INNOVAZIONE E RICERCA
PER LA PRATICA CLINICA

XIV Workshop Nazionale

**TERAPIA
E PREVENZIONE
DELL'INFEZIONE
DA HIV
E MICRORGANISMI
EMERGENTI**

FIRENZE
28 febbraio • 1 marzo 2022

HYBRID EDITION

STRATEGIE TERAPEUTICHE NEL PAZIENTE CON VIREMIA NON RILEVABILE

Dr Barbara Rossetti

Disclosure

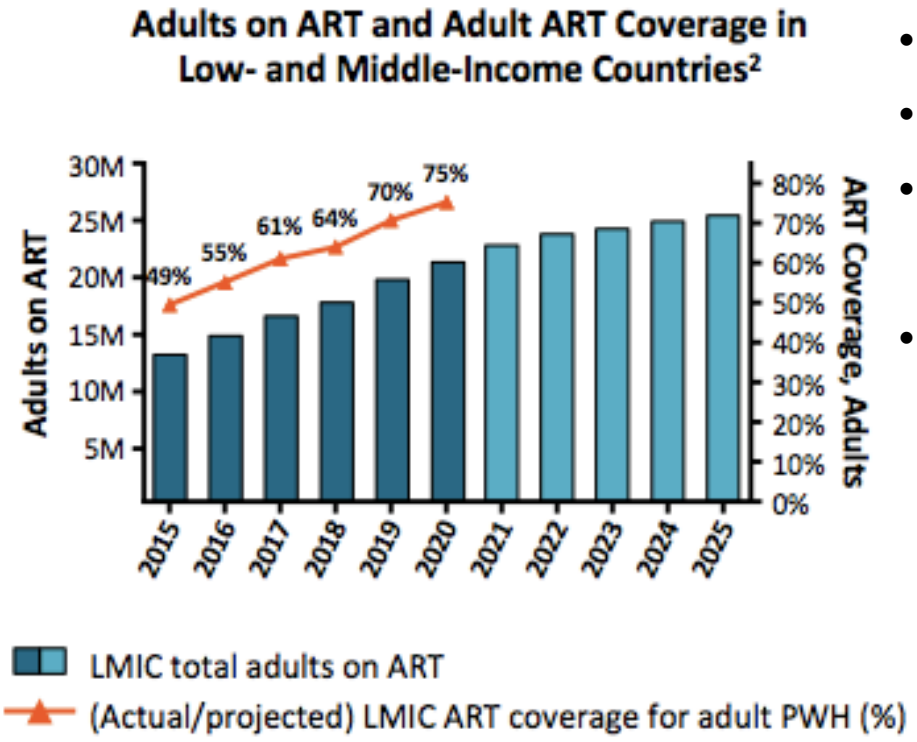
Grants for educational activities, personal fees for advisory boards and speakers bureau

- Abbvie
- Gilead Sciences
- Janssen-Cilag
- Merck Sharp and Dohme
- ViiV Healthcare
- Bristol-Myers Squibb
- Menarini

Study grant/support to my istitution

- Gilead Sciences
- Janssen-Cilag

Global antiretroviral coverage



- 37.7 million people vith HIV in 2020
- 36 million adults
- 74% of adults and 54% of children on ART
- 2030 UNAIDS target: 95% on ART

Ref. Clintonhealthaccess.org/2021-hiv-market-report-the-state-of-the-hiv-market-in-low-and-middle-income-countries/

Reasons to Consider an ART Switch in PLWH With Viral Suppression

- To simplify a regimen (eg, reduce pill burden or dosing frequency)
- To enhance tolerability or decrease short- or long-term toxicities
- To prevent or mitigate drug-drug interactions
- To eliminate food/fluid requirements
- To switch to a long-acting injectable regimen for relief of pill fatigue or potential stigma associated with daily oral medications
- To allow for optimal ART use during pregnancy or in whom pregnancy may occur
- To reduce costs

Clinical trials exploring switching strategies have generally defined suppression as an HIV-VL < 50 copies/mL for at least 6 months

EACS, v.11-2021; DHHS, 2022

General aim of regimen optimization: maintain viral suppression

Characteristics to consider in all people with HIV

- **Review treatment history**
- HIV genotype results
- HLA-B 5701 status
- Individual preferences
- Anticipated adherence

Regimen-specific considerations

- Regimen's barrier to resistance
- DDI
- Potential AEs and drug toxicities
- Convenience
- Cost and access

Presence of specific conditions/ factors

- Comorbid conditions
- Pregnancy or wish to become pregnant
- Coinfections: **HBV**, HCV, TB

Reasons to Consider an ART Switch in PLWH With Viral Suppression

- To simplify a regimen (eg, reduce pill burden or dosing frequency)
- To prevent long term toxicity or decrease short- or long-term toxicities
- To prevent or mitigate drug–drug interactions
- To eliminate food/fluid requirements
- To switch to a long-acting injectable regimen for relief of pill fatigue or potential stigma associated with daily oral medications
- To allow for optimal ART use during pregnancy or in whom pregnancy may occur
- To reduce costs

EACS, v.11-2021; DHHS, 2022

Switching from Suppressive ART to an STR: Non-inferior Efficacy at 48 Wks Across All Phase III Studies

Primary endpoint: proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Wk 48

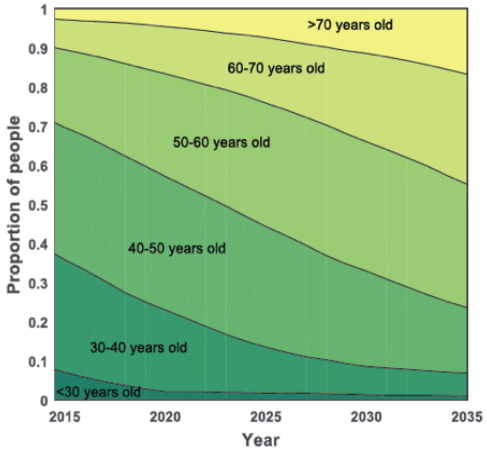
Key Studies*	Switch From	Switch to	Masking	Noninferiority Shown?
380-1878[1]	bPI + 2 NRTIs (n = 287)	BIC/F/TAF (n = 290)	Open-label	✓
380-1844[2]	DTG/ABC/3TC (n = 281)	BIC/F/TAF (n = 282)	Double-blind	✓
380-1961[3]	E/c/F/(TAF or TDF) or ATV/r + F/TDF (n = 236)	BIC/F/TAF (n = 234)	Open-label	✓
EMERALD[4]	bPI + F/TDF (n = 378)	DRV/c/FTC/TAF (n = 763)	Open-label	✓
DRIVE-SHIFT[5]	bPI or EVG/c or NNRTI + 2 NRTIs (n = 223)	DOR/3TC/TDF (n = 447)	Open-label	✓
TANGO[6]	FTC/TAF-based ART (n = 372)	DTG/3TC (n = 369)	Open-label	✓
STRIIVING[7]	bPI or NNRTI or INSTI + 2 NRTIs (n = 278)	DTG/ABC/3TC (n = 275)	Open-label	✓
SWORD-1/2[8]	bPI or NNRTI or INSTI + 2 NRTIs (n = 511)	DTG + RPV (n = 513)	Open-label	✓
GS-109[9]	EVG/c or EFV or ATV/r + FTC/TDF (n= 447)	EVG/c/FTC/TAF (n = 959)	Open-label	✓
GS-1216[10]	RPV/FTC/TDF (n = 314)	RPV/FTC/TAF (n = 316)	Double-blind	✓
GS-1160[11]	EFV/FTC/TDF (n = 437)	RPV/FTC/TAF (n = 438)	Double-blind	✓

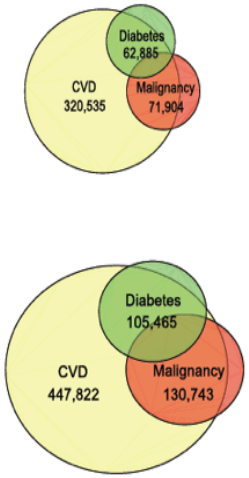
References

1. Daar. Lancet HIV. 2018;5:e347. 2. Molina. Lancet HIV 2018;5:e357. 3. Kityo. CROI 2018. Abstract 500. 4. Orkin. Lancet HIV 2018;5:e23. 5. Johnson. JAIDS. 2019;81:463. 6. van Wyk. Clin Infect Dis 2020;71:1920. 7. Trottier. Antivir Ther 2017;22:295. 8. Llibre. Lancet 2018;391:839. 9. Mills. Lancet Infect Dis 2016;16:43. 10. Hagins. HIV Med 2018; 19:724. 11. DeJesus. Lancet HIV 2017;4:e205.

Ageing and CV risk

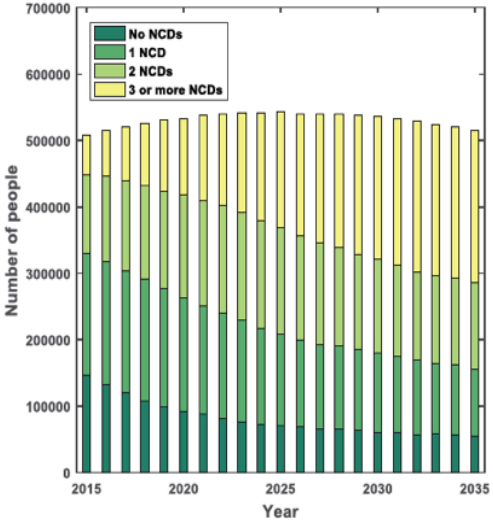
Age distribution of HIV positive patients on HIV therapy in USA Proportion of pts >50 y: **39%** (2015) and **74%** (2035)





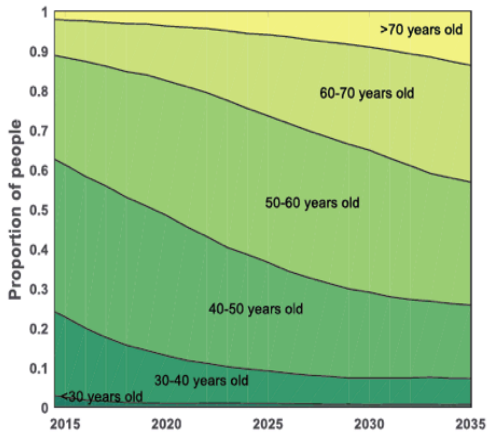
Number of co-morbidities in HIV patients on HIV therapy

