10° WORKSHOP NAZIONALE CISAI

MILANO

PREVENZIONE E GESTIONE DELLE CO-MORBIDITÀ ASSOCIATE ALL'INFEZIONE DA HIV

PRESIDENTI
PAOLO BONFANTI
ANTONIO DI BIAGIO

30 SETTEMBRE
1 OTTOBRE
2021

CISAI

FONDAZIONE ASIA

Duplice o triplice terapia: meno farmaci, meno effetti collaterali?

Simona Di Giambenedetto

CISAI
FONDAZIONE ASIA

Disclosures

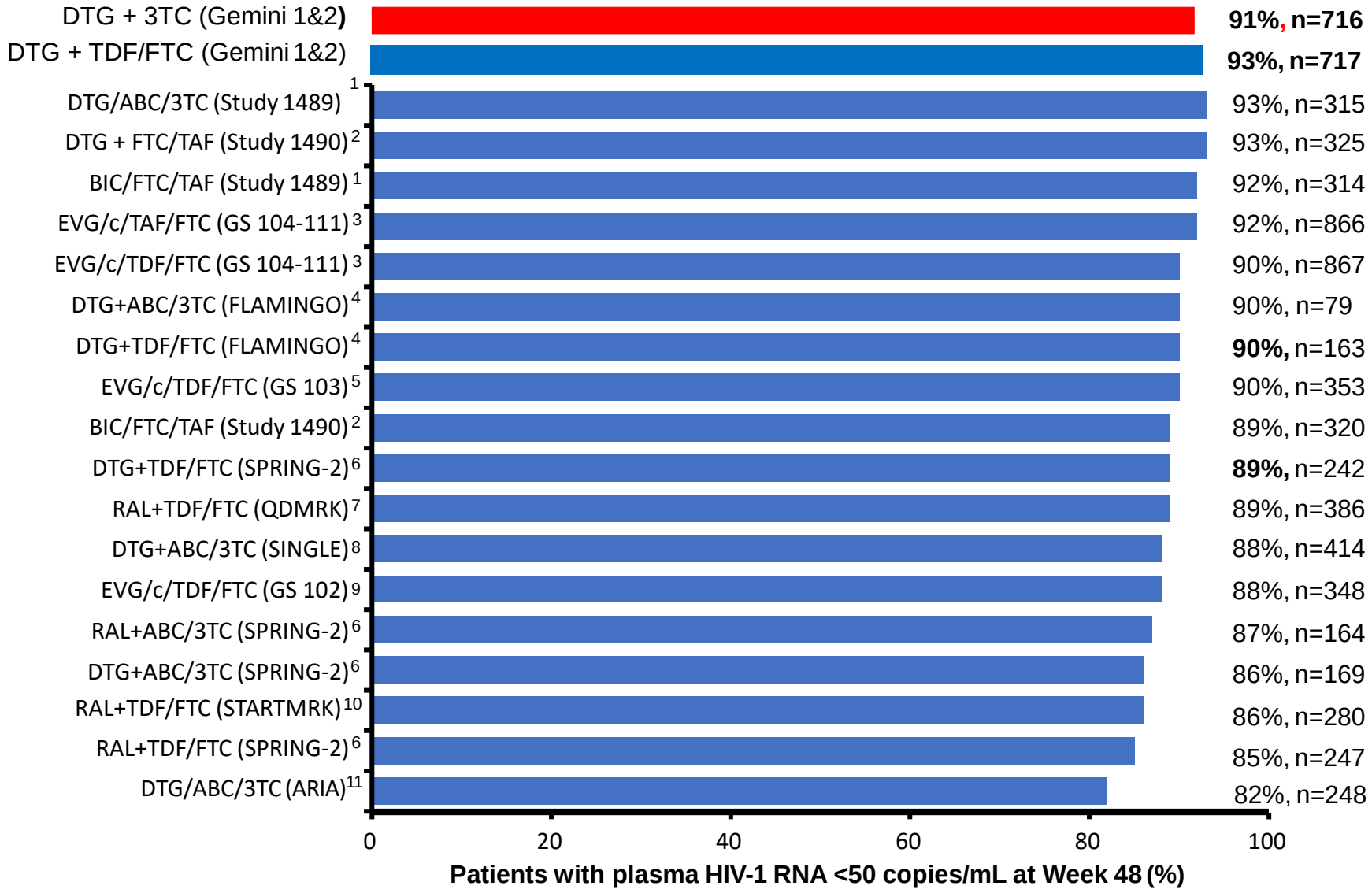
I have received funding for Advisory Boards, Speaker Panels and for preparation of educational materials from the following:

Gilead Sciences
ViiV Healthcare
Janssen-Cilag
Merck Sharp & Dohme

Strategie per successo della terapia ARV

- Iniziare bene…e presto
- Farmaci con alta efficacia e tollerabilità
- TERAPIA PERSONALIZZATA

Modern HIV Therapy: Progress and Prospects



COMPARATIVE EFFICACY AND SAFETY OF A COMBINATION THERAPY OF DOLUTEGRAVIR AND LAMIVUDINE VS 3-DRUG ANTIRETROVIRAL REGIMENS IN TREATMENT-NAIVE HIV-1 INFECTED PATIENTS AT 96 WEEKS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Katharina Nickel,[1] Nicholas J. Halfpenny,[2] Sonya J. Snedecor,[3] Yogesh Suresh Punekar[4]

[1]Pharmerit International, Berlin, Germany; [2]Pharmerit International, Rotterdam, the Netherlands; [3]Pharmerit International, Bethesda, MD, USA;

23rd International AIDS Conference; July 6-10, 2020; Virtual

Introduction

- Traditional antiretroviral therapy for patients living with HIV (PLHIV) includes combinations of 3 or more antiretroviral drugs (ARVs). Recent arrival of the 2-drug regimen (2DR) of DTG+3TC has demonstrated non-inferiority to 3-drug regimens (3DRs) in treatment-naive PLHIV up to Week 96 in the GEMINI-1 and GEMINI-2 studies.

- A previous Network Meta-analysis (NMA) showed DTG+3TC having comparable efficacy and safety to the guideline-recommended 3DRs at Week 48[1]
- The objective of this analysis was to evaluate efficacy and safety of DTG+3TC compared to standard of care 3DRs up to Week 96 in treatment-naive PLHIV

1. Radford M et al. AIDS. 2019;33:739-1749.

Nickel et al. AIDS 2020: Virtual. Poster PDB0104.

Methods

Systematic Literature Review

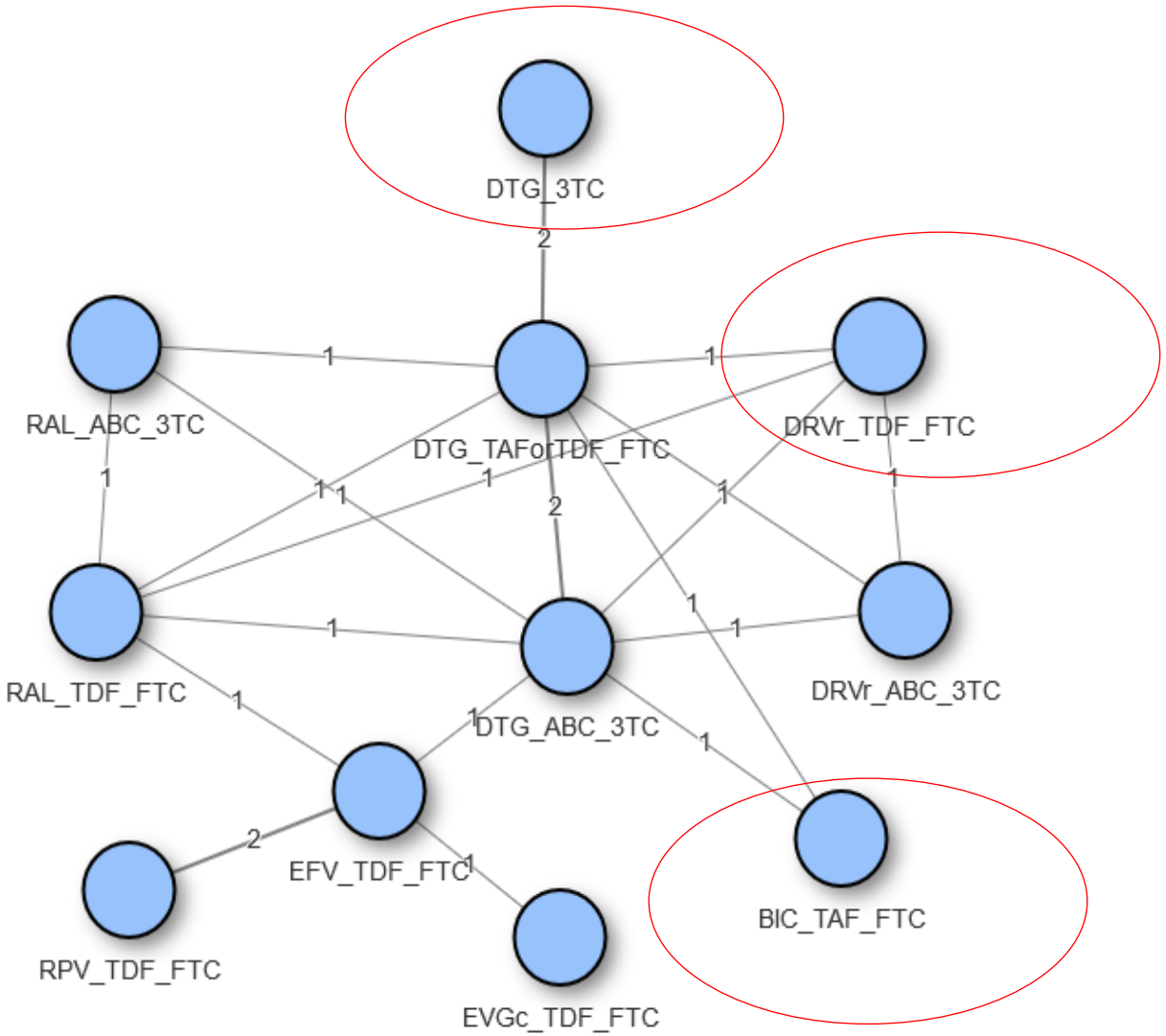
- The previously published SLR was updated on July 19, 2019, using PubMed, Embase and Cochrane databases to identify Phase 3/4 RCTs evaluating the efficacy and/or safety of DTG+3TC vs. guideline-recommended 3DRs among treatment-naive adult or adolescent (≥13 years) PLHIV[1]
- Regimens of interest were core agents recommended by DHHS or EACS guidelines[2,3]

