Terapia di prima linea: quali considerazioni nella scelta del trattamento ottimale

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Disclosures

- **Grants for educational activities**
  - ❖ Janssen-Cilag
  - ❖ Merck Sharp and Dohme
  - ❖ ViiV Healthcare
  - ❖ Gilead

- **Personal fees for advisory boards and speakers bureau**
  - ❖ Janssen-Cilag
  - ❖ Merck Sharp and Dohme
  - ❖ ViiV Healthcare
  - ❖ Gilead

La storia della terapia antiretrovirale si è sviluppata seguendo quelle tappe che corrispondevano alle esigenze del momento:

-affrontando e cercando di risolvere questioni dapprima legate alla barriera genetica dei farmaci,

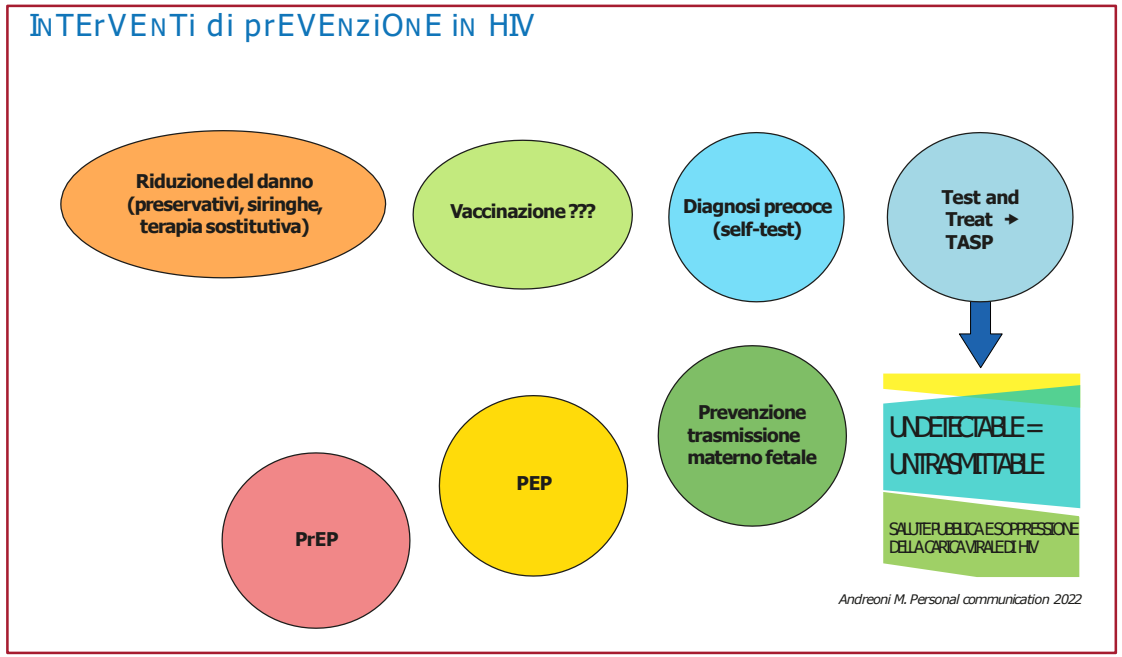
-poi alla loro potenza-tossicità,

-per arrivare oggi al focus delle terapia « del futuro» dove in discussione non è nella potenza né la tossicità

LE TappE dEl succEssO NEll a sfida a HIV

Quarant'anni di lotta a questa malattia rappresentano un fondamentale insegnamento in termini di prevenzione con una forte potenzialità di intervento per molte altre malattie infettive. La riduzione del danno si applica oggi all'HIV ma anche alle epatiti. La diagnosi precoce è un elemento fondamentale per la prevenzione di qualsiasi malattia trasmissibile.

La strategia di *treatment as prevention* (TASP) insegna come il trattamento non sia finalizzato solo alla cura del singolo ma abbia un impatto anche sulla comunità, in termini di riduzione della circolazione del virus. Il concetto di *Undetectable equals*

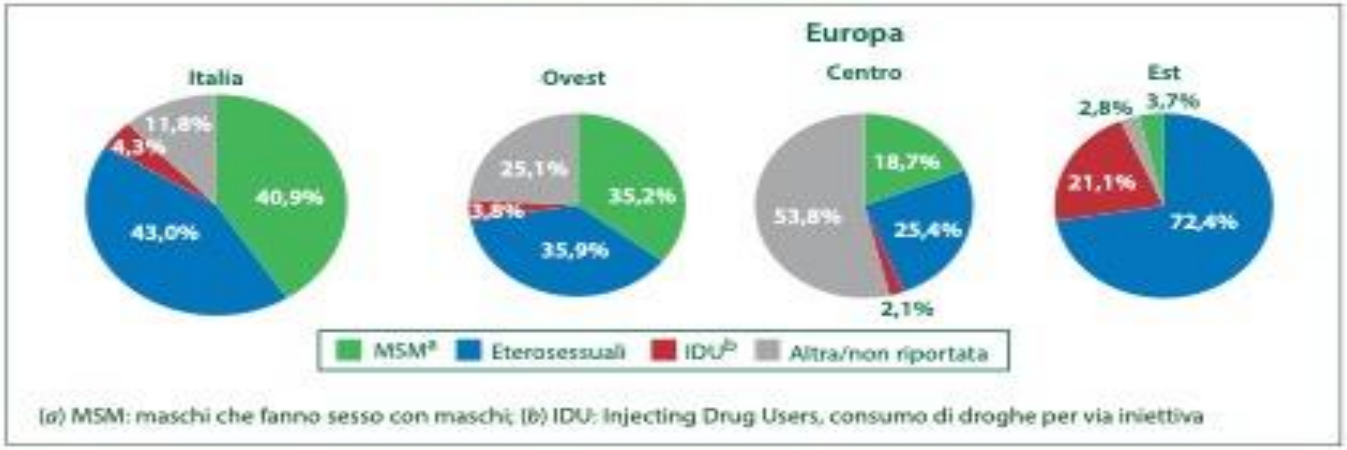


Untrasmittable (U=U), secondo cui un soggetto trattato non trasmette più l'infezione, ha importanti implicazioni non solo sul piano clinico ma anche in termini di salute pubblica e di riduzione dello stigma e della discriminazione.

Gli interventi di prevenzione della trasmissione materno-fetale, la profilassi pre-esposizione, la prevenzione post-esposizione: sono tutti argomenti messi in campo nella lotta contro l'infezione da HIV e rappresentano un esempio che può essere di volta in volta riproposto nei confronti di altre infezioni virali.

AGGIORNAMENTO DELLE NUOVE DIAGNOSI DI INFEZIONE DA HIV E DEI CASI DI AIDS IN ITALIA AL 31 DICEMBRE 2022

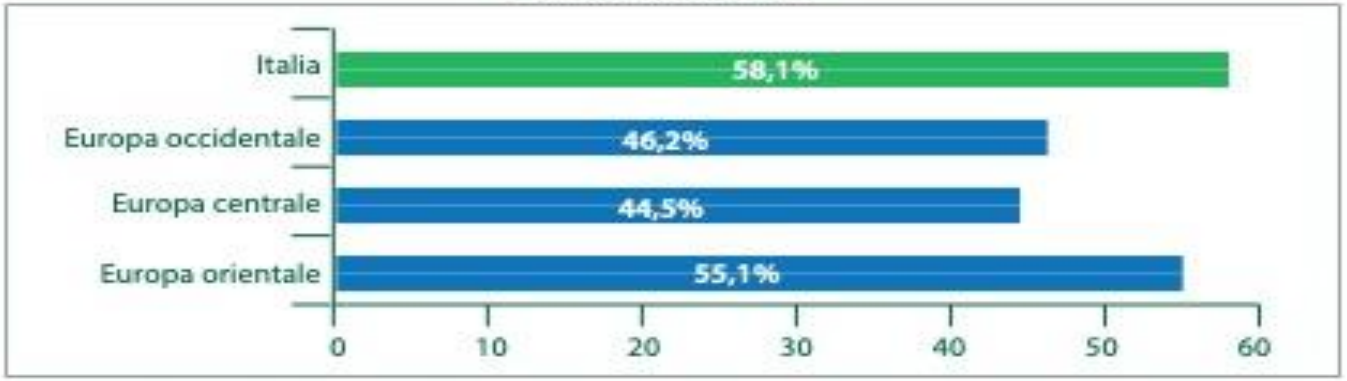
Modalità di trasmissione 2022



(a) MSM: maschi che fanno sesso con maschi; (b) IDU: Injecting Drug Users, consumo di droghe per via iniettiva

Distribuzione percentuale delle nuove diagnosi di infezione da HIV per modalità di trasmissione 2022.
Fonti: Sistema di Sorveglianza HIV nazionale, *ECDC/WHO. HIV/AIDS Surveillance in Europe 2023-2022 data (1)*

Late presenters* 2022



(*) Late presenters: nuove diagnosi di infezione da HIV con numero di linfociti CD4 <350 cell/µl.
Fonti: Sistema di Sorveglianza HIV nazionale, *ECDC/WHO. HIV/AIDS Surveillance in Europe 2023-2022 data (1)*

Strategie per successo della terapia ARV

- Iniziare bene…e presto
- Farmaci con alta efficacia e tollerabilità
- Terapia Personalizzata

KEY POINTS

- **PLWH da trial clinico**
- **PLWH late presenter**
- **PLWH con fallimento alla PREP**