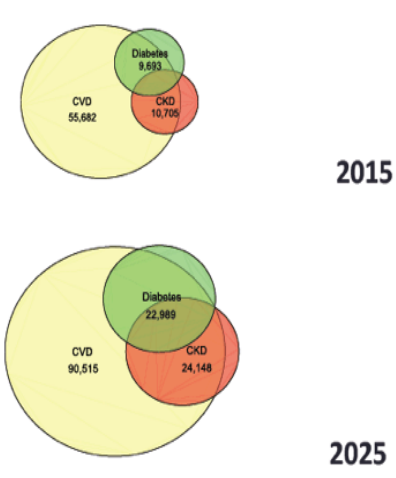
Proportion of pts with ≥3 co-morbidities: **11%** (2015) and **44%** (2035)



Co-morbidity burden driven by **cardiovascular diseases** (HT, dyslipidemia, stroke, MI), **diabetes**, **malignancy**

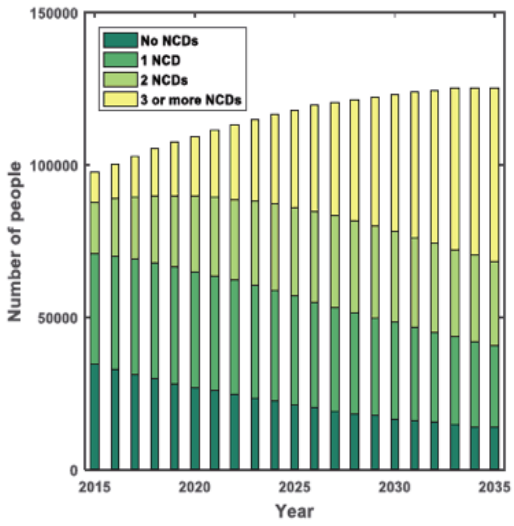
Age distribution of HIV positive patients on HIV therapy in Italy Proportion of pts >50 y: **30%** (2015) and **76%** (2035)





Number of co-morbidities in HIV patients on HIV therapy

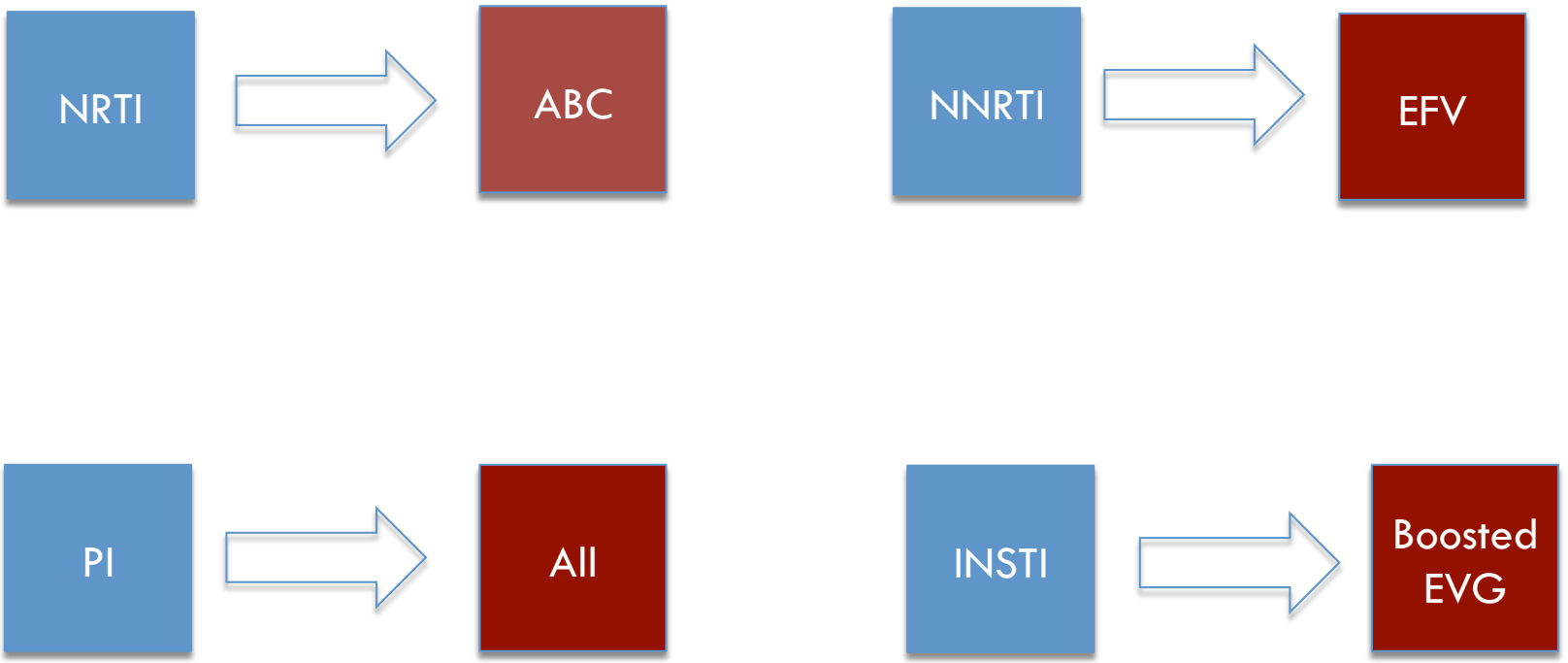
Proportion of pts with ≥3 co-morbidities: **10%** (2015) and **46%** (2035)



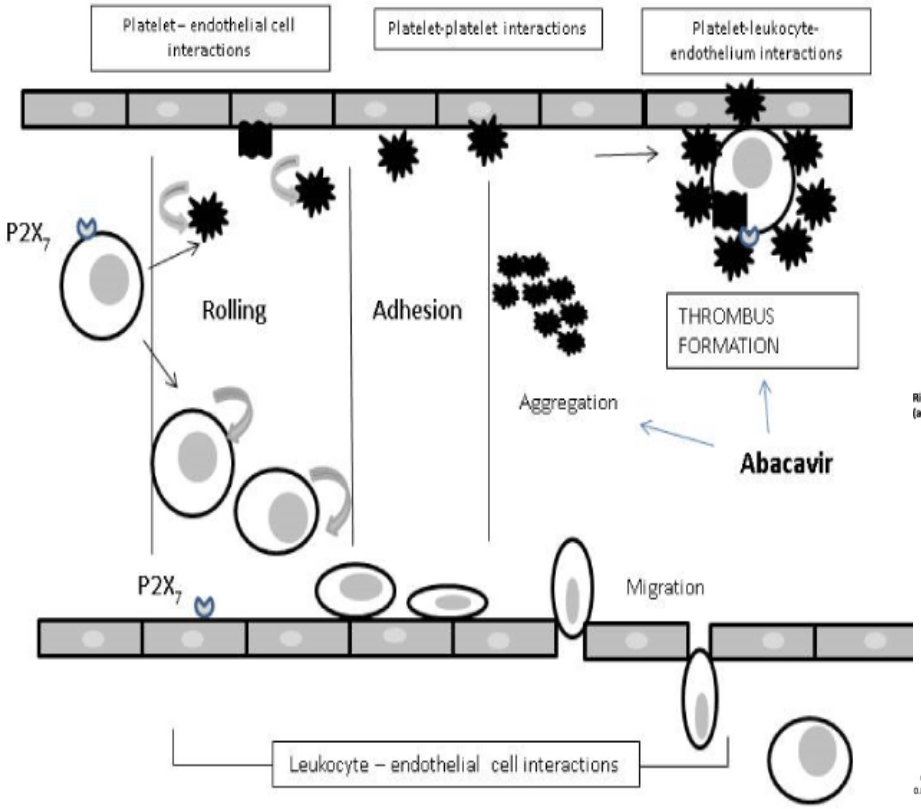
Co-morbidity burden driven by **cardiovascular diseases** (HT, dyslipidemia, stroke, MI), **diabetes**, **chronic kidney disease**

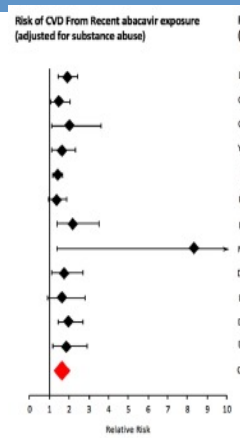
Smit M et al. Lancet Inf Dis 2015 e HIV Glasgow 2016

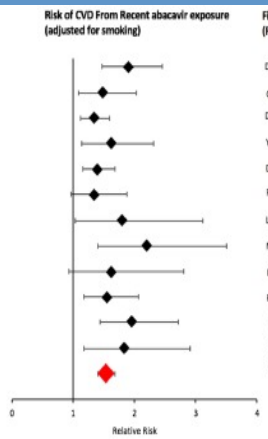
Cardiovascular risk

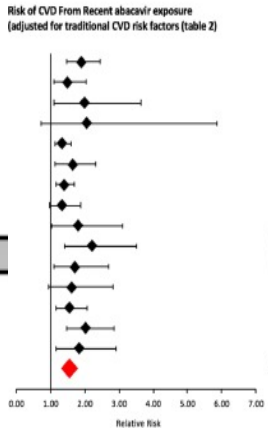


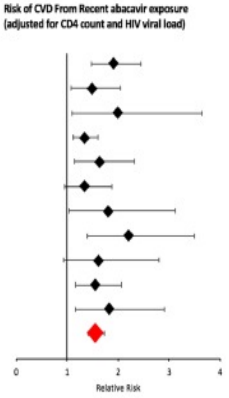
ABC











Consider switch to 2DR or TDF/TAF based regimens

Alvarez A et al. AIDS, 2017. K Dorjee, et al. International Journal of Antimicrobial Agents, 2018. EACS 2021, GL

Does DTG/3TC or DTG/RPV Work in Switch Therapy?