Endpoints and Statistical Analysis

- Endpoints included in efficacy analyses were virologic suppression, defined as proportion of subjects with HIV-1 RNA ≤50 copies/mL and CD4 cell change, defined as mean CD4 cell change from baseline after initiating therapy
- Endpoints included in the safety analysis were discontinuation rates, adverse events (AEs), drug-related AEs and serious AEs. Safety endpoints were reported as odds ratios

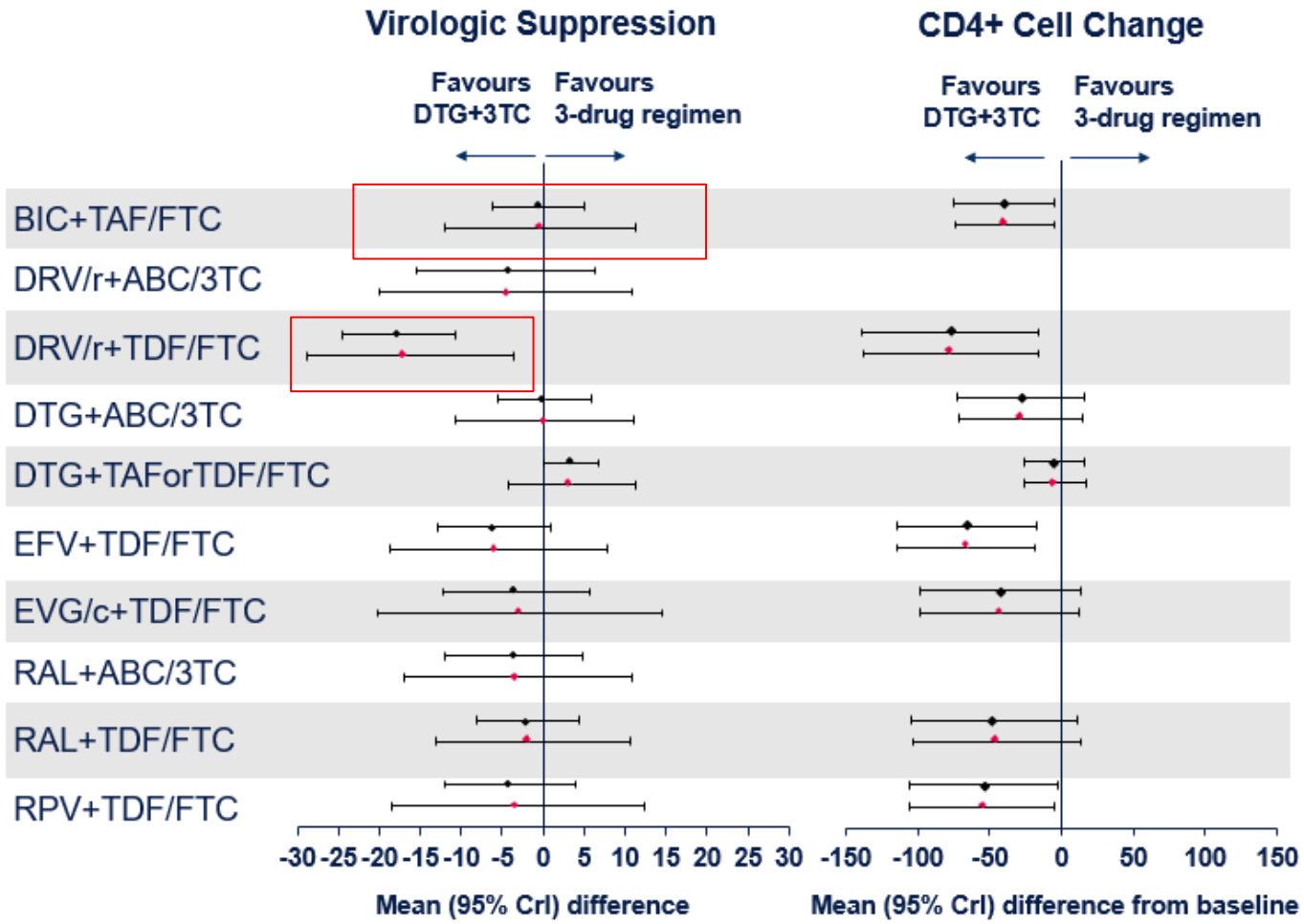
1. Radford M et al. *AIDS*. 2019;33:1739-1749. **2.** DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC). Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2019. **3.** European AIDS Clinical Society. Guidelines, Version 10.0. 2019.

Network of Studies



Nickel et al. AIDS 2020: Virtual. Poster PDB0104.

Efficacy Endpoint Results for NMA Week 96



Fixed effects model is represented first, with a black filled symbol. Random effects model is represented below, with a red filled symbol. Error bars represent 95% credible intervals.

Nickel et al. AIDS 2020: Virtual. Poster PDB0104.

Efficacy Results

- **Virologic suppression (VS)** achieved by DTG+3TC was superior to DRV/r+TDF/FTC and comparable to other 3DRs. The probability of DTG+3TC achieving better VS ranged from 2.5% with DTG+TAForTDF/FTC to 95.4% with EFV+TDF/FTC

- Stratified by baseline viral load of >100,000 RNA copies/mL and ≤100,000 RNA copies/mL or CD4 >200 cells/µL and ≤200 cells/µL, DTG+3TC was broadly comparable to all the 3DRs also reporting those subgroup data with some significant differences

- **Mean CD4 cell changes** with DTG+3TC were statistically significantly higher from baseline when compared to BIC+TAF/FTC, DRV/r+TDF/FTC, EFV+TDF/FTC and RPV+TDF/FTC. DTG+3TC was otherwise comparable with all other regimens

Nickel et al. AIDS 2020: Virtual. Poster PDB0104.

Triplice e duplice nel paziente naive

Cosa si intende per Rapid-ART

- Con il termine di Rapid-ART si intende un intervento sanitario che porti ad un inizio rapido della terapia antivirale in soggetti sieropositivi, idealmente prima dei risultati degli esami ematochimici classici (genotipo HIV, HLA, viremia e conta CD4+).

- Benchè il termine di per sé non ponga limiti cronologici, esempio più lampante della strategia in questione è rappresentato dal Test&Treat, l'inizio della terapia il giorno stesso della conferma della positività al test sierologico per HIV.

Rapid Start – Potential Benefits and Limitations

Potential Benefits

- Better clinical outcomes due to less time off ART
- Engagement opportunity to increase retention in care
- Shorter time to treatment decreases anxiety, increases trust
- Public health benefit: decreased transmission risk

Potential Limitations

- ART may not be optimized (renal insufficiency)
- OIs requiring delayed ART may not be ruled out
- Less time to address barriers to ART and adherence
- Risk of resistance if low barrier regimen used
- Requires change in work-flow with rapid access (access, appointment scheduling, staffing)

Further implementation research will continue to provide a better understanding of benefits and limitations in real world settings

DHHS, IAS-USA, EACS

Recommendations for Rapid/Immediate ART Initiation

IAS-USA 2020[1]	DHHS 2019[2, 3]	EACS 2020[4]
• ART initiation, including rapid start, is recommended for all infected ambulatory patients committed to starting ART* or for those with unclear HIV diagnosis • Only triple therapy is recommended for rapid ART start	• ART should be started immediately or as soon as possible after diagnosis for adults and children of all ages • Only triple therapy is recommended for rapid ART start	• ART is recommended in all adult PLWH irrespective of CD4 counts • If ART is to be initiated before genotypic testing results are available, it is recommended to select a first line regimen with a high barrier to resistance
Recommended Regimens		
BIC/FTC/TAF	**BIC/FTC/TAF**	**BIC/FTC/TAF**
DTG + TAF/FTC or TDF/(FTC or 3TC)	DTG + TAF/FTC or TDF/(FTC or 3TC)	DTG + TAF/FTC or TDF/(FTC or 3TC) or ABC/3TC†
	DRV/b + TAF/FTC or TDF/(FTC or 3TC)	PI/b + TAF/FTC or TDF/(FTC or 3TC) or ABC/3TC†

* Unless the patient has symptoms that suggest an opportunistic infection for which immediate ART is contraindicated
DHHS: NNRTIs should not be used because of concerns about transmitted drug resistance. Transmitted mutations conferring NNRTI–R are more likely than those associated with PI or INSTI-R
DHHS: Preferred regimens for children ≤ 12 years in addition to those above include: two NRTIs plus RAL or EVG/c or LPV/r, ATV/r, or NVP depending on age and weight
† For primary HIV infection, a combination of TDF or TAF, FTC, and either DRV/b, DTG or BIC should be considered for treatment initiation prior to genotype testing results. PI/b + TAF/FTC or TDF/FTC or ABC/3TC and regimens with TDF/3TC and ABC/3TC are only recommended by EACS for rapid initiation in PLWH with chronic infection. ABC contraindicated if HLA-B*57:01 positive. Even if HLA-B*57:01 negative, counselling on HSR risk still mandatory. ABC should be used with caution in persons with a high CVD risk (> 10%).

