10° CONGRESSO NAZIONALE
ICAR
Italian Conference on AIDS and Antiviral Research

associazione NADIR onlus SPECIAL EVENT

NADIR'S 20th: Is Italy focused in achieving the 4th 90?

Chairs: F. Schloesser (Roma), S. Vella (Roma)

Are Italian multi-class resistant patients becoming a neglected population?

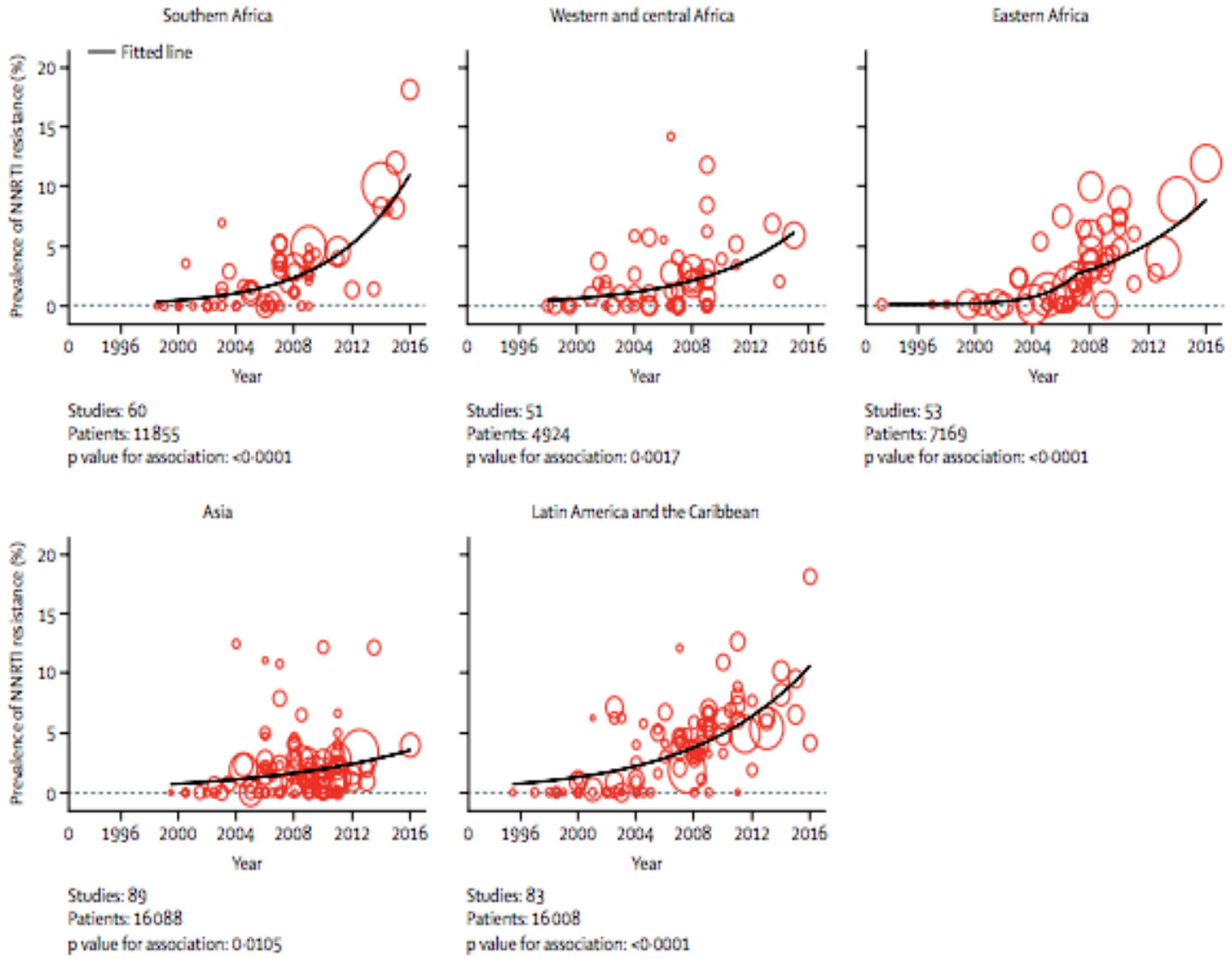
Antonella Castagna

Disclosures

I have received funding for Advisory Boards, Speaker Panels and for preparation of educational materials from the following:

Gilead Sciences
ViiV Healthcare
Janssen-Cilag
Merck Sharp & Dohme

HIV-1 drug resistance in low-income and middle-income countries

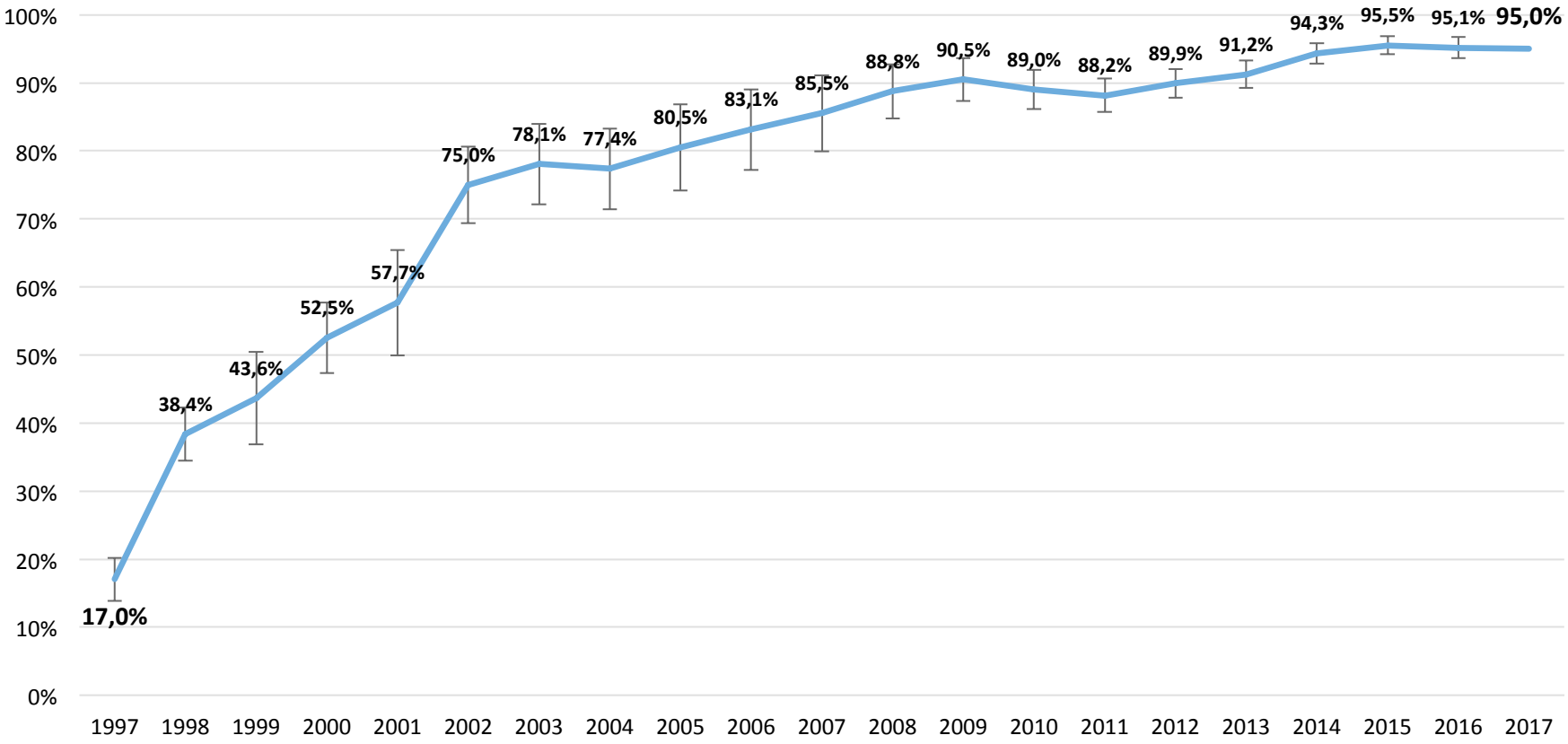


Some LMICs might be reaching WHO's 10% threshold for changing first-line non-nucleoside reverse NNRTI based ART to integrase inhibitor-based ART. Gupta J LID 2018

