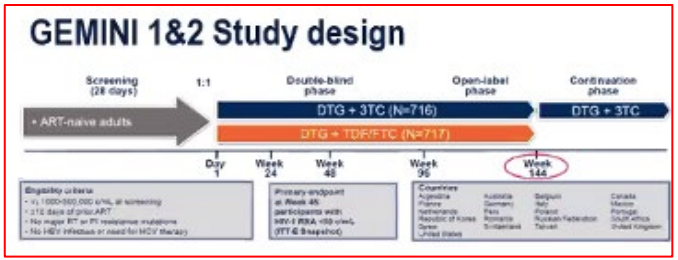
Virologic Failure With BIC/FTC/TAF at Wk 240 (n = 6)[1]

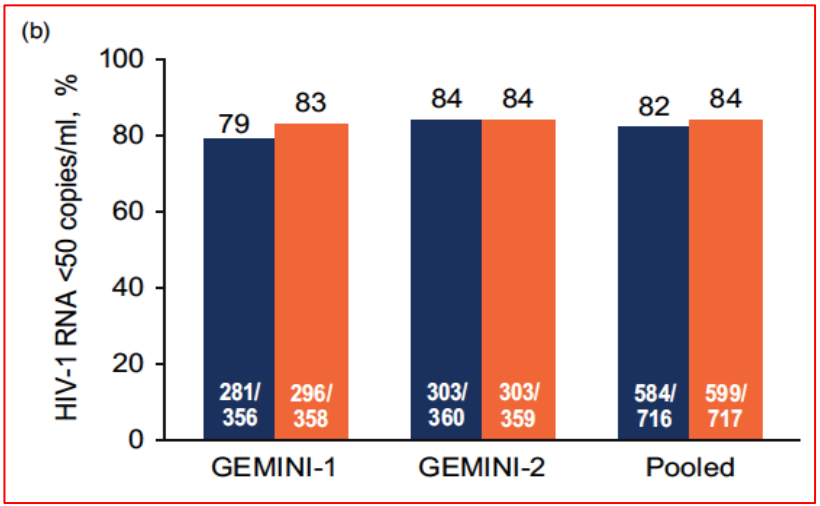
PT	Adherence, % (Blinded/ OLE)	BL HIV-1 RNA, c/mL	BL CD4+ Count, Cells/mm^3	HIV-1 RNA, c/mL	
				Wk 240	Wk 252
1	96/96	≤100,000	200 to <350	897	<50
2	91/92	>100,000 - 400,000	200 to <350	128	<50
3	99/99	≤100,000	350 to <500	317	<50
4	93/93	>100,000 -400,000	50 to <200	53	<50
5	86/87	≤100,000	200 to <350	141	<50
6	99/98	>400,000	200 to <350	133	Lost to f/u

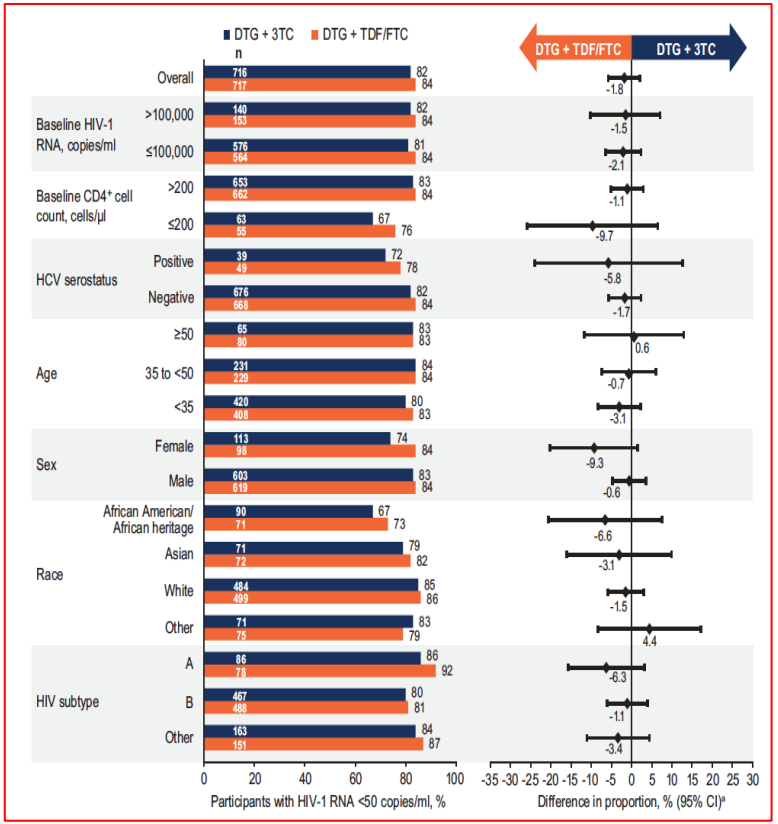
Resistance Through Wk 240,[1] n	BIC/FTC/TAF (n = 634)
Met resistance testing criteria	9
▪ NRTI resistance detected	0
▪ INSTI resistance detected	0

1. Orkin. Lancet HIV. 2020;7:e389. 2. Sax. AIDS 2022. Abstr EPB150.

Three-year durable efficacy of dolutegravir plus lamivudine in antiretroviral therapy – naive adults with HIV-1 infection





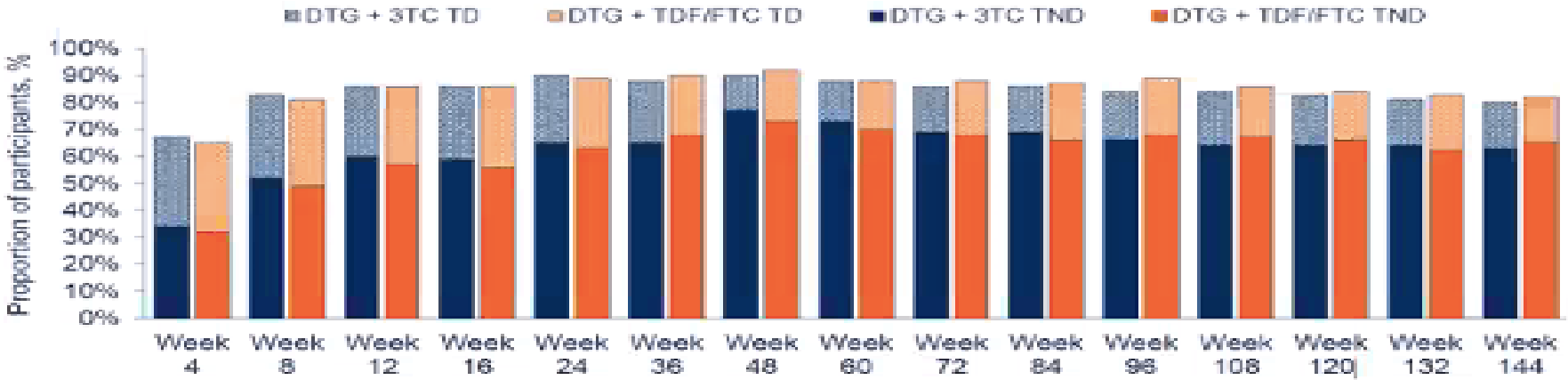


12 DTG +3TC participants and 9 DTG+TDF/FTC participants met protocol-defined confirmed virologic withdrawal criteria; none developed treatment-emergent resistance

AIDS 2022, **36**:39–48

DTG+3TC IN GEMINI-1 & -2: HIV-1 REPLICATION AT <50 C/ML AND VL 'BLIPS' THROUGH 144 WKS

Mark Underwood,[1] Rimgaile Urbaityte,[2] Ruolan Wang,[1] Joe Horton,[3] Linshan Yuan,[4] Brian Wynne,[1] Justin Koteff,[1] Jean van Wyk,[5] Choy Man,[1] Jörg Sievers[5]



