OSPEDALE
SAN RAFFAELE

NUOVE STRATEGIE
TERAPEUTICHE
PAZIENTE-ORIENTATE:
PRESENTE E FUTURO(1)

Seminario NADIR – 22 settembre 2017

Il nuovo volto della terapia

cART evolution/revolution: stato dell'arte e odierne direzioni

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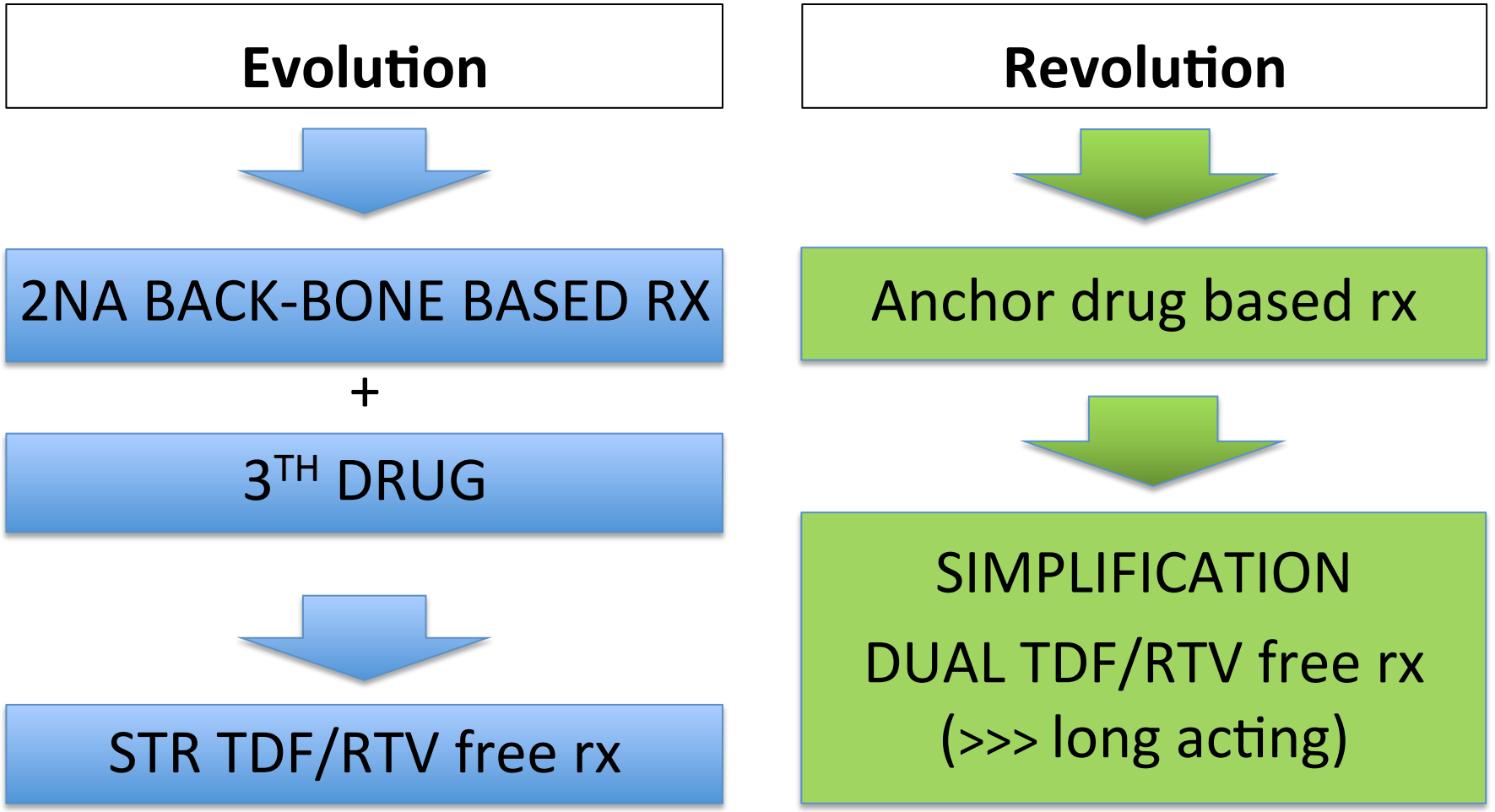
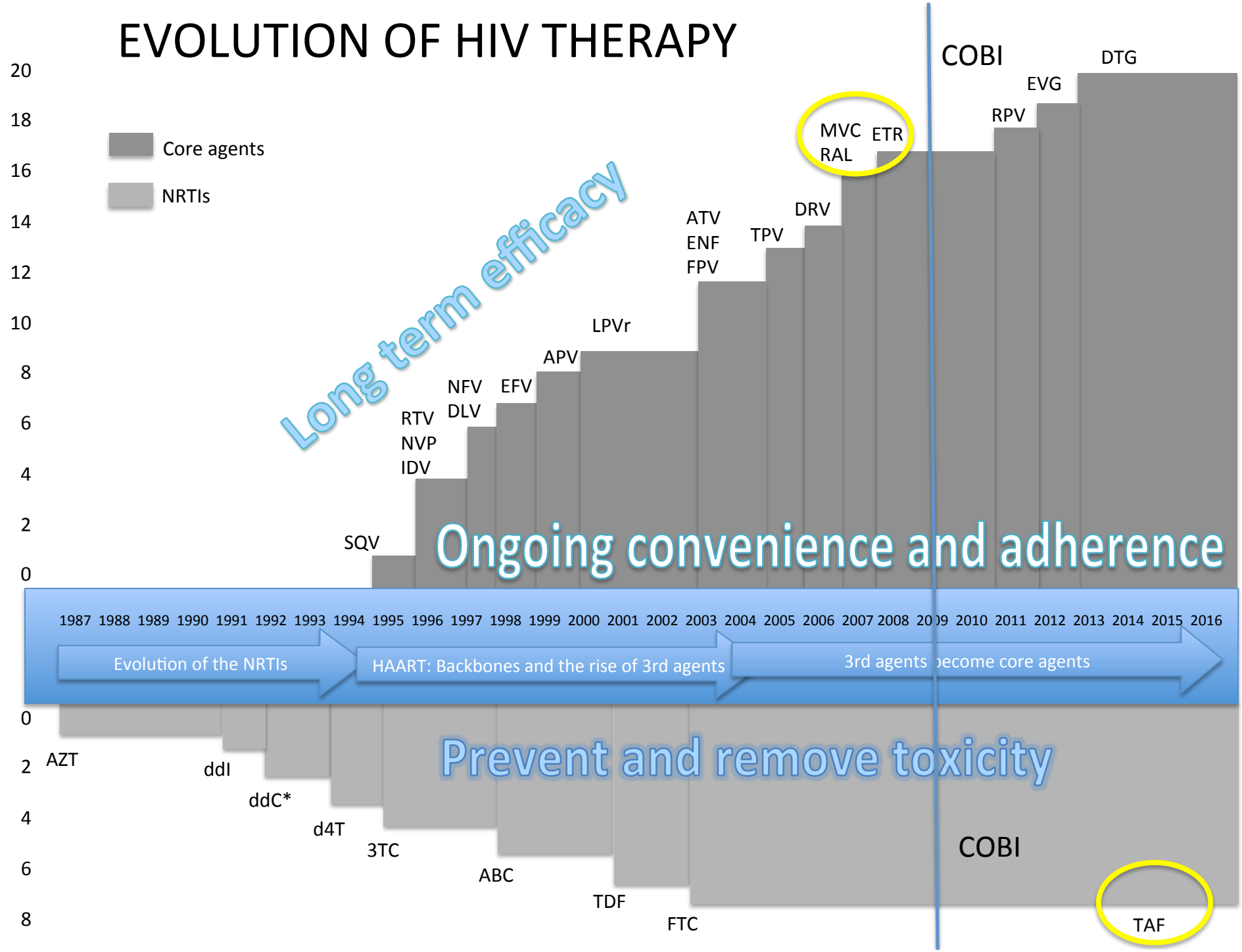
Ospedale San Raffaele Milano

cART long term strategy: the two main ways




EVOLUTION OF HIV THERAPY
Core agents
NRTIs
Long term efficacy
Ongoing convenience and adherence
Prevent and remove toxicity
COBI
COBI
SQV
RTV
NVP
IDV
NFV
DLV
EFV
APV
LPVr
ATV
ENF
FPV
TPV
DRV
MVC
RAL
ETR
RPV
EVG
DTG
TAF
AZT
ddI
ddC*
d4T
3TC
ABC
TDF
FTC
1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016
Evolution of the NRTIs
HAART: Backbones and the rise of 3rd agents
3rd agents become core agents

cART today: minimun required

- Triple combination TDF/RTV free
- OD Rx (better STR)
- Efficacy >90% HIV-RNA<50 copie/mL (↑)
- Good tolerability
- Flat price (chipper?!?)

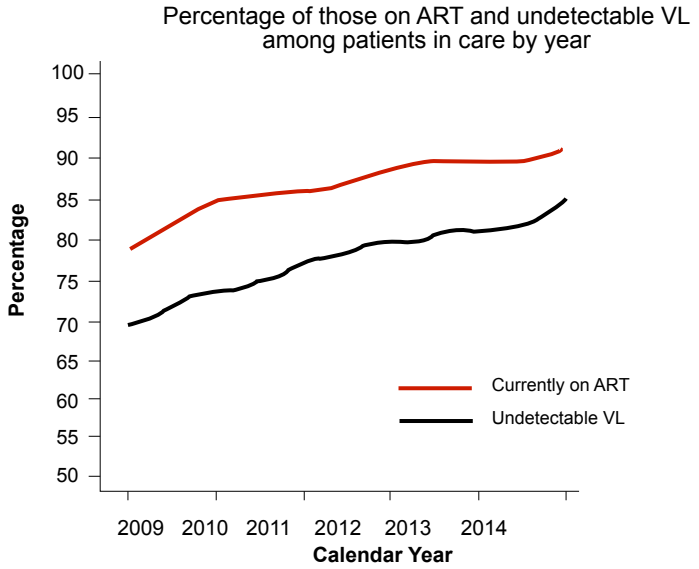
TOWARD 100% of HIV-RNA <50 copie/mL

‡

HIV Viral Load in US Clinics Over Time: Trends and Predictors

CFAR Network of Integrated Clinical Systems (CNICS)

- 31,055 subjects in CNICS cohort with VL values collected between 1997-2015 at 8 sites across US
- Outcome: undetectable VL defined as <400 copies/ml to exclude VL blips
- Results:
  - 82% men, 55% non-white, mean age 39
  - PLWH with undetectable VL increased from 30% in 1997 to 87% in 2014
  - In multivariate models of PLWH on ART after 2010, older age, white race, male sex, and better adherence were associated with undetectable VL ($p<0.05$), as was integrase inhibitor use ($p<0.001$)
  - Mean adherence did not increase nor did current substance use decrease in more recent years



Viral suppression rates have improved dramatically in recent years, likely due to increased use of integrase inhibitors.

