XI Workshop Nazionale
Innovazione e Ricerca per la Pratica Clinica
TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI E DELLE INFEZIONI VIRALI. 11-12 Gennaio 2021

HIV: LA PRATICA CLINICA AI TEMPI DEL COVID: la terapia a 3 farmaci

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- ViiV
- Angelini

La gestione del paziente con infezione da HIV in era COVID

Paziente

- Difficoltà a raggiungere il centro clinico
- Difficoltà nel farmacy refill
- Paura del COVID
- Riduzione screening per altre patologie

Centro Clinico

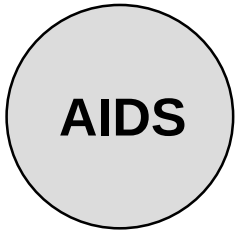
- Riduzione attività ambulatoriale
- Riduzione controlli co-morbilità
- Riduzione presenza medici esperti

- Naive patient
- Experienced patient

What can PLHIV expect from Antiretroviral therapy?

Rapid ART initiation

High genetic barrier to resistance



Use in patients with high viral load and/or low CD4 count

Recommended Regimens for Initiation of Antiretroviral Therapy in Most PLWH

IAS-USA 2020[1]	DHHS 2019[2]	EACS 2020[3*]
BIC/FTC/TAF	**BIC/FTC/TAF**	**BIC/FTC/TAF**
DTG + FTC/TAF or FTC†/TDF	DTG/3TC/ABC	DTG + ABC/3TC or DTG/ABC/3TC
DTG/3TC	DTG + FTC/TAF or FTC†/TDF	DTG + TAF/FTC or TDF/FTC or TDF/3TC
	RAL + FTC/TAF or FTC†/TDF	RAL + TAF/FTC or TDF/FTC or 3TC
Recommended for rapid start‡	**DTG/3TC**	**DTG+3TC or DTG/3TC**

Guidelines recommendations for DTG/3TC come with restrictions

- DTG/3TC (or DTG+3TC) is not recommended when ART needs to be initiated before genotypic testing results are available[1,2,3] nor in the following scenarios:
  - Chronic hepatitis B coinfection[1,2,3]
  - HIV RNA level >500,000 c/mL[1,2,3]
  - Treatment of an active opportunistic infection[1]
  - Perhaps a CD4 <200/μL (although unclear)[1]
- Close monitoring for adherence and virological response is needed with DTG/3TC[1]

* EACS: 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.
† 3TC may substitute for FTC or vice versa
‡ Additional regimens that can be considered for rapid start include (DRV/r or DRV/c) plus (TAF or TDF)a plus (3TC or FTC) per DHHS and PI/b combined with TDF/FTC, TAF/FTC, TDF/3TC or ABC/3TC per EACS

1. Saag MS et al. JAMA 2020 Oct 14 doi: 10.1001/jama.2020.17025 (Online ahead of print)
2. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, December 2019. Accessed November 2020
3. EACS. Guidelines Version 10.1, October 2020. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

Tabella 9 - Numero e percentuale di nuove diagnosi di infezione da HIV per concomitante diagnosi di AIDS, classi di CD4 (< 200, 200-349, 350-499 e ≥ 500 cell/µL) , genere, età, modalità di trasmissione, nazionalità (2019)

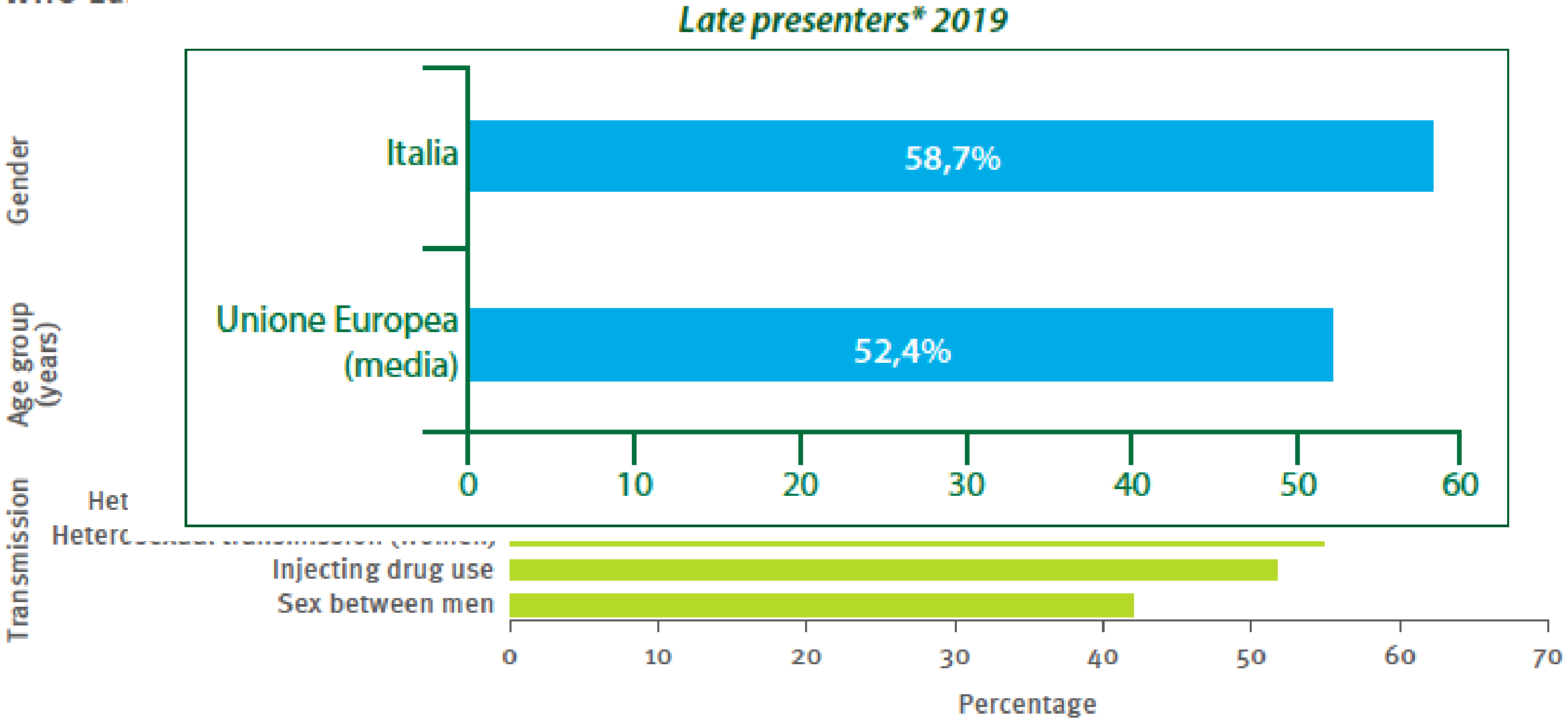
	AIDS		Totale casi con stadio clinico riportato	Numero CD4								Totale casi con CD4 riportati	Totale casi con CD4 non riportati[c]	Totale
				< 200		200-349		350-499		≥ 500				
Caratteristiche	n.	% riga[a]	n.	n.	% riga[b]	n.	% riga[b]	n.	% riga[b]	n.	% riga[b]	n.	n.	n.
Genere[d]														
Maschi	426	24,9	1.710	715	40,2	331	18,6	301	16,9	431	24,2	1.778	247	2.025
Femmine	88	20,9	422	168	37,7	92	20,6	91	20,4	95	21,3	446	60	506
Classe d'età[e]														
< 25	8	5,6	144	25	16,3	31	20,3	38	24,8	59	38,6	153	44	197
25-50	299	21,5	1.389	511	35,3	277	19,2	272	18,8	386	26,7	1.446	193	1.639
50	207	34,8	594	347	55,5	115	18,4	82	13,1	81	13,0	625	65	690
Modalità di trasmissione														
MSM	179	18,5	966	301	30,3	205	20,6	202	20,3	287	28,8	995	74	1.069
Eterosessuali maschi	189	33,3	567	315	53,5	91	15,4	78	13,2	105	17,8	589	48	637
Eterosessuali femmine	82	21,0	390	150	36,9	87	21,4	83	20,4	86	21,2	406	28	434
IDU	22	24,7	89	40	44,0	15	16,5	14	15,4	22	24,2	91	56	147
Non riportata	42	35,0	120	77	53,8	25	17,5	15	10,5	26	18,2	143	101	244
Nazionalità														
Italiana	385	24,3	1.582	663	40,3	294	17,9	285	17,3	402	24,5	1.644	240	1.884
Straniera	128	23,7	540	217	38,2	126	22,2	104	18,3	121	21,3	568	67	635
Non riportata	1	10,0	10	3	25,0	3	25,0	3	25,0	3	25,0	12	0	12
Concomitante diagnosi di AIDS														
SI				457	89,4	35	6,8	12	2,3	7	1,4	511	3	514
No				392	24,4	364	22,6	364	22,6	489	30,4	1609	9	1.618
Non riportato				34	32,7	24	23,1	16	15,4	30	28,8	104	295	399
Totale	**514**	**24,1**	**2.132**	**883**	**39,7**	**423**	**19,0**	**392**	**17,6**	**526**	**23,7**	**2.224**	**307**	**2.531**

CD4 <200 : 39,7%

CD4 <350: 58,7%

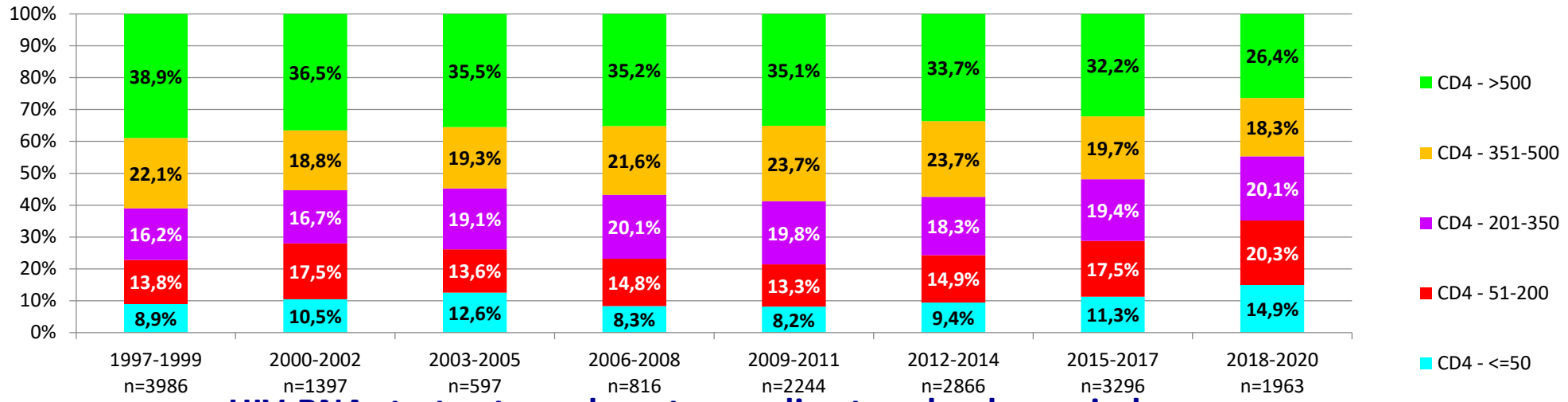
AIDS: 24,1%

Fig. C. Proportion of people diagnosed late (CD4 cell count < 350 per mm³) by gender, age and transmission, WHO Eu