1. Saag MS, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2020 Recommendations of the International Antiviral Society–USA Panel. JAMA. Published online October 14, 2020. https://jamanetwork.com/journals/jama/fullarticle/2771873
2. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, December 2019. Accessed October 2020
3. DHHS. Guidelines for the use of Antiretroviral Agents in Pediatric HIV Infection, April 2020. Accessed October 2020.
4. EACS. Guidelines Version 10.1, October 2020. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

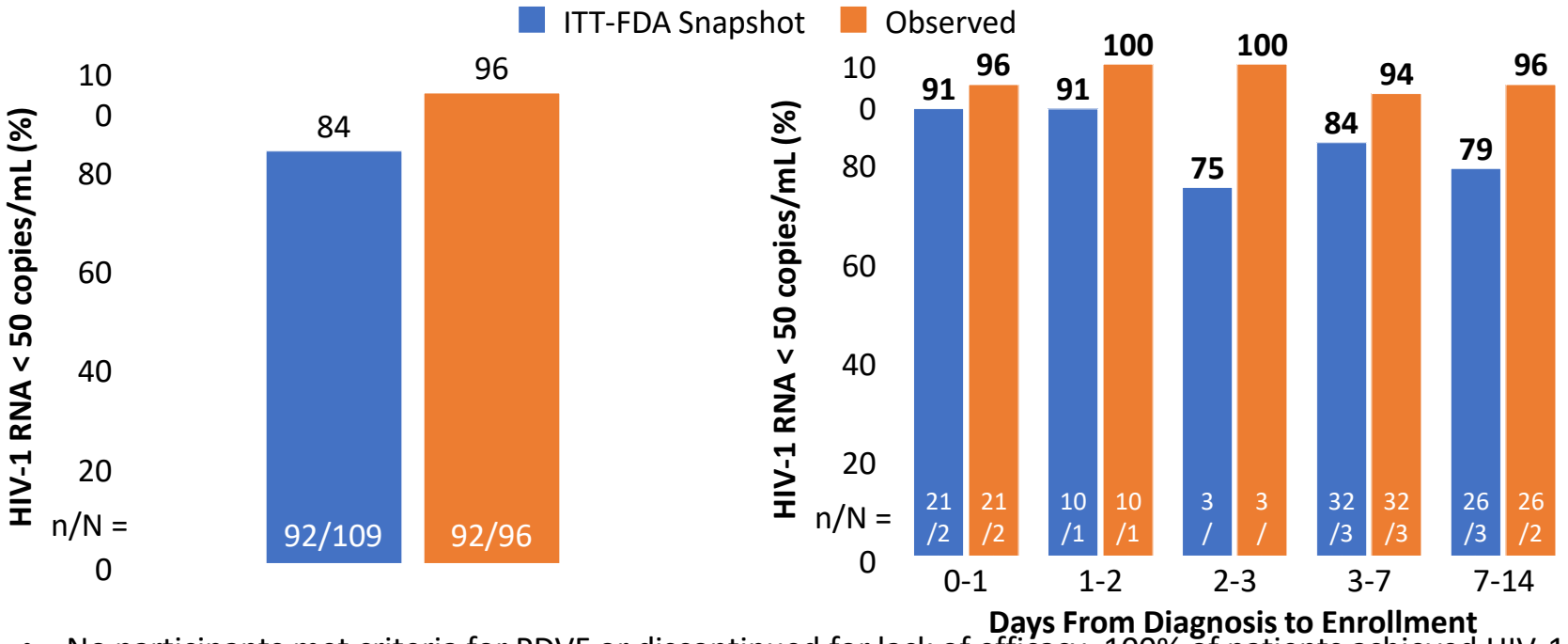
DIAMOND: Single-Arm Trial of DRV/COBI/FTC/TAF for Rapid ART Initiation

First dose received within 24 hrs of screening/baseline visit and before results of baseline safety/resistance lab tests available.
Safety assessment of baseline lab data conducted at Day 3 (+ 1 wk).
Baseline resistance data reviewed at Wk 4 (± 1 wk).

- Primary endpoint: HIV-1 RNA < 50 copies/mL by ITT-FDA Snapshot at Wk 48
- Additional analyses: safety, HIV-1 RNA < 200 copies/mL by ITT-FDA Snapshot, HIV-1 RNA < 50 copies/mL and < 200 copies/mL by observed algorithm (ie, excluding patients with missing data)

Huhn. Clin Infect Dis. 2019;[Epub].

DIAMOND: Virologic Efficacy at Wk 48



- No participants met criteria for PDVF or discontinued for lack of efficacy; 100% of patients achieved HIV-1 RNA < 200 copies/mL in the observed analysis

Huhn. Clin Infect Dis. 2019;[Epub].

DIAMOND: Safety Through Wk 48 in All Patients

- No drug-related serious AEs
- 3 participants discontinued due to pre-specified safety criteria
  - All 3 had transaminase levels at least 2.5x ULN at BL which had normalized by time of d/c
- No cases of IRIS despite HIV-1 RNA ≥ 100,000 c/mL or CD4+ cell count < 200 cells/mm^3 at BL in 25% and 21% of patients, respectively

AE	All Patients (N = 109)
Any, n (%)	92 (84)
Any related occurring in ≥ 2%, %	
▪ Diarrhea	12
▪ Nausea	12
▪ Rash	5
▪ Vomiting	4
▪ Fatigue	3
Any serious, n (%)	10 (9)
Any related, n (%)	36 (33)
▪ Grade ≥ 2	7 (6)
▪ Grade ≥ 3	2 (2)
▪ Grade ≥ 4	0

Huhn. Clin Infect Dis. 2019;[Epub].

Treatment | DTG + 3TC

‡

STAT: Phase 3b, open-label, single-arm study (USA, W48)

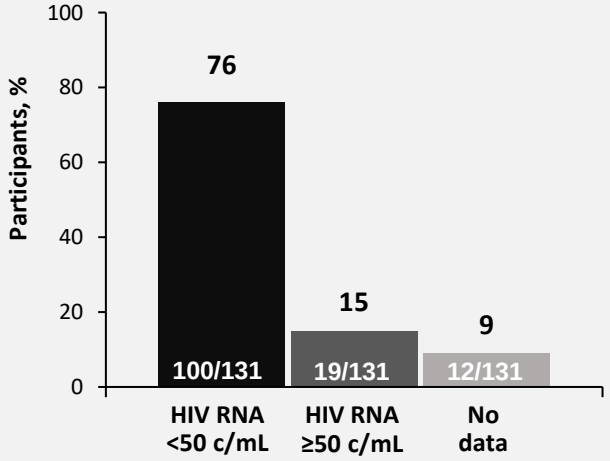
DTG/3TC for Rapid Start

ART-naïve adult PLWH (diagnosed ≤14 days of study entry) N=131 → DTG/3TC

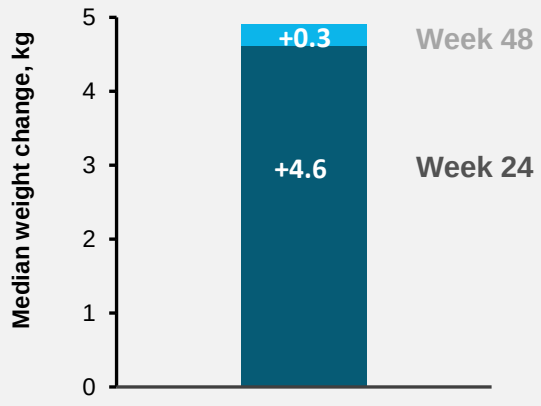
Key Secondary Outcomes at W48
Proportion of participants with plasma HIV-1 RNA <50 c/mL: FDA snapshot, ITT-E M=F, Observed analyses. Safety (AEs, DRAEs, discontinuations)

2019–2020

HIV-1 RNA <50 c/mL, W48 (FDA Snapshot)



Weight Increase, W48



Efficacy <50 c/mL, Observed Analysis: **97% (107/110)**
Efficacy <50 c/mL, ITT-E (M=F) Analysis: **82% (107/131)**

Grade 2–5 DRAEs (2%); serious AEs (2%)

10 (8%) PLWH switched from DTG/3TC by W48

- 5 HBV, 1 M184V, 1 AE (rash), 2 withdrew, 1 pregnancy
- 9/10 switched to 3-drug regimen
- +2 switches post-W48 (lack of efficacy; nonadherence)

