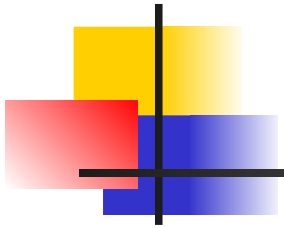

A New Era in ART: Tailored 2DR´s

Jose M Gatell MD, PHD
Senior Global Medical Director. ViiV Healthcare
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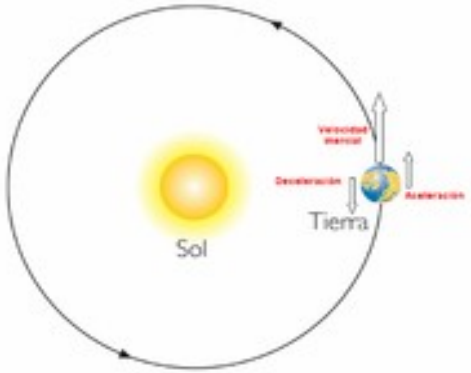
Potential conflicts of interest:

Since May 1st 2018 Dr. Gatell is a ViiV Healthcare fulltime employee (Senior Global Medical Director)

Challenging dogmas & introducing new paradigms: Never easy

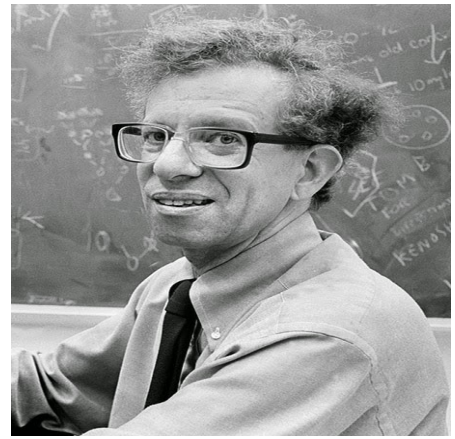


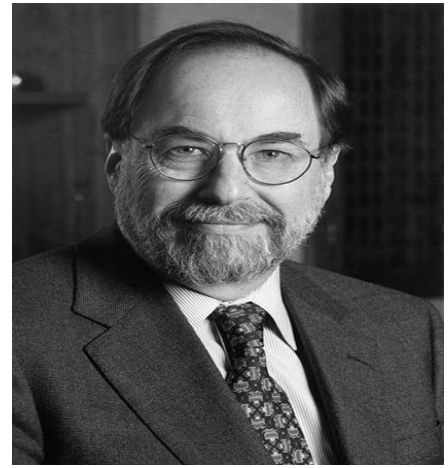
1633

Reverse transcription (1970)

RNA ⟶ DNA

Only reabilitated in 1939 (Pius XII) and 1992 (Jean Paul II)

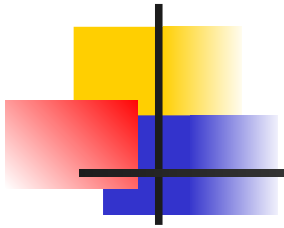




Nobel laureates, 1975

Look at the forest, not only at one tree

A New Era in ART: Tailored 2DR´s



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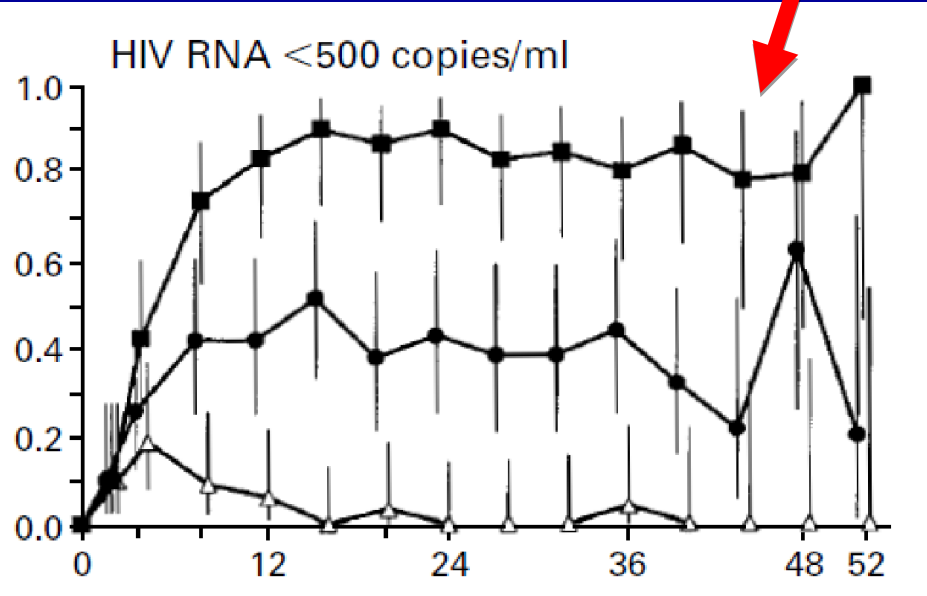
9. Cost-efficacy issues & guidelines
10. In summary ……..

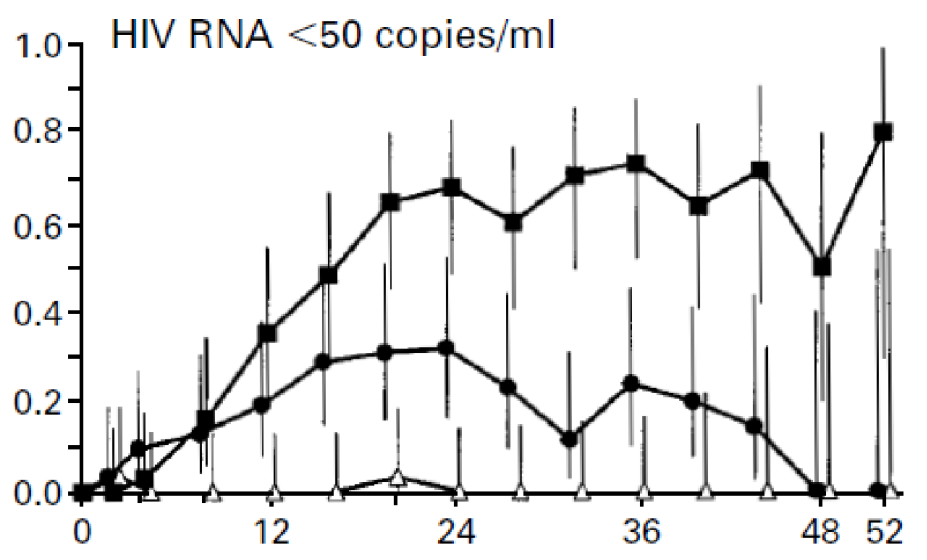
The New England Journal of Medicine

3 is a magic number ?

TREATMENT WITH INDINAVIR, ZIDOVUDINE, AND LAMIVUDINE IN ADULTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND PRIOR ANTIRETROVIRAL THERAPY

ROY M. GULICK, M.D., M.P.H., JOHN W. MELLORS, M.D., DIANE HAVLIR, M.D., JOSEPH J. ERON, M.D., CHARLES GONZALEZ, M.D., DEBORAH MCMAHON, M.D., DOUGLAS D. RICHMAN, M.D., FRED T. VALENTINE, M.D., LESLIE JONAS, B.S., ANNE MEIBOHM, PH.D., EMILIO A. EMINI, PH.D., AND JEFFREY A. CHODAKEWITZ, M.D.

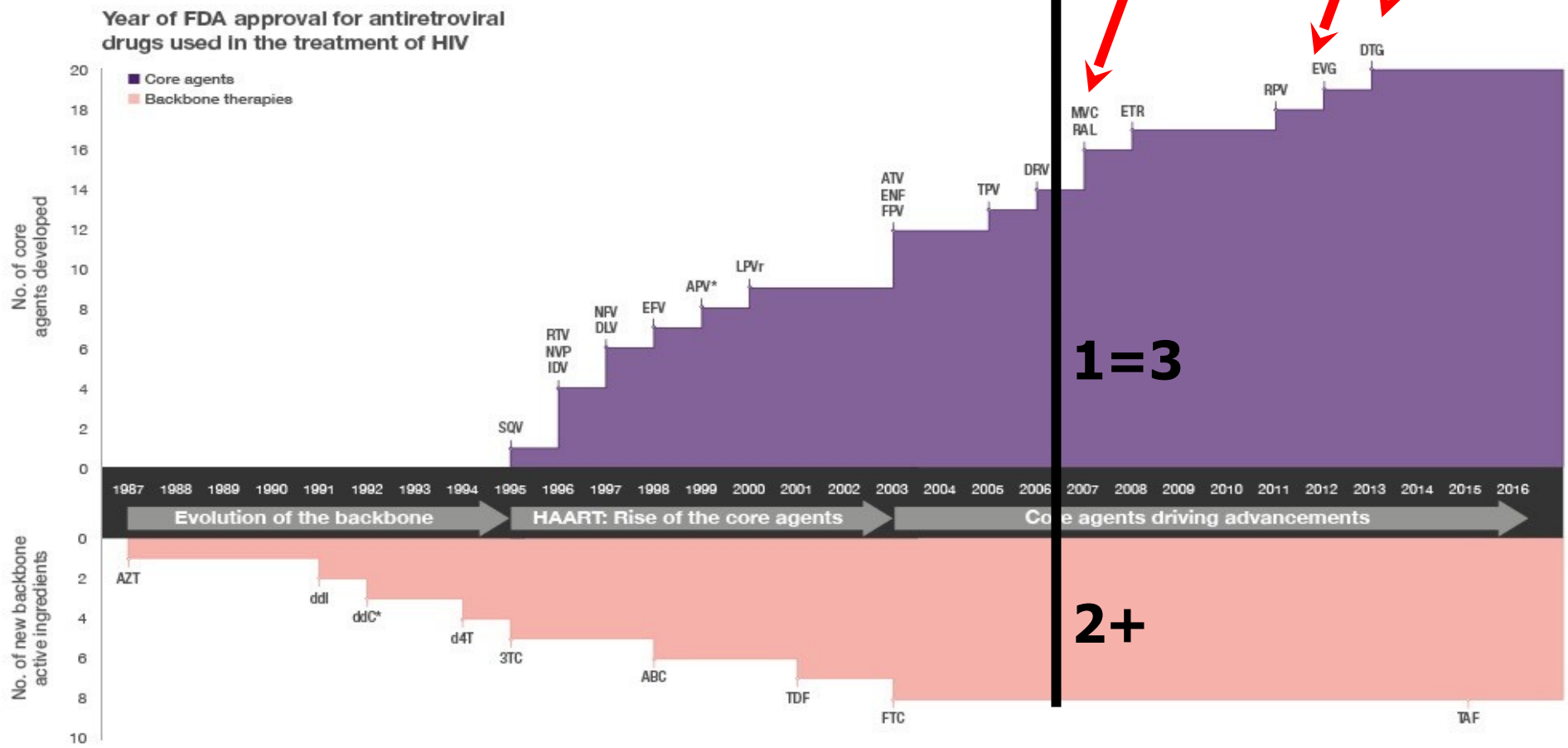




■ Three drugs
● Indinavir
△ Zidovudine–lamivudine

Gulick et al. N Engl J Med 1997; 337:734-9

THE EVOLUTION OF HIV THERAPY

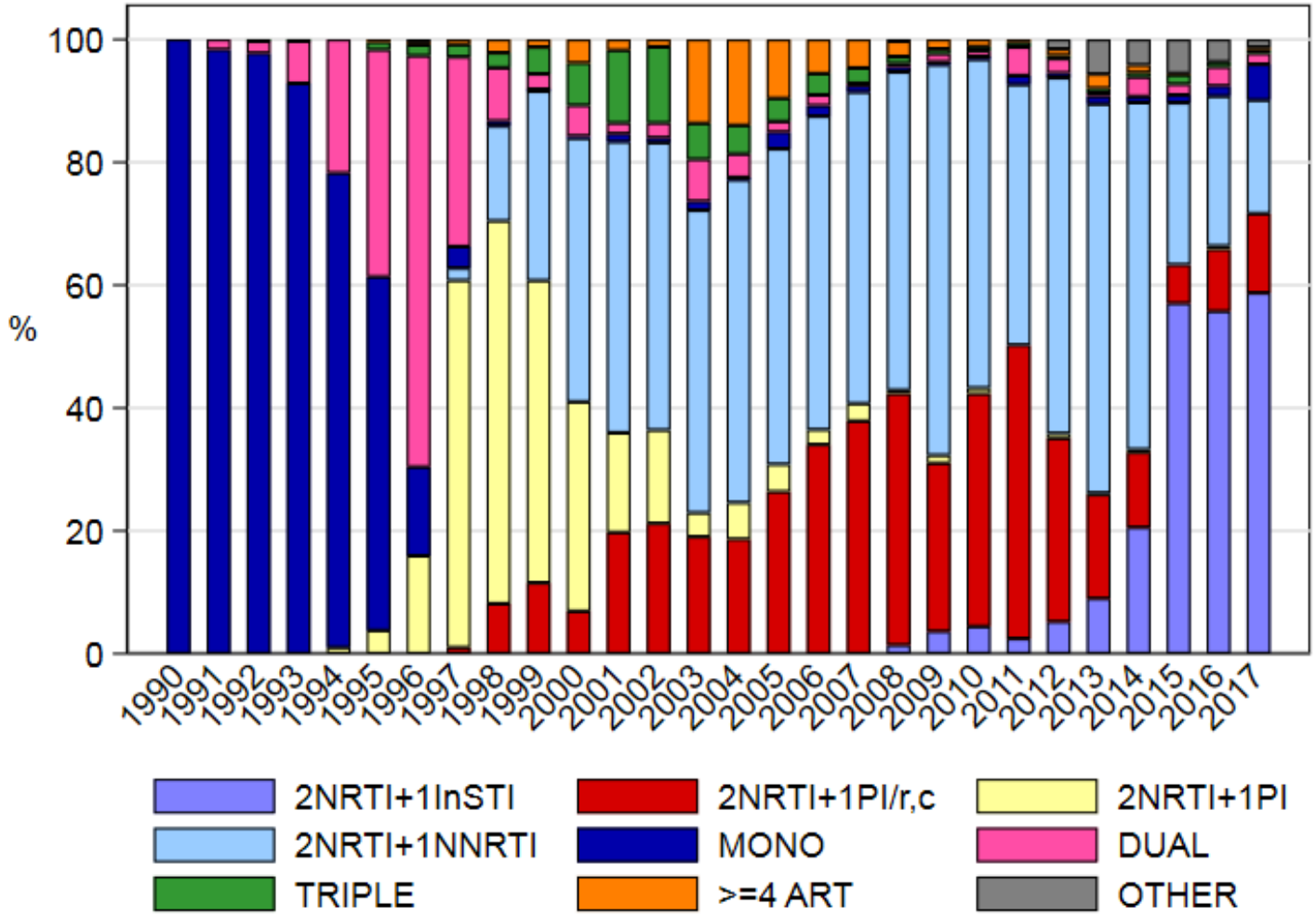


*No longer marketed in the United States of America

3TC = lamivudine; ABC = abacavir; APV = amprenavir; ATV = atazanavir; AZT = azidothymidine; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DRV = darunavir; DTG = dolutegravir; ENF = enfuvirtide; ETR = etravirine; EVF = efavirenz; EVG = elvitegravir; FPV = fosamprenavir; FTC = emtricitabine; HAART = highly active antiretroviral therapy; IDV = indinavir; LPVr = lopinavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir

FDA. Antiretroviral drugs used in the treatment of HIV infection http://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm118915.htm Accessed August 2015
FDA news release November 2015 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm471300.htm Accessed November 2015

The Constant Evolution of Initial ART at the Hospital Clinic of Barcelona, Spain (1990-2017)

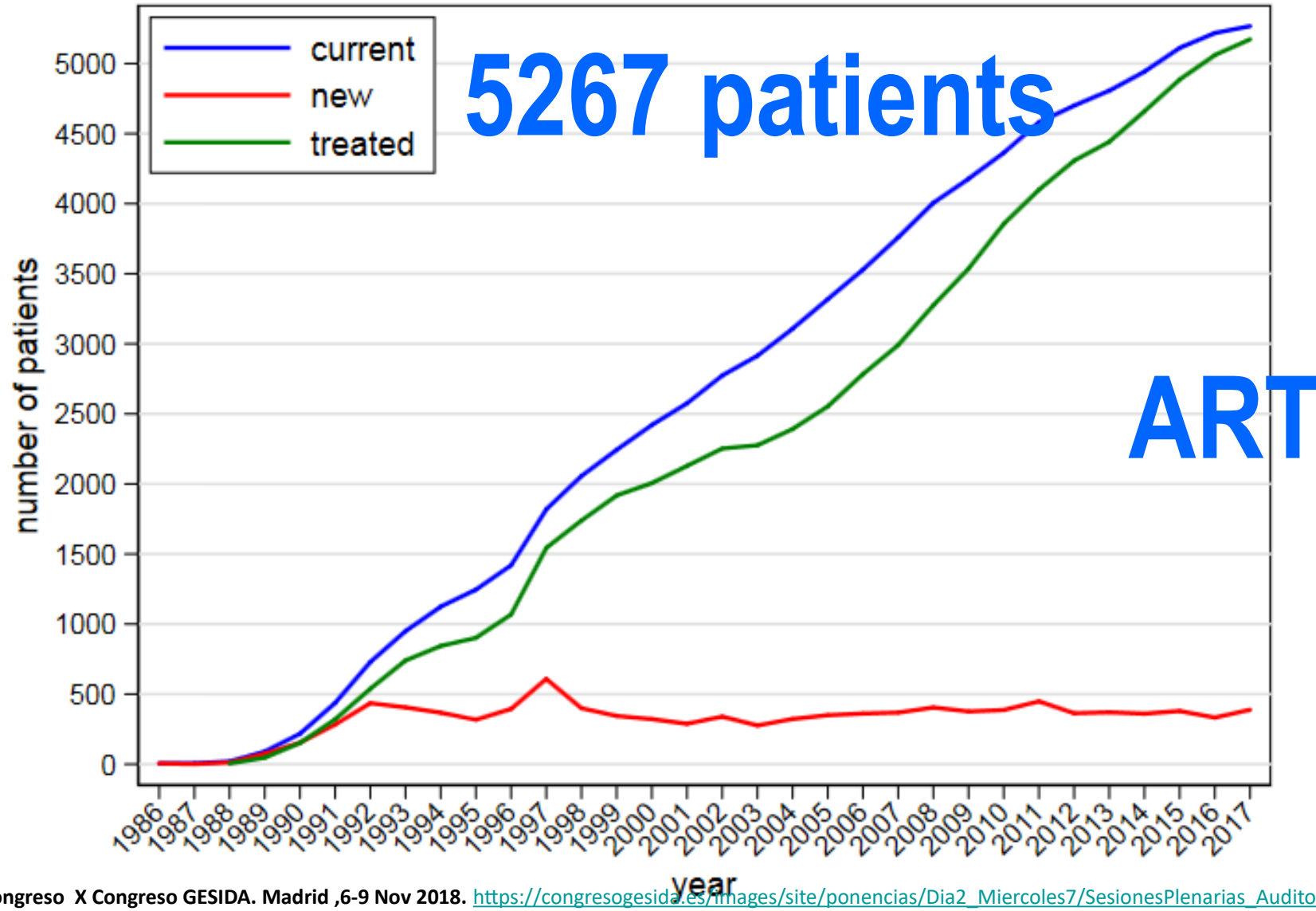


InSTI = 60%

Miro JM. Congreso X Congreso GESIDA. Madrid ,6-9 Nov 2018

Number of new and accumulated HIV-infected patients and patients on ART at the H. Clinic of Barcelona (1986-2017)

