IL PAZIENTE HTE: ADERENZA E NUOVI TARGET TERAPEUTICI

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Consultancy for ViiV, MSD

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Who Are HTE People?

- Older people with HIV treated in early days of ART with less potent regimens that had low resistance barriers
- Younger people with perinatal HIV infection, now young adults
- Patients with MDR

HTE definitions

- HTE PWH with LTO defined as having 2 or less available classes with 2 or less active drugs per class based on genotypic data and cumulative antiretroviral resistance

Def1) A composite of 2 or more of the below will define those HTE adults living with HIV-1 infection:

1A) Current regimen indicative of HTE
Regimen includes ≥3 drugs, including one or more of the following: DTG BID or DRV BID or T20; ETV + DTG BID or MVC or boosted DRV BID or T20

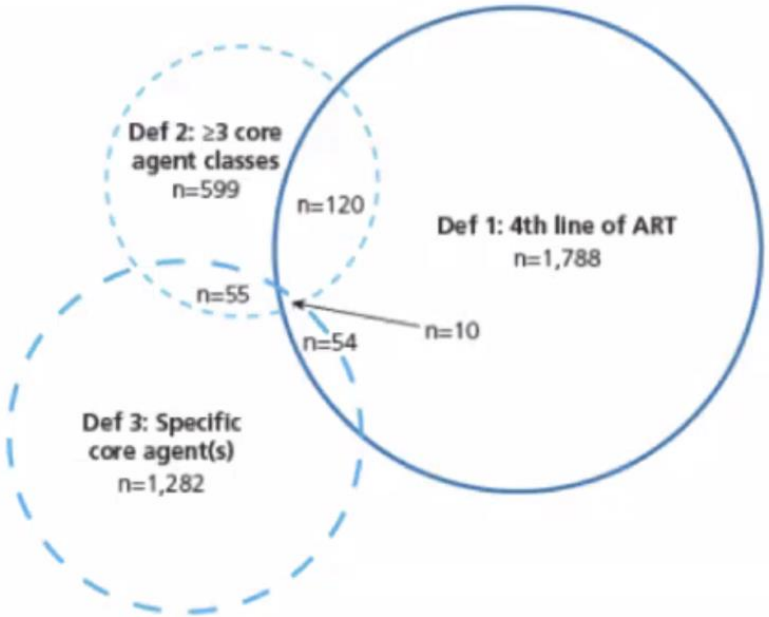
1B) At least 3 core ARV classes prior to current regimen
last drug regimen included ≥3 drugs

1C) Individuals who had at least 4 anchor agent switches at any previous time
with the 4th or subsequent regimen including one of the following: DTG BID or DRV BID or T20; ETV + DTG BID or MVC or boosted DRV BID or T20; ≥2 core agents + any other ARV;

1D) Virologic failure prior to class switch
Pts have recorded history of ≥3 virologic failure followed by a treatment switch (within 90 days)

Bajema. AIDS. 2020;34:2051; Lo Caputo S et al, ICAR 2021, OC56

HTE definitions



- PLWH with exposure to at least three core agent classes prior to their baseline regimen. Core agent classes included NNRTI, PI, INSTI, fusion inhibitors and CCR5 antagonists.
- PLWH on a regimen indicative of HTE:
  - -dolutegravir with twice daily dosing;
  - - darunavir with twice daily dosing;
  - - etravirine;
  - - both an INSTI and a PI;
  - - maraviroc;
  - - enfuvirtide

Two or less ARV drug classes with at least one active drug remaining	≤2 ARV drug classes with at least one active drug (or 2 active NRTIs) remaining, out of NRTIs, NNRTIs, PIs, or other ARVs (INSTIs, maraviroc, or enfuvirtide as a fourth combined class); NRTIs and PIs were only considered if recommended in EACS guidelines
At least 4 ART anchor agent switches	Individuals with ≥4 ART anchor agent switches
Regimen with at least 4 ARVs	Individuals who ever used a regimen with ≥4 ARVs
Composite definition for HTE	Everyone with GRT results and known resistance to the 3 original ARV classes (NRTIs, NNRTIs, and PIs), or else anyone who fulfilled the criteria for at least 2 of the 3 HTE definitions

Hsu et al., 22nd International AIDS Conference 2018; Hsu et al., BMC Infectious Diseases (2023); Pelchen-Matthews et al., J Acquir Immune Defic Syndr 2021.

4-ART classes resistance

- Estimated prevalence in Italy 1-3%
- To better characterize this population of PLWH-4DR and meet their needs, the Italian PRESTIGIO registry (39 participating centers, 229 PLWH enrolled) was established.

		Overall (n=229)
Age (years)		58,3 (53,6 – 61,6) min = 24,2 max = 81,3
Gender	Male	166 (72,5%)
	Female	63 (27,5%)
Nationality	Italian	210 (91,7%)
	Other	19 (8,3%)
Ethnicity	Caucasian	218 (95,2%)
	Black	9 (3,9%)
	Hispanic	2 (0,9%)

Data updated to March 1st, 2023

Prestigio Registry Update of March 1st, 2023

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journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

Prevalence of acquired resistance mutations in a large cohort of perinatally infected HIV-1 patients☆

R. Ungaro [1, †], L. Taramasso [1, 2, †], B. Bruzzone [3], I. Vicenti [4], L. Galli [5], V. Borghi [6], D. Francisci [7], M. Pecorari [8], A. Zoncada [9], A.P. Callegaro [10], E. Paolini [11], L. Monno [12], S. Bonora [13], A. Di Biagio [14, *] on behalf of the ARCA Study Group*