18 (14%) participants discontinued the study

- 11% lost to follow-up or withdrew consent
- 3% investigator decision

No treatment-emergent resistance detected

The efficacy of DTG/3TC for rapid start was 76% (FDA Snapshot) after 48 weeks
Weight gain was +4.9 kg; treatment modifications due to baseline lab results (HBV, M184V) in 5%

AE, adverse event; BL, baseline; DRAE, drug-related adverse event; ITT-E, intent to treat–exposed; M=F, missing=failure

Rolle CP, et al. IAS v2021, PEB182

Lineeguida EACS 2019

A) Recommended regimens (one of the following to be selected) *,**

Out of the recommended regimens in PLWH starting ART, we favour the use of an unboosted INSTI with a high genetic barrier (DTG or BIC) as preferred third agent. Tailoring antiretroviral regimens for each individual is essential as other classes of third agents (e.g. PI/b) might be indicated in the presence of resistance

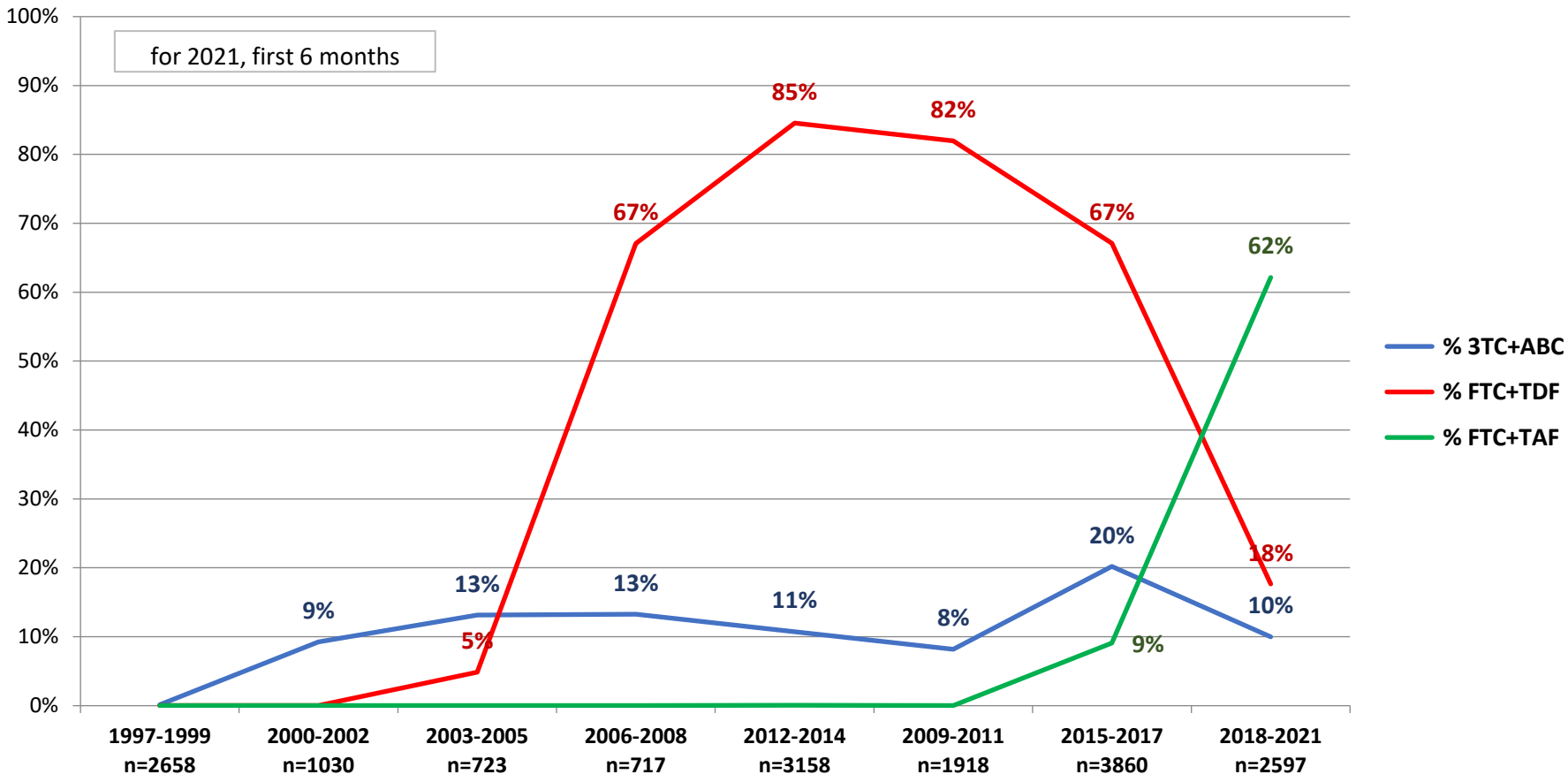
* Only drugs currently licensed for initiation of therapy by the EMA are taken into consideration (in alphabetical order)

** 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-naïve PLWH receiving either a single pill or two pills qd

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens		
2 NRTIs + INSTI (PREFERRED)		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk)
TAF/FTC or TDF/FTC or TDF/3TC + DTG		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) III Weight increase
TAF/FTC/BIC		
TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or bid		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
DTG + 3TC	HBsAg negative HIV-VL < 500,000 copies/mL CD4 count > 200 cells/µL	
2 NRTIs + NNRTI		
TAF/FTC or TDF/FTC or TDF/3TC + DOR TDF/3TC/DOR		II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) V (DOR: HIV-2)
TAF/FTC or TDF/FTC or TDF/3TC + RPV TAF/FTC/RPV TDF/FTC/RPV	CD4 count > 200 cells/µL HIV-VL < 100,000 copies/mL Not on proton pump inhibitor With food	II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (RPV: HIV-2)
2 NRTIs + PI/r or PI/c		
TAF/FTC or TDF/FTC or TDF/3TC + DRV/c or DRV/r TAF/FTC/DRV/c	With food	II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (DRV/r: cardiovascular risk)
Alternative regimens		
2 NRTIs + INSTI		
ABC/3TC + RAL qd or bid	HBsAg negative HLA-B*57:01 negative	I (ABC: HLA-B*57:01, cardiovascular risk) IV (RAL: dosing)
TDF/FTC/EVG/c TAF/FTC/EVG/c	With food	II (TDF: prodrug types. Renal and bone toxicity) VIII (EVG/c: use in renal impairment)
2 NRTIs + NNRTI		
ABC/3TC +EFV	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL At bed time or 2 hours before dinner	I (ABC: HLA-B*57:01, cardiovascular risk) IX (EFV: suicidality. HIV-2 or HIV-1 group 0)
TAF/FTC or TDF/FTC or TDF/3TC + EFV TDF/FTC/EFV	At bed time or 2 hours before dinner	II TDF: prodrug types. Renal and bone toxicity. TAF dosing) IX (EFV: suicidality. HIV-2 or HIV-1 group 0)

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



Jul 2021 Report

Pratica clinica

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

- 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-1

- Nel gruppo BIC, la probabilità di rimanere virologicamente soppressi a 12 mesi è risultata essere del 91%.

- Non sono stati riscontrate sospensioni del regime.

- I due casi di FV (mancata soppressione a 6 mesi) hanno mantenuto il regime e hanno ottenuto nei mesi successivi la soppressione dell'HIV-RNA.

Risultati-2

- Dal punto di vista immunologico, i pazienti nel gruppo BIC hanno 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 a 12 mesi è risultato correlato ad un più alto zenith della carica virale (per 0.1 log10 copies/ml in più, +15.3 cell/mm3, 95%CI 1.8-28.8, p=0.030), ulteriormente confermando l'efficacia del regime nei pazienti con malattia avanzata.

