HIV: Terapie nel fallimento virologico

Sergio Lo Caputo

Malattie Infettive A.O.U. Policlinico Foggia

Università Di Foggia

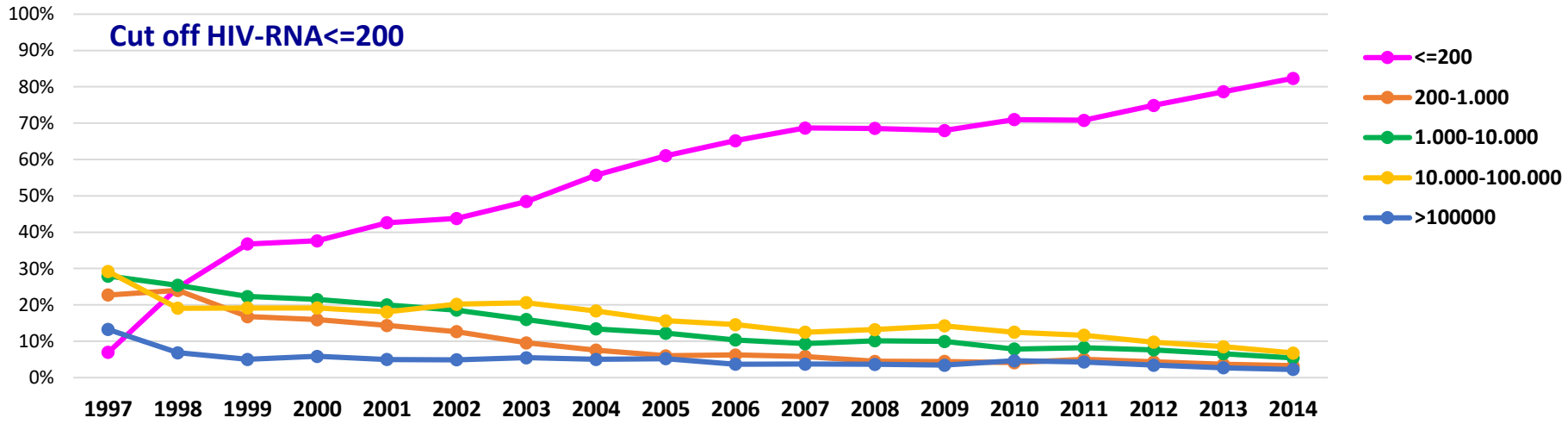
Università di Foggia

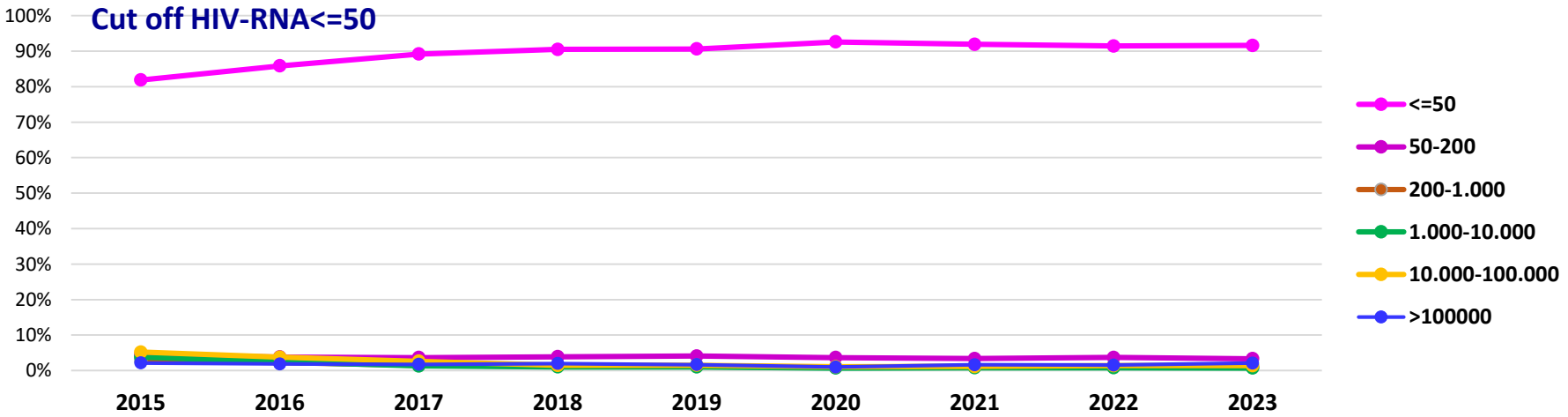
Disclosure

- Has been advisor for Gilead,ViiV, Janssen-Cilag, GSK, Astra Zeneca and MSD
- Had received speakers' honoraria from Gilead, ViiV, Astra Zeneca, MSD and Janssen-Cilag, GSK, Angelini, Menarini