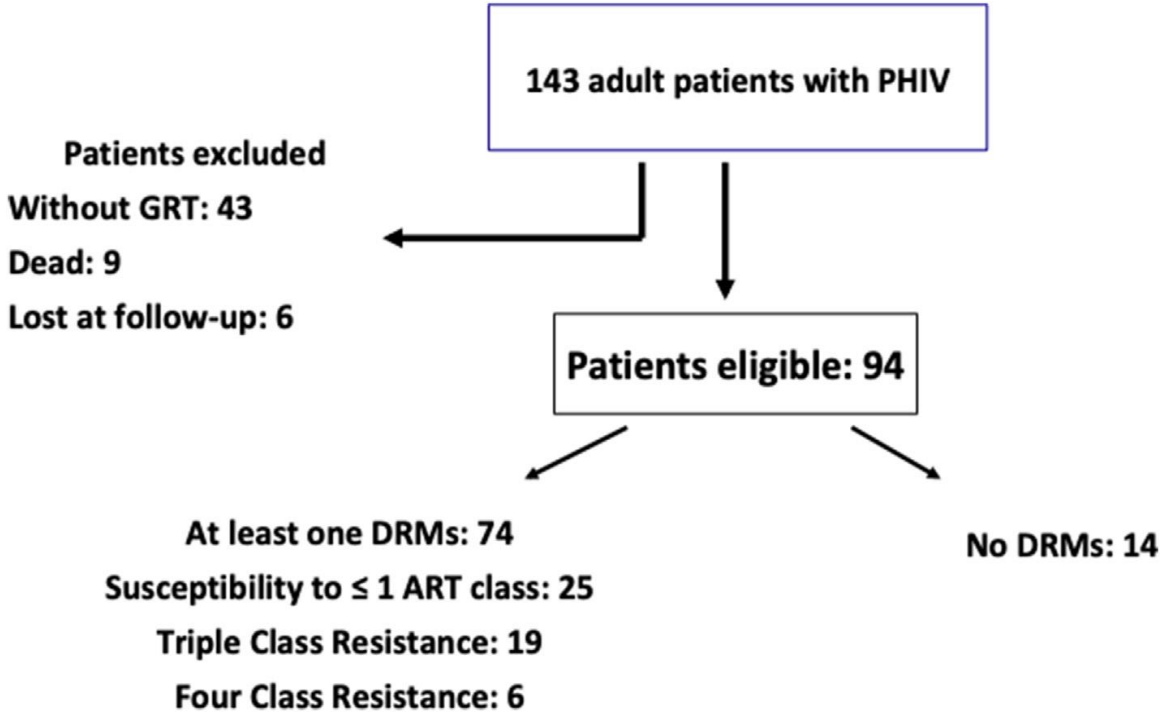


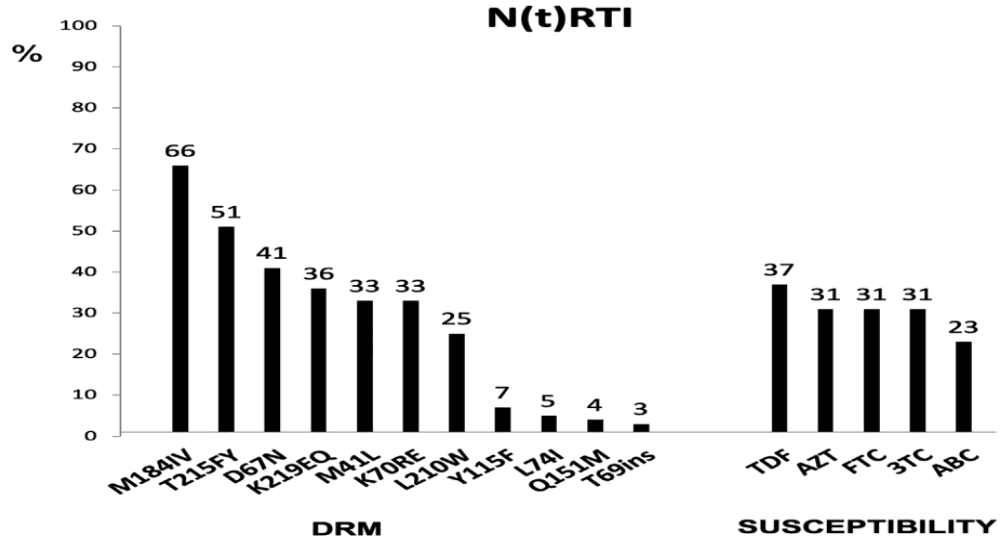
Fig. 1. Patient disposition. ART, antiretroviral therapy; DRM, drug resistance mutation; GRT, genotypic resistance test; PHIV, perinatal HIV-1.

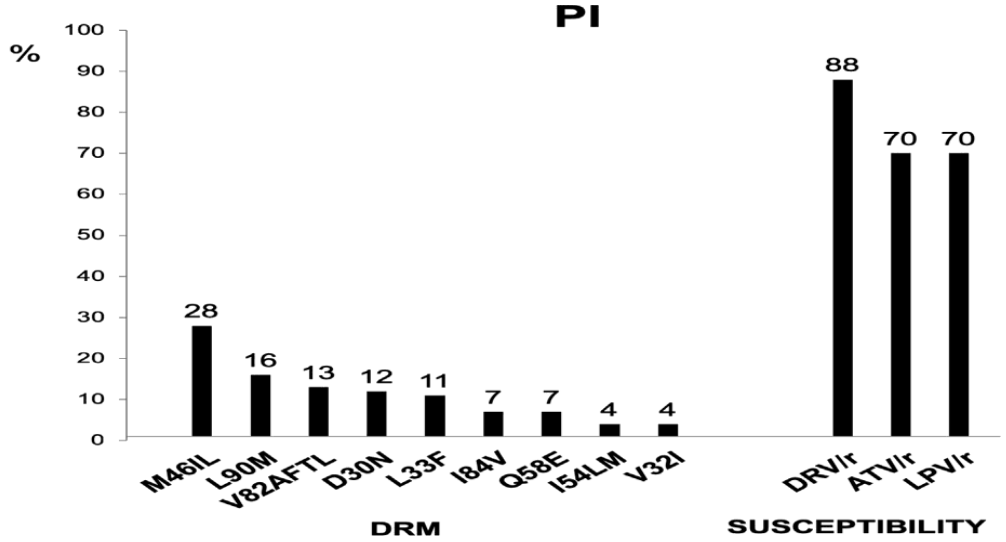
Table 1
Demographics of 94 perinatal HIV-infected patients in ARCA cohort

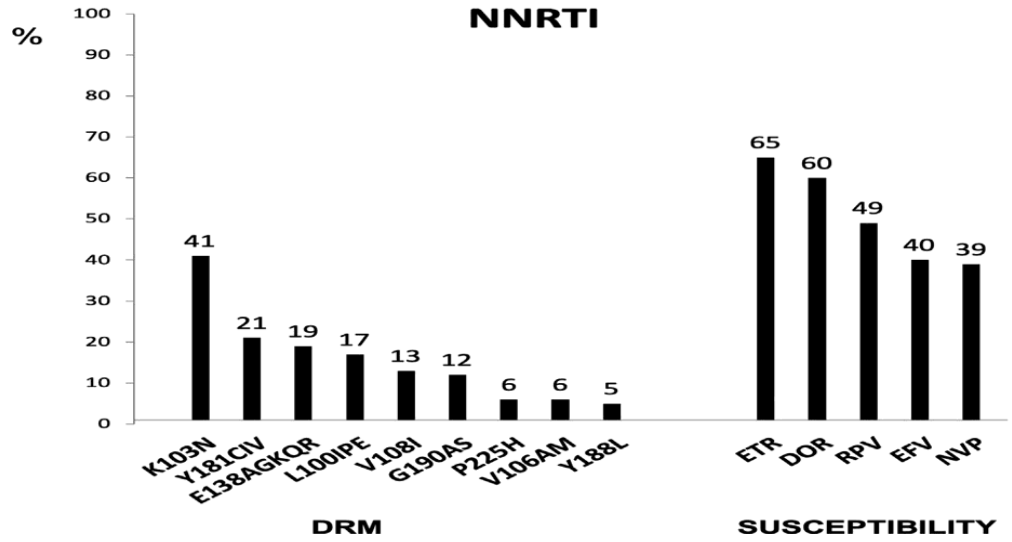
Characteristic	Value
Age	
18–24 years	30 (32)
25–29 years	34 (36)
≥30 years	30 (32)
Ethnicity	
White	88 (94)
African	4 (4)
Hispanic	2 (2)
Sex	
Male	46 (49)
Female	48 (51)
Serology	
HCV-Ab[a]	10 (11)
HBsAg[b]	1 (1)
Last virus load	
≤50 copies/mL	56 (60)
>50 copies/mL	38 (40)
Virus load zenith >100 000 copies/mL[c]	49 (59)
Last $CD4^+$ count	
<200 cells/mm^3	8 (8)
200–499 cells/mm^3	25 (27)
≥500 cells/mm^3	61 (65)
$CD4^+$ nadir <200 cells/mm^3[d]	15 (16)
No. of regimen switches (ART and cART)	
1–5	55 (58)
6–10	24 (25)
≥11	15 (16)
Last available ART regimen[e]	
Monotherapy	6 (8)
Dual therapy	4 (5)
2 N(t)RTIs	16 (22)
2 N(t)RTI + INSTI	5 (7)
2 N(t)RTI + PI	17 (23)
2 N(t)RTI + NNRTI	17 (23)
Multiregimen	8 (11)

ART, antiretroviral therapy; cART, combined antiretroviral therapy; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; INSTI, integrase strand transfer inhibitors; N(t)RTI, nucleos(t)ide inhibitors; NNRTI, nonnucleoside inhibitors; PI, protease inhibitor.