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

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

Proportion of patients with a VL<=80 copies/mL at 12 months from starting their first ART regimen by calendar year of initiation



Jan 2018 Report

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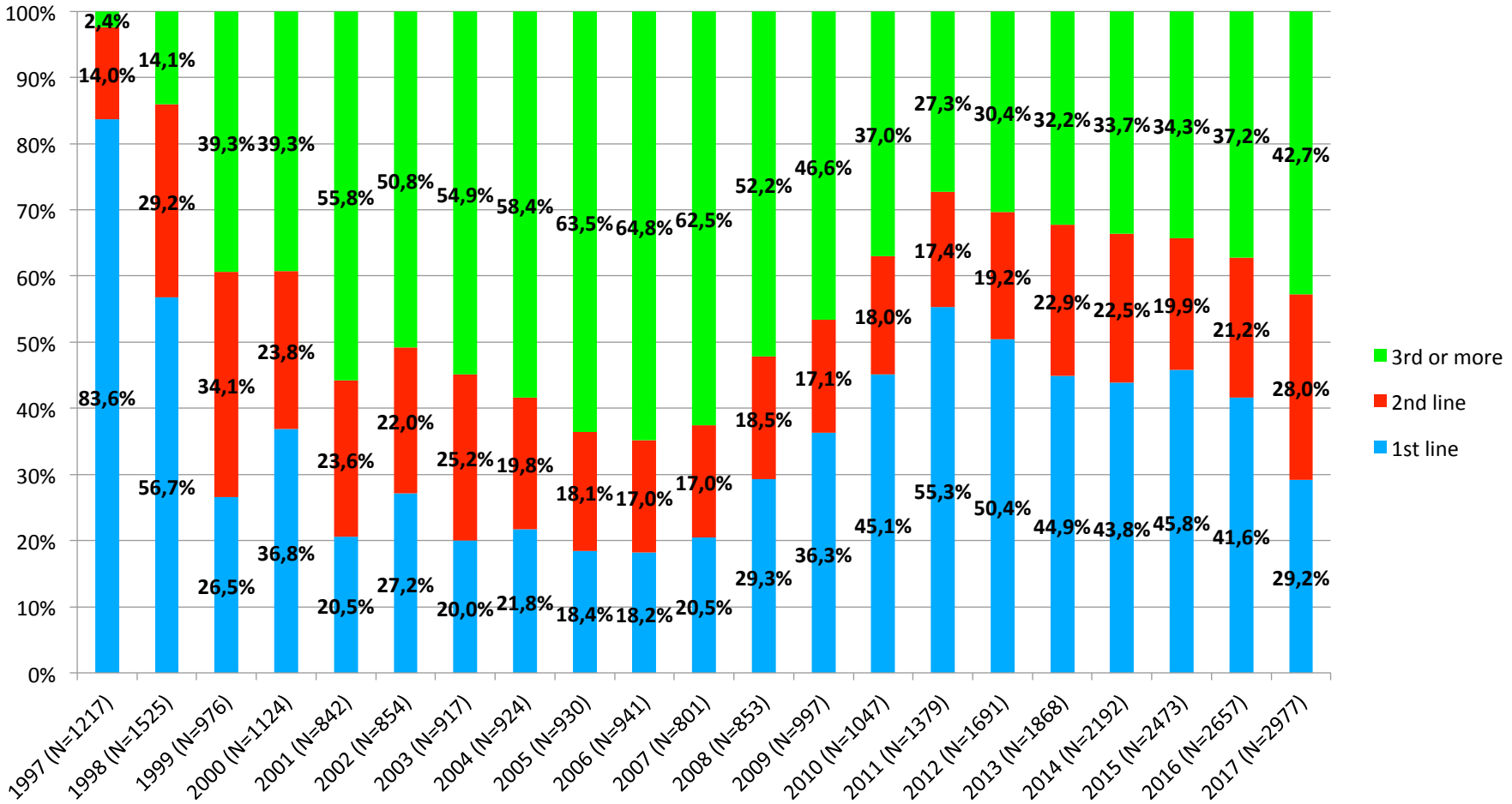
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Proportion of patients under different ART regimen lines according to calendar year



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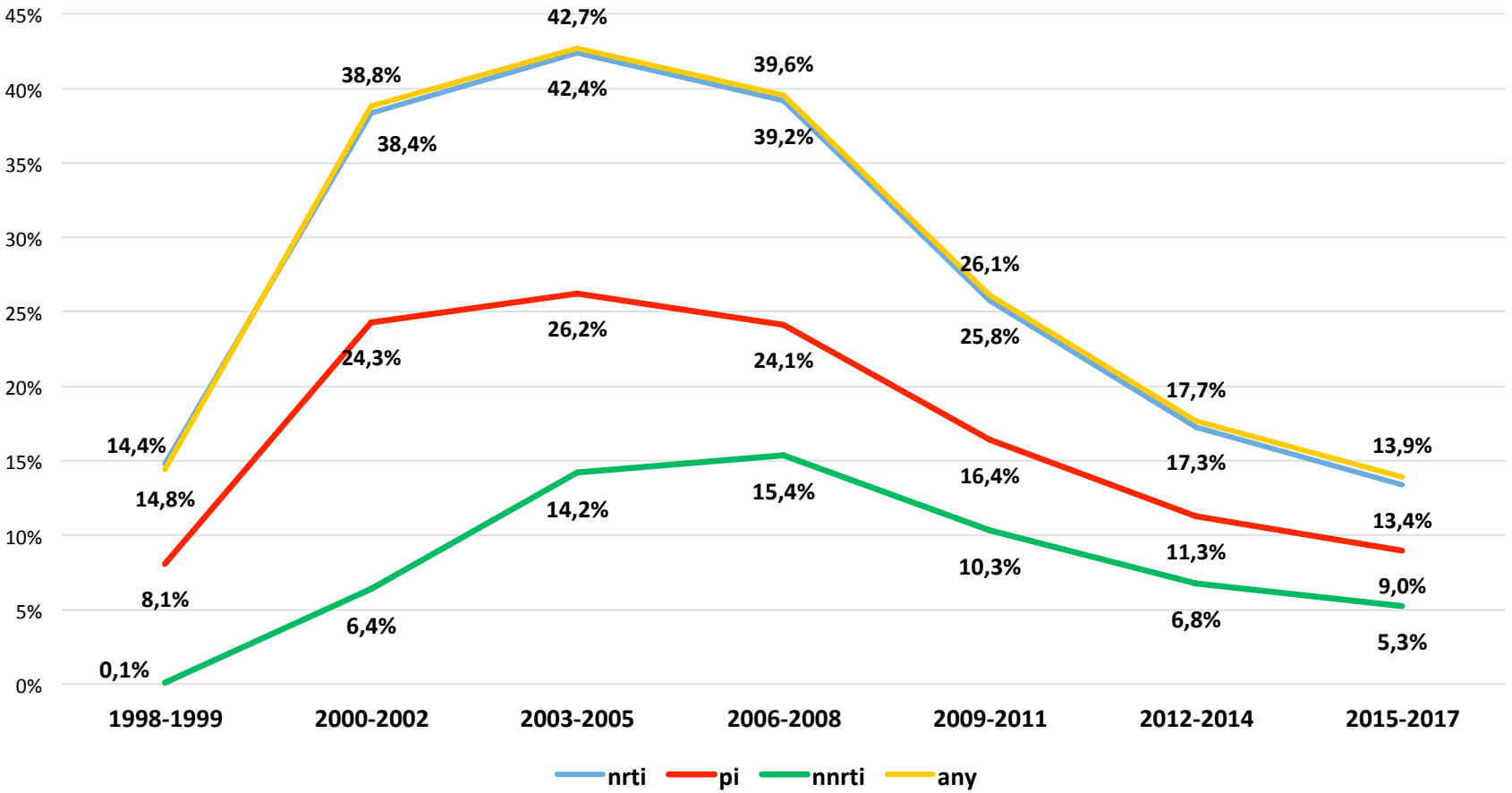
ITALIAN COHORT NAIVE ANTIRETROVIRALS