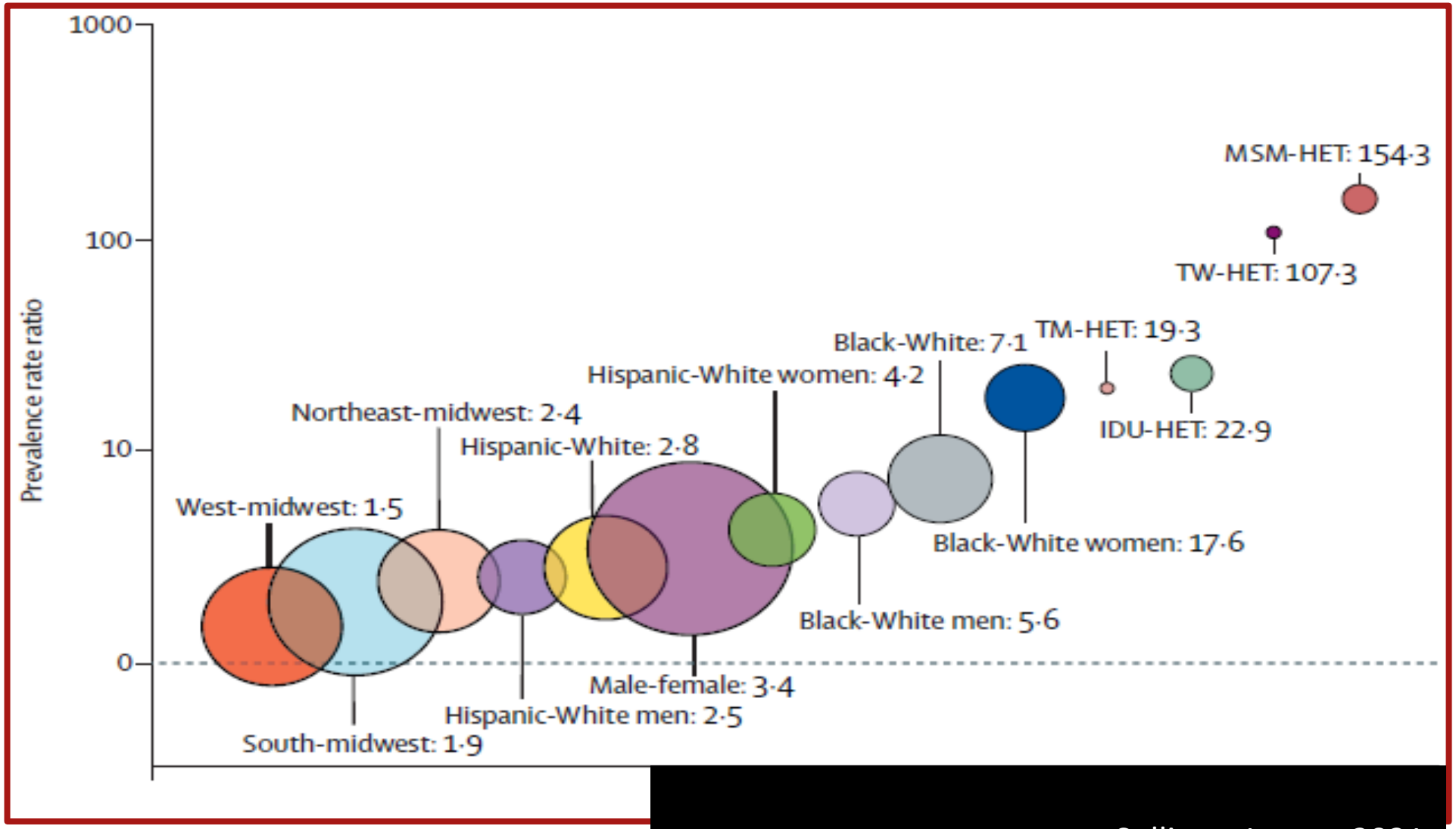
- Hanno mostrato inoltre un incremento del rapport CD4/CD8 a 6 (+0.12, p=0.005) e 12 mesi (+0.20, p=0.001). L'incremento del rapport CD4/CD8 è risultato invece correlato al valore del rapport stesso alla diagnosi (per 0.10 in più, +0.20, 95%CI 0.04-0.27, p=0.013).

Conclusioni

- Anche nella pratica clinica della nostra coorte multicentrica, BIC/FTC/TAF si è dimostrato un regime efficace e sicuro, con incrementi significativi dei parametri immunologici, in particolare in pazienti con malattia avanzata.

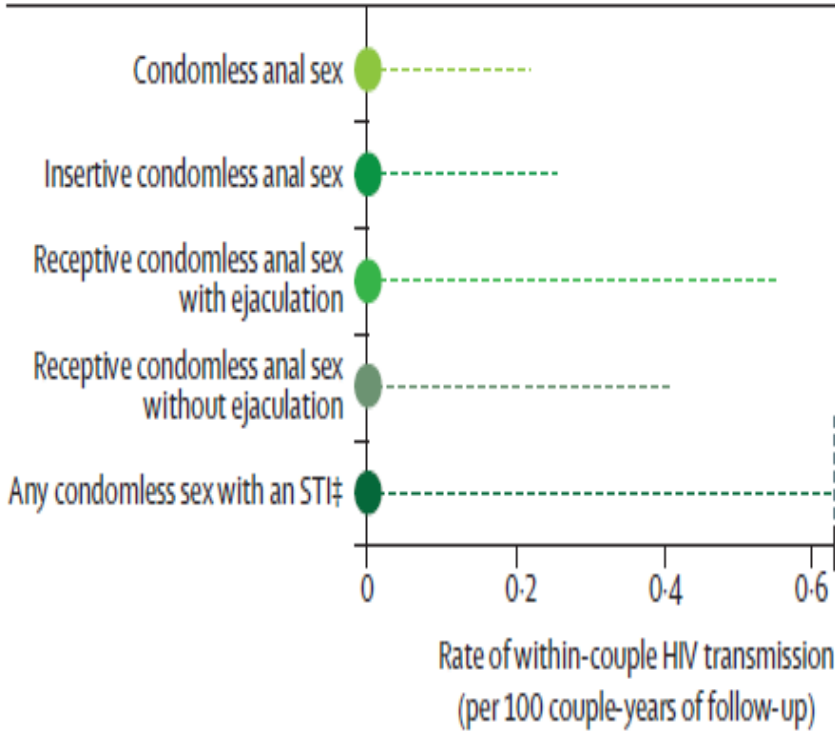
- Avere a disposizione regimi così efficaci e tollerabili in tutte le classi di pazienti naive al trattamento rappresenta un’arma fondamentale per i clinici, in particolare in periodi di difficile accesso al trattamento come durante la pandemia.

Magnitude of disparity in USA



Sullivan, Lancet 2021

Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER)

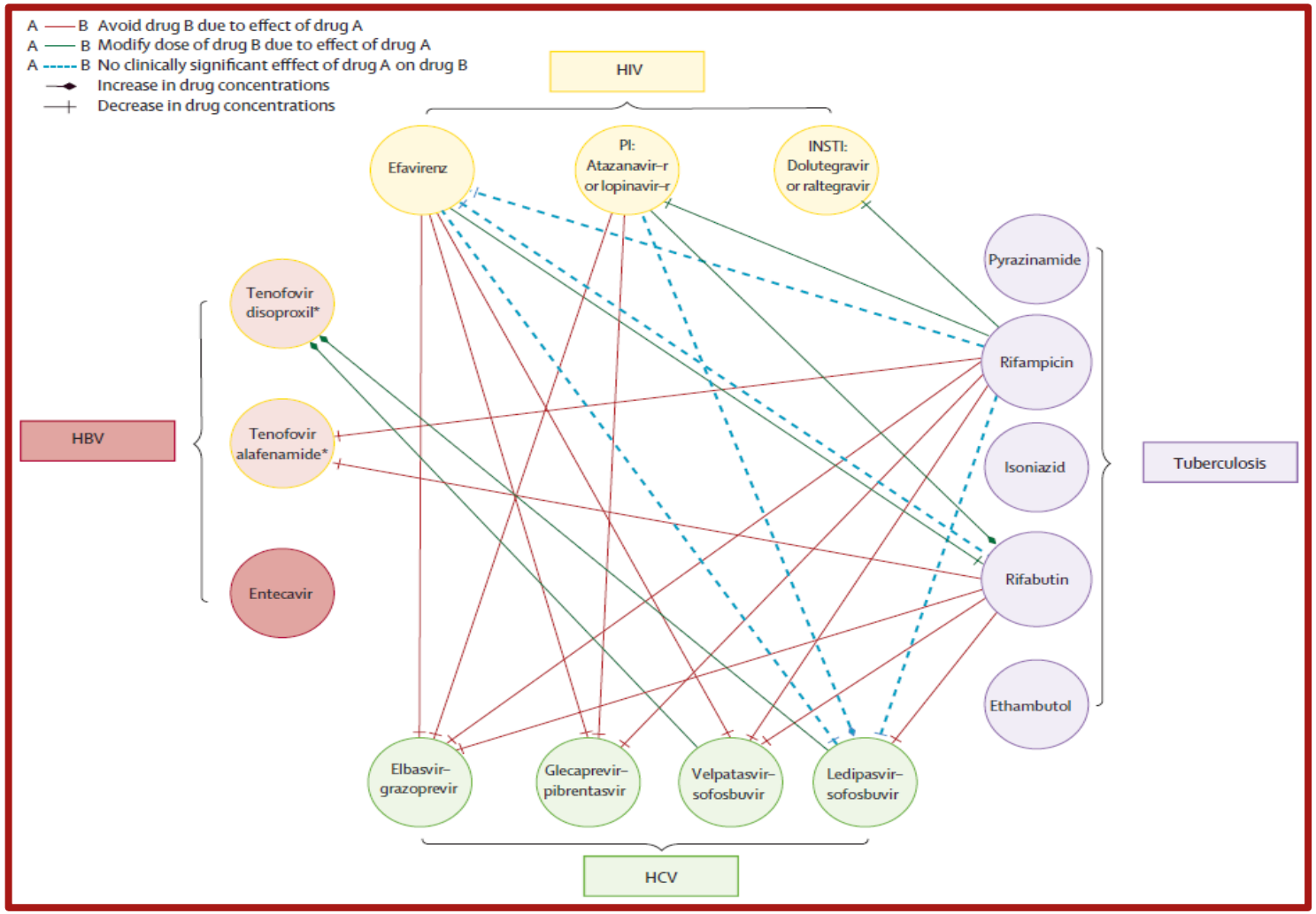


	Number of linked transmissions	Upper 95% CI limit*	Couple-years of follow-up	Number of condomless sex acts	HIV-negative men reporting sex act, n/N (%)†
Condomless anal sex	0	0·23	1593	76088	778/779 (99·9%)
Insertive condomless anal sex	0	0·27	1343	52087	709/777 (91·2%)
Receptive condomless anal sex with ejaculation	0	0·57	650	20487	436/776 (56·2%)
Receptive condomless anal sex without ejaculation	0	0·43	865	22995	577/773 (74·6%)
Any condomless sex with an STI‡	0	3·17	116	6090	NA

- **Three or more drugs 92%**
- **Dual therapy 5%**
- **Monotherapy 2%**

AJ Rodger, Lancet 2019

Complexities in the treatment of OI



U Arora, Lancet Infect Dis 2020

Triplice e duplice nel paziente semplificato

Ottimizzazione a viremia soppressa

- La prolungata sopravvivenza dei pazienti HIV+, garantita dai moderni farmaci antiretrovirali, ha consentito di constatare l'importanza dell'ottimizzazione della terapia, al fine di:

- Ovviare a una tossicità in atto (switch reattivo);
- Prevenire una tossicità prevedibile (switch preventivo o proattivo);
- Evitare il rischio di interazioni farmacologiche;
- Ridurre il pill-burden;
- Migliorare la compliance.