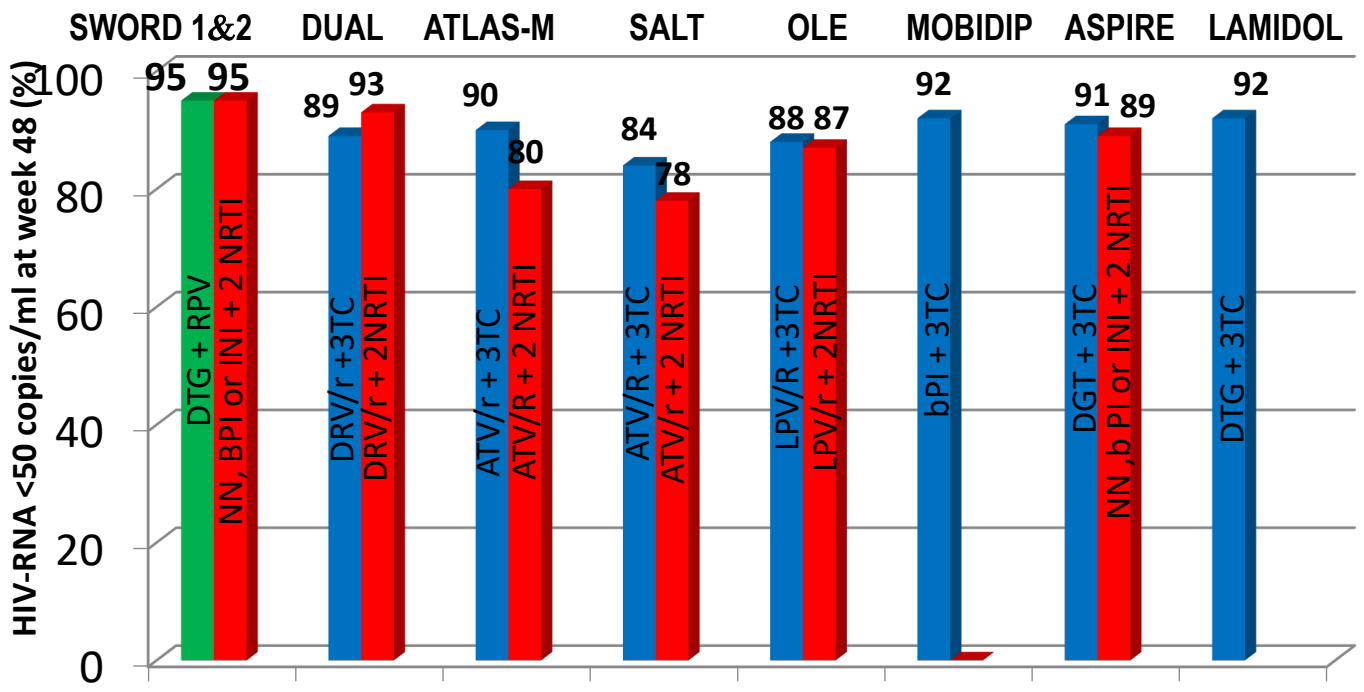
% calculated for DTG/3TC and DTG+FTC/TDF, respectively N 716 and N 717 ITT-E population

Proportions[a] of Participants With TND by BL Subgroups Were Similar Across Arms at Week 144

- At whs 144 similar proportions of ITT-E Overall participants with TND receiving DTG + 3TC vs DTG + TDF/FTC by Snapshot (63% [451/716] vs 65% [465/717]), or for Observed (OBS) population (77% [451/584] vs 78% [465/599])
- Proportions with TND within subgroups generally similar between arms

Underwood et al. IAS 2021; Virtual. Poster PEB163

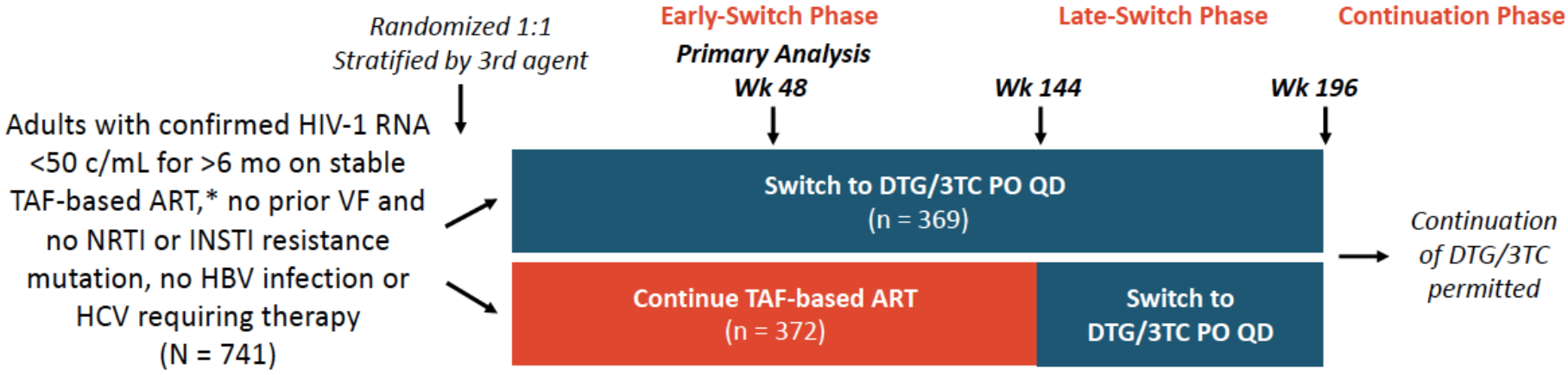
Efficay and safety of therapy from major switching studies with dual antiretroviral regimens



N	513 511	126 123	133 133	143 143	118 121	131	44 45	110
VF	0.6 1.2	3.2 1.6	1.5 4.5	4.2 2.8	2.5 2.5	3,1	2.3 2.2	3.6
AE%	3.3 0.6	0.8 1.6	3.0 6.0	2.1 7.1	0.8 3.3	0	2.3 4.4	2.7

TANGO: Wk 144 Analysis of Switch to DTG/3TC vs Continued 3- or 4-Drug TAF-Based Regimen

- Multicenter, randomized, open-label noninferiority phase III study



*Patients eligible if initial regimen was TAF/FTC with PI, NNRTI, or INSTI, or TDF switched to TAF ≥3 mo prior to screening with no other regimen changes.

- DTG/3TC met primary endpoint of noninferiority in maintaining virologic suppression vs TAF-based ART at Wk 48 by FDA Snapshot in ITT-E, and also at Wk 96[1,2]

- **Current analysis includes assessment of virologic outcomes, weight, and metabolic, renal, and inflammatory biomarkers at Wk 144[3]**

1. van Wyk. Clin Infect Dis. 2020;71:1920. 2. Wang. IAS 2021. Abstr OAB0301. 3. Osiyemi. IDWeek 2021. Abstr 900.

TANGO: Wk 144 Virologic Outcomes by FDA Snapshot

Snapshot Outcome, n (%)	ITT-E		Efficacy Evaluable*	
	DTG/3TC (n = 369)	TAF-Based ART (n = 372)	DTG/3TC (n = 364)	TAF-Based ART (n = 370)
HIV-1 RNA <50 c/mL	317 (86)	304 (82)	317 (87)	304 (82)
HIV-1 RNA ≥50 c/mL	1 (<1)	5 (1)	1 (<1)	5 (1)
▪ Data in window	0	0	0	0
▪ D/c for lack of efficacy	0	4 (1)	0	4 (1)
▪ D/c for other reason	1 (<1)	0	1 (<1)	0
▪ Change in ART	0	1 (<1)	0	1 (<1)
No virologic data	51 (14)	63 (17)	46 (13)	61 (16)
▪ Non–COVID-19 related	46 (12)	61 (16)	46 (13)	61 (16)
– D/c due to AE or death†	23 (6)	6 (2)	23 (6)	6 (2)
– D/c for other reason‡	22 (6)	55 (15)	23 (6)	55 (15)
– Missing data but on study	1 (<1)	0	1 (<1)	0
▪ COVID-19 related	5 (1)	2 (<1)	NA	NA
– D/c due to AE or death	0	0	NA	NA
– D/c for other reason‡	2 (<1)	2 (<1)	NA	NA
– Missing data but on study	3 (<1)	0	NA	NA