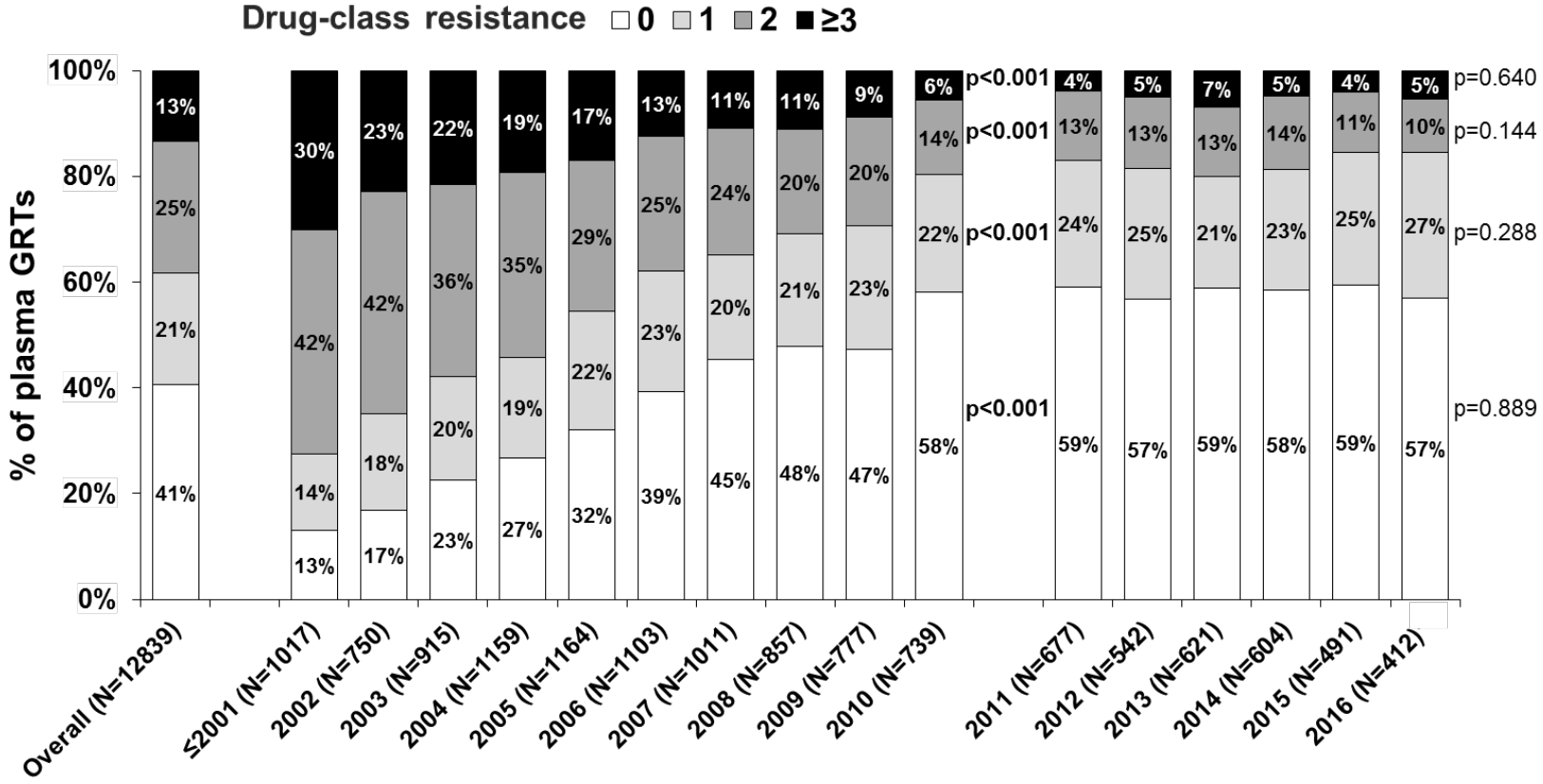
Proportion with evidence of previous virological failure to specific drug classes for patients in in follow up, according to calendar period



Jan 2018 Report

Beyond 2010, prevalence of resistance remained stable from 2011 to 2016.

Prevalence of resistance to any drug-class among ART-experienced HIV-1 infected patients with virologic failure over the years.



Analysis performed on 12839 sequences of protease, reverse transcriptase or integrase, from drug-experienced HIV-1 infected patients (N=6147). P-values by Chi-squared test for trend; statistically significant tests ($p<0.05$) are indicated in boldface. Sequences performed from 1999 to 2001 were grouped.

Armenia et al., oral presentation at EACS 2017 & IDRW 2017

Multiple drug class-wide resistance associated with poorer survival after treatment failure in a cohort of HIV-infected patients

Mauro Zaccarelli[a], Valerio Tozzi[a], Patrizia Lorenzini[a], Maria P. Trotta[a], Federica Forbici[b], Ubaldo Visco-Comandini[a], Caterina Gori[b], Pasquale Narciso[a], Carlo F. Perno[b] and Andrea Antinori[a] for the Collaborative Group for Clinical Use of HIV Genotype Resistance Test (GRT) at National Institute for Infectious Diseases 'Lazzaro Spallanzani'