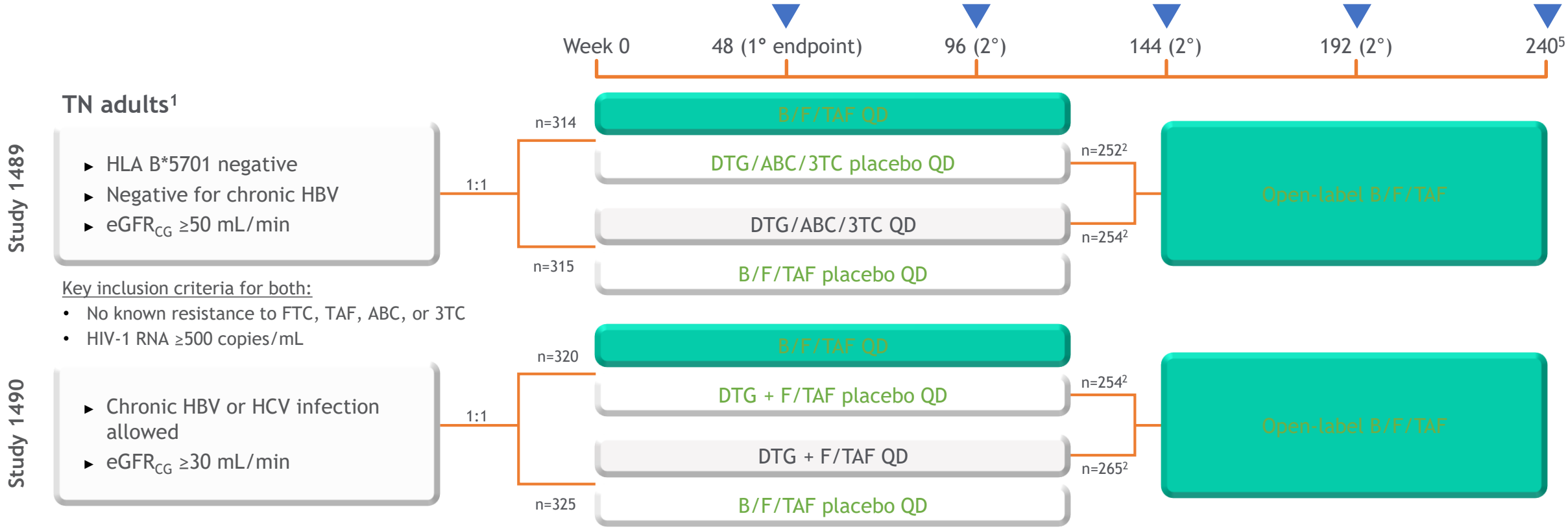
Regimen	Main requirements	Additional guidance (see footnotes)
Recommended regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk) II (Weight increase (DTG))
TAF/FTC/BIC		II (Weight increase (BIC, TAF))
TAF/FTC or TDF/XTC + DTG		II (Weight increase (DTG, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing)
TAF/FTC or TDF/XTC + RAL qd or bid		II (Weight increase (RAL, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
XTC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL Not recommended after PrEP failure	II (Weight increase (DTG)) V (3TC/DTG not after PrEP failure)
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + DOR or TDF/3TC/DOR		II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (DOR: caveats, HIV-2)
Alternative regimens		
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner	II (Weight increase (TAF) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (EFV: neuro-psychiatric adverse events. HIV-2 or HIV-1 group 0, dosing)
TAF/FTC or TDF/XTC + RPV or TAF/FTC/RPV or TDF/FTC/RPV	CD4 count > 200 cells/µL HIV-VL < 100,000 copies/mL Not on gastric pH increasing agents With food	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VIII (RPV: HIV-2)
2 NRTIs + PI/r or PI/c		
TAF/FTC or TDF/XTC + DRV/c or DRV/r or TAF/FTC/DRV/c	With food	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IX (DRV/r: cardiovascular risk) X (Boosted regimens and drug-drug interactions)

Lineeguida EACS Ottobre 2023

PLWH da trial clinico

Long-Term Follow-up on the Efficacy of B/F/TAF in TN PLWH

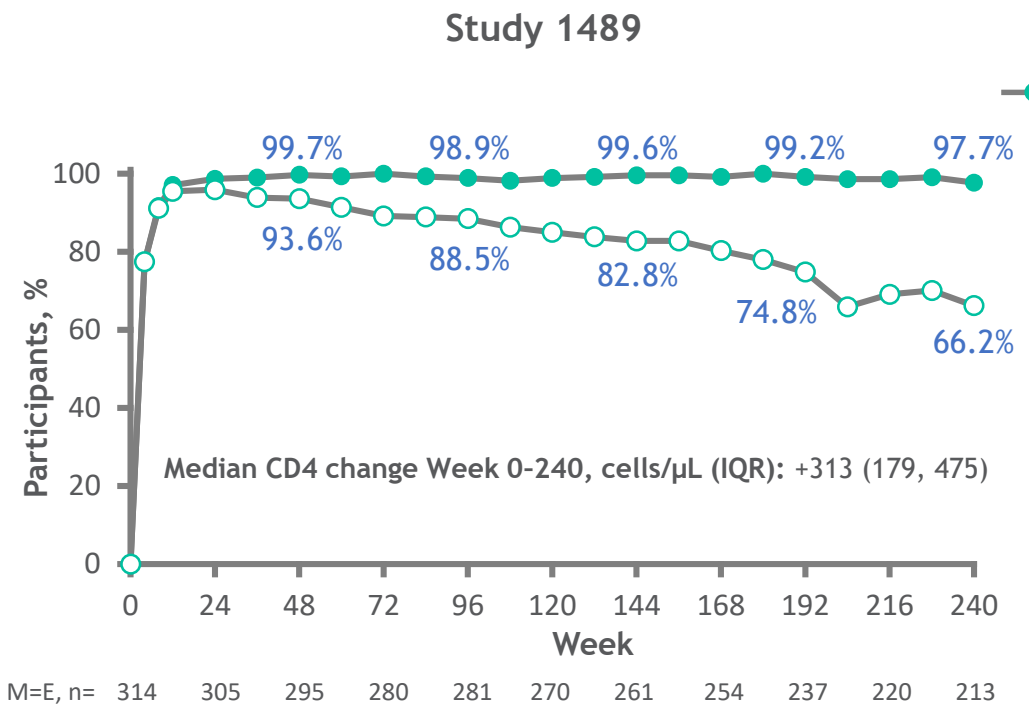
The open-label extensions of Studies 1489 (n=252) and 1490 (n=254) have investigated the efficacy of B/F/TAF (HIV-1 RNA <50 c/mL) in TN PLWH up to Week 240

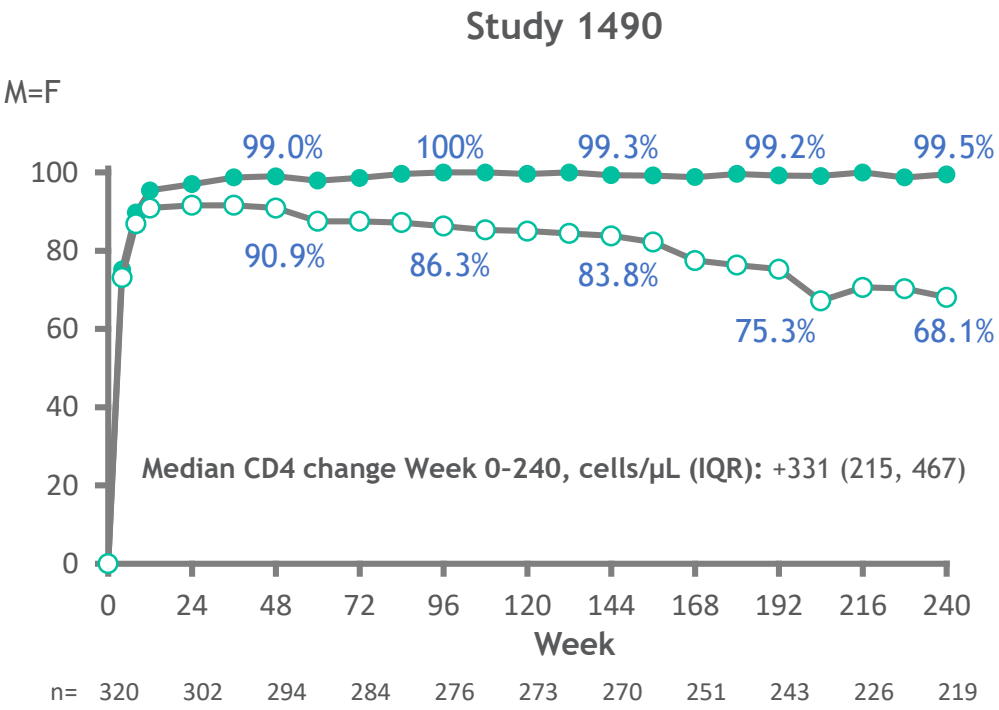


eGFR$_{CG}$: estimated glomerular filtration rate by Cockcroft-Gault equation; HLA: human leukocyte antigen; QD: once per day; TN: treatment-naïve; VS: virological suppression.
1. Arribas J, *et al.* viAS 2021 (Abstract PEB151; poster presentation). 2. Workowski K, *et al.* vCROI 2021 (Abstract 415; poster presentation). 3. Gallant J, *et al. Lancet* 2017; 390:2063-2072. 4. Sax P, *et al. Lancet* 2017; 390:2073-2821; 5. Wohl D, *et al.* CROI 2022 (abstract 494; oral presentation). 6. Sax, et al. EClinicalMedicine (The Lancet) 2023;59:101991

5-Year Outcomes Demonstrate the Durable Efficacy of B/F/TAF in TN PLWH

In Studies 1489 and 1490 there were high rates of virological suppression[a] (M=E and M=F) through 5 years of follow-up among TN PLWH originally randomised to B/F/TAF