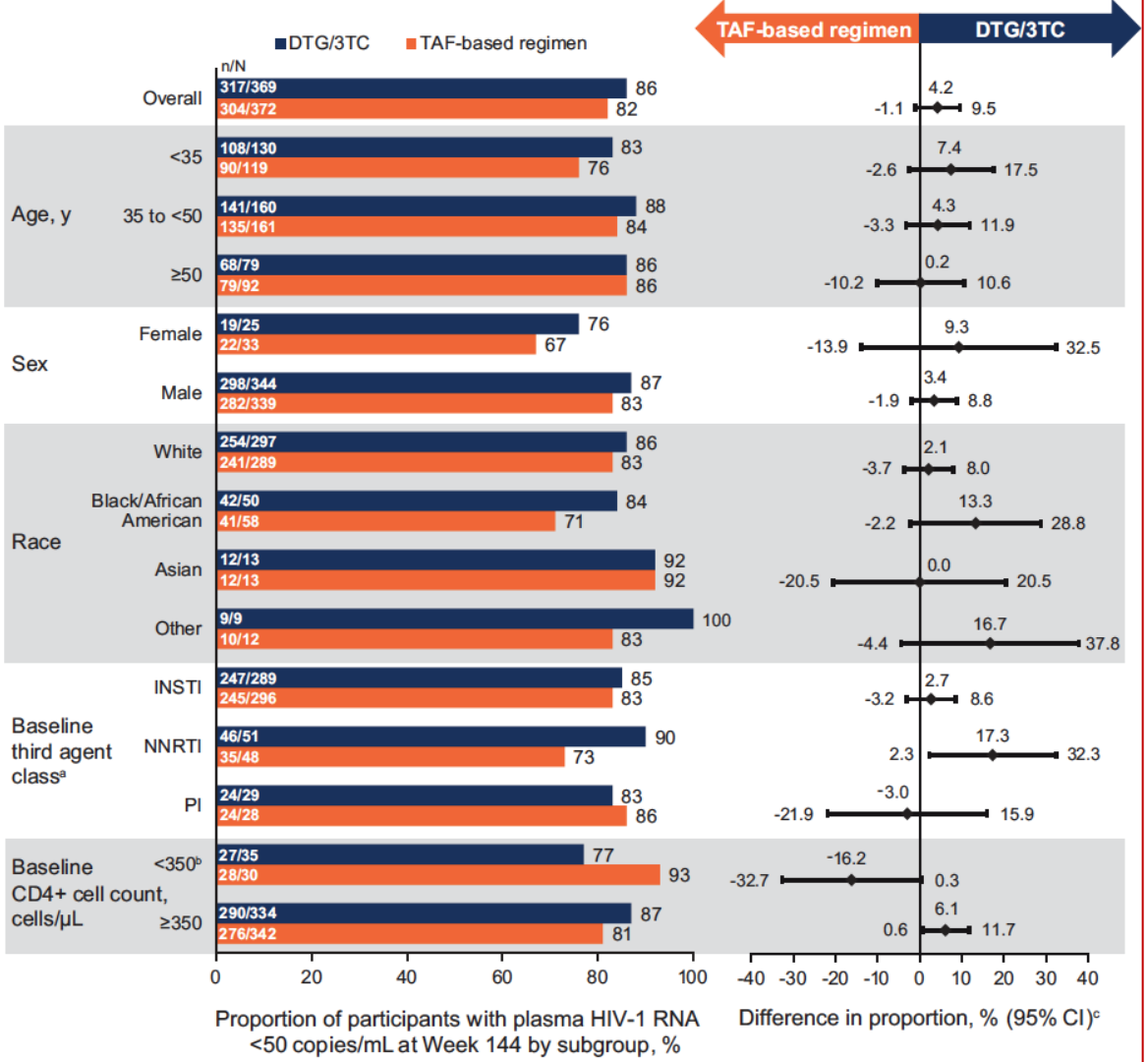
Adjusted differences at Wk 144

- HIV-1 RNA ≥50 c/mL: -1.1% (95% CI: -2.4 to 0.2)
- HIV-1 RNA <50 c/mL: 4.2% (95% CI: -1.1 to 9.5)

*Sensitivity analysis excluded 5 and 2 individuals in DTG/3TC and TAF-based ART arms, respectively, as no Wk 144 data due COVID-19 pandemic effects.
†3 fatal AEs unrelated to study drug treatment (homicide, ischemic hepatitis, and acute intoxication, in DTG/3TC group).
‡Other reasons for d/c included protocol deviation, physician decision, lost to follow-up, patient withdrawal, and lack of efficacy (2 patients in TAF-based ART arm)

- **DTG/3TC demonstrated continued non-inferiority in virologic and immunologic outcomes at Wk 144**

Osiyemi. IDWeek 2021. Abstr 900.



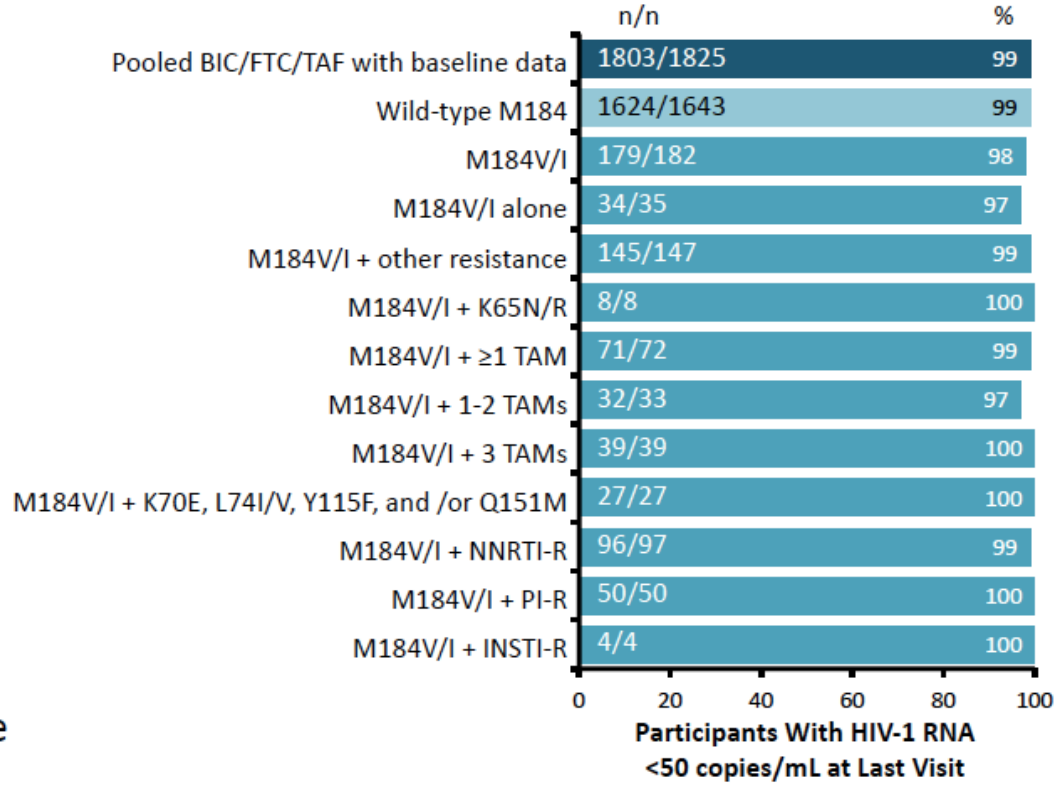
TANGO: participants with HIV-1 RNA levels <50 cs/mL (Snapshot; ITT-E) across subgroups at week 144

In all 8 Snapshot nonresponders receiving DTG/3TCwith a baseline CD4+ cell count <350/µL, Snapshot nonresponse occurred for nonvirologic reasons

CID 2022;75(6):975–86

Switching to BIC/FTC/TAF in Patients With History of or Archived M184V/I

- Pooled data from 6 trials of switch to BIC/FTC/TAF in virologically suppressed PWH
- Preexisting resistance by historical GT and/or baseline proviral DNA
- N =1825 switched to BIC/FTC/TAF with baseline GT and follow-up HIV-1 RNA data available
  - n =182 (10%) with preexisting M184V/I
  - No treatment-emergent resistance to BIC/FTC/TAF

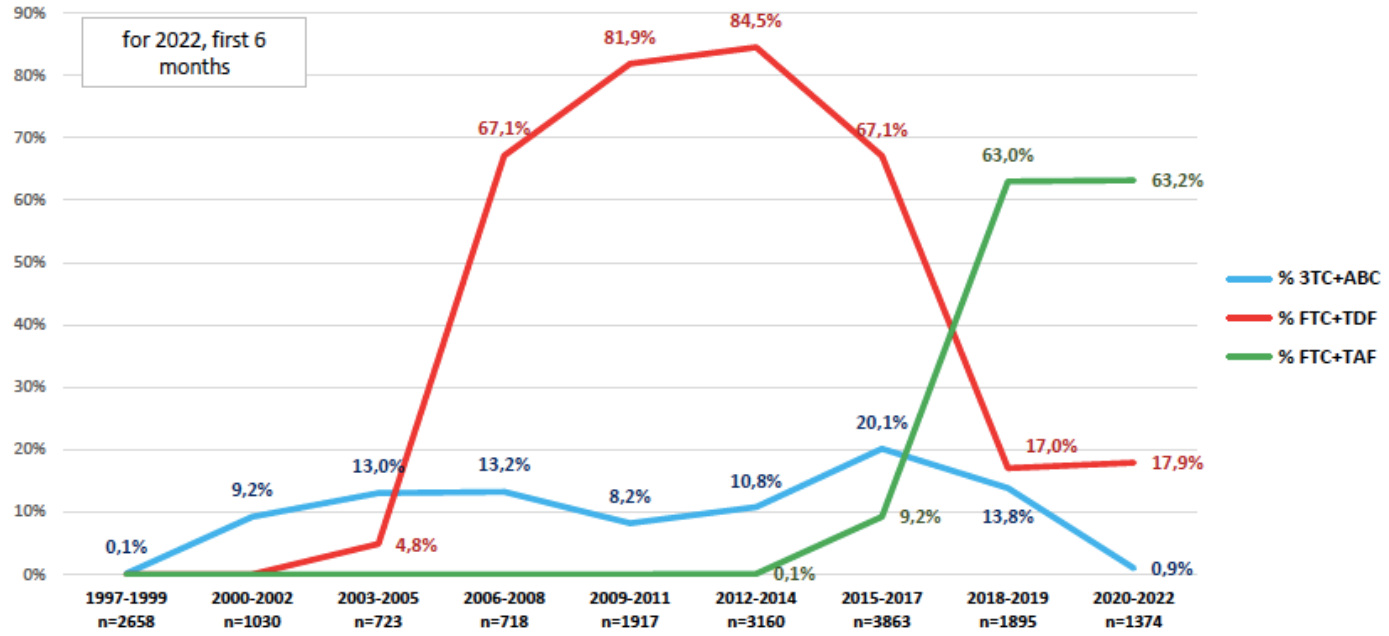


Sax. AIDS. 2022;36:1511

How Confident Are We With the Efficacy and Safety of Oral Two-Drug Regimens?