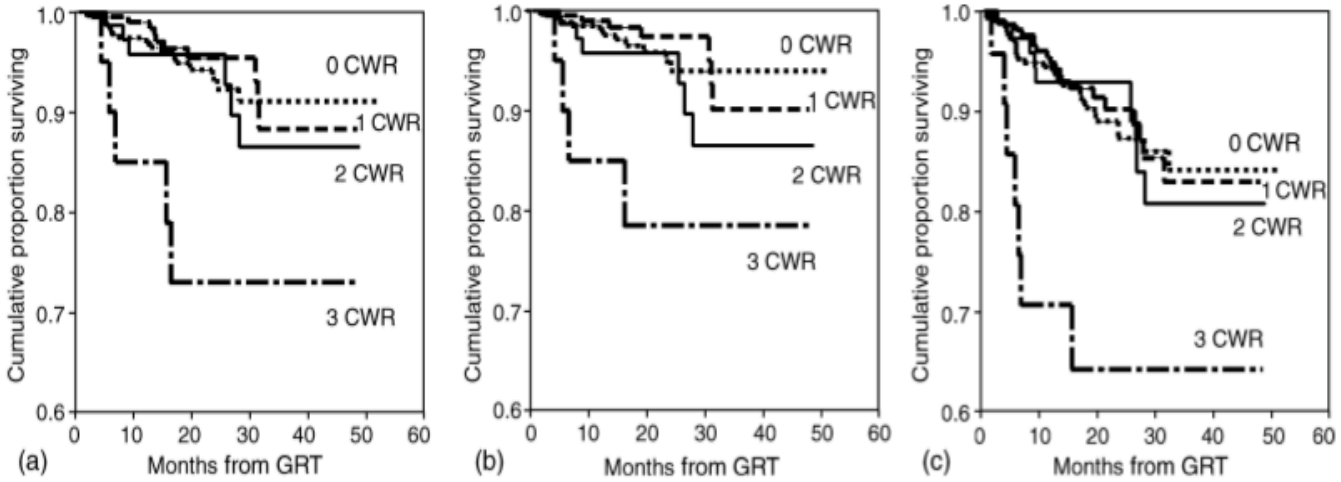


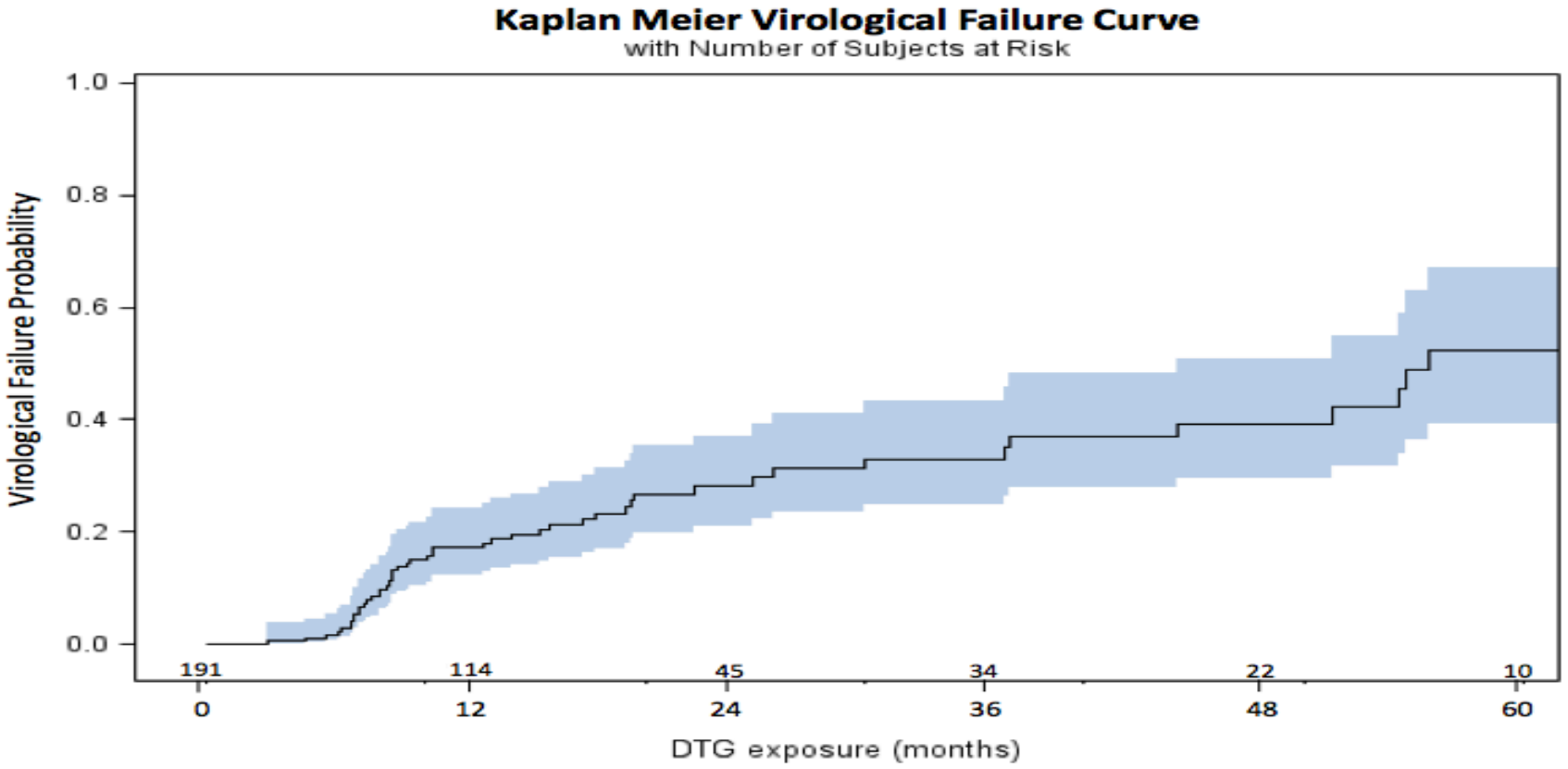
Fig. 3. Kaplan–Meier cumulative probability of surviving (a), an AIDS-related death (b) or surviving or remaining free from AIDS events (c) in patients with none, one, two or three three CWR. (a,b) At times 0, 1, 2 or 3 years, the numbers of patients at risk with 0 CWR were 306, 226, 100, 31, respectively; with 1 CWR were 215, 168, 69, 25, respectively; with 2 CWR were 78, 62, 38, 17, respectively; and with three CWR were 24, 16, 12, 7, respectively. (c) At times 0, 1, 2 or 3 years, the numbers of patients at risk with 0 CWR were 306, 218, 95, 28, respectively; with 1 CWR were 215, 163, 67, 24, respectively; with 2 CWR were 78, 60, 36, 15, respectively; and with three CWR 24, 13, 9, 5, respectively. CWR, class-wide resistance; GRT, genotypic resistance testing.

AIDS 2005

Long-term efficacy of dolutegravir in treatment-experienced failing subjects with HIV-1 integrase strand inhibitor (INSTI)-resistant virus

Antonella Castagna[1*], Micol Ferrara[2], Laura Galli[3], Laura Comi[4], Gaetana Sterrantino[5], Giovanni Cenderello[6], Mauro Zaccarelli[7], Emanuele Focà[8], Andrea Roncadori[9], Adriano Lazzarin[3] on behalf of the PRESTIGIO Study Group†