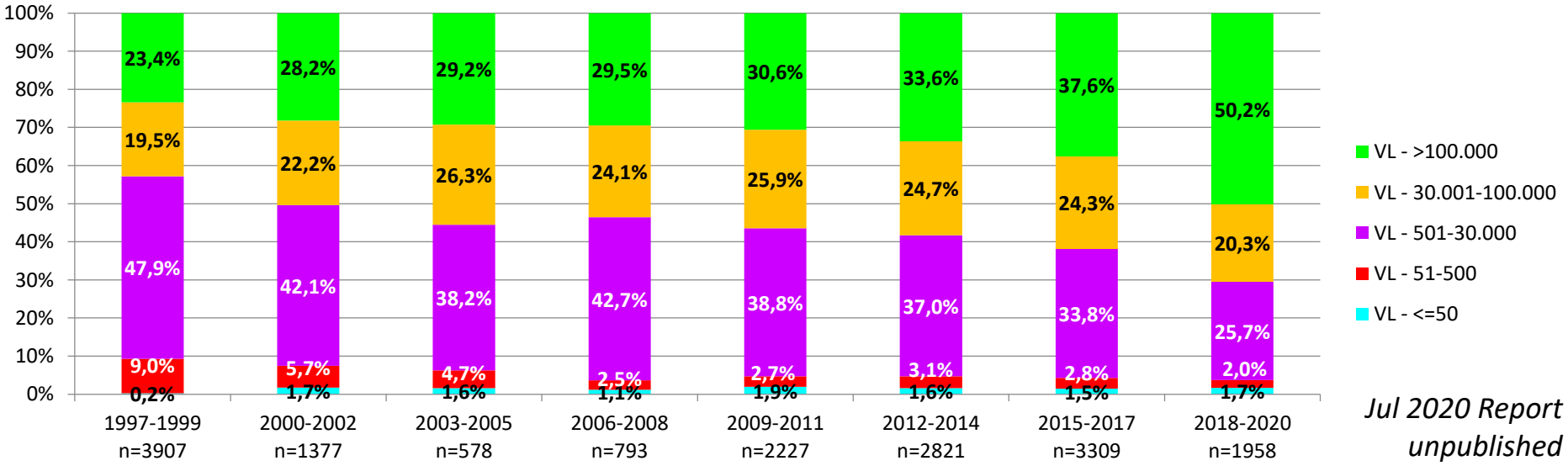


Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

CD4 cells/mmc count strata at enrolment according to calendar period



HIV-RNA strata at enrolment according to calendar period

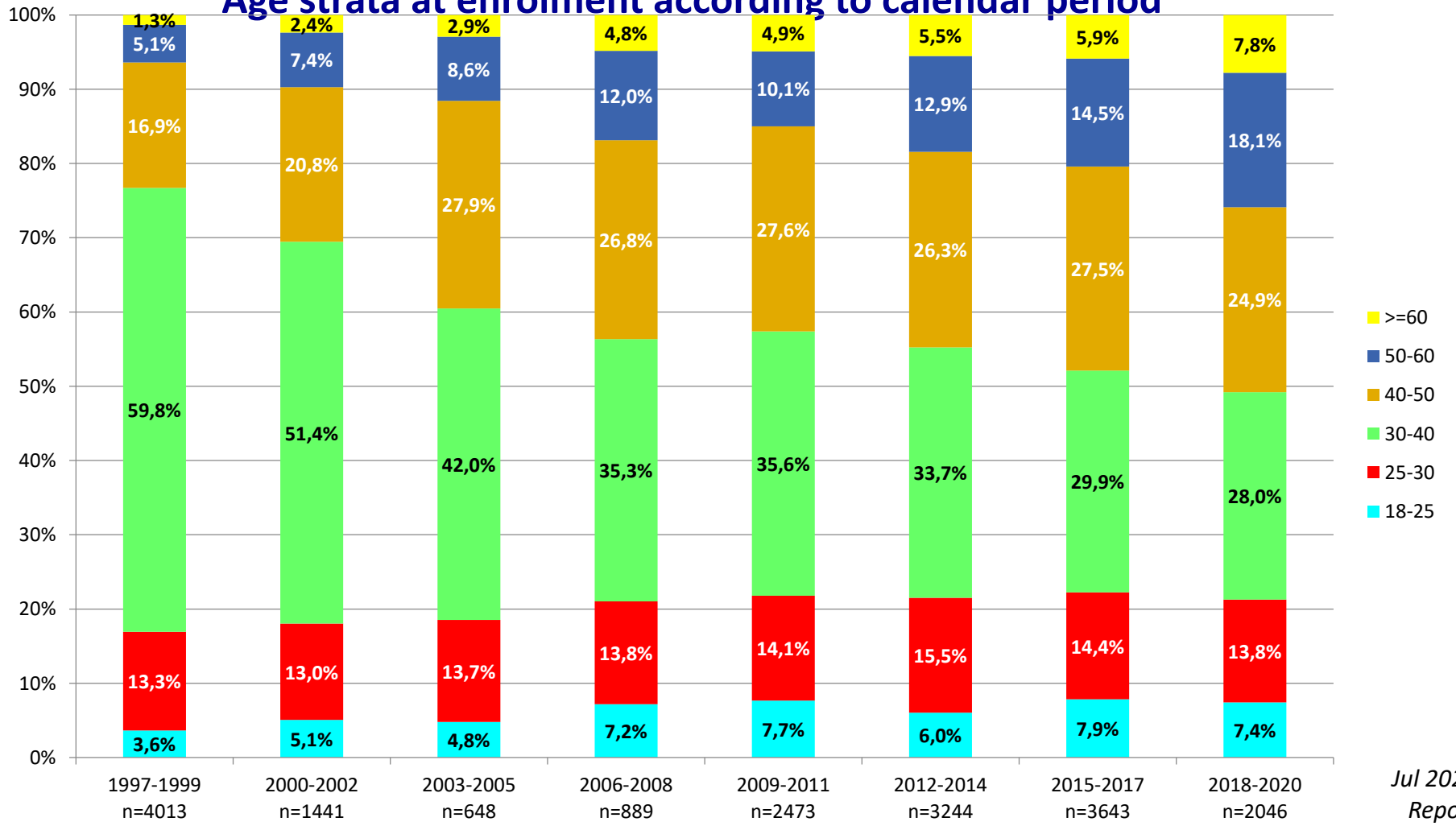


Jul 2020 Report unpublished

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I. C. O. N. A. Naive Antiretrovirals

Age strata at enrolment according to calendar period



Jul 2020 Report unpublished

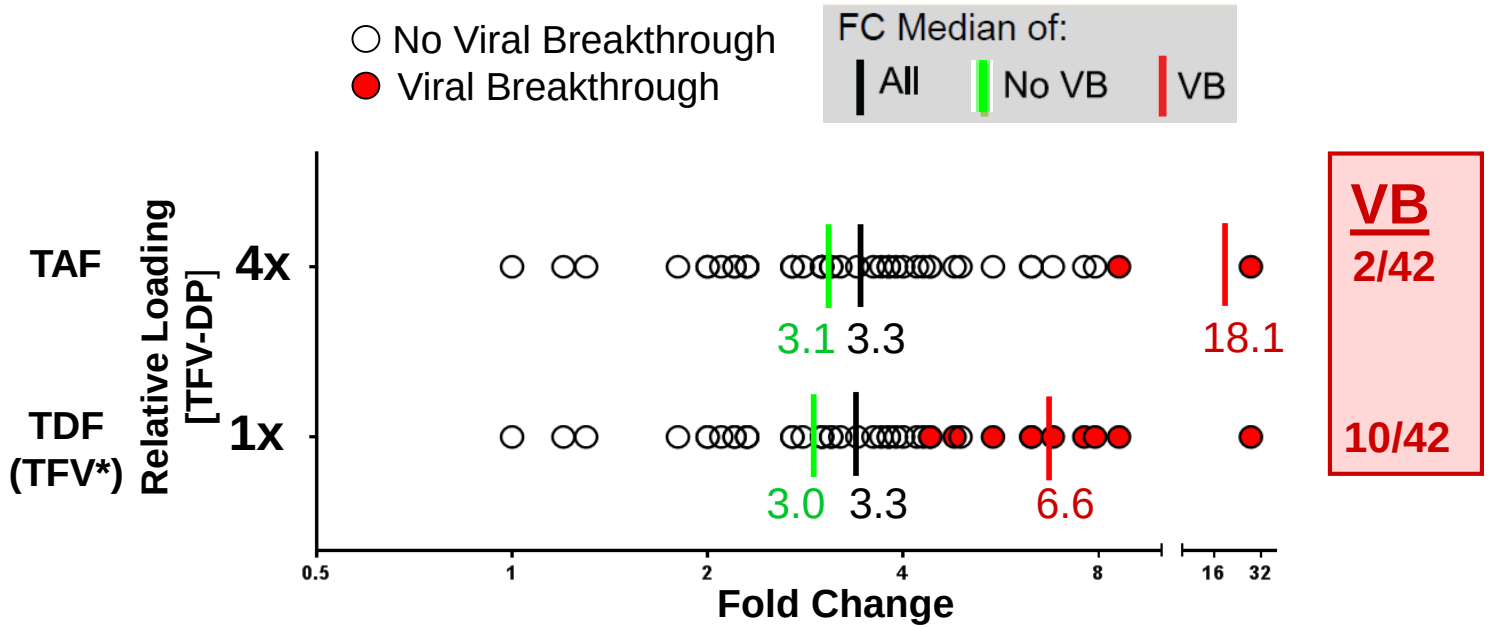
‡

Antiviral Activity of TAF Against HIV-1 with K65R ± M184V/I

***in vitro assessment of* TAF activity evaluating phenotypic range of resistance and resistance barrier against 42 K65R patient-derived HIV-1 viruses compared to TDF**

Mutant Class	N	Median EC_{50} Fold-Change Compared to Wild-Type		
		TAF	ABC	FTC
All viruses	42	3.3	11.8	>186
K65R	14	3.5	3.9	11.4
K65R + M184V/I	28	3.3	15.8	>186

- Increased resistance with M184V seen for ABC
- Decreased resistance with M184V seen for TAF



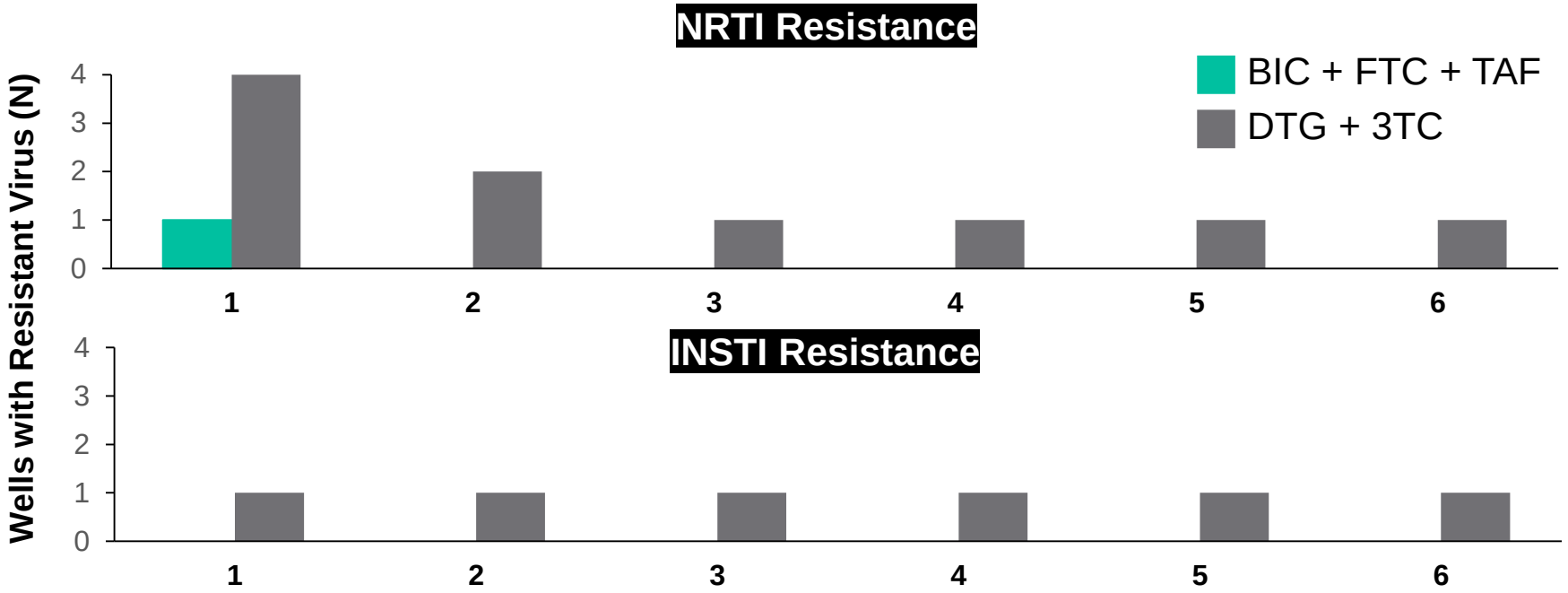
- TAF resulted in fewer viral breakthroughs of K65R-containing HIV-1 (2/42 vs. 10/42)

VB, viral breakthrough; *TFV is the *in vitro* equivalent of TDF

Cox S, et al. CROI 2019. Seattle, WA. Poster 546

Analysis with Wild-type HIV-1 (HIV IIIb strain): Emergent Resistance

In vitro simulation of B/F/TAF vs DTG+3TC’s “forgiveness” (extent of viral breakthrough/rebound and resistance emergence) under sub-optimal drug adherence conditions of up to 3 consecutive missed doses



- More resistance with DTG+3TC (14/144) vs BIC+FTC+TAF (1/144)
- BIC+FTC+TAF: M184V/I occurred once and was in the 3 missed doses experiments

In vitro emergent drug resistance was less common with BIC+FTC+TAF compared to DTG+3TC in wild-type HIV

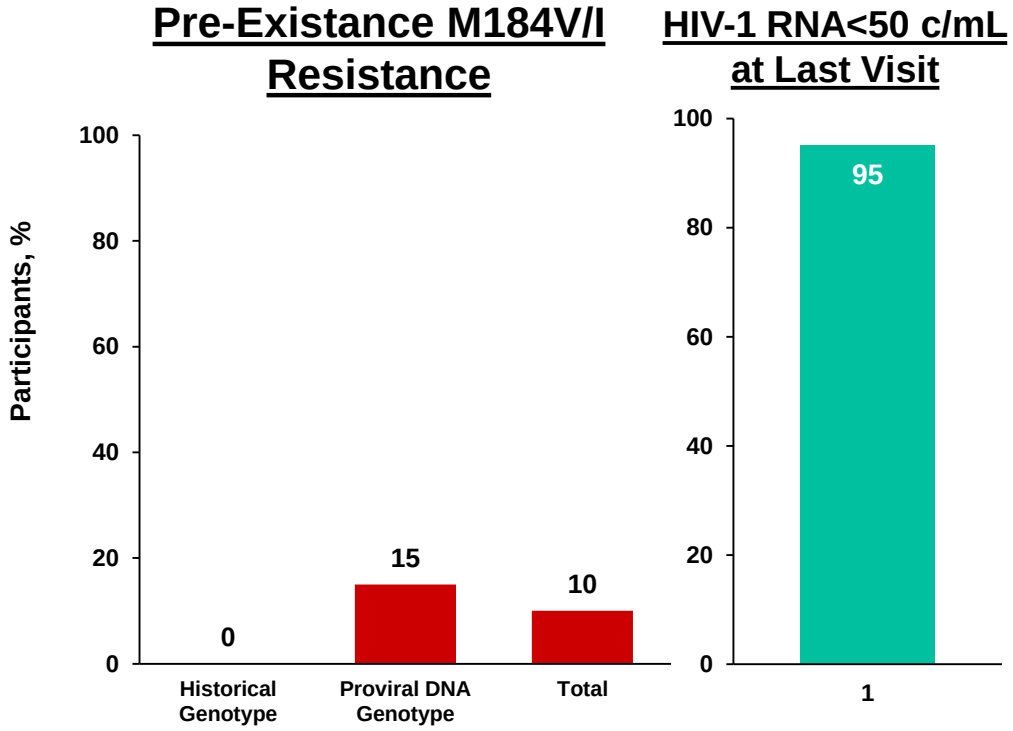
* M184V and M184I cause high-level resistance to FTC and 3TC and increased sensitivity to TAF
† R263K and S153F have been previously selected by DTG and cause reduced susceptibility to DTG. The well with R263K in IN also had T215A and K219R present.