[a] Percentages calculated on total of available HCV serology ($n = 88$).
[b] Percentages calculated on total of available HBV serology ($n = 91$).
[c] Percentage calculated on total of available HIV virus load zenith values ($n = 83$).
[d] Percentage calculated on total of available $CD4^+$ nadir values ($n = 93$).
[e] Percentages calculated on total of last available ART regimen ($n = 73$).







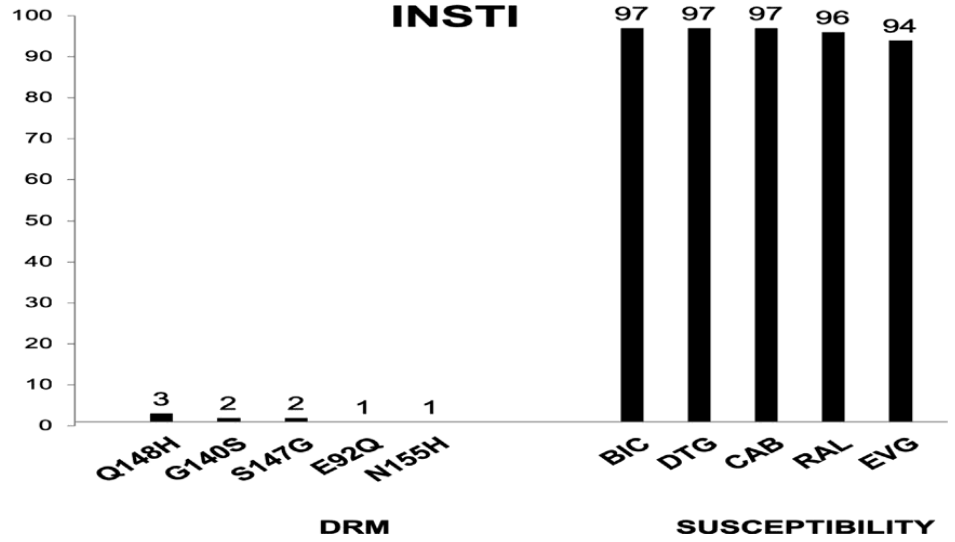


Fig. 2. Prevalence of DRM and residual susceptibility to antiretroviral therapy. 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; BIC, bictegravir; CAB, cabotegravir; DOR, doravirine; DRM, drug resistance mutation; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitors; LPV, lopinavir; N(t)RTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitors; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir;/r, ritonavir booster; RPV, rilpivirine; TDF, tenofovir.

Which factors are associated with the risk of becoming HTE?

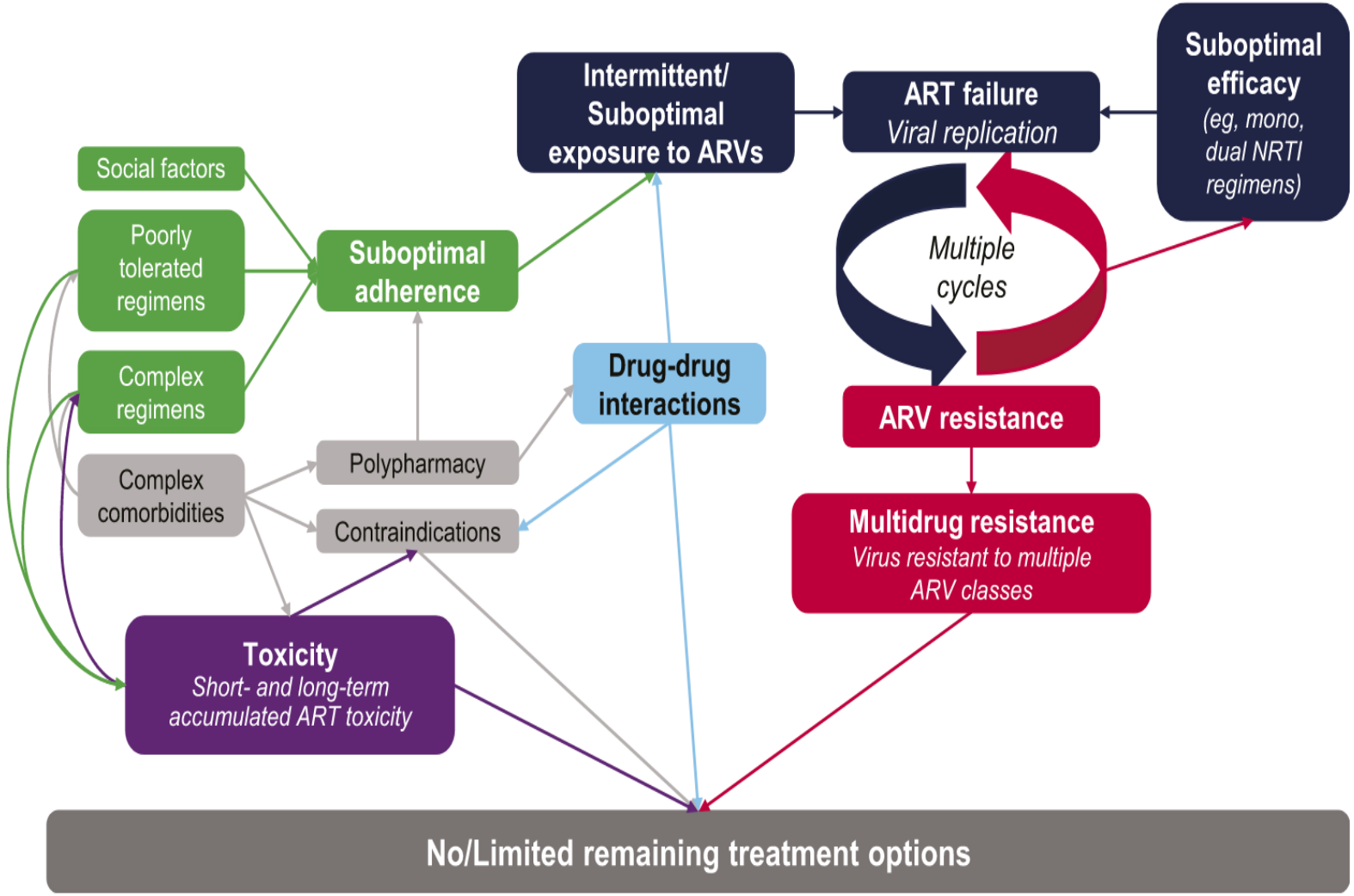


Figure 1. Clinical challenges to optimal ARV treatment in heavily treatment-experienced persons with HIV. ART, antiretroviral therapy; ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor.

Aberg 2023, Antiv Ther.

