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Azienda Ospedaliero - Universitaria di Ferrara

università di ferrara
DA SEICENTO ANNI GUARDIAMO AVANTI.

Novità in Infettivologia. Autumn 2018

I nuovi farmaci antiretrovirali

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Azienda Ospedaliero Universitaria – Ferrara

Bologna, 23 novembre 2018

Nuovi farmaci antiretrovirali

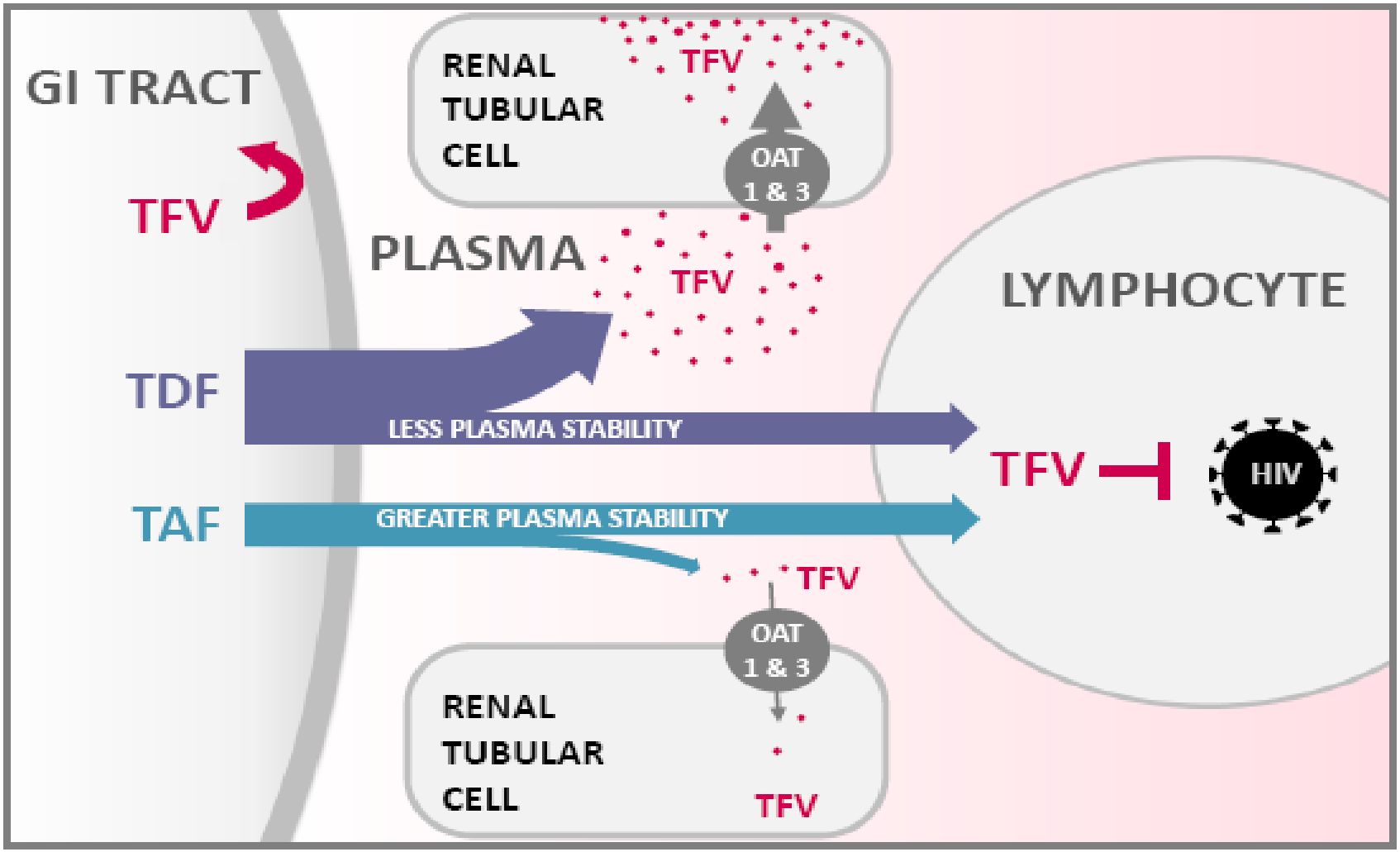
- **Farmaci di recente introduzione**
- **Farmaci di prossima introduzione**
- **Nuove formulazioni**
- **Nuove classi**

NRTI – TAF (tenofovir alafenamide)

TDF (tenofovir disoproxil fumarato)

- ***Tossicità renale***
  tubulopatia prossimale
  ipofosfatemia, fosfaturia, proteinuria
- ***Tossicità ossea***
  < densità minerale ossea, osteomalacia ,
  > rischio fratture

Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide

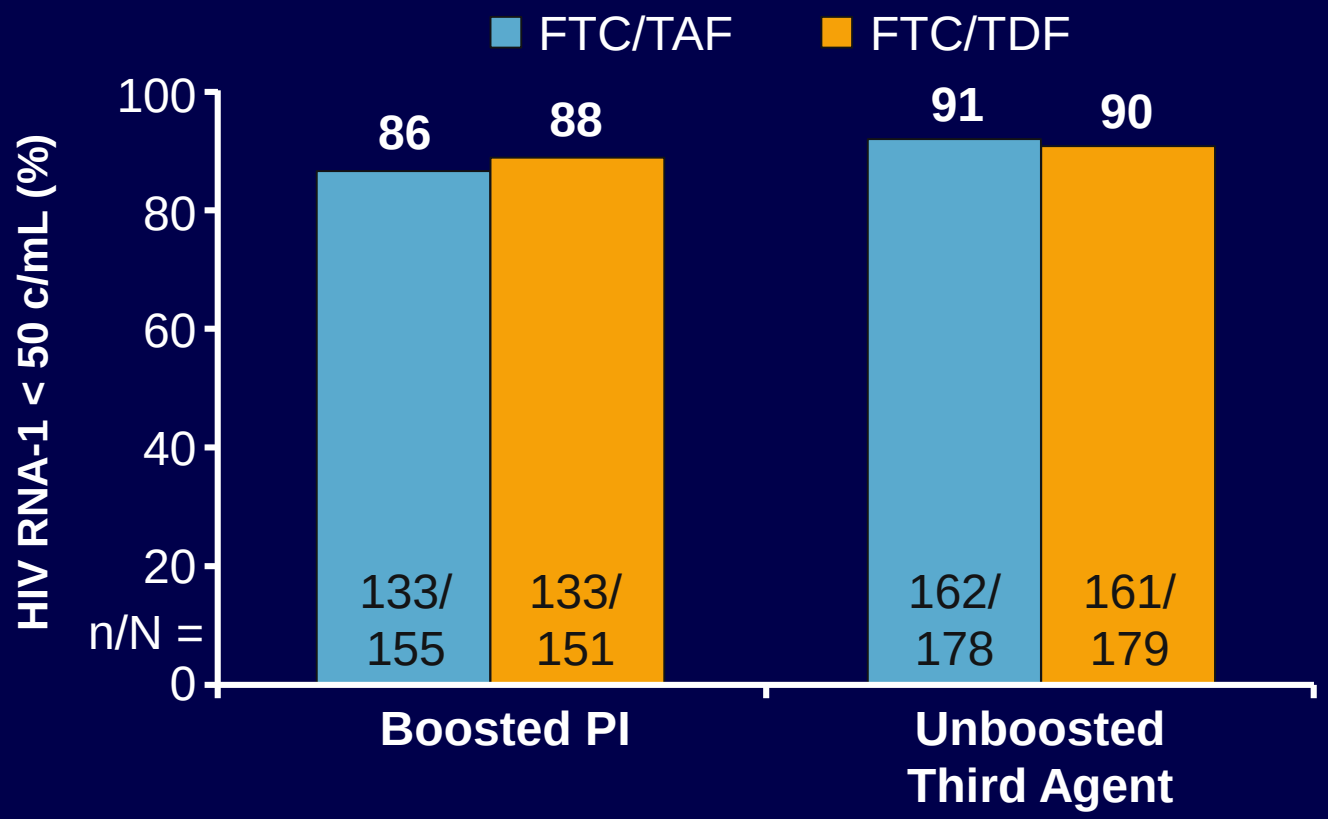


TAF 25 mg results in 80-90% lower TFV plasma levels

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Switch From TDF- to TAF-Containing ART: Virologic Efficacy at Wk 96 by Third Agent