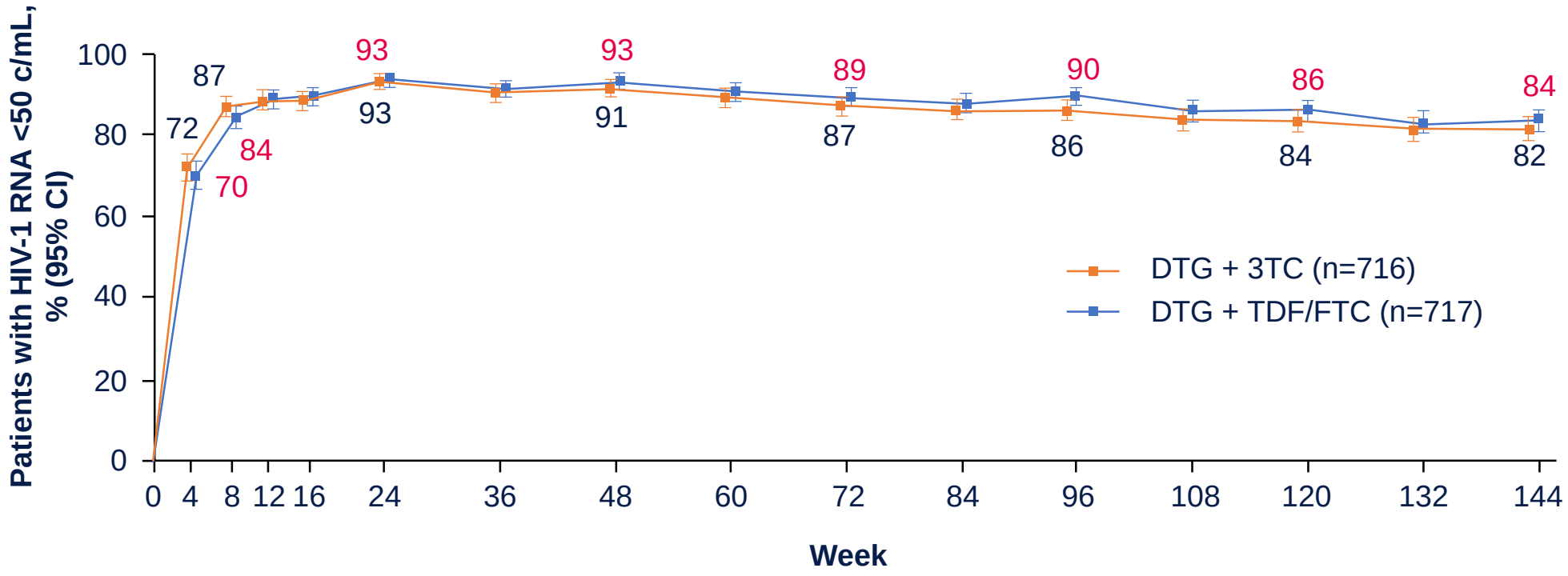




[a] HIV-1 RNA <50 copies/mL calculated using FDA Snapshot algorithm; includes only participants initially randomised to B/F/TAF
IQR: interquartile range; M=E: missing=excluded; M+F: missing=failure; TN: treatment-naïve.
1. Wohl D, et al. CROI 2022 (abstract 494; oral presentation); 2. Sax, et al. EClinicalMedicine (The Lancet) 2023;59:101991

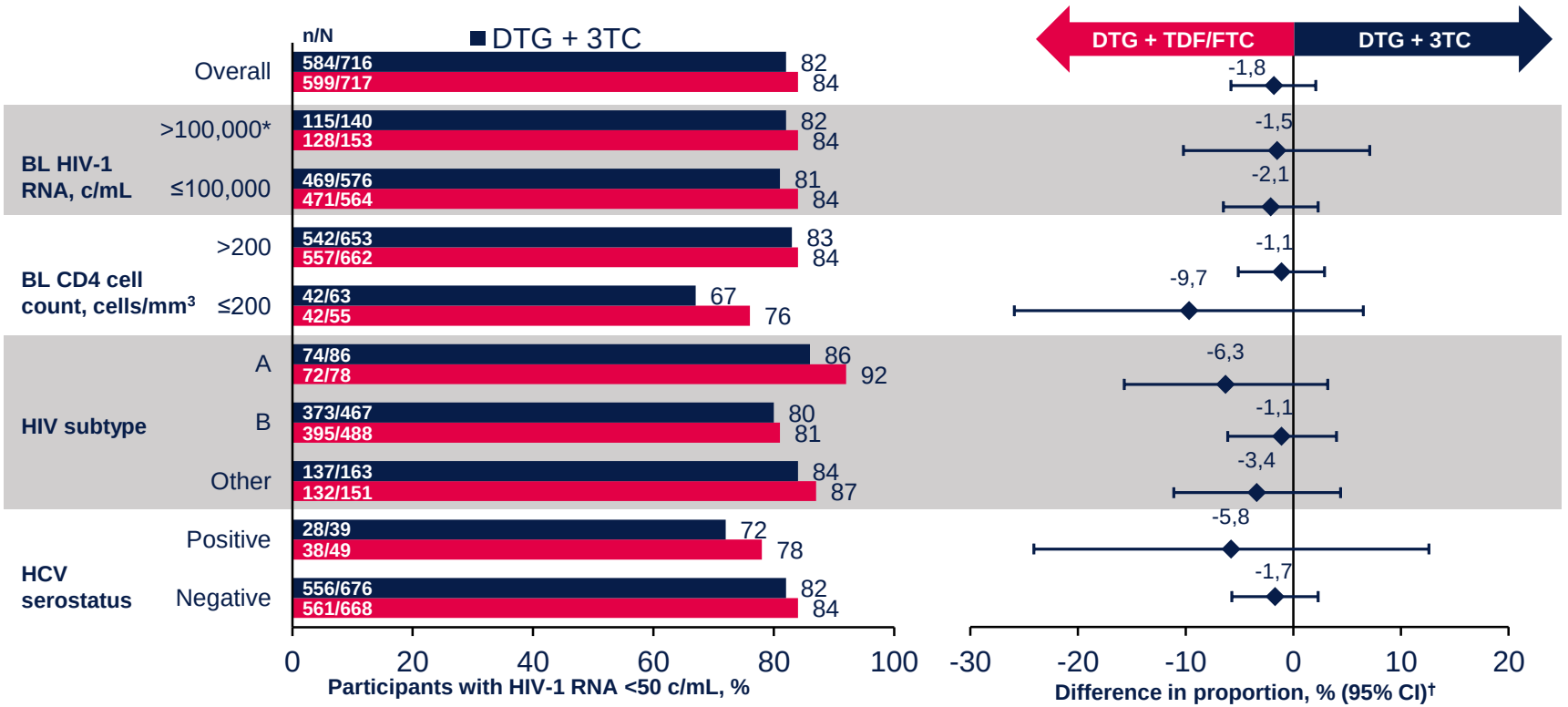
GEMINI-1 and -2: Pooled Snapshot Analysis Through Week 144 (ITT-E Population)

- DTG + 3TC was non-inferior to DTG + TDF/FTC in the pooled ITT-E population analysis through Week 144



Cahn P, et al. AIDS 2022;36:39–48

GEMINI-1 and -2: HIV-1 RNA <50 c/mL Across Baseline Disease Subgroups at Week 144



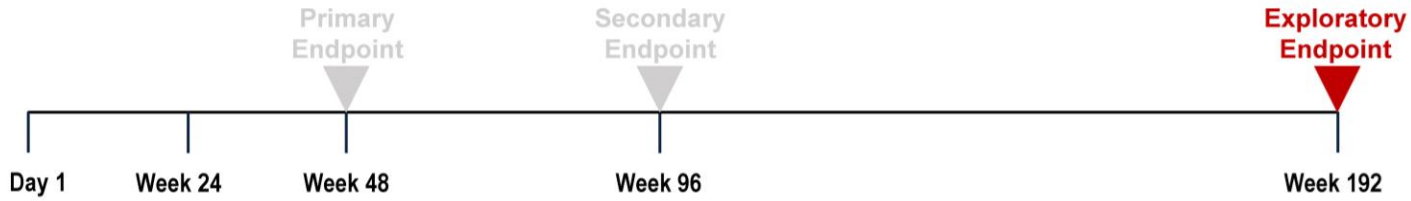
*Includes values for HIV-1 RNA >250,000 c/mL (DTG + 3TC, 41/51 [80%]; DTG + TDF/FTC, 37/46 [80%]), HIV-1 RNA >400,000 c/mL (DTG + 3TC, 15/18 [83%]; DTG + TDF/FTC, 19/24 [79%]), and HIV-1 RNA >500,000 c/mL (DTG + 3TC, 10/13 [77%]; DTG + TDF/FTC, 12/15 [80%]); †Adjusted difference for overall population (DTG + 3TC − DTG + TDF/FTC), unadjusted difference for subgroups calculated by proportion on DTG + 3TC − proportion on DTG + TDF/FTC

Orkin C, et al. CROI 2021. Slides 1991

DRIVE-FORWARD AND DRIVE-AHEAD: Randomized, Double-Blind, Phase 3 Trials in Treatment-Naïve Adults

Key Inclusion Criteria

- ≥18 years of age
- HIV-1 RNA ≥1000 copies/mL
- No prior antiretroviral treatment
- No known resistance to any of the trial drugs
- Creatinine clearance ≥50 mL/min



DRIVE-FORWARD

Stratified by:

- HIV-1 RNA (≤100,000 or >100,000 copies/mL)
- NRTI backbone therapy (TDF/FTC or abacavir/3TC)

DRIVE-AHEAD

Stratified by:

- HIV-1 RNA (≤100,000 or >100,000 copies/mL)
- Chronic hepatitis B and/or C infection status (yes or no)

Randomized, Double-Blind Base Trial	Open-Label Trial Extension
Group 1: DOR QD + 2 NRTIs[a]	Open-Label DOR QD + 2 NRTIs[a]
Group 2: DRV/r QD + 2 NRTIs[a]	
Group 1: DOR/3TC/TDF QD	Open-Label DOR/3TC/TDF
Group 2: EFV/FTC/TDF QD	

Inclusion Criteria for Extension

- Completed Week 96 visit
- Provided informed consent and is a clinically appropriate candidate
- Derived benefit from the base study

3TC, Lamivudine; DOR, doravirine; DRV/r, ritonavir-boosted darunavir; EFV, efavirenz; FTC, emtricitabine; NRTI, nucleos(t)ide reverse transcriptase inhibitor; TDF, tenofovir disoproxil fumarate; QD, once daily; [a]NRTIs were TDF/FTC or abacavir/3TC.