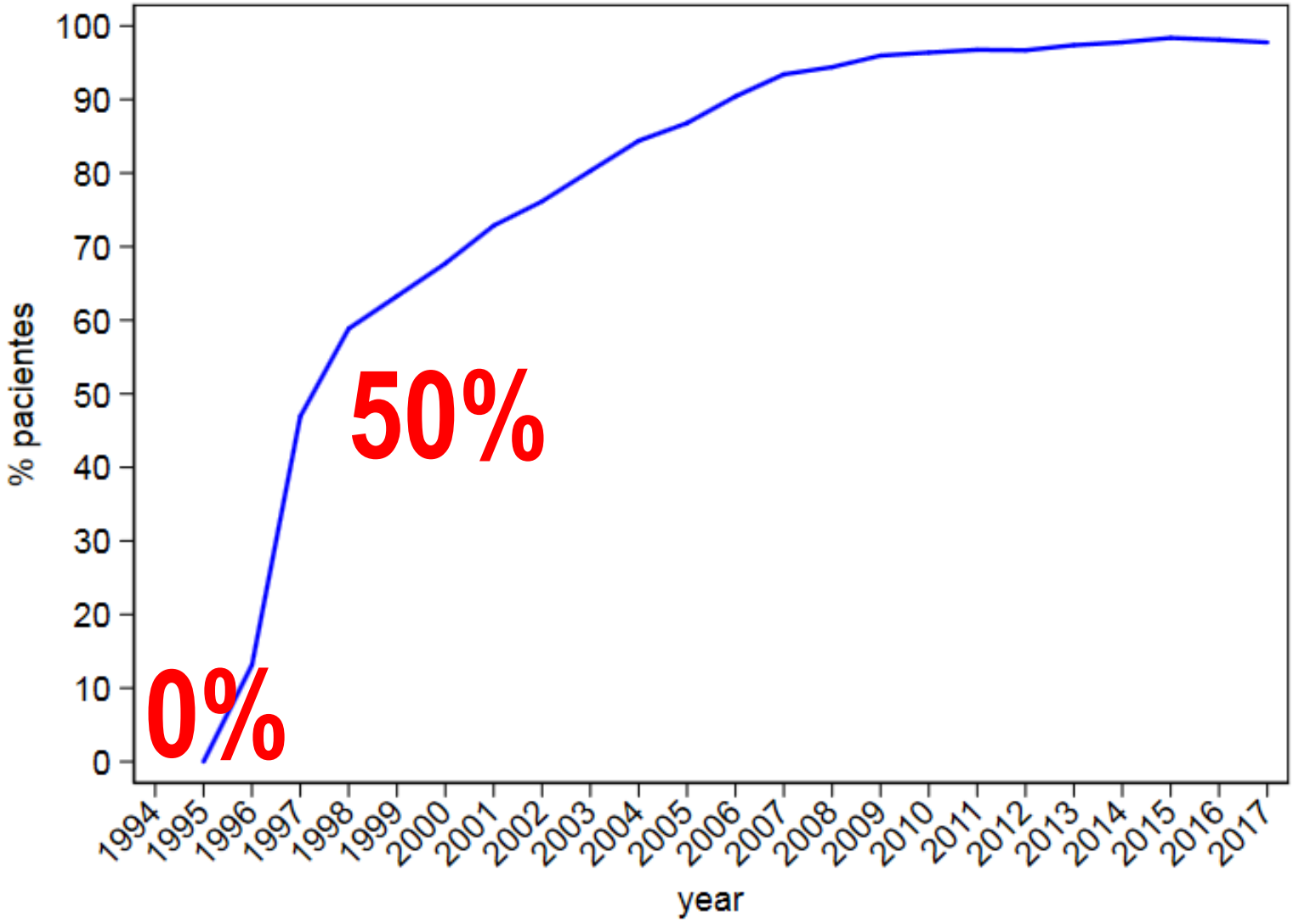
9



Miro JM. Congreso X Congreso GESIDA. Madrid ,6-9 Nov 2018. https://congresogesida.es/images/site/ponencias/Dia2_Miercoles7/SesionesPlenarias_Auditorio/JMMiro.pdf

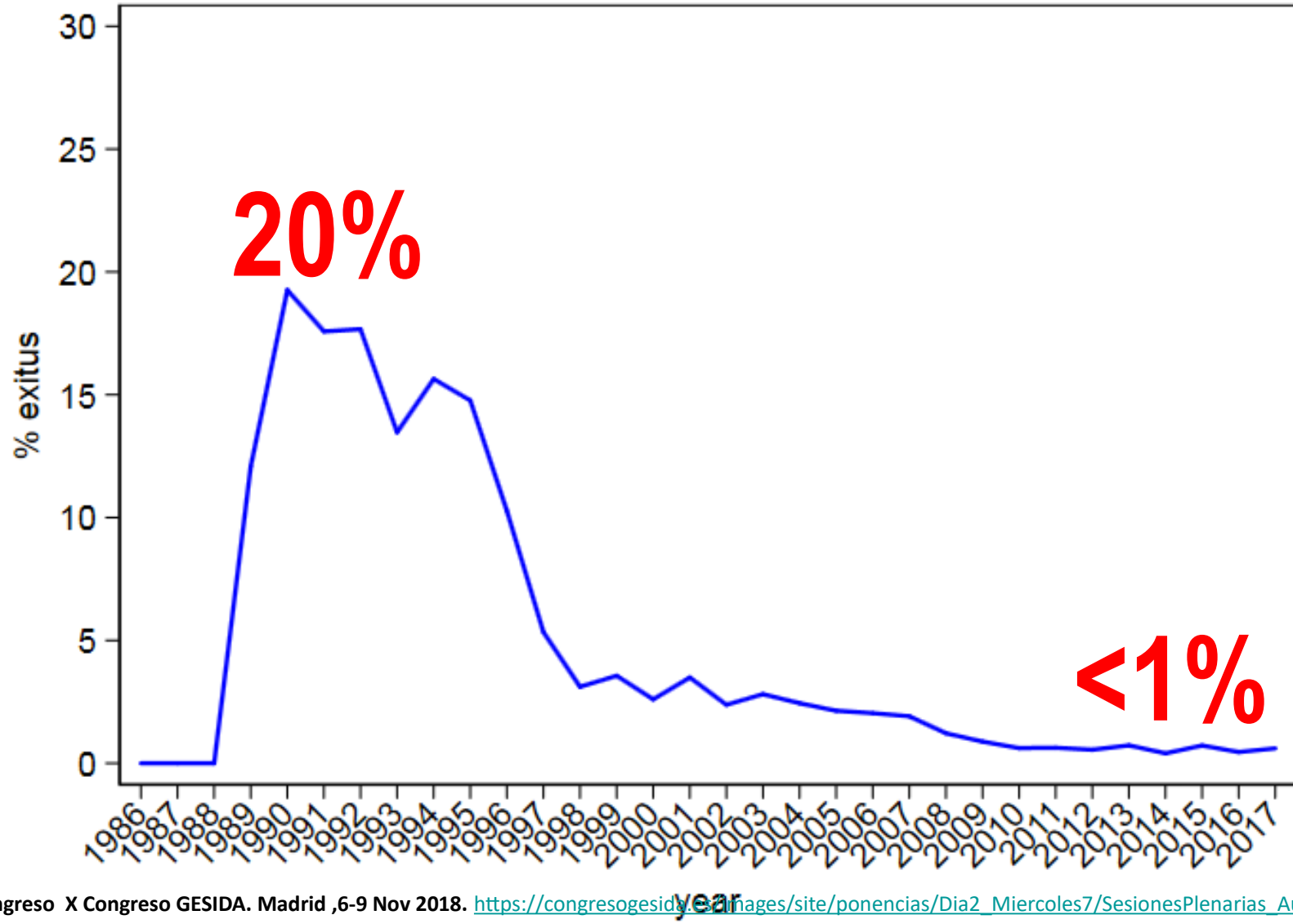
P

(<400 c/mL) on ART at the H. Clinic of Barcelona (1995-2017)

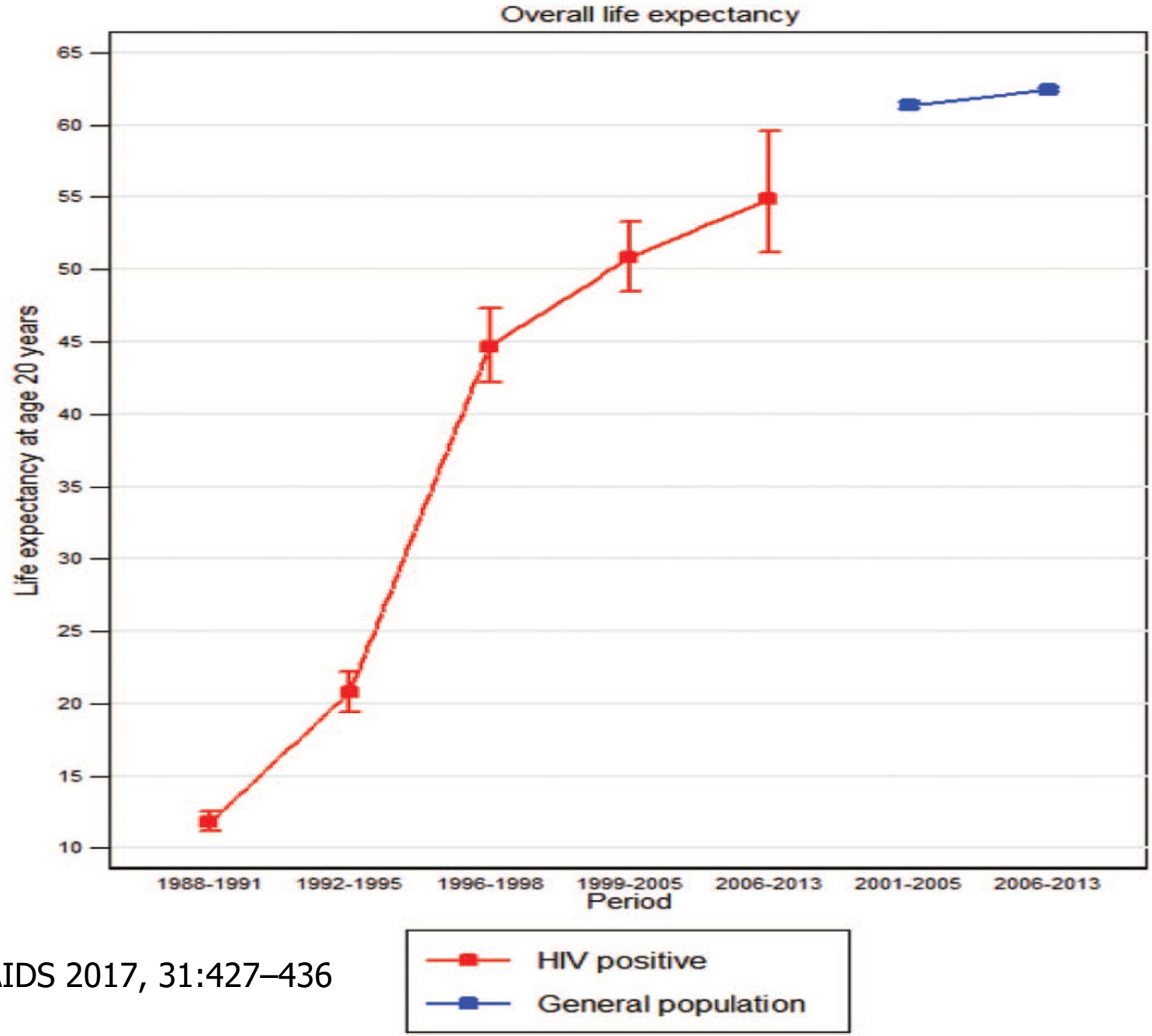


Miro JM. Congreso X Congreso GESIDA. Madrid ,6-9 Nov 2018. https://congresogesida.es/images/site/ponencias/Dia2_Miercoles7/SesionesPlenarias_Auditorio/JMMiro.pdf

Annual mortality rates in the cohort of HIV-infected patients of the H. Clinic of Barcelona (1986-2017)



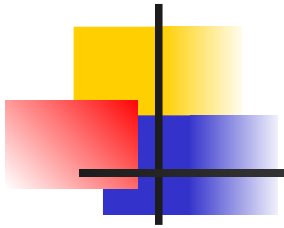
Miro JM. Congreso X Congreso GESIDA. Madrid ,6-9 Nov 2018. https://congresogesida.es/images/site/ponencias/Dia2_Miercoles7/SesionesPlenarias_Auditorio/JMMiro.pdf



Gueler et al. AIDS 2017, 31:427–436

Fig. 2. Life expectancy at age 20 years in patients enrolled in the Swiss HIV Cohort Study, from monotherapy (1988–1991) to recent combination ART era (2006–2013), and in a matched sample from the general Swiss population (2001–2013). ART,

A New Era in ART: Tailored 2DR´s



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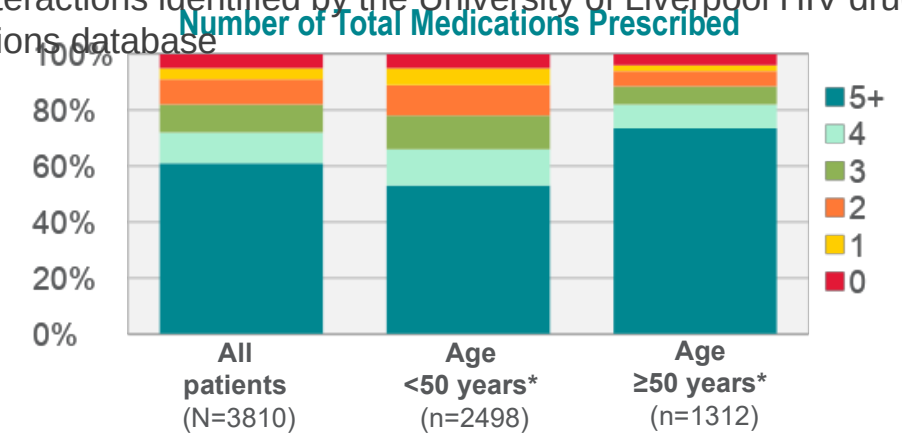
HIV Outpatient Study (HOPS): ARV/Non-ARV Drug Interactions

- Prospective, observational, US-based cohort of 3810 adults with HIV (2006–2010)
- Cohort data accrued longitudinally since 1993
- Describes the extent of polypharmacy and risks of potentially significant ARV/non-ARV drug interactions in people of different ages
- Drug interactions identified by the University of Liverpool HIV drug interactions database



*Age at patient midpoint of observation

LIMITATIONS OF THE STUDY

- Concurrent medications may not have actually been taken by the patient as prescribed
- Drug interactions may be underestimated because OTC and herbal medicines not systematically quantitated and interactions between non-ARVs were not examined
- University of Liverpool HIV drug interactions database may differ from the US labeling or guidelines for the relevant products
- Did not examine relationship between clinical endpoints and possible interactions

RESULTS

Of the patients prescribed an ARV/non-ARV combination during the 5-year period:

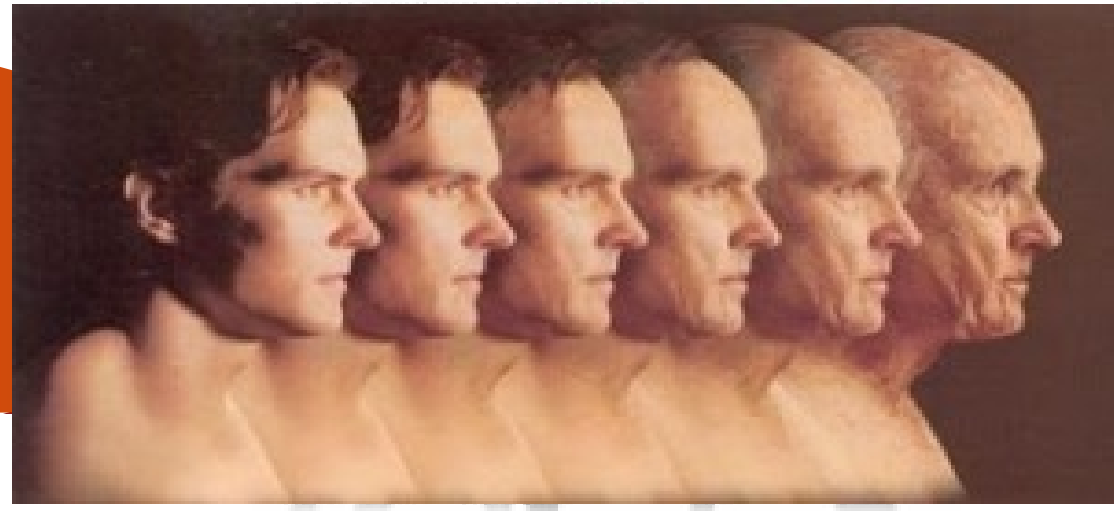
- **267 (7%)** had combinations that were contraindicated; **1267 (33%)** had combinations with moderate or high evidence of interaction
  - Older patients (≥50 years) were more likely to experience one of the above
- **1494 (39%)** patients were prescribed ≥5 non-ARV medications. Of those:
  - **706 (54%)** of patients were ≥50 years
  - **788 (32%)** of patients were <50 years

ARV, antiretroviral; OTC, over-the-counter; US, United States.

Holtzman C, et al. *J Gen Intern Med.* 2013;28(10):1302-1310.

Co-morbidities in HIV patients

Traditional risk factors



HIV

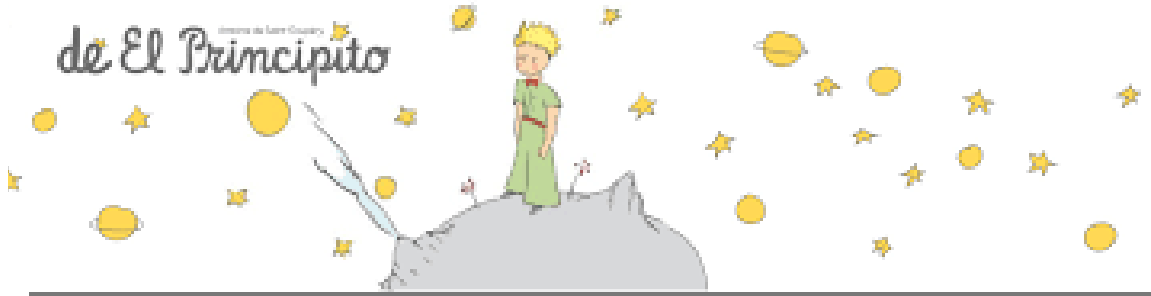
TOXICITY

Residual replication/reservoirs
Chronic inflammation & immunoactivation
Statins for all. Reprieve study ?

cART for life….

But can be optimized

Potentially dysfunctional trios….



David. Michelangelo Buonarroti
Galleria dell´Accademia.

La perfección no se alcanza cuando no hay nada más que añadir, sino cuando no hay nada más que quitar.