JAC 2017

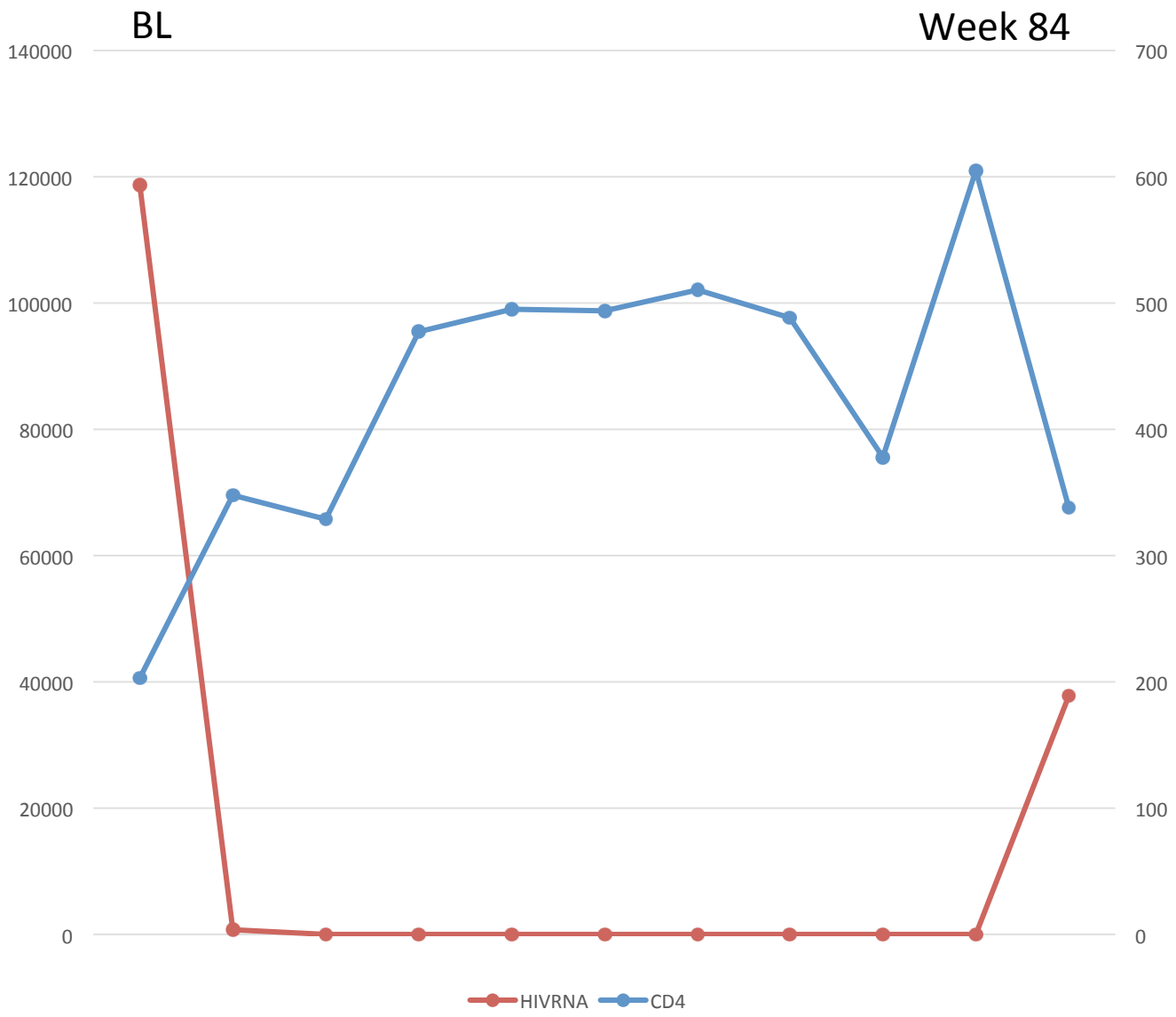


VF probabilities were 17%, 28%, 33%, 39% and 52% at 12, 24, 36, 48, 60 months since DTG 50mg BID start, respectively.

Prevent failure on those on effective salvage therapy

Maria, 34 anni
Trasmissione verticale
HTE-MDR
Holding with DTG DRV

DTG 50 mg BID
MVC 150 mg
ATV/cobi 300/150 mg
TAF/FTC
Farmaco sperimentale



Transmission of HIV-1 drug resistance mutations within partner-pairs: A cross- sectional study of a primary HIV infection cohort

Author summary

Why was this study done?

- Previous studies have shown that virus factors like replication capacity (the ability of a virus to multiply) can impact the likelihood of HIV-1 transmission.
- Little is known about whether HIV-1 drug-resistance mutations impact the likelihood of HIV transmission.

What did the researchers do and find?

- We identified 31 participants with primary HIV-1 infection and their partners.
- We found that five transmitting partners, none of whom had taken antiretroviral (ARV) therapy at the time of specimen collection, had 10 drug resistance mutations that made up more than 95% of the transmitter's viral population; all of these mutations were found in their recipient partners.
- We identified another 14 mutations at low frequencies (1.0%–11.8%) in nine transmitting partners; two of these low frequency mutations were also detected in two recipient partners.

What do these findings mean?

- Our findings suggest that HIV-1 drug resistance may be spread to and by people who have never taken ARV medications.

Stekler JD Plos Med 2018

We describe the third case report of seroconversion with multidrugresistant (MDR)-HIV despite pre-exposure prophylaxis.

A 34 year-old white MSM started daily FTC/TDF in February 2016 after being provided 11 refills

In March 2017, he developed fevers, chills, myalgias and was assessed, but no HIV test was sent

In April 2017, he presented for evaluation of anal condylomata, at which visit an automated HIV antigen/antibody test was sent and was reactive (day 0).

On day 2, his HIV-1 RNA was 27 316 copies/ml, and genotyping subsequently revealed significant mutations in the reverse transcriptase gene, including M184V, K65R , K70T, 103N mutation

Given his infection with a MDR virus, the patient was started on dolutegravir, rilpivirine, and darunavir/cobicistat, beginning on day 13.

Plasma HIV-1 RNA decreased to less than 20 copies/ml by day 66, at which point his regimen was simplified to rilpivirine and dolutegravir.

Thaden JT et al, AIDS 2018

PRESTIGIO

POPOLAZIONE

Il registro Italiano PRESTIGIO include i pazienti seguiti regolarmente secondo i principi di buona pratica clinica nei centri italiani di Malattie Infettive di tutte le regioni italiane e con le seguenti caratteristiche:

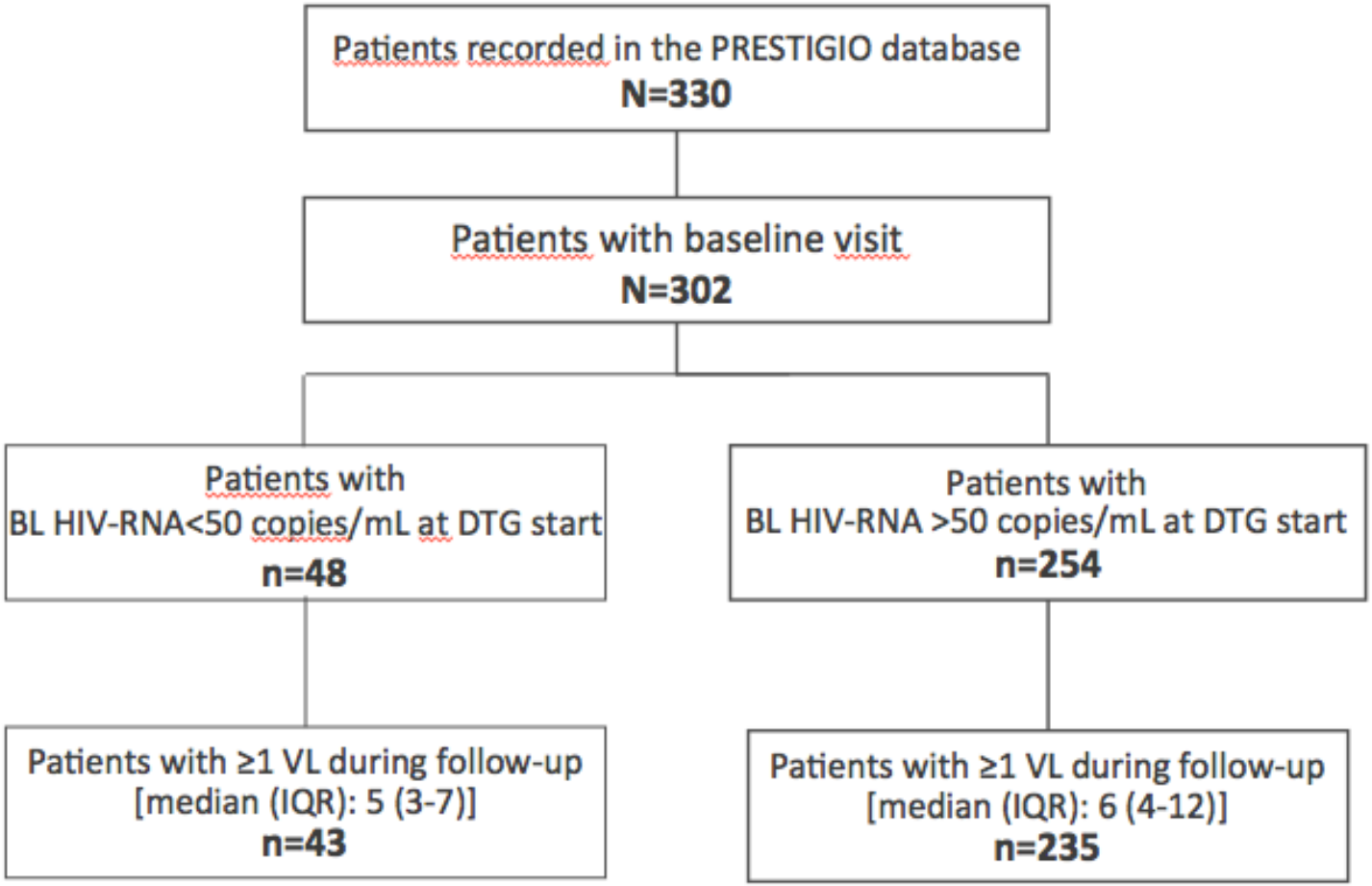
- soggetti con infezione da virus HIV-1;
- età >14 anni;
- resistenza documentata alle 4 classi di farmaci antiretrovirali (NRTI, NNRTI, PI, INI), definita come resistenza (almeno intermedia) ad almeno uno dei farmaci di ciascuna classe secondo l'algoritmo di Stanford. La resistenza può essere documentata sia al momento dell'inclusione nello studio o documentata precedentemente, nel corso della storia terapeutica del paziente.