Molina JM – DRIVE-FORWARD and DRIVE-AHEAD 192-week Data, Oral Presentation EACS 2021

DRIVE-FORWARD AND DRIVE-AHEAD Week 192 Participant Demographics and Baseline Characteristics

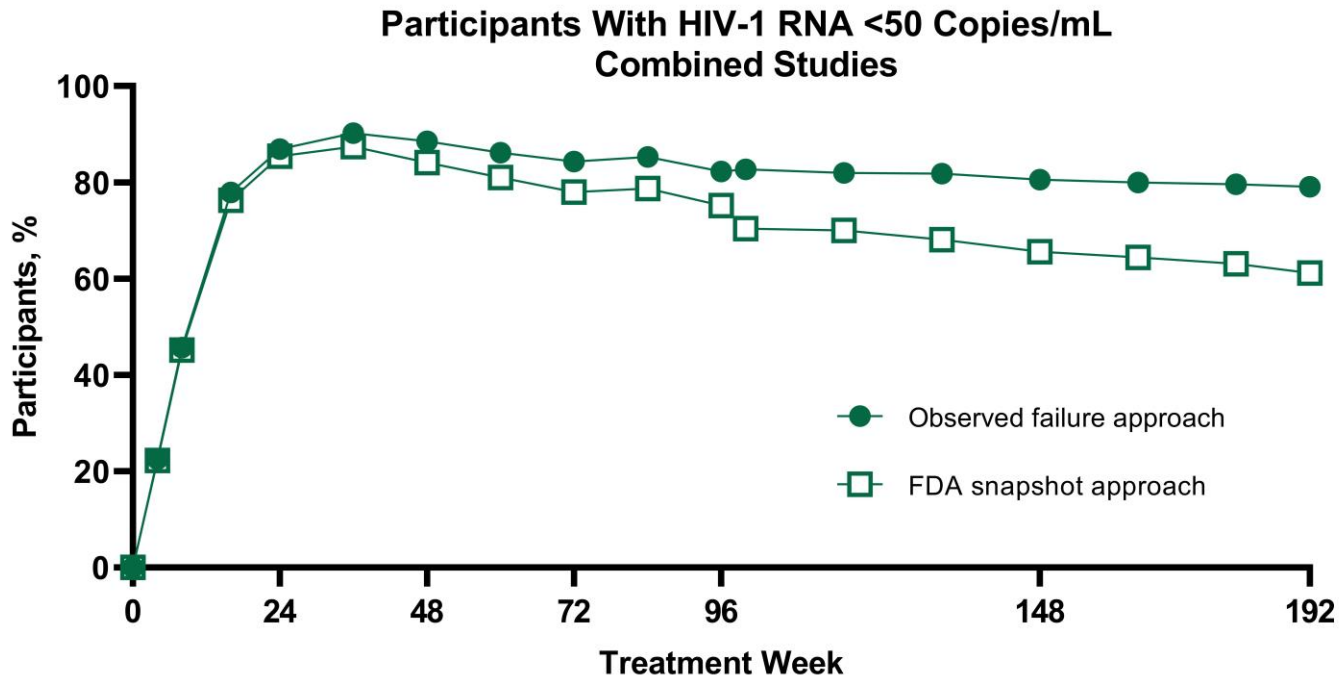
	DRIVE-FORWARD DOR + 2 NRTIs[a] (N =383)	DRIVE-AHEAD DOR/3TC/TDF (N = 364)	Combined Studies (N=747)
Age, median (range), y	33.0 (18, 68)	32.0 (18, 70)	32.0 (18, 70)
Male, n (%)	319 (83.3)	305 (83.8)	624 (83.5)
Race, n (%)			
White	280 (73.1)	176 (48.4)	456 (61.0)
Black or African American	86 (22.5)	68 (18.7)	154 (20.6)
Asian	7 (1.8)	59 (16.2)	66 (8.8)
Other race[b]	10 (2.6)	61 (16.8)	71 (9.5)
TDF included in regimen, n (%)	333 (86.9)	364 (100)	697 (93.3)
Hepatitis B and/or C, n (%)	11 (2.9)	11 (3.0)	22 (2.9)
Plasma HIV-1 RNA			
Median (range), $\log_{10}$ copies/mL	4.4 (2.0, 6.4)	4.4 (2.4, 6.1)	4.4 (2.0, 6.4)
≤100,000 copies/mL, n (%)	300 (78.3)	291 (79.9)	591 (79.1)
CD4+ T-cell counts			
Median (range), cells/mm^3	410.0 (19, 1822)	413.5 (19, 1399)	412.0 (19, 1822)
>200 cells/mm^3 , n (%)	341 (89.0)	320 (87.9)	661 (88.5)

[a]NRTIs were TDF/FTC or abacavir/3TC; [b]Other race includes American Indian, Alaska native, Hawaiian native or Other Pacific Islander and multiracial.

Molina JM – DRIVE-FORWARD and DRIVE-AHEAD 192-week Data, Oral Presentation EACS 2021

DRIVE-FORWARD and DRIVE-AHEAD Week 192 Efficacy Outcomes Through Week 192: DOR Regimen

- At Week 192, HIV-1 RNA <50 copies/mL was maintained in most participants: 79.1% by observed failure approach and 61.2% by FDA snapshot approach
- At Week 192, the mean increase from baseline in CD4+ T-cell count was 236.2 cells/mm^3 (95% CI: 216.8, 255.6)



Observed failure approach, n/N =	638/734	628/710	578/686	559/679	490/608	457/578
FDA snapshot approach, n/N =	638/747	628/747	578/741	559/743	490/747	457/747

Observed failure approach: baseline value was carried forward for virologic failures; other missing values were excluded from analysis; [a]NRTIs were TDF/FTC or abacavir/3TC.

Molina JM – DRIVE-FORWARD and DRIVE-AHEAD 192-week Oral Presentation Data, EACS 2021

PLWH di pratica clinica

Comparing the efficacy and safety of a first line regimen with emtricitabine/tenofovir alafenamide fumarate plus either bictegravir or dolutegravir: results from clinical practice

A. Ciccullo et al. Int J Antimicrob Agents. 2024 Jan;63(1):107040.

Variables	BIC group (n=187)	DTG group (n=140)	p
Age, median (IQR)	42 (33-52)	45 (34-55)	0.088
Male sex, n (%)	149 (79.7)	114 (81.4)	0.351
HIV risk factors: - MSM - Heterosexual - IDUs - Other/Unknown	 84 (44.9) 89 (47.6) 6 (3.2) 8 (4.3)	 70 (50.0) 45 (32.1) 8 (5.7) 17 (12.1)	0.001
CDC stage C, n (%)	34 (18.2)	22 (15.7)	0.461
Median log10 HIV-RNA copies/ml (IQR)	4.97 (4.28-5.51)	5.31 (4.65-5.76)	0.005
Median CD4+ cell at baseline (IQR)	340 (130-553)	120 (30-358)	<0001
Median CD4/CD8 ratio	0.25 (0.09-0.40)	0.17 (0.07-0.23)	0.275
HCV coinfected	4 (2.1)	2 (1.4)	0.351
HBV coinfected	3 (1.6)	1 (0.7)	0.594
Primary infection	12 (6.4)	2 (1.4)	0.517

Results/ Snapshot virological efficacy 6m

- At 6 months, among PLWHIV with available exams, 85.7% of individuals in the DTG group and 87.2% of those in the BIC group achieved a HIV-RNA below 50 copies/mL.

- **Considering those achieving TND at 6 months, 39% of those with DTG vs 13% of those in the BIC group (p<0.001).**

- *Starting BIC (vs DTG) was significantly associated with a lower probability of achieving TND after 6 months (OR 0.23, 95%CI 0.12-0.45, p<0.001)*

- In the BIC group, starting with a higher CD4+ cell count was associated with higher probability of TND after 6 months (per 100 cell more, B 0.3, aHR 1.01, p=0.022)

Results/ Snapshot virological efficacy 12m

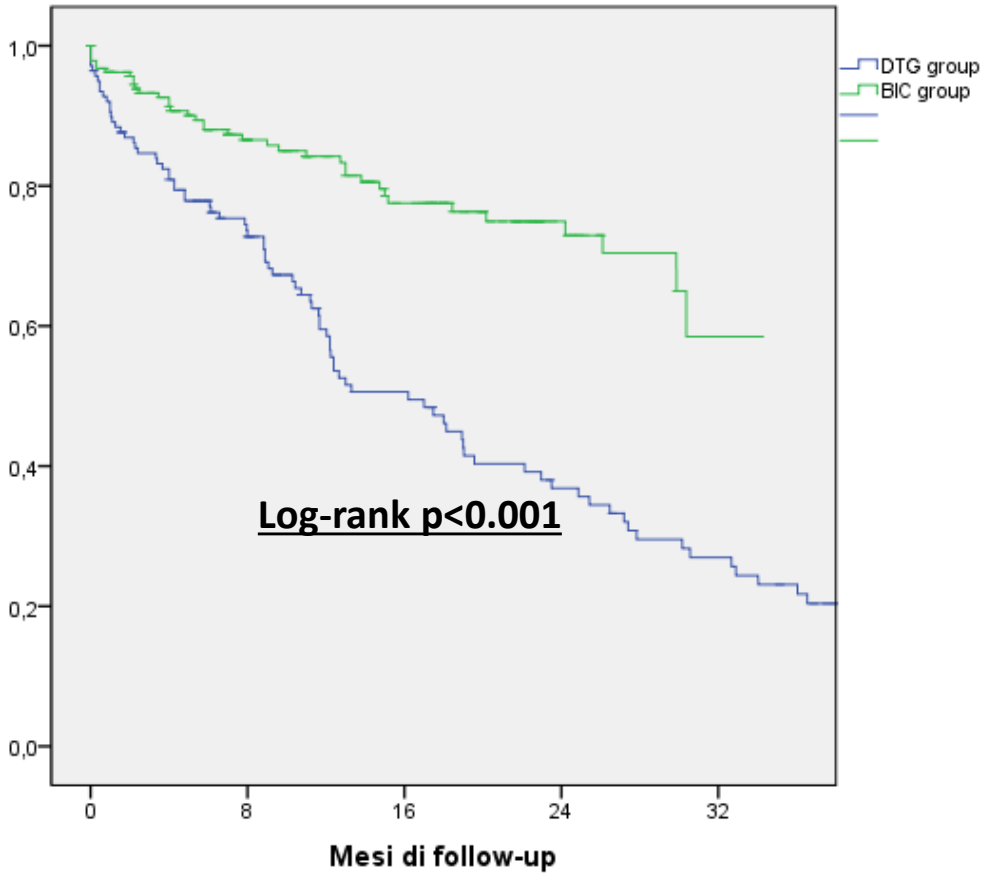
- At 12 months, 90.0% of individuals in the DTG group and 86.7% of those in the BIC group achieved a HIV-RNA below 50 copies/mL.