- Had received support for travel meetings from Gilead, Janssen-Cilag, and ViiV
- Had received grant for research from Gilead

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

HIV-RNA strata (copies/mL) in all PWH in follow-up according to calendar year

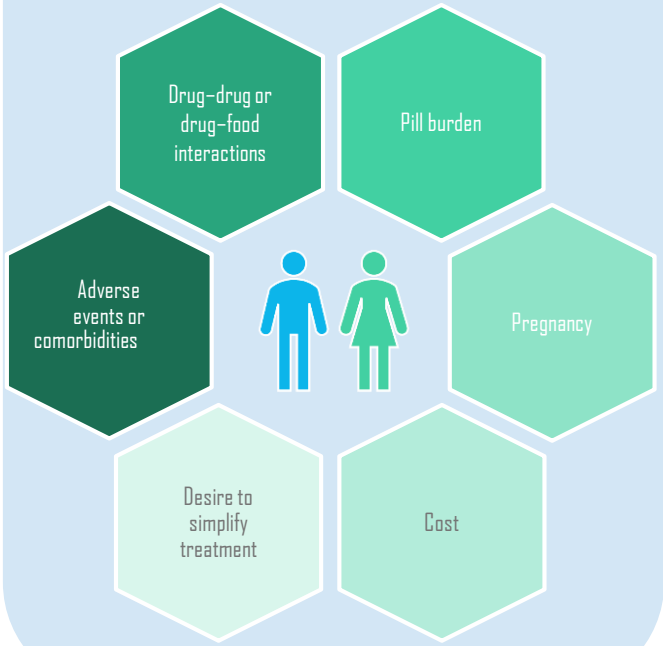




Dec 2023

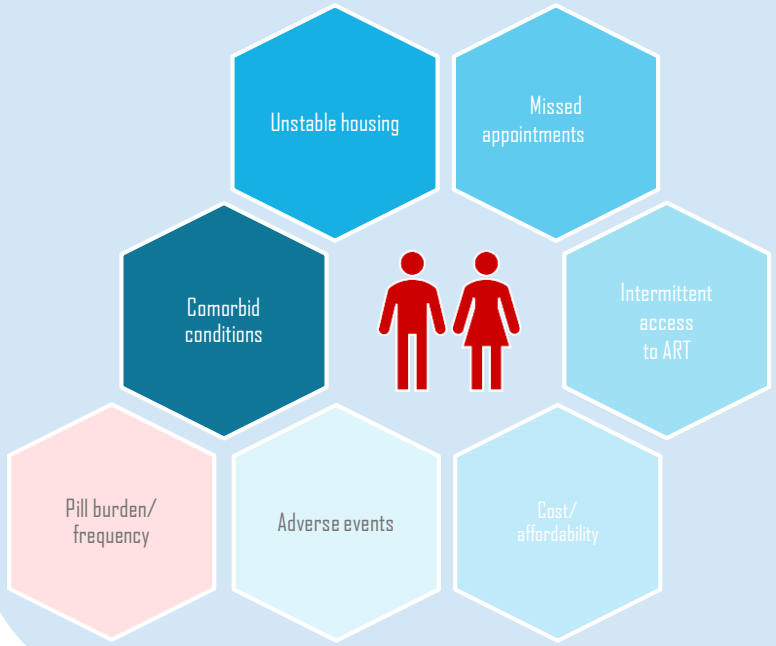
Understanding Treatment-Experienced PLWH