Le strategie di ottimizzazione possono prevedere la riduzione del numero di compresse (STR) o la riduzione del numero di molecole (2DR)

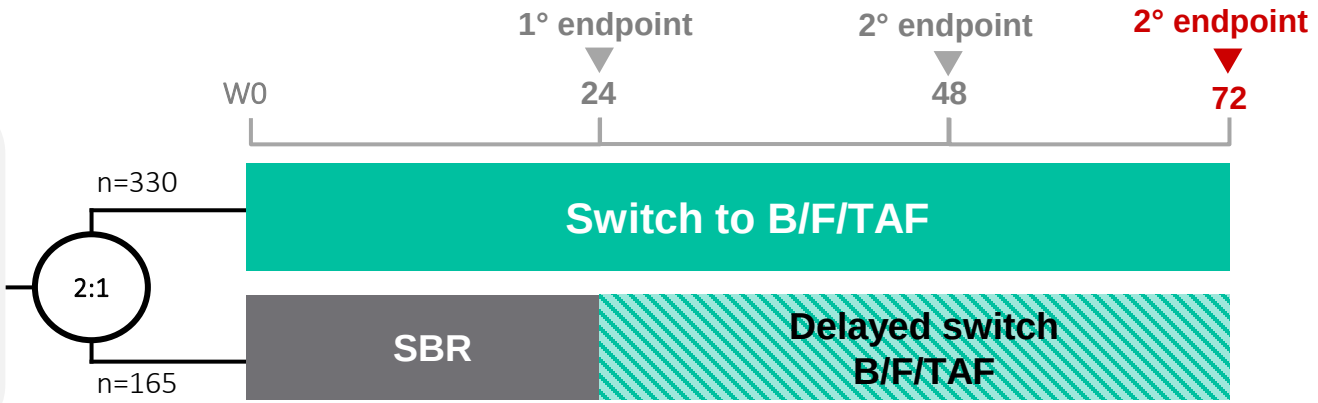
Switch to B/F/TAF in Virologically Suppressed Black American Adult PLWH

BRAAVE 2020: Switch to B/F/TAF in Black American Adults, W72 (End of Study)

HIV suppressed Black American adults on 2 NRTIs + third agent*

- Self-described as Black American, or mixed race, including Black
- Suppressed ≥6 months
- $eGFR_{CG}$ ≥50 mL/min

Study Design



ARV resistance criteria at baseline

Excluded
- NRTI-R
  - K65R/N/R
  - T69 insertions
  - ≥3 TAMs
- Primary INSTI-R

Included
- NRTI-R
  - M184V/I
  - 1–2 TAMs
  - Other substitutions
- NNRTI-R
- PI-R

Endpoints

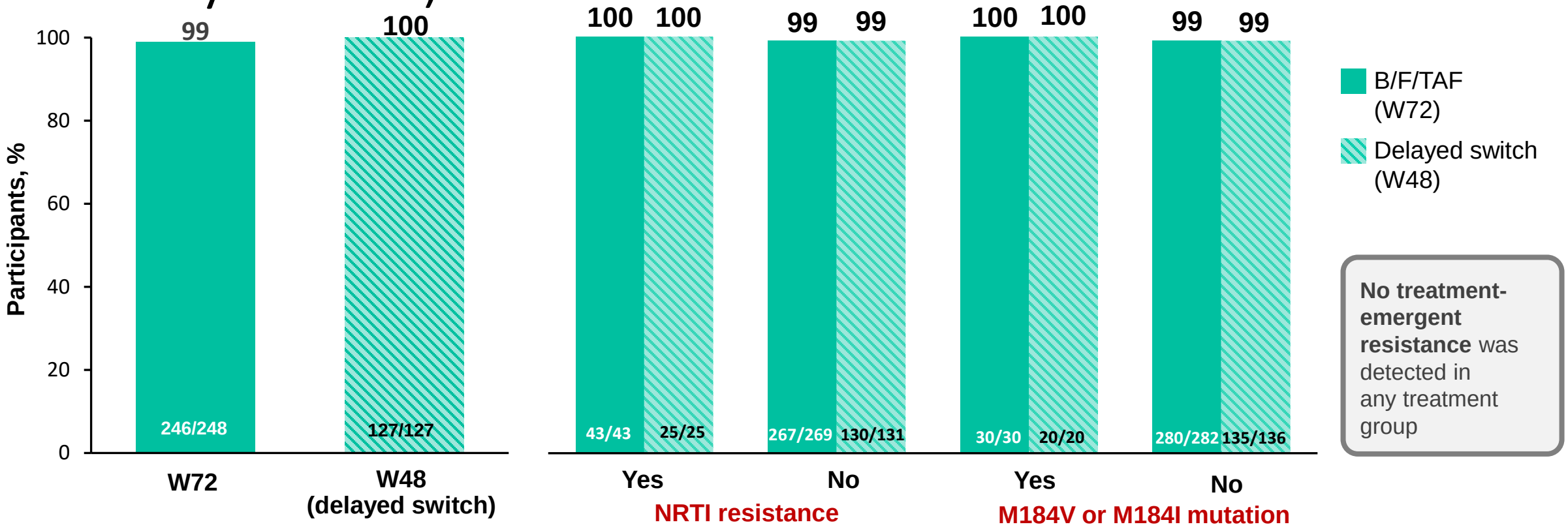
Primary
- HIV-1 RNA ≥50 c/mL at W24 by FDA Snapshot analysis

Secondary
- HIV-1 RNA <50 c/mL at W24 by FDA Snapshot analysis
- Change from baseline in CD4 count at W24
- Efficacy/safety through W48/W72

COVID-19 operational impact: Some visits between W48 and W72 were virtual due to the COVID-19 pandemic

Kumar P, et al. vIAS 2021, PEB161

HIV-1 RNA <50 c/mL at W72 (M=E, Full Analysis Set)



No treatment-emergent resistance was detected in any treatment group

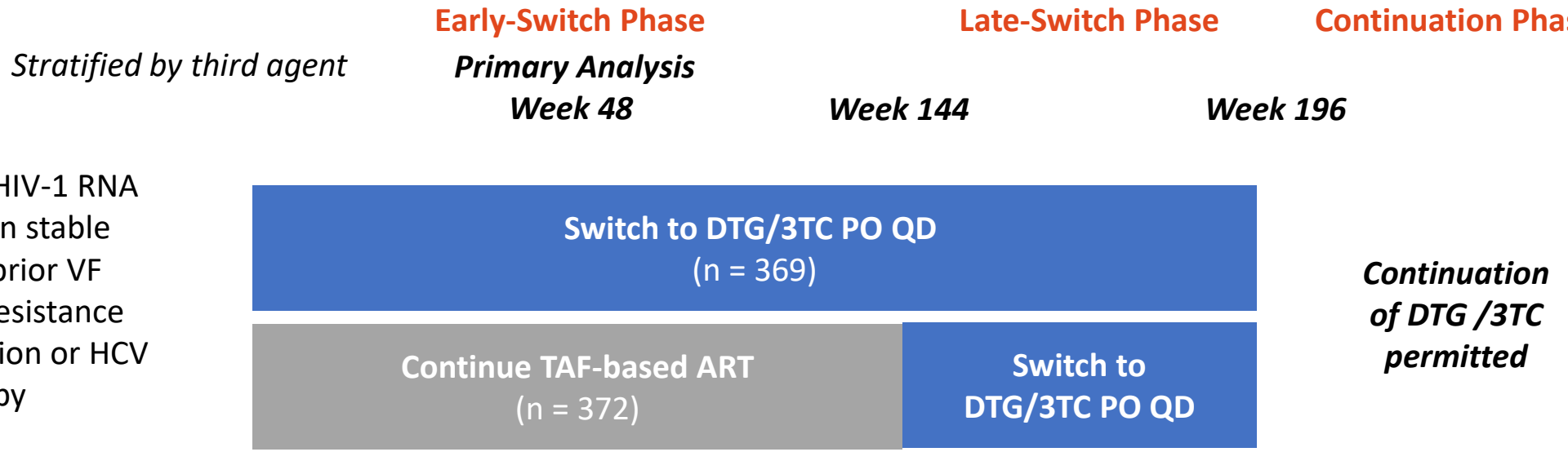
Virologic suppression was maintained in Black American adults on B/F/TAF despite pre-existing NRTI resistance, including M184V/I

Full Analysis Set: Denominator for percentage is number of participants in B/F/TAF with non-missing HIV-1 RNA value at each visit