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of of patients treated with TDF/FTC or TAF/FTC or ABC/3TC as firstline backbone, according to calendar period



Jun 2022 Report

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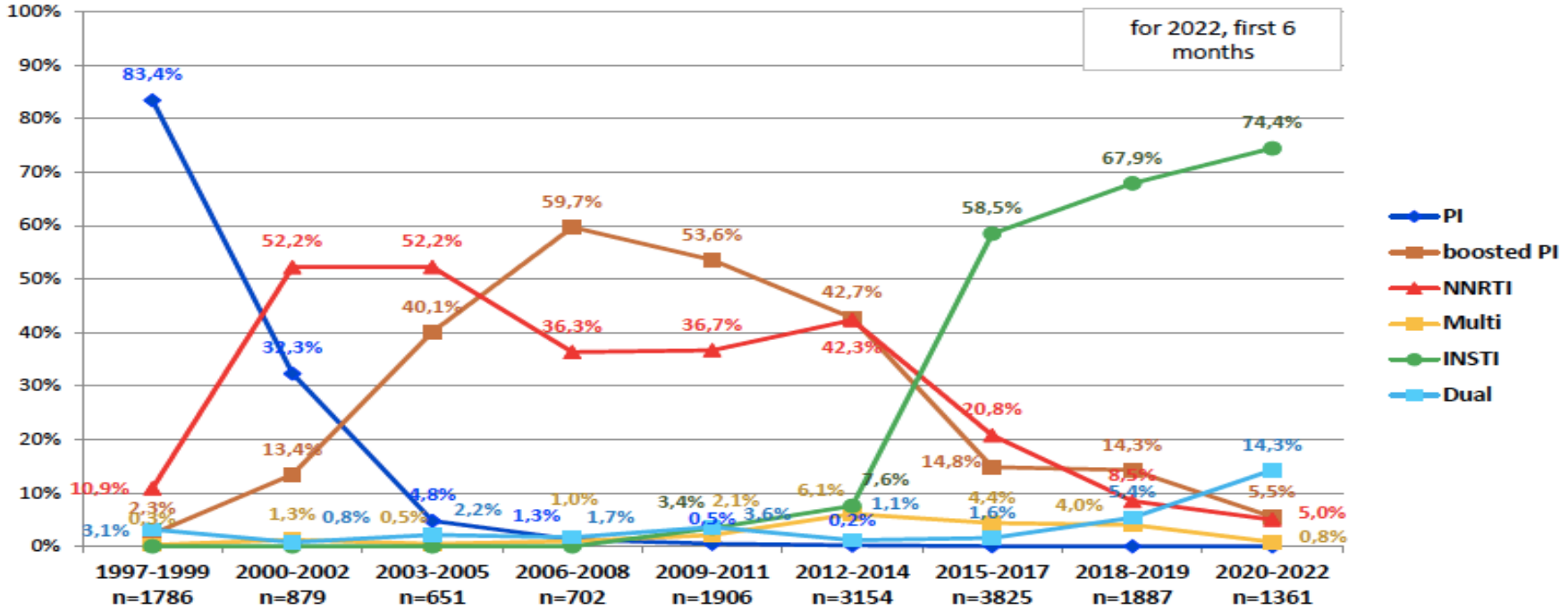
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of usage of different ART classes as third drug in first line regimen according to calendar period of starting (NRTIs not considered)



Jun 2022 Report

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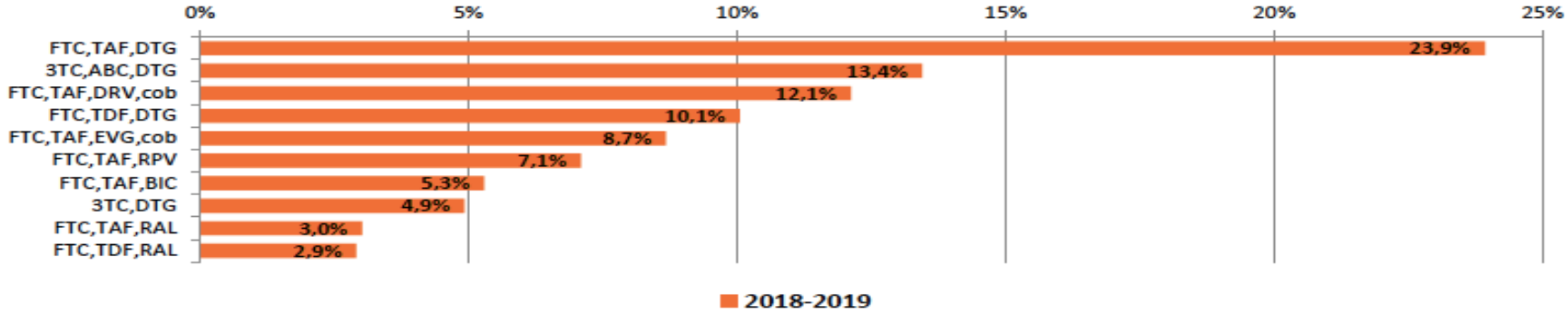
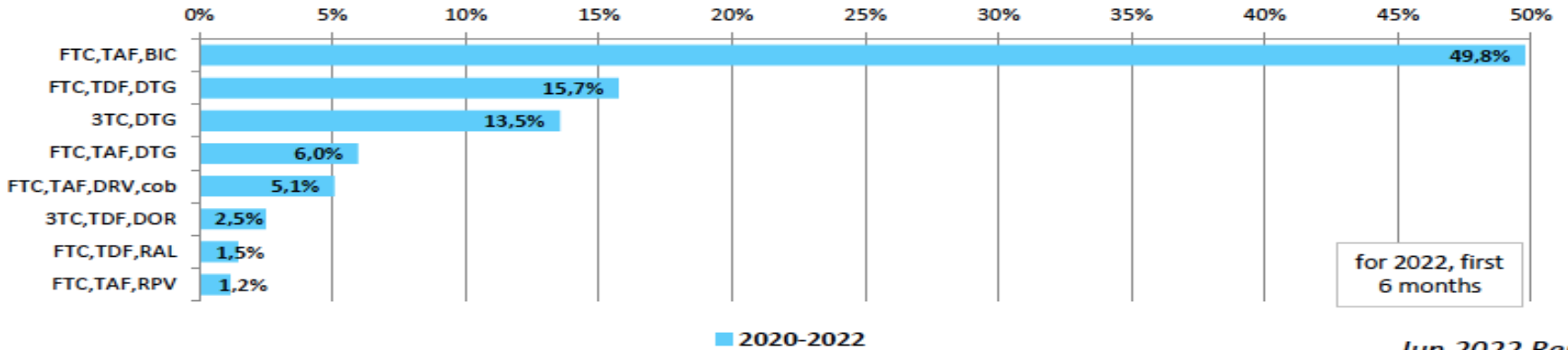
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Most frequent regimens used in first line according to calendar period of starting