Simoni JM, et al. CROI 2016. Boston, MA. #1034

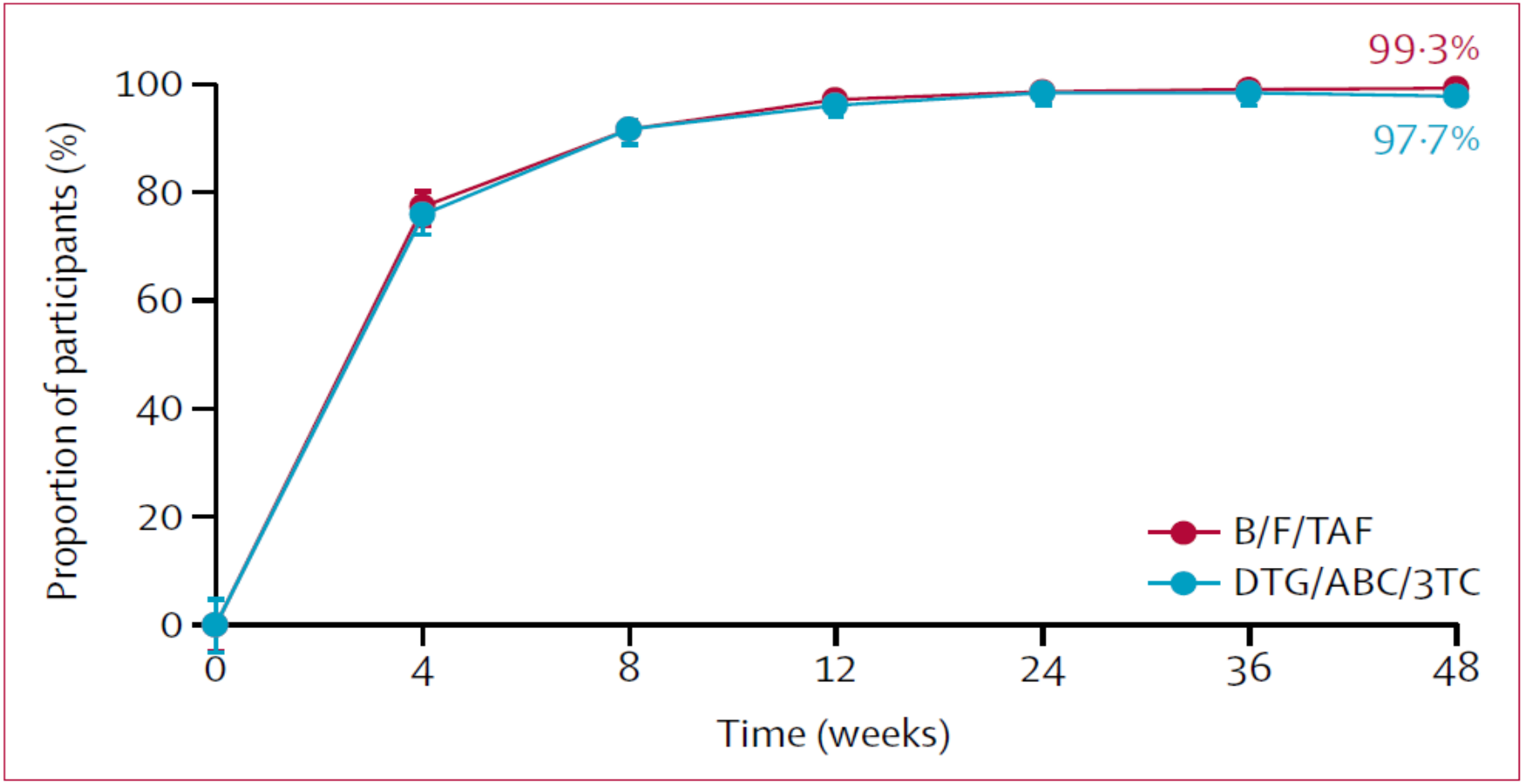


***Figure 2*: Proportion of participants with HIV-1 RNA less than 50 copies per mL**
Missing-as-excluded analysis. Error bars represent 95% CIs. B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine.

Gallant J, Lazzarin A et al. The Lancet 2017 Aug 31: 1-10

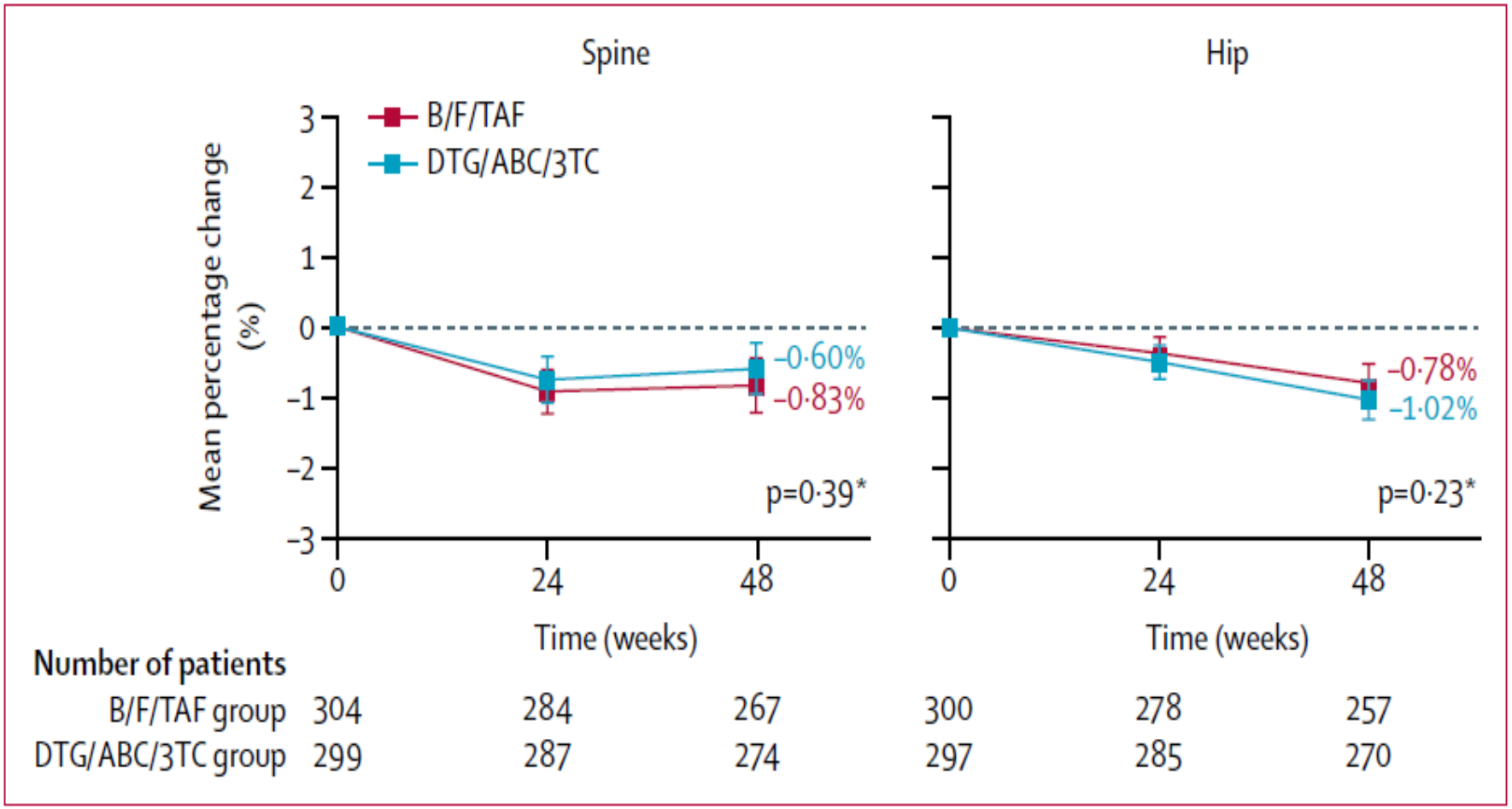


***Figure 3*: Mean percentage change from baseline in hip and lumbar spine bone mineral density**

As determined by dual energy X-ray absorptiometry scan. Error bars represent 95% CIs. B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine. *B/F/TAF versus DTG/ABC/3TC at week 48 by ANOVA.

Gallant J, Lazzarin A et al. The Lancet 2017 Aug 31: 1-10

	B/F/TAF group (n=314)	DTG/ABC/3TC group (n=315)	p value*
Serum creatinine (mg/dL)			
Baseline	0·90 (0·80 to 1·00)	0·91 (0·81 to 0·99)	0·92
Change at week 48	0·11 (0·03 to 0·17)	0·11 (0·03 to 0·18)	0·78
eGFR (mL/min)†			
Baseline	125·9 (107·7 to 146·3)	123·0 (107·0 to 144·3)	0·76
Change at week 48	−10·5 (19·5 to 0·2)	−10·8 (−21·6 to −2·4)	0·20
Urine albumin to creatinine ratio (mg/g)			
Baseline	5·5 (3·7 to 9·2)	5·4 (3·7 to 9·1)	0·72
Percentage change at week 48	0·6% (−32·0 to 48·9)	6·2% (−23·6 to 57·7)	0·11
Urine β2-microglobulin to creatinine ratio (µg/g)			
Baseline	108·1 (71·7 to 184·4)	109·8 (77·6 to 191·8)	0·92
Percentage change at week 48	−23·0% (−57·2 to 19·8)	−18·1% (−54·2 to 17·4)	0·40
Urine retinol binding protein to creatinine ratio (µg/g)			
Baseline	81·0 (58·3 to 122·4)	83·7 (59·8 to 120·4)	0·55
Percentage change at week 48	13·6% (−20·9 to 63·6)	19·9% (−16·0 to 58·9)	0·34

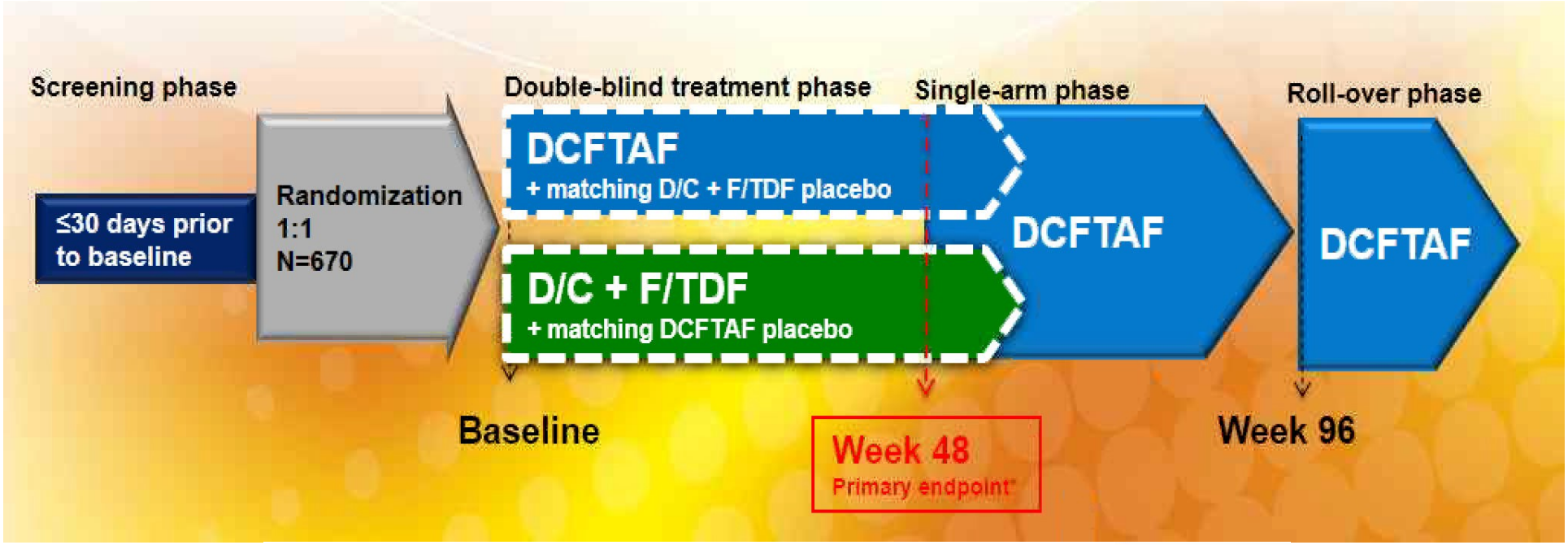
Data are median (IQR), unless otherwise specified. B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine. eGFR=estimated glomerular filtration rate. *p values for B/F/TAF versus DTG/ABC/3TC from two-sided Wilcoxon rank-sum tests. †Calculated with the Cockcroft–Gault formula.