Bajema. IAS 2019. Abstr MOPEB246.

Lower baseline CD4 nadir and higher baseline maximum HIV RNA level were significantly associated with greater risk of becoming HTxE

Table 2. *Adjusted hazard ratios (aHR) of incident HTxE PWH according to calendar period, demographic and clinical characteristics**

Variable	aHR*	P-value	95% CI	
Age at entry (per 10 years)	1.13	0.001	1.05	1.22
Female	0.72	0.001	0.59	0.87
Race/Ethnicity (reference: White)				
Black	0.92	0.29	0.78	1.07
Hispanic	0.82	0.19	0.62	1.10
Other/Missing	0.77	0.24	0.50	1.19
Entry year				
2000-2002	5.75	<0.001	4.25	7.78
2003-2005	4.20	<0.001	3.07	5.75
2006-2008 (reference)	--	--	--	--
2009-2011	0.20	<0.001	0.09	0.42
2012-2014	0.26	<0.001	0.13	0.51
2015-2017	0.36	0.02	0.15	0.84
Baseline nadir CD4 (per 100 cells/mm³ increase)	0.82	<0.001	0.78	0.87
Baseline maximum HIV RNA (per 10-fold increase copies/ml)	1.37	<0.001	1.26	1.49
ART naive at CNICS entry	0.34	<0.001	0.29	0.40
Prior single/dual NRTI treatment	2.47	<0.001	2.14	2.83

* N=887 events due to censoring

Factors associated with the cumulative MDR-HIV (<3 vs. ≥3)

Adjusted* Odds Ratio (AOR) of having MDR (>=3, N=1408) vs. not having (<3, N=5386)

		AOR	P value	[95% Conf.	Interval]
Sex	**M vs. F**	**1.53**	**<0.001**	**1.29**	**1.81**
Risk factor	**Heterosexual (ref)**				
	Homosexual	0.96	0.750	0.75	1.23
	IDU	0.81	0.072	0.65	1.02
	Sexual	0.91	0.659	0.61	1.37
	Vertical	**3.32**	**<0.001**	**1.71**	**6.44**
	Other/unknown	**0.77**	**0.042**	**0.60**	**0.99**
HCV	**Negative (ref)**				
	Positive	**0.70**	**0.001**	**0.57**	**0.86**
	Unknown	0.85	0.326	0.60	1.18
Nadir CD4	**<200 (ref)**				
	≥200	**0.78**	**0.001**	**0.68**	**0.91**
Year of first treatment start	**<2008 (ref)**				
	≥2008	**0.59**	**0.015**	**0.38**	**0.90**
Number of PIs previously administered	**per 1 increase**	**1.65**	**<0.001**	**1.55**	**1.75**
Number of NRTIs previously administered	**per 1 increase**	**1.12**	**<0.001**	**1.05**	**1.18**
Number of NNRTIs previously administered	**per 1 increase**	**1.75**	**<0.001**	**1.57**	**1.95**
Previous INIs exposure	**Yes vs No**	**1.46**	**0.008**	**1.10**	**1.93**
Previous T20 exposure	**Yes vs No**	**2.03**	**<0.001**	**1.48**	**2.78**

*Adjusted for: age; sex; nationality; risk factor; subtype; HBV coinfection; HCV coinfection; zenith viremia; nadir CD4; AIDS events; years of first treatment start; number of previously experienced PIs, NRTIs, NNRTIs; previous exposure to INIs, T20 and MVC; *center.*

Chi è la persona HTE oggi?

- **PLWHIV con viremia <50 copie/ml**
- **PLWHIV con viremia >50 copie/ml**

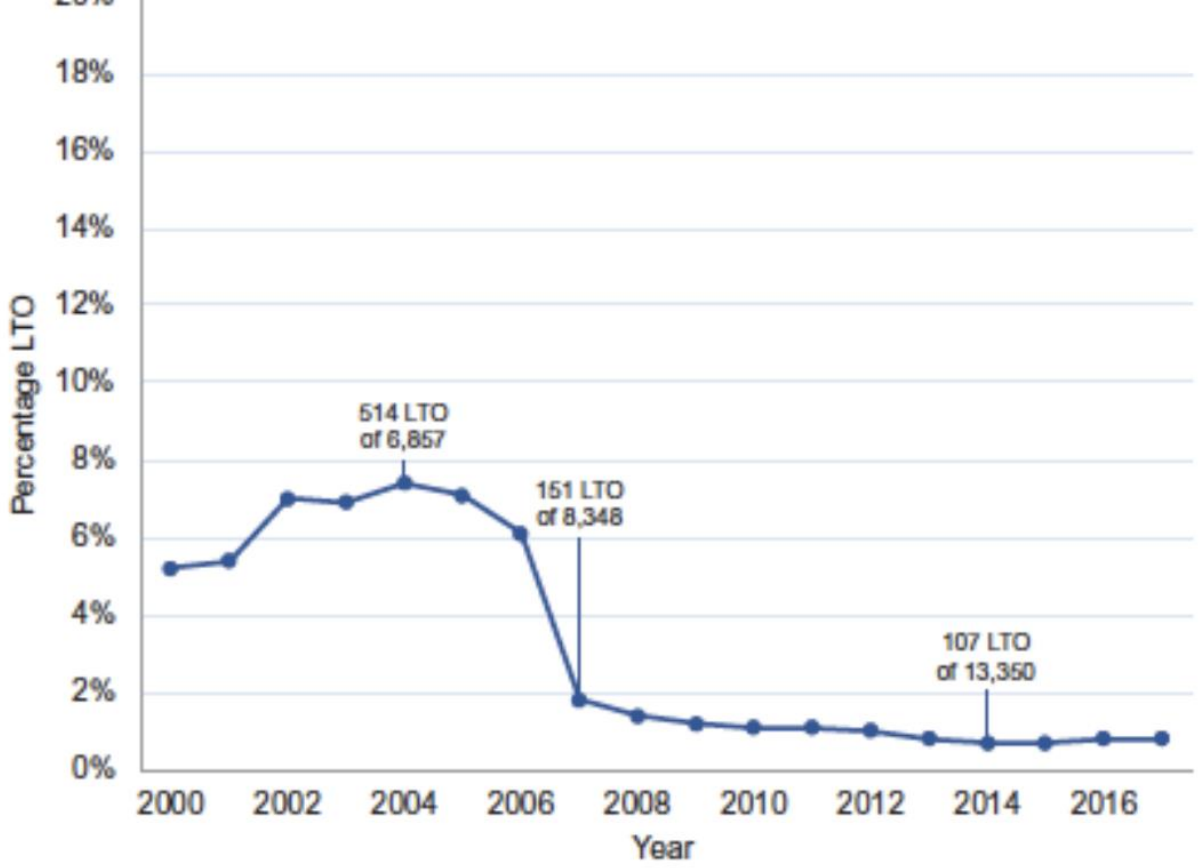
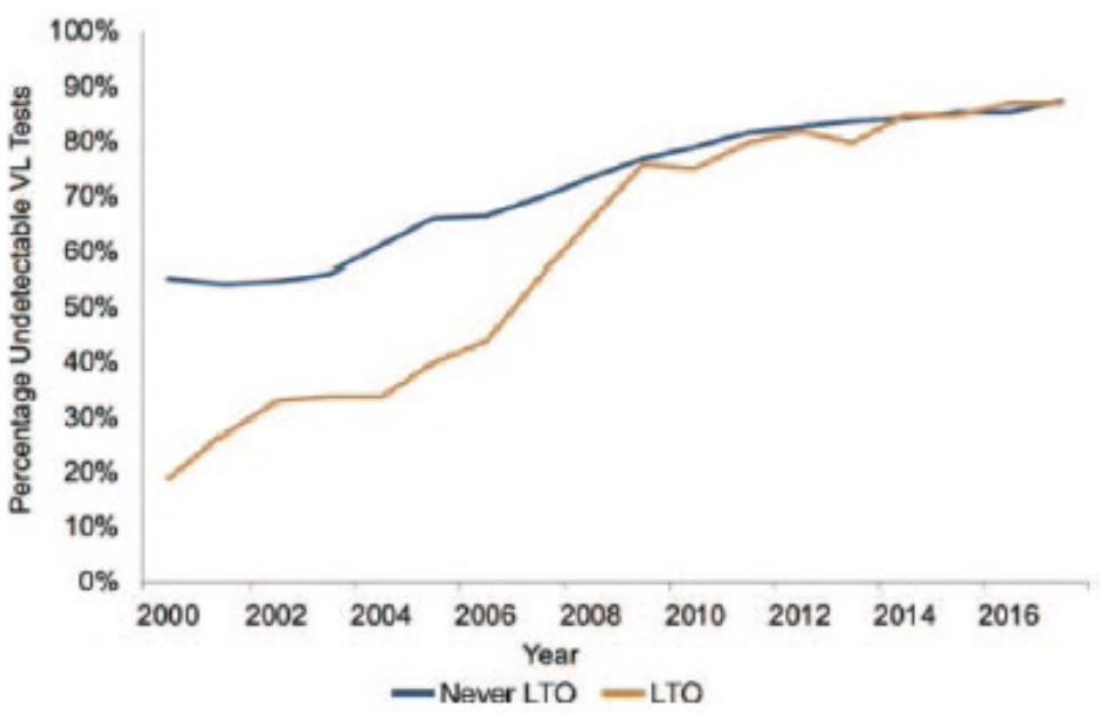