Kumar P, et al. vIAS 2021, PEB161

TANGO: Study Design

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



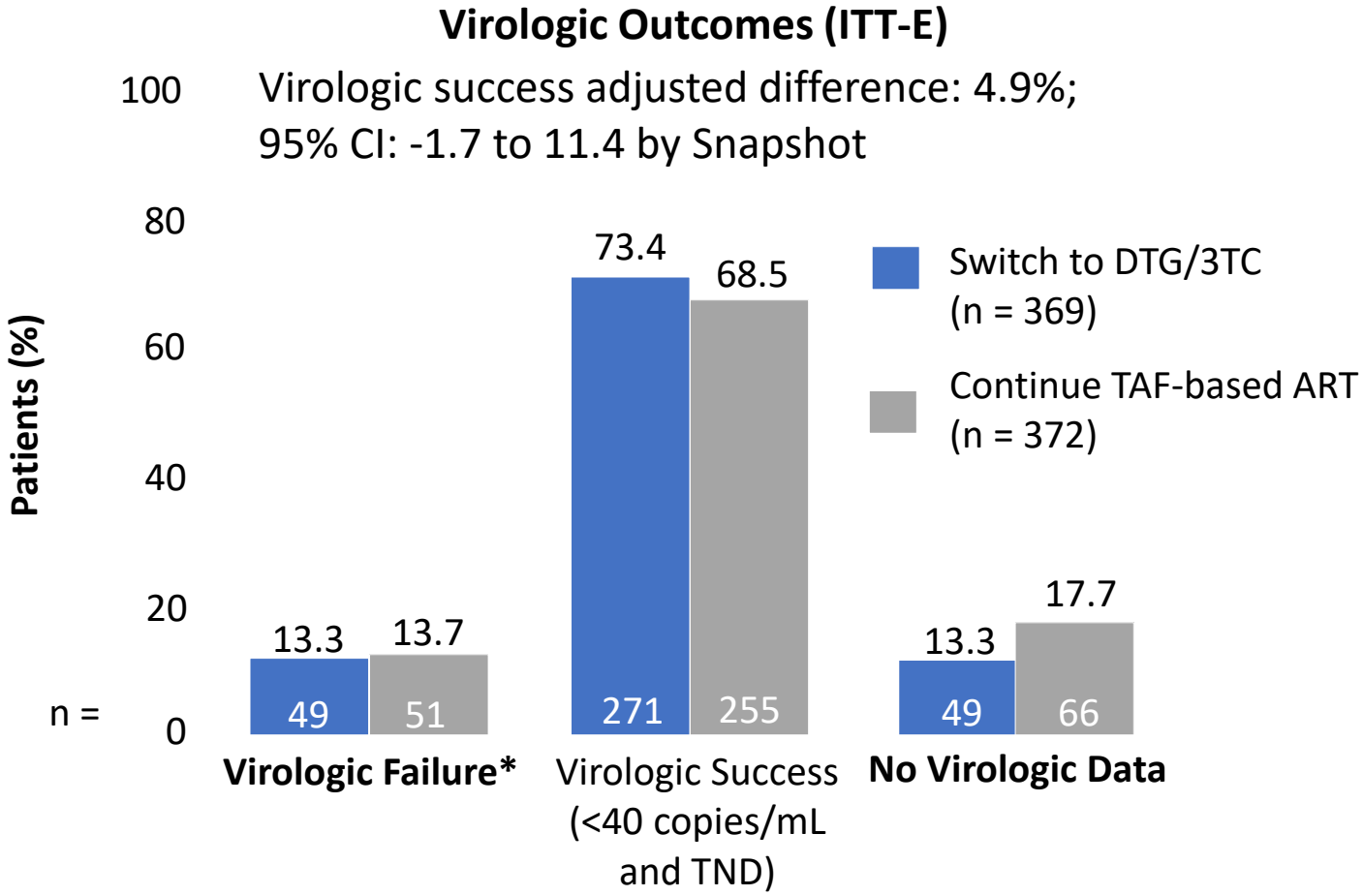
*Patients eligible if initial regimen was TAF/FTC with PI, NNRTI, or INSTI, or TDF switched to TAF ≥3 mo prior to screening with no other regimen changes.

- Primary endpoint from previous analysis: virologic failure at Week 48 (FDA Snapshot in ITT-E)
  - Noninferiority margin: 4%

van Wyk. Clin Infect Dis. 2020;71:1920. Wang. IAS 2021. Abstr OAB0301.

Slide credit: clinicaloptions.com

TANGO Post-Hoc Analysis: Virologic Outcomes by FDA Snapshot at Week 96



- Protocol-defined CVW (2 consecutive HIV-1 RNA ≥50 c/mL with the second one ≥200 c/mL) in 0 and 3 patients in DTG/3TC arm vs TAF-based ART arm
  - No NRTI- or INSTI-associated resistance at baseline or failure for 3 CVWs
- 7 patients with preexisting archived mutations maintained HIV-1 RNA <50 copies/mL on last visit
  - 3/4 patients on DTG/3TC and 2/3 on TAF-based ART with TND at baseline and through all visits

*Defined as one of 1) Data in window and VL <40 c/mL and TD 2) Data in window and VL ≥40 c/mL 3) Discontinued for lack of efficacy 4) Discontinued for other reason, with VL ≥40 or VL <40 c/mL and TD 5) Change in ART

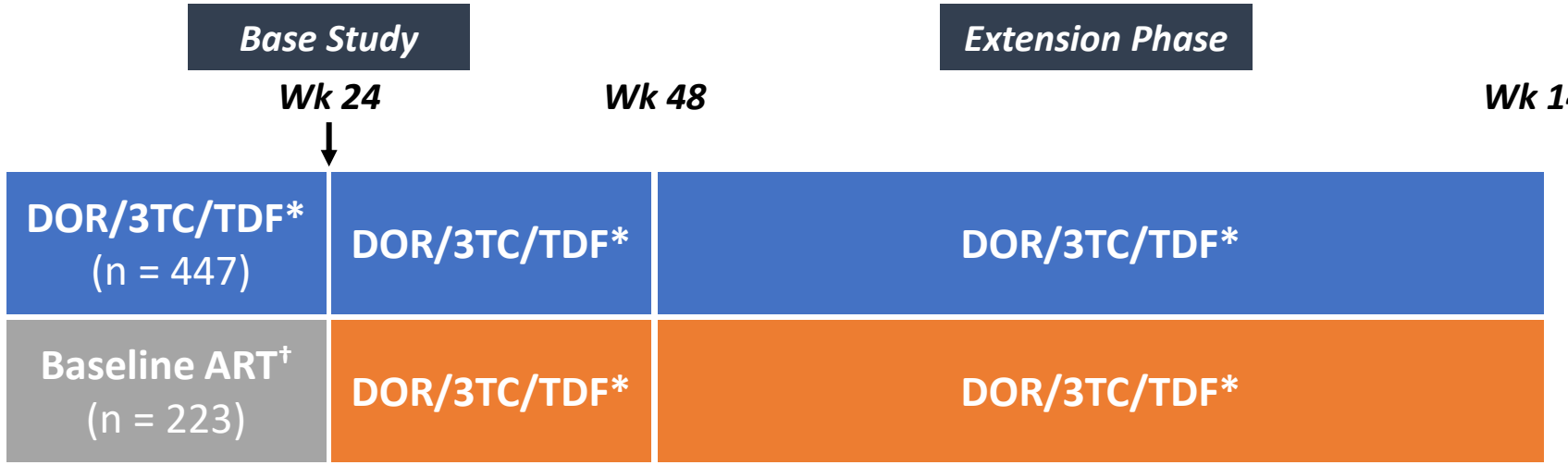
Wang. IAS 2021. Abstr OAB0301.

Slide credit: clinicaloptions.com

DRIVE-SHIFT: Switch to DOR/3TC/TDF vs Continuation of Baseline ART in Virologically Suppressed Adults

- International, randomized, open-label phase III noninferiority study[1-3]

Adults with HIV-1 RNA < 40 c/mL, stable ART for ≥ 6 mos, and eGFR ≥ 50 mL/min; no prior VF or resistance to study drugs (N = 670)



*DOR/3TC/TDF dosing: 100/300/300 mg QD.
†2 NRTIs + boosted PI (ATV, DRV, or LPV), EVG/COBI, or NNRTI (EFV, NVP, or RPV).