Suppressed PLWH
May still be dealing with:

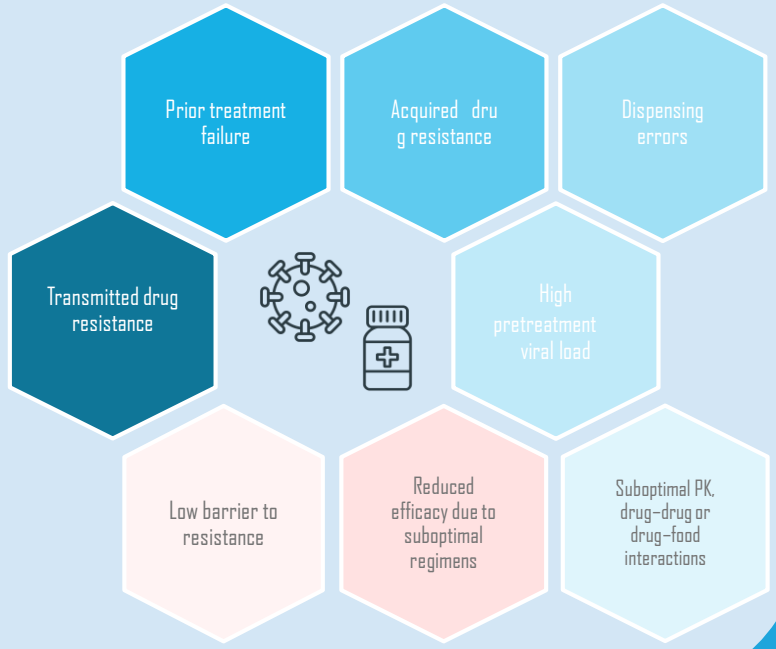


PLWH experiencing virologic failure
Virologic failure may be associated with a variety of factors, including:

Adherence/patient-related factors



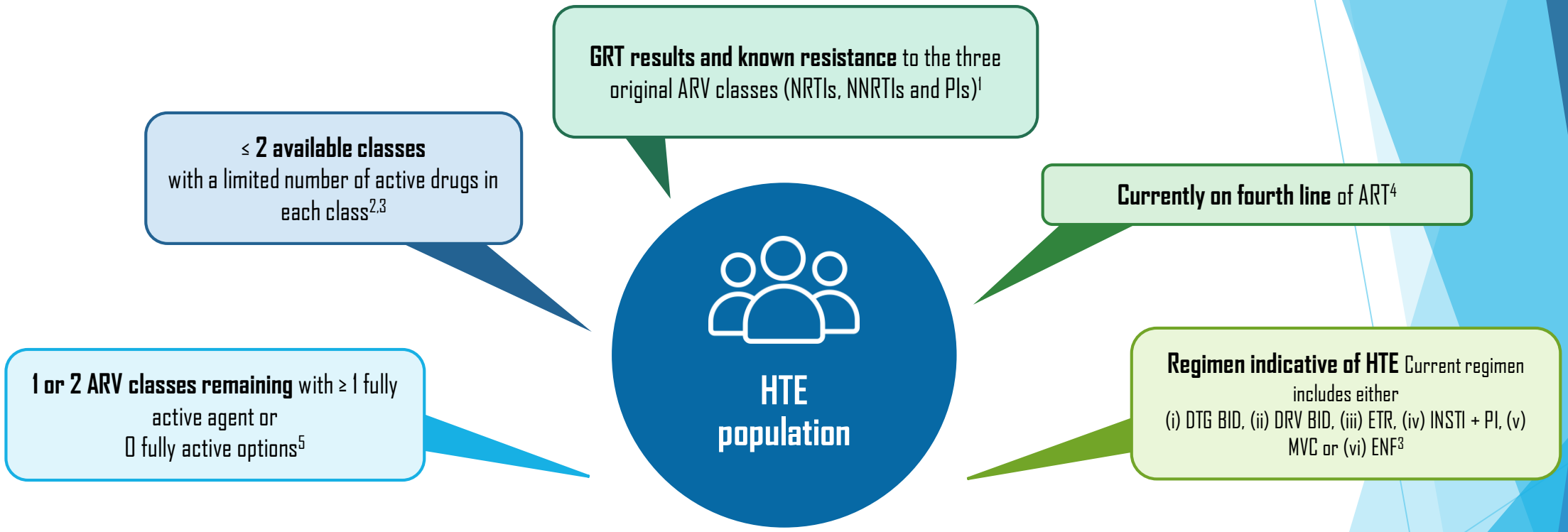
HIV- or ARV-related factors



PK, pharmacokinetics

DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV, June 2021. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf (accessed March 03, 2022)