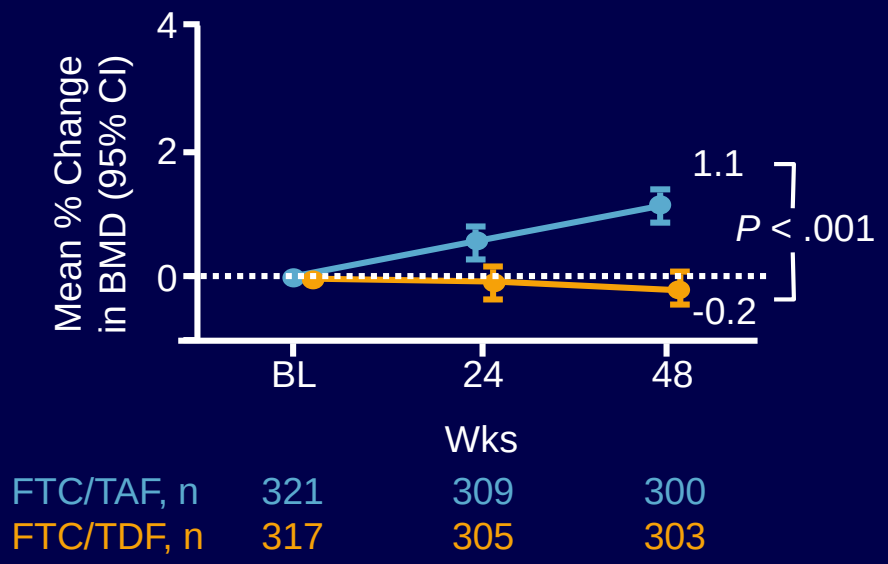
- Comparable virologic success rates by third agent, independent of NRTI pair

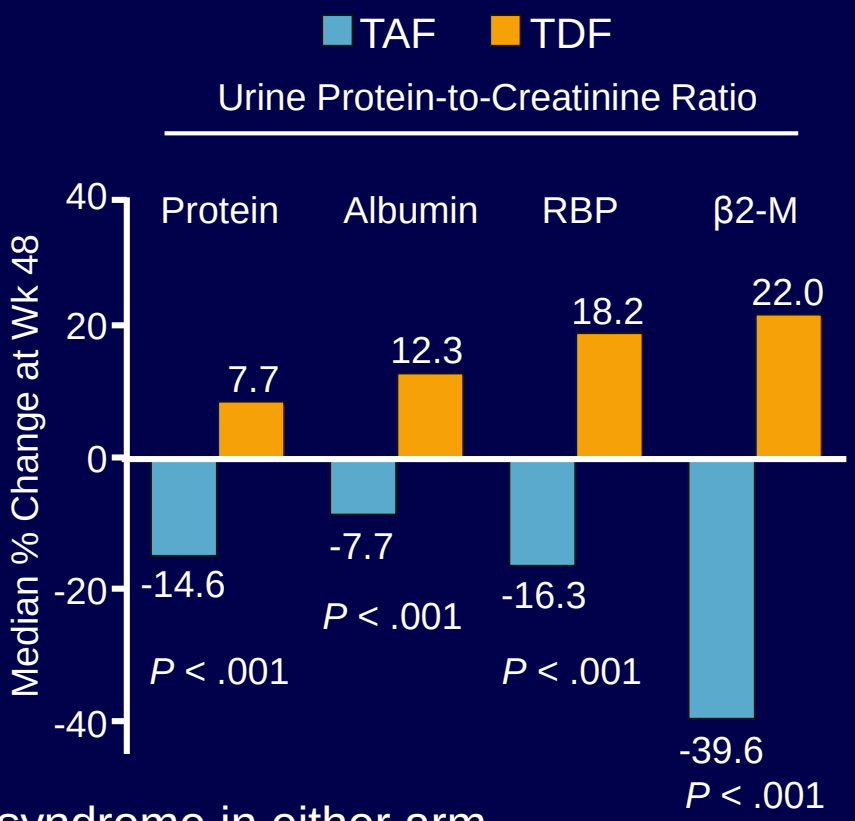


Raffi F, et al. HIV Glasgow 2016. Abstract O125.

GS-1089: Renal and Bone Outcomes With Switch From TDF- to TAF-Containing ART

- Significant improvement in BMD and proteinuria





No proximal renal tubulopathy or Fanconi syndrome in either arm

Gallant JE, et al. CROI 2016. Abstract 29.
Gallant JE, et al. Lancet HIV. 2016;3:e158-e165.

NRTI – TAF (tenofovir alafenamide)

***TAF da non utilizzare*:**

- **con eGFR < 30 ml**
- **nella PREP**

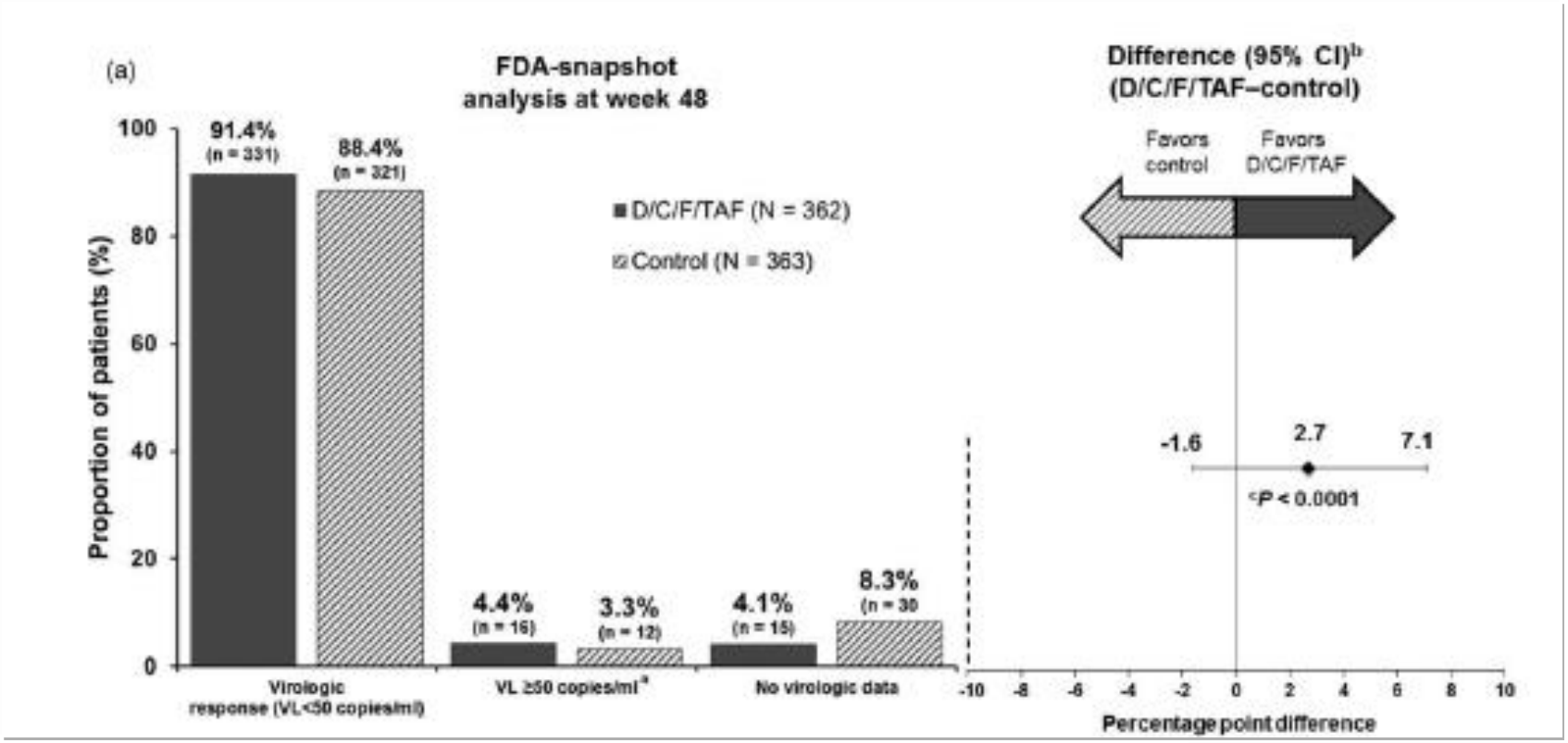
TAF ha sostituito TDF in:

- **TAF/FTC** **Descovy**
- **TAF/FTC/RPV** **Odefsey**
- **TAF/FTC/E/C** **Genvoya**

- **TAF/FTC/DRV/C** **Symtuza**

AMBER: DRV/COBI/FTC/TAF vs DRV/COBI + FTC/TDF for Treatment-Naive Pts

- **Lower rate of AE-related d/c for DRV/COBI/FTC/TAF vs DRV/COBI + FTC/TDF (1.9% vs 4.4%)**
- **Hip/spine BMD changes more favorable with DRV/COBI/FTC/TAF**
- **Significantly higher eGFR by serum creatinine (*P* < .0001) and cystatin c (*P* = .001) with DRV/COBI/FTC/TAF**