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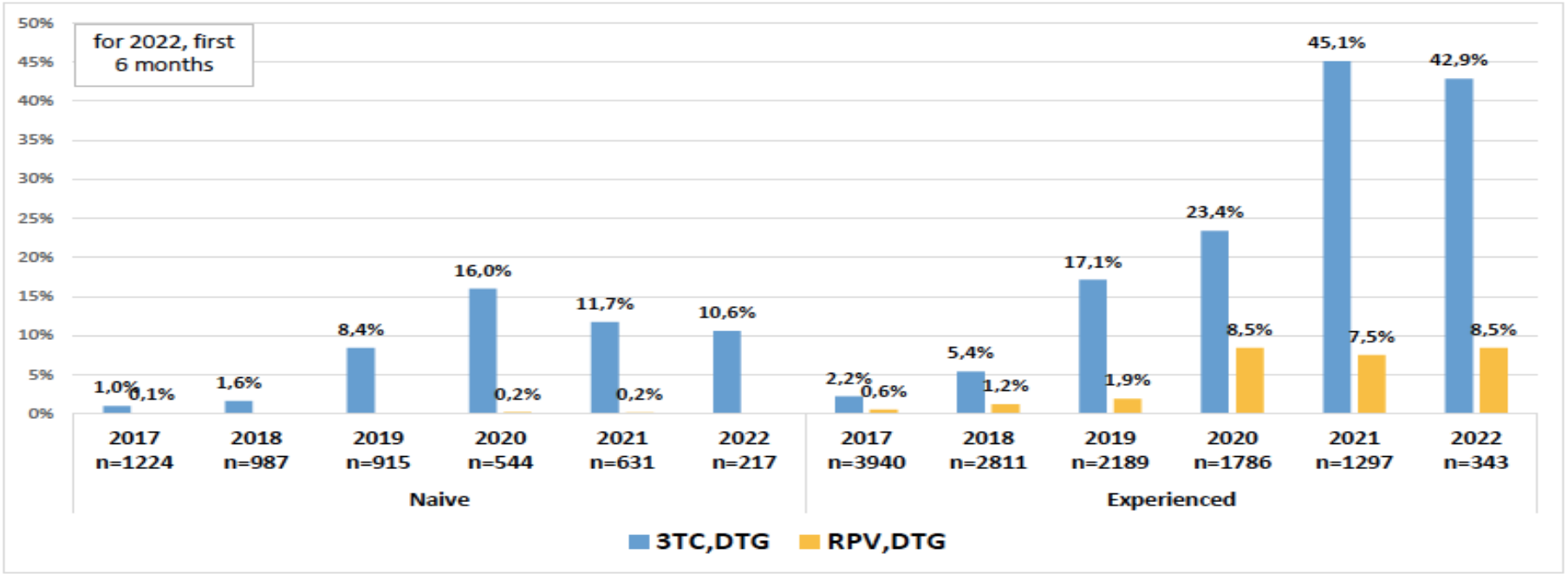
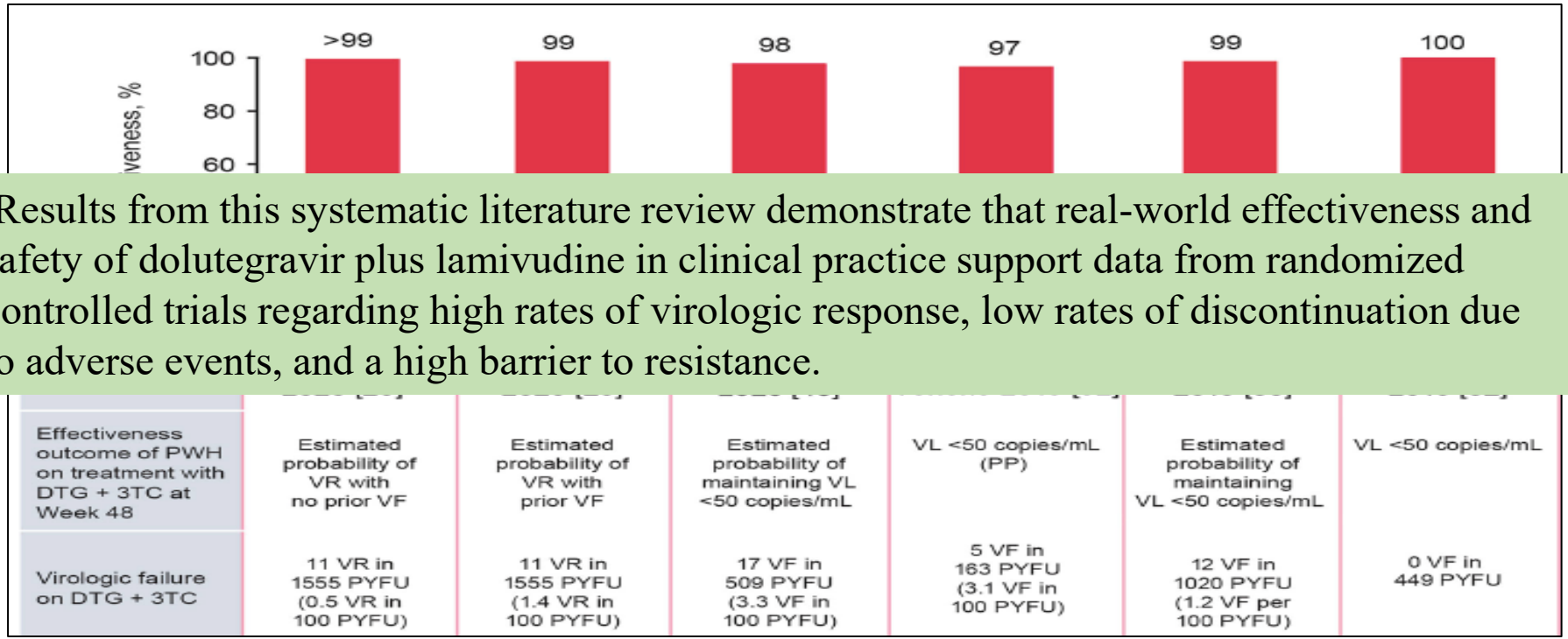
DTG+3TC and DTG+RPV dual therapies used in naïve and experienced patients from 2017 to 2022



Jun 2022 Report

HIV Treatment with the Two-Drug Regimen Dolutegravir Plus Lamivudine in Real-world Clinical Practice: A Systematic Literature Review



Results from this systematic literature review demonstrate that real-world effectiveness and safety of dolutegravir plus lamivudine in clinical practice support data from randomized controlled trials regarding high rates of virologic response, low rates of discontinuation due to adverse events, and a high barrier to resistance.

Effectiveness outcome of PWH on treatment with DTG + 3TC at Week 48	Estimated probability of VR with no prior VF	Estimated probability of VR with prior VF	Estimated probability of maintaining VL <50 copies/mL	VL <50 copies/mL (PP)	Estimated probability of maintaining VL <50 copies/mL	VL <50 copies/mL
Virologic failure on DTG + 3TC	11 VR in 1555 PYFU (0.5 VR in 100 PYFU)	11 VR in 1555 PYFU (1.4 VR in 100 PYFU)	17 VF in 509 PYFU (3.3 VF in 100 PYFU)	5 VF in 163 PYFU (3.1 VF in 100 PYFU)	12 VF in 1020 PYFU (1.2 VF per 100 PYFU)	0 VF in 449 PYFU

Proportion of PWH in switch cohorts treated with DTG/3TC reporting effectiveness at Week 48. Data included for studies with N>100 pts

Infect Dis Ther (2021) 10:2051–2070

What could be the main concerns?

- Immune activation/inflammation
- Residual viral burden
- Forgiveness

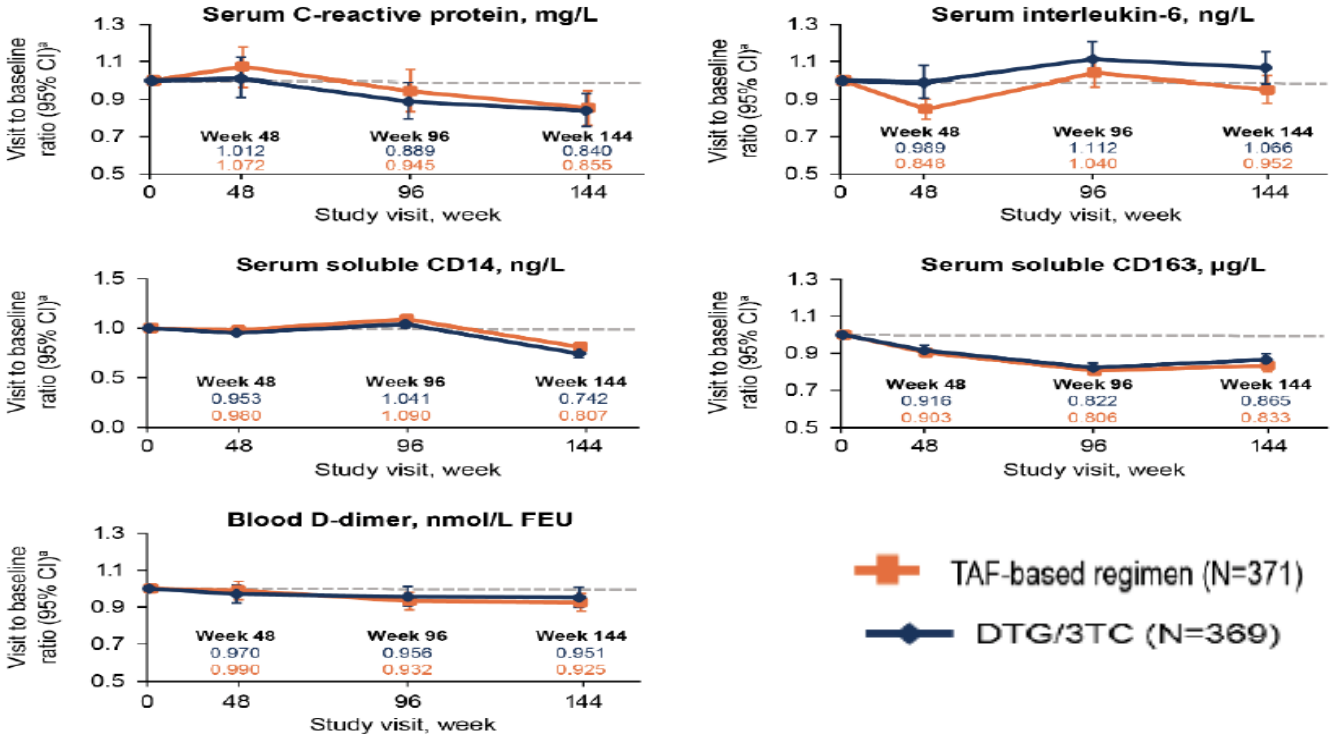
and not forgetting……..

- *Rapid start?*
- *Women with childbearing potential?*
- *Opportunistic infection/TB?*
- *Neurocognitive impairment?*

What could be the main concerns?