PRESTIGIO

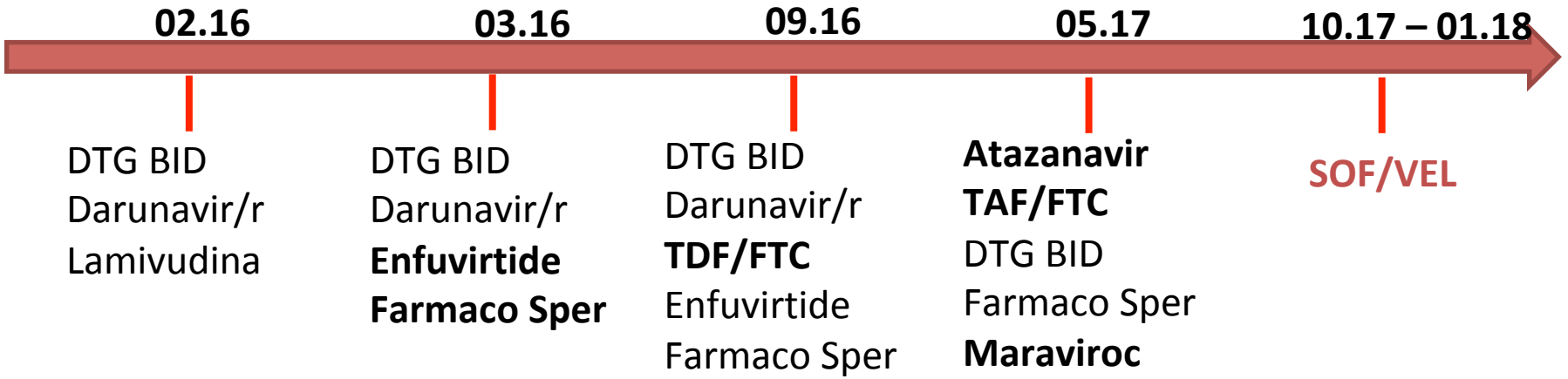
Aggiornamento status centri partecipanti registro

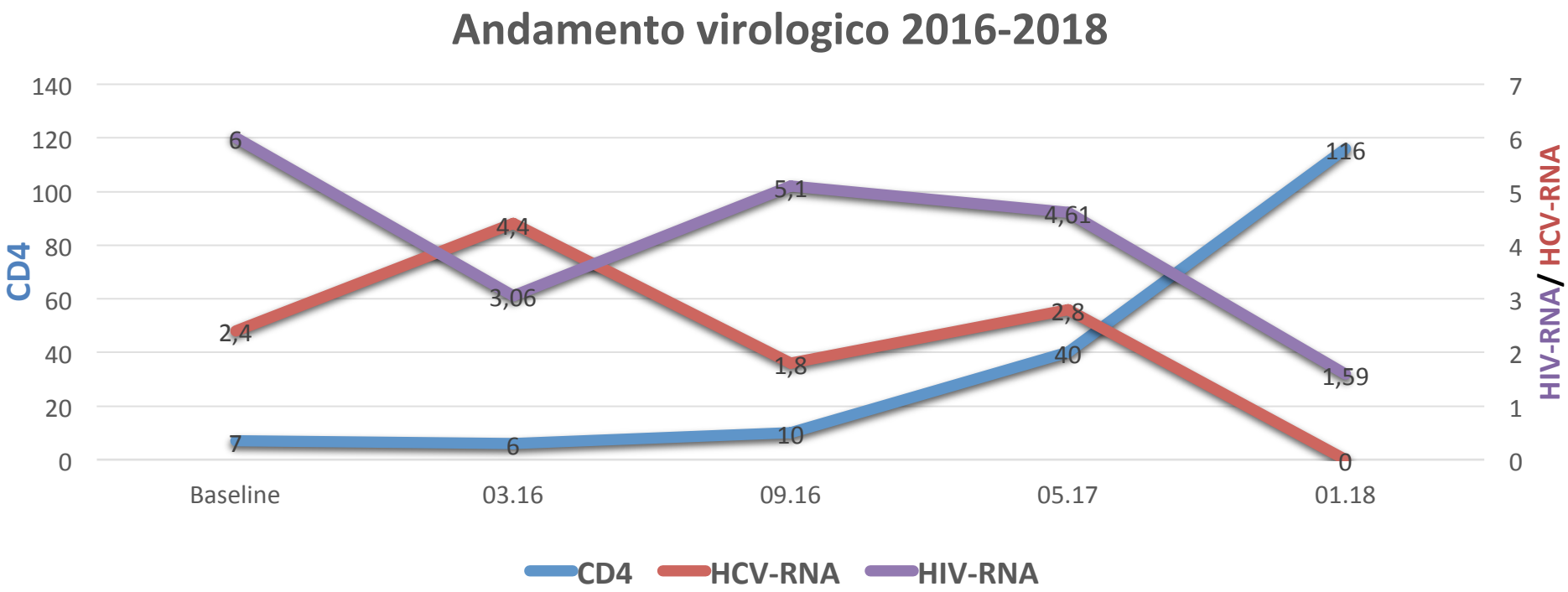
- Approvazione del CE e contratto firmato
- In attesa di approvazione del CE
- Approvazione del CE e contratto da firmare
- Parere sospensivo CE, in attesa di presa d'atto

PRESTIGIO: patients disposition (19 january 2018)



Ferrara M. et al, ICAR 2018





Proper managing of those with limited therapeutic options

#449LB

LONG-ACTING IBALIZUMAB IN PATIENTS WITH MULTI-DRUG RESISTANT HIV-1: A 24-WEEK STUDY

S. LEWIS[1], J. FESSEL[2], B. EMU[3], S. SCHRADER[4], P. KUMAR[5], G. RICHMOND[6], S. WEINHEIMER[1], C. MARSOLAIS[7]

[1]TaiMed Biologics, Irvine, CA, [2]Kaiser Foundation Res. Inst., San Francisco, CA, [3]Yale School of Medicine, New Haven, CT, [4]Schrader Clinic, Houston, TX, [5]Georgetown University, Washington, DC, [6]Gary Richmond, PA, Fort Lauderdale, FL, [7]Theratechnologies, Montreal, Canada.

Methods

TMB-301 is a single arm, 24-week study of IBA plus optimized background regimen (OBR) in treatment-experienced patients infected with MDR HIV-1.

Patients receiving their current failing ARV therapy, or no therapy, were monitored during a 7-day control period. Thereafter, a loading dose of 2,000 mg of intravenous (IV) IBA was the only ARV agent added to their regimen for 7 days. IBA was continued at doses of 800 mg IV every 2 weeks through 24 weeks on study treatment.

The primary efficacy endpoint was the proportion of patients achieving a ≥ 0.5 $\log_{10}$ decrease in HIV-1 RNA 7 days after initiating IBA therapy (Day 14 of study). OBR was initiated at Day 14.

Secondary endpoints included proportion of patients with RNA HIV-1 levels <50 and <200 copies/mL and mean change from Baseline in viral load and $CD4^+$ T cell count at Week 24 as well as an assessment of safety and tolerability.