Fig. 1. Annual prevalence of persons with HIV with limited treatment options among antiretroviral therapy-experienced persons in care by year (2000–2017).



Percentage of undetectable HIV viral load tests by year among antiretroviral-experienced persons with HIV by limited treatment option statusM (2000–2017).

AIDS 2020, **34**:2051–2059

Conclusion: Results of this large multicenter study show a dramatic decline in the prevalence of PWH with LTO to less than 1% with the availability of more potent drugs and a marked increase in virologic suppression in the current ART era.

GD, 1960, HIV RNA <50 Copie/mL dal 2010, in terapia con DRV/r 600 mg x 2 + DTG (prima RAL)

Sottotipo: B

Tropismo virale: N.D.

Sequenza RT: NRTI

Drug	20%	
	Resistance	Mutations
Lamivudina	R	D67G · S68G · K70R · L74I · M184V · T215Y · K219E
Abacavir	R	D67G · S68G · K70R · L74I · M184V · T215Y · K219E
Stavudina	R	D67G · S68G · K70R · L74I · M184V · T215Y · K219E
Didanosine	R	D67G · S68G · K70R · L74I · M184V · T215Y · K219E
Emtricitabina	R	D67G · S68G · K70R · L74I · M184V · T215Y · K219E
Tenofovir	I	D67G · S68G · K70R · L74I · M184V · T215Y · K219E
Zidovudine	R	D67G · S68G · K70R · L74I · M184V · T215Y · K219E

Sequenza RT: NNRTI

Drug	20%	
	Resistance	Mutations
Rilpivirina	R	L100I · K103N
Etravirina	I	L100I · K103N
Efavirenz	R	L100I · K103N
Nevirapine	R	L100I · K103N
Doravirine	I	L100I · K103N

Sequenza Proteasi (PR)

Drug	20%	
	Resistance	Mutations
Atazanavir/r	R	V32I · M46I · V82A · L90M
Darunavir/r	I	V32I · M46I · V82A · L90M
Fosamprenavir/r	R	V32I · M46I · V82A · L90M
Indinavir/r	R	V32I · M46I · V82A · L90M
Lopinavir/r	R	V32I · M46I · V82A · L90M
Nelfinavir	R	V32I · M46I · V82A · L90M
Saquinavir/r	R	V32I · M46I · V82A · L90M
Tipranavir/r	R	V32I · M46I · V82A · L90M

Sequenza Integrasi (IN)

Drug	20%	
	Resistance	Mutations
Bictegravir	S	-
Dolutegravir	S	-
Elvitegravir	S	-
Raltegravir	S	-
Cabotegravir	S	-

DNA

Simplification strategies for HTE PWH with VL <50 copie/ml

- HTE PWH are often treated with complex regimen
- Many concerns about simplification strategies in this population (few therapeutic alternatives)
- Studies are needed
- Maintain high genetic barrier

THERAPEUTIC ADVANCES in
Infectious Disease

Original Research

Evaluation of treatment simplification strategies in patients living with HIV with multi-drug resistance

Taylor N. Harris and Lindsey R. Buscemi

Ther Adv Infect Dis

2023, Vol. 10: 1–8

DOI: 10.1177/20499361221149869

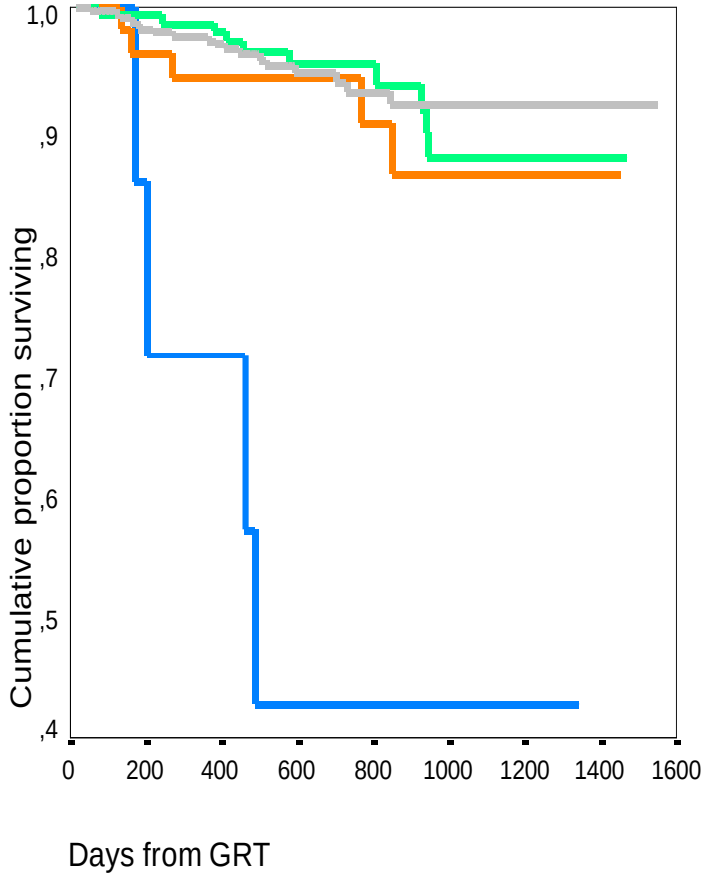
Table 2. Clinical outcomes.