AMBER study group

AIDS 2018, Vol 32 No 11

NNRTI - Doravirina

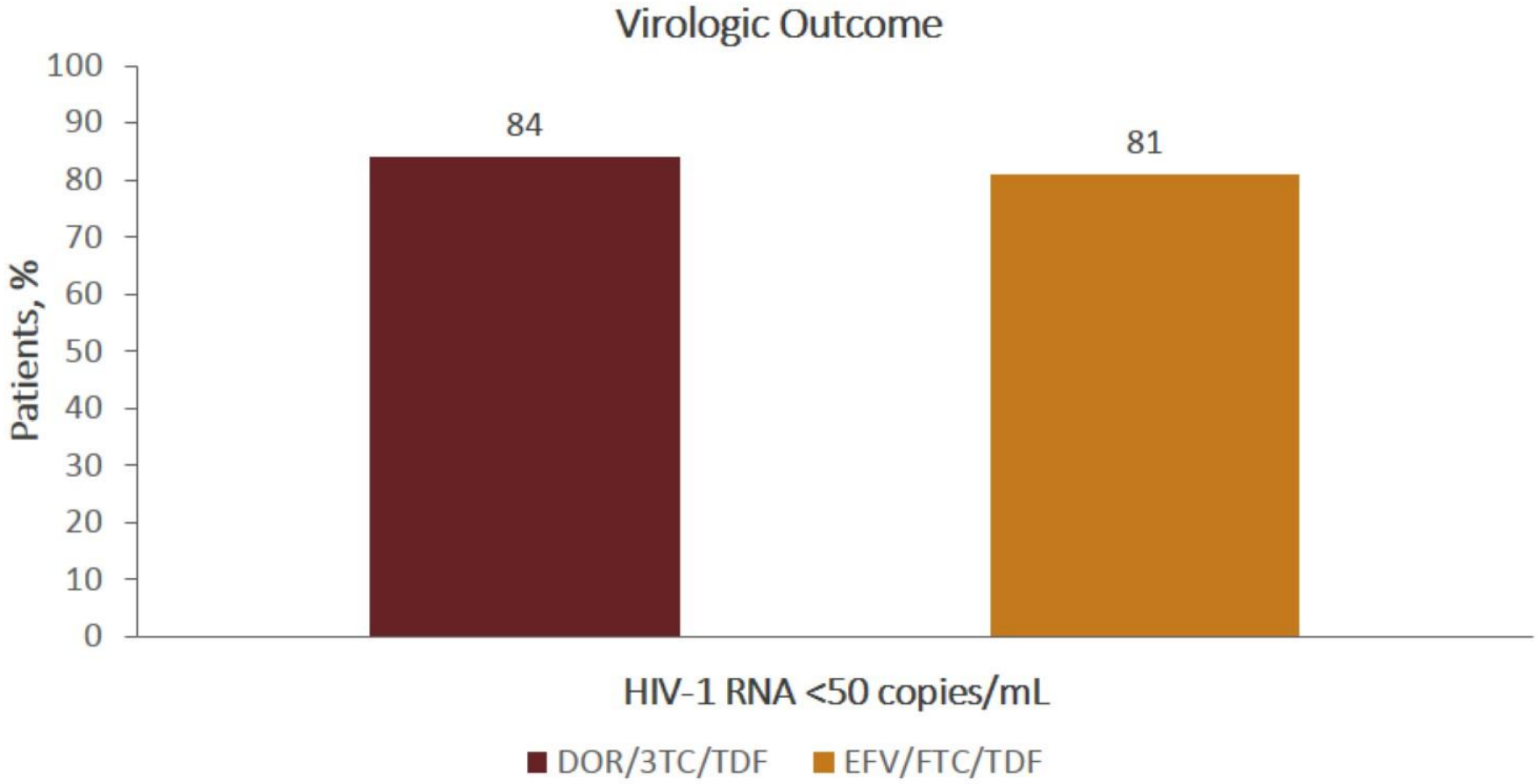
- **Attiva su ceppi HIV resistenti a NNRTI di prima generazione (103N, 181C, 190A, 101K,138K)**

- **Metabolizzata da CYP3A4, non da CYP450**
- **Scarse interazioni con altri farmaci**

- **Dose once daily senza restrizioni per il cibo**

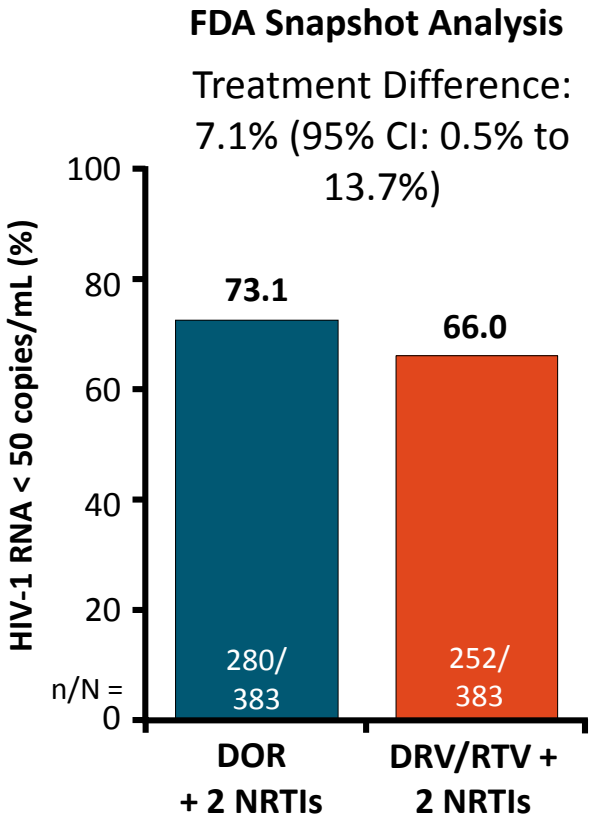
DOR/3TC/TDF vs EFV/FTC/TDF

Virologic Outcome at wk 48



Squires KE, et al. IAS 2017. Abstract 5585.

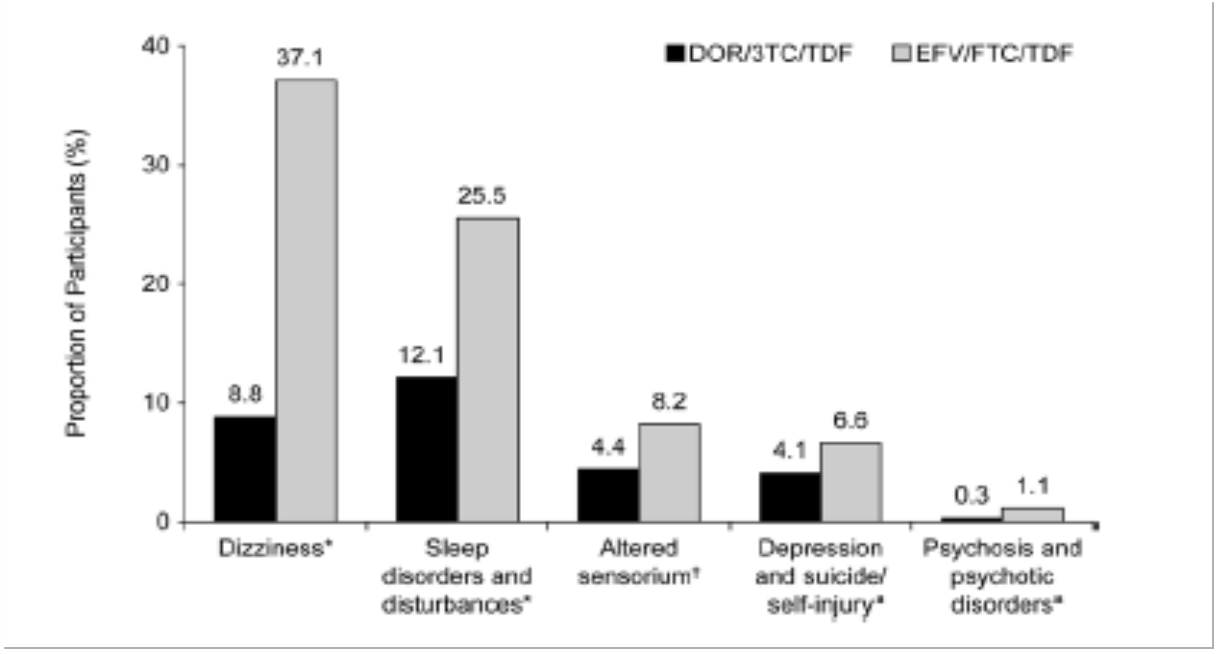
DRIVE-FORWARD: Virologic Outcomes at Wk 96