- **Considering those achieving TND at 12 months, 54% of those with DTG vs 17% of those in the BIC group (p<0.001).**

- *Starting BIC (vs DTG) was significantly associated with a lower probability of achieving TND after 12 months (OR 0.18, 95%CI 0.09-0.34, p<0.001)*

- In the BIC group, starting with a higher CD4+ cell count was associated with higher probability of TND after 12 months (per 100 cell more, B 0.6, aHR 1.01, p=0.001)

Results/TD

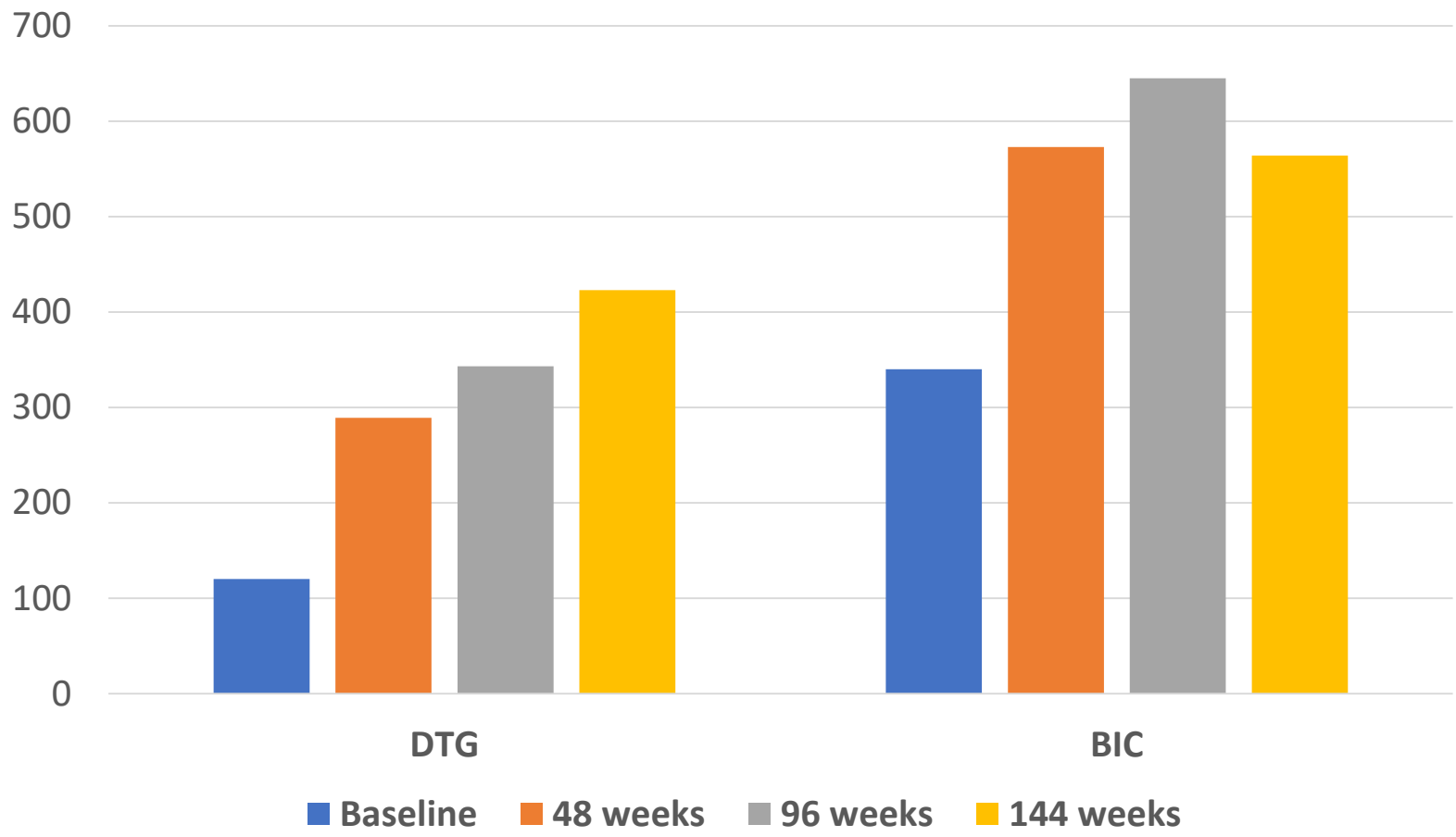


We observed 88 TD in the DTG group and 38 in the BIC group.

In the **DTG** group, main reasons for TD were: **switch to STR/2DR in 36% of PLWHIV**, CNS toxicity (5.0) and death (4.3).

In the **BIC** group main reasons were: switch to 2DR (11.3), Hypersensitivity (2.1), NON-CNS toxicity (2.1)

Results/Immunological



Comparing the efficacy and safety of dolutegravir+lamivudine vs bictegravir/emtricitabine/tenofovir alafenamide fumarate as first-line regimens in clinical practice

A. Ciccullo. Personal DATA

- Studio di pratica clinica su PLWHIV naive che hanno iniziato all’interno della coorte una terapia di prima linea con BIC/FTC/TAF o DTG/3TC

- Sono stati analizzati 44 pazienti, 22 per gruppo

Variables	Overall (n=44)	DTG group (n=22)	BIC group (n=22)	P
Males, n (%)	33 (75.0)	17 (77.3)	16 (72.7)	0.500
Years of age, median (IQR)	44 (31-56)	35 (25-53)	50 (36-57)	0.035
AIDS-defining event at diagnosis, n (%)	8 (18.2)	0	8 (36.4)	0.002
Anti-HCV antibodies, n (%)	0	0	0	/
HBV-coinfection, n (%)	0	0	0	/
Peak HIV-RNA, log10 copies/ml, median (IQR)	4.97 (4.61-5.33)	4.77 (4.38-4.99)	5.27 (4.97-5.86)	<0.001
Nadir CD4+ cell count, cell/mm3, median (IQR)	246 (89-417)	328 (243-460)	97 (43-268)	0.001
Baseline CD4/CD8 ratio, median (IQR)	0.34 (0.15-0.51)	0.45 (0.33-0.74)	0.21 (0.09-0.41)	0.009

Risultati

- In un tempo di osservazione cumulativo di 52 PYFU abbiamo osservato 1 FV nel gruppo DTG e 2 nel gruppo BIC; tutti sono stati correlati a aderenza subottimale e tutti e 3 i pazienti hanno ottenuto la soppressione virologica nelle settimane successive.

- **Nel gruppo BIC, la probabilità di risultare virologicamente soppressi a 12 mesi è risultata essere del 91% vs il 95% del gruppo DTG (log-rank 0.643).**

- Per quanto concerne le interruzioni dei regimi, abbiamo osservato 1 sola interruzione di DTG-3TC dovuta ad intolleranza gastrointestinale.

Risultati

- Dal punto di vista immunologico, i pazienti nel gruppo DTG hanno mostrato un incremento significativo della conta dei CD4+ sia a 6 mesi (+89 cell/mm3, p=0.001) che a 12 mesi (+203 cell/mm3, p=0.001); similmente il gruppo BIC ha mostrato un incremento significativo della conta dei CD4+ sia a 6 mesi (+115 cell/mm3, p=0.001) che a 12 mesi (+218 cell/mm3, p=0.001).

- L'incremento nel gruppo DTG è risultato più pronunciato nei pazienti più giovani (per ogni anno d'età in più, +6.6 cell/mm3, p=0.030).

- Entrambi i gruppi hanno inoltre mostrato un incremento del rapporto CD4/CD8 a 12 mesi: +0.20 (p=0.001) per il gruppo BIC vs +0.31 (p=0.005) per il gruppo DTG.

Conclusioni

- Nella pratica clinica della nostra coorte multicentrica, sia DTG/3TC che BIC/FTC/TAF si sono dimostrati regimi efficaci e sicuri, con incrementi significativi dei parametri immunologici.

- Le differenze nei due gruppi sono evidentemente dovuti alle differenti indicazioni delle linee guida.

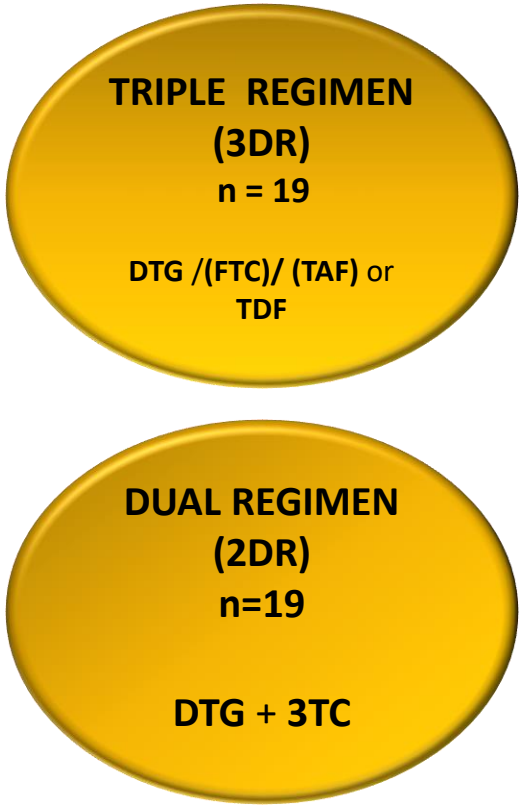
- Avere a disposizione regimi così efficaci e tollerabili in tutte le classi di pazienti naive al trattamento rappresenta un’arma fondamentale per i clinici, in particolare in periodi di difficile accesso al trattamento come durante la pandemia.

HIV-DNA DECAY IN ART-NAIVE PATIENTS STARTING DOLUTEGRAVIR PLUS LAMIVUDINE VS TRIPLE THERAPY

F. Lombardi et al. Infez Med 2020 Sep 1;28(3):461-463

METHODS

- Prospective and longitudinal study
- Total blood associated HIV-DNA as a marker of viral reservoir
- Quantification of total blood-associated HIV-DNA by droplet digital PCR, home-made protocol targeting the HIV-1 LTR region.
  Detecion limits : 32 copies/10^6 leukocytes
- Quantification at two time points:
  I. Before starting therapy (baseline, **BL**)
  II. Virological success (**VS**) (HIV-RNA < 50 copies/mL)
- Results expressed as $\log_{10}$ HIV-DNA copies/10^6 leukocytes.