Table 4: **Changes in quantitative measures of proteinuria**

Gallant J, Lazzarin A et al. The Lancet 2017 Aug 31: 1-10

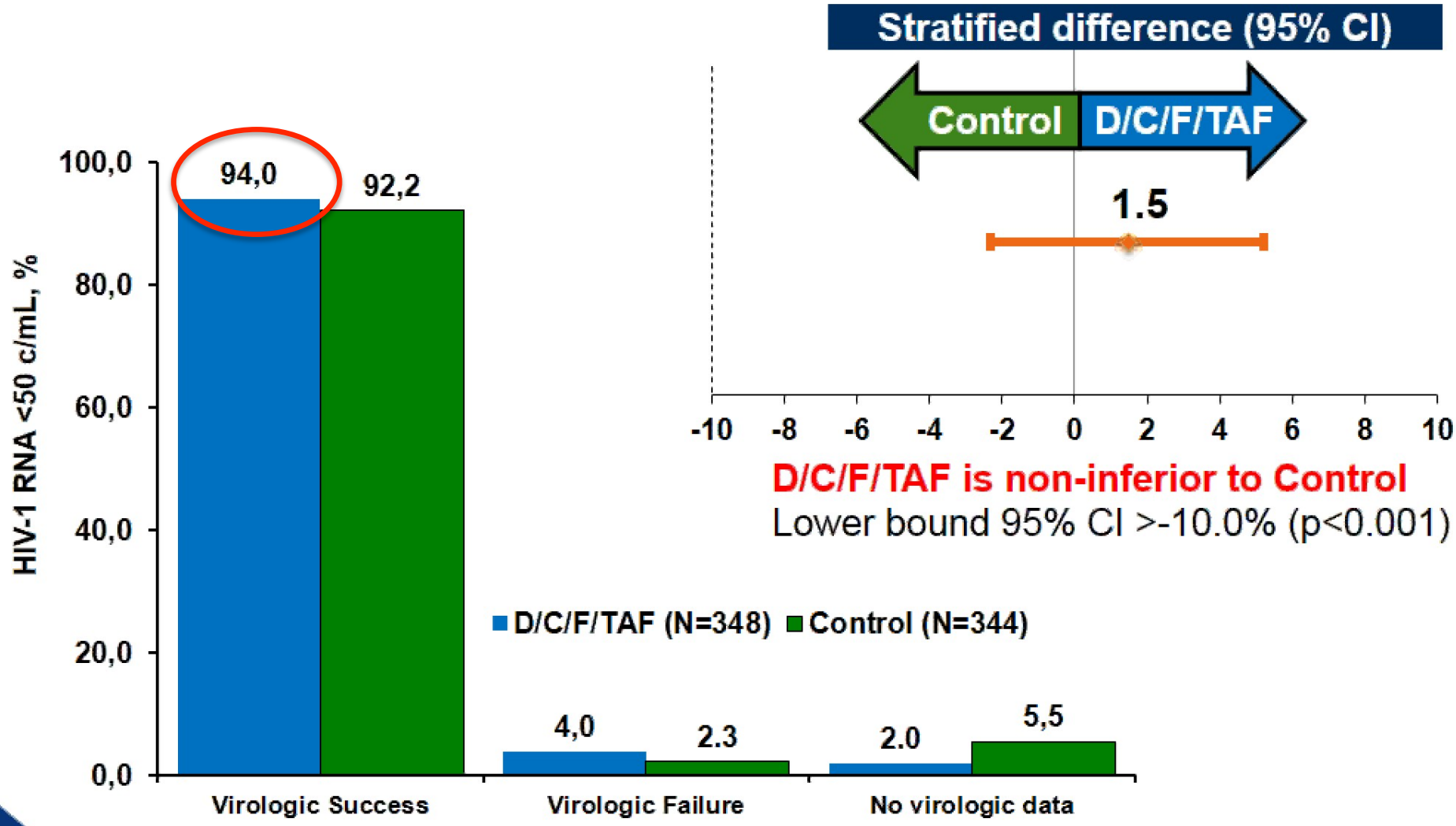
The fate of all boosted PI will be the same?

AMBER



Phase III trial in ART-naïve patients

FDA Snapshot @W48 (<50 copies/mL) (PP)



Source: TEFVR02

AMBER

Renal Adverse Events of Interest for renal proximal tubulopathy (PRT)

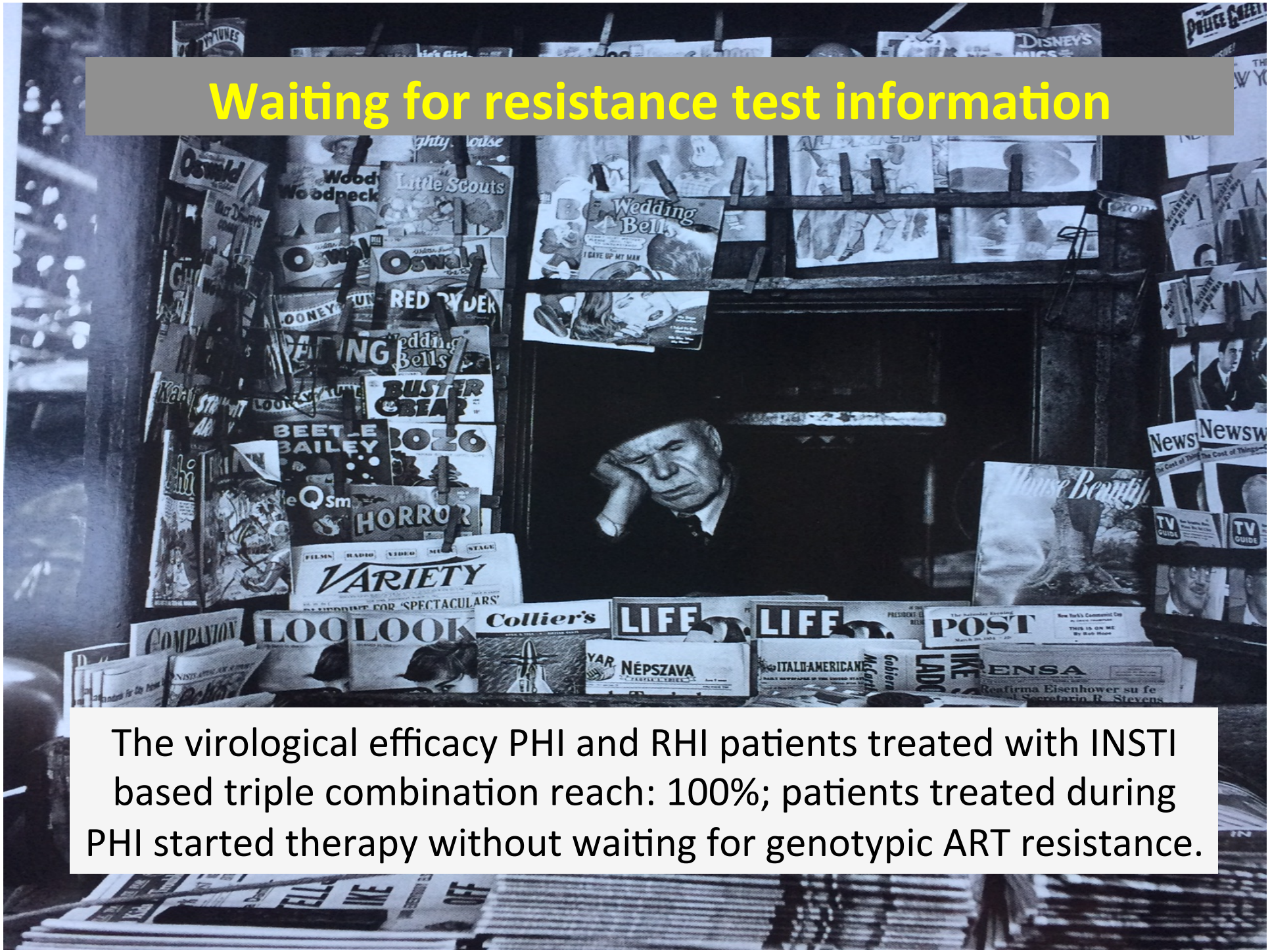
	Any AEOI	Related	≥Grade 3	≥Grade 4	Permanent Stop
D/C/F/TAF (N=362)					
Any Renal AEOI	**2 (0.6%)**	**1 (0.3%)**	**0**	**0**	**1 (0.1%)**
Laboratory related events	1 (0.3%)	1 (0.3%)	0	0	0
Clinical events	**1 (0.3%)**	**0**	**0**	**0**	**0**
Polyuria	1 (0.1%)	0	0	0	0
Control (N=363)					
Any Renal AEOI	**8 (2.2%)**	**3 (0.8%)**	**0**	**0**	**0**
Laboratory related events	8 (2.2%)	3 (0.8%)	0	0	0
Clinical events	0	**0**	0	0	0

No subjects had a renal AEOI consistent with a PRT

Laboratory events were assesed by a separate algorithm, see later

Source: TSFAE35a

Waiting for resistance test information



The virological efficacy PHI and RHI patients treated with INSTI based triple combination reach: 100%; patients treated during PHI started therapy without waiting for genotypic ART resistance.

Low genetic barrier can determine NNRTI FAIL?