Mulato A, et al. IAS 2019. Mexico City, Mexico. TUPEB244

‡

Resistance Analysis and Virologic Outcomes After >2 Years

Resistance Class	Genotype Source			HIV-1 RNA <50c/mL at Last Visit
	Historical (n=280)	Proviral DNA (n=298)	Total (n=445)*	
NRTI-R	3% (9)	22% (67)	**16%** (70)	**96%** (67/70)
NNRTI-R	15% (42)	24% (72)	**21%** (92)	**99%** (91/92)
PI-R	4% (12)	9% (28)	**8**% (37)	**100%** (37/37)
	Historical (n=23)	Proviral DNA (n=298)	Total (n=445)	
INSTI-R	4% (1)†	2% (6)	**2%** (6)	**100%** (6/6)
Any Class	18% (51)	44% (132)	**36%** (159)	**97%** (155/159)



B/F/TAF may be an effective treatment option for suppressed patients with certain pre-existing resistance mutations including M184V/I

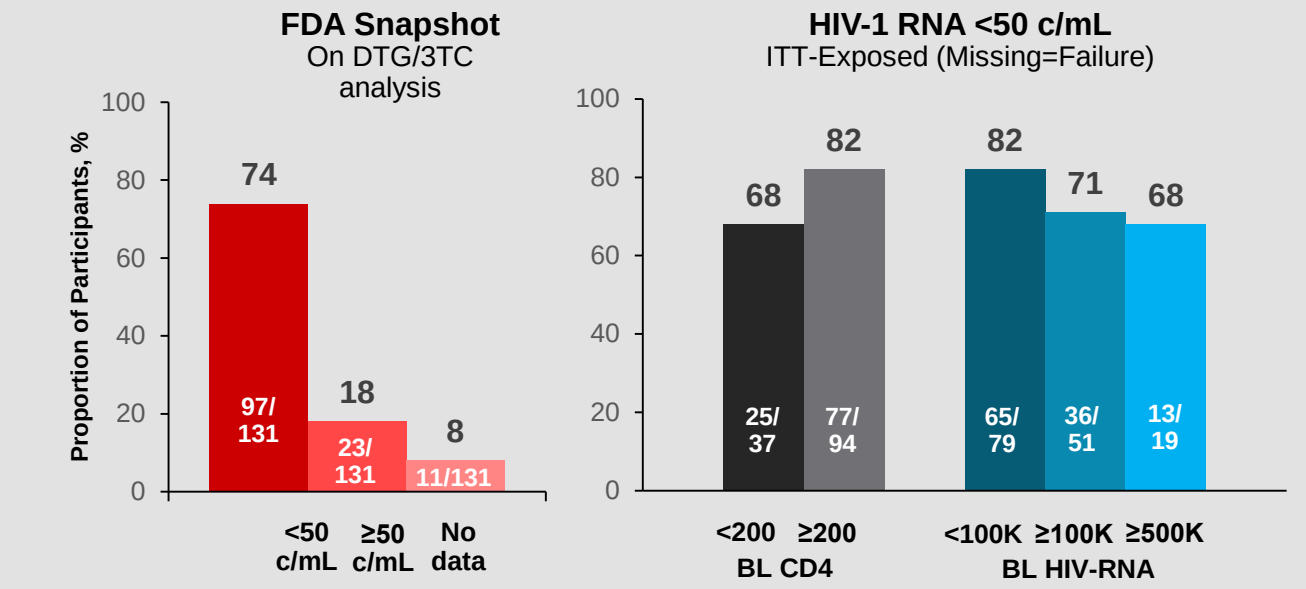
* Total represents participants with either historical or proviral genotypes
† Only 23 adults had INSTI historical genotypic results

Andreatta K, et al. CROI 2019. Seattle, WA. Poster 552

DTG/3TC as a First-Line Regimen in a Test and Treat (within 14 Days) Strategy

Evaluation of efficacy and safety of DTG/3TC initiated within 14 days of diagnosis in ART-naïve adults where baseline laboratory results are not available (N=131)

Efficacy at Week 24



- 87% (97/111) achieved HIV-1 RNA <50 c/mL in the Observed analysis while still on DTG/3TC
- No treatment-emergent resistance detected

Safety

- Grade 2-5 drug-related AEs (2%) and serious AEs (2%)
- 8 (6%) participants switched from DTG/3TC
  - 5 HBV, 1 M184V, 1 adverse event (rash), 1 withdrew
  - 7/8 switched to 3-drug regimen
- 15 (11%) participants discontinued the study
  - 9% loss to follow-up or withdrew consent
  - 2% investigator decision
- Absolute median increase in weight: +4.6 kg

DTG/3TC in a test and treat setting required treatment modifications as a result of baseline HBV coinfection and NRTI resistance

Rolle CP et al. HIV Drug Therapy 2020. Glasgow. P020

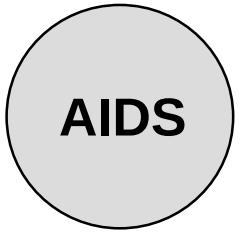
BL, baseline. ITT, intention to treat

What can PLHIV expect from Antiretroviral therapy?

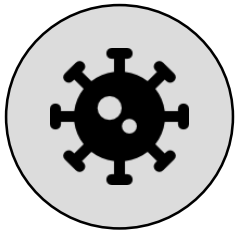
Rapid ART initiation

High genetic barrier to resistance

Long-term, durable efficacy

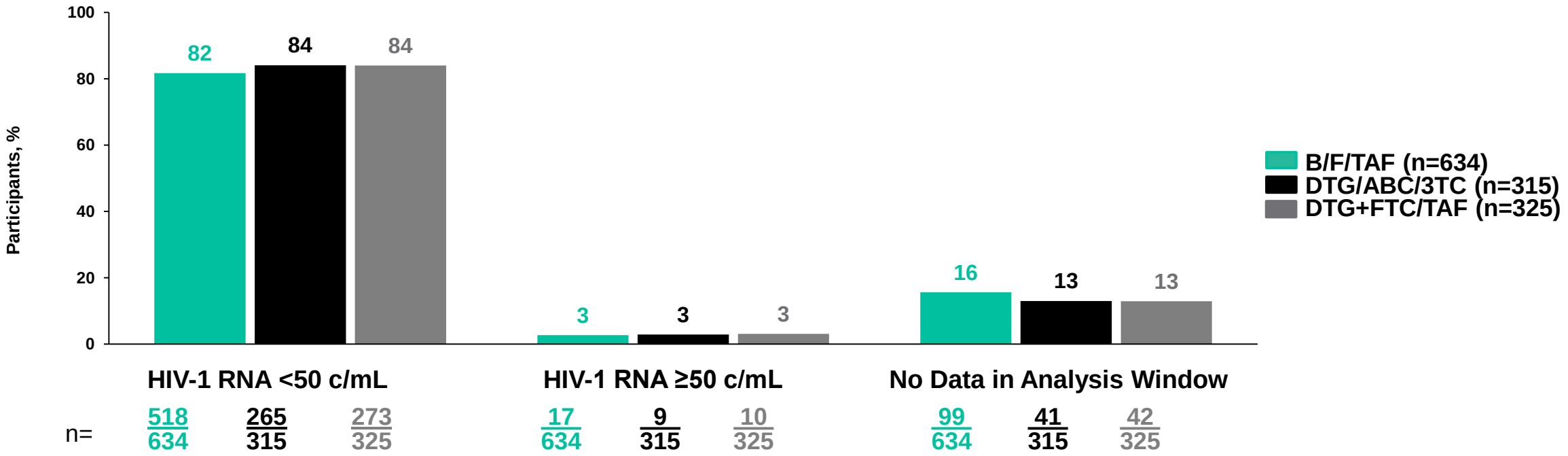


Use in patients with high viral load and/or low CD4 count



Reduction of HIV-1 DNA and immune activation

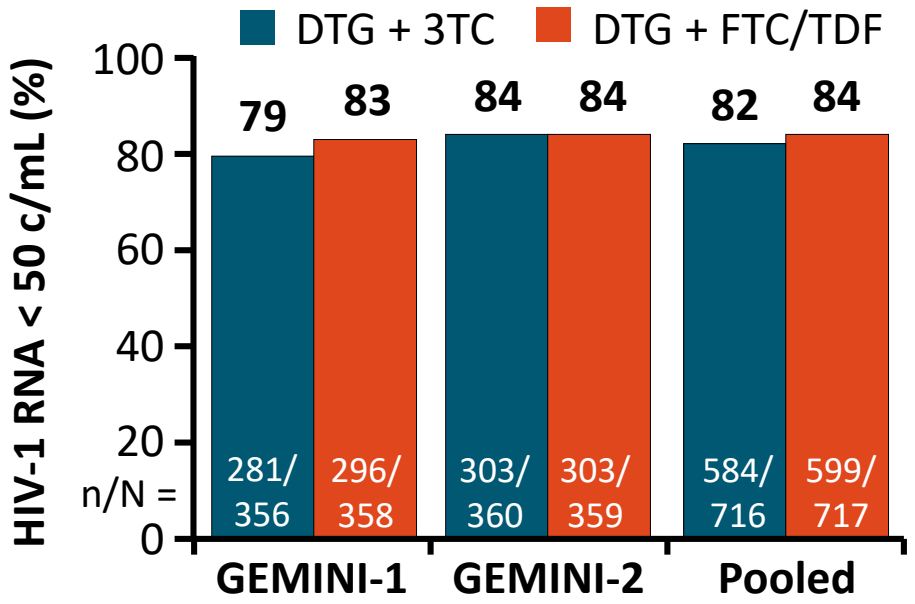
Virologic Outcomes by FDA Snapshot at Week 144

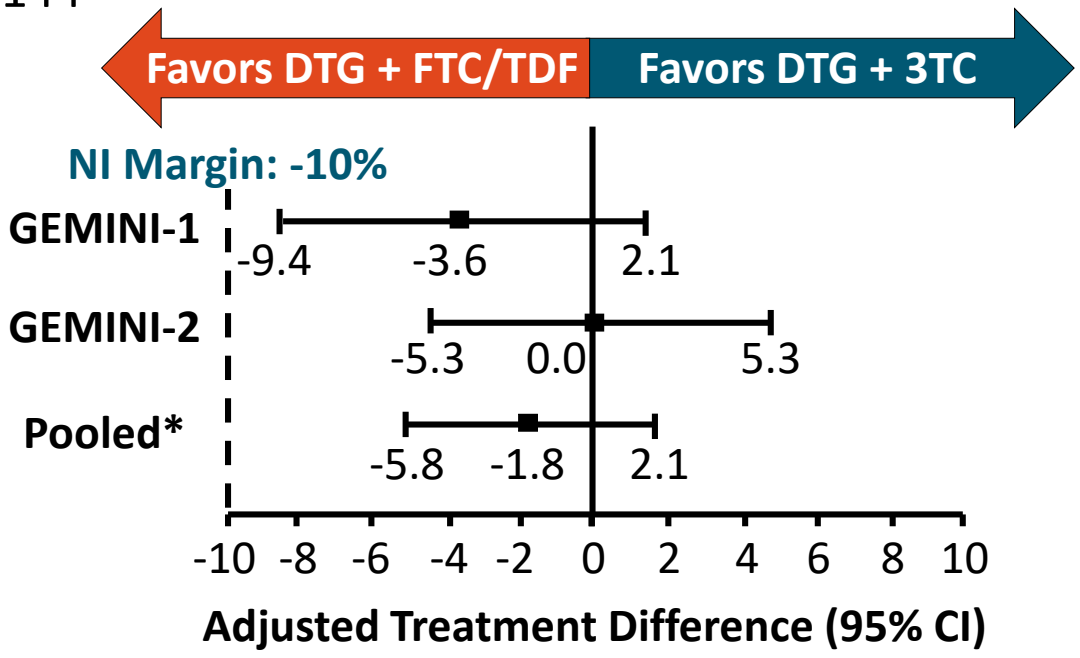


Orkin C, et al. EACS 2019. Basel, Switzerland. PE3/14

GEMINI-1 and -2: Viral Suppression Through Wk 144 With DTG + 3TC vs DTG + FTC/TDF as Initial ART

- Parallel, international, randomized, double-blind phase III noninferiority studies comparing initial ART with DTG + 3TC (n = 716) vs DTG + FTC/TDF (n = 717)
  - DTG + 3TC noninferior at Wk 48 primary analysis (HIV-1 RNA < 50 copies/mL by ITT-E Snapshot)[1] and at Wk 96[2]; current analysis through Wk 144[3]





*Adjusted for BL HIV-1 RNA (≤ 100,000 vs > 100,000 copies/mL), BL CD4+ cell count (≤ 200 vs > 200 cells/mm^3) and study (GEMINI-1 vs GEMINI-2).