–Antoine de Saint-Exupéry

Isla Juan Fernandez

Robinson Crusoe

OPINION

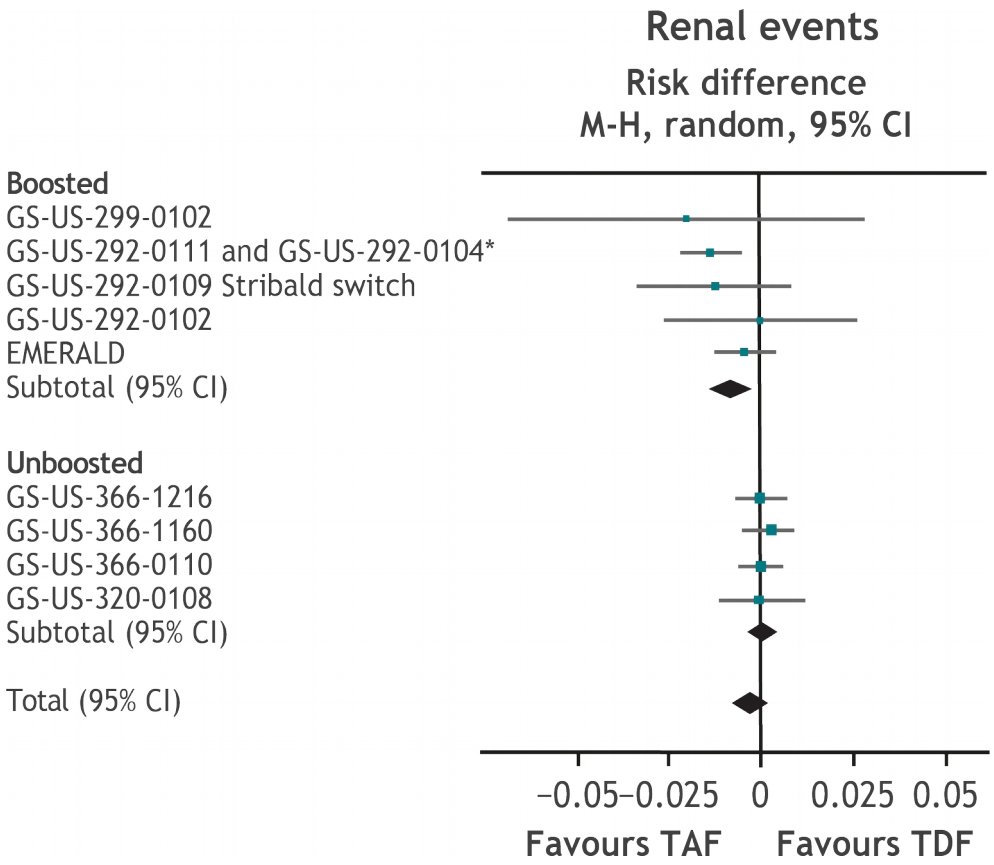
Twenty years of boosting antiretroviral agents: where are we today?

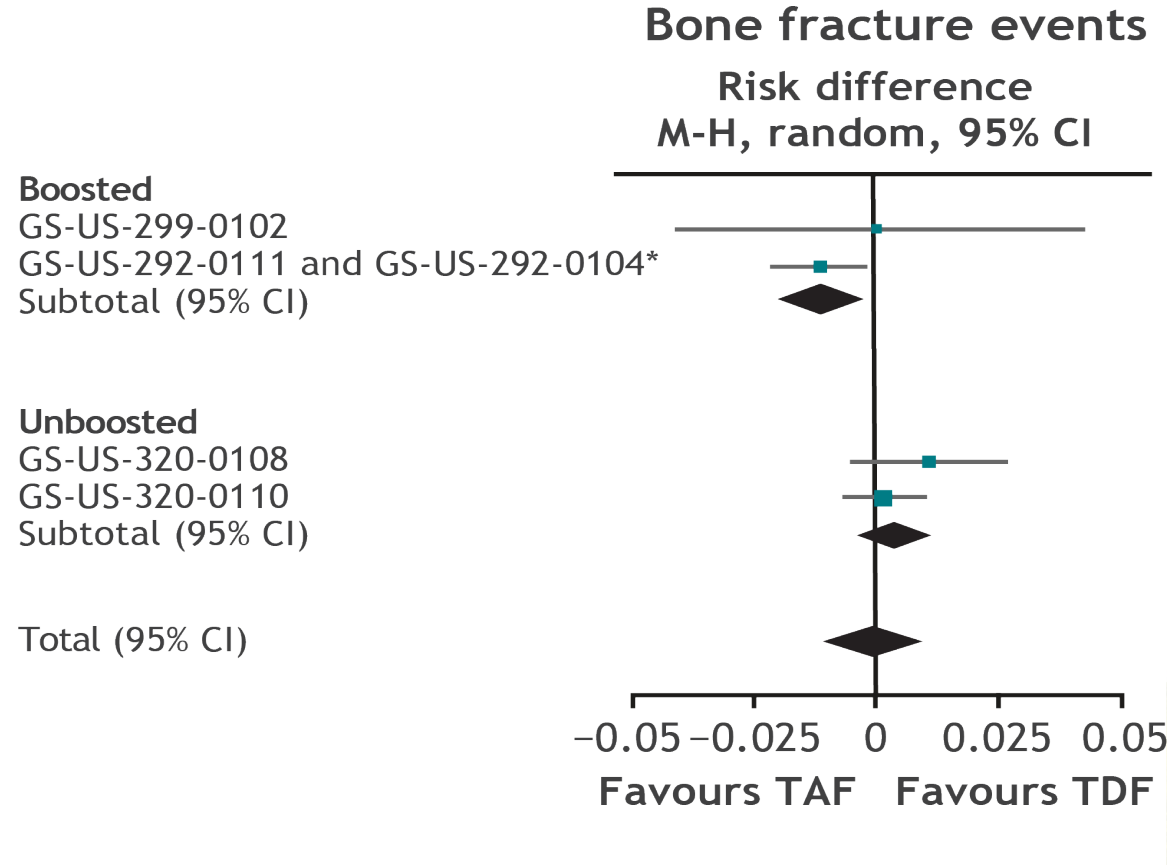
Marta Boffito[a,b], David Back[c] and José M. Gatell[d]

AIDS 2015, **29**:2229–2233

Boosters are responsible of a wide range of DDI´s increase toxicity of TDF and are largely avoidable in 2018

TDF: renal events & bone fracture events





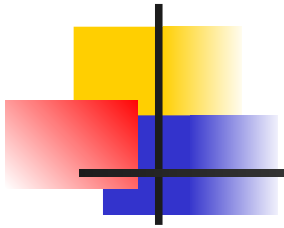
3235 PLHIV in boosted trials, 2803 PLHIV in unboosted trials

1897 PLHIV in boosted trials, 1298 PLHIV in unboosted trials

CI, confidence interval; M-H, Mantel–Haenszel method; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

Hill A, et al. J Virus Erad 2018;4:72–79.

A New Era in ART: Tailored 2DR´s



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Couples selected almost at random.
Most likely would never work ¡¡¡

Believe it or not, a carefully selected couple may work iiiii

Succesfull 2DR *vs.* 3DR in RCT

PI/r based

Naïve

- GARDEL (LPV/r + 3TC)
- KALEA (LPV/r + TDF)
- ANDES (DRV/r + 3TC)

Switching in suppressed patients

- OLE (LPV/r + 3TC)
- ATLAS-M (ATV/r + 3TC)
- SALT (ATV/r + 3TC)
- DUAL-GESIDA (DRV/r + 3TC)

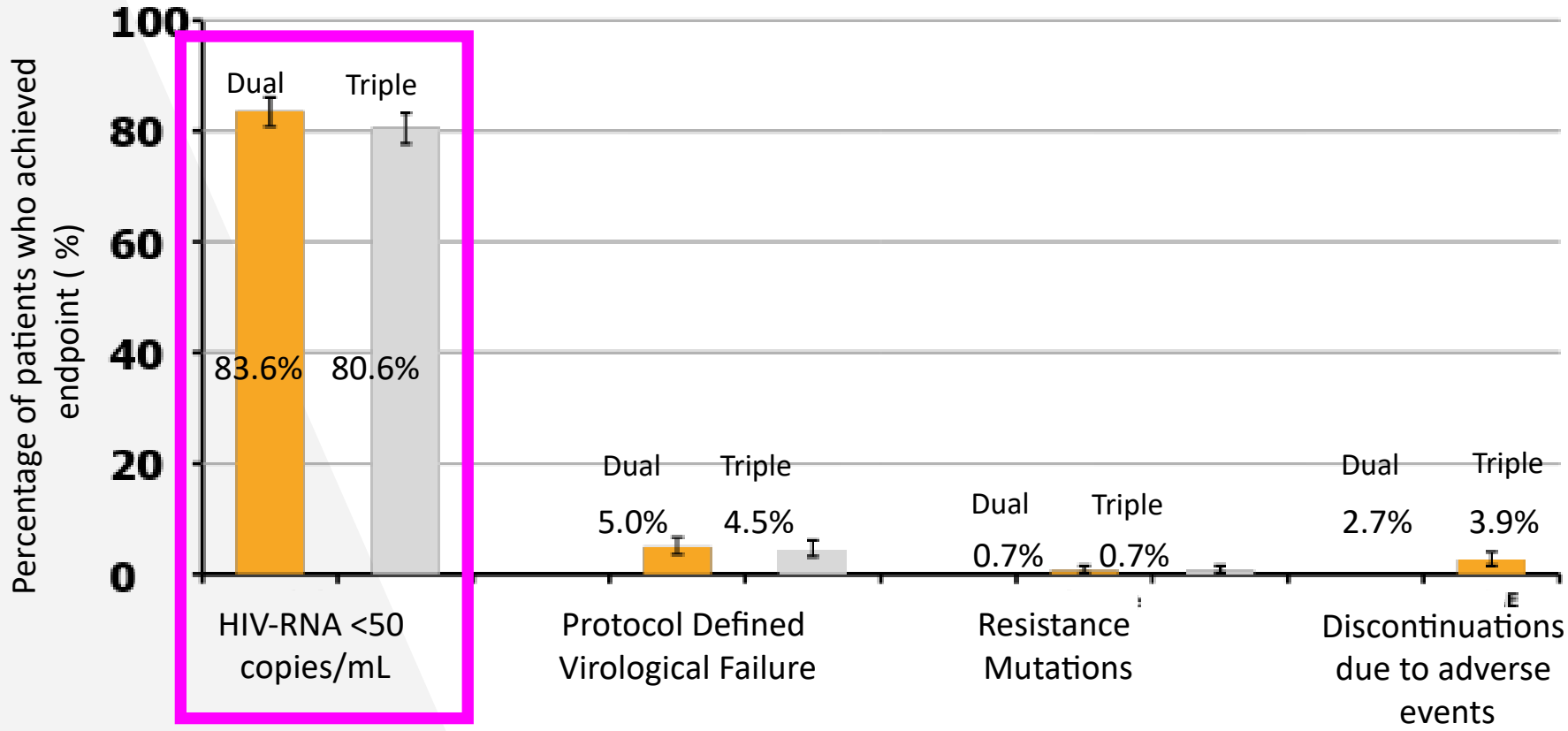
Miro JM. Congreso X Congreso GESIDA. Madrid ,6-9 Nov 2018. https://congresogesida.es/images/site/ponencias/Dia2_Miercoles7/SesionesPlenarias_Auditorio/JMMiro.pdf

bPI-based 2DC: Trial Designs

Study	Follow Up Week	Dual	Triple	Treatment History
GARDEL (n=306)	96	LPV/r + 3TC	LPV/r + 2 NRTI	Naïve
KALEAD (n=152)	24	LPV/r + TDF	LPV/r + 2 NRTI	Naïve
ANDES (n=145)	48	DRV/r + 3TC	DRV/r + 3TC/TDF	Naïve
OLE (n=250)	48	LPV/r + 3TC	LPV/r + 2 NRTI	Switch
ATLAS-M (n=266)	96	ATV/r + 3TC	ATV/r + 2 NRTI	Switch
SALT (n=267)	96	ATV/r + 3TC	ATV/r + 2 NRTI	Switch
DUAL-GESIDA (n=249)	48	DRV/r + 3TC	DRV/r + 2 NRTI	Switch
Total (n=1635)				

Liev Z et al. HIV Glasgow. October 28-31, 2018

bPI-based 2DC: Summary Findings



Only few NRTI mutations in 2D and TT arms (M184V). No major PI mutations.

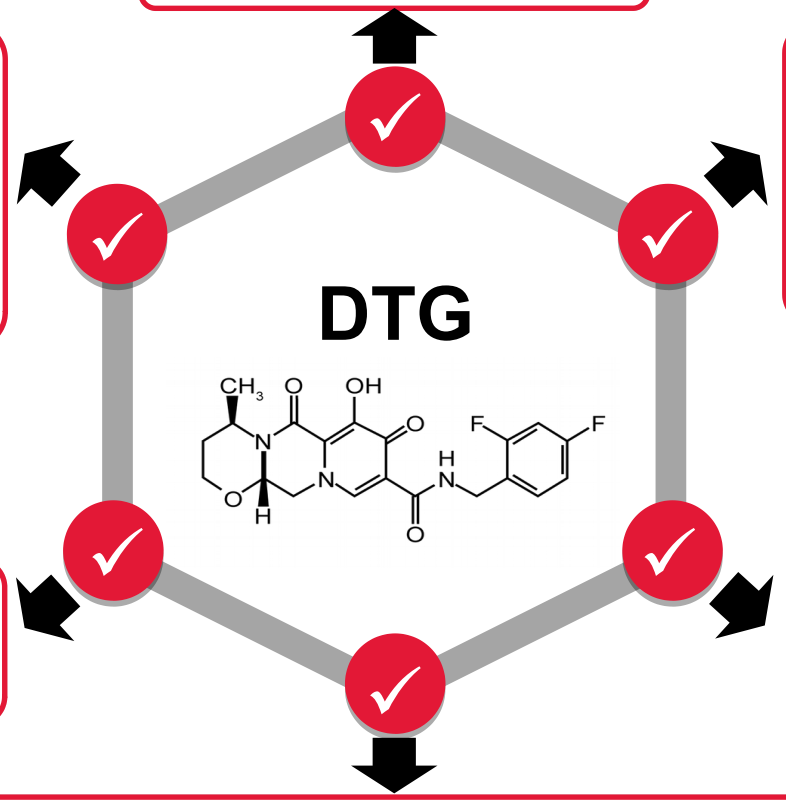
DTG as a Core Agent to Support 2DRs

Rapid and potent antiviral activity[1]

Breadth and depth of clinical trial data[2,7–9]
- DTG superior versus EFV and DRV/r in treatment-naïve subjects, ATV and RTV and TDF/FTC in treatment-naïve women and RAL in treatment-experienced subjects

High barrier to resistance[2,3]
- *In vitro* findings supported by Phase III data

Long binding to WT INI[4]
- Dissociation from mutant INI–DNA complexes slower versus RAL or EVG



Well tolerated
- Few discontinuations due to AEs in INI-naïve clinical trials[2, 7–10]

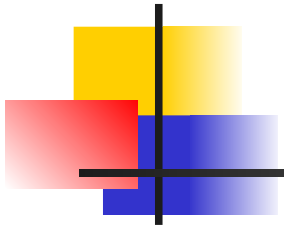
DDIs
- Booster-free
- Few clinically significant DDIs

Long half-life; low variability in exposure
- DTG (50 mg QD) exposures 19-fold above IC_{90}[5]
- Long 'tail' – drug plasma concentrations up to 216 hours post dose[6]

IC_{50}, half-maximal inhibitory concentration
WT, wild-type

1. Min S, et al. AIDS 2011;25:1737–45; 2. Cahn P, et al. Lancet 2013;382:700–8; 3. Kobayashi M, et al. Antimicrob Agents Chemother 2011;55:813–21; 4. Hightower KE, et al. Antimicrob Agents Chemother 2011;5:4552–9; 5. van Lunzen J, et al. Lancet Infect Dis 2012;12:111–8; 6. Elliot E, et al. IWCPHIV 2015. Abstract 13; 7. Walmsley S, et al. N Engl J Med 2013;369:1807–18; 8. Clotet B, et al. Lancet 2014;383:2222–31; 9. Orrell C, et al. Lancet HIV 2017;4:e536-46; 10. Raffi F, et al. Lancet 2013;381:735–43

A New Era in ART: Tailored 2DR´s



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Succesfull 2DR *vs.* 3DR in RCT

DTG-based

Naïve (+ 3TC)

- PADDLE (pilot single arm)
- ACTG A5353 (pilot single arm)
- **GEMINI 1+2 (phase III)**

Switching

- **SWORD 1+2 (DTG + RPV), TANGO**
- ASPIRE (DTG + 3TC)
- ANRS 167 LAMIDOL (single arm DTG + 3TC)
- DOLAM

Miro JM. Congreso X Congreso GESIDA. Madrid ,6-9 Nov 2018. https://congresogesida.es/images/site/ponencias/Dia2_Miercoles7/SesionesPlenarias_Auditorio/JMMiro.pdf

PADDLE: Viral Suppression at Week 48-96

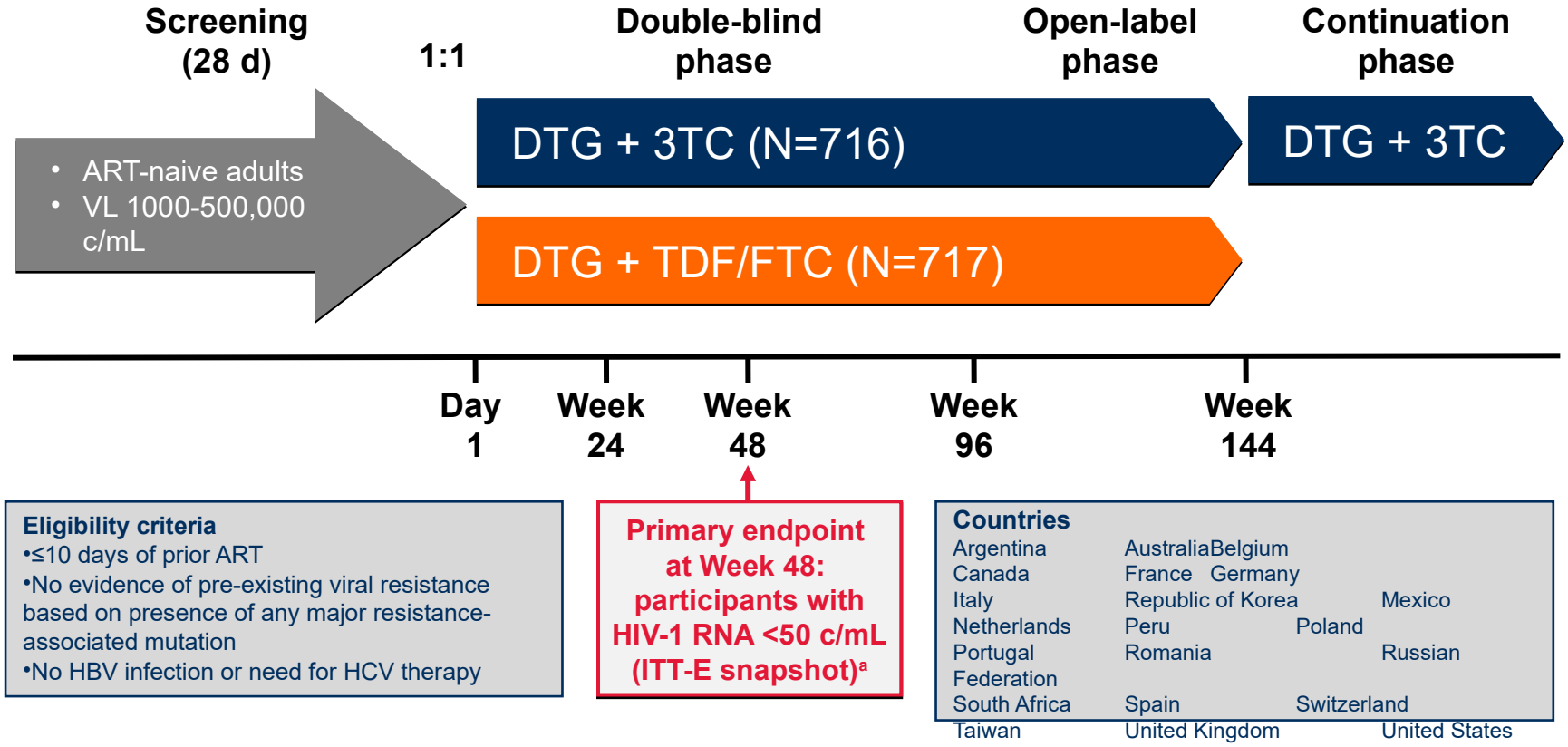
Patient	BL	Week 48	Week 60	Week 72	Week 84	Week 96
		HIV-1 Viral load (c/mL)				
1	10,909	<50	<50	<50	<50	<50
2	10,233	<50	<50	<50	<50	<50
3	**151,569**	<50	<50	<50	**55/<50***	<50
4	**148,370**	<50	<50	<50	<50	<50
5	20,544	<50	<50	<50	<50	<50
6	14,499	<50	<50	<50	<50	<50
7	18,597	<50	<50	<50	<50	<50
8	24,368	<50	<50	<50	<50	<50
9	10,832	Discontinuation at Week 48 due to SAE				
10	7,978	<50	<50	<50	<50	<50
11	**273,676**	<50	<50	<50	<50	**70/<50***
12	64,103	<50	<50	<50	<50	<50
13	33,829	<50	<50	<50	<50	<50
14	15,151	<50	<50	<50	<50	<50
15	23,400	<50	<50	<50	<50	<50
16	3,910	<50	<50	<50	<50	<50
17	25,828	<50	<50	<50	<50	<50
18	73,069	<50	<50	<50	<50	<50
19	**106,320**	Discontinuation at Week 48 due to PDVF				
20	7,368	<50	<50	<50	<50	<50

BL, baseline; PDVF, protocol-defined virologic failure
SAE, serious adverse event; SCR, screening; W, week

Figueroa MI, et al. IAS 2017. Poster MOPEB0287

GEMINI-1 and -2 Phase III Study Design

Identically designed, randomized, double-blind, parallel-group, multicenter, noninferiority studies



Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3).