HIV drug resistance detected during low-level viraemia is associated with subsequent virologic failure

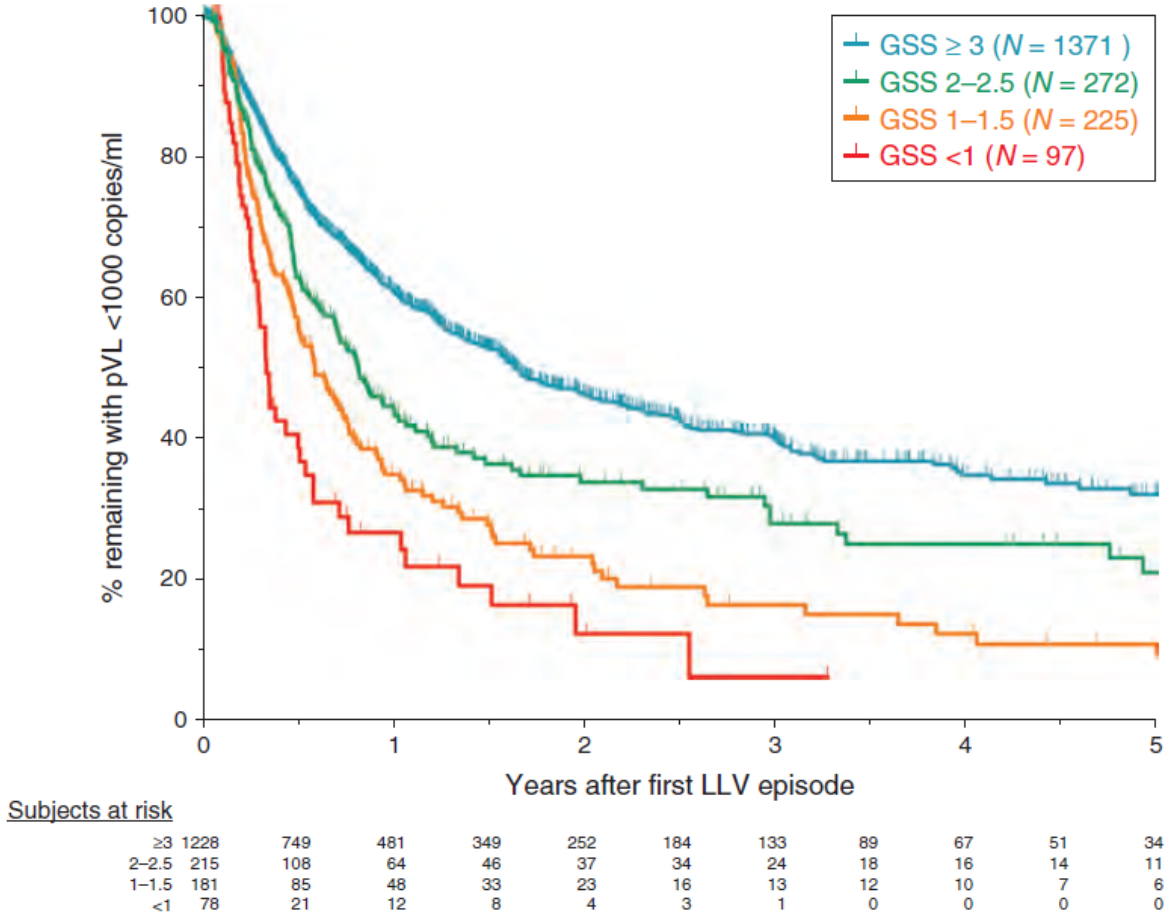
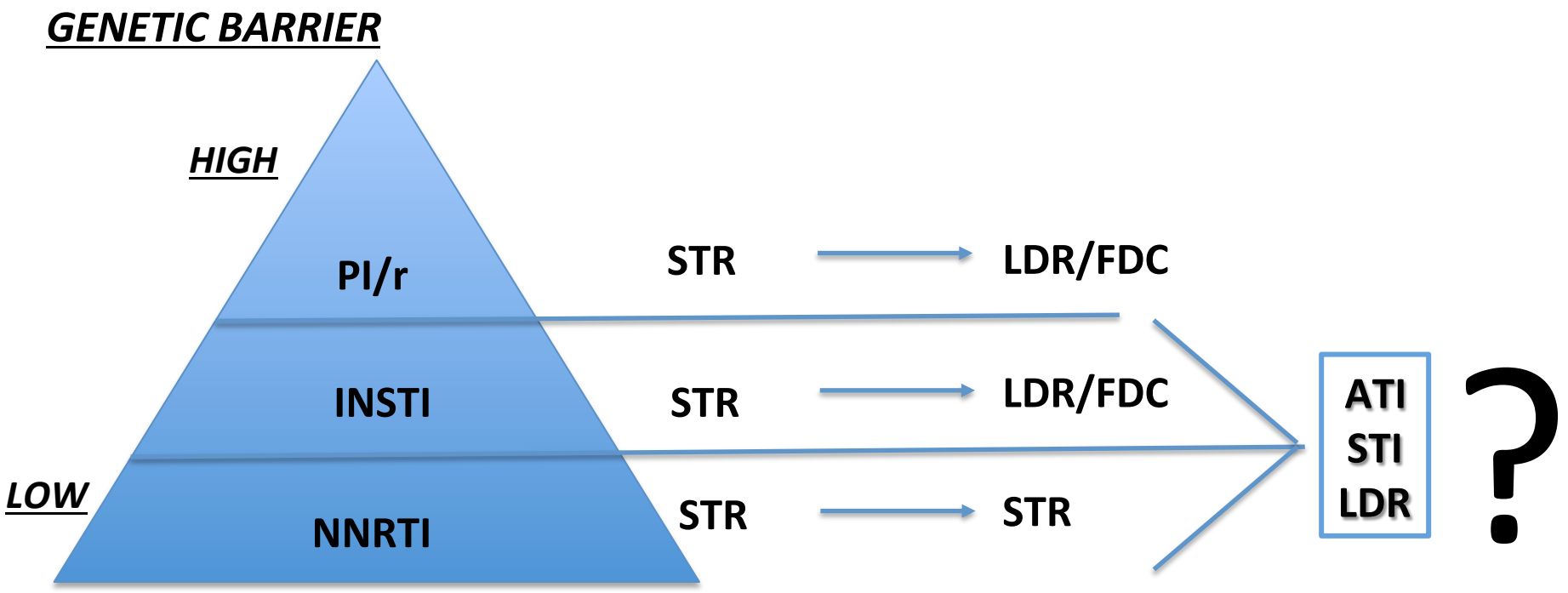


Fig. 1. Virologic failure was faster and more common in patients with lower genotypic susceptibility scores during low-level viraemia. Ka

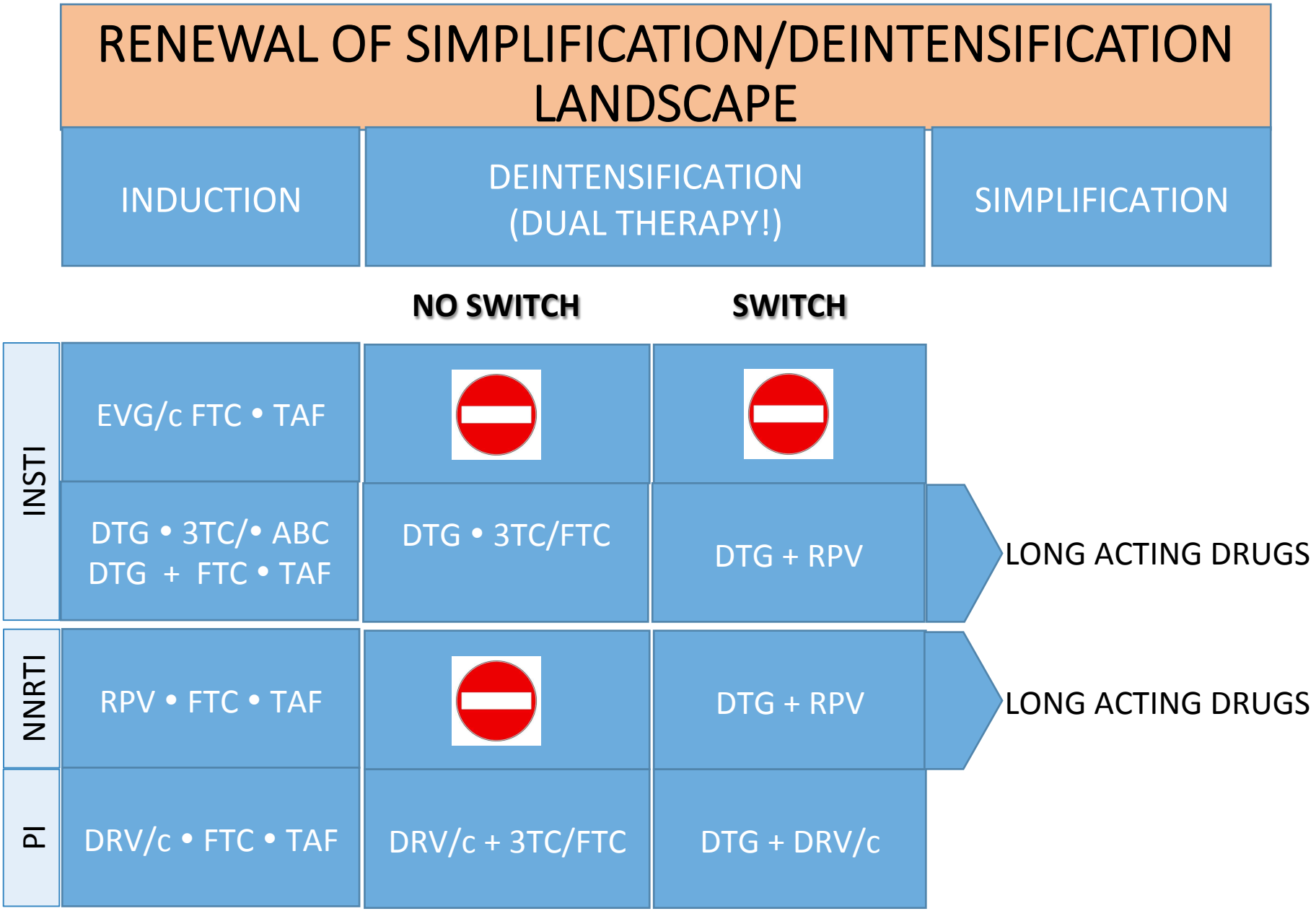
Swenson *et al.* *AIDS* 2014, **28**:1125–1134

cART maintenance and simplification:

the residual viraemia or/and the drug resistance genetic barrier should be the driver of the change of regimens?



RENEWAL OF SIMPLIFICATION/DEINTENSIFICATION LANDSCAPE

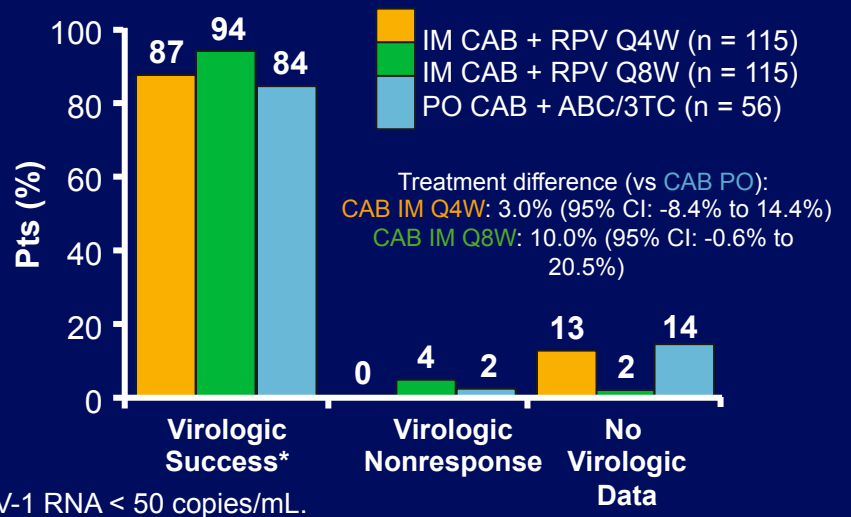


NEXT PREFERRED TDF FREE Rx

LATTE-2: 96-Wk Results for Cabotegravir IM + Rilpivirine IM as Long-Acting Maintenance ART

- **Cabotegravir:** INSTI formulated as PO tablet and for long-acting IM injection
- LATTE-2: phase IIb study in which pts randomized to CAB 400 mg + RPV 600 mg IM Q4W, CAB 600 mg + RPV 900 mg IM Q8W, or CAB 30 mg + ABC/3TC 600/300 mg PO QD after induction/virologic suppression with oral CAB + ABC/3TC (N = 309)

Wk 96 Virologic Efficacy



*HIV-1 RNA < 50 copies/mL.