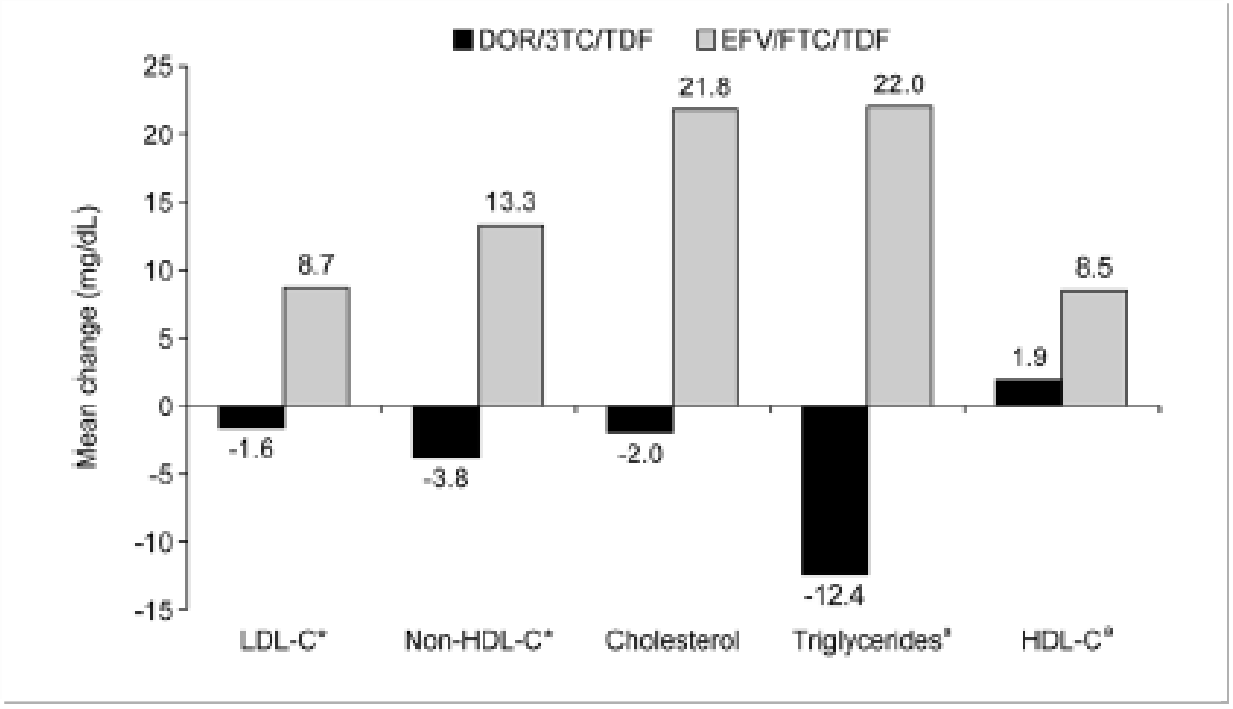


HIV-1 RNA < 50 copies/mL by Observed Failure Analysis, % (n)*	DOR	DRV/RTV
All participants	81.0 (342)	76.8 (323)
BL HIV-1 RNA, copies/mL		
▪≤ 100,000	**85.6 (264)**	**79.7 (282)**
▪> 100,000	**65.4 (78)**	**65.2 (72)**
▪≤ 500,000	**81.8 (325)**	**78.1 (311)**
▪> 500,000	**64.7 (17)**	**36.4 (11)**
BL CD4+ cell count, cells/mm^3		
▪≤ 50	80.0 (5)	52.9 (17)
▪51-200	71.0 (31)	65.8 (38)
▪> 200	82.0 (306)	79.9 (268)
NRTI		
▪TDF/FTC	**80.3 (295)**	**76.3 (283)**
▪ABC/3TC	**85.1 (47)**	**80.0 (40)**

*Discontinuation for lack of efficacy considered failure, other missing data excluded; n refers to total number of participants per subgroup.

Molina JM, et al. AIDS 2018. Abstract LBPEB017.





Doravirina

Effetti collaterali

Cefalea 13%

Diarrea 11%

Nausea 8%

DRIVE-AHEAD Study Group

NNRTI - Doravirina

- **Doravirina 100mg** ***Pifeltro***
- **DOR/3TC/TDF** ***Delstrigo***

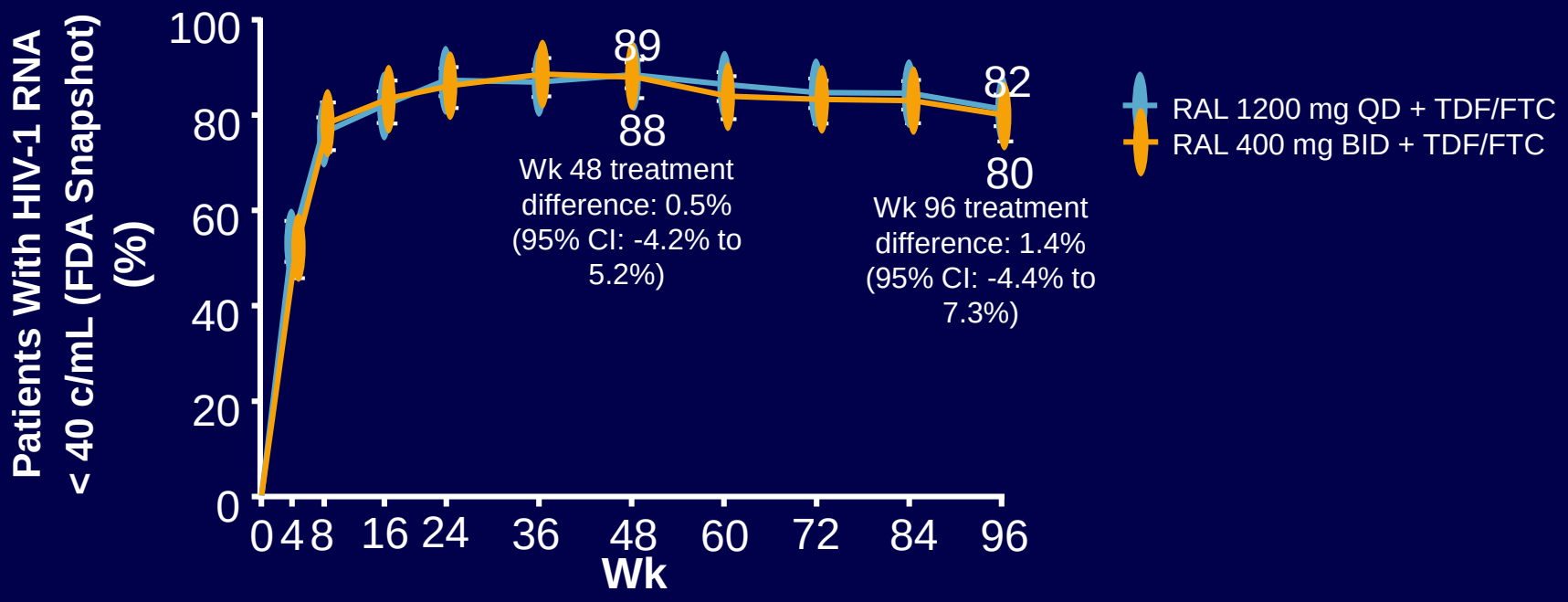
Why are INIs* first line?

*INI=integrase inhibitors

	Dolutegravir	Raltegravir	Elvitegravir/c	Bictegravir
Efficacy[1, 2, 3, 4]	✓✓	✓	✓	✓
Once daily dosing	✓	✓	✓	✓
Available as a STR	✓		✓	✓
High genetic barrier[1, 2, 3, 4]	✓			✓
Few drug interactions	✓	✓		✓
Tolerability		✓	✓	
Studies in women[5, 6]	✓		✓	

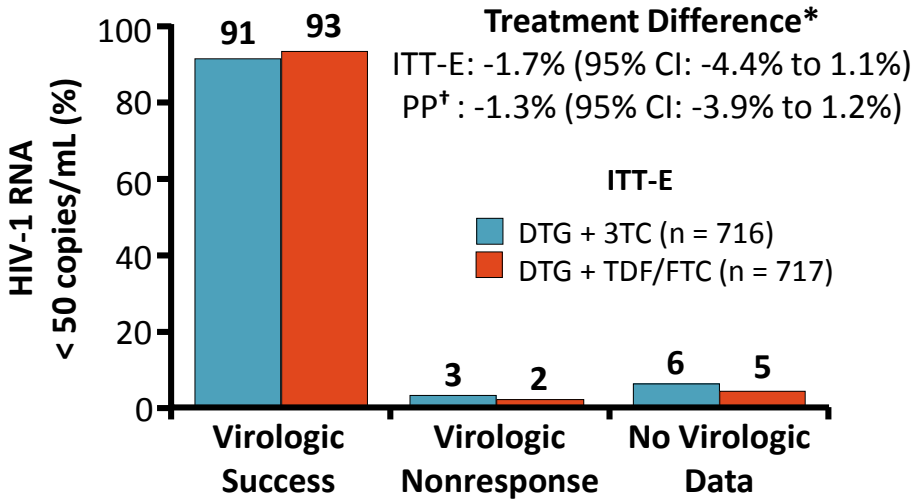
1. SINGLE study: Walmsley S et al. *NEJM* 2013; 2. SPRING-2 study: Raffi F et al. *Lancet* 2013. 3. FLAMINGO study. Molina JM et al. *Lancet HIV* 2015; 4. GS-1490. Sax PE et al. *Lancet* 2017; 5. ARIA study: Orrell C et al. *Lancet HIV* 2017; 6. WAVES study: Squires K et al. *Lancet HIV* 2016

ONCEMRK: RAL 1200 mg QD vs 400 mg BID With TDF/FTC at 96 Wks



Cahn P, et al. IAS 2017. Abstract TULBPEB20.