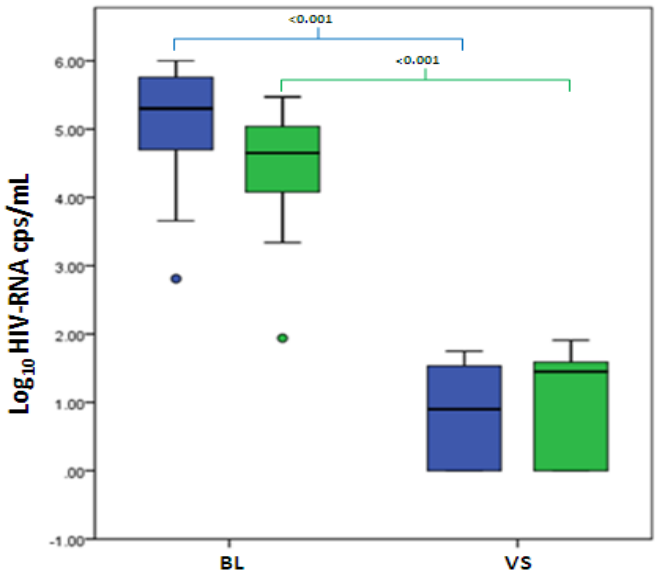


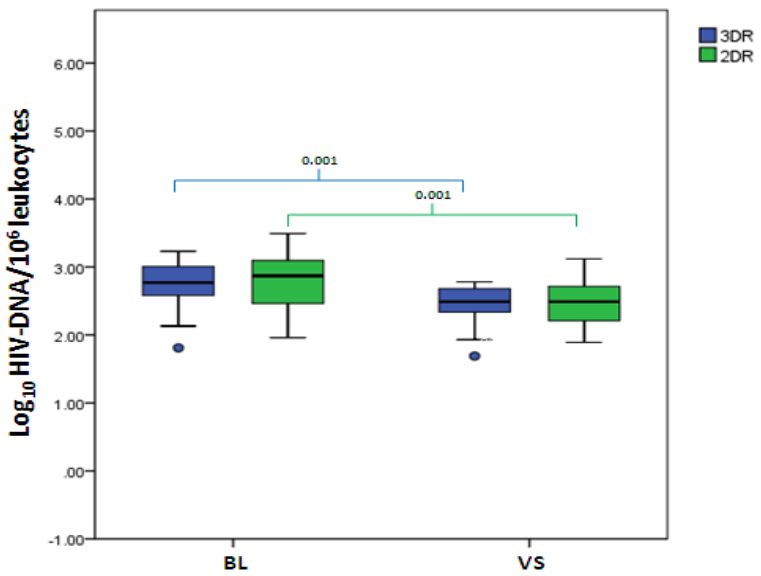
Results

BL characteristics

	3DR n=19	2DR n=19	p
Male gender, n (%)	17 (89.5)	17 (89.5)	1.000
Age, median (IQR) years	39.2 (32.1-47.5)	31.3 (23.2-39.3)	0.053
Caucasian, n(%)	16 (84.2)	14 (73.7)	0.426
Risk factor			0.475
Homo/bi-sexual	12 (63.2)	14 (73.7)	
Heterosexual	6 (31.6)	3 (15.8)	
Unknown	1 (5.3)	2 (10.5)	
HIV Subtype			0.234
B	9 (47.4)	6 (31.6)	
non-B	4 (21.1)	7 (36.8)	
Unknown	6 (31.6)	6 (31.6)	
CD4 count, median (IQR) cells/mm^3	251 (77-421)	397 (247-516)	0.061
CD8 count, median (IQR) cells/mm^3	908 (510-1351)	805 (624-960)	0.234
CD4/CD8, median (IQR)	0.24 (0.12-0.29)	0.47 (0.34-0.6)	**<0.001**
HIV-RNA, median (IQR), Log$_{10}$ copies/mL	5.3 (4.4-5.8)	4.6 (3.9-5.1)	**0.013**
HIV-DNA/10^6 leukocytes BL, median (IQR), Log$_{10}$ copies	2.77 (2.58-3.02)	2.90 (2.36-3.15)	0.795
CDC stage C, n (%)	5(26.3)	0 (0)	**0.008**
Starting first-line therapy within two months from HIV diagnosis, n (%)	16 (84.2)	16 (84.2)	1.000

HIV-RNA and HIV-DNA decay at BL and VS





	3DR n=19	2DR n=19	p
Time to virological success, median (IQR) days	64 (29-135)	55 (30- 125)	0.916
HIV-RNA, median (IQR), Log_{10} copies/mL	0.90 (0.00-1.59)	1.44 (0.00-1.62)	0.840
Delta Log HIV-RNA VS-BL, median (IQR)	-4.23 (-5.15 - (-3.48))	-3.62 (-3.9-(-3.09)	0.057
HIV-RNA, n(%)			0.516
Undetectable (0 copy/mL)	8 (42.1)	10 (52.6)	
Detectable (<50 copies/mL)	11 (57.9)	9 (47.4)	
HIV-DNA/10^6 leukocytes, median (IQR), Log_{10} copies	2.49 (2.25-2.69)	2.48 (2.19-2.72)	0.977
Delta log HIV-DNA VS-BL, mean (SD)	-0.27 (-0.48-(0.06))	-0.27 (-0.55-(0.04))	0.863
CD4 count, median (IQR) cells/mm^3	276 (236-624)	590 (362-661)	**0.025**
CD8 count, median (IQR) cells/mm^3	939 (687-1257)	905 (631-1134)	0.795
CD4/CD8, median (IQR)	0.35 (0.28-0.46)	0.65 (0.44-0.78)	**0.010**

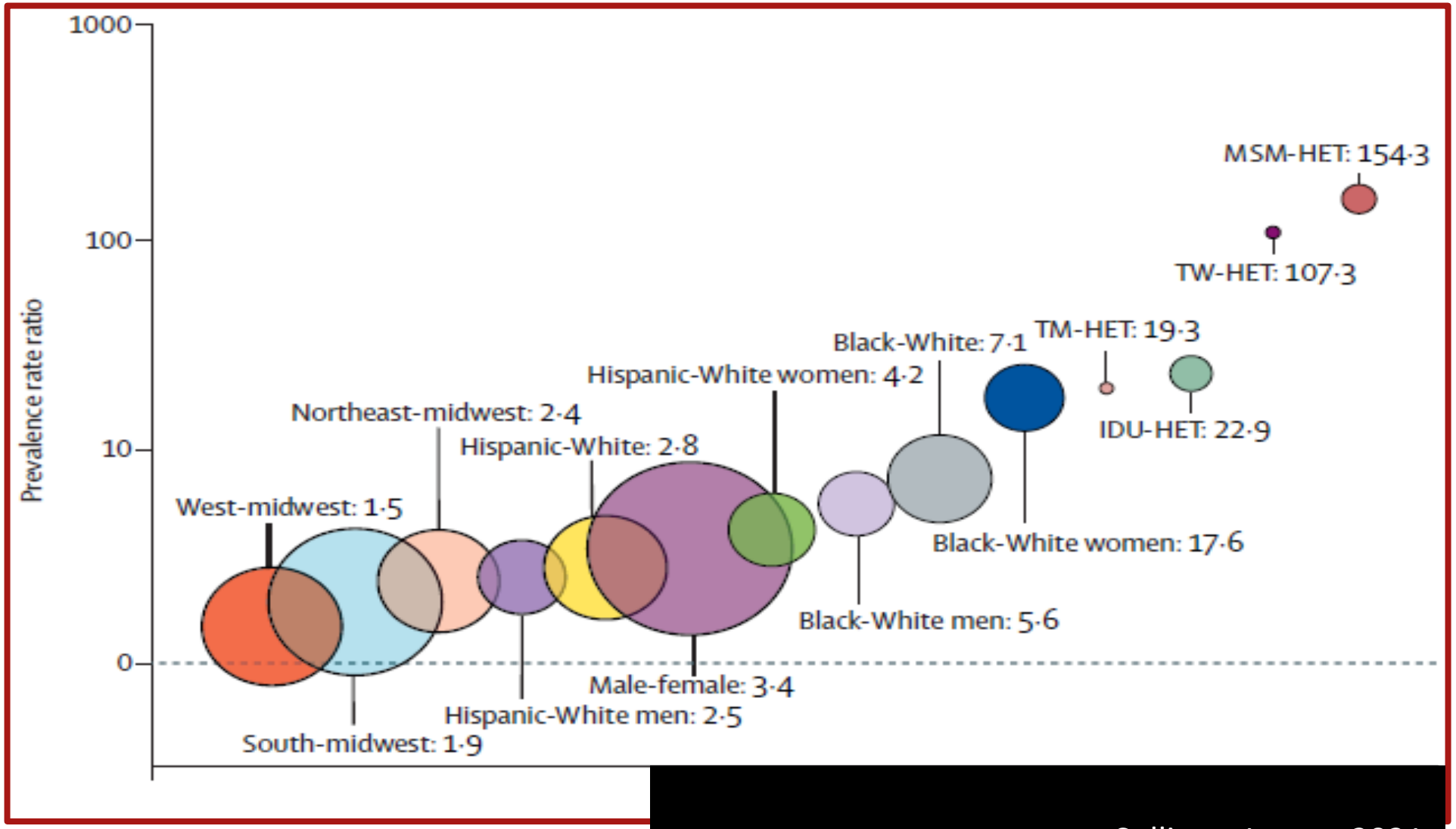
CONCLUSIONS

- Significantly HIV-DNA levels reduction at VS, which reached a comparable level between groups, and with a similar delta change At VS, HIV-DNA decay was similar in both groups
- At VS, both CD4 cells and CD4/CD8 ratio maintained higher levels in 2DR than 3DR
- Time to reach VS was similar between groups
- Direct correlation between BL HIV-RNA and BL HIV-DNA levels was observed
- There was no correlation between variables and HIV-DNA decay

Starting a DTG+3TC dual regimen did not show differences regarding the HIV-DNA dynamics as compared to starting a DTG-triple regimen in this clinical practice setting.
Our results add important new data that support the effectiveness of this approach on the cellular reservoir, which needs to be confirmed in larger cohorts.