- HIV-1 RNA < 50 c/mL: **90.8%** (immediate switch, Wk 48) vs **94.6%** (delayed switch, Wk 24)[3]
- Current analyses at Wk 144: plasma HIV-1 RNA, change in CD4+ cell count, PDVF and emergent resistance, fasting serum lipids, weight change, AEs[1]

1. Kumar. HIV Glasgow 2020. Abstr P037. 2. NCT02397096. 3. Johnson. JAIDS. 2019;81:463.

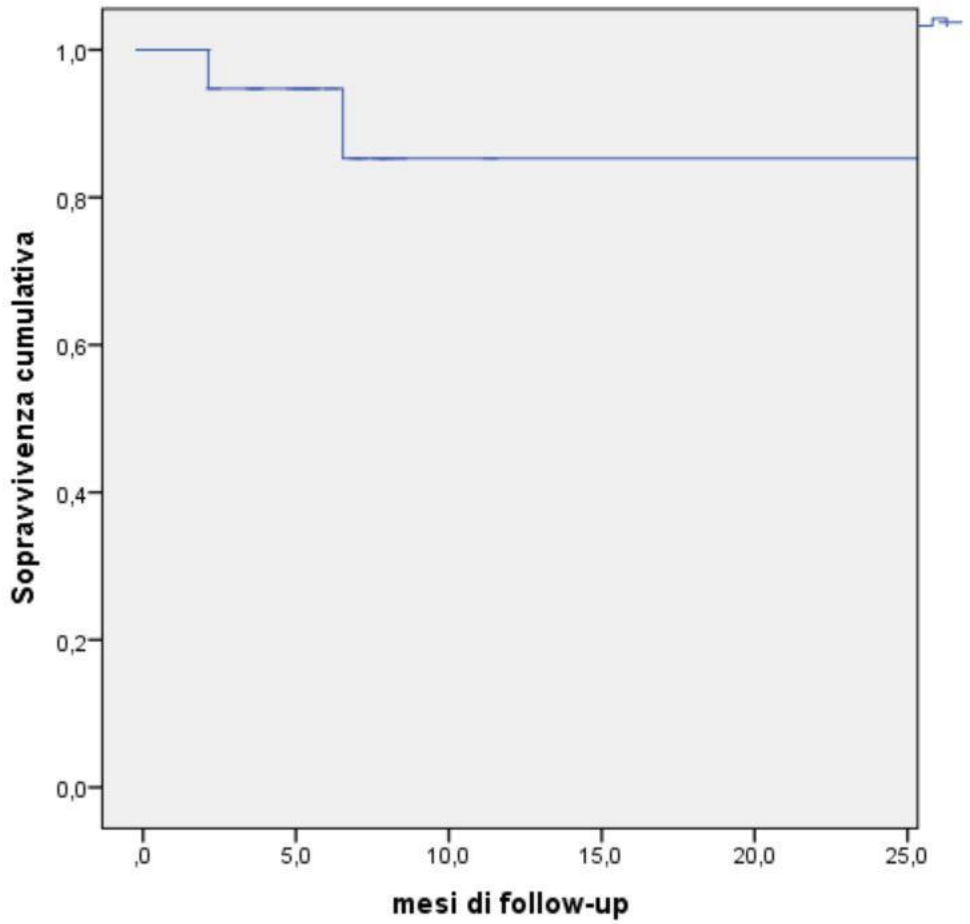
Real-life safety of doravirine in treatment-experienced, virologically suppressed PLWHIV

Ciccullo A, D'Angelillo A, Iannone V, Farinacci D, Lombardi F, Visconti E, Tamburrini E, Di Giambenedetto S

Variabili	N=36
Età, mediana (IQR)	52.5 (46.1 – 59.0)
Sesso maschile, n (%)	24 (66.7)
HIV risk factor: - Etero - MSM - IDU - Altro	 12 (33.3) 18 (50.0) 5 (13.9) 1 (2.8)
Anni di HIV, mediana (IQR)	11.0 (3.3 – 21.7)
Anni di ARV, mediana (IQR)	10.9 (3.3 – 18.0)
Pregresso evento AIDS, n (%)	14 (38.9)
Pregresso fallimento virologico, n (%)	8 (22.2)
HBsAg+, n (%)	3 (8.6)
Coinfezione HCV, n (%)	4 (11.8)
Nadir CD4+, mediana (IQR)	141 (43 - 275)
Zenith HIV-RNA, mediana (IQR)	5.29 (4.49 – 5.64)

Variabili	N=36
Pregresso uso RPV (storico)	28 (77.8)
Regime pre-switch: - 2NRTI+INI - 2NRTI+PI - 2NRTI+NNRTI - DTG+3TC - 4-drug - Naive	 12 (33.3) 8 (22.2) 11 (30.6) 1 (2.8) 1 (2.8) 3 (8.3)
Motivo start DOR: - Ottimizzazione - Tossicità - Naive - Altro	 27 (75.1) 3 (8.3) 3 (8.3) 3 (8.3)

Sopravvivenza del regime



Nella nostra analisi, a 12 mesi di follow-up, la probabilità di proseguire DOR è risultata pari a 85.3%

Sono state osservate 3 interruzioni durante 15.9 PYFU: una per fallimento virologico e due per intolleranze gastrointestinali.

Resistenze

Al genotipo storico, 5 pazienti (13.9%) presentavano una resistenza maggiore agli NNRTI:

- 3 pazienti E138A
- 1 paziente K103N
- 1 paziente Y188L

Nessuno dei pazienti con mutazione agli NNRTI ha interrotto il regime con DOR né ha presentato rialzi di HIV-RNA.

Come scegliere la terapia nei pazienti soppressi

- Ottima tollerabilità
- Buona efficacia
- Ridotti costi

Terapia personalizzata

HIV MEDICINE

British HIV Association
BHIVA

Lamivudine-based maintenance antiretroviral therapies in virologically-suppressed HIV-positive patients: derivation of a predictive score of virological failure

Borghetti et al. 2019

- Il genotipo da solo non è sufficiente a predire i fallimenti virologici.

- Necessità di integrare parametri viro-immunologici nel paziente.

- Selezionare con attenzione i pazienti che possono semplificare soprattutto ad un regime di «less-drug regimen» per far si che la terapia possa ridurre il rischio di fallimento nel FU a lungo termine.

Nucleoside Reverse-Transcriptase Inhibitor Resistance Mutations Predict Virological Failure in 669 Human Immunodeficiency Virus-Positive Patients During Lamivudine Plus Dolutegravir Maintenance Therapy in Clinical Practice

Exposure Variable	Models 1, 2, 4* aHR (95% CI)	*P* Value	Model 3** aHR (95% CI)	*P* Value	Model 5*** aHR (95% CI)	*P* Value
M184V/I (presence vs absence)			3.31 (1.02–10.74)	.046		
M184V/I with TAMs (presence vs absence)					4.63 (1.19–17.94)	.027
Previous failure on an INI-based regimen (at least 1 vs none)	5.84 (1.28–26.64)	.025	6.41 (1.36–30.18)	.019	5.51 (1.15–26.50)	.033
Time of virological suppression (>2 years vs ≤2)	0.29 (0.10–0.86)	.023	0.27 (0.09–0.80)	.018	0.23 (0.08–0.74)	.013

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; INI, integrase inhibitor; TAM, thymidine analog mutation.

NOTES: All Cox models were built after a stepwise selection of the following covariates (variables associated with the outcome at a $P > .05$ were excluded at each step): age, ethnicity, risk factor for HIV infection, detectable HIV-RNA at baseline, nadir CD4 and zenith HIV-RNA, viral subtype and HIV-RNA at last genotypic resistance test, time of viral suppression at baseline and previous virological failure (VF) with an INI-containing regimen. The variables representing RAMs were different according to the 5 models.

*In model 1, we used "presence of any NRTI-RAM versus none"; *in model 2, "presence of at least 1 TAM versus none"; *in model 4, "presence of M184V/I without TAMs versus all other combinations of RAMs or no RAMs". Because none of these variables was associated with VF, they were not included in their respective Cox models.

**Model 3 included the "presence of M184V/I versus absence of M184V/I."

***Model 5 included "presence of M184V/I plus at least 1 TAM versus all other combinations of RAMs or no RAMs."

338 patients with available genotype

A. Borghetti, OFID 2021

Algoritmo applicabile nella routine clinica che tiene conto di:

- Caratteristiche del ceppo virale (Sottotipo)
- Mutazione 184+TAM
- Storia immunovirologica del paziente (Nadir CD4+ , tempo dalla diagnosi e di soppressione virologica)
- Condizioni attuali (HIV-RNA allo switch non rilevabile)

Storia terapeutica - MF

- Dal 2000 al 2002 in terapia antiretrovirale con AZT/3TC + NVP
- Dal 2002 al 2005 in terapia antiretrovirale con AZT/3TC + EFV (fallimento con HIV-RNA: 58000 copie/ml)
- Dal 2005 al 2014 in terapia antiretrovirale con AZT/3TC ed inibitori delle proteasi.
- Dal 2014 TDF/FTC+RGV

- Genotipo del 2005:
  - Mutazioni maggiori per NRTI – L74V
  - Mutazioni maggiori per NNRTI – K103N
  - Mutazioni minori a PI – I13V, L63P

  - Soppresso stabilmente dal 2008 e CD4>400/mmc

- Semplifica, a viremia soppressa, nell’agosto 2015 a 3TC+DTG per grave sindrome metabolica

- Nel dicembre 2016 prima determinazione di HIV-RNA 112 cp/ml con successiva determinazione di 346 cp/ml.

Algoritmo - MF

Era opportuna una dual ?

- Paziente con 24 anni di infezione, con storia di pregresso fallimento virologico ma grave sindrome metabolica.
- Nadir CD4+ 20 cell/mm3
- Sottotipo F

totale_punteggio	Rischio_fallimento_2_anni
6	5,677362024

- Moderato rischio di fallimento virologico.
- Paziente con storia di fallimento virologico, basso nadir CD4+, genotipo non pulito.

Fallimento virologico con 2-DR con 3TC+DTG

Conclusioni

- La triplice terapia resta essenziale in popolazioni difficili (IO, fallimento virologico, presenza di mutazioni archiviate)

- Le duplici terapie sono molto efficaci e supportate da trials e studi di pratica clinica consolidati e soprattutto il futuro si baserà su DT

- La terapia ARV non può essere Standardizzata ma deve essere sempre più possibile Personalizzata

- Sia le Triplice che la Dual sono approcci terapeutici fondamentali per «long-life treatment»

Grazie per l’attenzione