Challenges With Defining the HTE Population



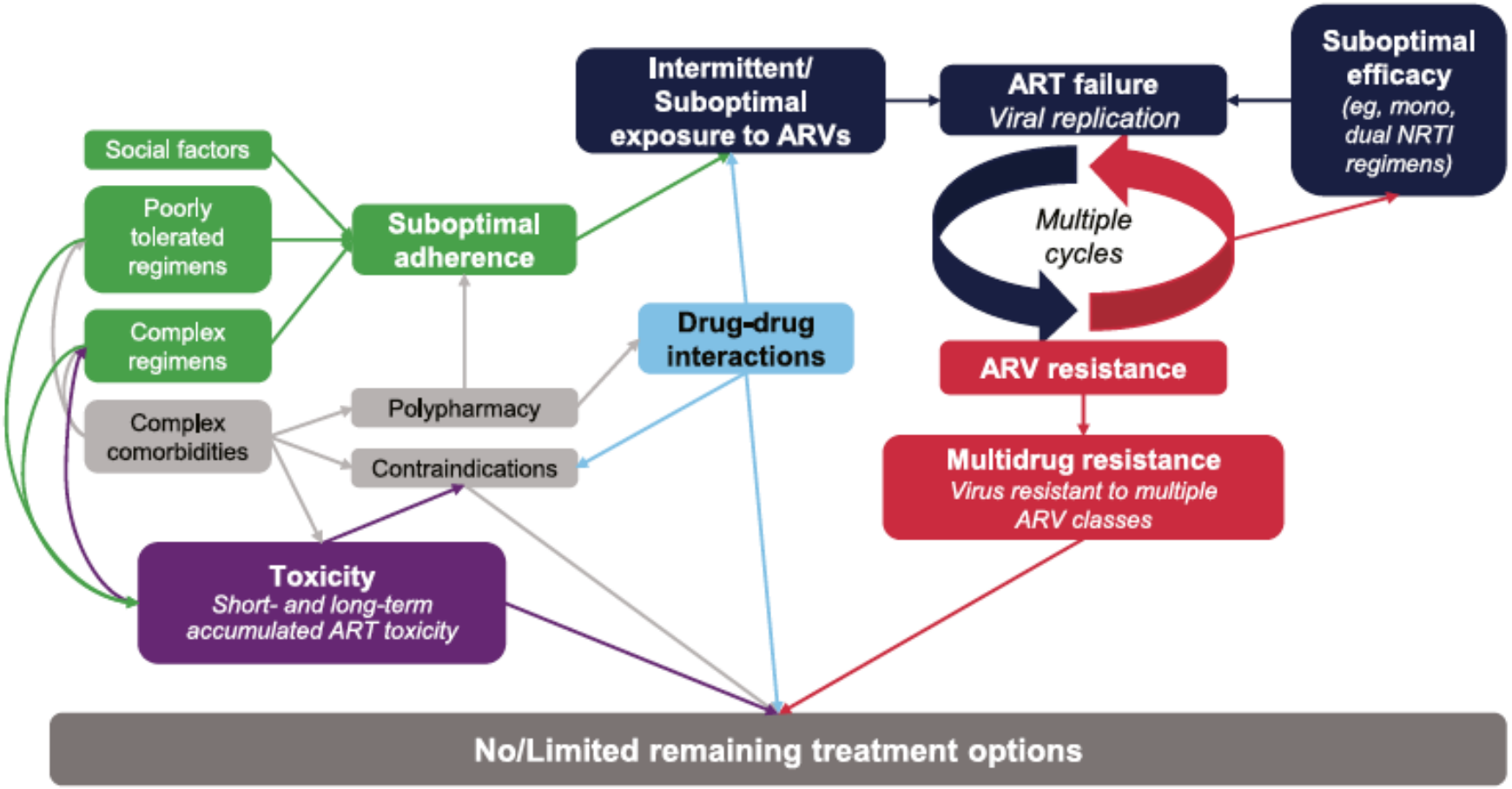
Various criteria have been used to define the HTE population across a range of studies