GEMINI-1 and -2: DTG + 3TC Noninferior to DTG + TDF/FTC in Treatment-Naive Patients at Wk 48



- **No treatment-emergent INSTI or NRTI mutations in patients with VF in either arm**
- **Confirmed VF with DTG + 3TC: n = 6**
- **Confirmed VF with DTG + TDF/FTC: n = 4**
- **Bone and kidney safety markers more favorable with DTG + 3TC vs DTG + TDF/FTC**

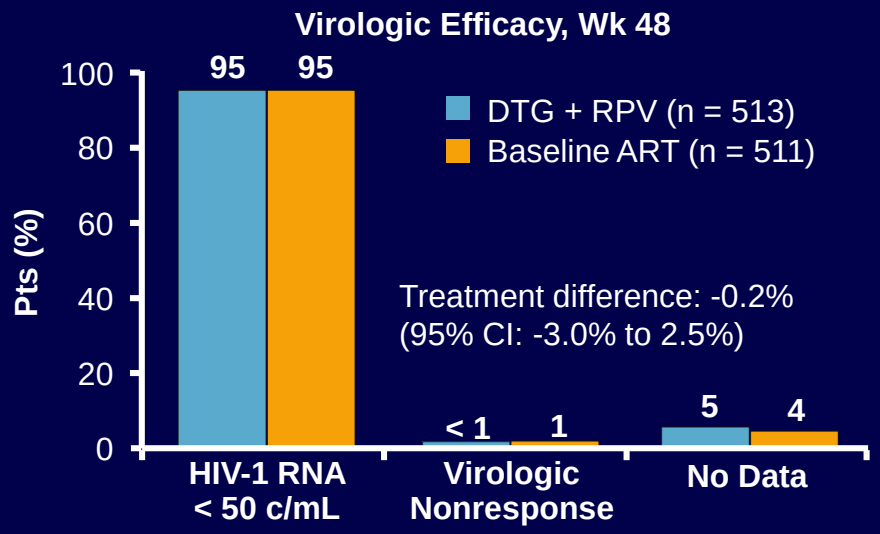
*Adjusted for HIV-1 RNA (≤ vs > 100,000 copies/mL), CD4+ cell count(≤ vs > 200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2). †PP = the ITT-E population excluding significant protocol violations.

DTG + 3TC was noninferior vs 3-drug therapy, no resistance in either arm

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.

SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV in Pts With No Previous VF

- **Randomized, open-label phase III trials in which virologically suppressed pts with no previous virologic failure continued with baseline ART or switched to DTG + RPV (N = 1024)[1]**
  - 72% of pts receiving TDF at baseline



- 1 pt receiving DTG + RPV with virologic withdrawal at Wk 36 had K101K/E mutation
  - Documented nonadherence at virologic failure; resuppressed with continued DTG + RPV; no INSTI resistance
- AE rates similar between treatment arms through Wk 52
  - Numerically higher rate of withdrawal for AEs with switch: 3% vs < 1%
- For pts on TDF-containing regimens at BL (n = 102), improvements in BMD with switch[2]

Slide credit: clinicaloptions.com

1. Llibre JM, et al. Lancet. 2018;[Epub ahead of print]. 2. McComsey G, et al. IAS 2017. Abstract TUPDB0205LB.

DTG/RPV FDA Approved for Maintenance Therapy *JULUCA*

- **Once-daily single-tablet regimen of DTG and RPV**
  - **First 2-drug STR FDA approved for use as a complete regimen in the US**

Key US Label Information	
Indication	▪ **For pts who have been virologically suppressed for ≥ 6 mos** ▪ **Pts must have no history of treatment failure and no resistance to DTG or RPV**
Administration requirements	▪ **Must be taken with a meal**
Key DDIs	▪ **Separate dose of DTG/RPV and antacid/polyvalent cation–containing medications** ▪ **Avoid PPIs (eg, omeprazole, pantoprazole)**
Dose adjustments	▪ **None required for pts with mild/moderate renal impairment; in pts with CrCl < 30 mL/min, increase monitoring for AEs**
DHHS	▪ **Consider when NRTIs not desirable**

DTG/RPV [package insert]. November 2017.

A real-life analysis of dolutegravir adverse effects in a cohort of naïve and experienced HIV-infected patients

Margherita Digaetano[1], Caterina Monari[2], Carlotta Rogati[1], Marianna Menozzi[1], Antonella Santoro[1], Aurora Bonazza[1], Federica Carli[1], Vanni Borghi[1], Cristina Mussini[1]

This study shows a lower percentage of DTG interruption due to AEs compared to the literature reported rates (7 vs 10.5%). However, we obtained similar results in appearance of NAEs (5 vs 5.4%).

DTG discontinuation rate due to AEs results to be *higher* in ***naïve*** vs experienced patients (12.7% vs 6.2%, p<0.05) and *higher* in patients with **TDF/TAF** vs ABC-backbone (13% vs 6%, p<0.05)

HIV Drug Therapy GLASGOW 2018

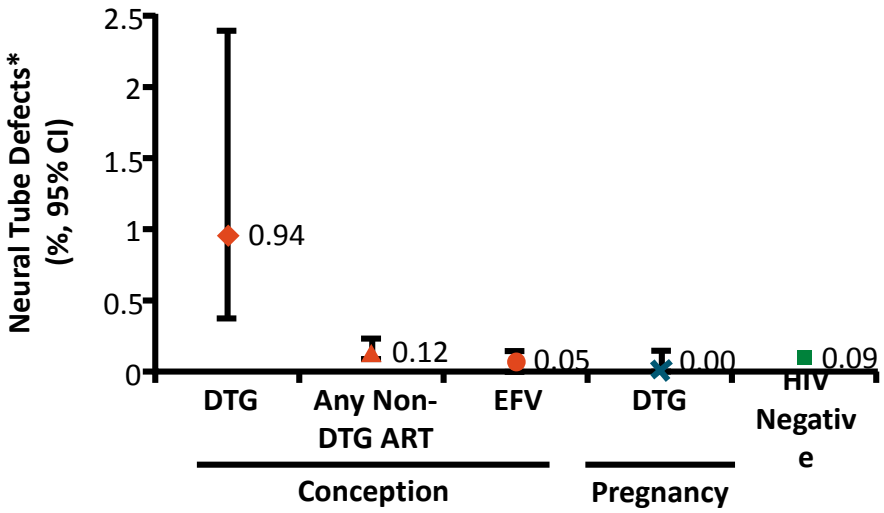
Switch to dolutegravir (DTG) from a boosted protease inhibitor (PI/r) associated with significant weight gain over 48 weeks in NEAT-022, a randomised 96-week trial

Laura Waters[1],

- **Factors associated with BMI gain on DTG in multivariable analysis:**
  - Framingham >15% (P=0.042) & hypertension (P=0.035). **Protective** factors were switching from PIs other than DRV/ATV (P=0.032), current smoking (P=0.006), daily exercise (P=0.036), and HDL-chol (P<0.001)
- **After adjustment for baseline BMI, switching from darunavir was the only independent factor associated with BMI gain (P=0.018).**

Tsepamo: Neural Tube Defects and DTG Exposure

- Unplanned analysis of ongoing birth outcomes surveillance study among Botswanan women ± HIV infection[1,2]



*In 89,064 births as of **May 1, 2018.**

- At latest analysis on **July 15, 2018**[2]
  - NTD prevalence with DTG exposure **at conception**: 4/596 (0.67%; 95% CI: 0.26% to 1.7%)
  - NTD prevalence with DTG started **during pregnancy**: 1/3104 (0.03%; 95% CI: 0.01% to 0.18%)
- Next formal analysis to occur after **March 31, 2019,** which will include 72% of national births

1. Zash R, et al. N Engl J Med. 2018;[Epub ahead of print]. 2. Zash R, et al. AIDS 2018. Session TUSY15.

Slide credit: clinicaloptions.com

Table. Neural Tube Defects in Infants in Tsepamo and the Four New Cohorts

Treatments in the Cohorts	Births, n	Neural Tube Defects, n	Rate, %
Tsepamo			
None (HIV-negative women)	66,057	61	0.09
Dolutegravir at time of conception	4	4	0.94
Dolutegravir after conception	2812	0	0.00
Canada			
Dolutegravir any time during pregnancy	75	0	0.00
Frankfurt			
Dolutegravir any time during pregnancy	1	0	0.00
Eastern and Central Europe			
Dolutegravir any time during pregnancy	28	0	0.00
Gilead Global			
Bictegravir or elvitegravir any time during pregnancy	650	1	0.00

Guidance on the Use of DTG in Women

DTG may be used

Use DTG or another option

Do not use DTG

Currently Receiving DTG?	Pregnancy Status	Recommendation on DTG		
		DHHS[1]	BHIVA[2]	WHO[3]
No	Early pregnancy*			
	Late pregnancy†			
	Childbearing potential, no contraception			
	Childbearing potential, effective contraception			
Yes	Early pregnancy*			
	Late pregnancy†			
	Childbearing potential, no contraception			
	Childbearing potential, effective contraception			

*DHHS: < 8 wks from last menstrual period; BHIVA and WHO: first trimester.

†DHHS: ≥ 8 wks from last menstrual period; BHIVA and WHO: second and third trimesters.