1. Cahn. Lancet. 2019;393:143. 2. Cahn. JAIDS.2020;83:310. 3. Cahn. HIV Glasgow 2020. Abstr P018.

Slide credit: clinicaloptions.com

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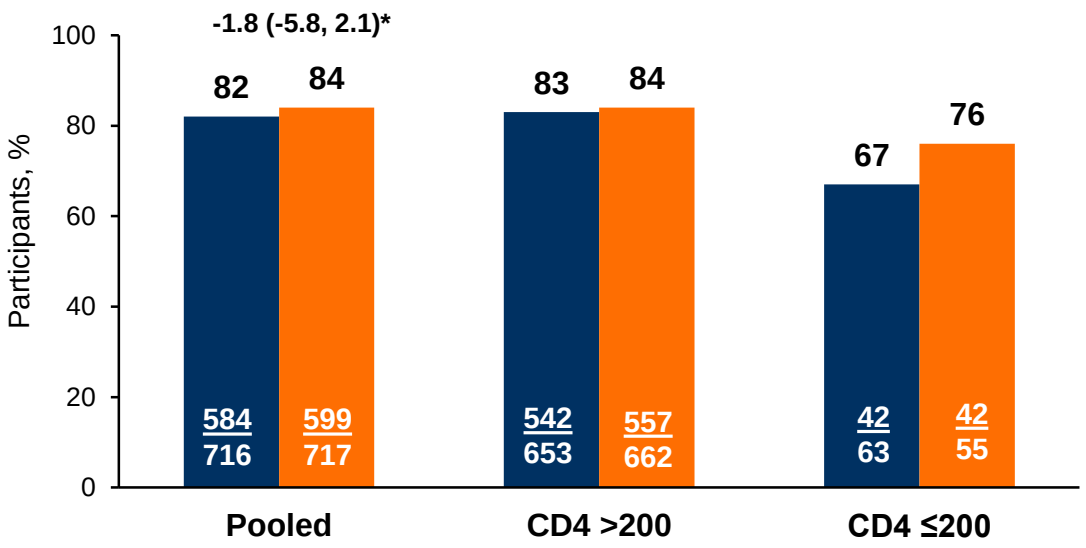
Open Label Phase: Efficacy and Overall Weight Change at Week 144

HIV-1 RNA <50 c/mL: Snapshot Analysis



Resistance

- 1 DTG+3TC participant with reported non-adherence and BL VL 93,515 c/mL & CD4 393 cells/mm^3 developed RT resistance which evolved to 2-class resistance despite maintaining VL <200 c/mL
  - Suppressed <50 c/mL from W4 to W120 with viral rebound to 61,927 c/mL at W132 and resuppressed to <200 c/mL

W132	**RT:**	**M184V**	**VL 61,927 c/mL**
W144	**IN:**	**R263R/K**	**VL 135 c/mL**

  - ria of consecutive VL ≥200 c/mL where only 1st sample would have been tested for resistance†

Weight: Mean Change from Baseline

- +3.7kg (DTG+3TC) and +2.4kg (DTG+FTC/TDF) at W144
  - Not reported: p-value, variance (IQR), subgroup analysis (sex/race)

At W144 DTG+3TC maintained non-inferior efficacy but showed lower viral suppression rates in participants with baseline CD4 ≤200 cells/mm^3

2-class treatment emergent resistance observed in one DTG+3TC participant

CI, confidence interval; IQR, interquartile range; VL, viral load (HIV-1 RNA)
*Adjusted treatment difference (95% CI)
†Protocol required discontinuation if VL decrease < 1log10 by W12 (except if <200 c/mL by W12), confirmed rebound ≥200 c/mL at/after W24 with first initial suspected VL sample used for resistance testing

‡

Open Label Phase: Safety at Week 144

n (%) or mean change from baseline	DTG+3TC (N=716)	DTG+FTC/TDF (N=717)
Drug-related AEs Any grade 2-5	146 (20%) 58 (8%)	192 (27%) 69 (10%)
AEs leading to discontinuation	31 (4%)	33 (5%)
Any serious AE	76 (11%)	85 (12%)
Serum creatinine, µmol/L*	+12.6	+15.5
Serum creatinine, mg/dL*	+0.14	+0.18
GFR from cystatin C, mL/min/1.73m^2*	+12.2	+10.6
TC:HDL-C ratio*	-0.2	-0.4
Weight, kg†	+3.7	+2.4

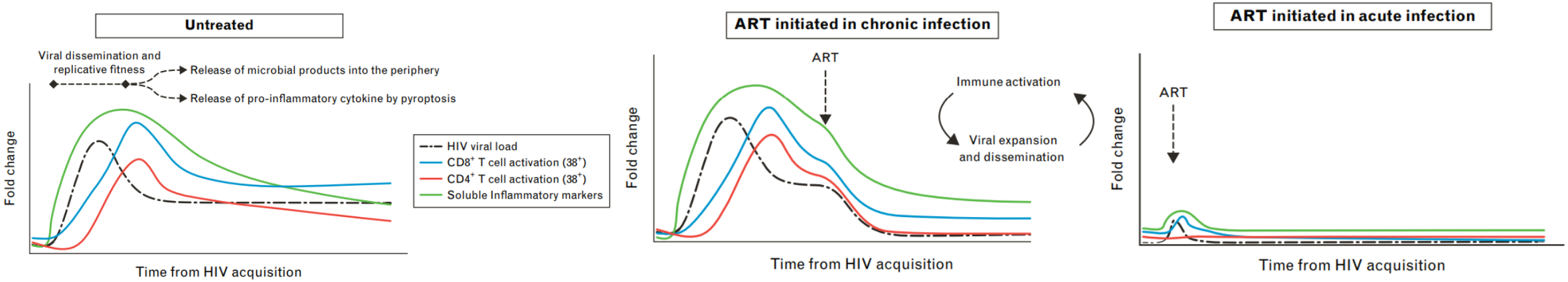
- Majority of drug-related AEs were mild in severity
- Findings were consistent with W48 and W96 for lipids and renal and bone biomarkers

Overall safety and tolerability were comparable between DTG+3TC and DTG + F/TDF

AE, adverse event; TC, total cholesterol; HDL-C high density lipoprotein cholesterol
**P* <0.01; †No p-value reported

Cahn P, et al. HIV Drug Therapy 2020. Glasgow. Poster #018

ART initiation, particularly during acute infection, reduces immune activation in PLHIV



Initiating ART during acute infection attenuates inflammation more than initiating ART in chronic HIV infection[1]

Early ART initiation has been associated with (vs baseline):[2]

- ↓ sCD14 and CRP levels
- ↑ CD4 cell count
- Normalisation of TNF, sIL-6R, and D-dimer levels

ART, antiretroviral therapy; CD4, cluster of differentiation 4; CRP, C-reactive protein; sCD14, soluble CD14; sIL-6R, soluble interleukin 6 receptor; TNF, tumour necrosis factor.

1. Krebs J et al. *Curr Opin HIV AIDS* 2016;11:163–172; 2. Sereti et al. *Clin Infect Dis* 2016;64:124–131.

Long-term effects of triple therapy on immune recovery are well characterised

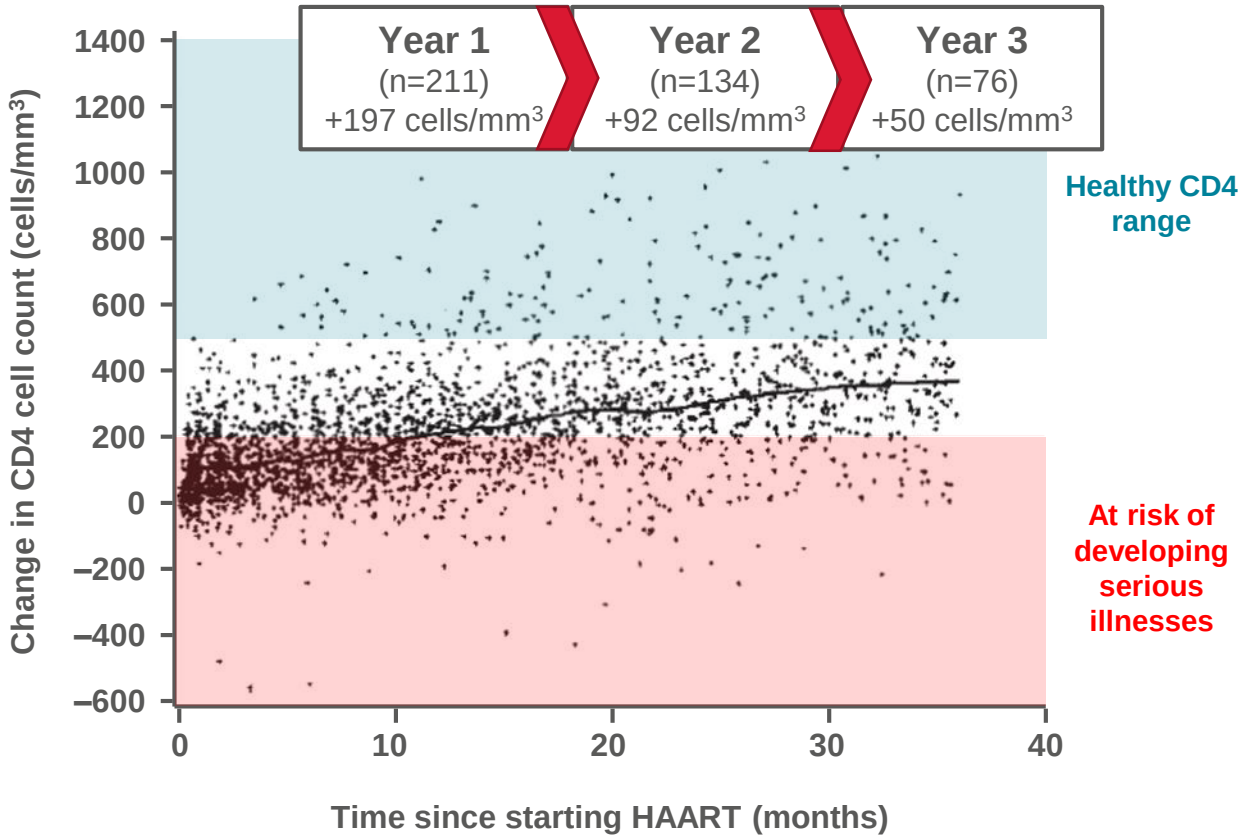
Median follow-up of 237 treatment-naïve PLHIV initiating a triple therapy-based regimen and whose VL remained at <500 copies/mL for a prolonged period[1]

- Rapid ↑CD4 cell counts in the first month, followed by a less rapid but continued CD4 increase
- After 2 years of HAART, CD4 levels:
  - Increased by 319 (range -224–1546) cells/mm^3
  - >500 cells/mm^3 in 40% of participants

Factors negatively impacting CD4 recovery[2]

- Low proportion of naïve cells among CD4+ T-lymphocytes
- Persistent viral replication
- Immune activation, microbial translocation
- Older age, HCV co-infection
- Pre-therapeutic low CD4+ T-cell nadir

Individual changes in CD4 count from baseline[a]



[a]Locally weighted robust scatter-plot smoothing (Lowess) estimate of the overall trend.

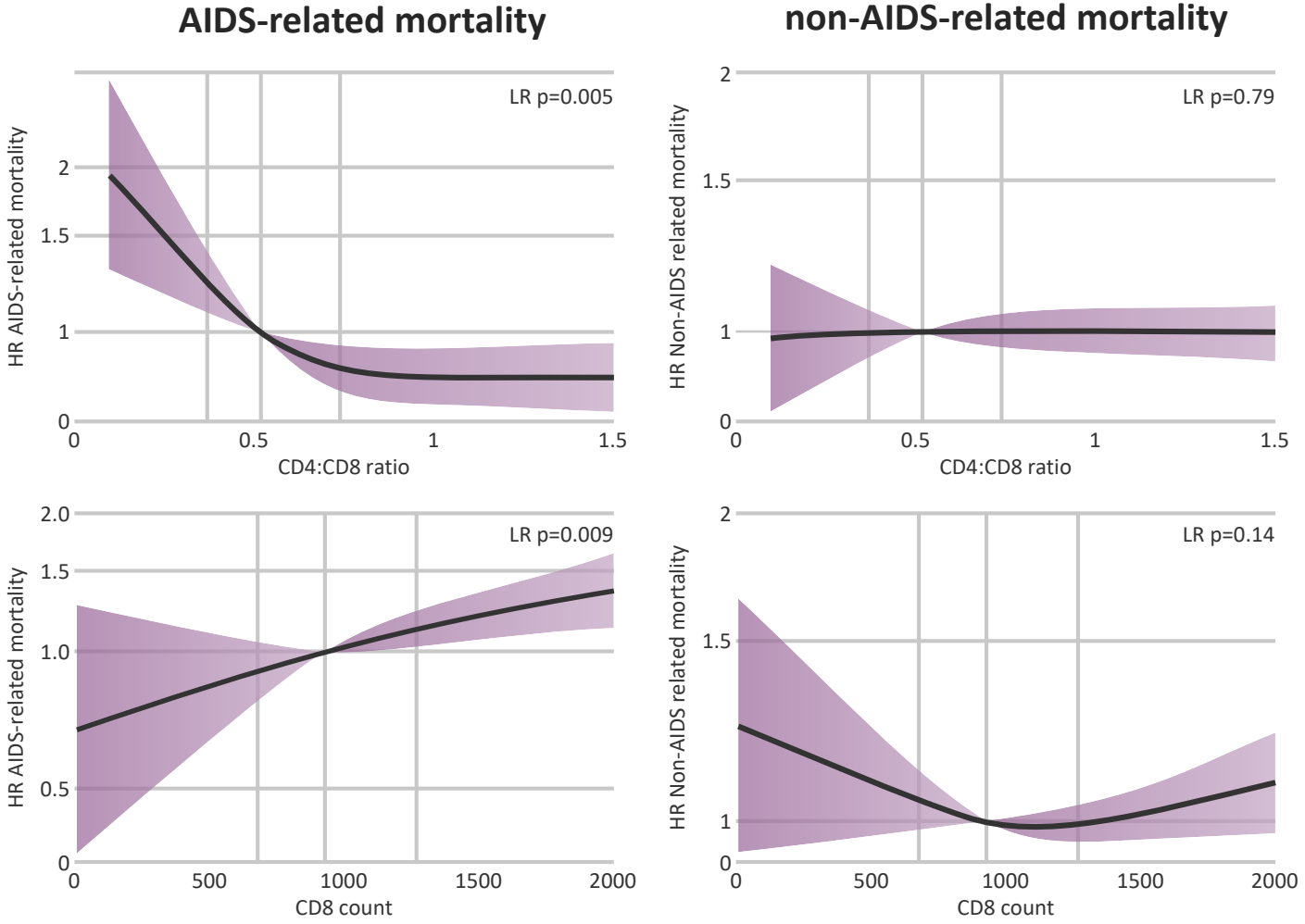
CD4, cluster of differentiation 4; HAART, highly-active antiretroviral therapy; HCV, hepatitis C virus; PLHIV, people living with HIV; VL, viral load.

1. Smith C, et al. *AIDS* 2003;17:963–9; 2. Corbeau P, et al. *Blood* 2011;117:5582–90.

CD4:CD8 ratio and CD8 as prognostic markers for mortality in ART-treated PLHIV

CD4:CD8 ratio

CD8 count



- Cohort of 49,865 PLHIV starting ART between 1996 and 2010
- Follow-up started at CD4 ≥350 cells/µL and VS*
- 276,526 person-years of follow-up

AIDS-related mortality declined with increasing CD4:CD8 ratio (LR p<0.005) and decreasing CD8 count (LR p=0.009)

Non-AIDS-related mortality was not significantly associated with CD4:CD8 or CD8 count

Plots of adjusted hazard ratio (HR) of AIDS-related (left panels) and non-AIDS-related (right panels) mortality with median as comparator for CD4:CD8 ratio (upper panels) and CD8 count (lower panels) with 95% confidence intervals. Modelled using cubic splines. The vertical lines indicate the median and interquartile range.

*Virologic suppression defined as HIV RNA lower than the limit of detection of the assay or <200 copies/µL.

HR; Hazard ratio, LR; Likelihood ratio; PLHIV, people living with HIV; VS, virologic suppression.