Criteria	Evidence
Long-term **durability**?	**Yes**, DTG/RPV 3 yr[1], DTG/3TC 3 yr[2]
More sensitive viral markers (ie, target not detected, IL-6)?	**No difference** between 3DR and 2DR[2,3]
Frequency of **blips** similar with DTG + 3TC or DTG/RPV vs DTG-based 3DR?	**No difference** in blip frequency[4,5]
Barrier to resistance of DTG + 3TC and DTG/RPV high enough?	**Excellent barrier;** no resistance for DTG/3TC in 3 yr, infrequent DTG/RPV[1,2]
Safety and tolerability?	**Better outcomes** for DTG/3TC and DTG/RPV renal and bone markers vs TDF[1,2]
Efficacy in case of M184VI?	**Yes,** DTG/3TC[6,7]

1. Van Wyk. J Acquir Immune Defic. 2020;85:325. 2. Cahn. Virtual HIV Glasgow 2020. Poster P018. 4. Underwood. EACS 2019. Slides PS8/2. 5. Wang. HIV Glasgow 2018. Poster P313. 6. Blick. EACS 2021. Abstr PE 2/65 . 7. Hocqueloux. EACS 2021. Abstr OS1/2. 8. Wang. EACS 2021. Abstr PE2_70

SWORD-1 and -2: Switch to DTG + RPV vs Continuation of Baseline ART in Virologically Suppressed Adults

- Parallel, randomized, open-label, multicenter phase III noninferiority studies in adults on stable ART (INSTI, NNRTI, or PI + 2 NRTIs) with HIV-1 RNA <50 copies/mL for ≥6 mo[1-3]
- Primary endpoint: At Wk 48, HIV-1 RNA <50 copies/mL maintained in 95% of patients in each arm adjusted treatment difference: -0.2% (95% CI: -3.0% to 2.5%)[2]; at Wk 100, HIV-1 RNA <50 copies/mL maintained in 89% (95% CI: 86%-92%) of early-switch arm vs 93% (95% CI: 91%-95%) in late-switch arm[3]
- 10/990 (1%) confirmed virologic withdrawals through Wk 100[1]
  - Treatment-emergent NNRTI resistance mutations documented in 3/10, all from early switch arm*

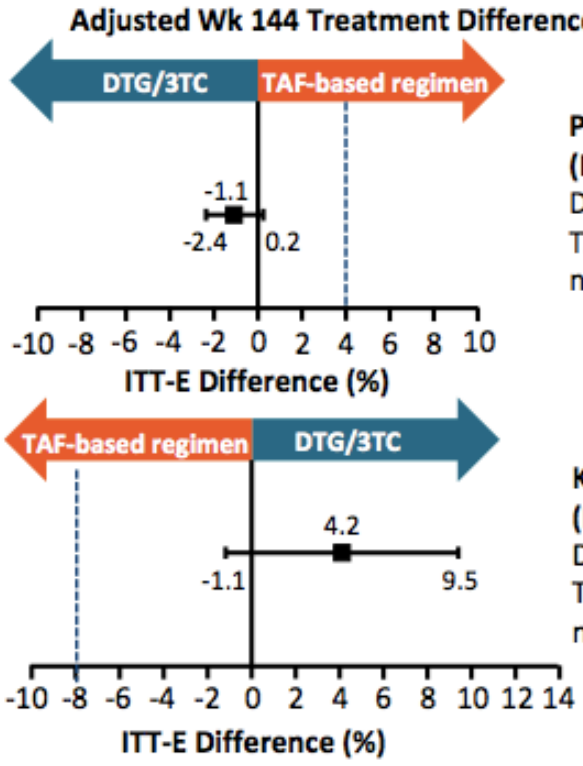
Time of Failure	Previous Regimen	Mutations at Baseline		Mutations at Confirmed Virologic Withdrawal	
		NNRTI	INSTI	NNRTI	INSTI
Wk 36	EFV/FTC/TDF	None	None	K101K/E	None
Wk 88	DTG/ABC/3TC	None	None	E138E/A	None
Wk 100	EFV/FTC/TDF	K101E, E138A	G193E	K101E, E138A, M230M/L	Assay failure

*For these 3 patients, HIV-1 RNA at last measurement: <50 copies/mL, 55 copies/mL, 300 copies/mL, respectively.

1. Aboud. AIDS 2018. Abstr THPEB047. 2. Llibre. Lancet. 2018;391:839. 3. Aboud. Lancet HIV. 2019;6:e576.

TANGO: Viral Suppression Through Wk 144 With Switch to DTG/3TC in Virologically Suppressed Patients

- Randomized, open-label, phase III trial
  - Adults with HIV-1 RNA <50 copies/mL for >6 mo on stable TAF-based regimen
  - No prior VF or NRTI or INSTI RAMs; no HBV
- FTC/TAF + PI, INSTI, or NNRTI as initial regimen
- Randomized to DTG/3TC or to continue their TAF-based regimen
- Who was in TANGO?
  - Baseline regimens (FTC/TAF +): INSTI 79% (66% EVG/COBI), RPV 12%, boosted DRV 7%
  - Median ART duration: 34-35 mo (~3 yr)



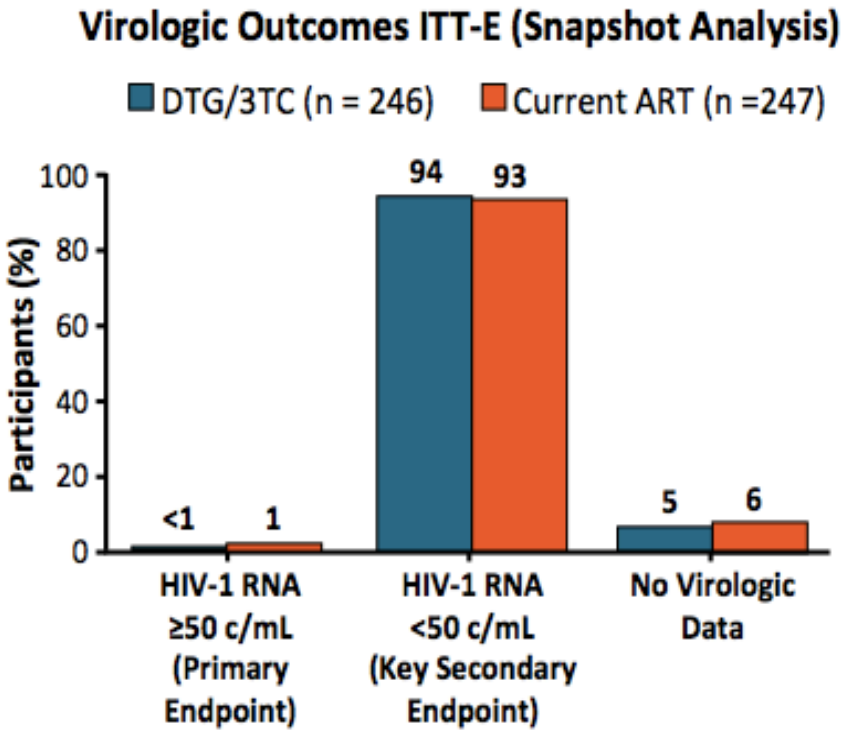
Primary endpoint (HIV-1 RNA ≥50 c/mL): DTG/3TC noninferior to TAF-based regimen (4% noninferiority margin)

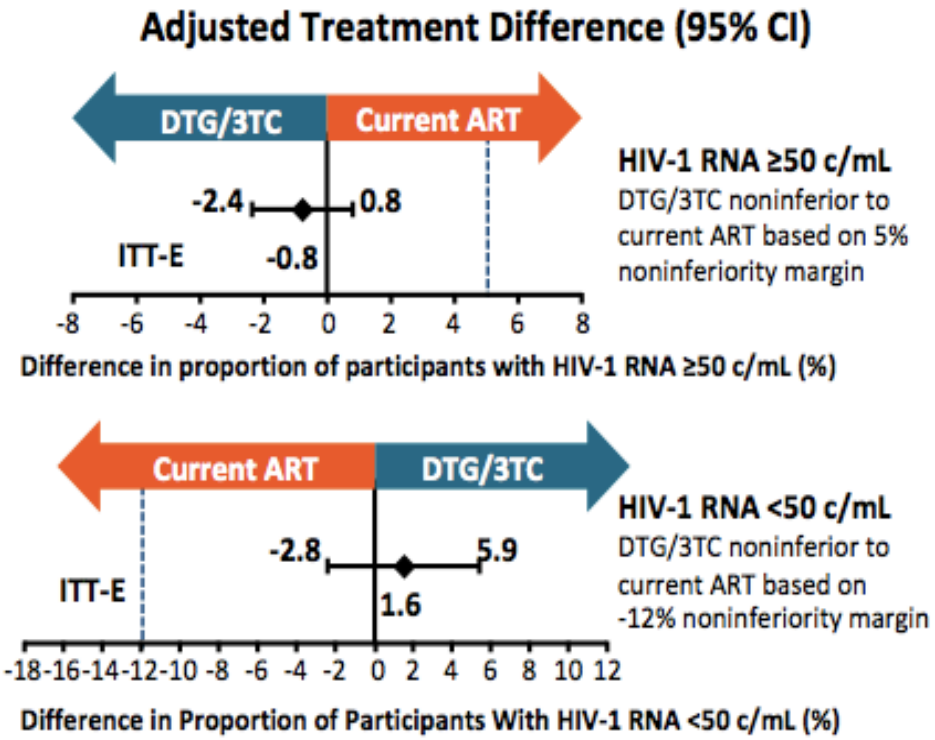
Key secondary endpoint (HIV-1 RNA <50 c/mL): DTG/3TC noninferior to TAF-based regimen (-8% noninferiority margin)

van Wyk. IAS 2021. Abstr PEB164.

Slide credit: clinicaloptions.com

SALSA: Virologic Outcomes at Wk 48 (ITT-E)





- No resistance mutations or confirmed virologic withdrawals through Wk 48

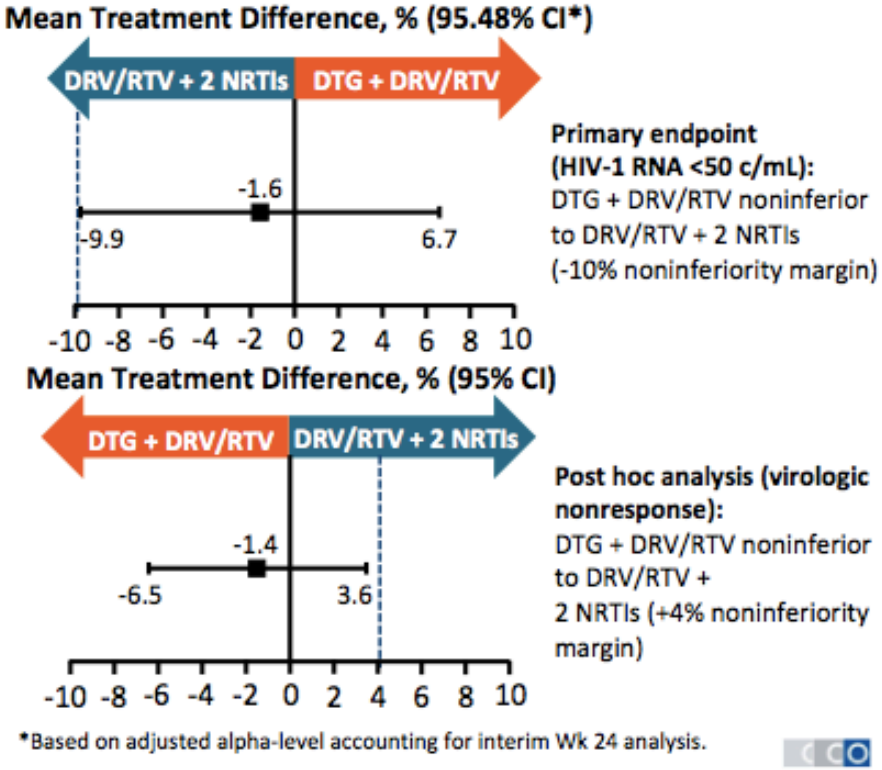
Llibre. IAS 2021. Abstr OALB0303.