Slide credit: clinicaloptions.com

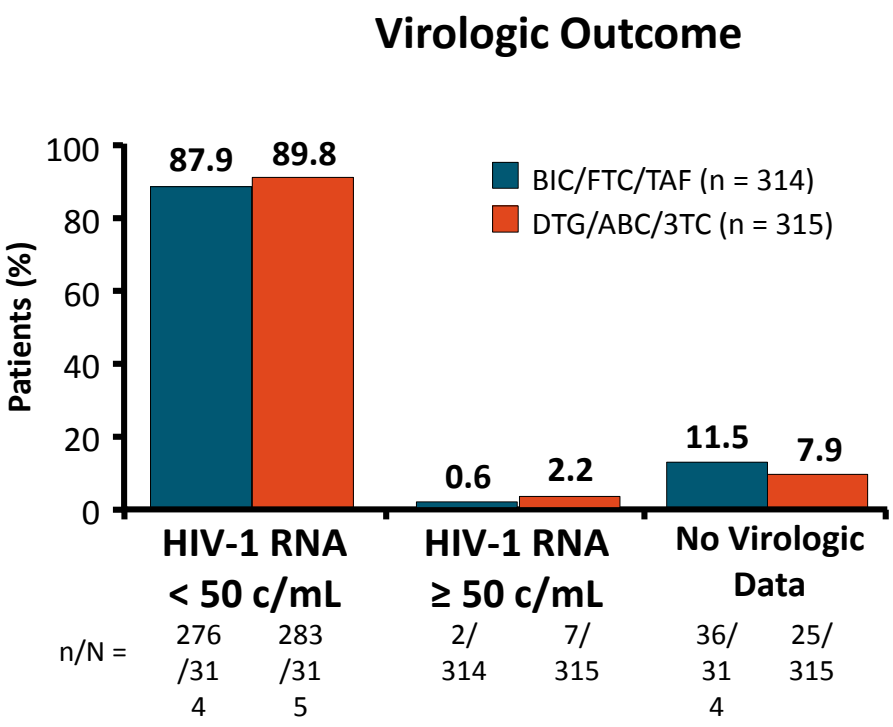
References in slidenotes. Adapted from Doherty M, et al. AIDS 2018. Session TUSY15.

INSTI- Bictegravir

- **Attivo verso virus resistenti INSTI**
- **Elevata barriera genetica**
- **Scarse interazioni**
- **Non booster**

- **Coformulato :BIC/FTC/TAF** ***Biktarvy***

GS-1489: Virologic Outcomes at Wk 96



- **Noninferiority of BIC/FTC/TAF vs DTG/ABC/3TC confirmed in additional analyses**
- **No treatment-emergent resistance detected in any patient through Wk 96**

Wohl. IDWeek 2018. Abstr LB4. Reproduced with permission.

Nuovi farmaci antiretrovirali

- **Farmaci di recente introduzione**
- **Farmaci di prossima introduzione**
- **Nuove formulazioni**
- **Nuove classi**

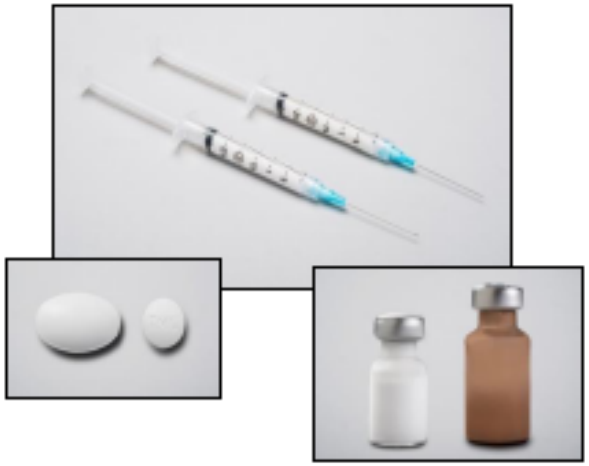
INSTI - Cabotegravir

- **Struttura e profilo resistenza simile a dolutegravir**

- **Nanoformulazione per somministrazione parenterale**

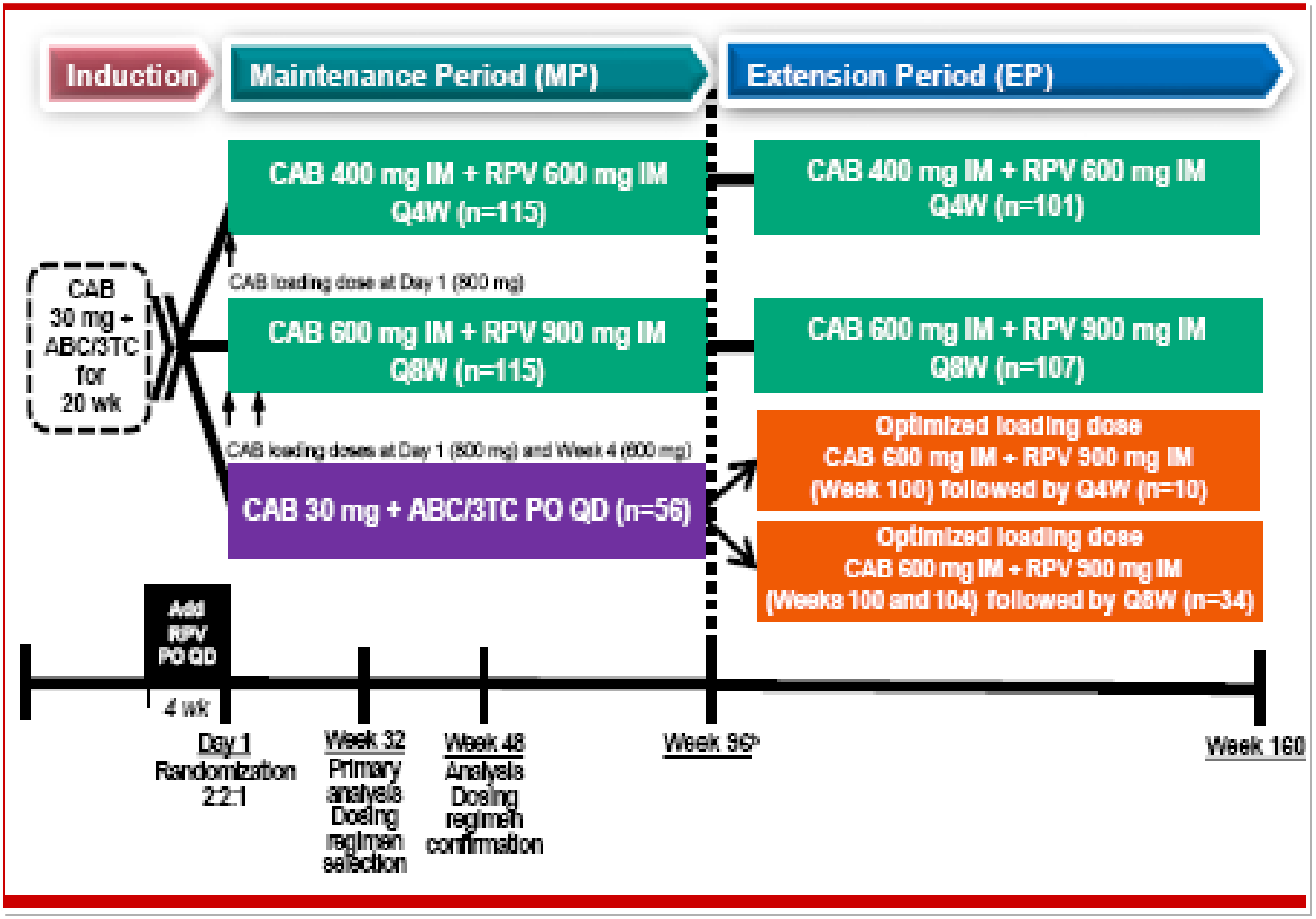
Long-acting injectables

- Cabotegravir (CAB) is an HIV-1 integrase inhibitor
  - Oral 30mg tablet ($t_{1/2}$ ~ 40 hours)
  - IM LA injection 200 mg/ml ($t_{1/2}$ ~20-40 days)
- Rilpivirine (RPV) is an HIV-1 NNRTI
  - Oral 25mg tablet ($t_{1/2}$ ~ 50 hours)
  - IM LA injection 300mg /ml ($t_{1/2}$ ~ 30-90 days)
- Oral 2DR CAB + RPV proof of efficacy through week 144 in LATTE[1]