Trickey A et al Clin Infect Dis. 2017 Sep 15;65(6):959-966

CD4:CD8 ratios continued to increase in PLHIV who maintained triple therapy ART after viral suppression

Linear mixed model regression analysis of association between CD4 and CD8+ cells and type of ART regimen started after switch

	Unadjusted coefficient	95% CI	Adjusted coefficient	95%CI
CD4:CD8 ratio (log_{10})				
Regimen after switch				
Triple	+0.042	(+0.037, +0.047)	+0.056	(+0.047, +0.064)
2DC	–0.013	(–0.029, –0.003)	–0.029	(–0.056, –0.002)
Mono	–0.013	(–0.030, +0.005)	–0.011	(–0.044, +0.021)
CD8, cells/mm^3				
Regimen after switch				
Triple	–22.2	(–48.0, +3.7)	–25.7	(–51.6, +0.28)
2DC	+114.9	(–32.9, +197.0)	+110.4	(+27.3, +193.6)
Mono	+73.5	(–25.4, + 172.5)	+64.7	(–35.6, +165.0)
CD4, cells/mm^3				
Regimen after switch				
Triple	+46.7	(+40.3, +53.1)	+45.2	(+30.7, +59.6)
2DC	+7.6	(–13.5, +28.8)	+32.1	(–13.1, +77.3)
Mono	+23.6	(–1.40, +48.7)	+18.0	(–36.9, +72.9)

- Observational cohort included PLHIV (N=1,241) who achieved VL ≤ 50 copies/mL on a triple ART regimen and then switched to another regimen:
  - 1073 switched to triple ART regimen
  - 104 to dual ART regimen
  - 64 switched to monotherapy
- 6,528 CD4:CD8 ratio measurements were collected over a period of 24 months after the ART switch

- The slope of the CD4:CD8 ratio increased for people switching to triple therapy vs. two drug combinations
- CD8 count increased for participants switching to a two drug combinations

Unadjusted and adjusted coefficients from linear mixed model regression analysis to test the association between the dependent variable and type of regimen started after switch. Every model is adjusted for: age, gender, mode of HIV transmission, Italian nationality, previous AIDS event, years of HIV infection, HCV co-infection, HIV RNA and CD4 at cART initiation, CD4 and CD8 count at switch, reason for switch, months of viral suppression.
2DC, two drug combination; cART, combination ART, VL, viral load

Mussini C et al. BMC Med. 2018 May 29;16(1):79. doi: 10.1186/s12916-018-1046-2.

HIV-1 DNA changes in patients on suppressive triple antiretroviral therapy for ≥10 years

Triple therapy is associated with a reduction of the HIV-1 DNA reservoir (1/2)

Study design

Longitudinal study of HIV-1 DNA changes in participants on suppressive triple antiretroviral therapy for ≥10 years (n=30)

Aim

Long-term changes in total and episomal HIV-1 DNA in blood assessment

Inclusion/exclusion criteria

- Participants enrolled in ACTG A5001 cohort
- ART-naïve, plasma HIV-1 RNA suppressed (<50 copies/mL) from Week 32 of initial therapy for ≥10 years
- ≥1 PBMC and plasma samples: pre-ART; at Years 1 and 10

Participant characteristics (n=30)	
Pre-ART median age, years (Q1, Q3)	37 (31, 42)
Sex, male n, (%)	23 (77)
Race/ethnicity	
White, non-Hispanic	16 (53)
Black, non-Hispanic	5 (17)
Hispanic (regardless of race)	7 (23)
Pre-ART HIV-1 RNA (log_{10} copies/mL), median (Q1, Q3)	4.7 (4.3, 5.4)
Pre-ART CD4+ T-cells percent, median (Q1, Q3)	15 (10, 24)
Initial ARV regimen, n (%)	
EFV + 2/3 NRTI	16 (53)
ABC/AZT/3TC	8 (27)
EFV + NFV + 2 NRTI	4 (13)
NFV + 2 NRTI	2 (7)
ARV regimen at final time point, n (%)	
EFV + 2/3 NRTI	21 (70)
ATV/RTV + 2 NRTI	3 (10)
NVP + 2/3 NRTI	3 (10)
LPV/RTV + 2 NRTI	1 (3)
NFV + 2 NRTI	1 (3)
ABC 3TC EFV RAL	1 (3)

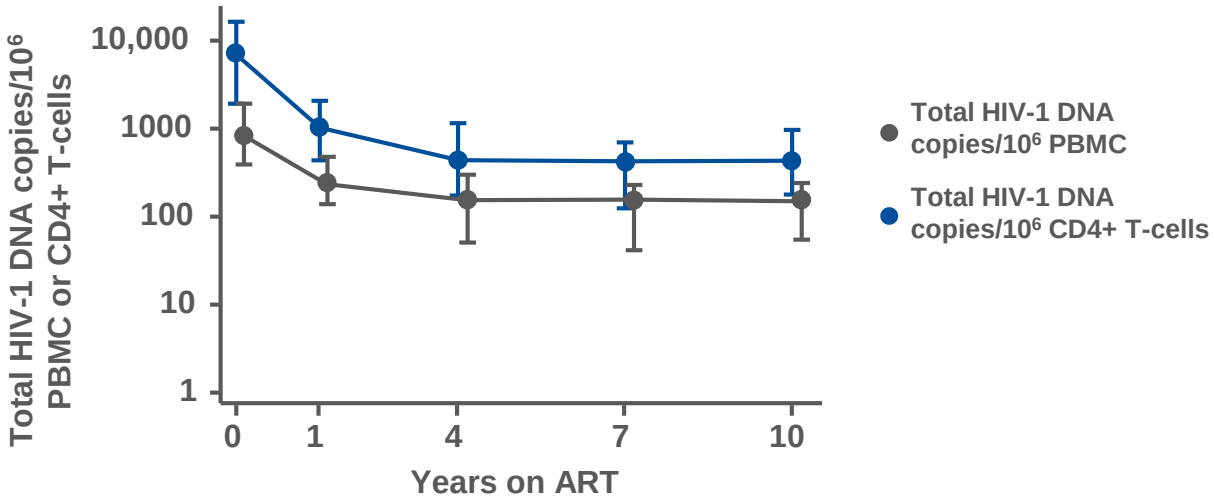
3TC, lamivudine; ABC, abacavir; CD4, cluster of differentiation 4; ACTG, AIDS Clinical Trial Group; ART, antiretroviral therapy; ATV, atazanavir; DNA, deoxyribonucleic acid; EFV, efavirenz; LPV, lopinavir; NFV, nelfinavir; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PBMC, peripheral blood mononuclear cell; Q, quartile; RAL, raltegravir; RNA, ribonucleic acid; RTV, ritonavir.

Besson GJ, et al. *Clin Infect Dis* 2014;59:1312–21.

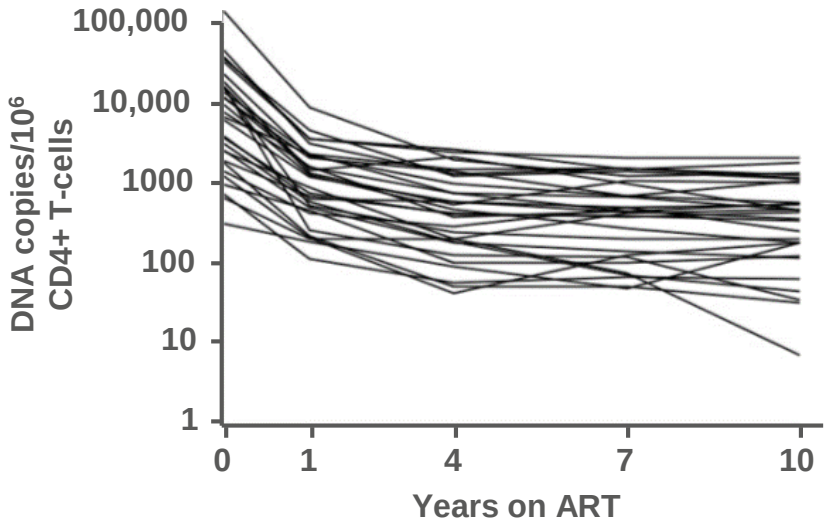
Triple therapy is associated with a reduction of the HIV-1 DNA reservoir (2/2)

- Initiating triple therapy in treatment-naïve patients led to a decrease of HIV-1 DNA reservoirs during the first five years, followed by stabilisation[1]

Total HIV-1 DNA over time (median [Q1, Q3])[1]



By-subject total HIV-1 DNA over time[1]



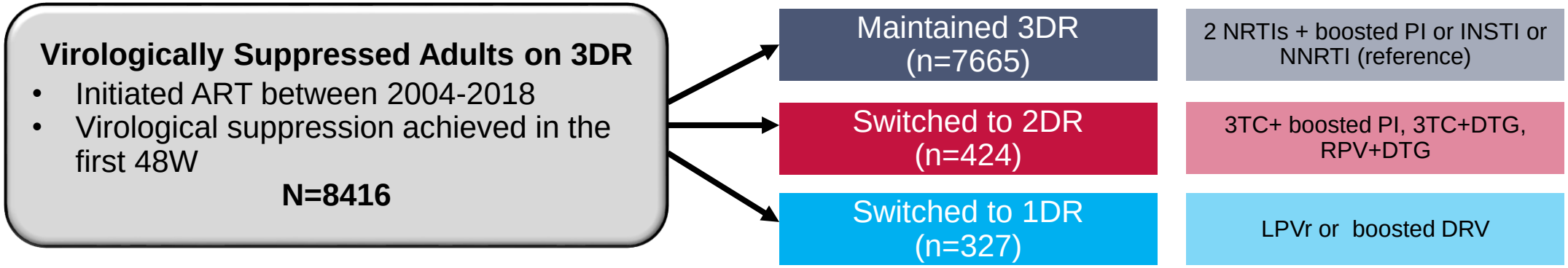
- Another study in a cohort of PHI patients (N=327) demonstrated that the earlier HAART is initiated after HIV infection, the faster the HIV-1 DNA levels decreased during the first eight months of treatment[2]

ART, antiretroviral therapy; CD4, cluster of differentiation 4; DNA, deoxyribonucleic acid; HAART, highly-active antiretroviral therapy; PHI, primary HIV infection; Q, quartile.

1. Besson GJ, et al. *Clin Infect Dis* 2014;59:1312–21; 2. Laanani M, et al. CROI 2015, #373.

Switch to 2DR vs Maintaining 3DR: Virologic Failure and Clinical Events

Retrospective analysis evaluating virological failure and clinical outcomes



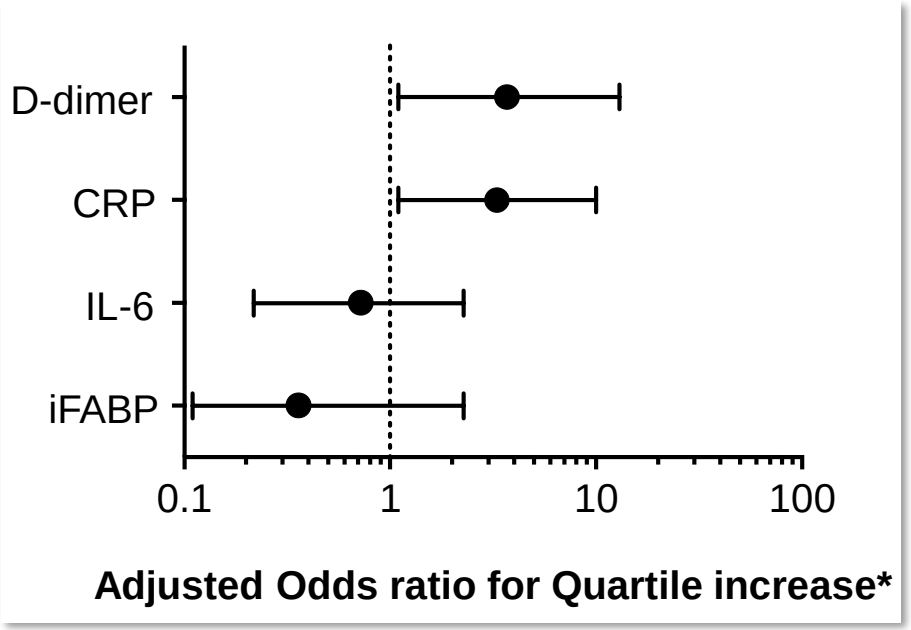
Outcome	Finding
Virological failure	• 3-fold greater risk with 1DR after 24 months of ART • No difference between 3DR and 2DR after 24 months of ART
Severe non-AIDS events **AIDS or AIDS related deaths** **All cause of death**	• Low absolute numbers of death and clinical events • No difference between regimens

CoRIS, Cohorte de la red de Investigacion en Sida

Serrano-Villar S, et al. AIDS 2020. Oral OAB0304

Switch to 2DR vs Maintaining 3DR: Inflammatory Markers

Inflammatory sub study comparing inflammatory markers in 148 PLWH with 612 prospectively stored samples and up to 8 years of follow-up; inclusion: longer follow-up and at least 3 samples



Compared to 3-drug combinations, 2-drug combinations were associated with a 2-3 fold higher probability of experiencing a D-dimer or CRP increase during follow-up

*Adjusted for age, sex, risk group, education level, AIDS, CD4 nadir, maximum HIV RNA, biomarker level at HIV RNA suppression, years of follow-up
iFABP, Intestinal fatty-acid binding protein; IL-6, interleukin-6; CoRIS, Cohorte de la red de Investigacion en Sida; CRP,C reactive protein

Serrano-Villar S, et al. AIDS 2020. Oral OAB0304

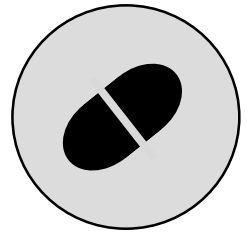
What can PLHIV expect from Antiretroviral therapy?