Slide credit: clinicaloptions.com

DUALIS: Viral Suppression Through Wk 48 With Switch to DTG + DRV/RTV in Virologically Suppressed Patients

- Randomized, open-label, multicenter phase III noninferiority trial
- PWH with HIV-1 RNA <50 c/mL on DRV/RTV + 2 NRTIs for ≥24 wk (1 blip of <200 c/mL permitted)
- Compared switch to DTG 50 mg + DRV/RTV 800/100 mg vs continue DRV/RTV + 2 NRTIs
- Primary endpoint: Wk 48 HIV-1 RNA <50 c/mL
- NRTI backbone change not considered failure

Wk 48 Virologic Outcome (FDA Snapshot, ITT), %	Switch to DTG + DRV/RTV	Cont. DRV/RTV + 2 NRTIs
HIV-1 RNA <50 c/mL	86.3	87.9
Snapshot virologic nonresponse	3.8	5.3
No data	9.9	6.8



Spinner. Open Forum Infect Dis. 2020;7:ofaa356.

Slide credit: clinicaloptions.com

Switches from PI or EFV

Study 1878: Switch From Boosted PI to BIC/FTC/TAF

	HIV-1 RNA <50c/mL at Last Visit, n/N (%)	Median Duration of BIC/FTC/TAF, Wk
All BIC/FTC/TAF	525/532 (99)	101
▪ No blips	486/492 (99)	98
▪ ≥1 blip	36/40 (98)	109
BL Resistance Data Available		
No primary resistance (PR, RT, INSTI)	279/281 (99)	96
Any primary resistance (PR, RT, INSTI)	212/217 (98)	108
NRTI-R	94/98 (96)	108
M184V/I	59/62 (95)	95
Any TAM	52/54 (96)	100
1-2 TAMs	31/33 (94)	107
≥3 TAMs	21/21 (100)	96
NNRTI-R	127/129 (98)	108
PI-R	52/52 (100)	103
INSTI-R	14/14 (100)	103

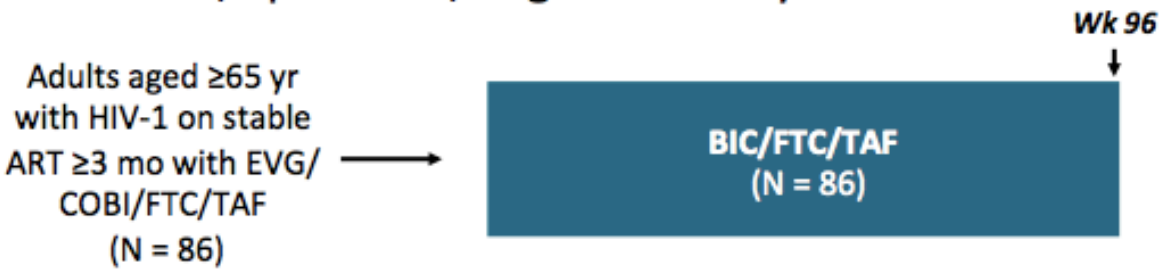
- BIC/FTC/TAF was highly effective even in those with baseline resistance and viral blips

Andreatta. EACS 2021. Abstr PE1/19.

Slide credit: clinicaloptions.com

Switch to BIC/FTC/TAF in Adults Aged ≥65 Yr

- Multicenter, open-label, single-arm study



- Primary endpoint: HIV-1 RNA <50 copies/mL at Wk 24 by FDA Snapshot
- Secondary endpoints: HIV-1 RNA <50 copies/mL at Wk 48, 72, 96; safety, tolerability
- Baseline characteristics: median age 69 yr, 87% men, 99% White, median eGFR 76 mL/min, 92% receiving EVG/COBI/FTC/TAF
  - Medications for comorbidities: CV (64%), GI (63%), CNS (44%), musculoskeletal (23%)

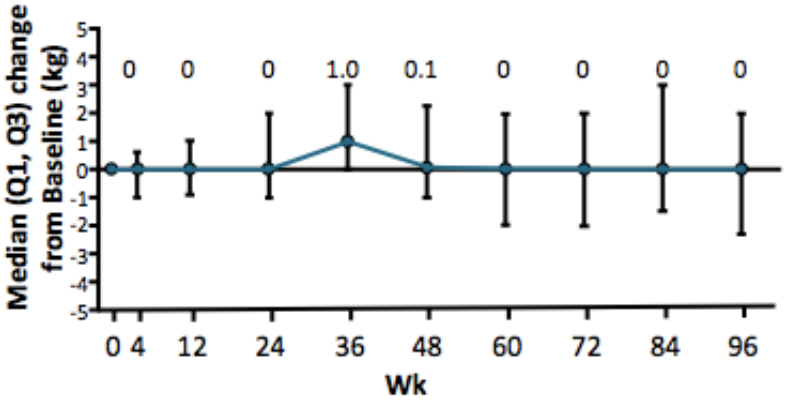
Maggiolo. IAS 2021. Abstr 784.

Slide credit: clinicaloptions.com

Maggiolo F, Infect Dis Ther (2021) 10:775–788

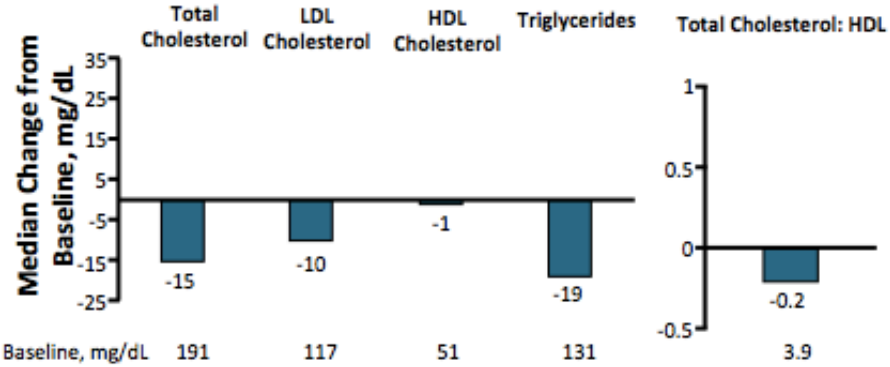
Switch to BIC/FTC/TAF in Adults ≥65 years: Wk 96 Weight and Lipid Changes

Median Weight Change from Baseline to Wk 69



- Median weight change at Wk 96 was 0.0kg (IQR: -2.3 to 2)

Changes in Fasting Lipids at Wk 96 (N = 56)



- Participants on lipid-modifying medication
  - At baseline: 42%
  - Initiated during study: 7%

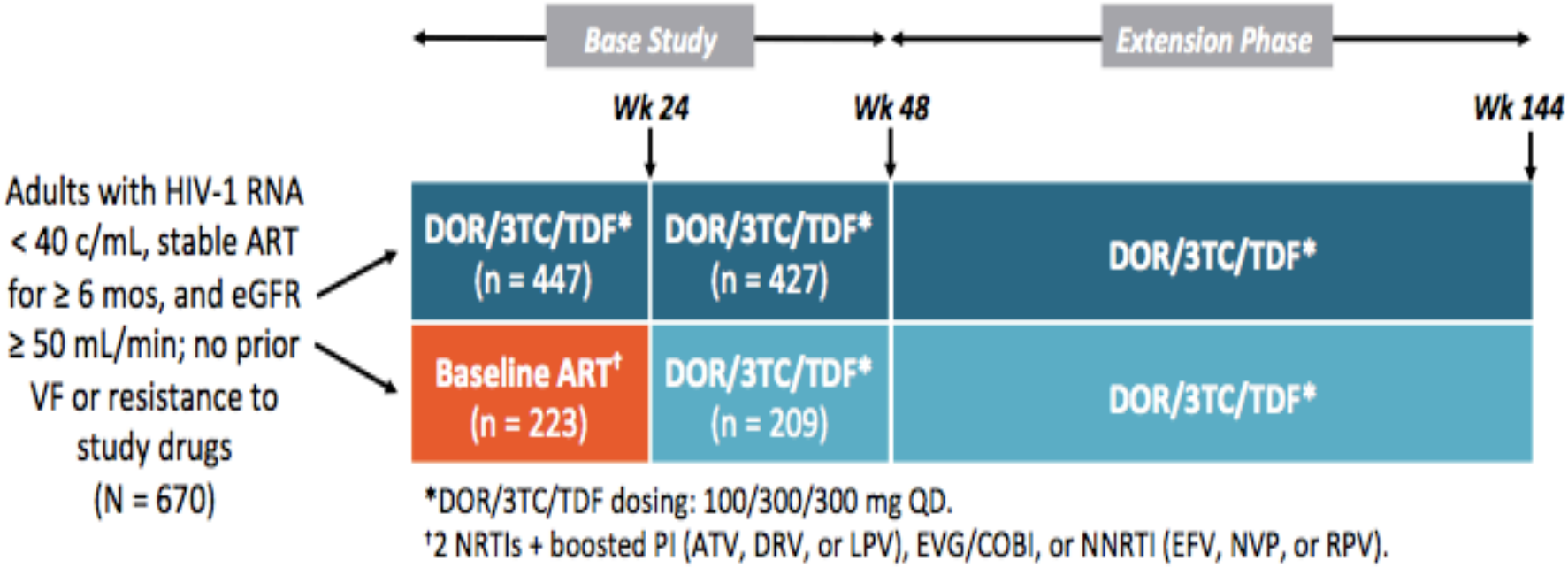
Maggiolo. IAS 2021. Abstr 784.