- At 96 wks, ~ 30% pts receiving IM injection experienced ISR
  - 99% of ISRs mild/moderate
- AEs leading to withdrawal
  - Pooled Q4W/Q8W IM arms, 4%; PO arm, 2%
- Withdrawals between Wks 48 and 96: CAB IM arms, n = 4 (n = 1 for AE, n = 3 withdrew consent); CAB PO arm, n = 3 (all withdrew consent)
- No additional PDVFs after Wk 48 in any arm
- ~ 88% of pts receiving IM CAB very satisfied to continue present treatment vs 43% receiving PO CAB

Eron J, et al. IAS 2017. Abstract MOAX0205LB. Margolis DA, et al. Lancet. 2017;[Epub ahead of print].

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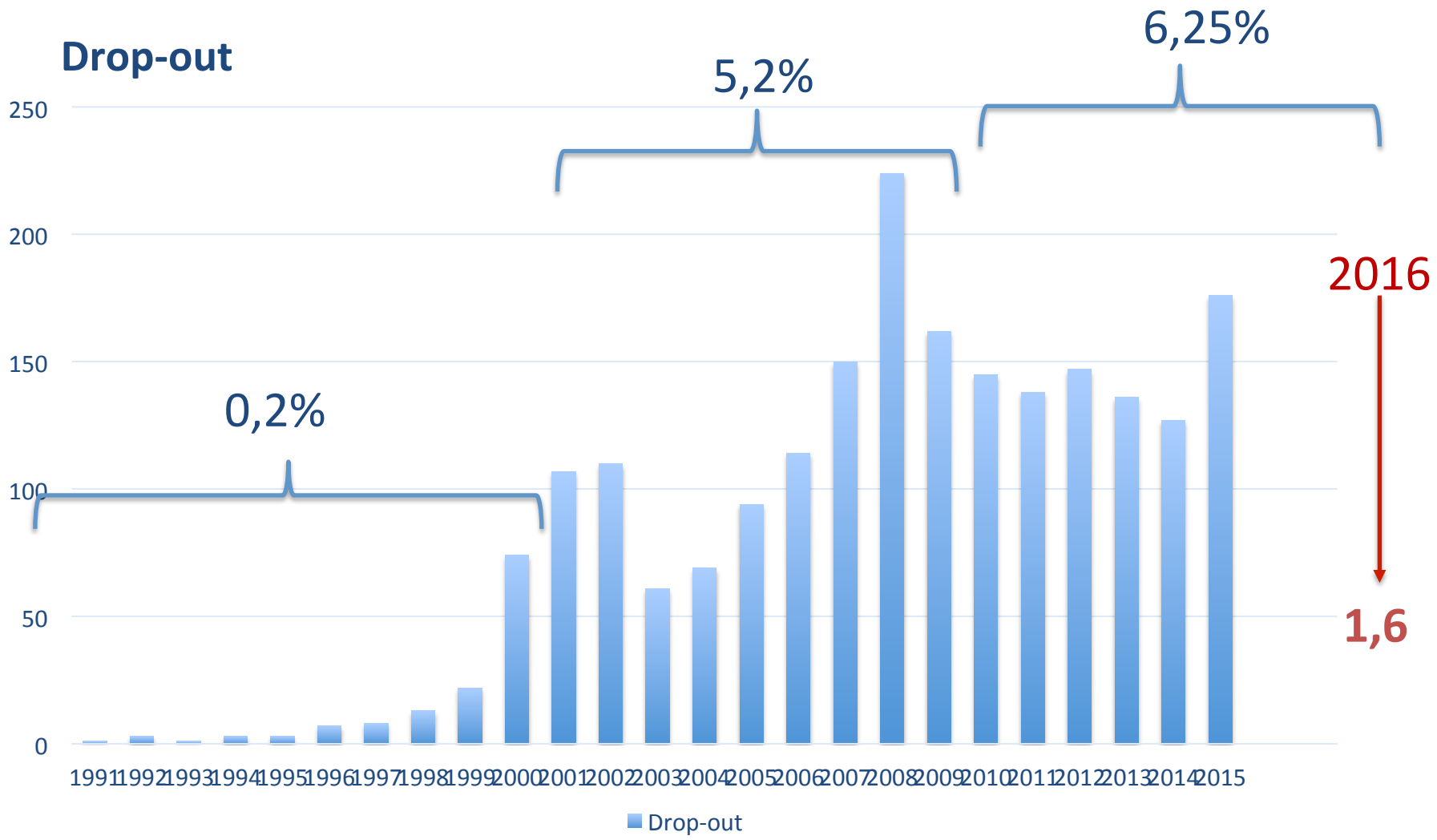
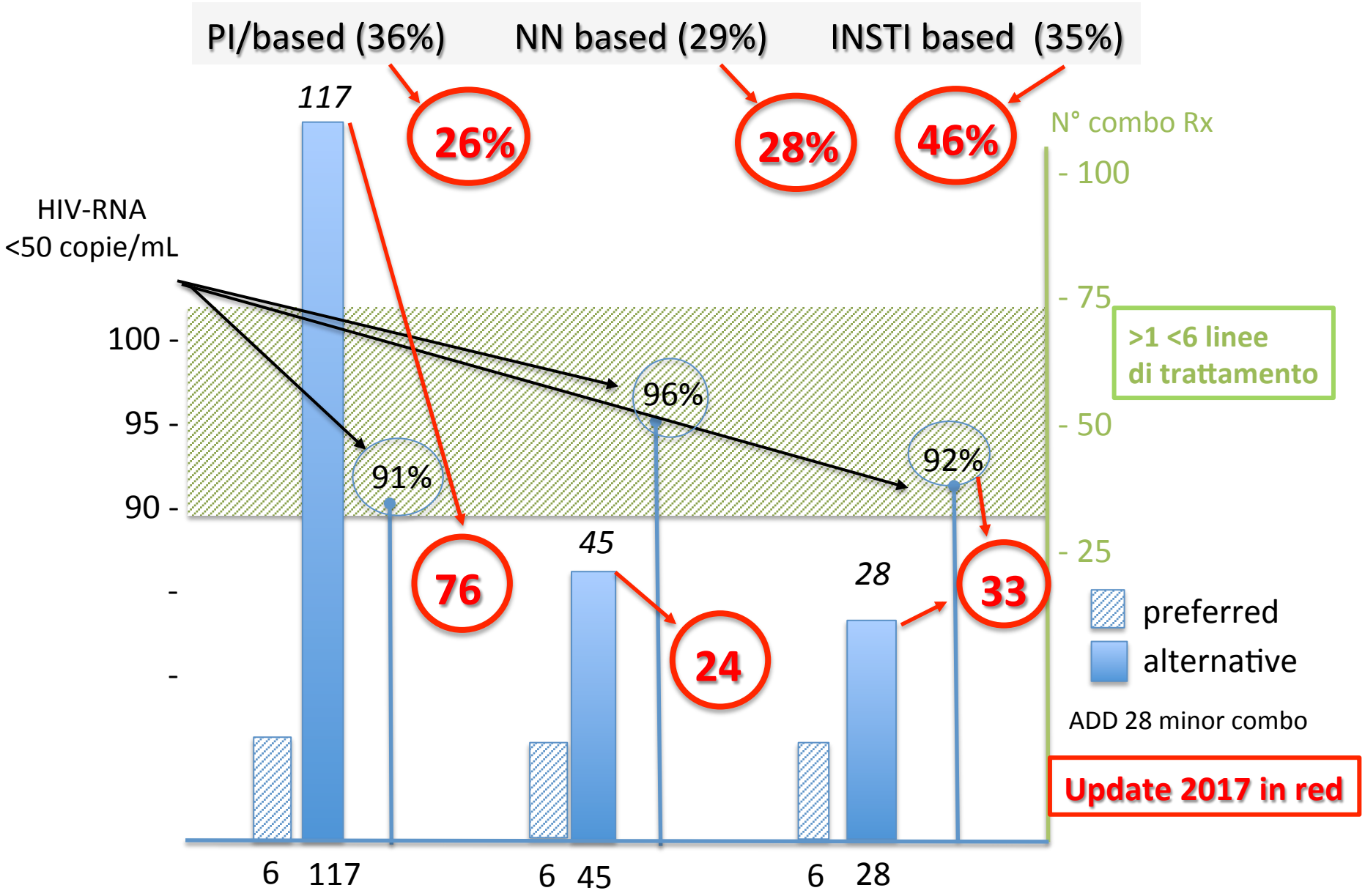
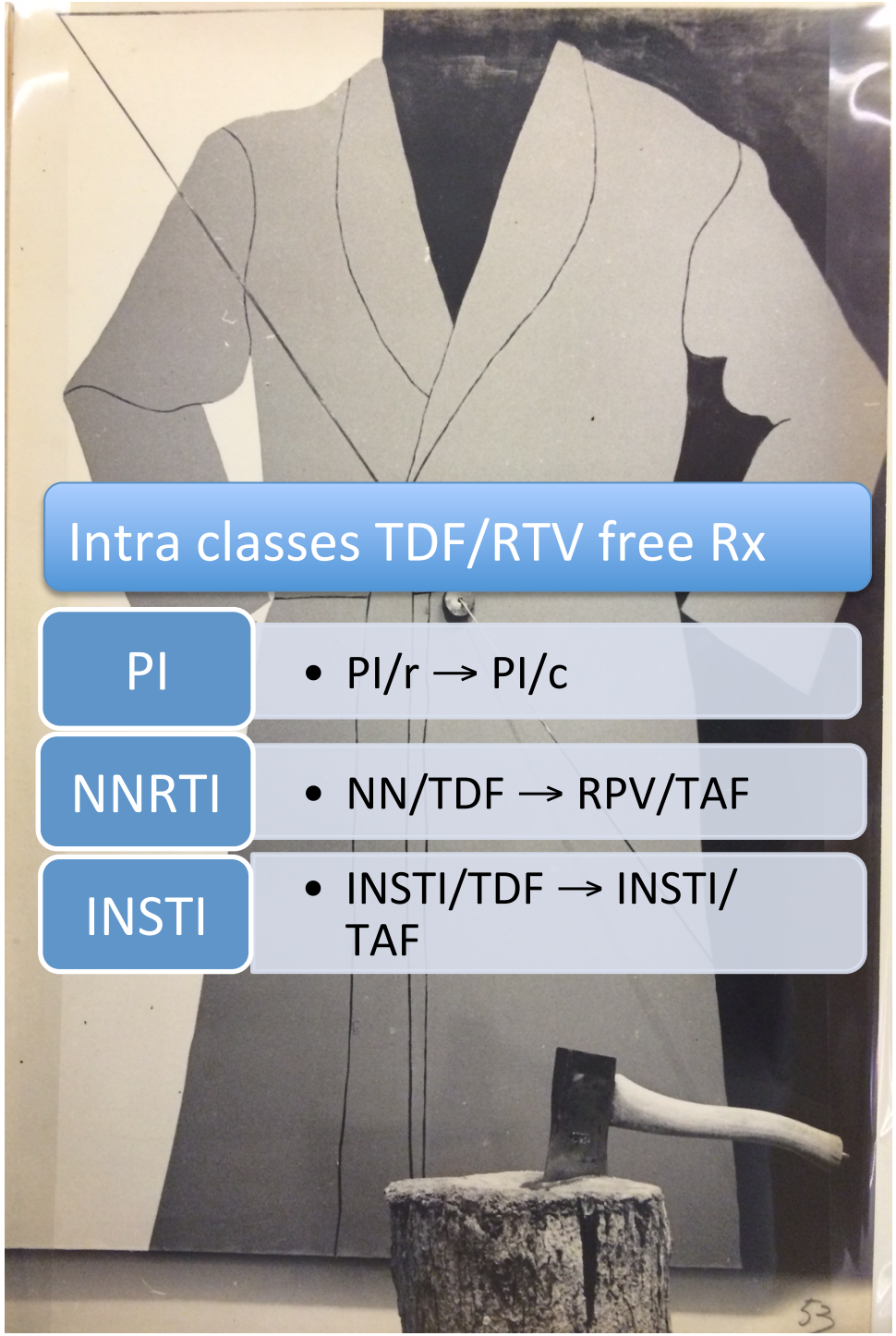
Rotting in real world
a …..waste……cohort
Putting in order with new cART options