[a]–10% noninferiority margin for individual studies.

Cahn P et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Cahn et al. Lancet. 2019;393(10167):143-155

Demographic and Baseline Characteristics for the Pooled GEMINI-1 and -2 Population

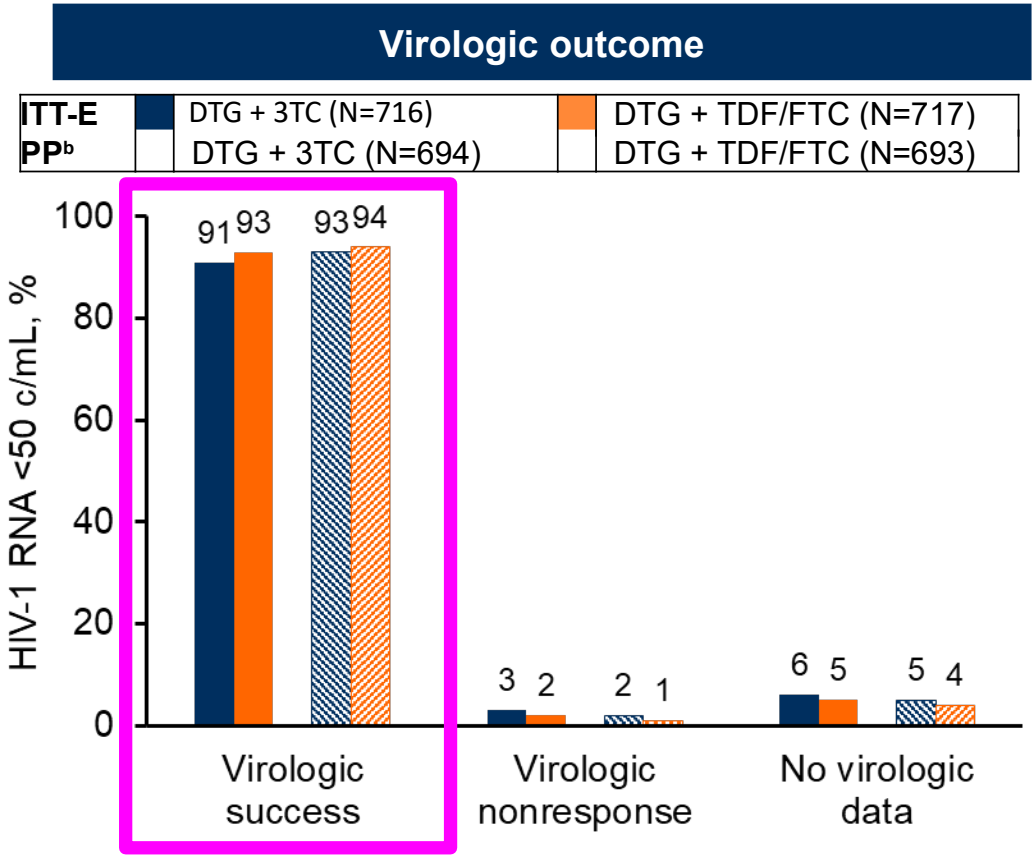
Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
Other	66 (9)	72 (10)
Ethnicity, n (%)		
Hispanic or Latino	215 (30)	232 (32)
Not Hispanic or Latino	501 (70)	485 (68)
HIV-1 RNA, median (range), log_{10} c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
≤100,000	576 (80)	564 (79)
>100,000[a]	140 (20)	153 (21)
CD4+ cell count, median (range), cells/mm^3	427.0 (19-1399)	438.0 (19-1497)
>200	653 (91)	662 (92)
≤200	63 (9)	55 (8)

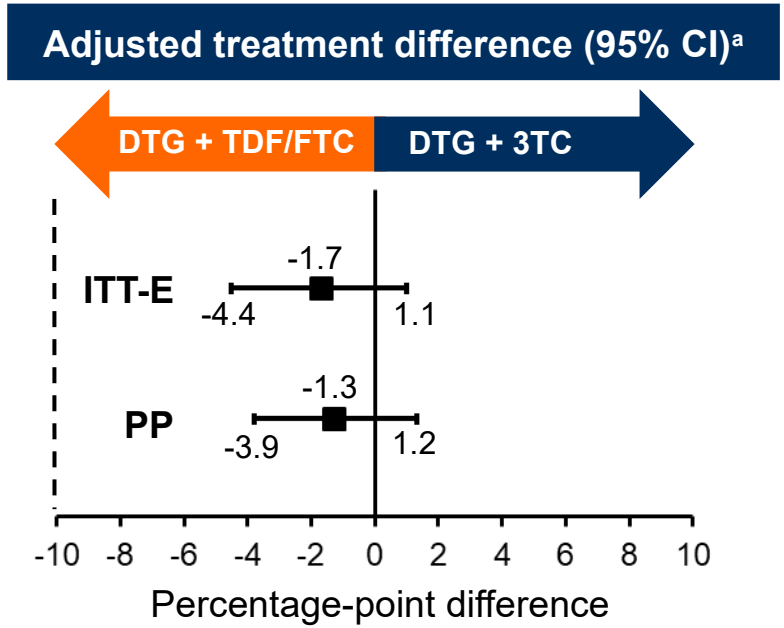
[a]2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL

Cahn P et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Cahn et al. Lancet. 2019;393(10167):143-155

Pooled Snapshot Outcomes at Week 48: ITT-E and Per Protocol Populations





DTG + 3TC is **non-inferior** to DTG + TDF/FTC with respect to proportion <50 c/mL at Week 48 (snapshot, ITT-E population) in both studies

[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL), CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2). [b]PP, per protocol: population consisted of participants in the ITT-E population except for significant protocol violators, which could potentially affect efficacy outcomes as determined by the medical monitor prior to database lock.

Cahn P et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Cahn et al. Lancet. 2019;393(10167):143-155

GEMINI-1 and -2: Adverse Events

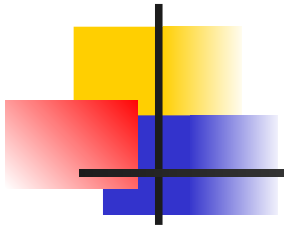
n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Any AE	543 (76)	579 (81)
AE occurring in ≥5% of subjects in either group		
Headache	71 (10)	75 (10)
Diarrhoea	68 (9)	77 (11)
Nasopharyngitis	55 (8)	78 (11)
Upper RTI	56 (8)	44 (6)
Nausea	27 (4)	53 (7)
Insomnia	27 (4)	45 (6)
Pharyngitis	36 (5)	32 (4)
Back pain	35 (5)	31 (4)
Drug-related AE	126 (18)	169 (24)
Grade 2–4 AE occurring in ≥1% of subjects	42 (6)	47 (7)
Headache	8 (1)	8 (1)
AE leading to withdrawal from the study	15 (2)	16 (2)
Neuropsychiatric AEs leading to withdrawal	6 (<1)	4 (<1)
Any serious AE*	50 (7)	55 (8)

Overall safety and tolerability profile at Week 48 was comparable between the two regimens. Fewer drug-related AEs were observed with DTG + 3TC

Pooled ITT-E Population
*2 deaths (acute myocardial infarction, n=1; Burkitt's lymphoma, n=1) in the GEMINI-2 study; both were in the DTG + 3TC group and were considered unrelated to the study drug regimen

Cahn P, et al. IAS 2018. TUAB0106LB

A New Era in ART: Tailored 2DR´s



1. 3DR´s (often with a booster). From year 1996 to 2018
2. Why to reduce exposure to antiretroviral agents ?
3. The proof of concept: PI/r+3TC
4. Evidence of DTG+3TC in naïve patients
5. Evidence of DTG+RPV or DTG+3TC in suppressed patients
6. Less than 3 drugs in salvage therapy ?
7. Reasonable concerns to be addressed
8. Unproven/misleading perceptions?
9. Cost-efficacy issues & guidelines
10. In summary ……..

Succesfull 2DR *vs.* 3DR in RCT

DTG-based

Naïve (+ 3TC)

- PADDLE (pilot single arm)
- ACTG A5353 (pilot single arm)
- **GEMINI 1+2 (phase III)**

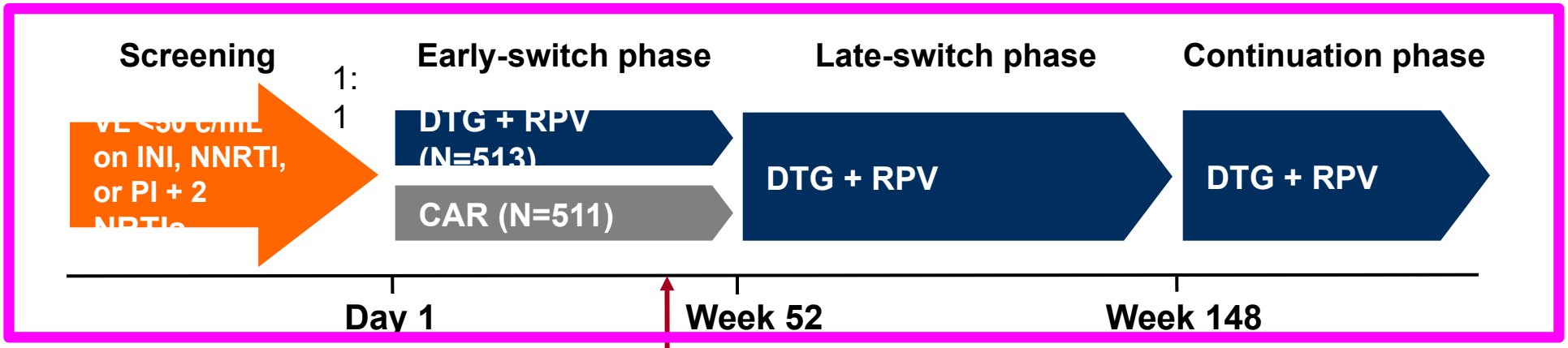
Switching (+ RPV or 3TC)

- ASPIRE (+ 3TC)
- ANRS 167 LAMIDOL (+3TC; pilot single arm)
- DOLAM (+3TC; pilot)
- **SWORD 1+2 (+ RPV; phase III)**
- **TANGO, SALSA (+3TC; phase III ongoing)**

Miro JM. Congreso X Congreso GESIDA. Madrid ,6-9 Nov 2018. https://congresogesida.es/images/site/ponencias/Dia2_Miercoles7/SesionesPlenarias_Auditorio/JMMiro.pdf

SWORD-1 and -2: Phase III Study Design

Identically designed, randomised, multicentre, open-label, parallel-group, non-inferiority studies



Inclusion criteria

- On stable CAR ≥6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA <50 c/mL during the 12 months before screening
- HBV-negative

Primary endpoint at 48 weeks: subjects with VL <50 c/mL (ITT-E snapshot)*

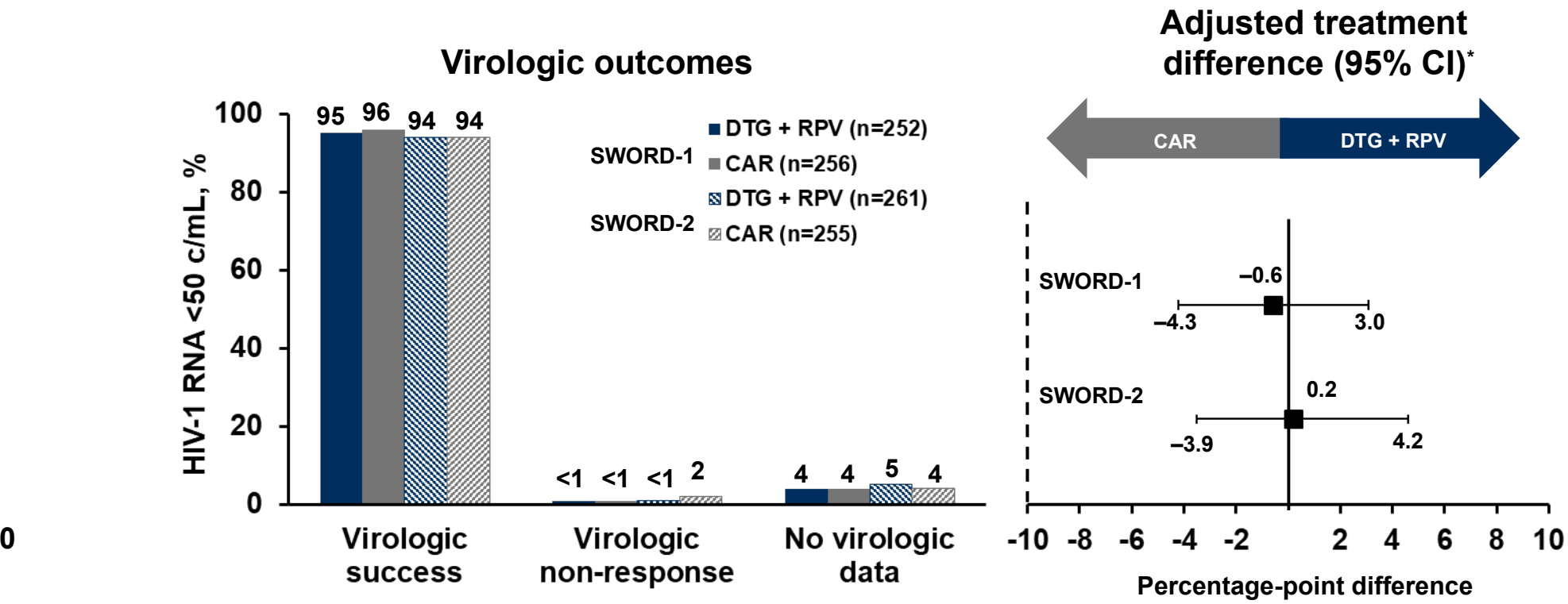
Countries:
Argentina, Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Russia, Spain, Taiwan, United Kingdom, United States

*8% non-inferiority margin for pooled data. -10% non-inferiority margin for individual studies

HBV, hepatitis B virus; ITT(-E), intent to treat (- exposed); NRTI, nucleoside reverse transcriptase inhibitor

Llibre JM, et al. CROI 2017. Oral Presentation 44LB
Llibre et al. Lancet. 2018;;391(10123):839-849

SWORD-1 and -2: Snapshot Outcomes at Week 48



DTG + RPV is **non-inferior** to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48 in both studies

*Adjusted for age and baseline third agent

Llibre JM, et al. CROI 2017. Oral Presentation 44LB
Llibre et al. Lancet. 2018;;391(10123):839-849

SWORD-1 and -2: Adverse Events Leading to Withdrawal at Week 48

	DTG + RPV (n=513) n (%)	CAR (n=511) n (%)
AEs leading to withdrawal from the study*	17 (3)	3 (1)
Psychiatric disorders	7 (1)	1 (<1)
Gastrointestinal disorders	7 (1)	0
Neoplasms (benign, malignant, or unspecified)	2 (<1)†	2 (<1)
Nervous system disorders	1 (<1)	0
Hepatobiliary disorders	1 (<1)	0
Respiratory, thoracic, or mediastinal disorders	1 (<1)	0

DTG + RPV safety profile was consistent with the respective labels of its components

*A subject might have had more than one adverse event that led to withdrawal;
†Llibre JM, et al. Lancet. 2018 Erratum: pii: S0140-6736(18)30200-9
Data pooled across SWORD-1 and -2

Llibre JM, et al. CROI 2017. Oral Presentation 44LB
Llibre et al. Lancet. 2018;;391(10123):839-849

A New Era in ART: Tailored 2DR´s

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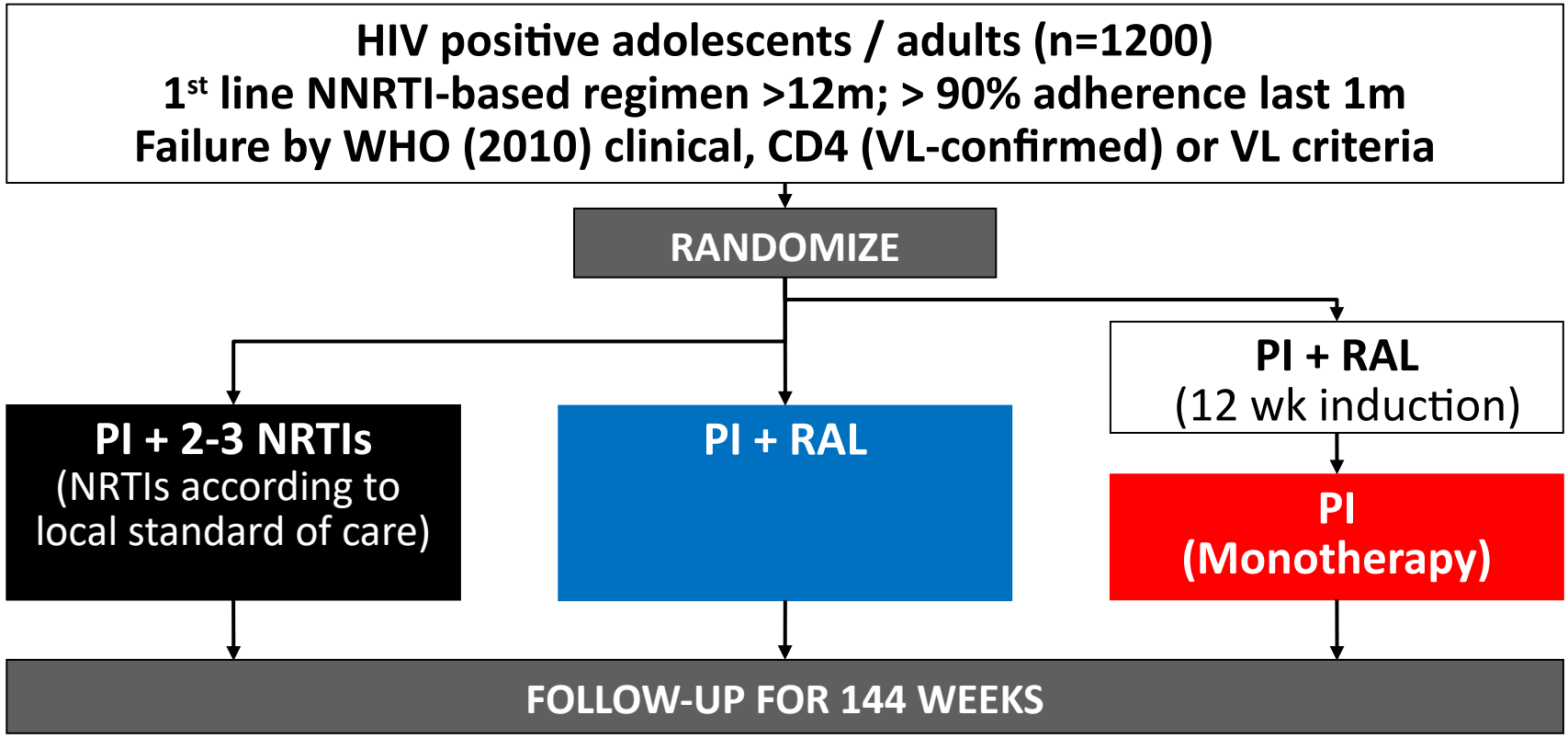
10. In summary ……..