Slide credit: clinicaloptions.com

Maggiolo F, Infect Dis Ther (2021) 10:775–788

DRIVE-SHIFT: DOR/3TC/TDF, Immediate-Switch vs Delayed-Switch

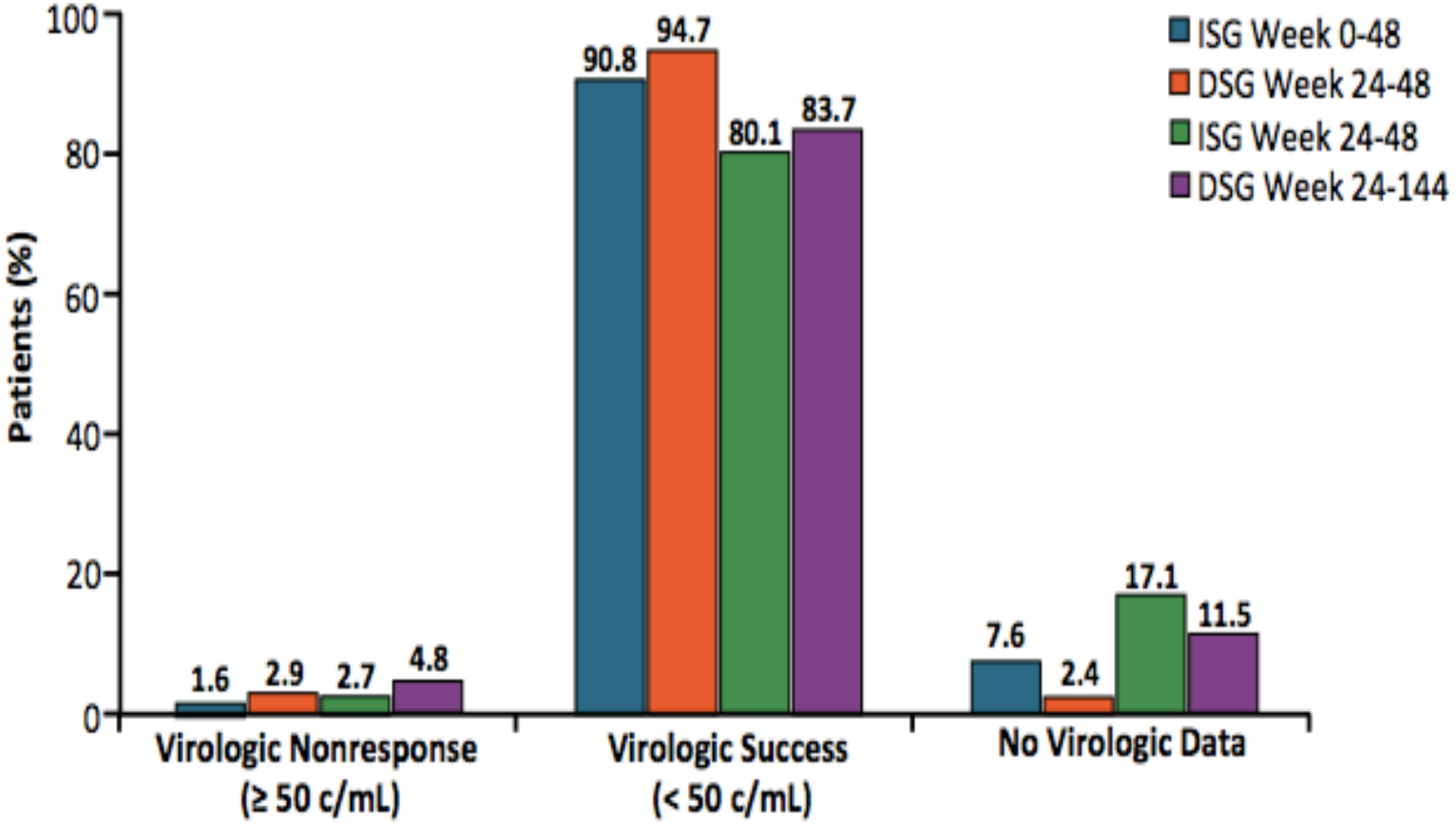
- International, randomized, open-label phase III noninferiority study[1,2]



- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 in **immediate switch arm** vs Wk 24 in **delayed switch arm**[2]

Kumar. J Acquir Immune Defic Syndr. 2021;87:801.

DRIVE-SHIFT: Efficacy of Switch to DOR/3TC/TDF at Wks 24, 48, and 144 vs Continued BL ART

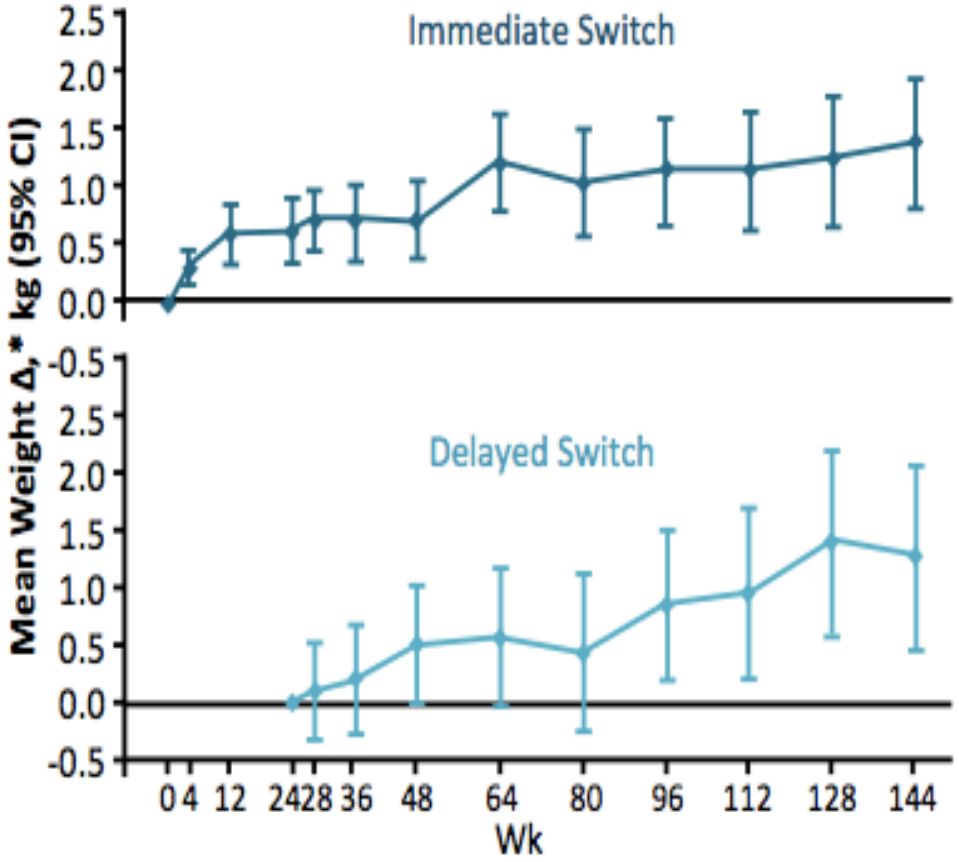


DSG, delayed-switch group (n = 209); ISG, immediate-switch group (n = 447)

Kumar. J Acquir Immune Defic Syndr. 2021;87:801.

Slide credit: clinicaloptions.com

DRIVE-SHIFT: Post-Switch Mean Weight Change



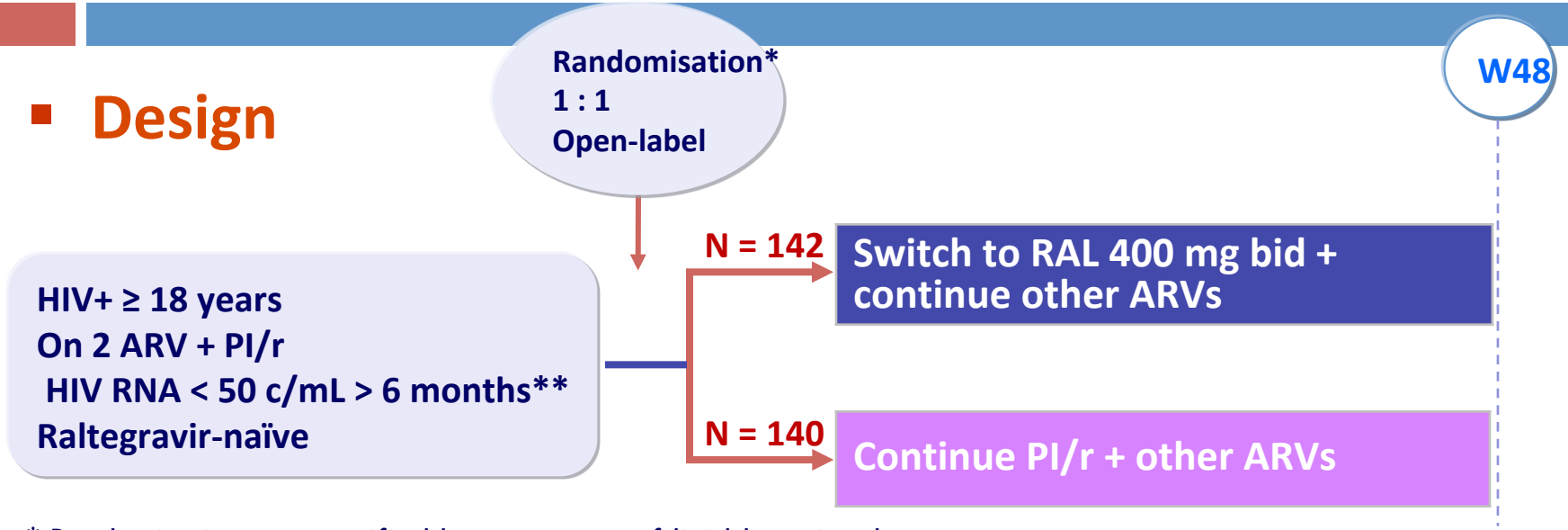
Mean Weight Δ,* kg (95% CI)	Immediate Switch	Delayed Switch
Wk 24	0.7 (0.4 to 0.9)	NA
Wk 48	0.7 (0.4 to 1.1)	0.5 (0 to 1.0)
Wk 96	1.1 (0.7 to 1.6)	0.8 (0.2 to 1.5)
Wk 144	1.4 (0.8 to 1.9)	1.2 (0.4 to 2.0)

*Adjusted for weight at switch, race (black vs nonblack), ethnicity (Hispanic vs other), sex, age, BL CD4+ cell count, and HIV-1 RNA.

Kumar. J Acquir Immune Defic Syndr. 2021;87:801.