- **Immune activation/inflammation**
- Residual viral burden
- Forgiveness

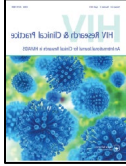
TANGO: Changes in Inflammatory Biomarkers From Baseline to Wk 144



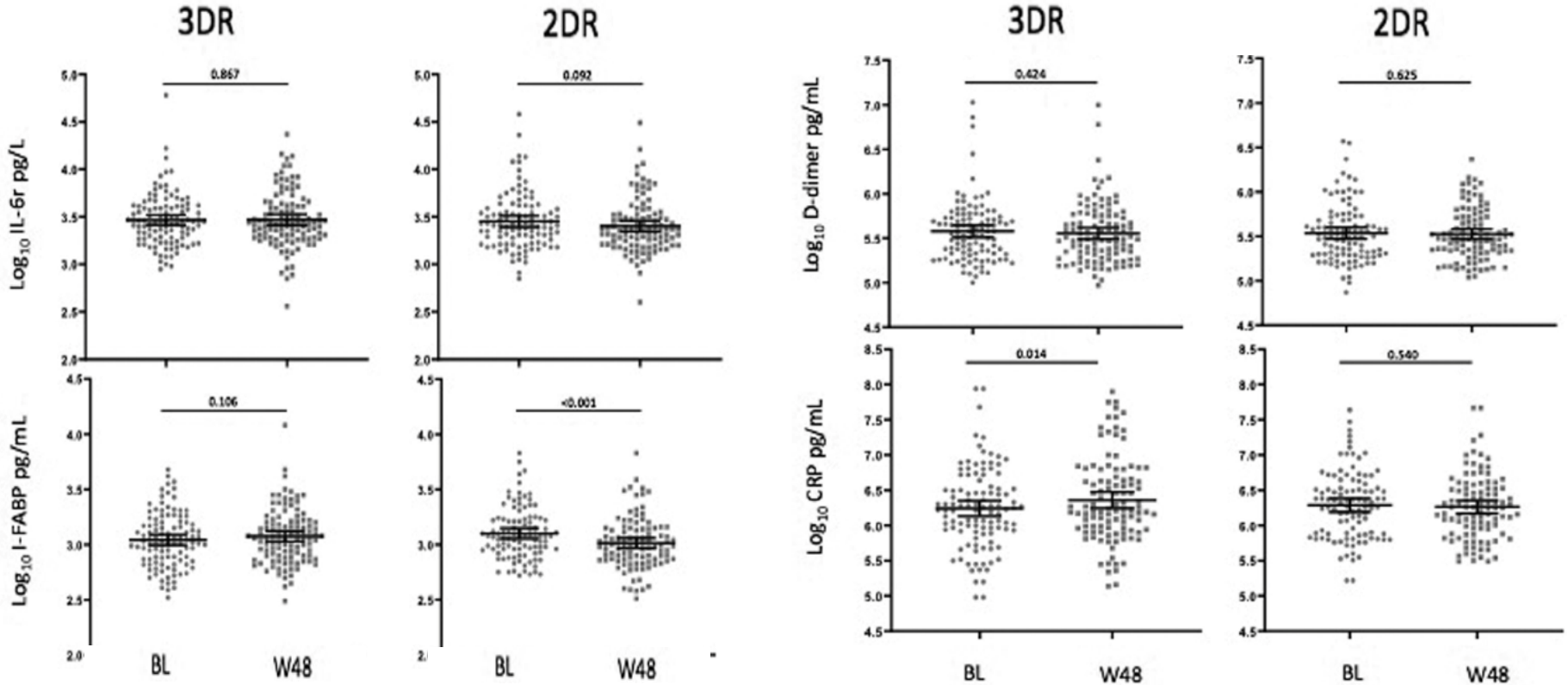
Small and comparable changes in inflammatory markers across treatment groups

Osiyemi. IDWeek 2021. Abstr 900. CID 2022;75(6):975–86

Inflammation markers in virologically suppressed HIV-Infected patients after switching to dolutegravir plus lamivudine vs continuing triple therapy: 48-week results in real-life setting



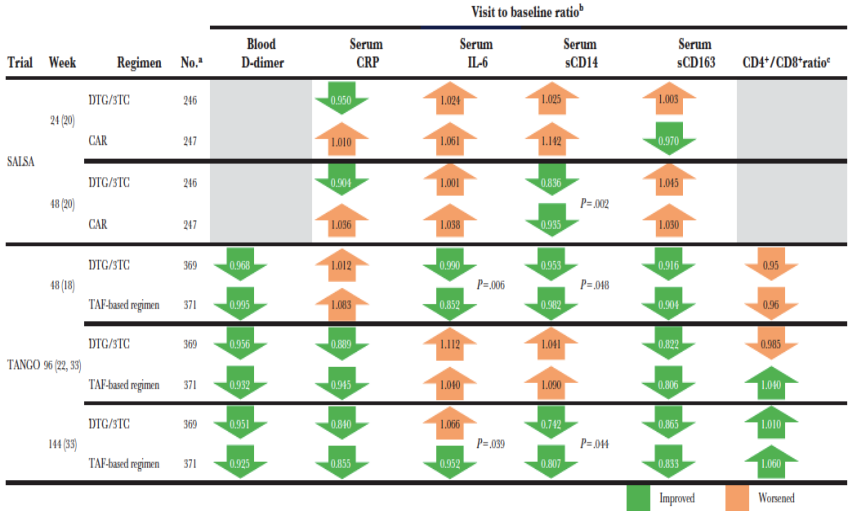
Study design: longitudinal study on 208 virologically-suppressed patients on stable 3-drug ART who switched at baseline to dolutegravir. lamivudine (2DR-group). Median time on ART= 13 yrs; Median N° of ART lines:6



HIV Research & Clinical Practice 2022; 23: 28-36

Changes in Inflammatory and Atherogenesis Biomarkers With the 2-Drug Regimen Dolutegravir Plus Lamivudine in Antiretroviral Therapy–Experienced, Virologically Suppressed People With HIV-1: A Systematic Literature Review

2 randomized controlled trials (RCTs) and 6 real-world evidence were analysed



Study	No.	Time point	Age, y	Baseline CD4+/CD8+ ratio	Time on ART, median (IQR)	Change from BL in CD4+/CD8+ ratio
Lombardi 2019 (29)	67	48 wk	Median (IQR), 49.4 (41.2-54.9)	Median (IQR), 0.83 (0.70-1.00)	10.9 (4.8-16.4) y	0.03[d] NS
Hidalgo-Tenorio 2019 (38)	177	48 wk	Mean (SD), 48.5 (14.2)	Mean (SD), 0.87 (0.5)	3 (4-18) y	0.06[d] $P=.023$
Taramasso 2019 (35)	22	12 mo	NR	NR	NR	0.26[d] $P<.05$
Baldin 2019 (36)	556	96 and 144 wk	Median (IQR), 51.7 (45.3-57.4)	Median (IQR), 0.85 (0.61-1.13)[e]	11.5 (6.1-18.3) y	0.06[b] 96 wk $P=.001$ 0.10[b] 144 wk $P=.002$
Reynes 2020 (37)	27	48 mo	Median, 59	Median, 0.84	215 (22-329) mo	0.14[b] P value NR
Maggiolo 2021(34)	218	60 mo	Median (IQR), 52 (12)	Median (IQR), 0.93 (0.70)	10.2 (13) y	0.21[b] $P<.0001$

Results show that dolutegravir plus lamivudine has a comparable impact on inflammatory and atherogenesis biomarkers vs 3/4DRs, with no consistent pattern of change after switch in virologically suppressed PWH.

Open Forum Infect Dis. 2022 Feb 10;9(4)

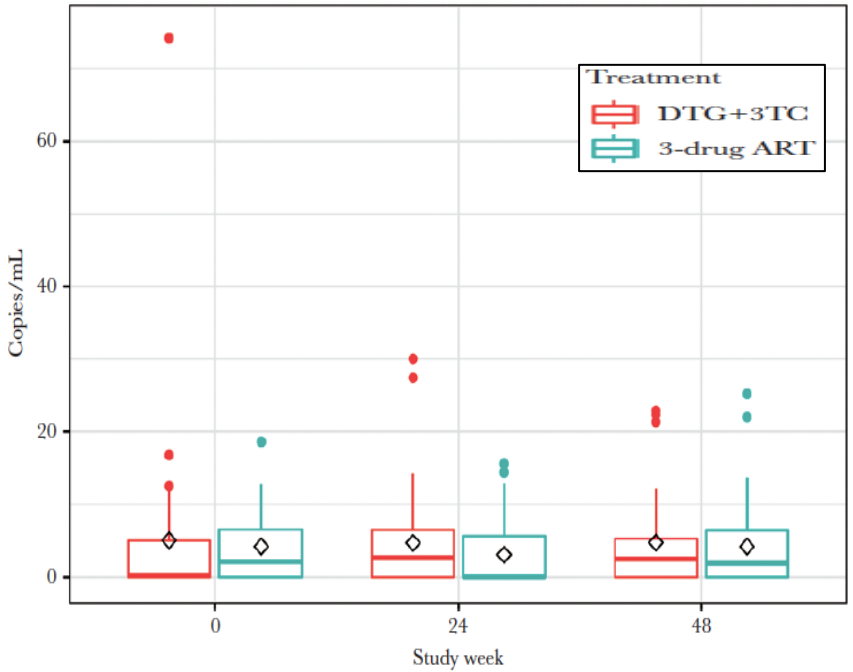
What could be the main concerns?