Study outcome	Simplified cohort (*N* = 28)	Non-simplified cohort (*N* = 22)	*p*-value
Viral suppression at most recent clinic visit, *n* (%)	24 (85.7)	16 (72.7)	0.302
⩾80% time suppressed over the past 2 years, *n* (%)	23 (82.1)	16 (72.7)	0.503
⩽50% time suppressed over the past 2 years, *n* (%)	4 (14.3)	4 (18.2)	0.718
Virologic failure, *n* (%)	3 (10.7)	5 (22.7)	0.277
Treatment-emergent resistance, *n* (%)	0	0	1.000

Which is the rate of AIDS events and death in HTE people?

Poor survival in drug-class multi-resistance

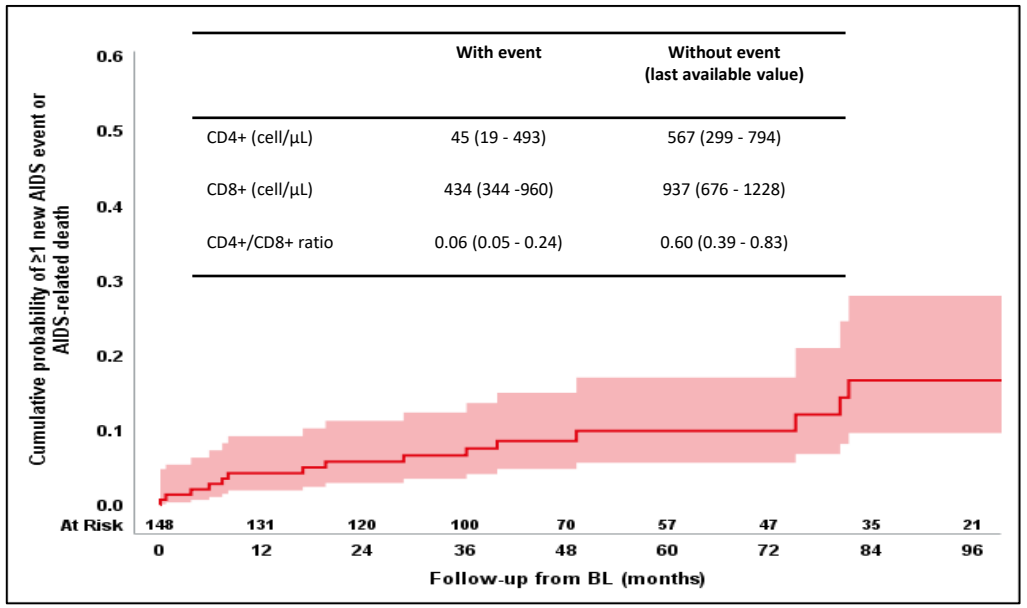
Logistic regression	Multivariate	P
CD4 time-dependent (per 50 cells increase)	0.79 (0.66-0.93)	0.006
Plasma HIV-RNA time-dependent (per 1 $\log_{10}$ increase)	1.14 (0.76-1.71)	0.539
Previous AIDS	2.29 (0.86-6.12)	0.098
LPV after GRT	0.57 (0.19-1.67)	0.302
3 drug class multi-resistance (DCMR)	12.29 (3.00-50.28)	<0.001



Zaccarelli, AIDS 2005

Time to occurrence of new AIDS/death or non-AIDS event/death among 148 PLWH and 4-class drug resistant virus

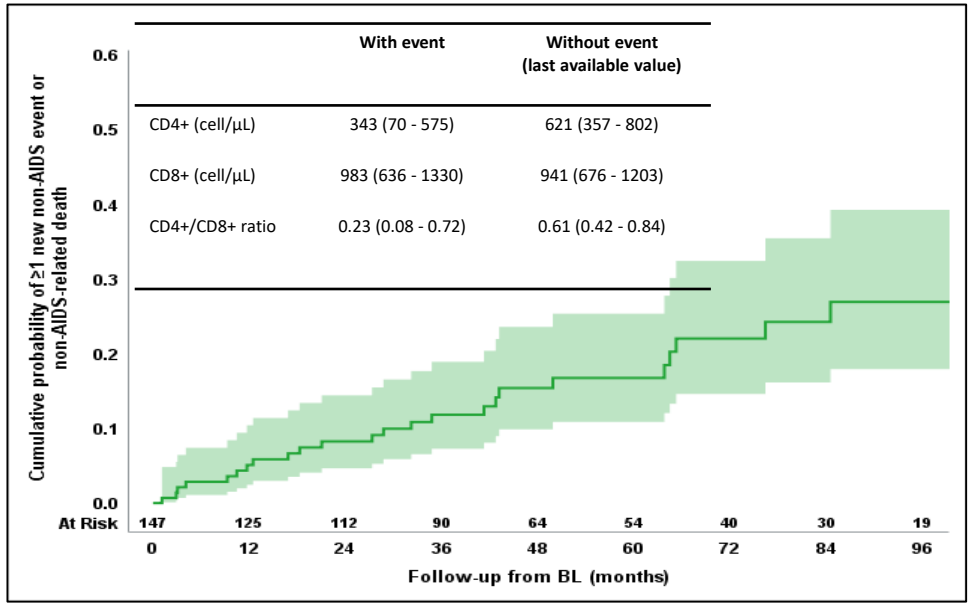
PRESTIGIO



	With event	Without event (last available value)
CD4+ (cell/µL)	45 (19 - 493)	567 (299 - 794)
CD8+ (cell/µL)	434 (344 -960)	937 (676 - 1228)
CD4+/CD8+ ratio	0.06 (0.05 - 0.24)	0.60 (0.39 - 0.83)

CUMULATIVE PROBABILITIES OF A NEW AIDS EVENT/AIDS-RELATED DEATH (95%CI)	
12 months	4.3% (1.9 - 9.2)
24 months	5.8% (2.9 - 11.3)
36 months	6.6% (3.5 - 12.4)
48 months	8.6% (4.8 - 15.0)

24 events in 15 pts: 3 mycobacteriosis, 3 pulmonary tuberculosis, 1 tuberculous meningoencephalitis, 2 NHL, 1 cutaneous KS, 2 esophageal candidiasis, 2 pneumocystis jirovecii, 1 disseminated herpes simplex, 1 wasting syndrome, 1 menigoencephalic cryptococcosis, 1 cytomegalovirus encephalitis and 6 AIDS related deaths.