SPIRAL Study: Switch PI/r to RAL

Design



* Randomisation was stratified by current use of lipid-lowering therapy

** Median time with virologic suppression was > 6 years

Endpoints

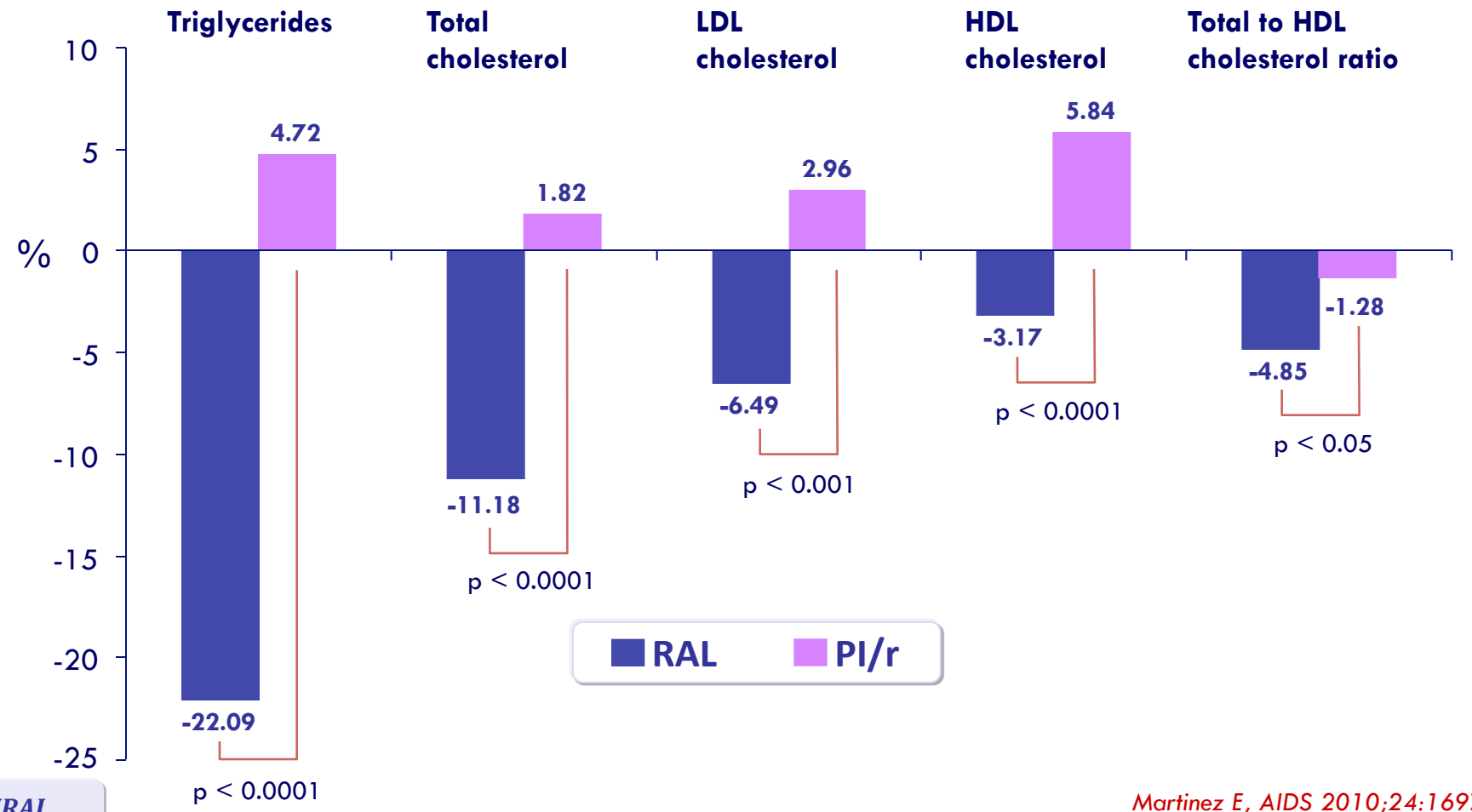
- Primary: non inferiority in the proportion of patients with treatment failure at W48* (non completer = failure, intent-to-treat analysis), lower limit of the 95% CI for the difference = - 12.5%, 80% power ;

  * events occurring in the 2 weeks after W48 were included in the analysis
- Secondary: virologic failure (confirmed HIV-1 RNA > 50 c/mL), CD4, fasting lipids, adverse events

SPIRAL

Martinez E, AIDS 2010;24:1697-1707

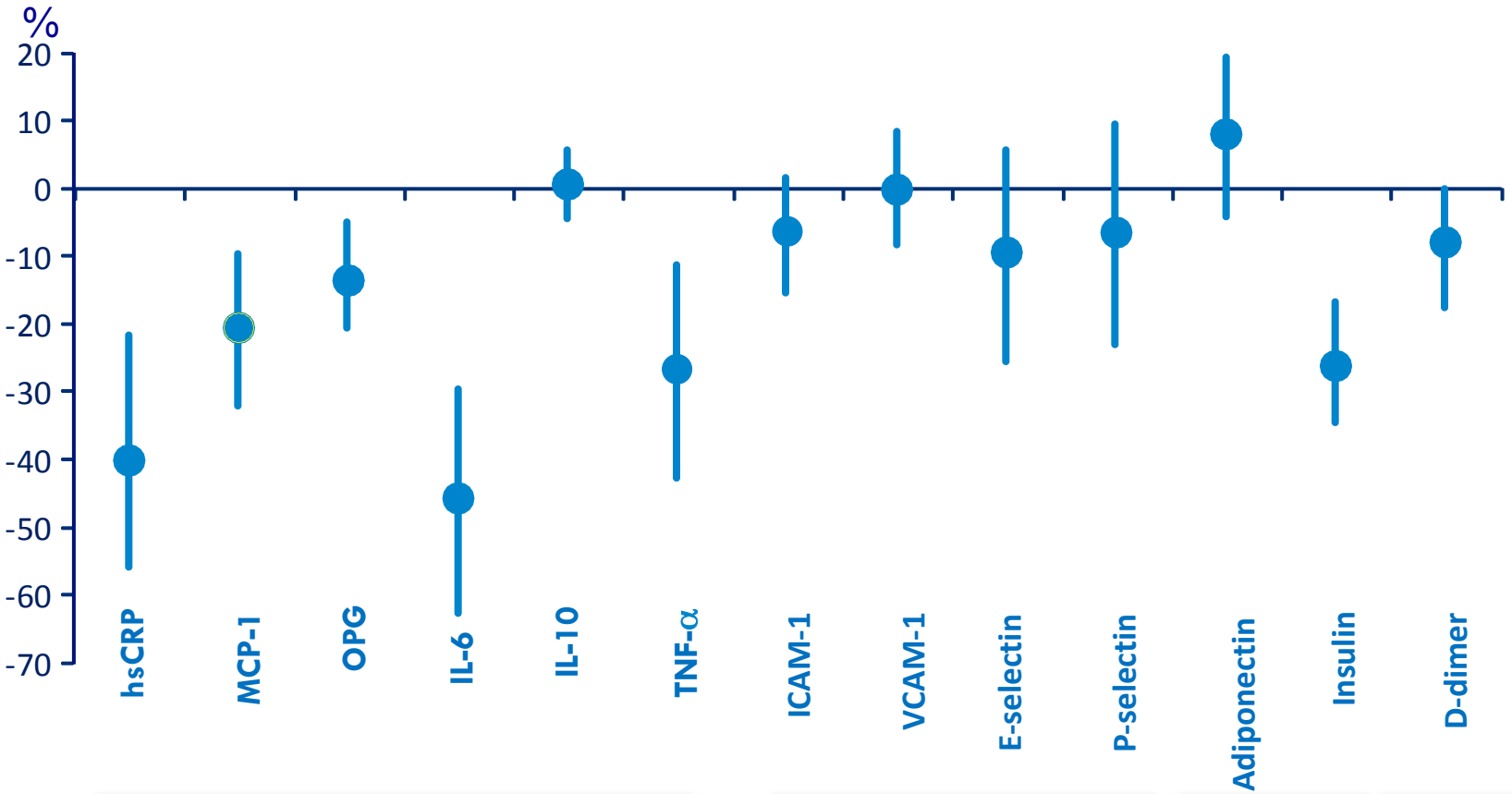
SPIRAL Study: Percentage changes in fasting lipid concentrations from baseline to W48



SPIRAL

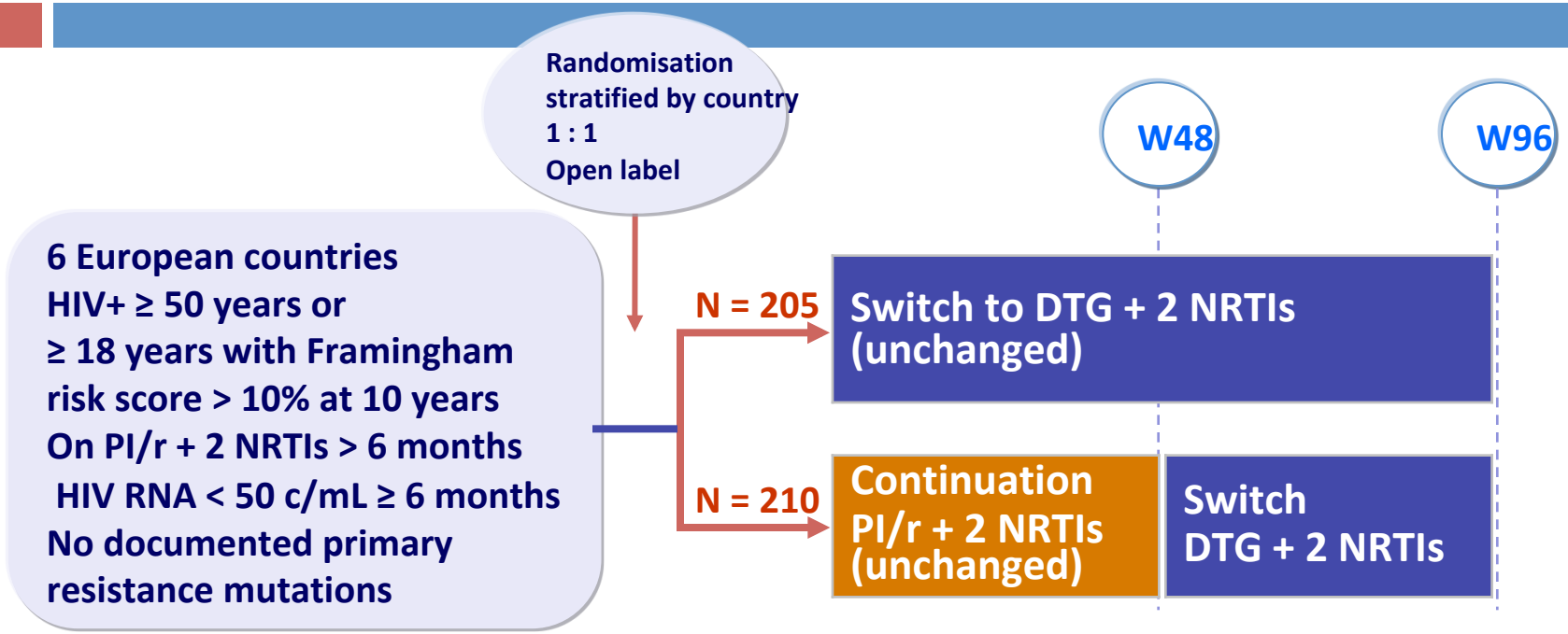
Martinez E, AIDS 2010;24:1697-1707

SPIRAL Study: Cardiovascular biomarkers



Martinez E, AIDS 2012;26:2315-26

NEAT 022 Study: Switch to DTG vs continuation of PI/r in patients with high cardiovascular risk