ID-OSR Cohort drop-out



cART > 1 < 6 treatment lines = 205 differente rx





Intra classes TDF/RTV free Rx

PI	• PI/r → PI/c
NNRTI	• NN/TDF → RPV/TAF
INSTI	• INSTI/TDF → INSTI/ TAF

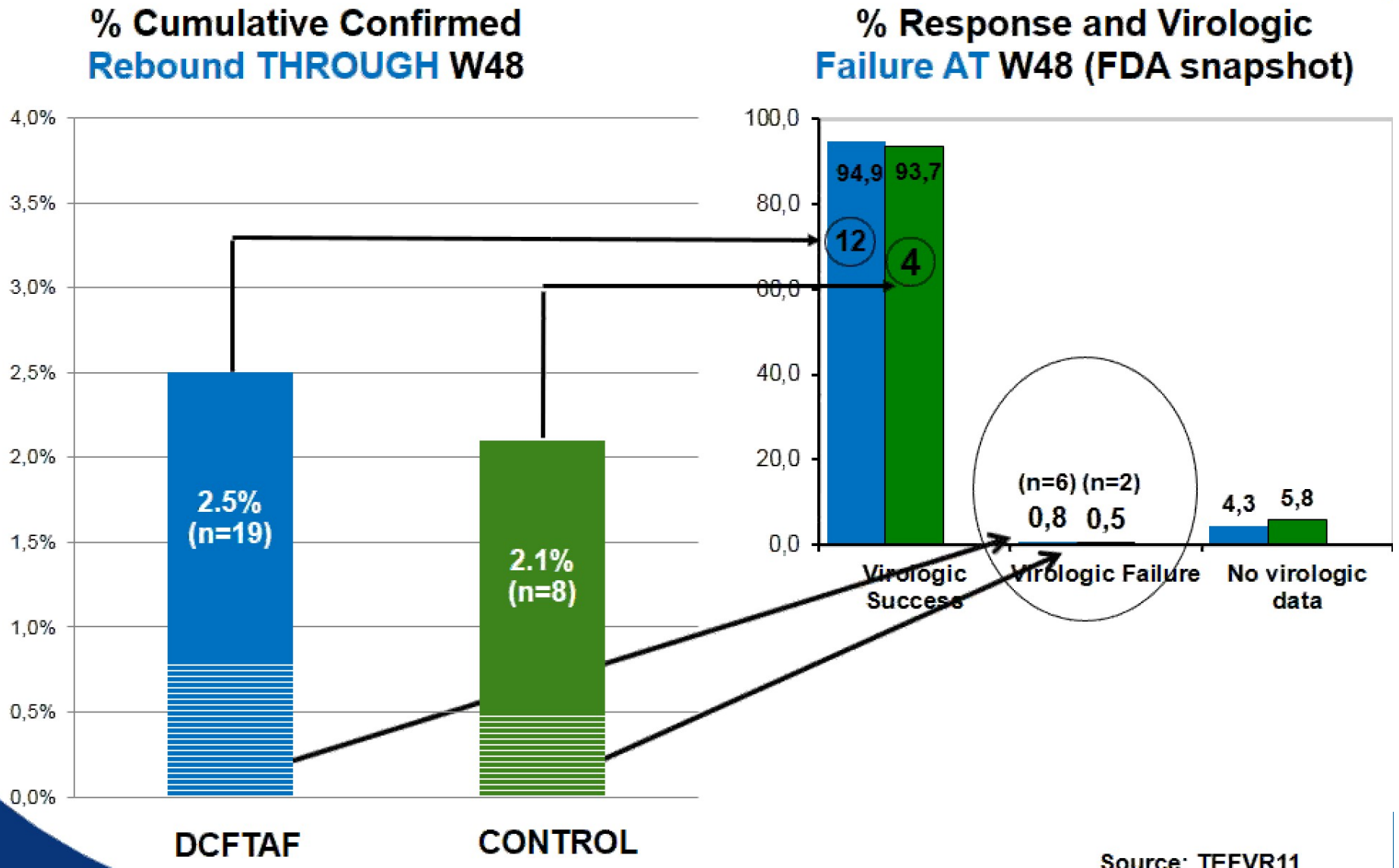
It's necessary a cART renewal in maintenance therapy today

Goal: Reduce the number of too tailored Rx out of fashion

Selection of:

1. • the best of the class as anchor drug
2. • TDF/RTV free Rx

Rebound vs. FDA Snapshot (ITT)



Source: TEFVR11


Father, forgive me, I still tenofovir!
Not yet TAF ?!?

STORE change all PI/r in DRV/c: maintaining tailored back-bone

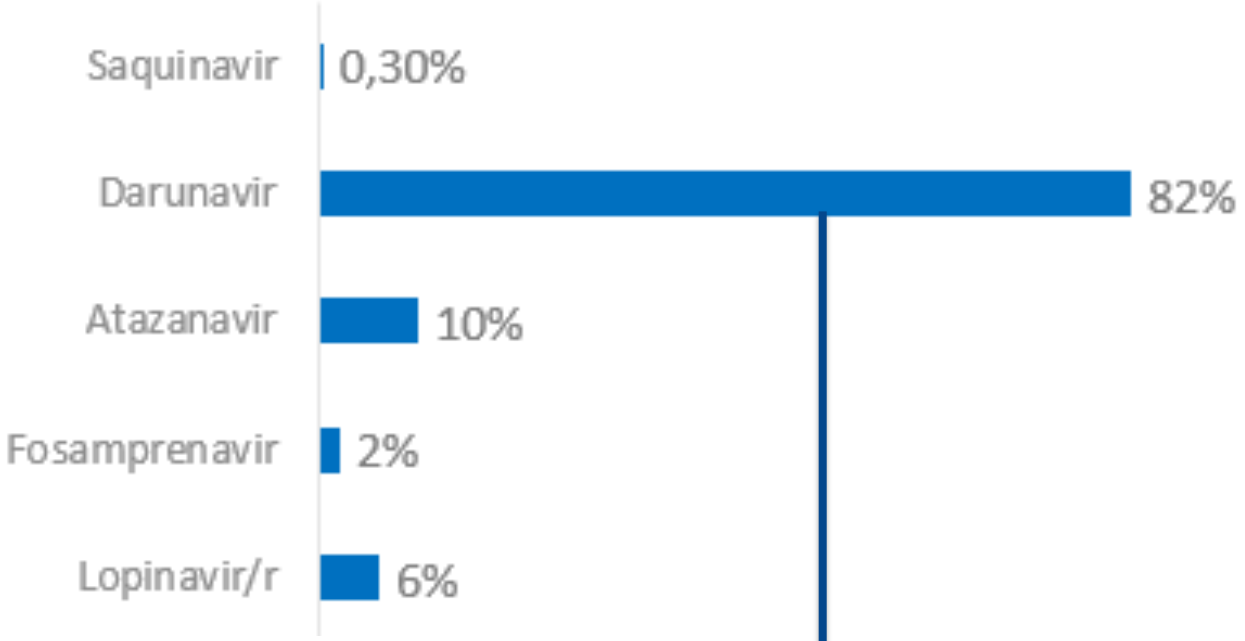
Backbone therapies during DRV/c treatment

TDF/FTC	42,4%
ABC/3TC	16,9%
3TC or FTC	13,7%
RAL	9,5%
MVC	4,7%
DTG	4,5%
ETR	1,0%
RPV	0,3%

Backbone therapies were not changed when switching

Total Dual Therapies = 33,7%

Ongoing PIs before switch to DRV/c



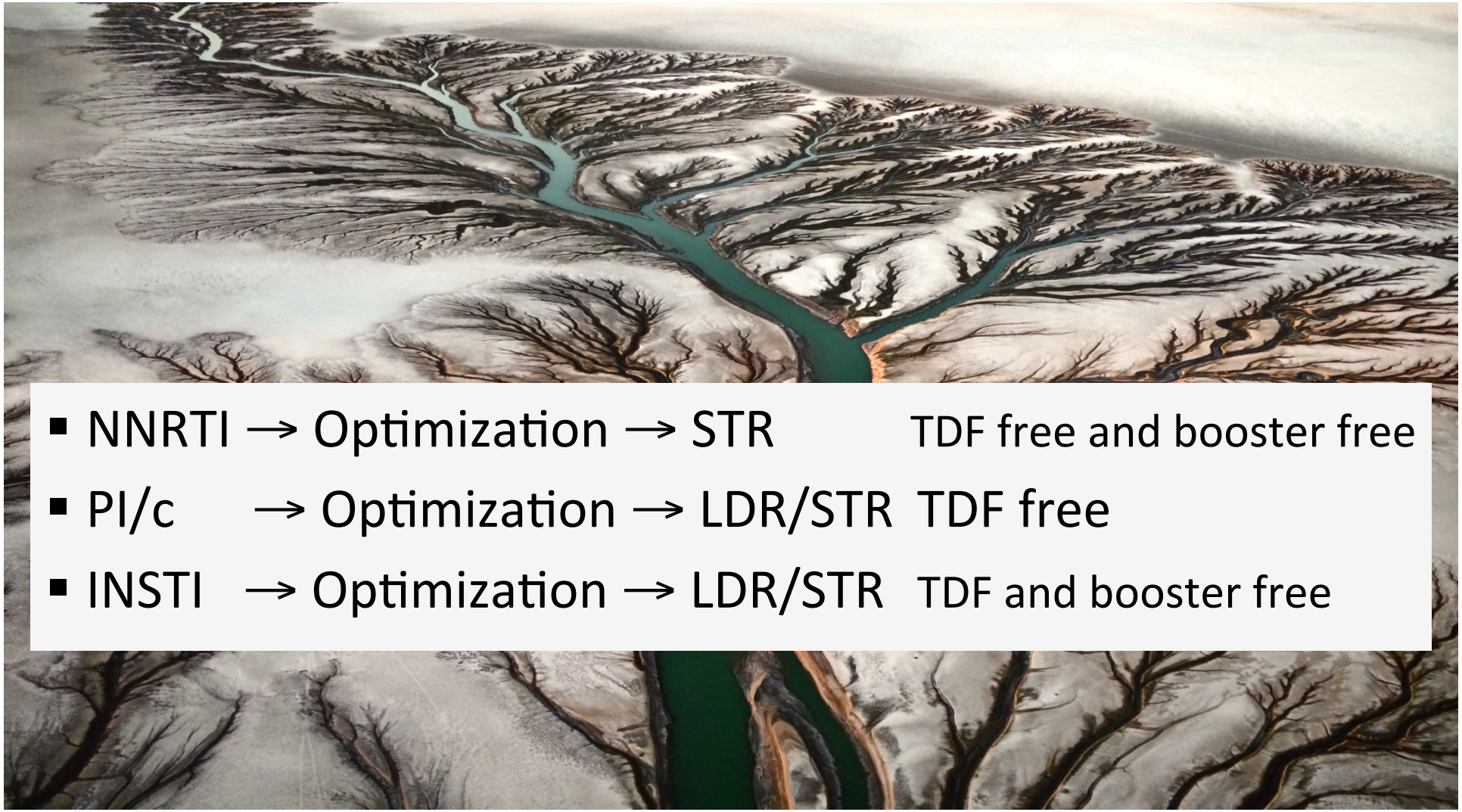
	N (%)
DRV as first PI	110 (39.9%)
DRV started as Naive	57 (20.7%)