Paton et al. NEJM, 2014

EARNEST Trial design



Primary outcome at week 96:

Good HIV disease control **– defined as all of:**

- Alive and no new WHO4 events from 0-96 weeks AND
- CD4 cell count > 250 cells/mm^3 at 96 weeks AND
- VL<10,000 c/ml OR >10,000 c/ml without PI res. mutations at 96 weeks

A New Era in ART: Tailored 2DR´s

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A New Era in ART: Tailored 2DR´s

7. Reasonable concerns to be addressed

- Longer follow-up (>= 2 years)
- Selection of resistance mutations in failing patients
- Real life data

PADDLE: Efficacy to Week 96

- Eighteen patients completed 48 weeks and were included in the extension phase. All patients completed week 96, 100% maintained plasma HIV-1 RNA <50 c/mL
- No new VFs, AIDS defining illnesses, or SAEs (related/possibly related to study drugs) were observed
- No treatment discontinuations were reported through the extension phase. Two Grade 3 laboratory abnormalities were reported (high cholesterol and proteinuria), but were considered unrelated to study drug

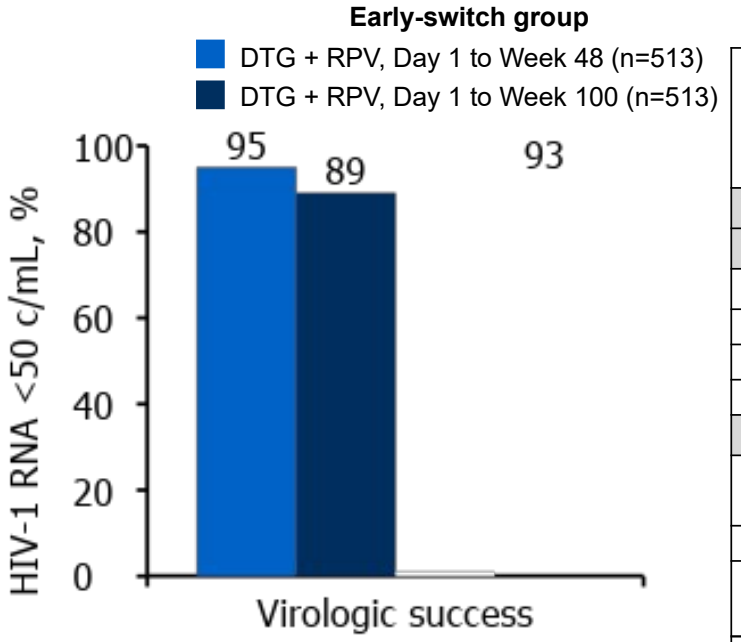
Patient	BL	Week 48	Week 60	Week 72	Week 84	Week 96
		HIV-1 Viral load (c/mL)				
1	10,909	<50	<50	<50	<50	<50
2	10,233	<50	<50	<50	<50	<50
3	**151,569**	<50	<50	<50	**55/<50***	<50
4	**148,370**	<50	<50	<50	<50	<50
5	20,544	<50	<50	<50	<50	<50
6	14,499	<50	<50	<50	<50	<50
7	18,597	<50	<50	<50	<50	<50
8	24,368	<50	<50	<50	<50	<50
9	10,832	Discontinuation at Week 48 due to SAE				
10	7,978	<50	<50	<50	<50	<50
11	**273,676**	<50	<50	<50	<50	**70/<50***
12	64,103	<50	<50	<50	<50	<50
13	33,829	<50	<50	<50	<50	<50
14	15,151	<50	<50	<50	<50	<50
15	23,400	<50	<50	<50	<50	<50
16	3,910	<50	<50	<50	<50	<50
17	25,828	<50	<50	<50	<50	<50
18	73,069	<50	<50	<50	<50	<50
19	**106,320**	Discontinuation at Week 48 due to PDVF				
20	7,368	<50	<50	<50	<50	<50

*Two patients required retest of viral load due to blips. VL retests were <50 c/mL

Figueroa MI, et al. IAS 2017. Poster MOPEB0287

Virologic Efficacy

- Through 100 weeks of treatment, DTG + RPV continued to be efficacious in the early-switch group
  - Virologic efficacy in the late-switch group at Week 100 was similar to that of the early-switch group at Week 48



n, %	Early-switch group		Late-switch group
	DTG + RPV Week 48	DTG + RPV Week 100	DTG + RPV Week 100
Virologic success	486 (95)	456 (89)	
Virologic nonresponse	3 (<1)	13 (3)	10 (2)
Data in window, not <50 c/mL	0	5 (<1)	3 (<1)
Discontinued for lack of efficacy	2 (<1)	7 (1)	3 (<1)
Discontinued while not <50 c/mL	1 (<1)	1 (<1)	0
Change in ART	0	0	4 (<1)
No virologic data	24 (5)	44 (9)	23 (5)
Discontinued because of AE or death	17 (3)	27 (5)	11 (2)
Discontinued for other reasons[a]	7 (1)	17 (3)	9 (2)
Missing data during window but on study	0	0	3 (<1)

[a]Other reasons for discontinuation while treated with DTG + RPV were lost to follow-up, n=3; protocol deviation, n=5 (prohibited medication use, n=3; pregnancy, n=2); withdrawal of consent, n=18 (participant relocated, n=5; travel burden, n=2; other, n=9); and investigator discretion, n=2.

Llibre et al. *Lancet*. 2018;391:839-849.

Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Poster THPEB047.

DTG + RPV: Low Rates of Confirmed Virologic Withdrawal Through Week 100

Week of failure	Previous regimen	Viral loads, copies/mL[b]	Resistance mutations[a]		Fold change
			Baseline (GenoSure[c])	Confirmed virologic withdrawal	
Week 24	EFV/TDF/FTC	88; 466	NNRTI: none INSTI: G193E	NNRTI: none INSTI: G193E	DTG, 1.02
Week 36	EFV/TDF/FTC	1,059,771; 1018; <50	NNRTI: none INSTI: none	NNRTI: K101K/E INSTI: none	RPV, 1.21
Week 64[d]	DTG/ABC/3TC	833; 1174; <50	NNRTI: none INSTI: N155N/H, G163G/R	INSTI resistance test failed	———
Week 76[d]	ATV, ABC/3TC	79; 162; 217	———	Test not performed[e]	———
Week 88	DTG/ABC/3TC	278; 2571; 55	NNRTI: none INSTI: none	NNRTI: E138E/A INSTI: none	RPV, 1.61 DTG, 0.72
Week 88	RPV/TDF/FTC	147; 289	———	Test not performed[e]	———
Week 100	EFV/TDF/FTC	651; 1105; 300	NNRTI: K101E, E138A INSTI: G193E	NNRTI: K101E, E138A, M230M/L INSTI resistance test failed	RPV, 31
Week 100	ATV, RTV, TDF/FTC	280; 225; 154	NNRTI: none INSTI: none	NNRTI: none INSTI: none	———

[a]Shading represents participants with treatment-emergent NNRTI resistance-associated mutations. Underlined value denotes viral load when participant met virologic withdrawal. [c]HIV-1 baseline resistance testing was performed on integrated HIV-1 proviral DNA using GenoSure Archive® assay (Monogram Biosciences, South San Francisco, CA). On-study resistance testing used standard plasma-based genotypic and phenotypic resistance testing. [d]Participants in the late-switch group. [e]Resistance testing not performed because of low viral load.

Aboud et al. AIDS 2018; Amsterdam, the Netherlands. Poster THPEB047.

Confirmed Virologic Withdrawals Through Week 48: ITT-E Population

- Low rates of virologic withdrawals were observed at Week 48

	GEMINI 1		GEMINI 2		Pooled	
Variable, n (%)	**DTG + 3TC (N=356)**	**DTG + TDF/FTC (N=358)**	**DTG + 3TC (N=360)**	**DTG + TDF/FTC (N=359)**	**DTG + 3TC (N=716)**	**DTG + TDF/FTC (N=717)**
CVW	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)
Treatment-emergent resistance	**0**	**0**	**0**	**0**	**0**	**0**

- No treatment-emergent INSTI mutations or NRTI mutations were observed among participants who met CVW (confirmed virologic failure) criteria

Confirmed virologic withdrawal criteria is defined as a second and consecutive HIV-1 RNA value meeting virologic non-response or rebound. Virologic non-response is defined as either a decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 12 with subsequent confirmation unless plasma HIV-1 RNA is <200 c/mL, or confirmed plasma HIV-1 RNA levels ≥200 c/mL on or after Week 24. Virologic rebound is defined as confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Resistance: DTG + 3TC

	Overall N	Study type	Resistance in DTG + 3TC arm, n
Treatment-naïve			
ACTG A5353[1]	**120**	Phase II, single-arm, pilot	**1 (M184V + R263R/K)**
PADDLE[2]	**20**	Single-arm pilot	**0**
GEMINI I and II[3]	**1,433**	Phase III, randomised, double-blind	**0**
Suppressed switch			
LAMIDOL[4]	**104**	Open-label, single-arm	**1 (L74V/L, M230I, V106I)**
ASPIRE[5]	**89**	Open-label, randomised	**0**
Real world			
Maggiolo [6]	**94**	Prospective cohort	**0**

NA, not available; NR, not reported

1. Taiwo B, et al. CID 2018;66:1689–97; 2. Cahn P, et al. J Int AIDS Soc 2017;20:216–78; 3. Cahn et al. AIDS 2018. Oral TUAB0106LB
4. Joly V, et al. EACS 2017. Poster PE9/11; 5. Taiwo B, et al. CID 2018;66:1794–7; 6.. Maggiolo F, et al. BMC Infect Dis 2017;17:215

Resistance: DTG + 3TC at HIV Glasgow 2018

	Overall N	Abstract	Study type	Resistance in DTG + 3TC arm, n
Treatment-naïve				
ACTG A5353[1]	**120**	O213	Pilot	***Already reported***
GEMINI I and II[2]	**1,433**	P021	RCT	**0**
Suppressed switch				
ASPIRE[3]	**89**	O145	RCT	**0**
Real world				
Maggiolo et al.[5]	**218**	P104	Prospective, multi-centre, cohort	***Not reported***

*Mutations that do not limit INI activity

1. Gillman J, et al. HIV Drug Therapy Glasgow. Abstract O213; 2. Orkin C, et al. HIV Drug Therapy Glasgow 2018. Abstract P021; 3. Taiwo B, et al. HIV Drug Therapy Glasgow 2018. Oral 145; 4. Hidalgo-Tenorio C, et al. HIV Drug Therapy Glasgow 2018. Abstract P094; 5. Maggiolo F, et al. HIV Drug Therapy Glasgow 2018. Poster 104; 6. Restelli S, et al. HIV Drug Therapy Glasgow 2018. Abstract P098

A New Era in ART: Tailored 2DR´s

ViiV Healthcare

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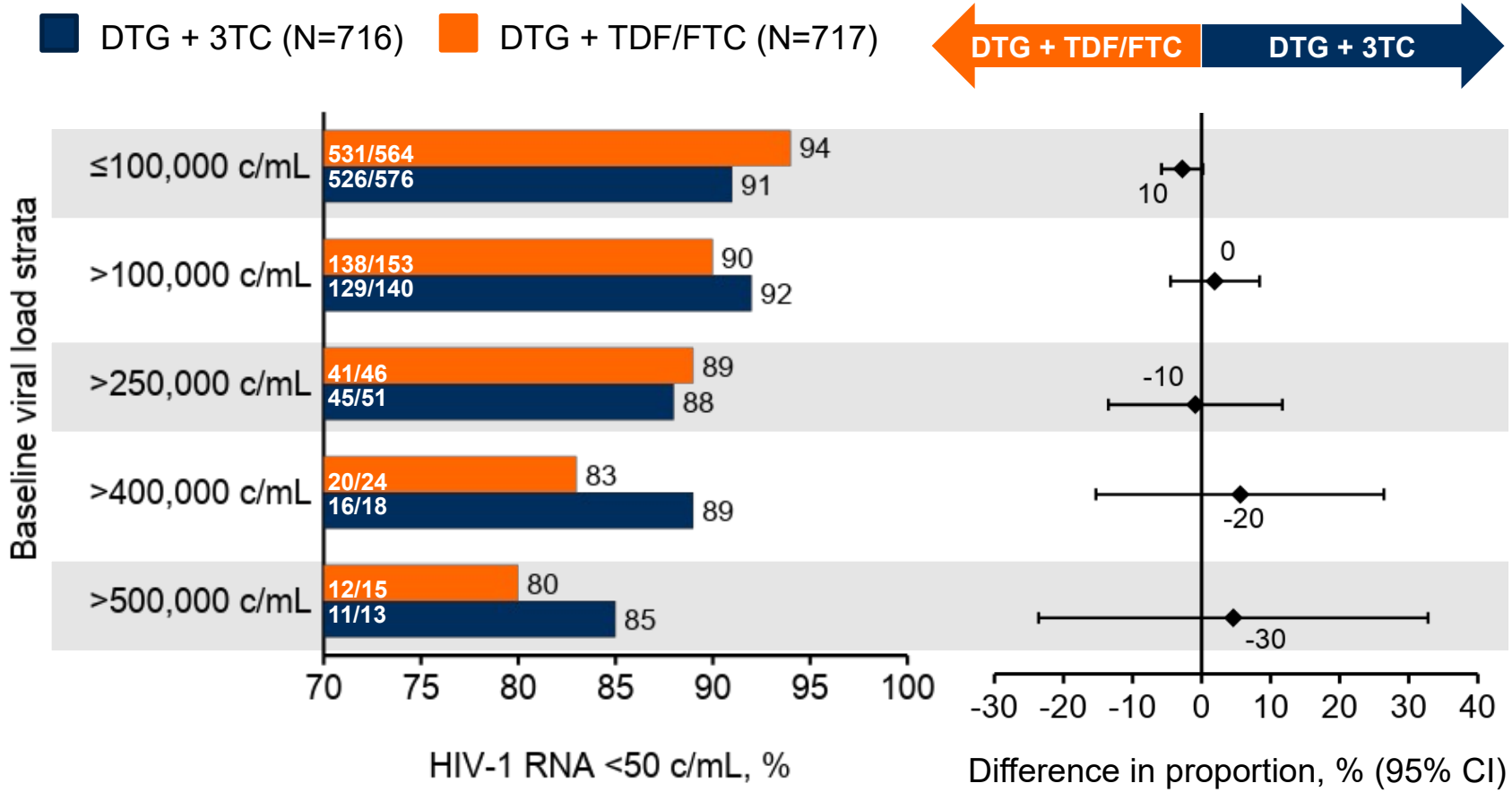
A New Era in ART: Tailored 2DR´s

8. Unproven/misleading perceptions?

Extreme phenotypes (VL, CD4´s)
Subclinical advantages (bone, renal biomarkers)
Blips without criteria of CVF or PDVF
Plasma viral load decay
Efficacy using ultrasensitive plasma VL
Reservoir size
Anatomical/physiological compartments
- Lymphatic tissue
- Genital (anal, vaginal) secretions
- CNS

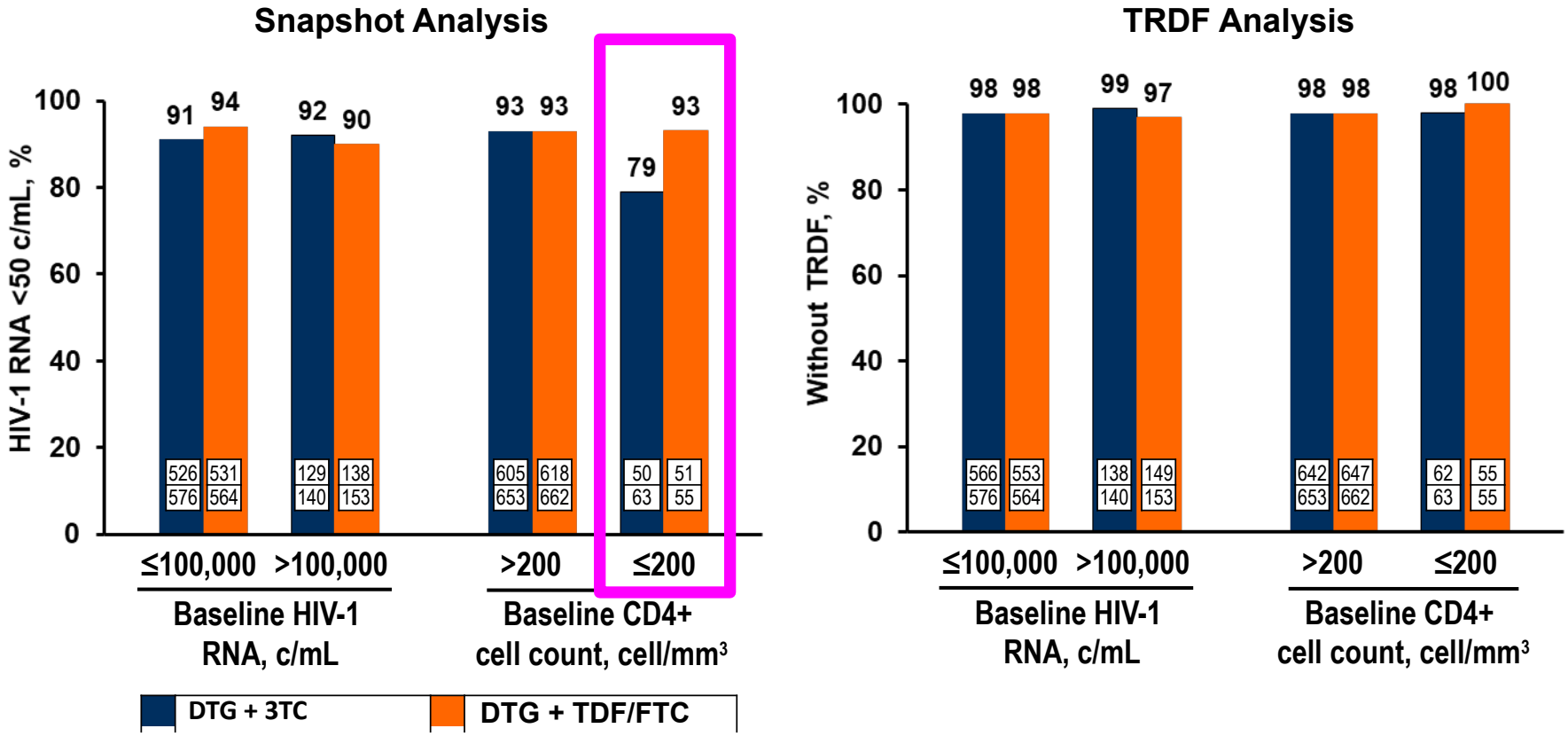
Chronic inflammation/immunoactivation
Test & treat (without or before receiving blood analysis)

Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis) by Baseline Plasma HIV-1 RNA



Eron et al. HIV DART and Emerging Viruses 2018; Miami, FL. Slides 7.