Rapid ART initiation

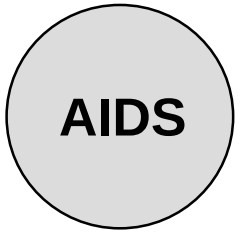
High genetic barrier to resistance

Long-term, durable efficacy

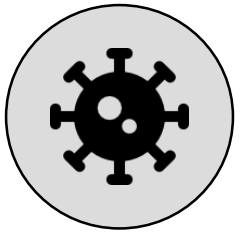
Established efficacy in special populations



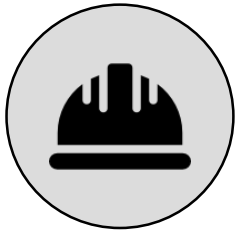
Simplicity of STR with once-daily dosing



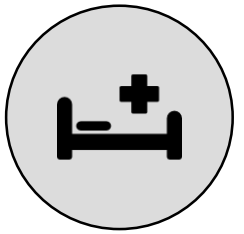
Use in patients with high viral load and/or low CD4 count



Reduction of HIV-1 DNA and immune activation



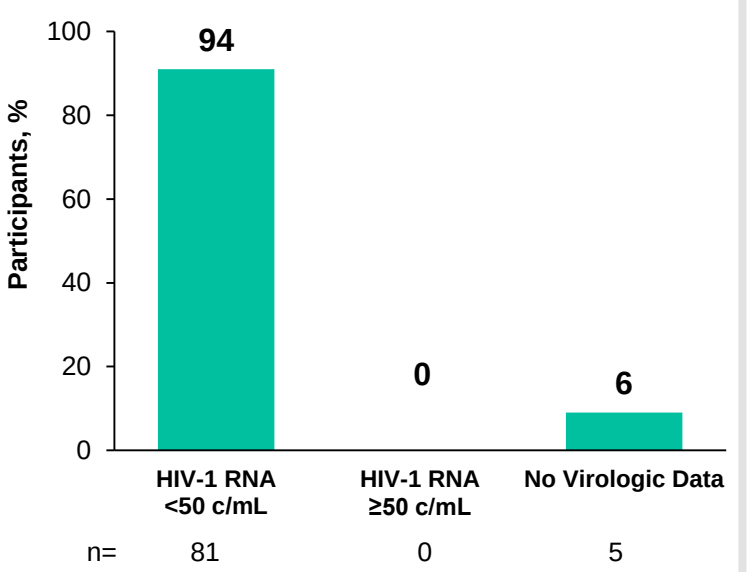
Favourable safety profile



Positive impact on AIDS- and non-AIDS related morbidity/mortality

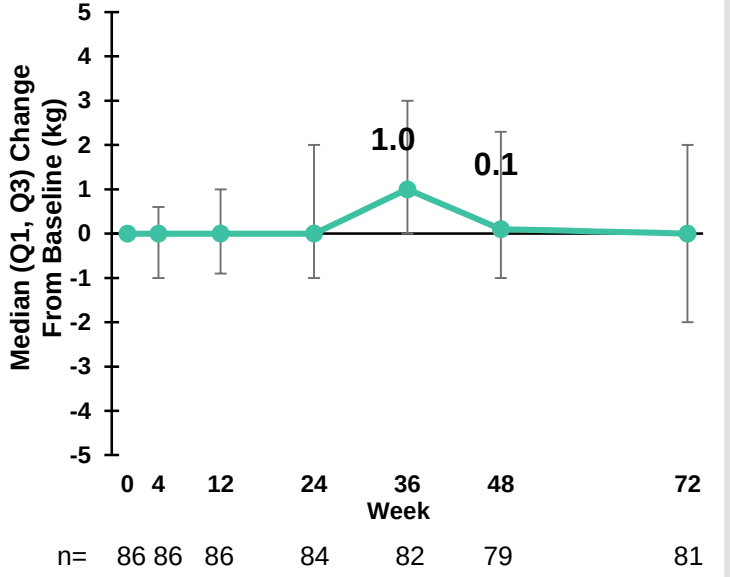
Efficacy, Weight Change and Safety through Week 72

Efficacy



- No treatment emergent resistance to any of the regimen components

Weight Change



- No change from baseline in median weight

Safety

Adverse Events, % (n)	B/F/TAF n = 86
Study drug-related AEs (grades 2, 3 or 4)	**4.7% (4)**
Study drug-related AEs (grades 3 or 4)	**2.3% (2)**
Any study drug-related serious AE	**0**
AE leading to study drug discontinuation	**4.7% (4)**
Drug-related	**2.3% (2)***
Renal AEs leading to study drug discontinuation	**0**
Death	**2†**

*1) abdominal discomfort (grade 2), 2) irritability and sleep disorder (grade 4)
†1) 77 yo male with pre-existing depressive disorder led to suicide via a benzodiazepine overdose (study day 427), 2) 72 yo male developed and succumbed to pneumonia secondary to COVID-19 infection (study day 672); Neither death study drug-related

B/F/TAF was highly effective with no virologic failure and no treatment emergent resistance and well-tolerated in virologically suppressed adults ≥65 years through W72

AE, adverse event

Maggiolo F, et al. HIV Drug Therapy 2020. Glasgow. P038

Summary of HIV Symptom Index Bothersome Symptoms B/F/TAF vs. DTG-based Regimens*

Favors B/F/TAF
No differences between arms
Favors DTG/ABC/3TC

	Study 1489 Treatment-naïve				Study 1844 Virologically suppressed			
	Week†			Longitudinal Model‡	Week†			Longitudinal Model‡
	4	12	48		4	12	48	
Nausea/vomiting	✓	✓		✓		✓	✓	✓
Loss of appetite		✓		✓		✓		✓
Difficulty sleeping		✓	✓			✓		✓
Fatigue/loss of energy	✓	✓	✓	✓	✓			
Dizzy/lightheadedness	✓		✓		✓			✓
Sad/down/depressed					✓		✓	✓
Nervous/anxious					✓	✓	✓	✓

✓ = Statistically significant ($p<0.05$), based on the adjusted logistic regression model, favoring the B/F/TAF group over the DTG/ABC/3TC group*

Across studies of treatment-naïve and virologically suppressed adults, bothersome symptoms were reported by fewer participants on B/F/TAF than those on DTG/ABC/3TC*

*Hair loss at Week 4 in Study 1844 was the only PRO that favored DTG/ABC/3TC

† Multivariate regression model controlled for age, sex, race, baseline HIV Symptom Index score, VACS Index, history of serious mental illness, baseline SF36 physical and mental scores, and years since diagnosis (for study 1844 only). ‡ Longitudinal modeling was performed using generalized mixed-effects models to show symptom patterns over each of the four study visits.

Wohl D, et al. The Patient 2018;11(5):561-573; Wohl D, et al. AIDS 2018. Amsterdam, NL. Poster TUPEB148

Patient-Reported Outcomes: Conclusions

- In head-to-head blinded, randomized, controlled trials of treatment-naïve and treatment-experienced adults with HIV, utilizing validated patient reported outcome tools resulted in
  - Favorable patient-reported outcomes reported when initiating or switching to B/F/TAF vs initiating or continuing DTG/ABC/3TC with less reports:
    - GI symptoms: nausea/vomiting and loss of appetite
    - Difficulty sleeping or poor sleep quality
    - Fatigue
    - Dizziness/light-headedness
    - Depression
    - Anxiety
- Patient-reported outcomes supplement spontaneous adverse events reporting in clinical trials and may further differentiate the safety and tolerability of the regimens

Wohl D, et al. The Patient 2018. https://doi.org/10.1007/s40271-018-0322-8
Wohl D, et al. AIDS 2018. Poster # PEB148

The battle

No TAF

TAF

Interim BHIVA guidance for the management of adults with HIV on antiretroviral treatment (ART) during the coronavirus pandemic

ART INITIATION

Critical requirements for initiating ART include:

- use of a regimen with a high barrier to resistance
- use of a well-tolerated regimen with high efficacy, a high barrier to resistance and low risk of toxicity
- need to minimise viral load and safety monitoring
- use of a regimen with few major drug–drug interactions and ideally a single tablet regimen without food requirements

Suggested first-line ART algorithm

Recommended: **BIC/FTC/TAF**

- Unless contra-indicated due to DDIs or a new diagnosis in a pregnant woman (follow BHIVA guidelines)

ART options should still be discussed and, where necessary, tailored according to patient needs and requirements

https://www.bhiva.org/file/5eac2b1e84f0f/BHIVA-interim-ART-guidelines-COVID-19-01052020.pdf

- Naive patient

- Experienced patient

Reasons to Consider an ART Switch During Viral Suppression

Appropriate

- To **simplify** a regimen by reducing pill burden and/or dosing frequency
- To enhance **tolerability** and/or decrease short- or long-term **toxicity**
- To prevent or mitigate **drug-drug interactions**
- To eliminate food or fluid requirements
- To allow for optimal use of ART **during pregnancy** or in cases where pregnancy may occur
- To **reduce costs**

Inappropriate

- To use the “newest” regimen
- To reduce costs at the price of a toxicity or intolerance risk for your patient

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

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

DHHS Guidelines. Dec 2019.

Interim BHIVA guidance for the management of adults with HIV on antiretroviral treatment (ART) during the coronavirus pandemic

ART MAINTENANCE

- Most PLHIV receiving ART are virally suppressed
- Usual efficacy and safety monitoring is six-monthly for PLHIV who are virologically stable on ART. Potential deferral for patients with good adherence, no tolerability/toxicity concerns and no DDIs issues
- No ART switch should be undertaken unless absolutely necessary (e.g. pregnancy, VF, tolerability/toxicities or DDIs issues)
- Non-essential monitoring should be deferred
- To reduce workloads for virology labs, viral resistance testing should be limited to:
  - BL testing for naïve
  - Patients with confirmed VL>200 cp/mL on a low genetic barrier regimen (pre-emptive switch to a high barrier regimen can be undertaken before results are available if clinically appropriate)
  - Patients reporting good adherence with new VL >1000 cp/mL on a high genetic barrier regimen

https://www.bhiva.org/file/5eac2b1e84f0f/BHIVA-interim-ART-guidelines-COVID-19-01052020.pdf

Key Recommendations for When and How to Switch ART Regimens

- Thorough review of treatment history required – regimen tolerability, co-medications, food requirements, costs, and results from prior resistance tests
- Follow-up HIV viral load in 1 month after *any* switch
- Switching after viral suppression
  - If HBSAg positive, include TAF or TDF whenever possible
  - If NRTI resistance in the past, do not switch from boosted PI to low genetic barrier drug (e.g., NNRTI or RAL)
  - Simplification to certain 2-drug regimens (DTG/3TC, DTG/RPV, boosted PI/3TC, eventually CAB/RPV) may be appropriate to manage toxicity or in response to patient preference, provided *both* drugs are active

Saag, Gandhi, Hoy et al, *JAMA*, 2020.

Effect of past virological failure on dolutegravir+lamivudine as maintenance regimen [ICONA]

Background: Dolutegravir (DTG)+lamivudine (3TC) was shown to be as effective as triple therapy in RCT on patients (pts) switching during virological suppression, but limited data are available about the use of this regimen in pts with previous virological failures (VF), since RCT excluded these pts.

Retrospective multi-cohort study across Italian infectious disease clinics **switching for the first time to DTG+3TC from any other regimen (baseline)**

Study population

- **PLWH >18 years old**
- **Enrolled in ICONA Foundation Study cohort or in 5 Italian monocentric Cohorts**
- **Starting DTG+3TC with HIV-RNA <50 cp/mL from any ART**

Endpoints

- **Viral rebound (confirmed HIV-RNA ≥50 c/mL)**
- **Viral blip (HIV-RNA ≥50 c/mL not confirmed by the following measurement)**

Definitions

- **Def 1**: Single HIV-RNA ≥1000 c/mL or confirmed HIV-RNA ≥50 c/mL on any ART
- **Def 2**: Single HIV-RNA ≥1000 c/mL or confirmed HIV-RNA ≥50 c/mL on a NRTI or INSTI-containing regimen and HIV-RNA ≥ 50 c/mL or a single HIV-RNA≥50 c/ml followed by change of ART

	Overall population N=966	No previous VF N=772	≥1 previous VF N=194	p-value
Female gender, n(%)	248 (25.7%)	189 (24.5%)	59 (30.4%)	0.091
Age, median (IQR)	51 (44-57)	50 (42-57)	53 (49- 58)	<0.001
Mode of HIV transmission, n(%)				<0.001
heterosexual	340 (35.2%)	274 (35.5%)	66 (34.0%)	
IVDU	146 (15.1%)	94 (12.2%)	52 (26.8%)	
MSM	356 (36.9%)	307 (39.8%)	49 (25.3%)	
Other/unknown	124 (12.8%)	97 (12.6%)	27 (13.9%)	
CDC stage C, n(%)	150 (15.5%)	107 (13.9%)	43 (22.2%)	0.017
HCV Ab, n(%)				<0.001
negative	753 (78.0%)	623 (80.7%)	130 (67.0%)	
positive	172 (17.8%)	111 (14.4%)	61 (31.4%)	
missing	41 (4.2%)	38 (4.9%)	3 (1.6%)	
HBsAg, n(%)				0.008
negative	834 (87.7%)	653 (86.3%)	181 (93.3%)	
positive	15 (1.6%)	11 (1.4%)	4 (2.1%)	
missing	102 (10.7%)	93 (12.3%)	9 (4.6%)	
Nadir CD4, cell/mmc, median (IQR)	247 (98-372)	268 (126-400)	165 (44-270)	<0.001
CD4 at switch, cell/mmc, median (IQR)	699 (541-888)	695 (545-898)	714 (525-864)	0.870
Years of HIV Infection, median (IQR)	12 (6-21)	9 (5-17)	22 (19-27)	<0.001
Years of ART, median (IQR)	8.4 (4.0-17.5)	6.6 (3.3-12.1)	18.9 (16.5-20.7)	<0.001
Years of viral suppression, median (IQR)	7.0 (3.4-12.0)	5.9 (2.9-10.6)	12.0 (8.4-14.3)	<0.001

20% had ≤1 VF; 8% had ≥2 VF

Gagliardini R et al. CROI 2020; Boston. Poster 0486

Effect of past virological failure on dolutegravir+lamivudine as maintenance regimen

Results

Def 1: Single HIV-RNA ≥1000 c/mL or confirmed HIV-RNA ≥50 c/mL on any ART

Viral Rebound [Def 1]	HR 95%CI	p-value	AHR 95%CI	p-value	AHR 95% CI (sensitivity analysis)	p-value
Previous VF 1 vs 0	2.81 (0.70-11.25)	0.144	2.87 (0.65-12.74)	0.166	3.71 (0.53-25.75)	0.185
Previous VF ≥ 1 vs 0	2.88 (0.74-11.13)	0.125	3.39 (0.77-14.90)	0.106	5.39 (0.99-29.30)	0.051

VR was detected in 11 pts over 1555 person-year-follow-up (PYFU): total incidence ratio (IR) was 0.7 x 100 PYFU (95% CI 0.4-1.3), 0.5 x 100 PYFU (0.2-1.1) in pts without previous failures and 1.4 x 100 PYFU (0.6-3.4) in pts with >=1 previous VF, with an estimated 1-year probability of 0.4% (0.1-1.4) and 1.3% (0.3-5.3) respectively (log-rank p=0.071)

Def 2: Single HIV-RNA ≥1000 c/mL or confirmed HIV-RNA ≥50 c/mL on a NRTI or INSTI-containing regimen and HIV-RNA ≥50 c/mL or a single HIV-RNA ≥50 c/ml followed by change of ART

Viral Rebound [Def 2]	HR 95%CI	p-value	AHR 95%CI	p-value	AHR 95% CI (sensitivity analysis)	p-value
Previous VF 1 vs 0	2.62 (0.93-7.42)	0.069	2.37 (0.75-7.51)	0.142	2.69 (0.53-13.60)	0.231
Previous VF ≥1 vs 0	1.88 (0.71-4.99)	0.204	2.36 (0.73-7.63)	0.152	4.32 (1.00-18.53)	0.049

With Def 2, VR was detected in 18 pts, IR 1.2 x 100 PYFU (0.7-1.9), 1.9 x 100 PYFU (0.6-1.8) in pts without previous failures and 1.9 x 100 PYFU (0.8-4.2) in pts with >=1 previous VF

By multivariate analysis, pts with 1 previous VF had higher risk of VR but not statistically significant throughout all the analyses (table), while having >=1 previous VF resulted to be associated to VR in the two sensitivity analyses.