- **Primary endpoints**
  - Proportion of patients with virological success at W48 (no consecutive HIV-1 RNA > 50 c/mL and no treatment discontinuation): non-inferiority of DTG, by ITT, Kaplan-Meier analysis; lower limit of the 95% CI for the difference = - 10%, power 90%
  - Mean percentage changes in fasting lipid total cholesterol at W48 (between treatment difference of 12%, 99% power)

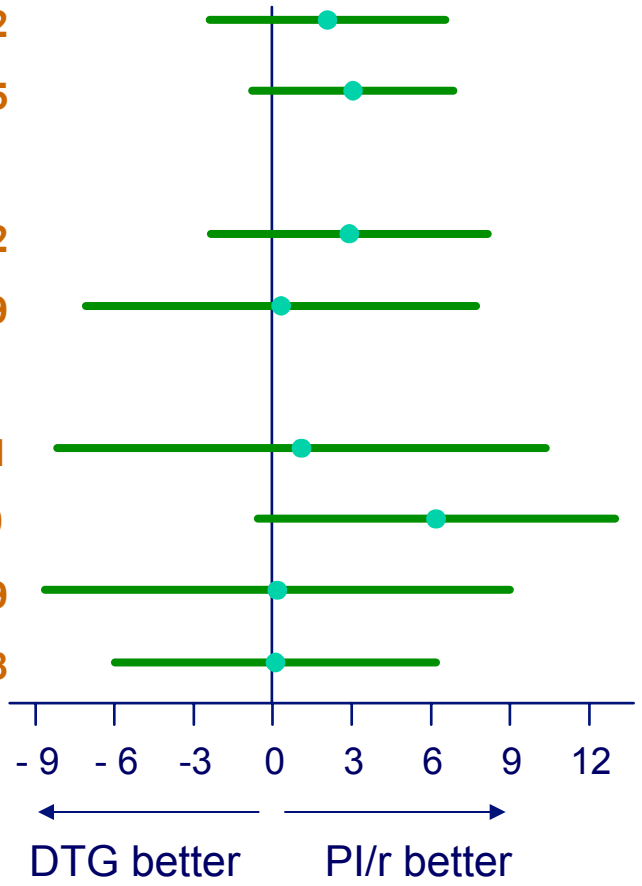
NEAT 022

Gatell JM. AIDS 2017;31:2503-14 ; Gatell JM. Clin Infect Dis 2019 ; 68 :597-606

NEAT 022 Study: Switch to DTG vs continuation of PI/r in patients with high cardiovascular risk

Treatment success at W48 (ITT, per-protocol and sub-groups)

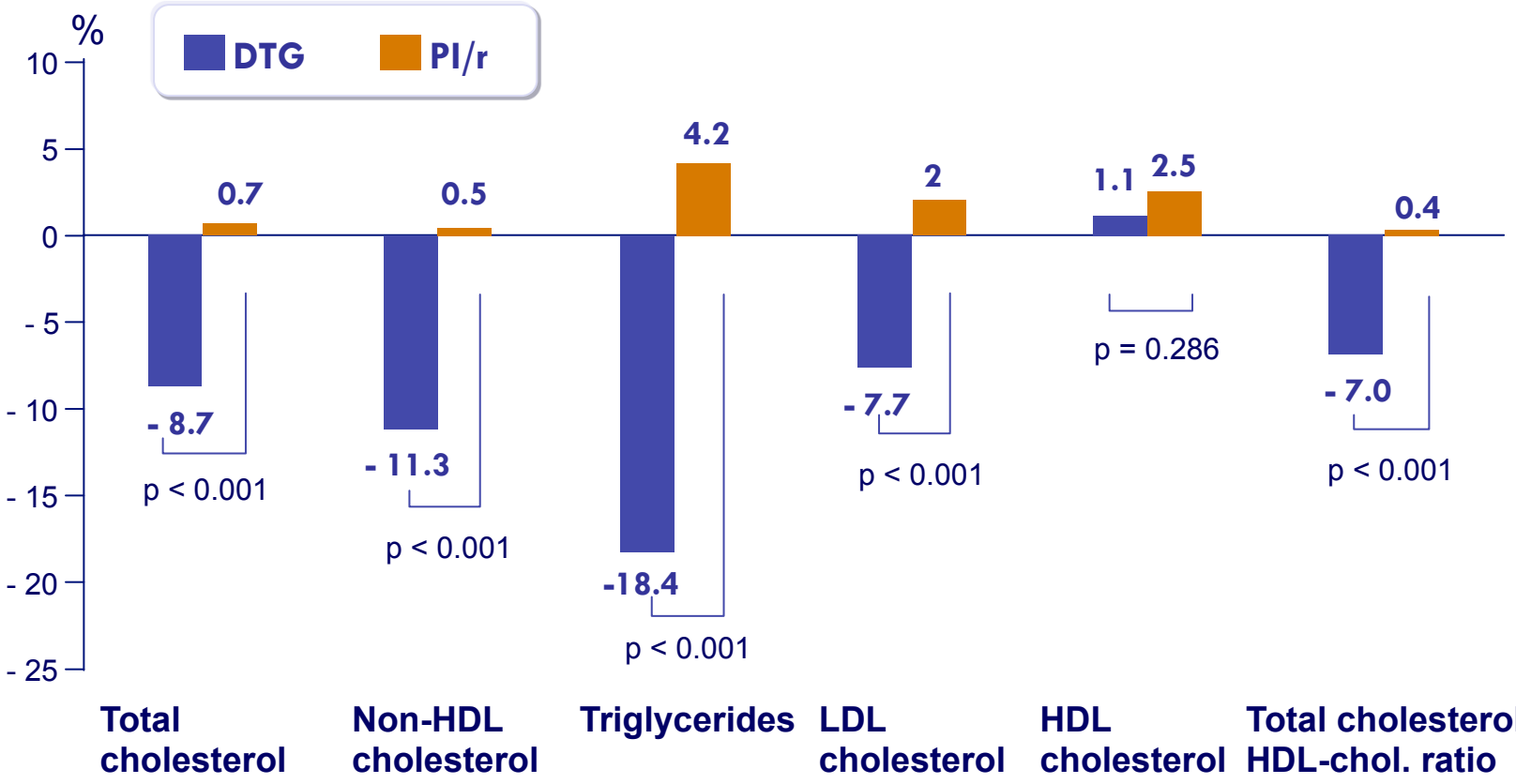
	% of patients	DTG Success (%)	PI/r Success (%)	Difference, % (95 % CI)	p for interaction
ITT analysis	100	**93.1**	**95.2**	2.1%	
Per-protocol analysis	97.3	**94.5**	**97.5**	3.0%	
Framingham 10-years CV risk					0.44
< 15%	53.0	**94.3**	**97.2**	2.9%	
≥ 15%	47.0	**92.5**	**92.9**	0.4%	
Country					1.00
United Kingdom	39.5	**89.0**	**90.1**	1.1%	
Spain	23.9	**93.8**	**100**	6.2%	
Germany	14.9	**96.7**	**96.9**	0.2%	
Belgium-France-Italy	21.7	**97.7**	**97.8**	0.1%	



Gatell JM. AIDS 2017;31:2503-14

NEAT 022 Study: Switch to DTG vs continuation of PI/r in patients with high cardiovascular risk

Fasting plasma lipids (mmol/L): mean percentage change at W48



- **No changes in the utilization of lipid lowering agents (around 30% in each arm, both at baseline and W48)**

NEAT 022

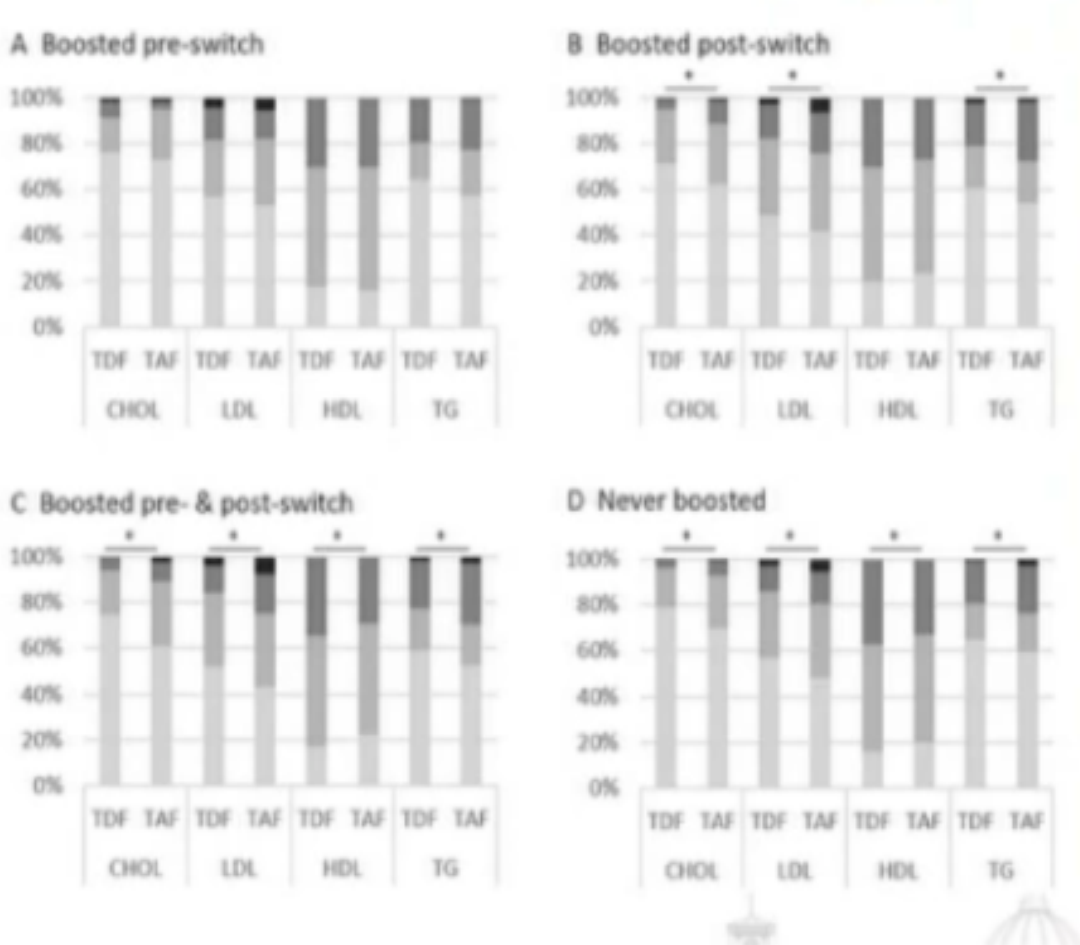
Gatell JM. AIDS 2017;31:2503-14

TAF and TDF

TDF could have an independent lipid-lowering effect

The switch from **TDF** to **TAF** is associated with less favourable lipid profiles, regardless of pharmaco-enhancers or third-agent use, however, less evident in people with higher lipid levels

TAF per se does not seem to influence lipid profiles



Hemkens LG, 2015; Brunet L, 2021; Taramasso L, 2019

Weight gain

- ✓ Association of BMI with all-cause mortality by sex, general population!