Pooled Outcomes at Week 48 Stratified by Baseline HIV-1 RNA and CD4+ Cell Count: Snapshot and TRDF Analysis



- 2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL. **Treatment related discontinuation = failure (TRDF)** population accounts for confirmed virologic withdrawal (CVW), withdrawal due to lack of efficacy, withdrawal due to treatment-related AE, and participants who met protocol-defined stopping criteria. **DTG + 3TC CD4 <200 Snapshot non-response (n=13): 1 CVW**, 3 with VL >50 in window **(2 of 3 re-suppressed),** 2 discontinued due to AE (TB, Chagas disease), 2 protocol violations, 2 lost to follow-up, 1 withdrew consent, 1 withdrew to start HCV treatment, 1 change in ART (incarcerated). **DTG + TDF/FTC < 200 Snapshot non-response (n=4):**1 investigator discretion, 1 withdrew consent, 1 lost to follow-up, 1 VL >50 (re-suppressed).

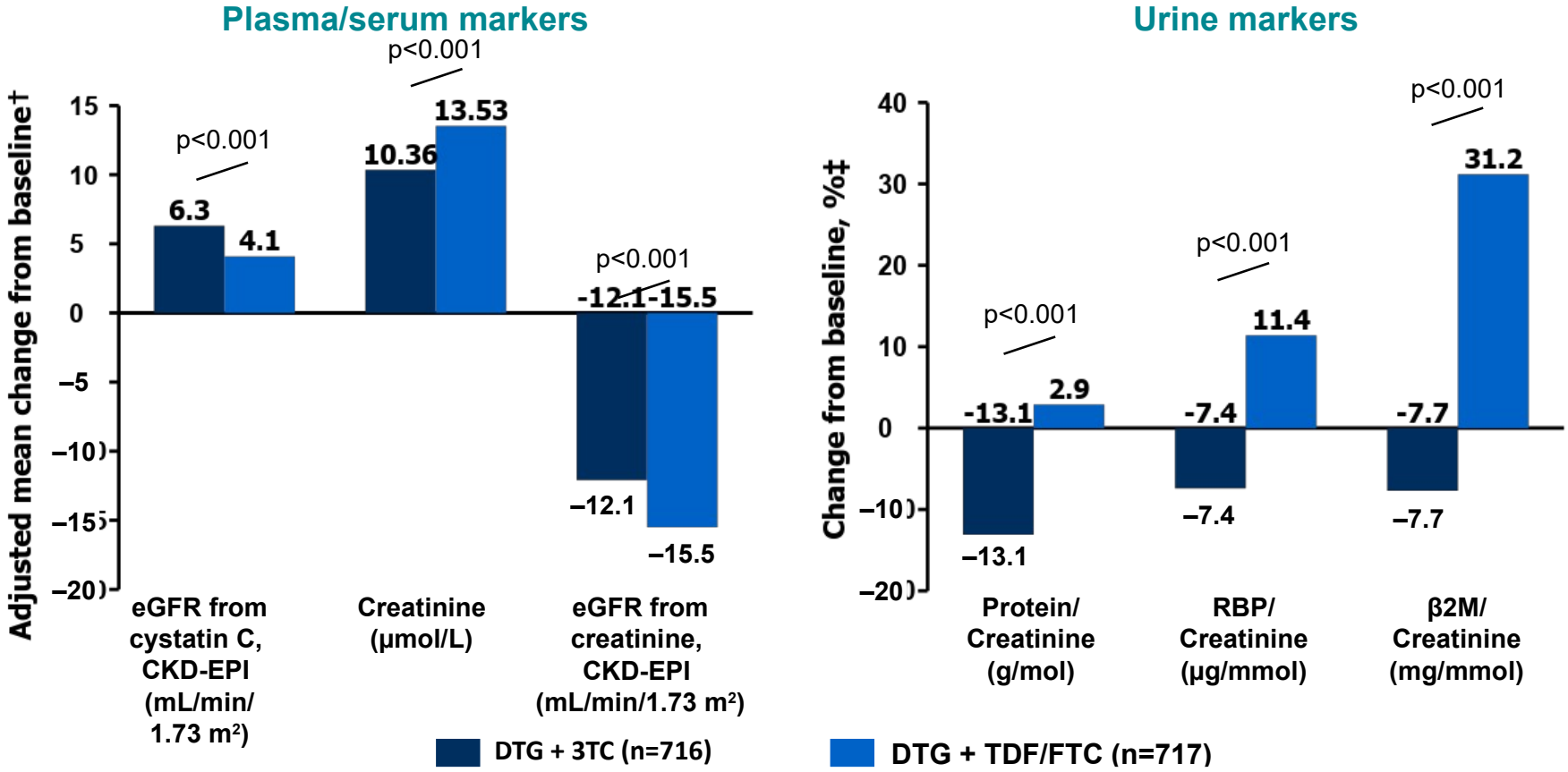
Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Reasons for snapshot failure in baseline CD4<200 copies/mL subgroup

DTG + 3TC (n=13/63)	DTG + TDF/FTC (n=4/55)
1 CVW	1 investigator discretion
3 with VL >50 in window (2 of 3 re-suppressed)	1 withdrew consent
2 discontinued due to AE (TB, Chagas disease)	1 lost to follow-up
2 protocol violations	1 VL >50 (re-suppressed)
2 lost to follow-up	
1 withdrew consent	
1 withdrew to start HCV treatment	
1 change in ART (incarcerated)	

Adapted from Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

GEMINI-1 and -2: Change in Renal Biomarkers at Week 48



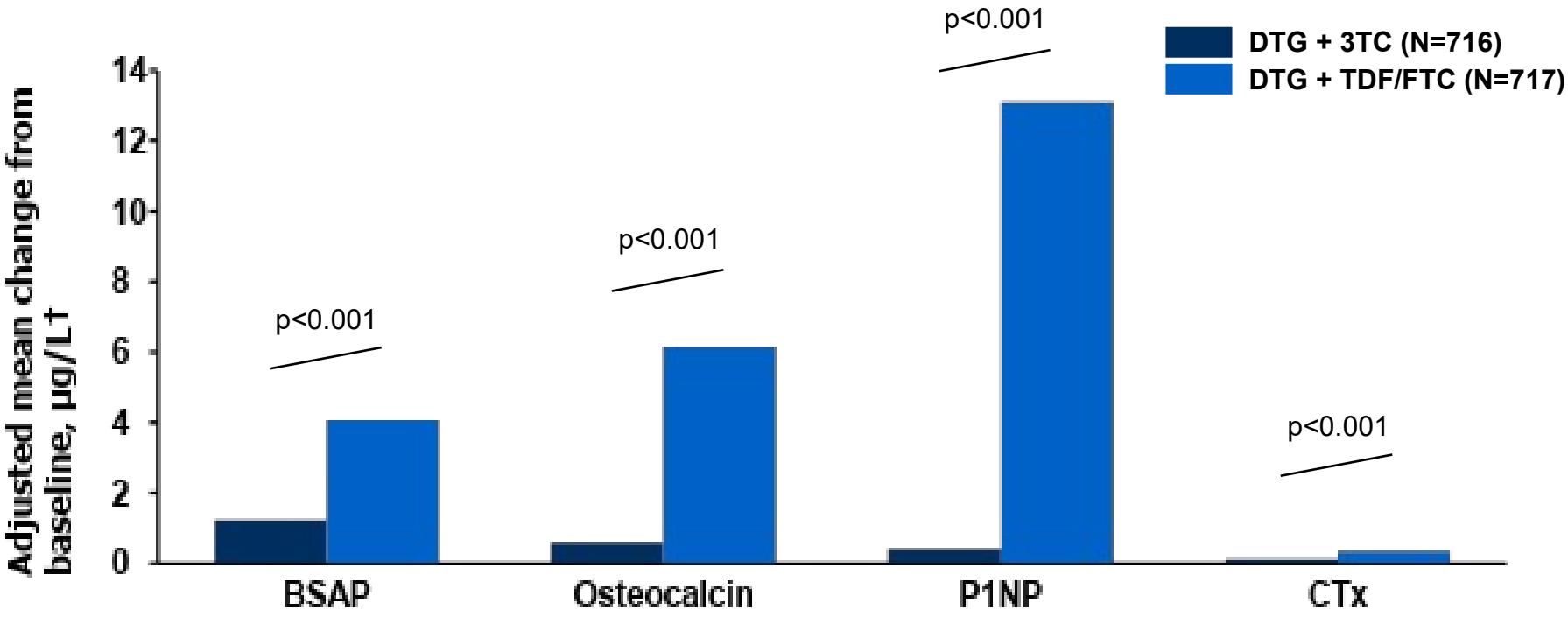
Change in renal biomarkers from baseline to Week 48 significantly favoured DTG + 3TC

Pooled ITT-E Population

†Estimated mean change from baseline at Week 48 in each arm calculated from ANCOVA model adjusting for: study, treatment, baseline plasma HIV-1 RNA, baseline CD4+ cell count, age, sex, race, presence of diabetes mellitus, presence of hypertension, and baseline biomarker value. Multiple imputed dataset (missing at random); ‡Estimated from geometric mean ratio for baseline and Week 48

Cahn P, et al. IAS 2018. TUAB0106LB

GEMINI-1 and -2: Change in Serum Bone Markers at Week 48



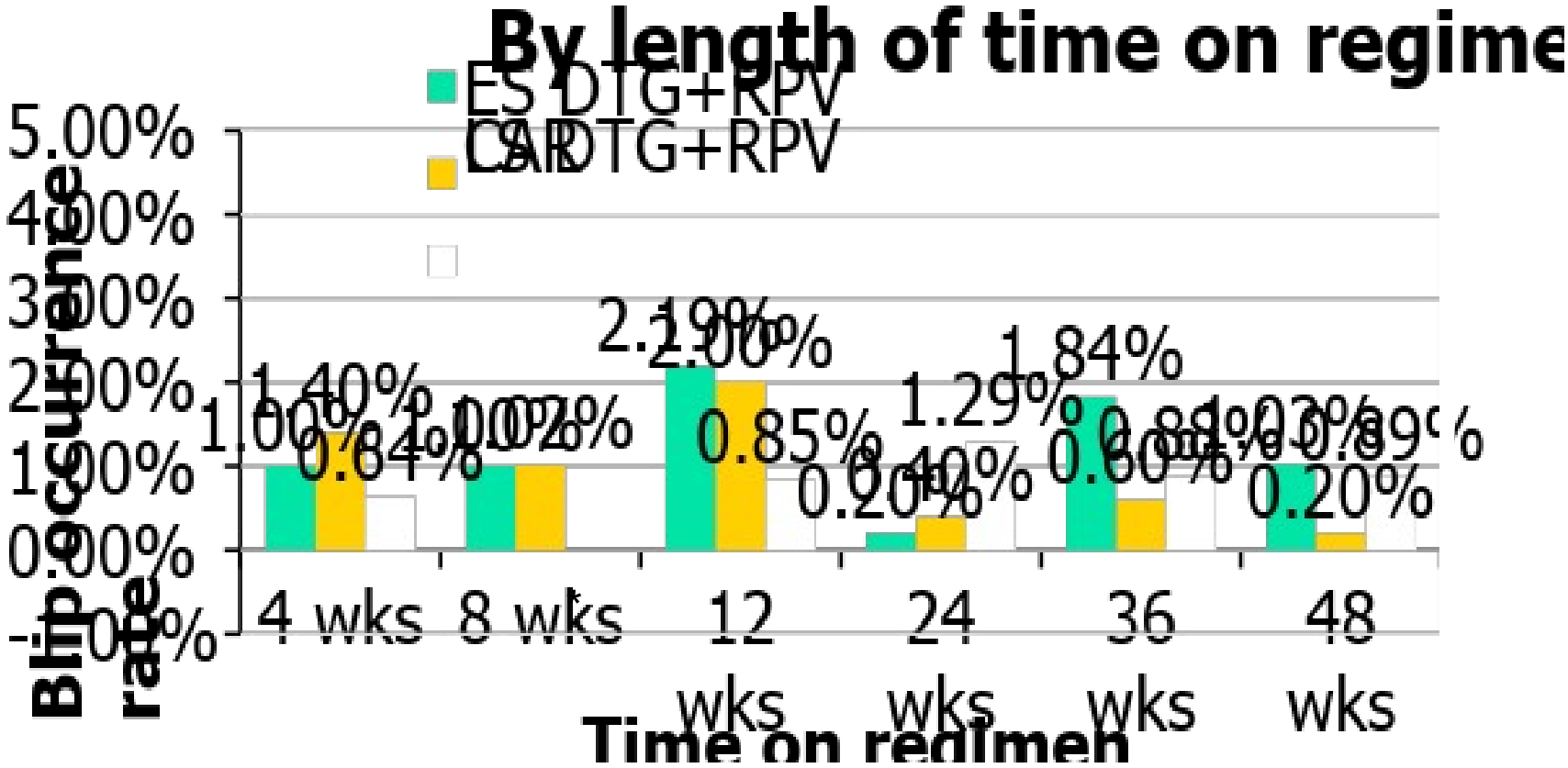
Change in bone biomarkers from baseline to Week 48 significantly favoured DTG + 3TC

Pooled ITT-E Population

†Estimated mean change from baseline at Week 48 in each arm calculated from ANCOVA model adjusting for study, treatment, baseline plasma HIV-1 RNA, baseline CD4+ cell count, age, sex, race, BMI, smoking status, current vitamin D use, and baseline biomarker value. Multiple imputed dataset (missing at random)

Cahn P, et al. IAS 2018. TUAB0106LB

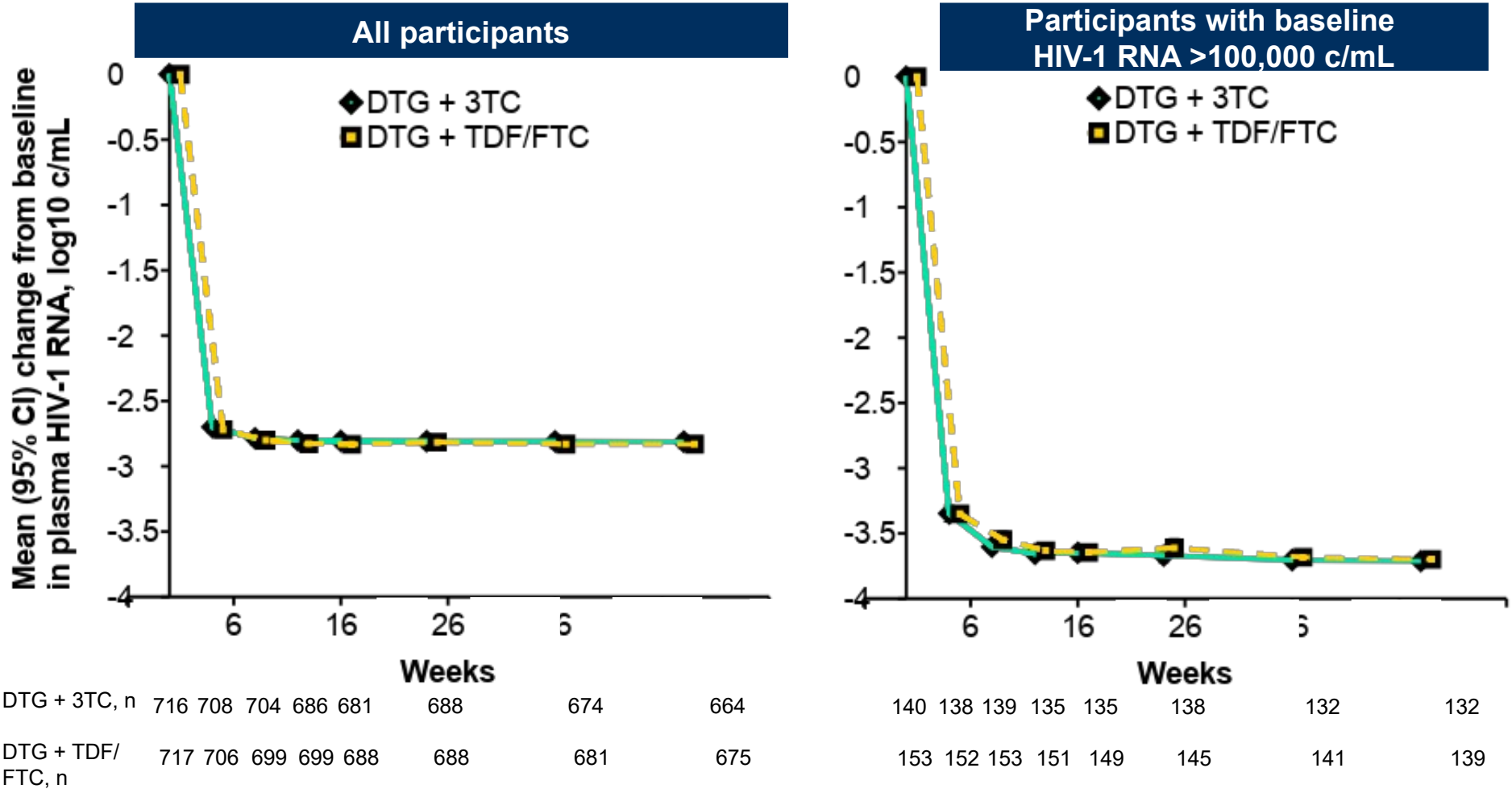
Rates of Blips Through Week 100



*There was no Week 8 visit for the late switch subjects.

Wang et al. HIV Glasgow; Glasgow, UK. Poster P313.

Viral Load Decline Through 48 Weeks in All Participants



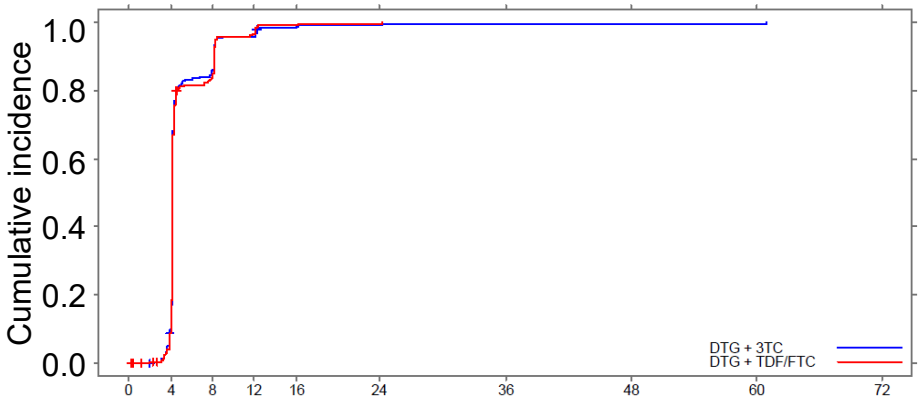
Error bars are too small to be seen for some data points.

Figure reproduced from Cahn et al. *Lancet.* 2018 [Epub ahead of print]. With permission from Elsevier.

Eron et al. HIV DART and Emerging Viruses 2018; Miami, FL. Slides 7.