Efficacy - % of virosuppressed patients – DRV/c RX (AMBER, EMERALD, STORE)

	V1	V2	V3 (W24)	V4 (W48)
AMBER	-	-	-	91,4%
EMERALD	-	-	-	94,9%
STORE	100% (N=337)	100% (N=316)	100% (N=79)	-

After EMERALD and STORE

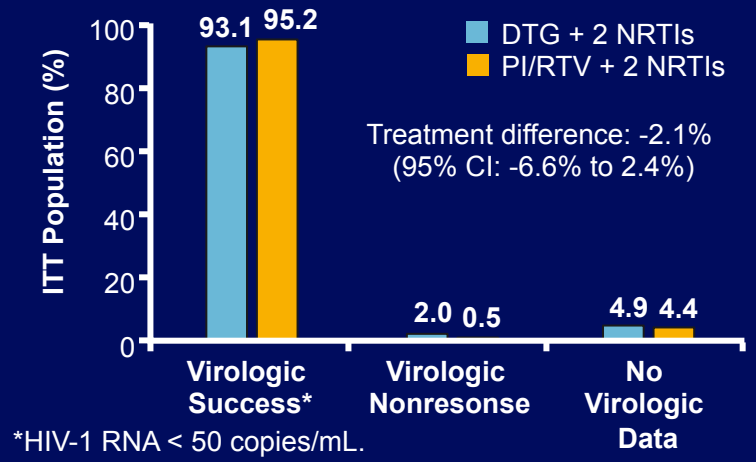
In HIV-RNA suppressed patients is it time for forced switch to standardize again the cART including intensification of the RX?



- NNRTI → Optimization → STR TDF free and booster free
- PI/c → Optimization → LDR/STR TDF free
- INSTI → Optimization → LDR/STR TDF and booster free

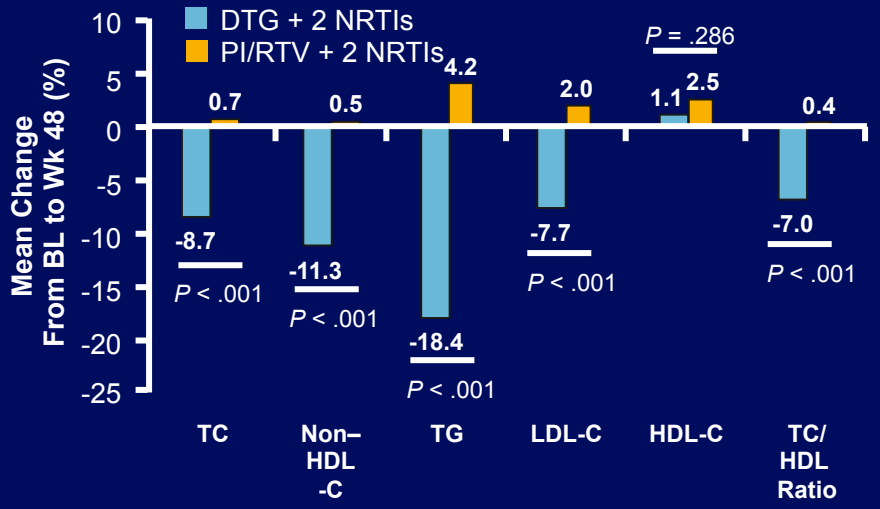
NEAT 022: Key Findings

- Switching to DTG noninferior to continuing boosted PI through Wk 48



*HIV-1 RNA < 50 copies/mL.

- Switching to DTG associated with improved lipid profile vs continuing boosted PI through Wk 48

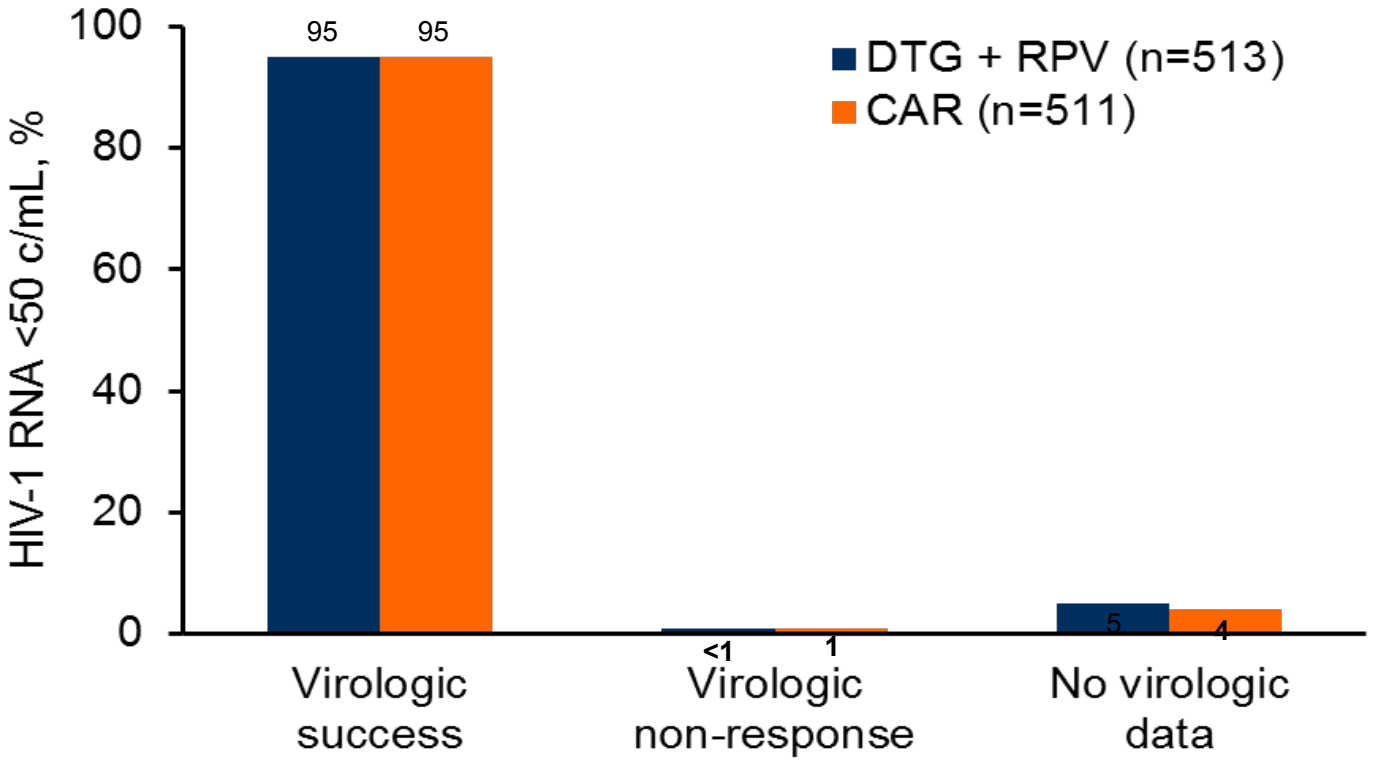


- No emergent resistance in pts with VF
- No significant differences in grade 3/4 AEs, serious AEs, AE-related d/c

Gatell JM, et al. IAS 2017. Abstract TUAB0102. Reproduced with permission.