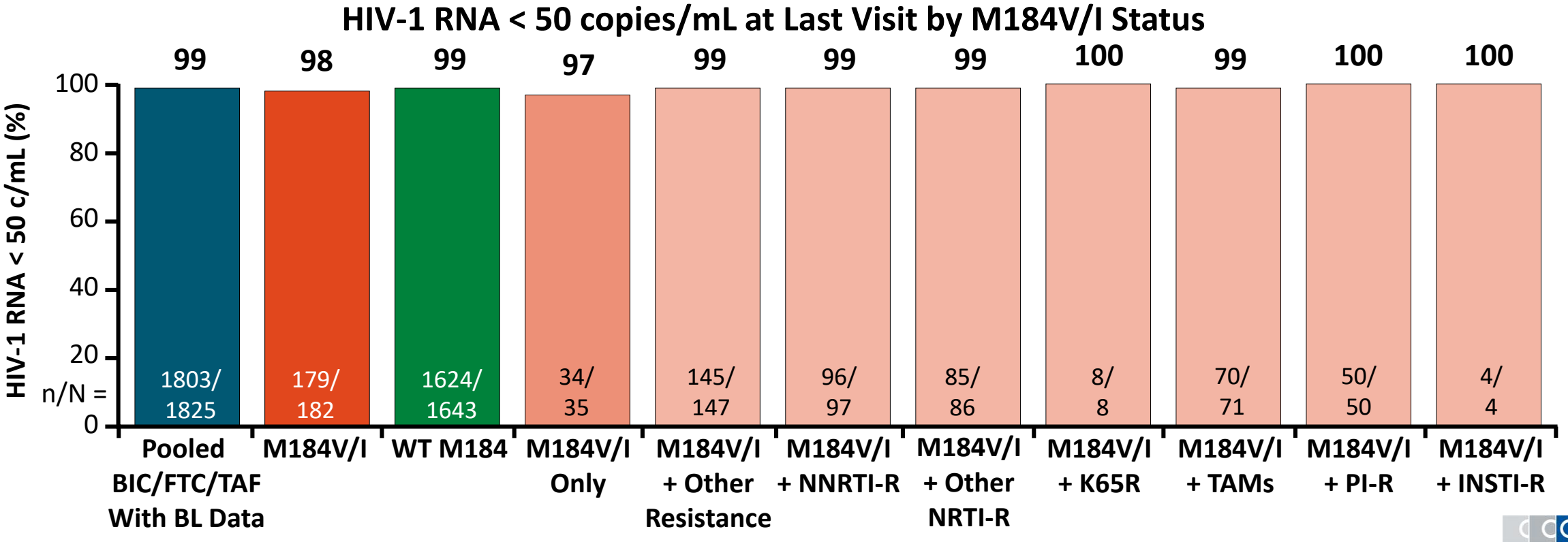
Conclusions

- DTG+3TC is prescribed in patients with history of previous VF (~20% of cases)
- Risk of viral rebound and viral blip is increased in patients with previous VF (esp. ≥1 VF), compared to those without previous VF
- 1-year probability of viral rebound was very low
- DTG+3TC should be cautiously used in patients with current viral suppression but a history of VF

Gagliardini R et al. CROI 2020; Boston. Poster 0486

Switch to BIC/FTC/TAF: Virologic Suppression by Preexisting M184V/I Status

- HIV-1 RNA ≥ 50 c/mL at last visit in 3 patients with M184V/I; HIV-1 RNA 2860 c/mL for n = 1 (poor adherence, undetectable plasma BIC but no emergent resistance) and HIV-1 RNA < 100 c/mL for n = 2 (resuppressed with BIC/FTC/TAF or ATV/RTV + FTC/TDF)



Andreatta. HIV Glasgow 2020. Abstr P123.

Slide credit: clinicaloptions.com

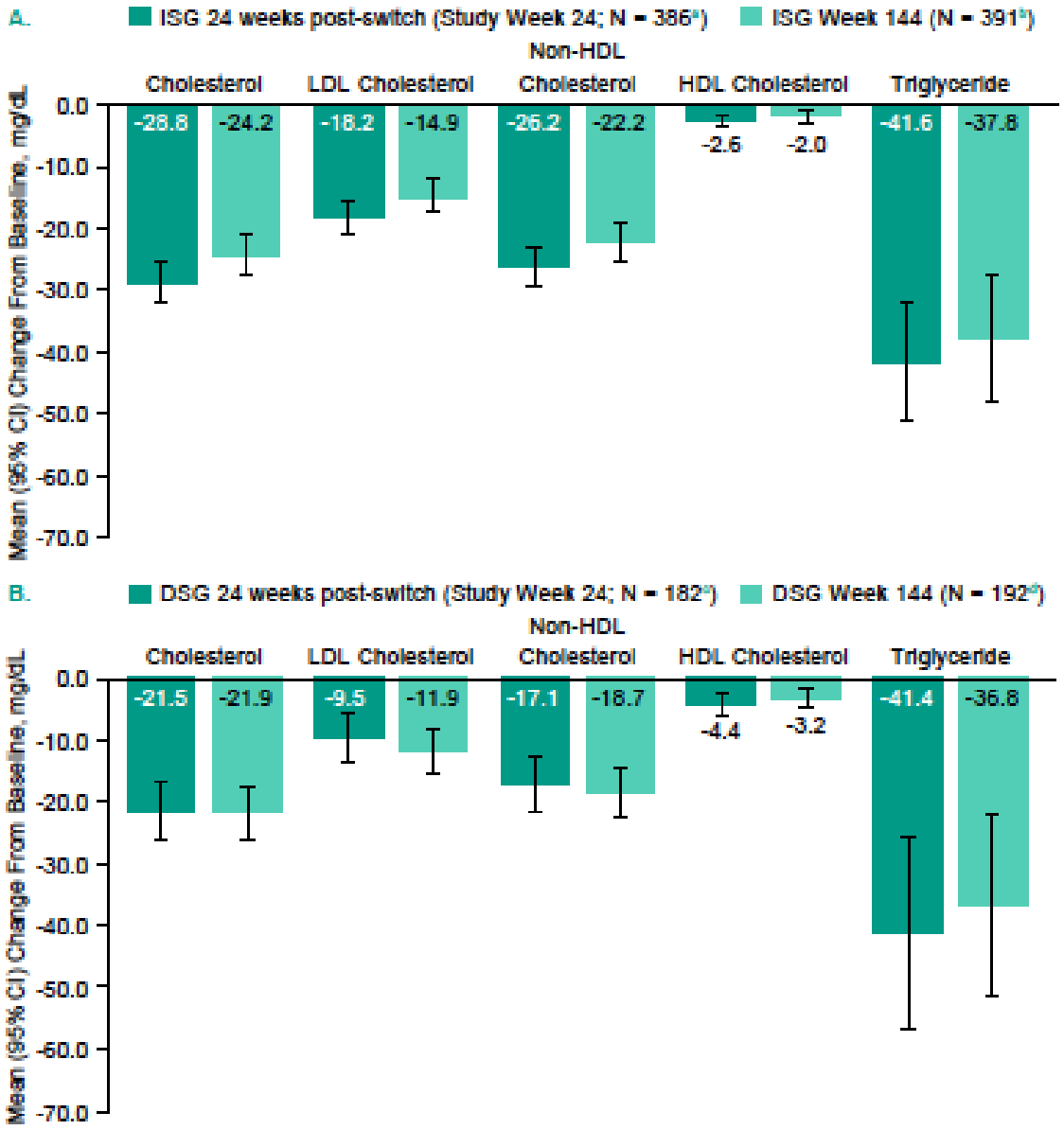
P037

Long-term Treatment Efficacy and Safety Following Switch to Doravirine/ Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF): Week 144 Results of the DRIVE-SHIFT Trial

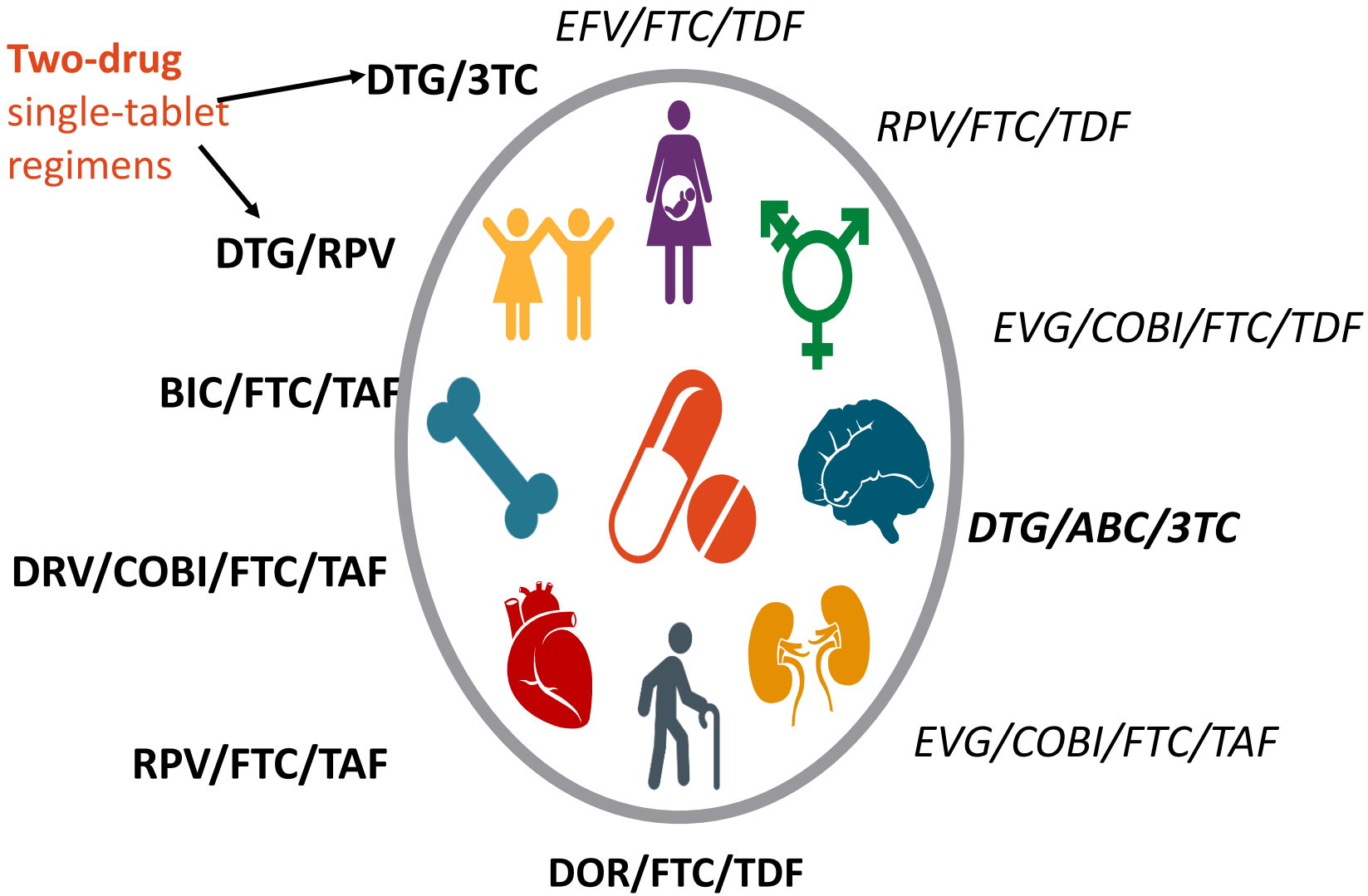
Conclusions

- Long-term virologic suppression was maintained in adults with HIV-1 who switched to DOR/3TC/TDF from a boosted PI, boosted elvitegravir or an NNRTI regimen
- Switching to DOR/3TC/TDF resulted in low rates of virologic failure with no evidence of resistance to doravirine
- Findings at Week 144 confirm previous data that show once-daily DOR/3TC/TDF is a generally well-tolerated option for maintaining viral suppression in adults considering a change in therapy
- DOR/3TC/TDF as switch therapy has a favourable lipid profile compared with baseline regimens and results in minimal weight gain