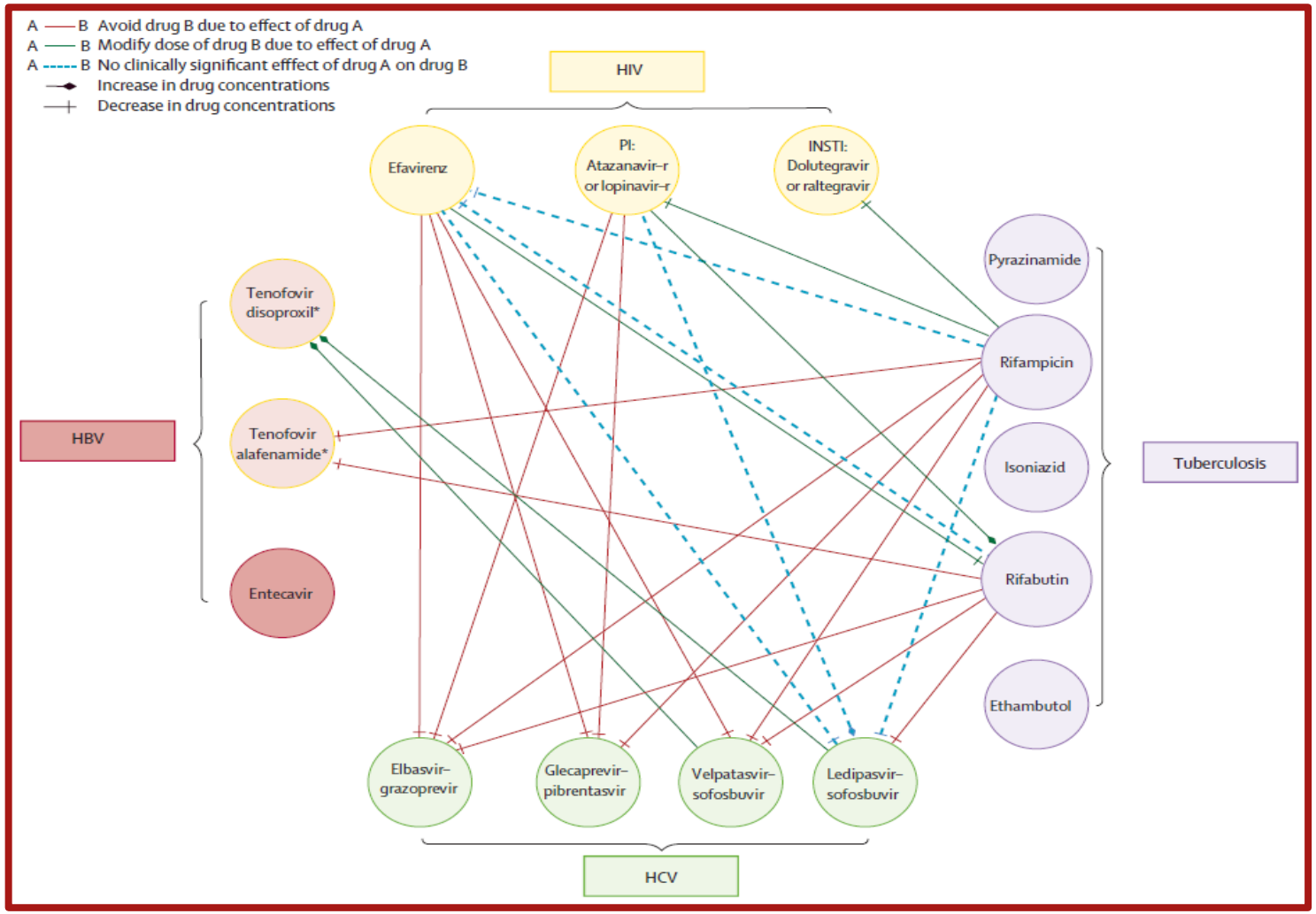
PLWH late presenter

Magnitude of disparity in USA



Sullivan, Lancet 2021

Complexities in the treatment of coinfection



U Arora, Lancet Infect Dis 2020

Open Forum Infectious Diseases

MAJOR ARTICLE

Advanced HIV Infection in Treatment-Naïve Individuals: Effectiveness and Persistence of Recommended 3-Drug Regimens

Karam Mounzer,[1] Laurence Brunet,[2] Jennifer S. Fusco,[2] Ian R. Mcnicholl,[3] Helena Diaz Cuervo,[4] MichaelEnsion,[5] Lewis Mccurdy,[6] and Gregory P. Fusco[2]

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- **The PWH included in this study were ART-naïve, at least 18 years of age, and had advanced HIV infection, defined as a CD4 cell count <200 cells/µL at the time of ART initiation between January 1, 2018, and July 31, 2019.**

Study population: 961 PWH

Table 1. Baseline Demographic and Clinical Characteristics

	B/F/TAF n = 416	bDRV n = 106	DTG n = 271	EVG/c n = 168
Age, median (IQR), y	36 (29–46)	35 (27–46)	36 (28–45)	37 (28–47)
Female, No. (%)	85 (20)	19 (18)	46 (17)	34 (20)
Black race, No. (%)	257 (62)	67 (63)	170 (63)	116 (69)
CD4 cell count, median (IQR), cells/µL	87 (33–155)	94 (30–151)	93 (38–153)	91 (26–145)
CD4 ≤50 cells/µL, No. (%)	151 (36)	35 (33)	82 (30)	64 (38)
Log_{10} viral load, median (IQR), copies/mL	5.3 (4.8–5.7)	5.4 (4.8–5.7)	5.3 (4.7–5.7)	5.2 (4.8–5.7)
Viral load ≥100 000 copies/mL, No. (%)	257 (62)	72 (68)	178 (66)	100 (60)
Hepatitis B coinfection, No. (%)	19 (5)	10 (9)	19 (7)	19 (11)
Single-tablet regimen, No. (%)	416 (100)	26 (25)	140 (52)	168 (100)
eGFR ≥90 mL/min/1.73 m^2, No. (%)	363 (87)	84 (79)	231 (85)	135 (80)

Abbreviations: B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bDRV, boosted darunavir; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat; IQR, interquartile range.

Open Forum Infectious Diseases
MAJOR ARTICLE

Advanced HIV Infection in Treatment-Naïve Individuals: Effectiveness and Persistence of Recommended 3-Drug Regimens

Karam Mounzer,[1,2] Laurence Brunet,[3a] Jennifer S. Fusco,[3,a] Ian R. Mcnicholl,[3] Helena Diaz Cuervo,[4] Michael Sension,[5] Lewis Mccurdy,[4] and Gregory P. Fusco[2,6]

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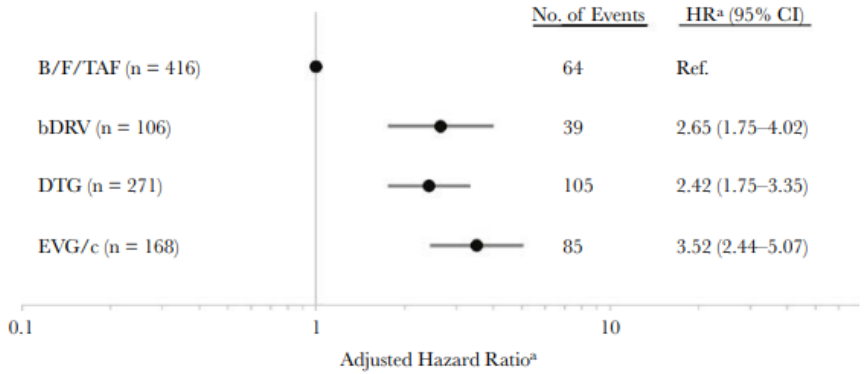


Figure 1. Adjusted[a] association between regimen and regimen discontinuation. [a]Estimated with a Cox proportional hazards model with stabilized inverse probability of treatment weights, controlling for baseline sex, Black race, hepatitis B, index year, age, CD4 cell count, and viral load. Abbreviations: B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bDRV, boosted darunavir; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat; HR, hazard ratio.

BIC: Out of 64 B/F/TAF discontinuers, no reason for discontinuation could be identified among 56%; a treatment-related reason (ie, unsuppressed at discontinuation or unfavorable event) was identified among 14%; the remaining 30% discontinued for other reasons (drug holiday, provider choice).

DRV: Out of 39 PWH who discontinued bDRV, 23% had no identifiable reason for discontinuation, 41% had a treatment-related reason, and 36% had another reason identified (simplification, drug holiday, patient/provider choice).

DTG: Out of 105 DTG discontinuers, 41% had no identifiable reason, 24% had a treatment-related reason, and 35% had another reason for discontinuation (simplification, access issues, drug holiday, provider choice).

Immunological recovery in PLWHIV starting dolutegravir plus lamivudine as first-line regimen: data from the ODOACRE cohort

Ciccullo A et. Poster Presentation ICAR 2022

Patients & Methods

Aim of the study was to confirm, in a real-life setting, the results of the GEMINI clinical trials evaluating the efficacy of DTG+3TC in treatment-naïve PLWHIV

Data from a **multicenter** cohort of **treatment-naïve PLWHIV** starting a first-line regimen with **DTG+3TC**, evaluating the virological efficacy and the immunological recovery.

Variables	N=45
Age (years), Median (IQR)	34 (28-50)
Males, n (%)	38 (84.4)
Risk factor for HIV infection, n (%): **- Heterosexual** **- MSM** **- IDU** **- Others**	 8 (17.8) 28 (62.2) 2 (4.4) 7 (15.6)
Anti-HCV antibodies positive, n (%)	0
CDC stage C, n (%)	0
CD4+ count (cell/μL), Median (IQR)	394 (293-508)
CD4/CD8 ratio, Median (IQR)	0.48 (0.38-0.68)
HIV-RNA (log10 copies/mL), Median (IQR)	4.61 (4.23-4.97)

Results/1

During a cumulative time of 64.67 Patient-Years of Follow-Up, we did not observe any adverse event leading to treatment discontinuation in our cohort.

All patients achieved virological suppression within a year from treatment initiation and maintained viral suppression during follow-up time with no viral blips registered.