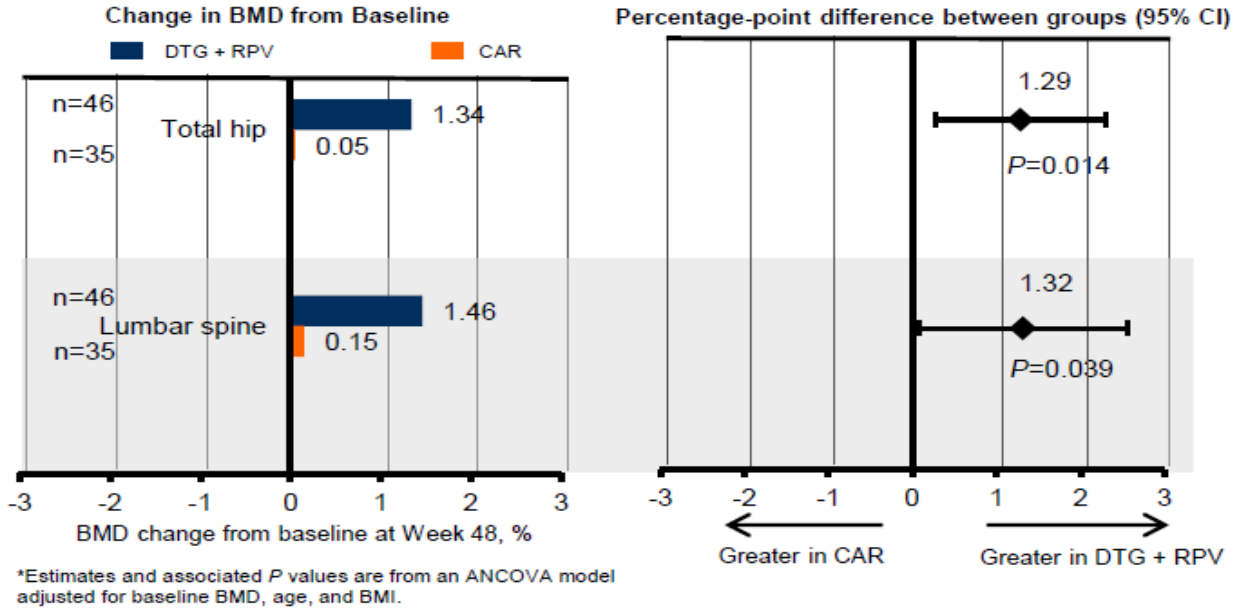
Slide credit: clinicaloptions.com

Studi SWORD 1 & 2. Risposta virologica a 48 settimane



Primary and Key Secondary Endpoints: Week 48*

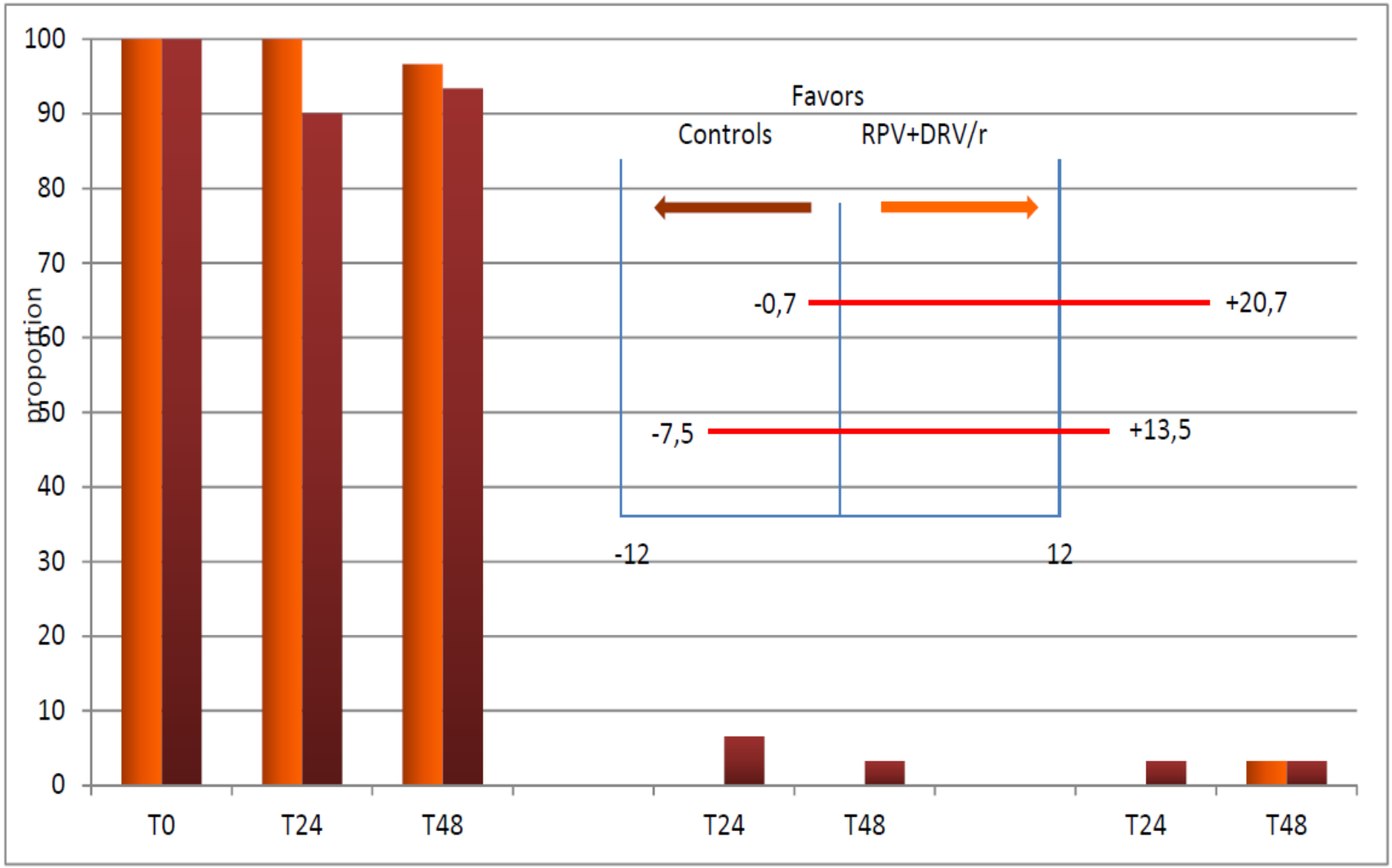
- DTG + RPV patients had an increase from Baseline to Week 48 in hip (1.34%) and spine (1.46%) BMD, which differed statistically significantly (*P*=0.014, *P*=0.039, respectively) from CAR patients



- The primary endpoint result was supported by the significantly greater percentage change from Baseline to Week 48 in the DTG + RPV group compared with the CAR group for BMD in both total hip and lumbar spine when expressed as T-scores or as Z-scores (data not shown)

McComsey et al. IAS 2017; Paris, France. Poster TUPDB0205LB.

Studio PROBE. Risposta virologica a 48 settimane



HIV-RNA < 50 copies/ml

HIV RNA > 50 copies/ml

No data

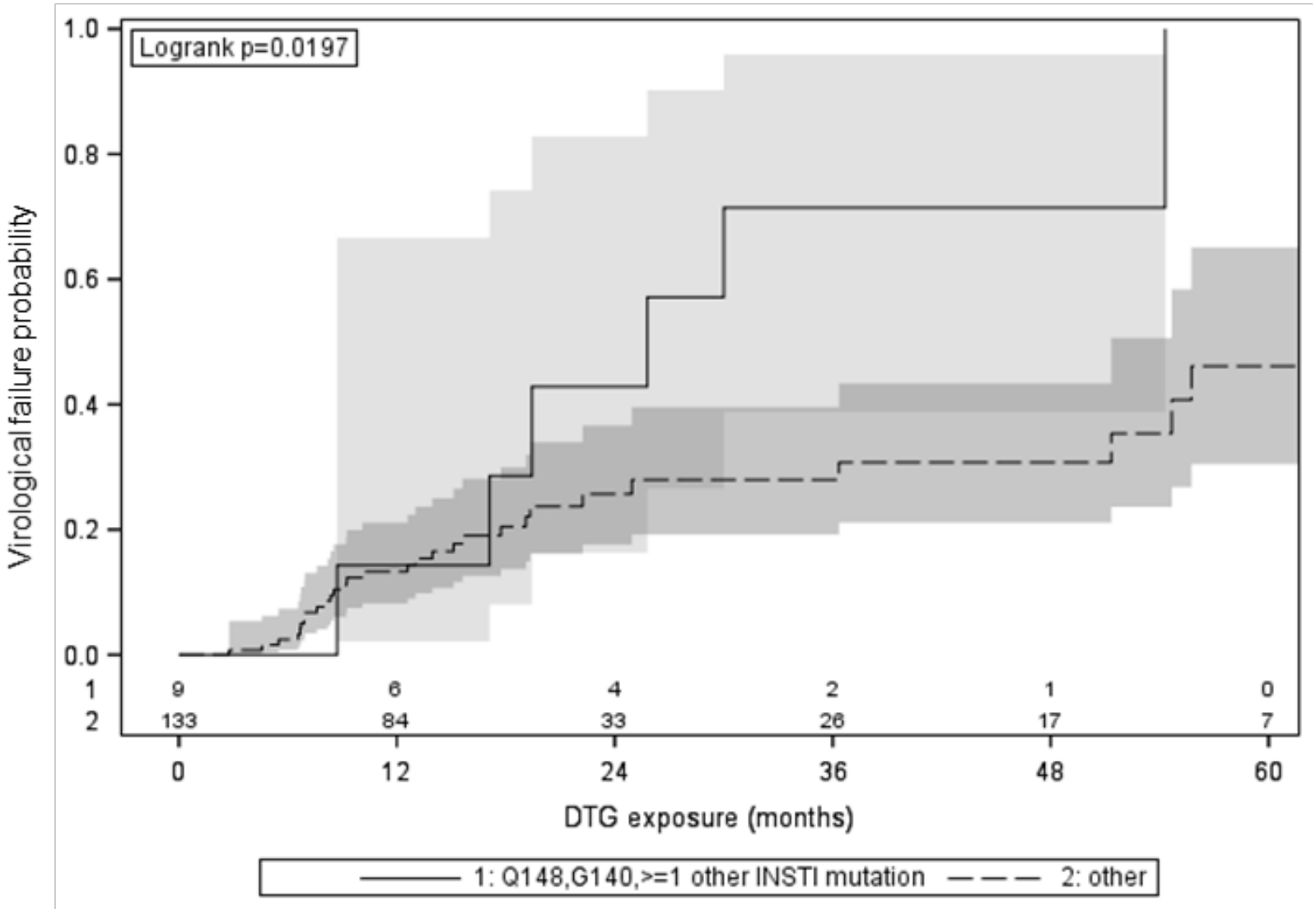
Avoid the change rules imposed by the spending review

Table 1. Key Safety Outcomes at Week 96

	Age ≥50 years			Age <50 years		
	FTC/TAF (n=150)	FTC/TDF (n=144)	P value	FTC/TAF (n=183)	FTC/TDF (n=186)	P value
Change in eGFR, median (mL/min)	+7.8	+3.7	<0.001	+10.6	+4.2	<0.001
Changes in Renal Biomarkers, median (%)						
Urine Protein: Creatinine Ratio	-21.2	+7.7	<0.001	-30.2	-1.4	<0.001
Urine Albumin: Creatinine Ratio	+5.8	+29.4	0.002	-1.0	+22.0	<0.001
Urine Retinol Binding Protein: Creatinine Ratio	-6.3	+57.8	<0.001	-3.5	+36.9	<0.001
Urine Beta-2-Microglobulin: Creatinine Ratio	-29.7	+54.7	<0.001	-29.8	+41.8	<0.001
PRT or Fanconi Syndrome	0	1		0	0	
Changes in BMD, mean (%)						
Spine	+2.69	+0.15	<0.001	+1.49	-0.41	<0.001
Hip	+1.59	-0.78	<0.001	+1.81	-0.08	<0.001

PRT = proximal renal tubulopathy


In HTE failing patiens
HAART optimization need tailored therapy
but following the SOC: 3-PSS-Rx



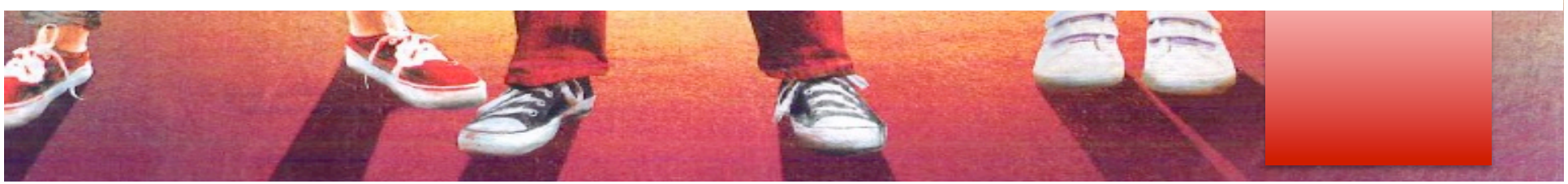
Castagna a et al. JAC 2017, in press

PRESTIGIO Study: Optimized Background therapy (82% with PI/r)

Optimized Background therapy		N=135
OBT > 3 drugs (including DTG)		50 (37%)
PI-sparing regimens		24 (18%)
NNRTI-sparing regimens		97 (72%)
NRTI-sparing regimens		66 (49%)
NRTI most frequently used		
	TDF	43 (32%)
	FTC	35 (26%)
	3TC	22 (16%)
NNRTI most frequently used		
	ETV	27 (20%)
	RPV	11 (8%)
PI/r most frequently used		
	DRV	93 (69%)
	ATV	10 (7%)
	LPV	7 (5%)
Enfuvirtide use		7 (5%)
Maraviroc use		35 (26%)

Castagna A. et al, ICAR 2016

Toward functional cure/eradication




?!? THE FUTURE YOU WANT ?!?
Tra cent’anni da oggi


FUORI