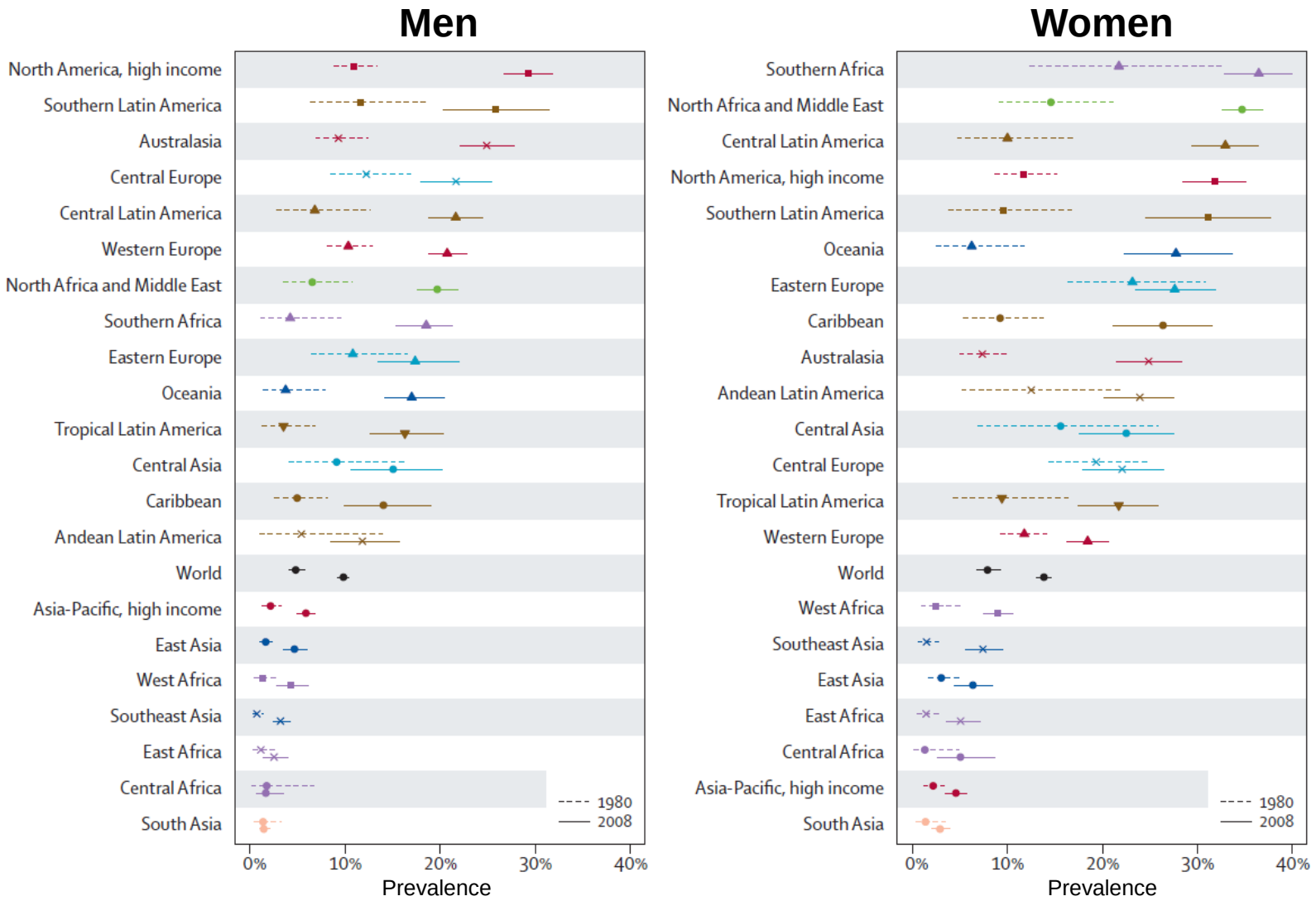
Figure 1. Change in Fasting Lipids After Switch to DOR/3TC/TDF at 24 Weeks Post-Switch and Study Week 144 in (A) ISG Participants and (B) DSG Participants



We Have Some Great Oral Fixed-Dose Combinations



The Global Obesity Pandemic: Prevalence by Geographic Location



- Marked increases in the prevalence of obesity both in high and low income regions
- Women are disproportionally affected in many areas

---- 1980
—— 2008

Finucane M, et al. Lancet 2011;377:557–567

Changes in weight and BMI with first-line doravirine-based therapy

Chloe Orkin[1], Richard Elion[2], Melanie Thompson[3], Juergen K Rockstroh[4], Fernando Alvarez Bognar[5], Zhi J Xu[6], Carey Hwang[7], Peter Sklar[7], Elizabeth A Martin[7]

Objective: To evaluate changes in weight and BMI in adults with HIV-1 at 1 and 2 years after starting an antiretroviral regimen that included doravirine, ritonavir-boosted darunavir, or efavirenz.
Design: Post-hoc analysis of pooled data from three randomized controlled trials.
Methods: We evaluated weight change from baseline, weight gain at least 10%, and increase in BMI after 48 and 96 weeks of treatment with doravirine, ritonavir-boosted darunavir, or efavirenz-based regimens. Risk factors for weight gain and metabolic outcomes associated with weight gain were also examined.

Conclusion: Weight gains over 96 weeks were low in all treatment groups and were similar to the average yearly change in adults without HIV-1. Significant weight gain and BMI class increase were similar across the treatment groups and were predicted by low baseline CD4 T-cell count and high baseline HIV-1 RNA

AIDS 2021 Jan 1;35(1):91-99

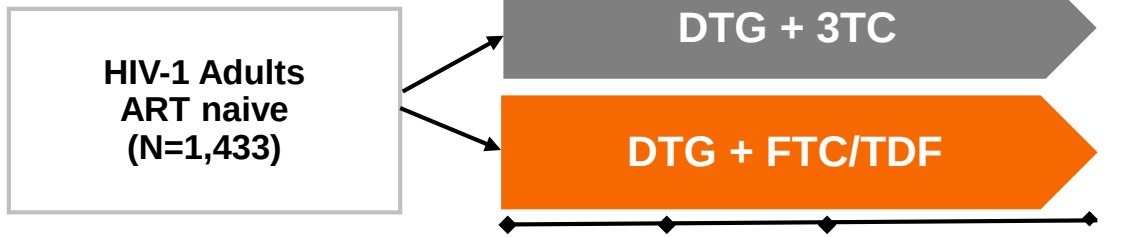
GEMINI: DTG + 3TC or DTG + FTC/TDF
TANGO: DTG/3TC or TAF-based regimen

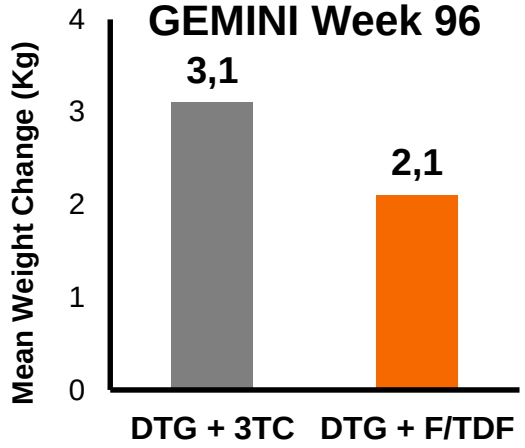
‡

Weight Analyses

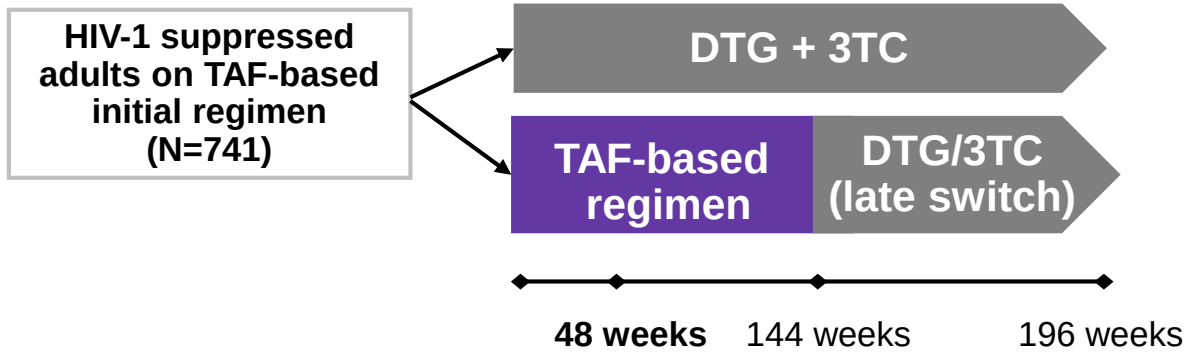
Evaluation of differences in the changes in body weight in GEMINI and TANGO

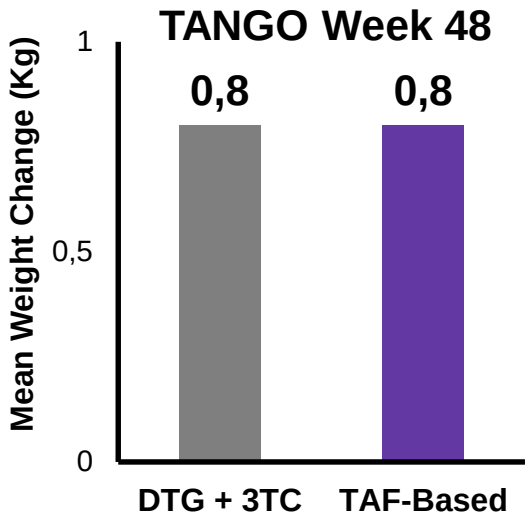
GEMINI[1,2]





TANGO[3]



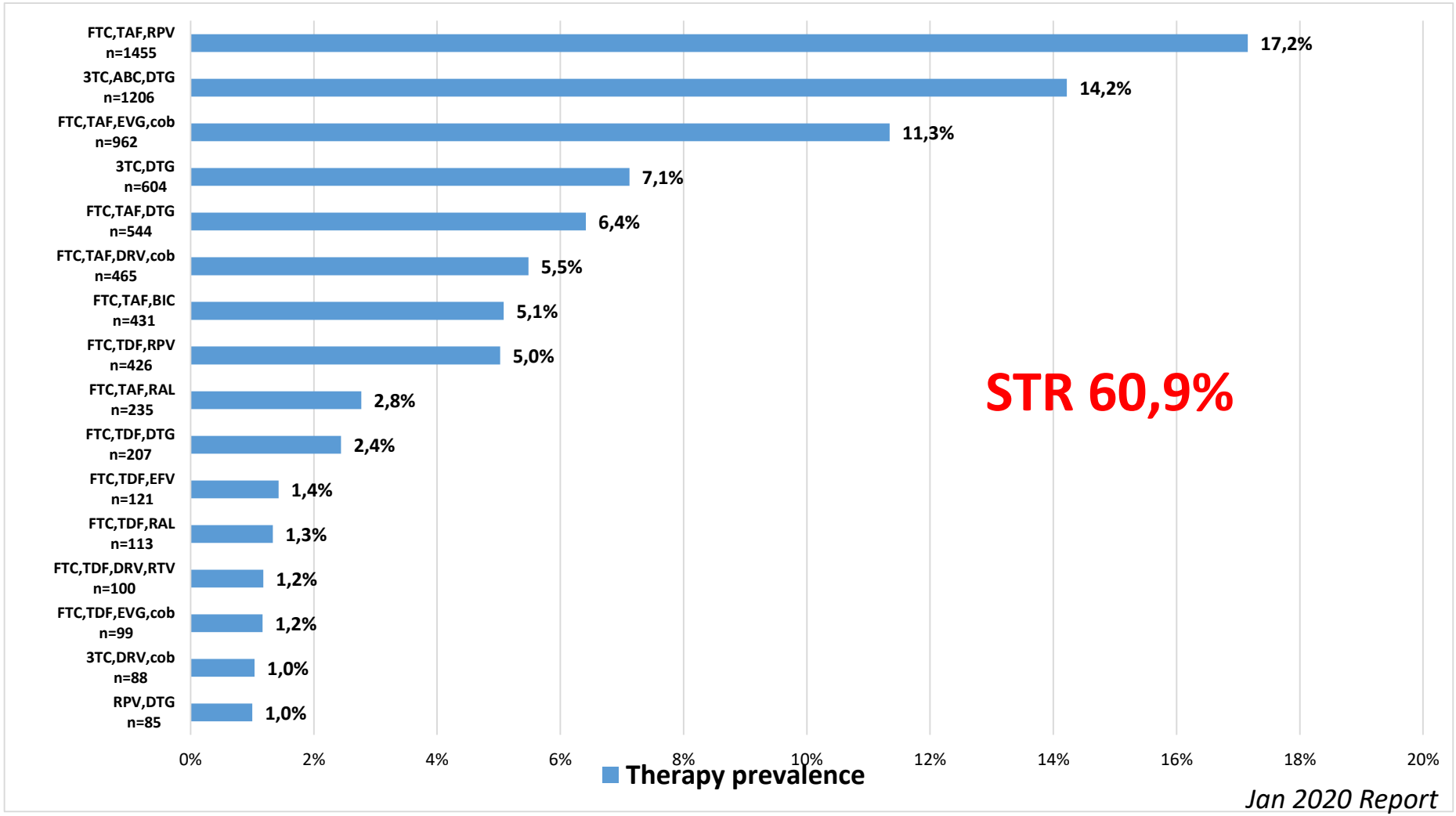


1. Cahn P, et al. IAS 2019. Mexico City, Mexico. Oral WEAB0404LB
2. Cahn P, et al. Lancet 2019;393:143–55
3. Van Wyk J, et al. IAS 2019. Mexico City, MX. Oral WEAB0403LB

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Italian Cohort I. C. O. N. A. Naive Antiretrovirals

All lines of therapies used in 2019 (n=7141, therapy prevalence >1%)



STR 60,9%

Jan 2020 Report

Optimal HIV management should be:

- **Potent**
- **Safe**
- **Tolerable**
- **Easy to adhere to…**

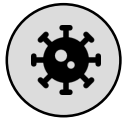
… to achieve sustained virological control[1]

The key goals of ART are[1]:

Maximal and durable suppression of plasma HIV RNA

Restoration and preservation of immunologic function

Reduction in HIV-associated morbidity and prolongation of the duration and quality of survival



Prevention of HIV transmission

The current goal of therapy is to 'go beyond undetectable' to support patients in reaching the fourth 90* in their lifetime[2]

*UNAIDS fourth 90: 90% of those with viral load suppression have a good quality of life
PLHIV, people living with HIV.
1. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Available at: https://files.aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Last accessed: March 2020; 2. Lazarus JV, et al. *BMC Medicine* 2016;14:94.