Time to Viral Suppression

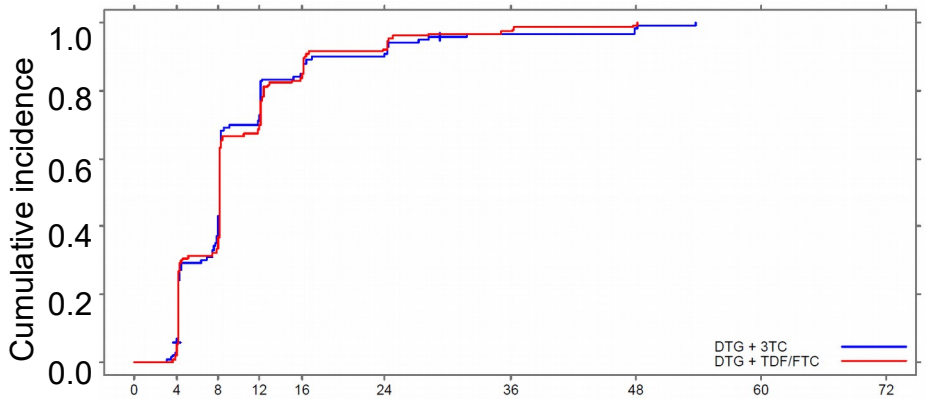
Participants with baseline HIV-1 RNA ≤100,000 c/mL



Time to viral suppression, weeks

Time to viral suppression	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Median (95% CI), days	29.0 (NE-NE)	29.0 (NE-NE)
Hazard ratio (95% CI)	0.99 (0.88-1.11)	

Participants with baseline HIV-1 RNA >100,000 c/mL

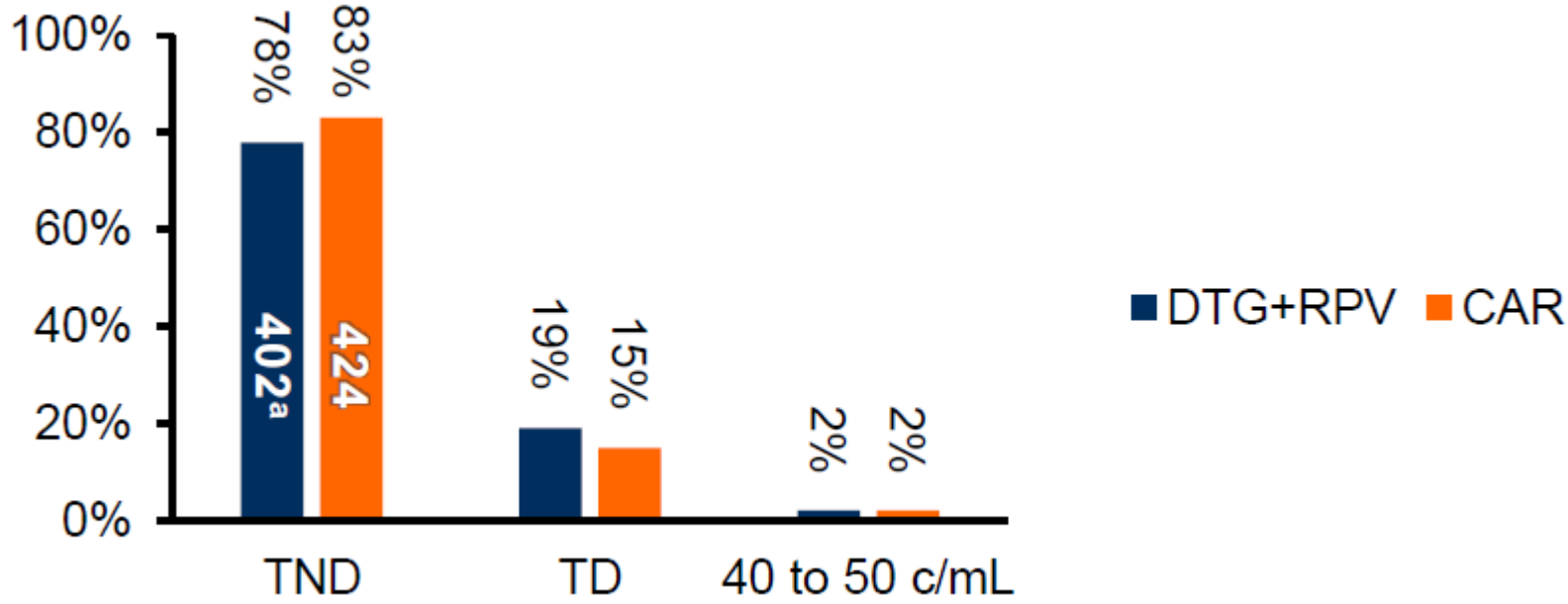


Time to viral suppression, weeks

Time to viral suppression	DTG + 3TC (N=140)	DTG + TDF/FTC (N=153)
Median (95% CI), days	57.0 (56.0-57.0)	57.0 (NE-NE)
Hazard ratio (95% CI)	1.00 (0.79-1.26)	

Eron et al. HIV DART and Emerging Viruses 2018; Miami, FL. Slides 7.

Proportions by VL Category <50 c/mL at Baseline



- At Baseline, slight numerical differences were observed within the VL categories <50 c/mL between the DTG + RPV and CAR arms

[a]The number of participants per category. Of four participants in the DTG + RPV arm with no Post-Baseline data, three had TND and one had TD at Baseline. Two with Baseline TND in CAR had no Post-Baseline VL, and are included here and per Snapshot algorithm in Table 2 (N=402 and N=424), but not in Table 1 analyses (TND DTG + RPV, N=399 and CAR, N=422).

Underwood et al. HIV Glasgow; Glasgow, UK. Poster P311.

Reduction in transmission – The Evidence

ACTG 076 (1994)[1]

68% reduction in maternal-infant transmission with zidovudine

San Francisco (1998)[2]

Maternal-infant transmission **approached zero** in cohort of pregnant women treated with triple ART

Rakai, Uganda (2000)[3]

No transmissions in serodifferent couples with VL <1,500 c/mL

Swiss Statement (2008)[4]

No transmissions likely with undetectable VL

ART, antiretroviral therapy

1. Connor et al. N Engl J Med 1994; 331:1173–80
2. Beckerman et al. IAS Geneva 1998. Poster 459
3. Quinn et al. N Engl J Med 2000; 342:921–9
4. Vernazza et al. Bulletin des médecins suisses 2008; 89:5

Reduction in transmission – The Evidence

HPTN 052 (2016)[1]

93% reduction in linked transmissions in serodifferent couples (transmissions occurred before VL was suppressed or from ART failure)

PARTNER & PARTNER-2 (2014–2018)[2,3]

No linked transmissions in MSM or heterosexual couples (even when STI present)

Opposites attract (2018)[4]

No linked transmissions in serodifferent MSM couples when VL <200 c/mL (even when STI present)

STI, sexually transmitted infection

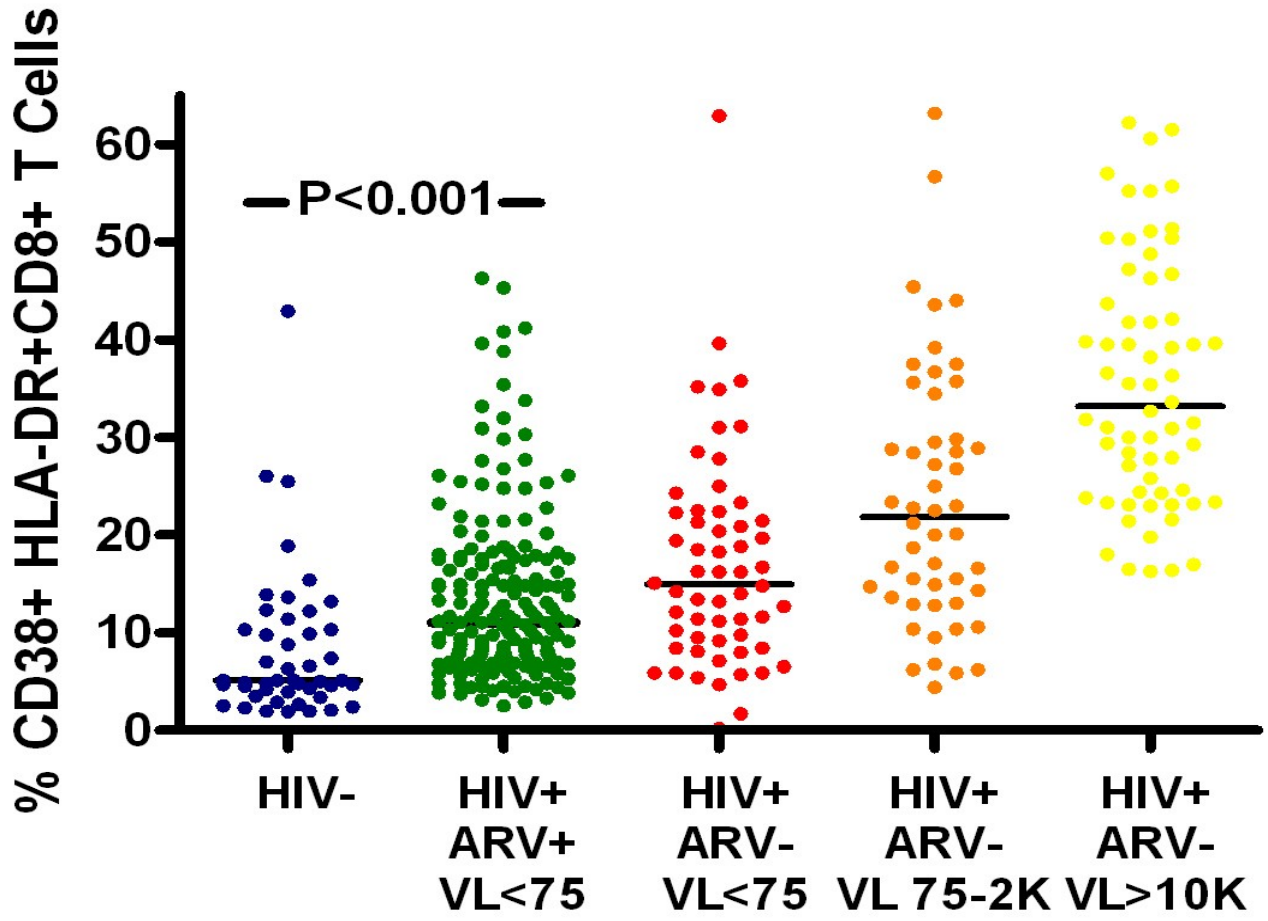
1. Cohen et al. N Engl J Med 2016;375:830–9
2. Rodger et al. JAMA. 2016;316:171–81
3. Rodger et al. IAS Amsterdam 2018. Abstract WEAX0104LB
4. Bavington et al. Lancet HIV 2018: e438–e447

Genital HIV-1 Shedding With Dolutegravir (DTG) Plus Lamivudine (3TC) Dual Therapy

Gianella et al
Aspire & ACTG 5353 studies
N= 31 (DTG+3TC) & 20 (3DR)

In conclusion, in this small pilot study, we did not detect concerning signals about the efficacy of the 2-drug regimen of DTG+3TC in controlling genital HIV RNA shedding, hence prevention of viral transmission, when HIV RNA is undetectable in blood plasma. These preliminary results suggest that DTG+3TC likely confers similar transmission prevention benefits as triple therapy.

….. but ART-suppressed Patients Have Persistently Abnormal T Cell Activation …….



Hunt et al, JID, 2003 and 2008

Association Between HIV Infection and IL-6, sCD14, and D-dimer Adjusted for (a) Age and Race-Ethnicity and (b) All Covariates

		Proportional Odds Ratio (95% CI)			
	Outcomes	**HIV-negative (Reference)**	**HIV-positive HIV-1 RNA <500 c/mL**	**HIV-positive HIV-1 RNA 500–9,999 c/mL**	**HIV-positive HIV-1 RNA ≥10,000 c/mL**
(a) Model (age, race-ethnicity adjusted)					
1	IL-6 quartiles	1	1.14 (0.96, 1.35)	1.32 (1.01, 1.73)	2.99 (2.32, 3.84)
2	sCD14 quartiles	1	0.93 (0.78, 1.10)	0.85 (0.65, 1.12)	2.05 (1.61, 2.62)
3	D-dimer quartiles	1	0.50 (0.42, 0.59)	0.88 (0.67, 1.16)	1.91 (1.49, 2.45)
(b) Model (fully adjusted)					
1	IL-6 quartiles	1	1.35 (1.11, 1.64)	1.46 (1.10, 1.95)	2.78 (2.11, 3.65)
2	sCD14 quartiles	1	0.77 (0.64, 0.93)	0.71 (0.54, 0.95)	1.49 (1.14, 1.94)
3	D-dimer quartiles	1	0.51 (0.43, 0.62)	0.95 (0.71, 1.26)	1.73 (1.32, 2.26)

There are no consistent data from large, well-designed studies to link low-level residual viraemia with persistent inflammation

Adapted from: So-Armah, KA. J Acquir Immune Defic Syndr 2016;72:206–13

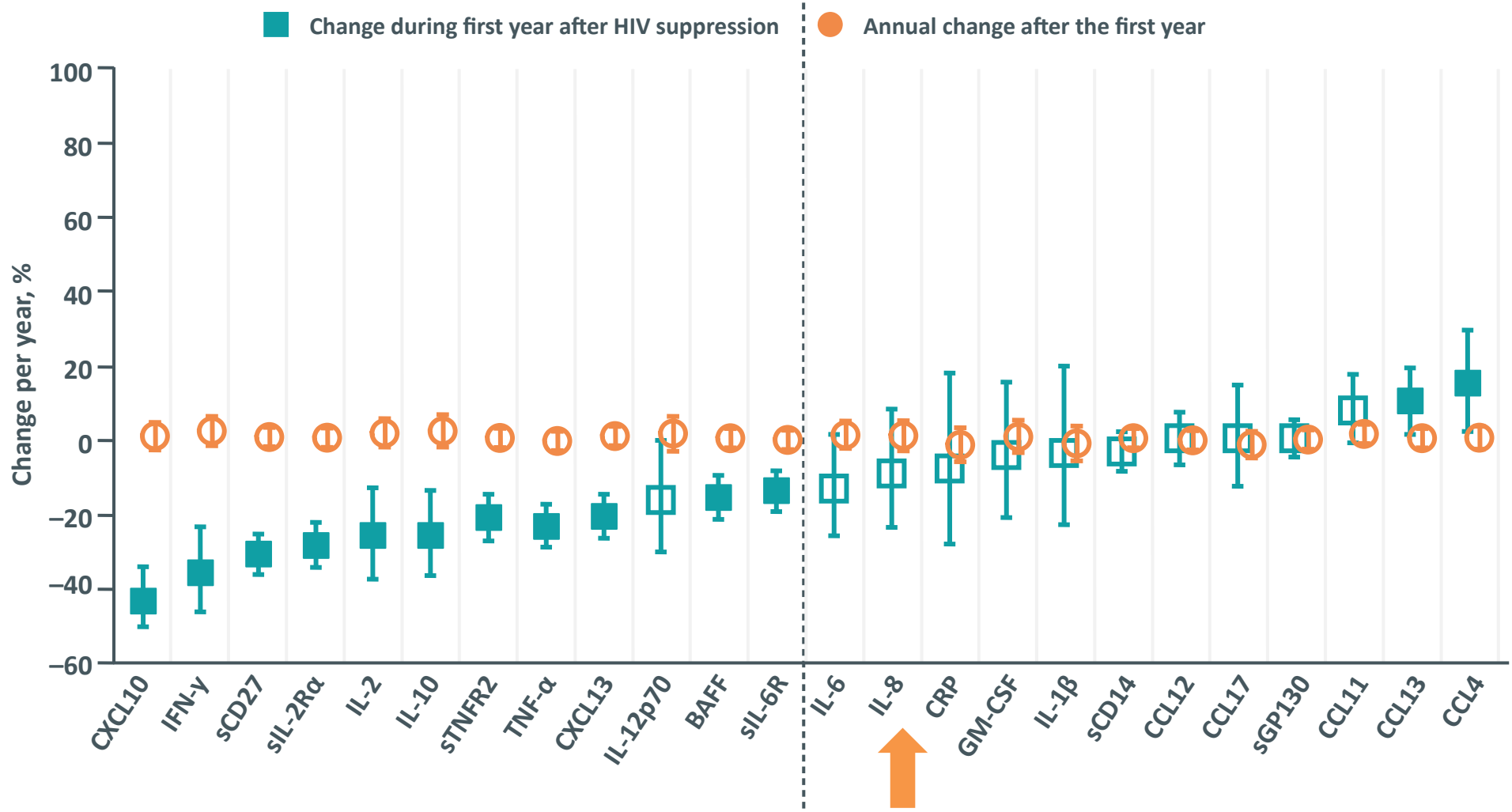
SWORD-1 and -2: Inflammatory Mediators at Week 48

No notable differences between the DTG + RPV and CAR groups in change from baseline to Week 48 for levels of inflammatory mediators

Inflammatory mediator and time point		DTG + RPV		CAR		Week 48 difference DTG + RPV – CAR (95%)
		n	Mean	n	Mean	
hsCRP, mg/L	Baseline*	512	2.81	505	2.77	
	Week 48	480	+0.11	482	+0.47	–0.36 (–1.2, 1.0)
IL-6, ng/L	Baseline*	512	2.19	503	2.25	
	Week 48	478	+0.04	480	–0.12	0.16 (–0.2, 0.4)
D-dimer, nmol/L FEU	Baseline*	504	1.87	496	1.80	
	Week 48	463	–0.01	466	–0.05	0.04 (–0.28, 0.34)
sCD163, µg/L	Baseline*	509	590.48	501	601.79	
	Week 48	477	+57.99	477	+54.10	3.89 (–22.4, 206.3)
sCD14, ng/mL	Baseline*	510	1,703.31	502	1,698.60	
	Week 48	479	+419.09	479	+778.15	–359.06 (–451.7, 2325.5)
sVCAM-1, µg/L	Baseline*	512	1,933.50	503	1,957.52	
	Week 48	479	–2.43	480	+63.57	–66.00 (–190.8, 4180.9)
iFABP, ng/mL	Baseline*	512	2.97	501	2.92	
	Week 48	478	–2.13	478	–1.47	–0.66 (–0.9, 0.3)

*Baseline values are actual values. iFABP is also known as FABP2
FEU, fibrinogen-equivalent units

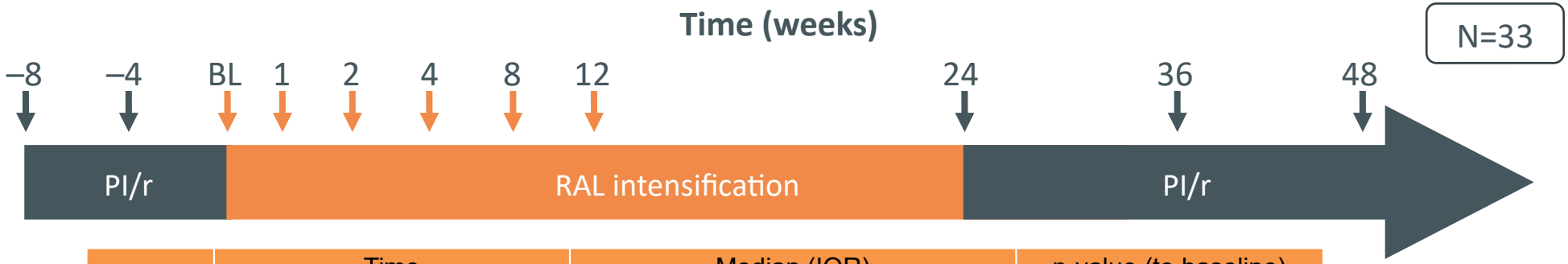
Adapted from: Orkin C, et al. EACS 2017. Poster BPD2/10



Filled markers represent differences that were statistically significant after Bonferroni adjustment ($p<0.002$)