GRT, genotypic resistance testing; HTE, heavily treatment-experienced

1. Pelchen-Matthews A, et al. JADIS 2021;87:806-817; 2. Bajema KJ, et al. IAS 2019, Poster MOPEB246; 3. Bajema K, et al. AIDS 2020;34:2051-2059; 4. Hsu R, et al. AIDS 2020, Poster PEB0234; 5. Kozal M, et al. N Engl J Med 2020;382:1232-1243

The evolution of clinical study design in heavily treatment-experienced persons with HIV: A critical review

Antiviral Therapy June 2023: 1–17

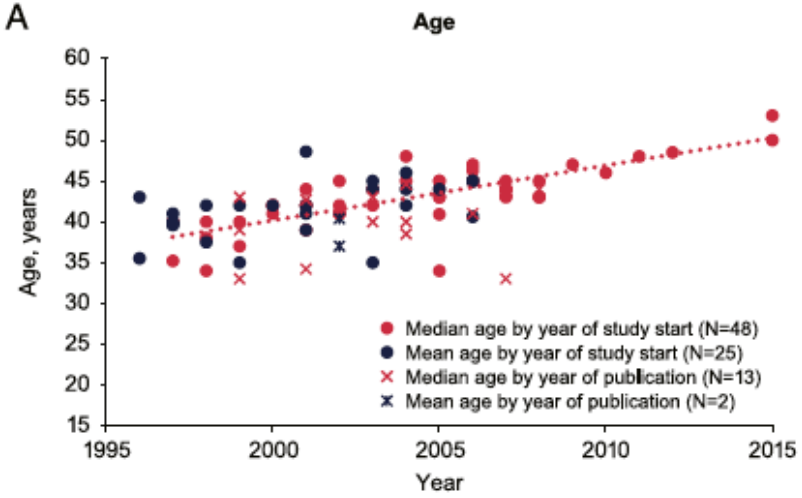


Clinical challenges to optimal ARV treatment in heavily treatment-experienced persons with HIV

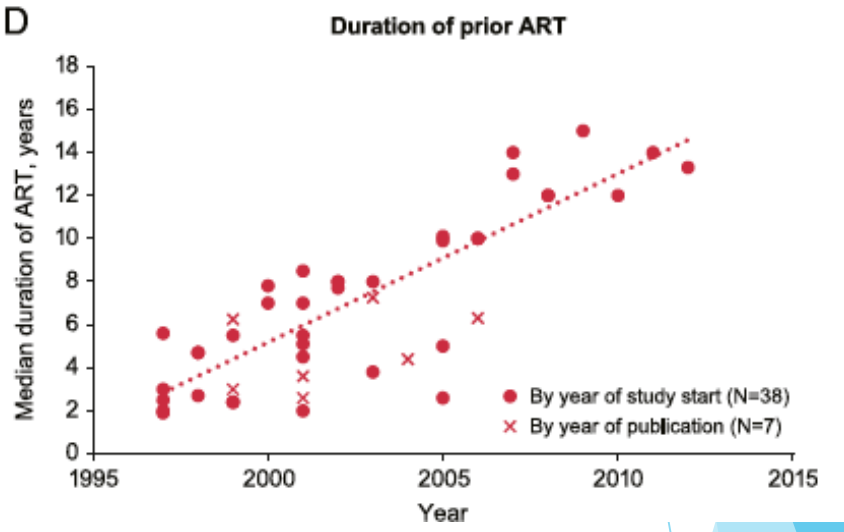
The evolution of clinical study design in heavily treatment-experienced persons with HIV: A critical review