At baseline, none of the analyzed PLWHIV presented resistance mutations to 3TC; interestingly 7 PLWHIV presented minor mutations in the integrase region.

Results/2

Figure 1. Median CD4+ cell count at the 3 timepoints.

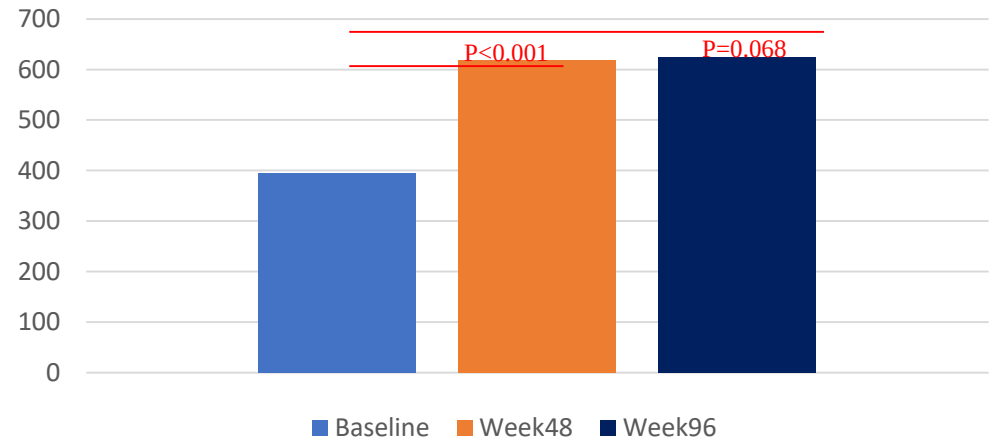
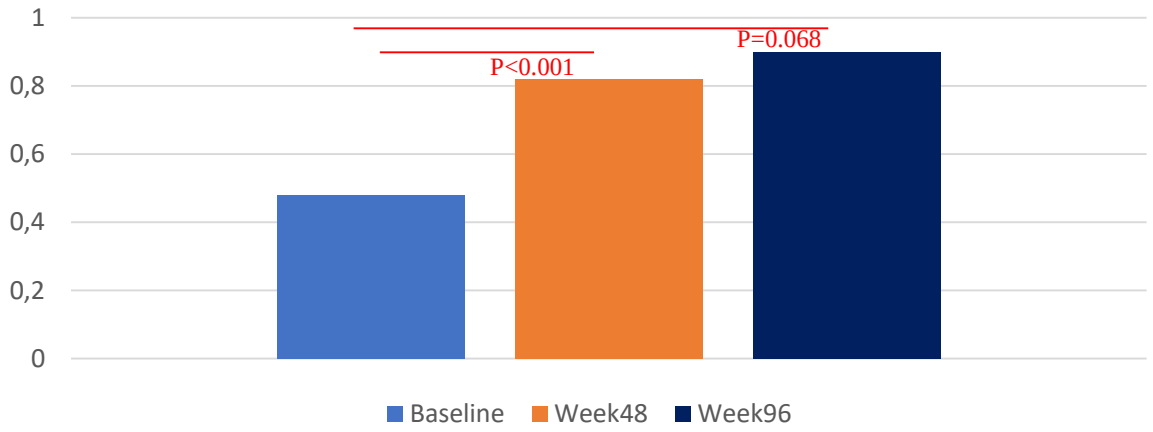


Figure 2. Median CD4/CD8 ratio at the 3 timepoints.



Regarding immunological parameters, we registered a significant improvement in both absolute CD4+ cell count (median increase +224 cell/mm3, p<0.001) and CD4/CD8 ratio (median increase +0.34, p<0.001) at week 48.

Moreover, we observed an improving trend in CD4+ cell count (median +230, p=0.068) and CD4/CD8 ratio (median +0.42, p=0.068) at week 96, although non-significant.

PLWH in corso di PrEP

Initial Combination Regimen for ART-naive Adults

Before selecting an ART regimen, it is critical to review:

- If a woman **wishes to conceive or is pregnant**: Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy
- If the person has an **opportunistic infection**: Initiation of ART regimen in persons with opportunistic infections
- If the person has **TB**: Antiretroviral regimens in TB/HIV co-infection
- If the person has potential **treatment limiting comorbidities**: Comorbidity section, dose adjustment for renal and liver impairment
- If the person is treated with **other medications**: Drug-drug interactions
- If the person has **Swallowing Difficulties:** Administration of ARVs in persons with swallowing difficulties
- If the person has **acquired HIV while on regular PrEP intake**: In this situation, change PrEP to a triple-drug ART regimen including a third drug with a high barrier to resistance (preferably, DTG, BIC or alternatively DRV/b) plus TDF/XTC without interrupting antiretrovirals. The danger of acute seroconversion syndrome and higher infectiousness would be arguments for immediate switch to triple therapy. ART should be adjusted if more extensive resistance is demonstrated by genotypic resistance analysis

- Only drugs currently licensed for initiation of therapy by the EMA are included (in alphabetical order)
- Recommended regimens should be considered first and are preferable for most persons. Antiretroviral drugs in the Recommended category provide a combination of essential characteristics for an optimal treatment such as long-term efficacy, barrier to resistance, safety, tolerability and few drug-drug interactions. Alternative regimens should be considered if recommended regimens are not feasible
- An increasing number of generic HIV drugs are now available, and their use can lead to large cost savings. The use of generic forms of drugs included in recommended regimens should therefore be encouraged, even if single tablet regimens are not used, as recent studies have shown similar virologic outcomes in ART-naive persons receiving either a single pill or two pills qd
- Tailoring antiretroviral regimens for each individual is essential in the presence of resistance
- For a wider review of possible drug-related adverse events, please see: Adverse Effects of ARVs and Drug Classes

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

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

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. Choice of ART during pregnancy should be guided by recommendations from the Perinatal Guidelines.

For people who do not have a history of CAB-LA use as PrEP, the following regimens are recommended:

INSTI plus Two NRTIs

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

INSTI plus One 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

For people with HIV and a history of CAB-LA use as PrEP, INSTI genotypic resistance testing should be performed before the start of ART. If treatment is begun prior to results of genotypic testing, the following regimen is recommended:

- DRV/c[b] or DRV/r with (TAF or TDF)[c] plus (FTC or 3TC)—pending the results of the genotype test **(AIII)**

Correspondence

Antiretroviral resistance and management after pre-exposure to prophylaxis

The Lancet HIV, Volume 8, Issue 3, March 2021, Pages e166-e174

	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

- 20 (91%) of 22 patients with previous PrEP use initiated antiretrovirals with a median time to treatment of 10 days (range 0–159).

- 3 months after starting antiretrovirals, **17 (85%) of these 20 patients were retained in care, of which 16 (94%) of the 17 patients retained in care had a viral load less than 200 copies per mL**.

- 16 (94%) of the 17 patients initiated a treatment backbone of tenofovir disoproxil fumarate and emtricitabine; one (6%) patient started on abacavir and lamivudine.

- Regarding third agent HIV medications, 11 (65%) were treated with darunavir and cobicistat, two (12%) with raltegravir, two (12%) with dolutegravir, one (6%) with darunavir and ritonavir, and one (6%) with raltegravir, darunavir, and cobicistat.

- for individuals with a newly diagnosed HIV infection and previous use of PrEP, management should consider the 23% emtricitabine resistance (and potentially up to 26%) and the higher proportion of genotypic resistance tests that did not amplify in this population. The lower proportion of genotypic resistance tests that amplified in this group might be due to a lower baseline HIV viral load. Even so, **we showed that HIV viral load suppression is achievable in this subgroup of HIV patients**.

Of 10 356 people with a new HIV diagnosis

4246 (40%) had an available genotype obtained within 30 days of diagnosis

Among them, 560 (13%) had AHI diag- nosed, 98 (2%) had the M184I/V mutation, 5 (0.1%) had the K65R mutation, and 2 (0.1%) had both.

PREP e ARV nel futuro:

-ruolo rapid ARV

-ruolo 2DR nel naive

Clinical Infectious Diseases

MAJOR ARTICLE

Preexposure Prophylaxis Use History in People With Antiretroviral Resistance at Human Immunodeficiency Virus (HIV) Diagnosis: Findings From New York City HIV Surveillance and Partner Services, 2015–2022

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Bureau of Hepatitis, HIV and STIs, New York City Department of Health and Mental Hygiene, Queens, New York, USA

Background. Drug resistance may be acquired in people starting human immunodeficiency virus (HIV) preexposure prophylaxis (PrEP) during undiagnosed infection. Population-based estimates of PrEP-related resistance are lacking.

Methods. We used New York City surveillance and partner services data to measure the effect of PrEP use (tenofovir disoproxil fumarate/tenofivir alafenamide fumarate with emtricitabine) history on the baseline prevalence of M184I/V mutations in people with HIV diagnosed in 2015–2022. PrEP use was categorized as "recent" (defined as PrEP stopped ≤90 days before diagnosis), "past" (PrEP stopped >90 days before diagnosis), or "no known use." Resistance-associated mutations were determined using the Stanford algorithm. We used log binomial regression to generate the adjusted relative risk (aRR) of M184I/V by PrEP use history in people with or without acute HIV infection (AHI).

Results. Of 4246 people with newly diagnosed HIV and a genotype obtained within ≤30 days of diagnosis, 560 (13%) had AHI; 136 (3%) reported recent and 124 (35%) past PrEP use; and 98 (2%) harbored M184I/V. In people with AHI, recent PrEP use was associated with a 6 times greater risk of M184I/V than no known use (aRR, 5.86 [95% confidence interval, 2.49–13.77]). Among people without AHI, the risk of M184I/V in recent users was 7 times that in people with no known use (aRR, 7.26 [95% confidence interval, 3.98–13.24]), and in past users, it was 4 times that in those with no known use (4.46 [2.15–9.24]).

Conclusions. PrEP use was strongly associated with baseline M184I/V in New York City, regardless of AHI status. Ordering a nucleic acid test when indicated after assessment of exposure, antiretroviral history, and AHI symptoms can decrease PrEP initiation in people with undetected infection.

Keywords. HIV; preexposure prophylaxis; drug resistance; resistance associated mutations; United States.

Grazie per l’attenzione