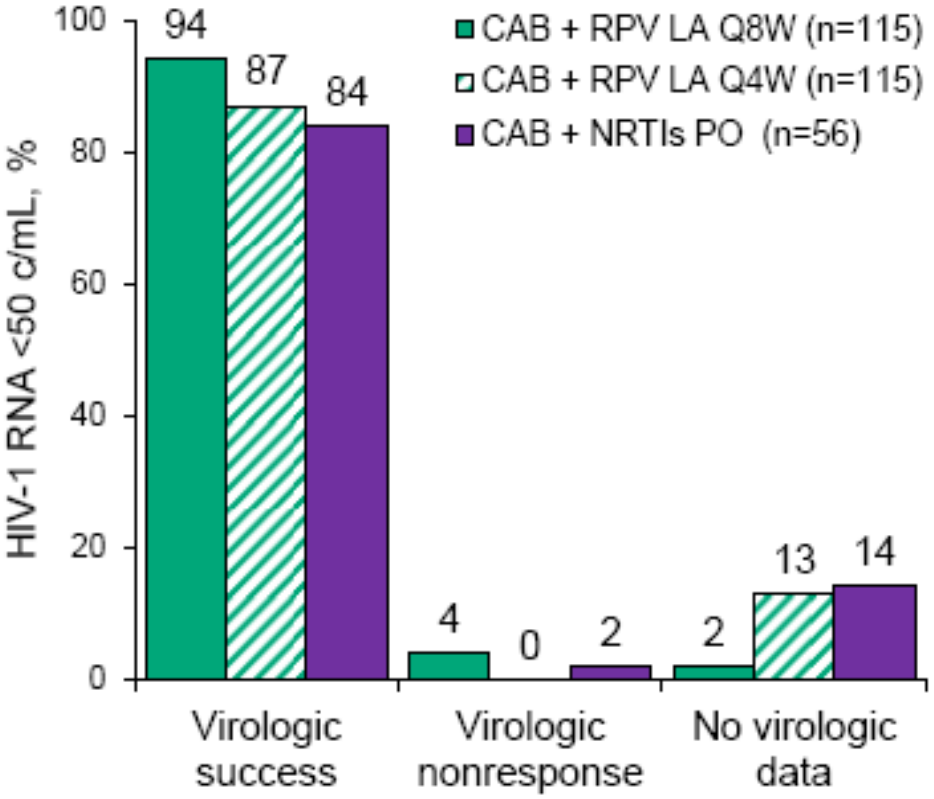
[1]Margolis D et al. Lancet ID 2015

CAB + RPV Studio LATTE 1 e 2

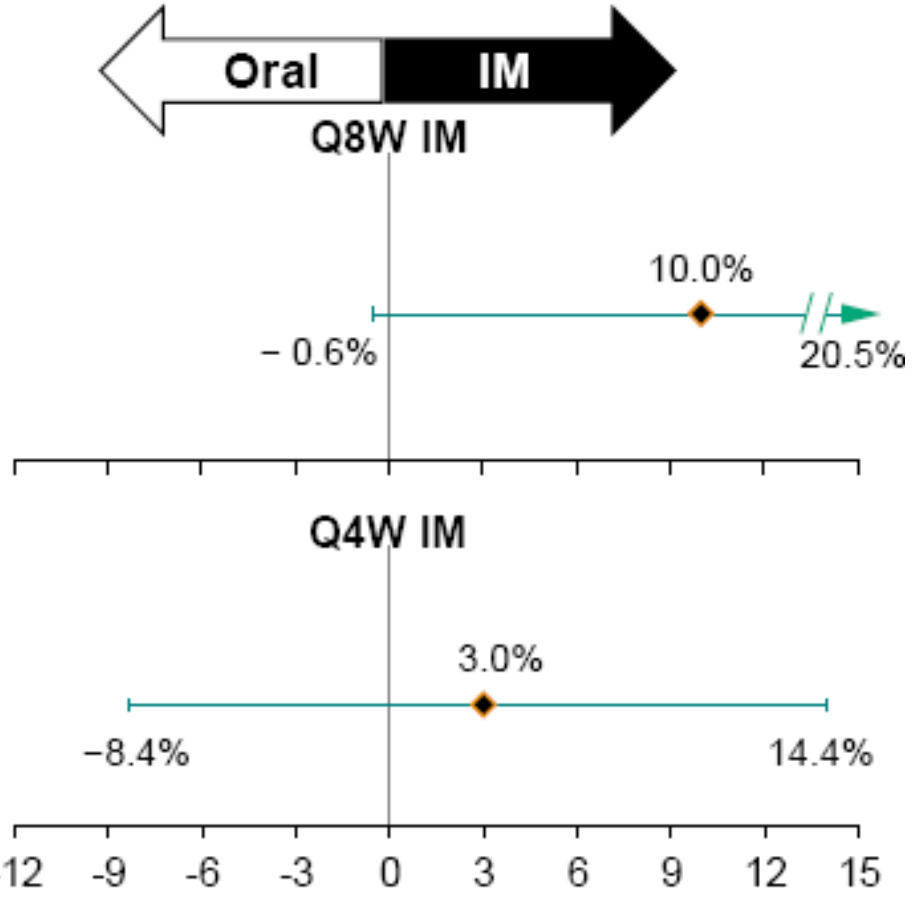


LATTE-2: Induction with CAB + NRTIs followed by LA CAB + RPV Maintenance w96

Virologic outcomes



Treatment differences (95% CI)



CAB, cabotegravir; CI, confidence interval; IM, intramuscular; ITT-ME, intent-to-treat maintenance exposed; LA, long acting; NRTI, nucleoside reverse transcriptase inhibitor; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB; Margolis D et al. Lancet 2017.

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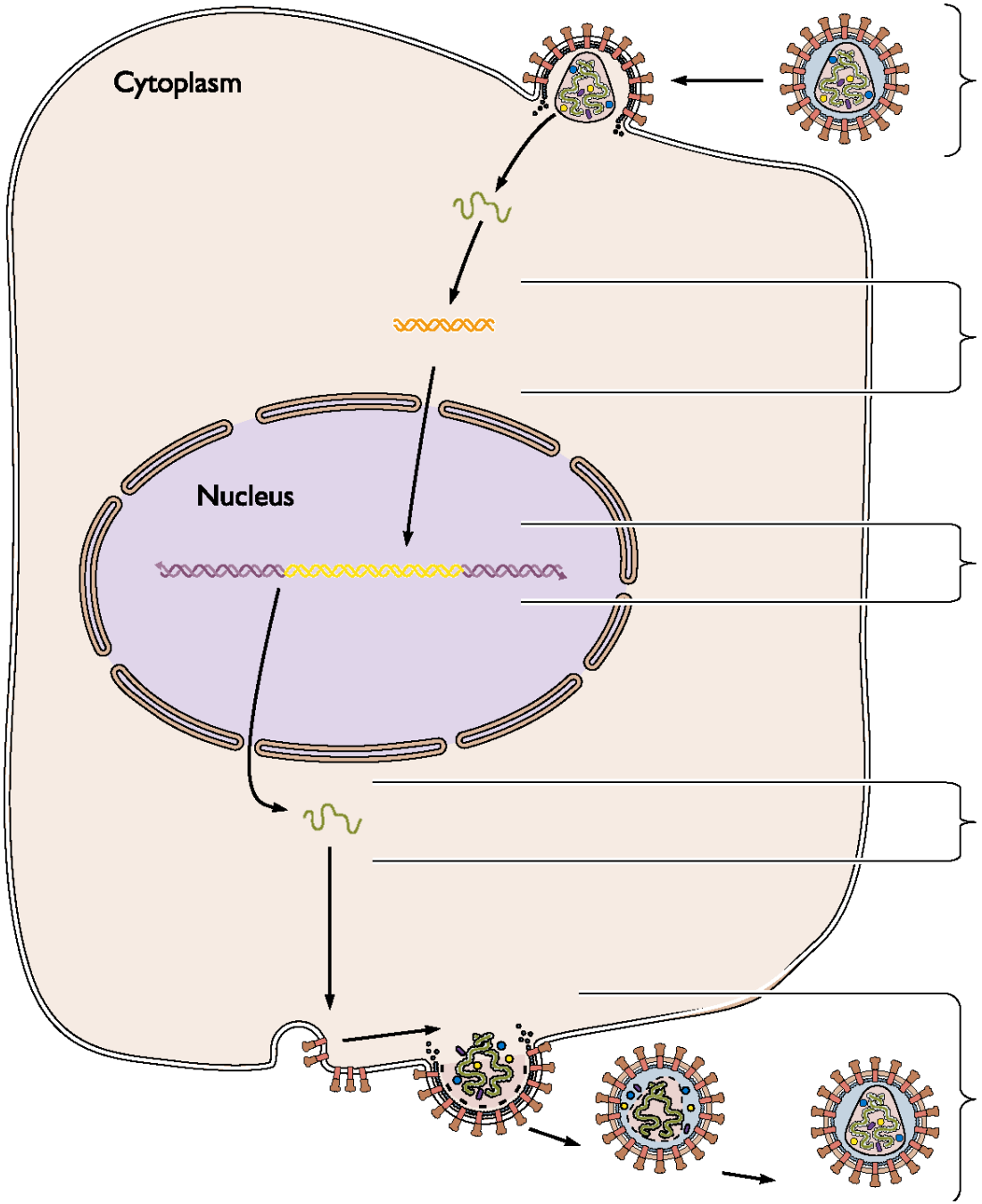


Cell attachment, fusion, and entry
- CD4 derivatives
- Polymers
- Plant lectins
- Bicyclams
- Chemokine analogs

Reverse transcription
- Nucleoside analog reverse transcriptase inhibitors: zidovudine, didanosine, zalcitabine, stavudine, lamivudine, acyclic nucleoside phosphonates
- Nonnucleoside reverse transcriptase inhibitors: nevirapine, delavirdine, loviride, efavirenz

Integration
- Integrase inhibitors

Transcription and posttranscriptional processing
- Tat inhibitors

Virion packaging and budding
- Protease inhibitors: saquinavir, ritonavir, indinavir, nelfinavir
- Nucleocapsid inhibitors

Fostemsavir

- **Profarmaco di temsavir**
- **Inibitore dell'attacco con il recettore CD4**

- ***Legame con gp120 envelope HIV***
- **Polimorfismi gp120 di HIV1/ non M resistenza naturale**