- Immune activation/inflammation
- **Residual viral burden**
- Forgiveness

Open Forum Infectious Diseases

BRIEF REPORT

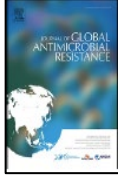
No Significant Changes to Residual Viremia After Switch to Dolutegravir and Lamivudine in a Randomized Trial



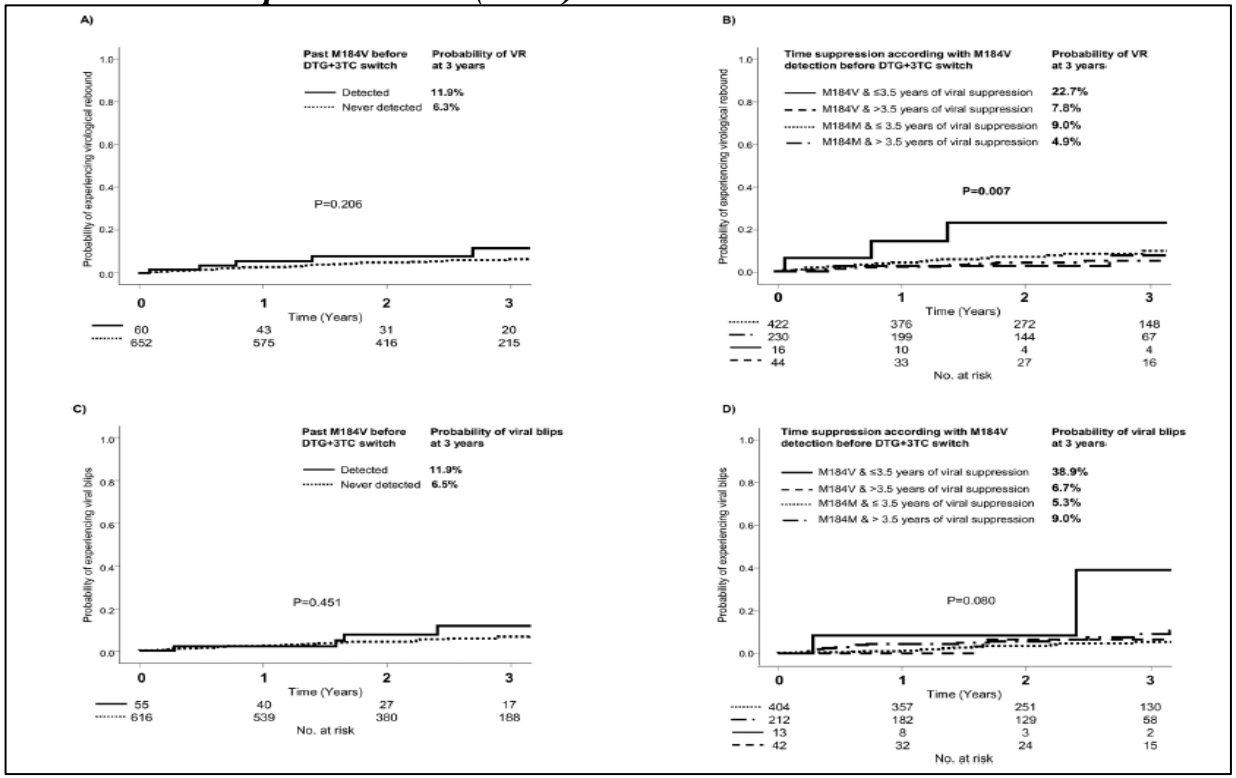
72 patients of the ASPIRE trial were included. At entry, levels of residual viremia did not differ significantly between arms (DTG+3TC vs 3-drug ART: mean, 5.0 vs 4.2 HIV-1 RNA copies/mL; P = .64). After randomization, no significant between group differences were found at either week 24 or 48.

Open Forum Infect Dis. 2019 Feb 11;6(3)

Virological efficacy of switch to DTG plus 3TC in a retrospective observational cohort of suppressed HIV-1 patients with or without past M184V: the LAMRES study



***Study design**: A total of 712 individuals followed in several clinical centres in France, Italy and Spain were analysed. Past M184V was present in 60 (8.4%) individuals.*



Results

By 3 years after switch, the overall probability of VR and blips was 6.7% and 6.9%, respectively, without any statistical significance according to the presence/absence of past M184V.

A significantly higher probability of VR was found in individuals harbouring M184V before DTG + 3TC with a duration of virological suppression (Ts) ≤.3.5 years compared to others

At VF: 1 pt with M184V; no resistances to INSTIs were found

What could be the main concerns?

- Immune activation/inflammation
- Residual viral burden
- **Forgiveness**

IMPACT OF TREATMENT ADHERENCE ON EFFICACY OF DTG + 3TC AND DTG + TDF/FTC: POOLED ANALYSIS OF THE GEMINI-1 AND -2 CLINICAL STUDIES

Mounir Ait-Khaled,[1] Juan Sierra Madero,[2] Vicente Estrada Perez,[3] Roberto Gulminetti,[4] Debbie Hagins,[5] Hung-Chin Tsai,[6] Choy Man,[7] Jörg Sievers,[1] Rimgaile Urbaityte,[8] Richard Grove,[8] Andrew Zolopa,[7] Brian Wynne,[7] Jean van Wyk[1]

Methods

- **Association between adherence and proportion of participants with HIV-1 RNA <50 c/mL was evaluated at Week 48** using the FDA Snapshot algorithm and an analysis based on the last available on-treatment viral load by Week 48 (assessment of virologic response not accounting for discontinuations for non-virologic reasons)
- **Percent adherence** calculated as:
  - **number of pills taken** (difference between the number of pills available and the number of pills returned) **per number of pills prescribed estimated using pill count data**
- Participants were **stratified by ≥90% vs <90% adherence**
- Unadjusted treatment differences with exact 95% CIs were derived for proportion of participants with HIV-1 RNA <50 c/mL using both FDA Snapshot endpoint and last available on-treatment viral load through Week 48

1. Cahn et al. *Lancet*. 2019;393:143-155. 2. Cahn et al. HIV Glasgow 2020; Virtual. Poster P018. 3. Altice et al. *Patient Prefer Adherence*. 2019;13:475-490. 4. Sax et al. *Lancet*. 2017;390:2073-2082.

Ait-Khaled et al. IDWeek 2020™; Virtual. Poster 1024.

Adherence Results in GEMINI-1 and -2 (ITT-E Population)

Snapshot Outcomes by Adherence Category

Outcomes, n (%)	DTG + 3TC ≥90% (N=679)	DTG + 3TC <90% (N=35)	DTG + TDF/FTC ≥90% (N=677)	DTG + TDF/FTC <90% (N=34)
HIV-1 RNA <50 c/mL	**631 (93)**	**24 (69)**	**647 (96)**	**22 (65)**
HIV-1 RNA ≥50 c/mL	**16 (2)**	**4 (11)**	**9 (1)**	**4 (12)**
Data in window and HIV-1 RNA ≥50 c/mL	8 (1)	0	4 (1)	1 (3)
Discontinued for lack of efficacy	3 (<1)	2 (6)	2 (<1)	0
Discontinued for other reason and HIV-1 RNA ≥50 c/mL	4 (1)	1 (3)	2 (<1)	3 (9)
Change in ART	1 (<1)	1 (3)	1 (<1)	0
No virologic data at Week 48	**32 (5)**	**7 (20)**	**21 (3)**	**8 (24)**
Discontinued study for AE or death	9 (1)	1 (3)	8 (1)	4 (12)
Discontinued study for other reason	21 (3)	6 (17)	13 (2)	4 (12)
On study but missing data in window	2 (<1)	0	0	0

- Baseline HIV-1 R … herence categories

Adherence results	DTG + TDF/FTC (N=717)
Adherence category,	
<90%	34 (5)
≥90%	677 (94)
HIV-1 RNA by adhere	
<90%	4.35 (3.07-5.88)
≥90%	4.48 (2.11-6.37)
CD4+ cell count by a… cells/mm³	
<90%	415.0 (19-929)
≥90%	440.0 (19-1497)

- A high proportion of pa… eatment adherence
- In each treatment gro…
- Demographics and bas… well balanced between treatment groups[1,2]

Ait-Khaled et al. IDWeek 2020™; Virtual. Poster 1024.

Discussion

- In this study, ***adherence level appeared to have a similar impact on the 2DR and 3DR***; overall, response rates were high in those with ≥90% adherence
  - Response rates were high in participants with <90% adherence
  - The high rates of response across adherence categories is supported by a real-world database analysis that suggests ≥80% adherence as a threshold for achieving virologic suppression[1]
- ***Limitations of this analysis include the small number of participants in the lower adherence*** subgroup and the difficulty in accurately measuring adherence[2]

Conclusions

- In the GEMINI studies, a lower proportion of participants with <90% adherence achieved HIV-1 RNA <50 c/mL at Wk 48 regardless of regimen
- The impact of lower adherence on virologic response was similar between treatment groups
- These results provide additional information about the robustness of DTG + 3TC compared with 3-drug DTG-containing regimens and suggest similar regimen forgiveness

1. Byrd et al. *J Acquir Immune Defic Syndr*. 2019;82:245-251. 2. Allice et al. *Patient Prefer Adherence*. 2019;13:475-490.