#449LB

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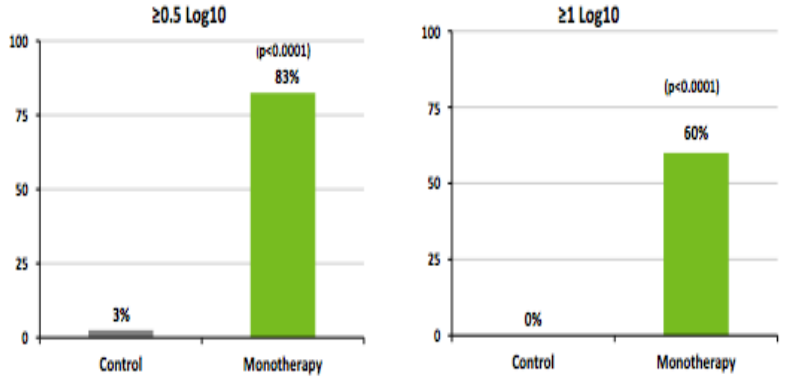
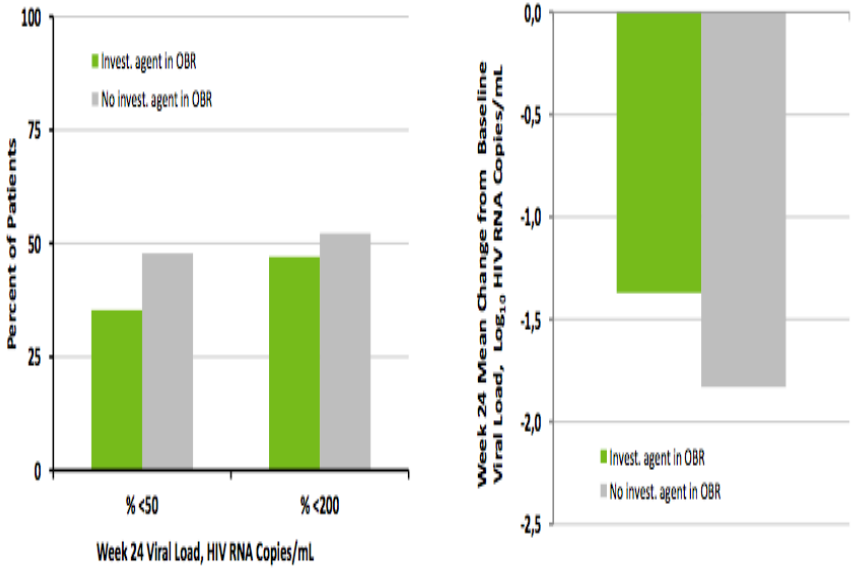
Efficacy at Day 14

Following 2000 mg loading dose of IBA (Day 7):



- Mean and median VL decrease was 1.1 $\log_{10}$ (p<0.0001)

Efficacy with (n=17) or without (n=23) investigational agent in OBR



Trogarzo™ is indicated for the treatment of multidrug-resistant HIV-1 infection. Image courtesy of Theratechnologies.

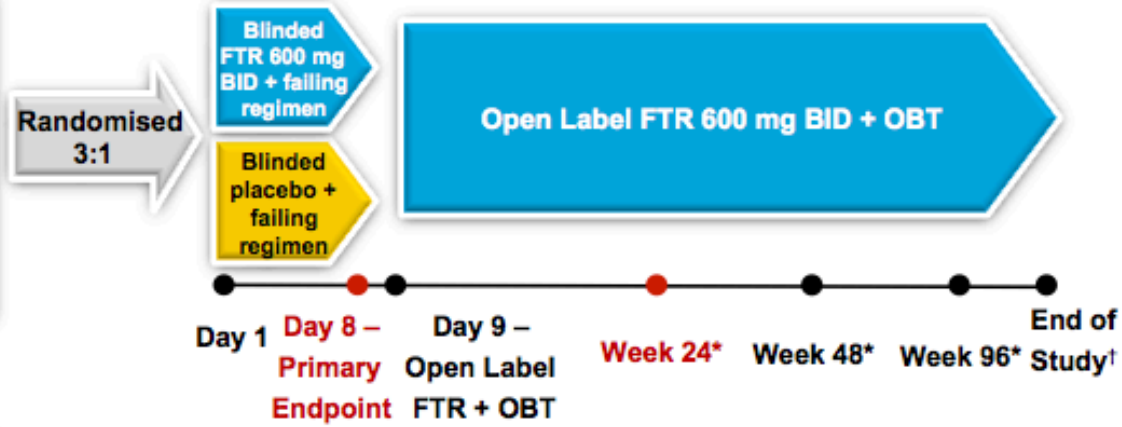
Study Design

BRIGHTE

BRIGHTE is an ongoing Phase 3 randomised, placebo-controlled, double blind trial

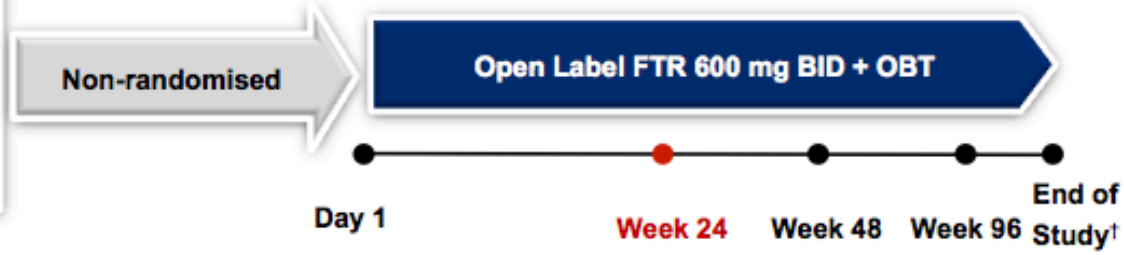
Randomised Cohort §:
HTE participants failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 1 or 2 ARV classes remaining & ≥1 fully active & available agent per class
- Unable to construct viable regimen from remaining agents



Non-randomised Cohort §:
HTE participants, failing current regimen with confirmed HIV-1 RNA ≥ 400 c/mL and:

- 0 ARV classes remaining and no remaining fully active approved agents‡



Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

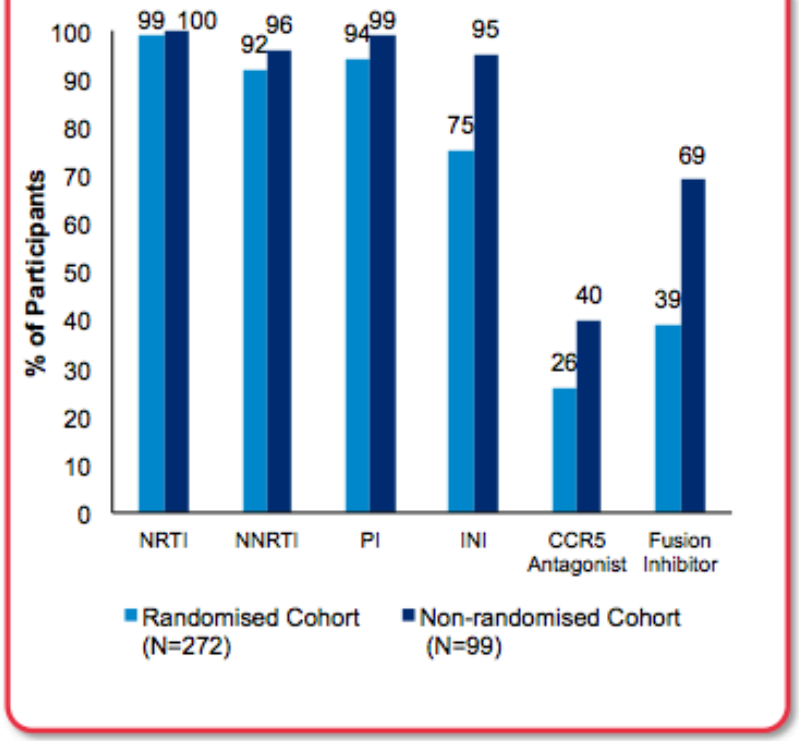
BRIGHTE Baseline Characteristics

Parameter	Randomised Cohort		Non-randomised Cohort	Total Treated Participants (N=371)
	Placebo BID (N=69)	FTR 600 mg BID (N=203)	FTR 600 mg BID (N=99)	
Age years, Median (range)	45 (19–66)	48 (18–73)	50 (17–72)	49 (17–73)
<50 years, [n(%)]	46 (67)	116 (57)	44 (44)	206 (56)
Sex, [n(%)]				
Male	57 (83)	143 (70)	89 (90)	289 (78)
Race, [n(%)]				
White	47 (68)	137 (67)	73 (74)	257 (69)
Black/African-American	18 (26)	42 (21)	23 (23)	83 (22)
HIV-1 RNA $\log_{10}$ c/mL, Median (range)	4.5 (1.6–6.9)	4.7 (1.6–6.4)	4.3 (1.6–6.6)	4.6 (1.6–6.9)
HIV-1 RNA c/mL, [n(%)]				
<400	7 (10)	14 (7)	4 (4)	25 (7)
400 – <1000	3 (4)	7 (3)	5 (5)	15 (4)
1000 – <100,000	35 (51)	126 (62)	75 (76)	236 (64)
≥100,000	24 (35)	56 (28)	15 (15)	95 (26)
CD4+ cells/µL, Median (range)	100 (0–915)	99 (0–1160)	41 (0–641)	80 (0–1160)
CD4+ cells/µL, [n(%)]				
<50	23 (33)	74 (36)	54 (55)	151 (41)
50 – <200	26 (38)	76 (37)	25 (25)	127 (34)

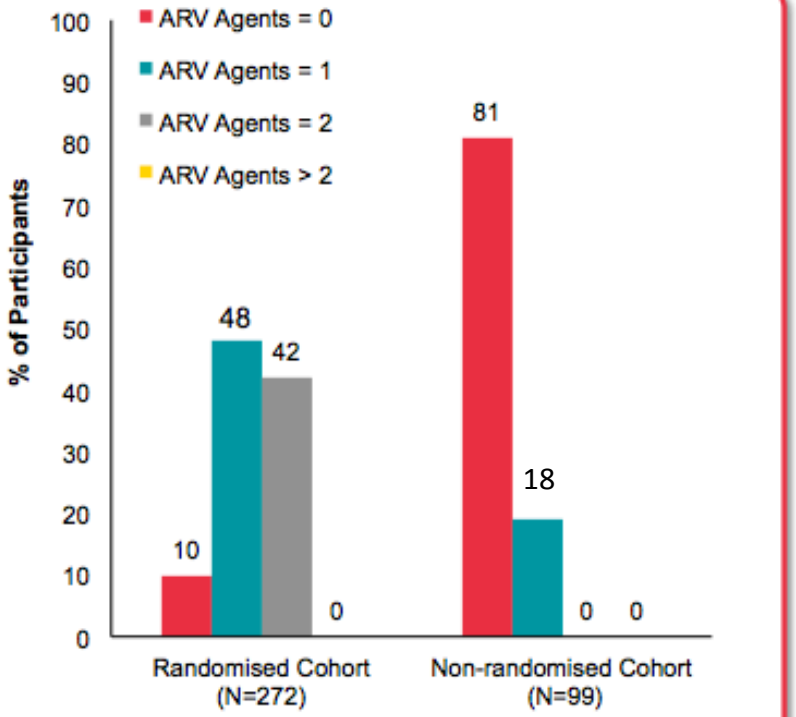
Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

Prior ARV Exposure and Initial OBT

Prior Exposure to ARVs



Fully Active and Available ARV Agents in Initial OBT



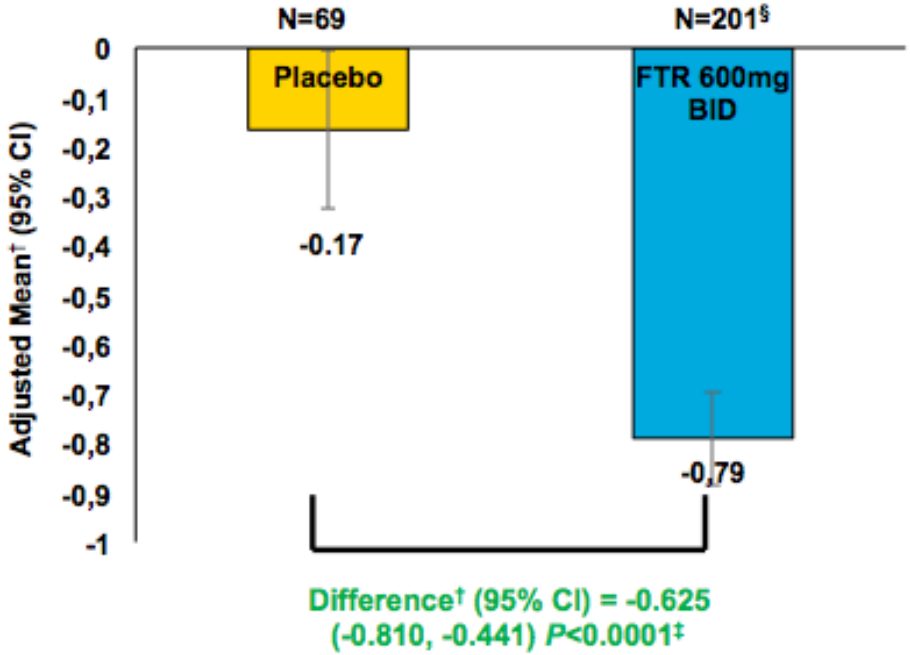
Baseline and emergent resistance analysis are currently ongoing; *13/19 received investigational ARV Ibalizumab. INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-NRTI; PI, protease inhibitor.

Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

BRIGHTE Primary Endpoint:

Adjusted Mean HIV-1 RNA log_{10} Change at Day 8

The primary endpoint was the adjusted mean plasma HIV-1 RNA log_{10} change from Day 1 at Day 8* in the Randomised Cohort (ITT-E)



FTR participants (ITT-E)

- >0.5 log_{10} decrease - **65%**
- >1 log_{10} decrease - **46%**

Subgroup: Baseline HIV-1 RNA >1000 c/mL (n=182), FTR demonstrated:

- Median decrease of **1 log_{10}**
- Adjusted mean decrease of **0.9 log_{10}**
- >0.5 log_{10} decrease - **68%**
- >1 log_{10} decrease - **50%**

*Day 8 window includes viral load between Day 6 to Day 10; participants who did not have a result in the Day 8 window had their last on treatment result carried forward (1 participant receiving FTR) or their Day 1 result carried forward (9 participants; 4 receiving placebo and 5 receiving FTR); †Mean adjusted by Day 1 log_{10} HIV-1 RNA; ‡hypothesis test: μFTR - μ placebo; *P* from Levene's test of homogeneity of variance 0.2082; §Two participants in the FTR arm, who had missing Day 1 HIV-1 RNA values, were not included in the analysis for the HIV-1 RNA log_{10} least squares mean change at Day 8.

ITT-E, intent to treat-exposed.

Kozal et al. EACS 2017; Milan, Italy. Oral PS8/5.

Investigational agents for treatment-experienced patients

Fostemsavir[1]

- Fostemsavir is an attachment inhibitor to gp120
- BRIGHTE: FTR in treatment-experienced, ≤2 active ARV classes (N=371)
- FTR mean HIV RNA decline of 0.79 $\log_{10}$ in 8 days functional monotherapy

Ibalizumab[2,3]

- Ibalizumab is a humanized monoclonal antibody to CD4 receptor
- TMB-301: ibalizumab in multi-drug resistant, treatment-experienced patients (N=40)[3]
- 83% achieved ≥0.5 $\log_{10}$ drop at Day 14

1. M Kozal, *et al.* EACS 2017, Milan, Italy; oral #PS8/5;
2. Lalezari J, *et al.* IDWeek 2016, New Orleans, LA, United States; abstract #LB-6;
3. Lewis S, *et al.* CROI 2017, Seattle, WA, United States; poster #449LB.