- **Pazienti multifalliti con virus multiresitenti**

- **Fostemsavir 1200mg/die per os + OBR**

BRIGHTE: Efficacy and Safety Outcomes With Fostemsavir OBR in Heavily Treatment–Experienced Patients

- Primary endpoint: adjusted* mean HIV-1 RNA $\log_{10}$ change at Day 8 in randomized ITT-E population
  - FTR vs PBO: -0.79 vs -0.17 (difference: -0.625; 95% CI: -0.810 to -0.441; *P* < .0001)
- **Randomized cohort (N = 272), Wk 24 virologic response rates**
  - **HIV-1 RNA < 40 copies/mL: 54%**
  - **HIV-1 RNA < 200 copies/mL: 71%**
  - **HIV-1 RNA < 400 copies/mL: 77%**
- **Most common grade 2-4 tx-related AEs were nausea, diarrhea, headache, vomiting, fatigue, asthenia**

Wk 24 Safety Event, n (%)	Randomized Cohort (n = 270)	Nonrandom. Cohort (n = 99)	All Treated Patients (N = 371)
Any event	243 (90)	93 (94)	338 (91)
Grade 2-4 tx-related AE	49 (18)	19 (19)	68 (18)
AE leading to d/c	12 (4)	9 (9)	21 (6)
Serious AE	73 (27)	37 (37)	112 (30)
Tx-related serious AE	6 (2)	3 (3)	9 (2)
Death†	8 (3)	9 (9)	17 (5)

Kozal M, et al. EACS 2017. Abstract PS8/5.

Slide credit: clinicaloptions.com

*Mean adjusted by HIV-1 RNA on Day 1. †12 of 17 deaths from AIDS-related events; 1 death from recurrent atypical mycobacterial infection due to IRIS.

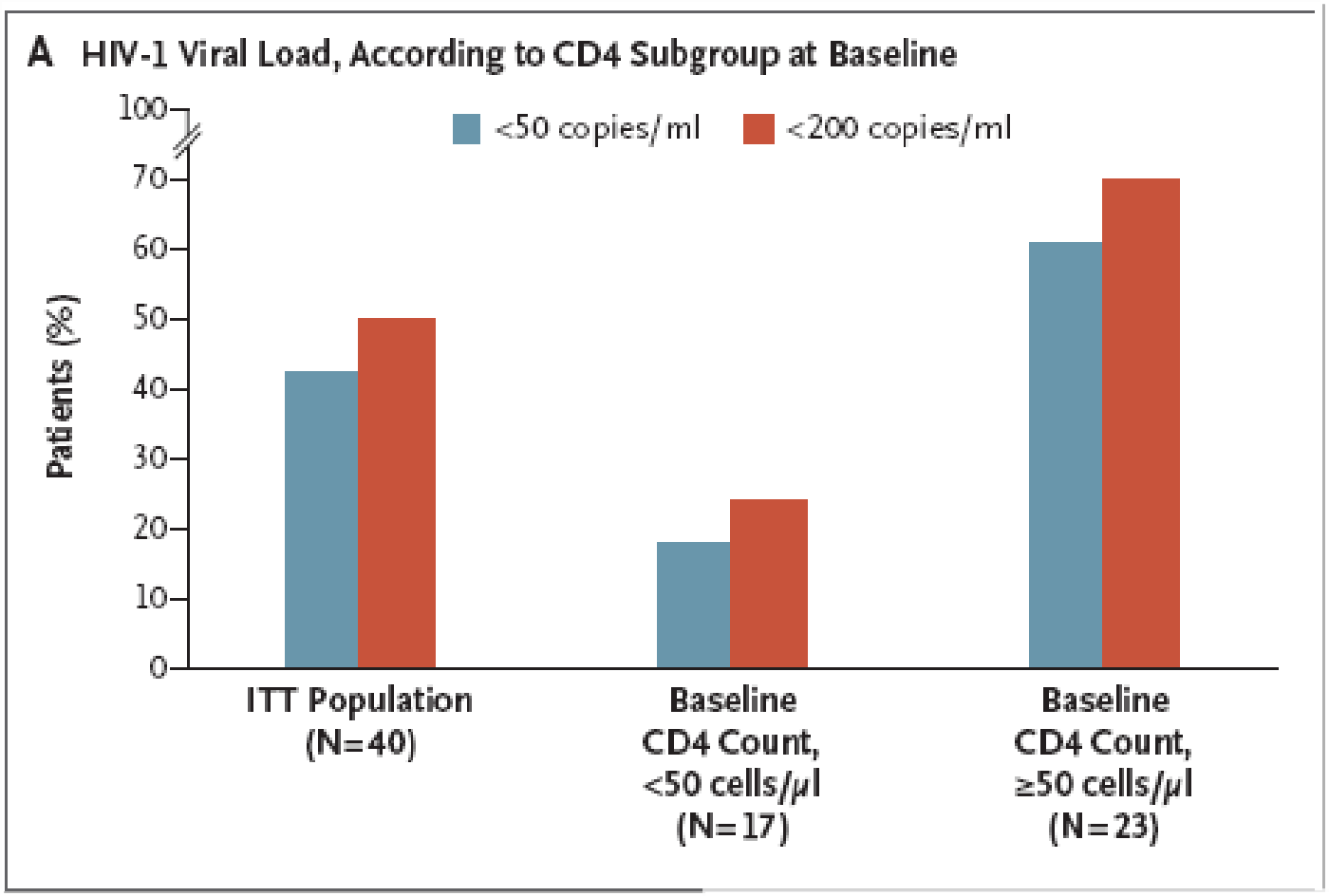
Ibazulimab (*Trogarzo*)

- **Anticorpo monoclonale umanizzato IG4**

- ***Si lega al recettore CD4 del linfocito T***
- **Blocca l'ingresso del virus impedendo i cambiamenti di conformazione post legame CD4-gp120**

- **Parenterale: 2000mg e.v. seguiti da 800 mg ogni 2w**

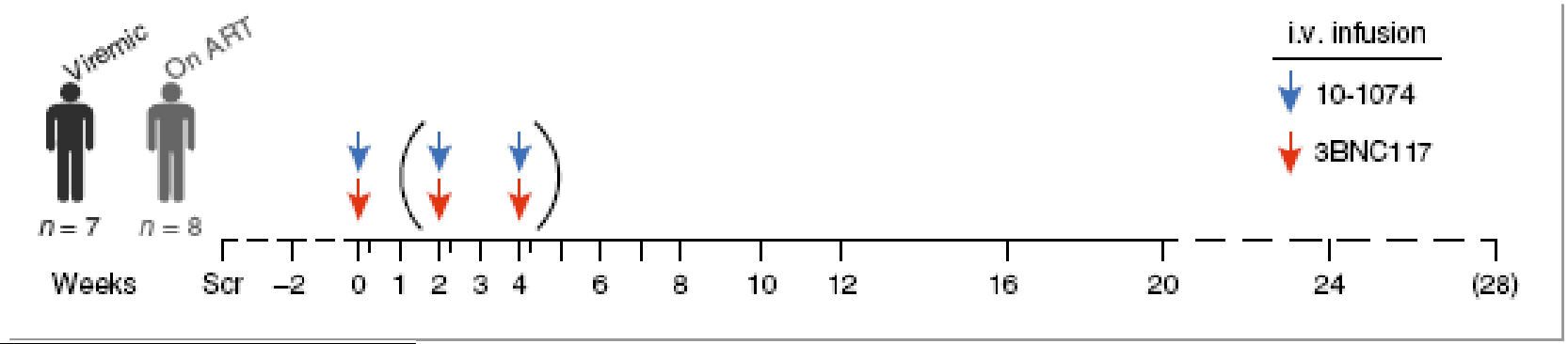
- **Pazienti multifalliti con virus multiresitenti**

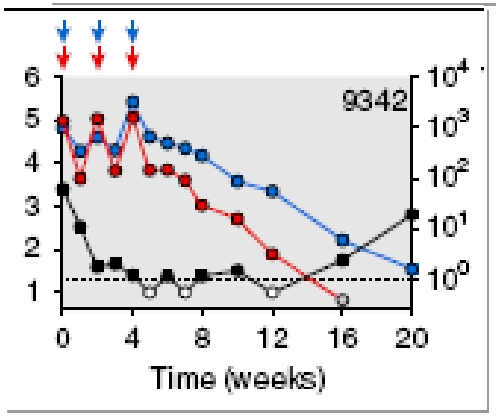

A HIV-1 Viral Load, According to CD4 Subgroup at Baseline
<50 copies/ml
<200 copies/ml
Patients (%)
100
70
60
50
40
30
20
10
0
ITT Population (N=40)
Baseline CD4 Count, <50 cells/μl (N=17)
Baseline CD4 Count, ≥50 cells/μl (N=23)

Safety and antiviral activity of combination HIV-1 broadly neutralizing antibodies in viremic individuals

Yotam Bar-On[1]

NATURE MEDICINE





HIV-1 VL (copies per ml)
3BNC117
10–1074

3BNC117 target recettore CD4

10-1074 target envelope HIV

4 HIV viremici HIV RNA -2.05 log/ml nei 3 mesi successivi


K·Haring
STOP AIDS