Adapted from: Wada NI, et al. AIDS 2015;29:463–71

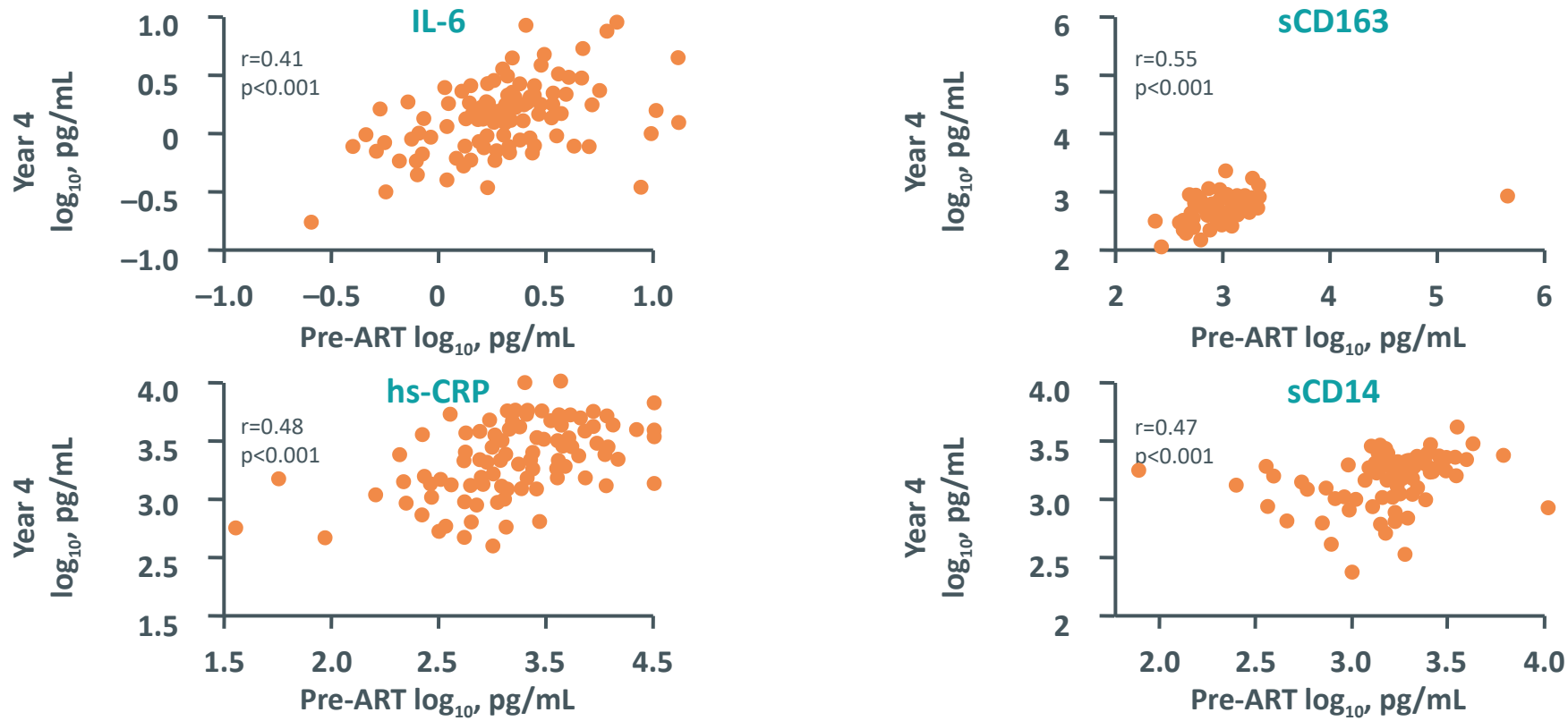
Impact of Intensification with RAL on HIV-1-infected Individuals Receiving Monotherapy with Boosted PIs



	Time	Median (IQR)	p-value (to baseline)
IL-6, ng/mL	Baseline	34 (18–46)	
	Week 24	43 (27–116)	0.02
	Week 48	30 (19–92)	1.00
	p-value (Week 24–48)		**0.26**
CRP, µg/mL	Baseline	1.18 (0.59–2.13)	
	Week 24	1.29 (0.70–2.92)	0.20
	Week 48	0.99 (0.40–2.52)	0.20
	p-value (Week 24–48)		**0.04**
D-dimer, ng/mL	Baseline	95 (58–129)	
	Week 24	112 (74–171)	0.14
	Week 48	153 (84–215)	0.02
	p-value (Week 24–48)		**0.09**

Adapted from: Puertas MC, et al. J Antimicrob Chemother 2018;73:1940–8. Supplementary Appendix

Correlation Between Pre- and On-ART Levels of Inflammatory Biomarkers



101 treatment-naïve participants who initiated ART and had plasma HIV-1 RNA levels consistently <50 c/mL at all time points ≥48 weeks

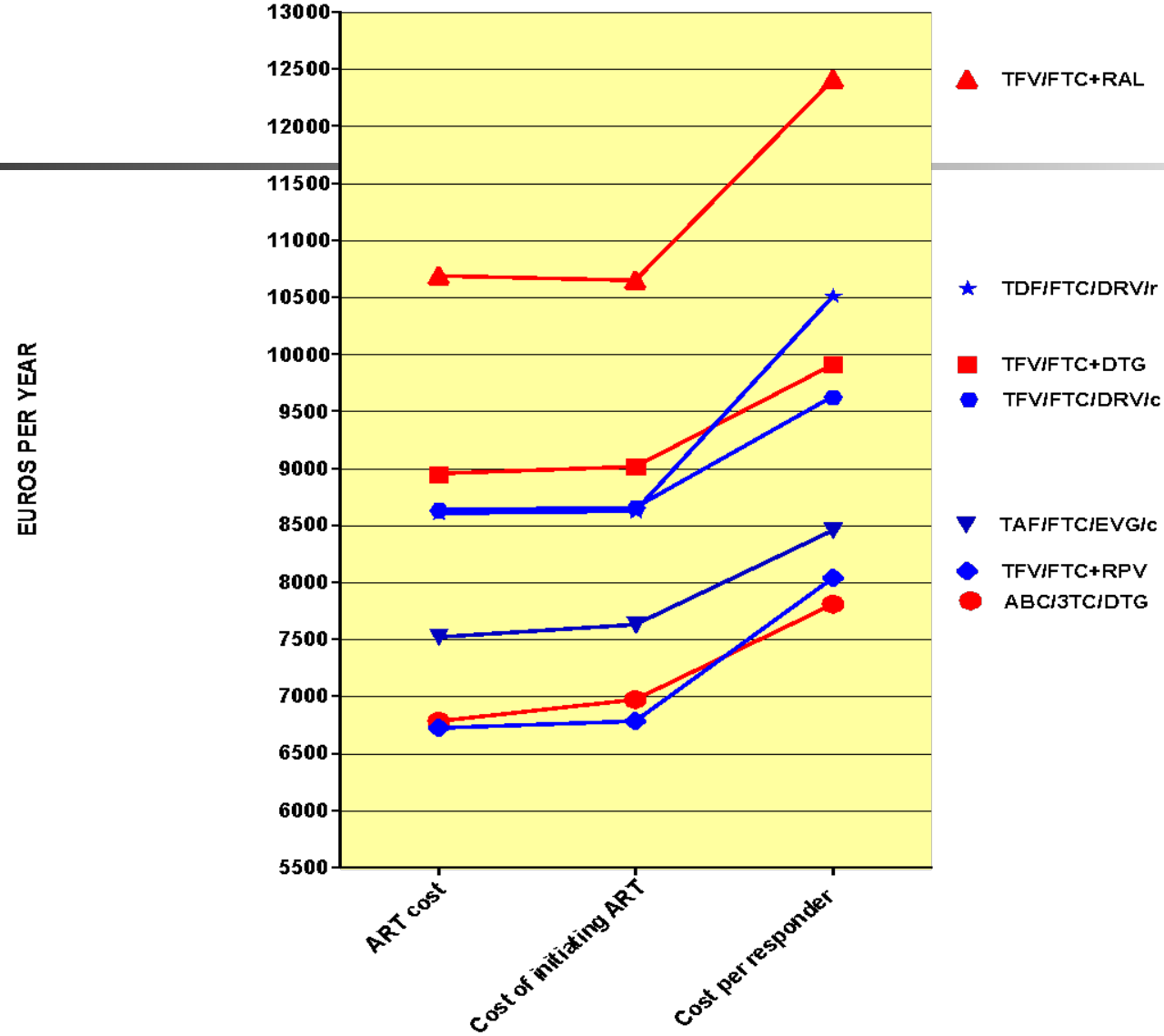
Adapted from: Gandhi RT, et al. PLoS Pathog 2017;13:e1006285

A New Era in ART: Tailored 2DR´s

ViiV Healthcare

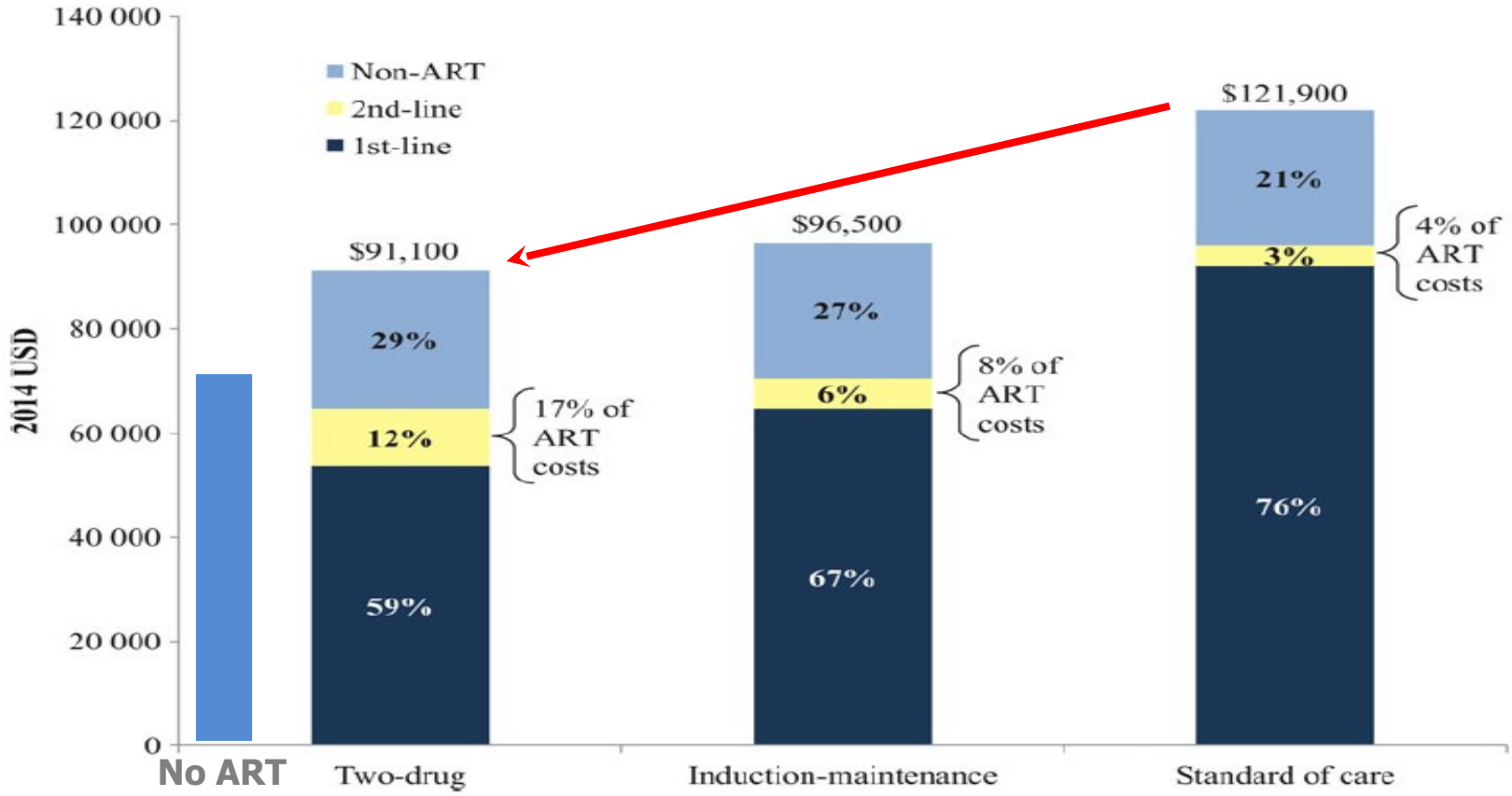
1. 3DR´s. From year 1996 to 2018
2. Why to reduce exposure to antiretroviral agents ?
3. The proof of concept: PR/r+3TC
4. DTG+3TC in naïve patients
5. DTG+RPV or DTG+3TC in suppressed patients
6. 2DR´s in salvage therapy ?
7. Reasonable concerns to be addressed
8. Unproven/misleading perceptions
9. **Cost-efficacy issues & guidelines**
10. In summary ……..

Perez-Molina, Blasco, .. Gatell et al. EIMC 2018



Pérez-Molina JA, Martínez E, Blasco AJ et al. Enferm Infecc Microbiol Clin. 2018; Jun 5. pii: S0213-005X(18)30185-X. doi: 10.1016/j.eimc.2018.04.010. [Epub ahead of print]

Conclusions. Should DTG + 3TC demonstrate high rates of virologic suppression, this regimen will be cost-effective and would save >$500 million in ART costs in the United States over 5 years.



lative discounted 5-year per-person costs (in 2014 US dollars [USD]) for the 2-drug, induction-maintenance, and standard-of-care strategies. Discounted costs line antiretroviral therapy (ART) costs (dark blue), second-line ART costs (yellow), and non-ART costs (light blue); the proportion of each cost category of total beled in each bar. Additionally, the proportion of 5-year ART costs comprised of second-line ART costs is shown.

Guidelines for 2019

GESIDA (Jan 2019)

EACS (Oct. 2018)

IAS-USA (July 2018)

DHHS (Oct. 2018)

WHO

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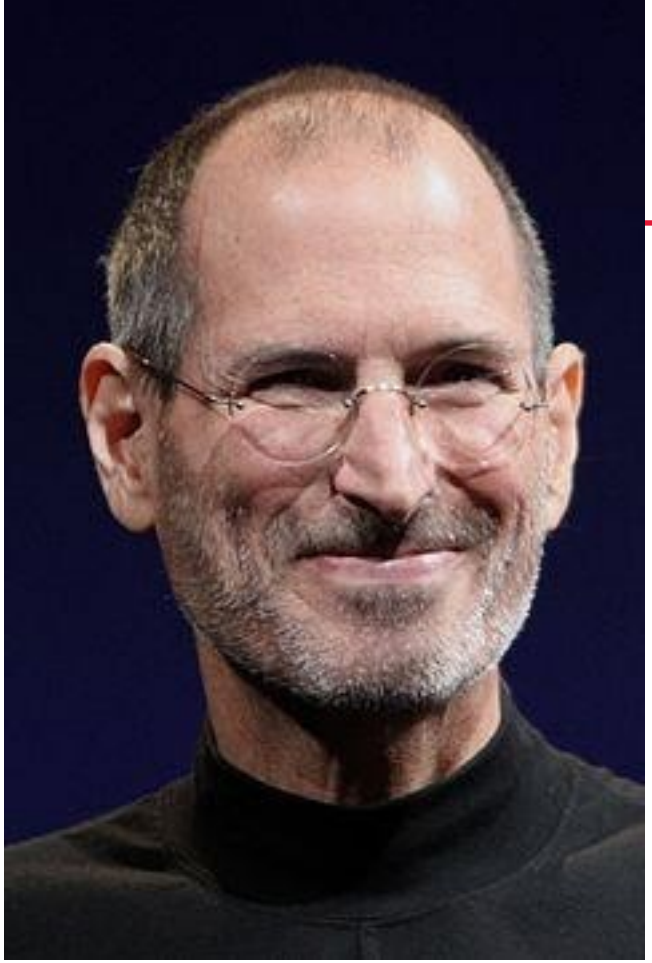
HE WHO IS FIXED TO A STAR DOES NOT CHANGE HIS MIND.

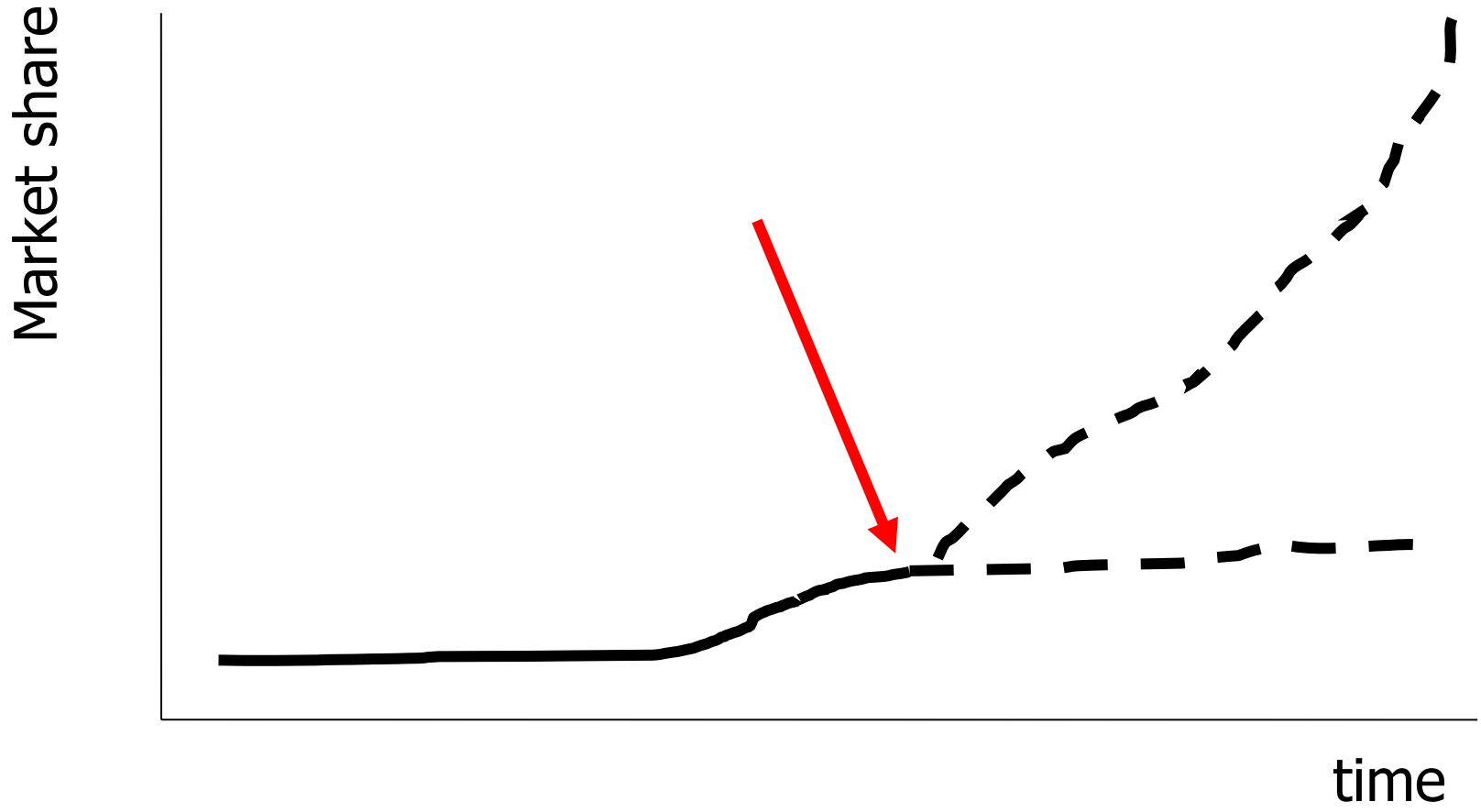
LEONARDO DA VINCI

BRIGHTDR



We are changing the world.
Yet, they have not realized

Digital photography / cellular phones




The dawn of a new day ……

7. Final considerations

Regimens other than "every day triple-drug regimens" could became a cost-effective option in a wider range of patients within next few years

Proof of concept already achieved

Pivotal phase III studies have meet primary endpoints (GEMINIs, SWORDs) and others (TANGO) are ongoing