The Global BMI Mortality Collaboration. The Lancet, 2016

NRTI

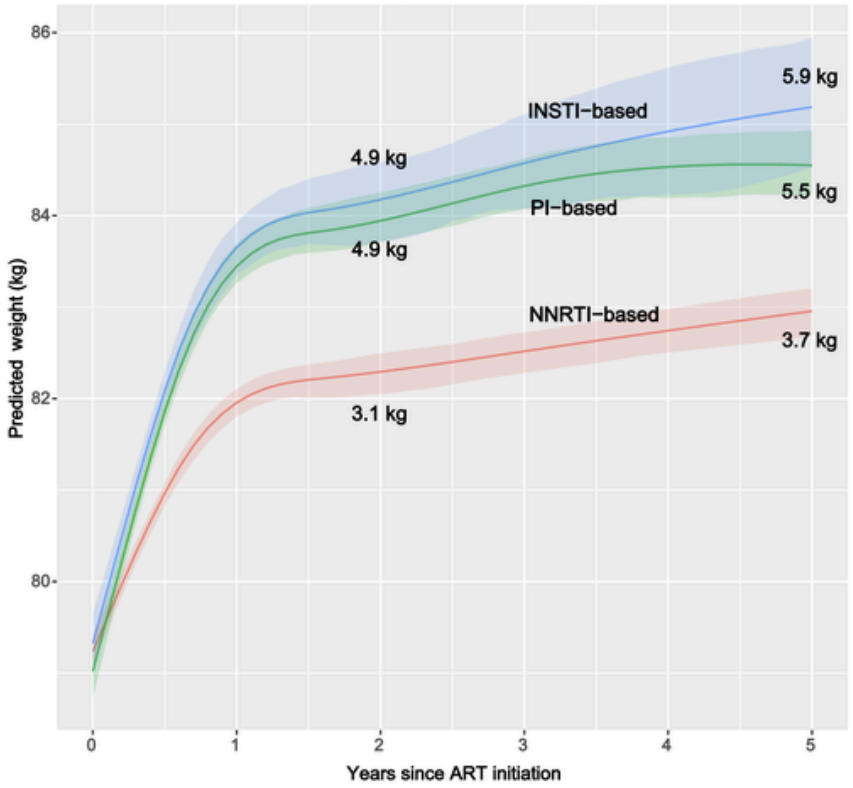
PI

NNRTI

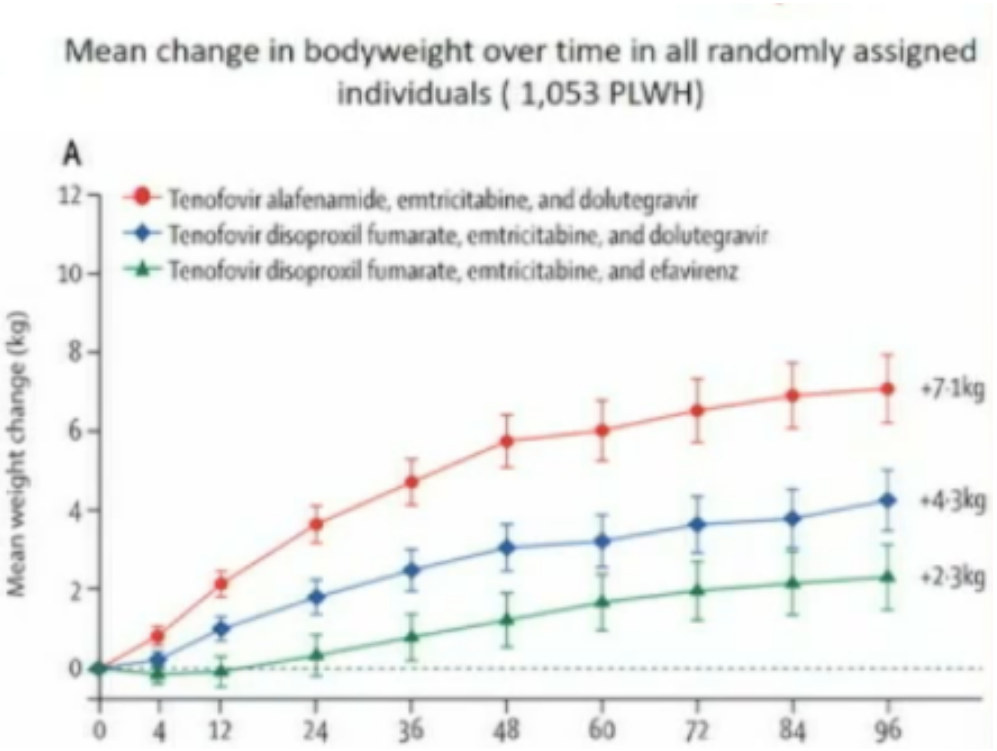
INSTI

Weight gain?

Weight over the first five-years of ART by regimen class (22,972 PLWH)



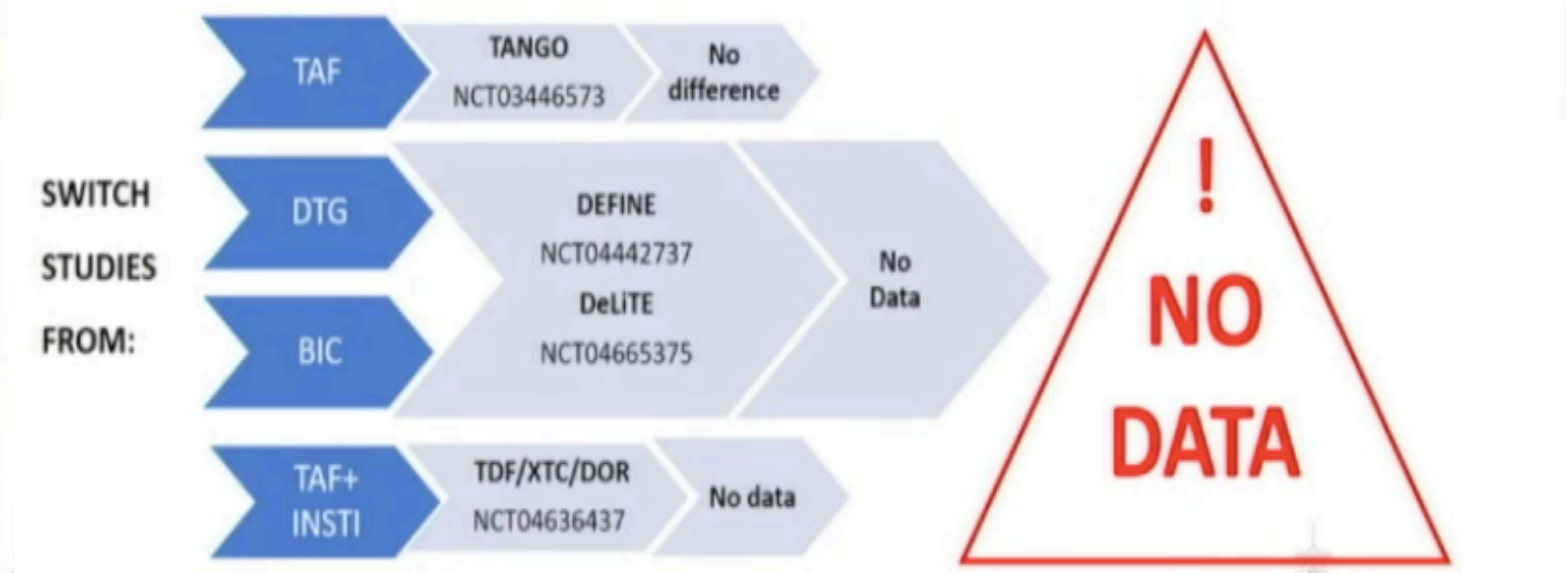
Mean change in bodyweight over time in all randomly assigned individuals (1,053 PLWH)



Bourgi K, et al., JIAS 2020, 23: e25484. Venter WDF, et al., Lancet HIV 2020; 7: e666–76.

Weight and switch

- ✓ Rilpivirine, doravirine and darunavir appear to be associated with smaller increases in weight



Sax PE, et al. CID, 2020. Shah S, et al. Drugs, 2021. van Wyk, J et al. CID 2020

Recommended Regimen Switch Strategies in the Setting of Viral Suppression

DHHS 2022

- **Within-class** switch strategies studied in individuals without underlying resistance include switching from:
  - TDF† or ABC‡ to TAF†
  - RAL§ to DTG
  - DTG, EVG/c, or RAL§ to BIC
  - EFV to RPV or DOR
  - ATV/c or ATV/r to ATV (with ABC/3TC)
- **Between-class** switch strategies studied in individuals without underlying resistance include switching from:
  - PI/b to INSTI (BIC, DTG, EVG)
  - PI/b to RPV or DOR
  - NNRTI to INSTI
  - PI/b with MVC

- **Two-Drug regimens**
  - DTG+RPV
  - DTG+3TC or FTC
  - bPI+3TC (in selected cases)
  - bDRV+DTG

Long-Acting CAB+RPV

EVG/c/TAF/FTC+DRV (In PLWH with history of resistance)

EACS 2021

Within-class or between-class switches are usually of low virological risk if components are of equal potency and in the absence of resistance (i.e. TDF/FTC -> TAF/FTC, EFV -> DOR or RPV)

TDF or TAF should not be discontinued in persons with chronic HBV

Dual therapies supported for switch by large RCTs or meta-analysis:

- DTG + RPV
- DTG + 3TC
- DRV/b + 3TC
- Long-acting CAB+RPV bi-monthly injections

Dual therapies supported only by small trials:

- DRV/b + RPV
- DRV/b + DTG

Monitoring after Switching Antiretroviral Therapy

- ✓ Closely monitoring for 3 months after switch to assess medication tolerance and to check efficacy
  - Clinic or telephone call 1 to 2 weeks
  - VL test to check for rebound viremia 4 to 8 weeks

DHHS, 2022

PROMEMORIA (GIANNI RODARI)

Ci sono cose da fare ogni giorno:
lavarsi, studiare, giocare,
preparare la tavola

a mezzogiorno.
Ci sono cose da fare di notte:
chiudere gli occhi, dormire

avere sogni da sognare,
orecchie per non sentire.
Ci sono cose da non fare mai,

ne' di giorno ne' di notte,
ne' per mare ne' per terra:
per esempio, la guerra.