Forgiveness of INSTI-Containing Regimens at Drug Concentrations Simulating Variable Adherence *In Vitro*

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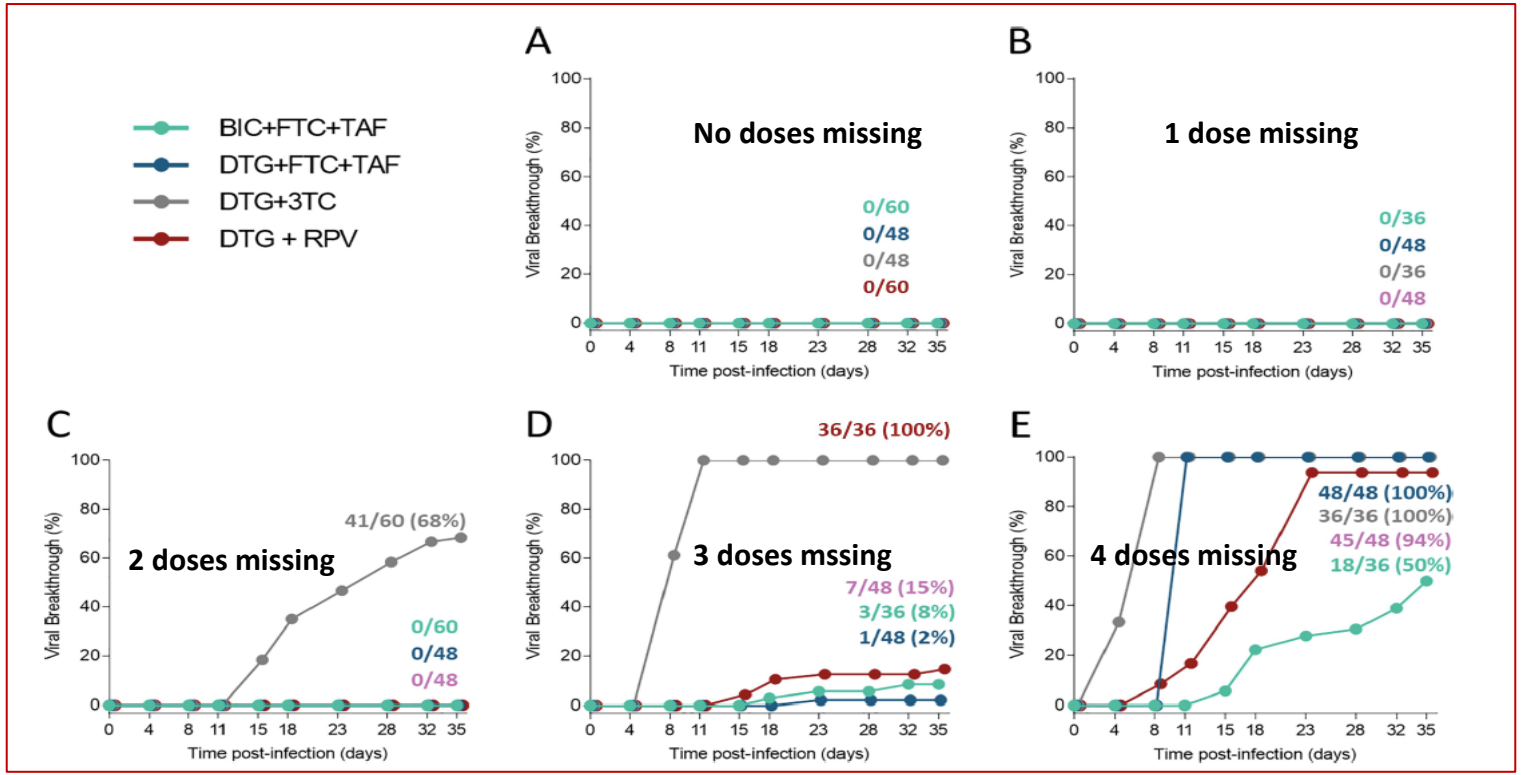
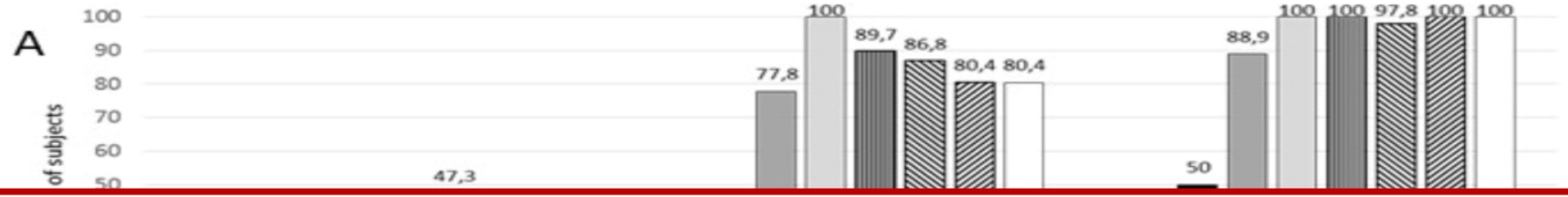
<u>Study design</u>: time to *in vitro* viral breakthrough (VB) and resistance barrier using simulated human drug exposures at either full or suboptimal treatment adherence to each regimen were compared



Antimicrob Agents Chemother. 2022 May 17;66(5):e0203821

Forgiveness to imperfect adherence to BIC/TAF/FTC

Study design: retrospective analysis of PDC. 281 adult PLWH were included, (75%M);median age of 49 years (IQR 43-58). Median follow-up of the cohort under B/F/TAF was 590 days (IQR 381-685) for a total of 343 patient/years



Conclusions: Adherence dynamics under B/F/TAF indicate that this regimen is highly forgiving and obtains desired virologic outcomes for adherence levels as low as 70%. Long-term success of ART needs well tolerated, effective regimens that are the least intrusive of the patient's lifestyle. In this context, an elevated forgiveness may be considered as an additional feature that can further improve long-term outcomes.

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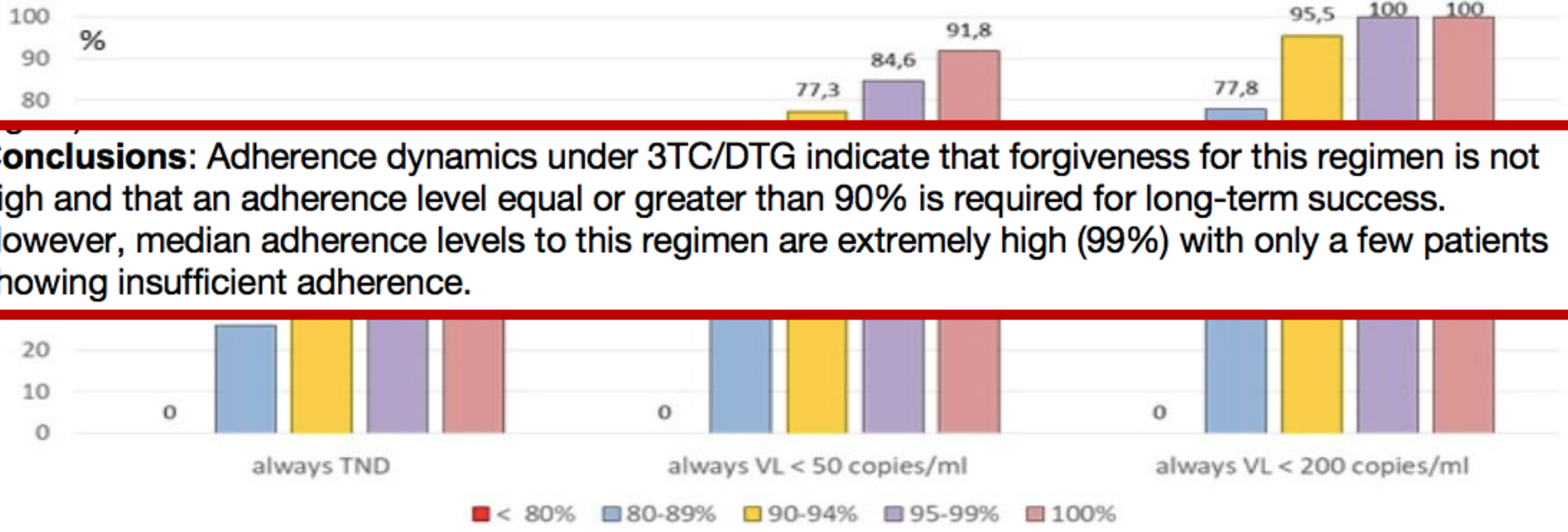
Adherence rates and forgiveness to uncomplete adherence to 3TC/DTG

Study design: retrospective study on 240 adult PLWH; (75% M) ;median age=52 years (IQR 43-58). Median follow-up under 3TC/DTG was 819 days (IQR 450-1459) with some PLWH followed for more of 5 years for a total of 681 patient/years



Conclusions: Adherence dynamics under 3TC/DTG indicate that forgiveness for this regimen is not high and that an adherence level equal or greater than 90% is required for long-term success. However, median adherence levels to this regimen are extremely high (99%) with only a few patients showing insufficient adherence.

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Take home messages

- Dual therapy is now incorporated into DHHS and EACS ART guideline recommendations for first-line and maintenance treatment
- DTG/3TC dual-therapy is effective as that with three drugs also in the real-world setting
- Although dual therapy is an attractive innovative option as it diminishes the life-time exposure to antiretroviral drugs with potential toxicity, the impact of a rebound in immune activation and on residual viremia are currently not well understood.
- Additional studies on the role of dual therapy in «difficult-to-treat» populations, such as patients with high viral load, advanced clinical stage, multiple comorbidities, aging population, pregnancy, etc, are needed.
- A dual therapy regimen reduces the drug burden, which can improve patient adherence and quality of life. However, forgiveness for this regimen is not high and high level (>90%) of adherence is required for long-term success
- Dual therapy is an innovative antiretroviral strategy that may be considered in a multifactorial approach to HIV treatment control in which the personalized target intervention represents the true paradigm shift.

Grazie per l'attenzione