	With event	Without event (last available value)
CD4+ (cell/µL)	343 (70 - 575)	621 (357 - 802)
CD8+ (cell/µL)	983 (636 - 1330)	941 (676 - 1203)
CD4+/CD8+ ratio	0.23 (0.08 - 0.72)	0.61 (0.42 - 0.84)

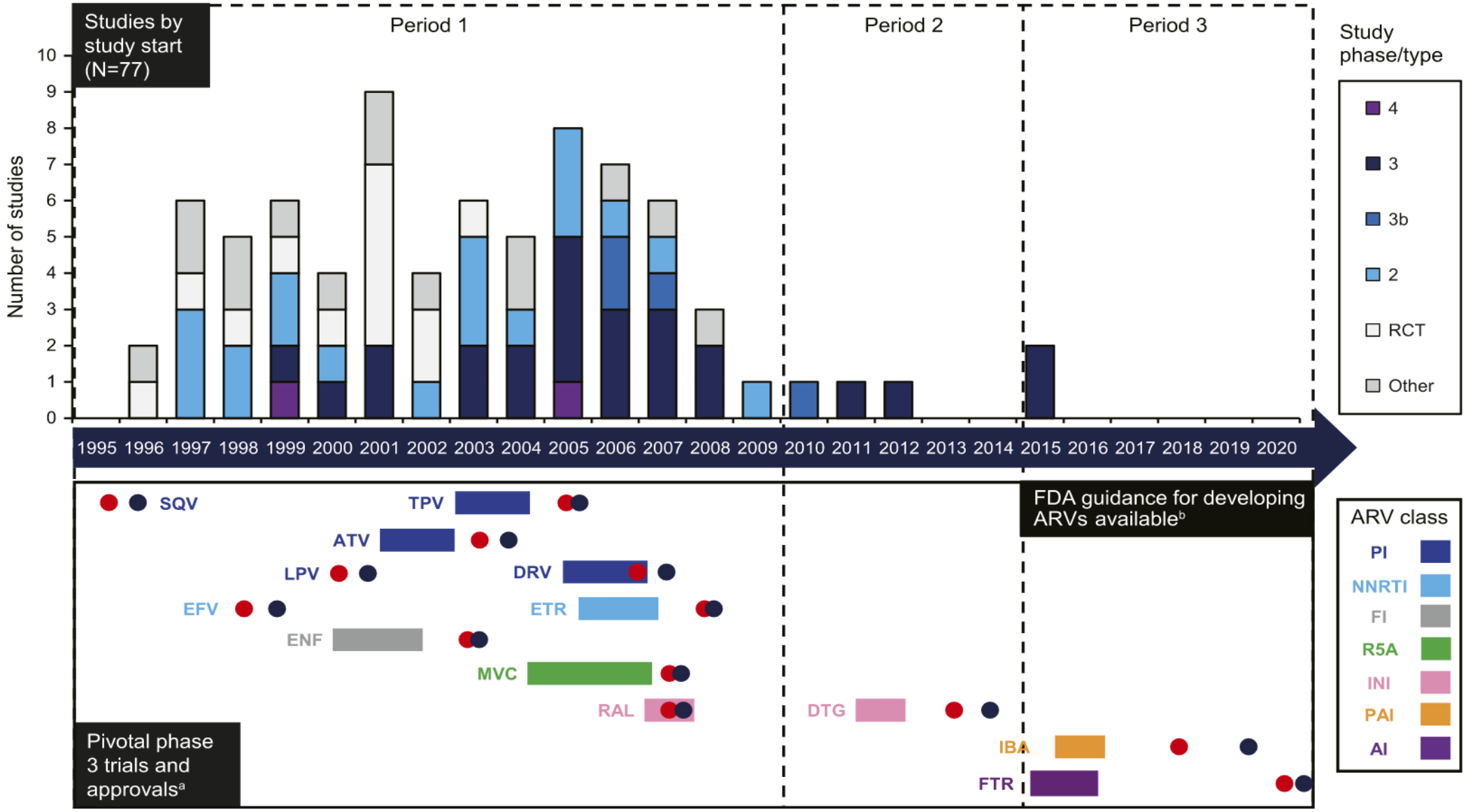
CUMULATIVE PROBABILITIES OF A NEW NON-AIDS EVENT/NON-AIDS-RELATED DEATH (95%CI)	
12 months	5.1% (2.5 - 10.4)
24 months	8.3% (4.7 - 14.5)
36 months	11.8% (7.3 - 18.9)
48 months	15.4% (9.9 - 23.6)

38 events in 26 pts : 3 HL, 3 anal cancer, 3 HCC, 2 prostate cancer, 1 lung cancer, 1 breast cancer, 1 laryngeal cancer, 1 conjunctival spinocellular carcinoma, 2 other malignancies. 6 MACE, 6 CKD, 3 cirrhosis and 6 non-AIDS related deaths.

L. Galli, OFID 2020

NUOVI TARGET TERAPEUTICI

Aberg 2023, Antiv Ther.

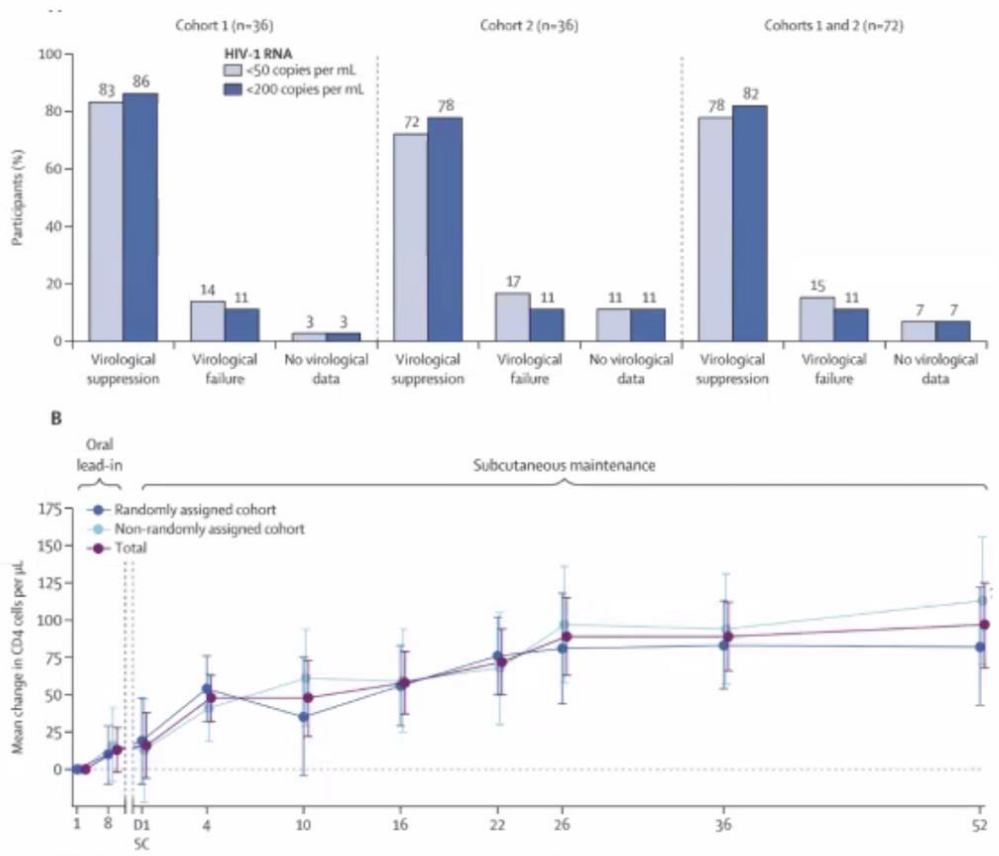


This review showed a dramatic reduction in the number of studies conducted in HTE participants after 2010.

Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial

Lancet HIV 2023; 10: e497–505

Published Online
July 11, 2023



Comment

Lenacapavir: an attractive option, but proceed with caution

- Lenacapavir is close to how we hoped a long-acting injectable antiretroviral would look
- We advise some caution before lenapacavir use is expanded more widely for the treatment of HIV.
  - Few women in the trials
  - Unrecognised severe adverse reactions (e.g. hypersensitivity reactions)

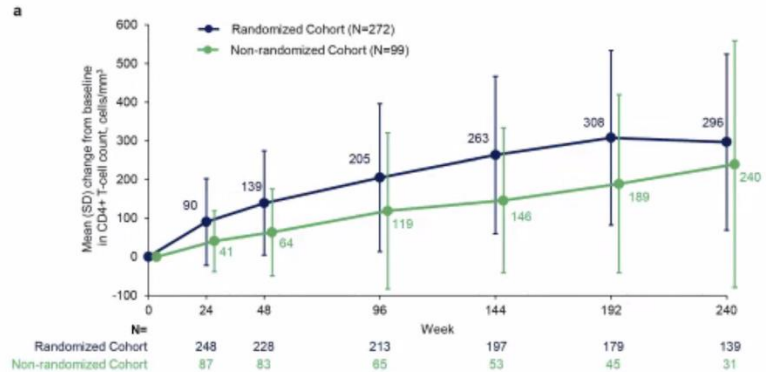
reactions and other clinically relevant adverse drug reactions been sufficiently ruled out? Further evaluation in larger and more diverse populations would be prudent to better establish the safety and toxicity profile of lenacapavir, especially before the requirement for initial oral lead-in dosing is abandoned.

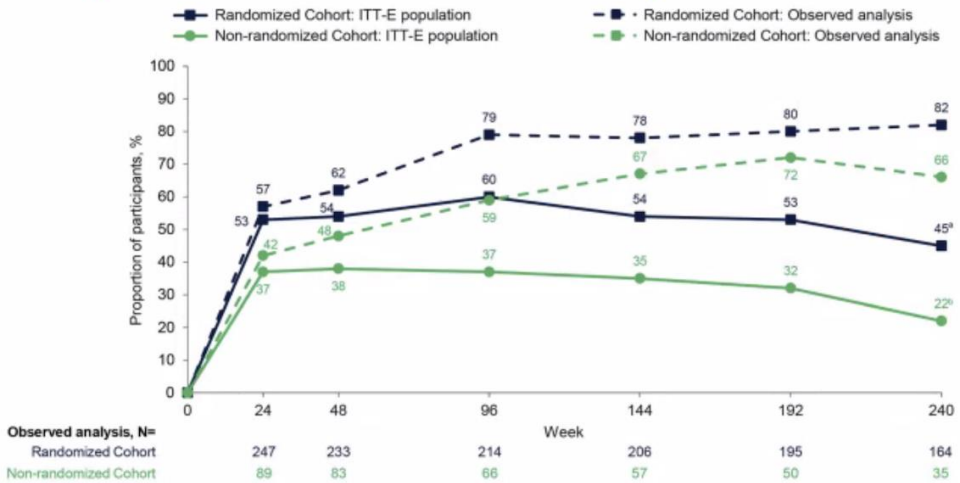
Infect Dis Ther
https://doi.org/10.1007/s40121-023-00870-6

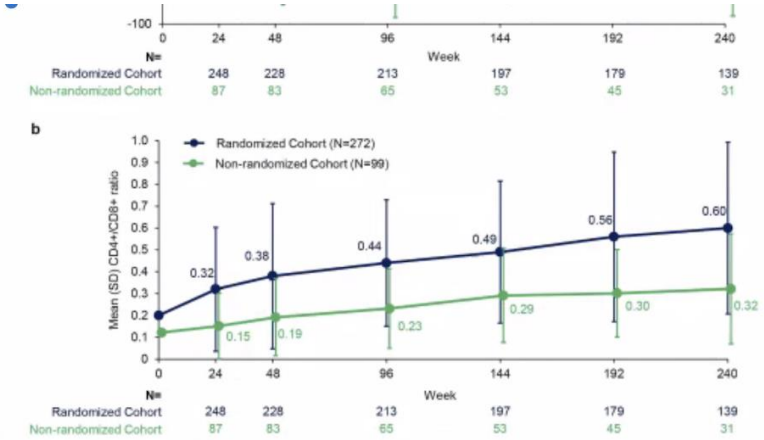
ORIGINAL RESEARCH

Week 240 Efficacy and Safety of Fostemsavir Plus Optimized Background Therapy in Heavily Treatment-Experienced Adults with HIV-1

Judith A. Aberg · Bronagh Shepherd · Marcia Wang · Jose V. Madruga ·







- Long-term efficacy and safety of fostemsavir + OBT in HTE adults with multidrug-resistant HIV-1 from the phase 3 BRIGHTE trial
  - At w240, 45% and 22% of the RC and NRC, had virologic response (Snapshot);
  - At w240, mean change from BL in CD4 T-cell count 296 cells/mm3 (RC) and 240 cells/mm3 (NRC); mean CD4/CD8 ratio increased between w96 and 240 (RC 0.44 to 0.60; NRC 0.23 to 0.32). Immunological response even those who were viremic might be directly related to its unique mechanism of action.
  - The safety and tolerability profile of fostemsavir +OBT remained consistent with prior observations through 96 weeks.

How manage new HTE people?

Box 7.2. Best practice for the management of individuals with multi-class virological failure (all GPPs)

- In individuals with ongoing viraemia and with few options to construct a fully suppressive regimen, referral for specialist advice and/or discussion in a multidisciplinary team 'virtual' clinic is imperative.
- In those with significant resistance, include at least two and preferably three fully active agents with at least one active boosted PI (preferably ritonavir- or cobicistat-boosted darunavir) and one agent with a novel mechanism of action (these may include INSTIs, CCR5 antagonists, molecules targeting glycoprotein 120 [gp120; fostemsavir], monoclonal antibodies targeting CD4 [ibalizumab], capsid inhibitors [lenacapavir], the fusion inhibitor T-20 or other investigational agents).
- Treatment interruption is not recommended.

BHIVA 2022

Individuals with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed

BHIVA British HIV Association

BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022

- We recommend accessing newer agents through research trials, expanded access and named individual programmes (GPP).
- We suggest that consideration, on an individual basis, should be given to whether inclusion of NRTIs with reduced activity on genotypic testing will provide additional antiviral activity; this may be the case where it is difficult to construct a regimen with fully active drugs including a boosted PI (Grade 2A).
- We recommend against discontinuing or interrupting ART (Grade 1B).
- We recommend against adding a single, fully active ARV because of the risk of further resistance (Grade 1D).
- We recommend against the use of maraviroc to increase the CD4 cell count where there is evidence for X4- or dual-tropic virus (Grade 1C).
- We recommend that in the context of triple-class failure and raltegravir-/elvitegravir-selected integrase resistance, twice-daily dolutegravir should be included as part of a new regimen where there is at least one fully active agent in the background regimen (Grade 1C).

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REVIEW

HIV: how to manage heavily treatment-experienced patients

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Key practice points

- Heavily treatment-experienced (HTE) patients with HIV are described as having two or less antiretroviral classes available for use with limited fully active agents within each class.
- Amongst HTE patients who are failing their regimen, barriers to adherence, pharmacokinetic barriers and drug interactions need to be addressed.

- When constructing a new regimen for an HTE patient, all genotypic, phenotypic and tropism testing must be reviewed as all resistance is cumulative, even if archived.
- One active medication should not be added to a failing regimen. Ideally, a regimen should incorporate at least two fully active medications.
- New and novel classes under development (attachment/post-attachment inhibitor, capsid inhibitor, nucleoside reverse transcriptase translocation inhibitor) can be used to construct a complete regimen for HTE patients.

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