Antiviral Therapy June 2023: 1–17

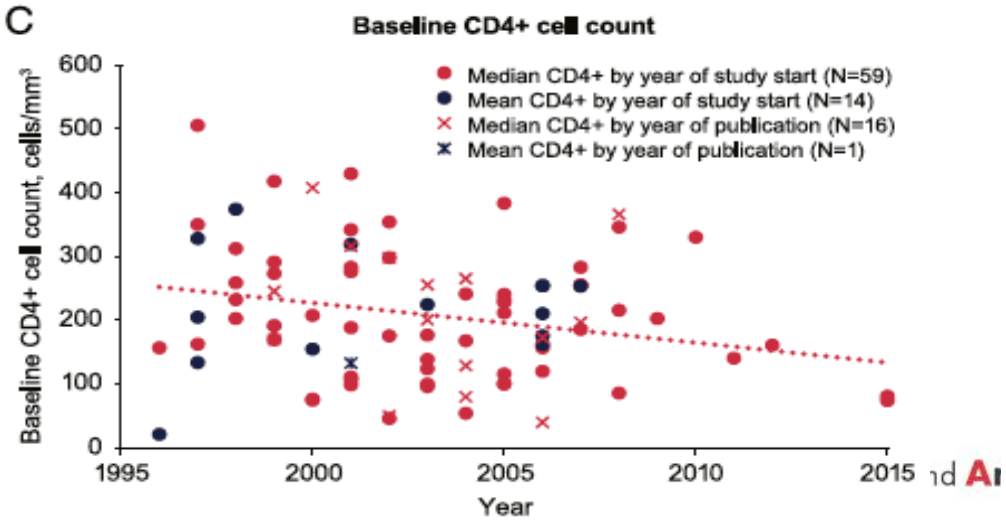
A



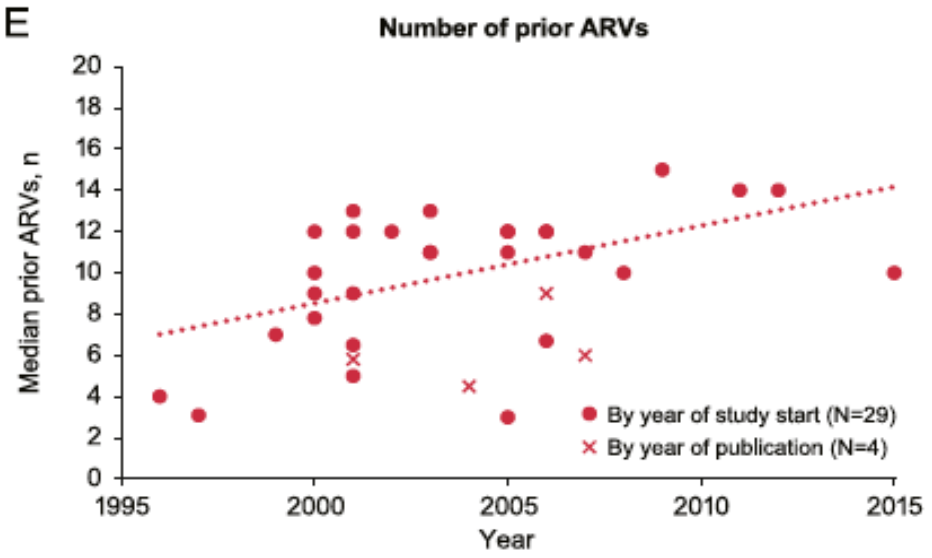
D



C



E



Characterization of Heavily Treatment-Experienced People With HIV and Impact on Health Care Resource Utilization in US Commercial and Medicare Advantage Health Plans

Julie Priest,[1] Erin Hulbert,[2] Bruce L. Gilliam,[1] and Tanya Burton[2]

Data from the national Optum Research Database between January 1, 2014, and March 31, 2018,

- ***HTE PWH (n = 2297) were older (53.5)***
- ***more likely to have HIV-related emergency department visits and inpatient stays***
- ***higher mean daily pill burden (9.7)***
- ***higher mortality rate (5.9% vs 2.9% and 2.3%) during follow-up***
- ***<200 CD4+ cells/mm3***

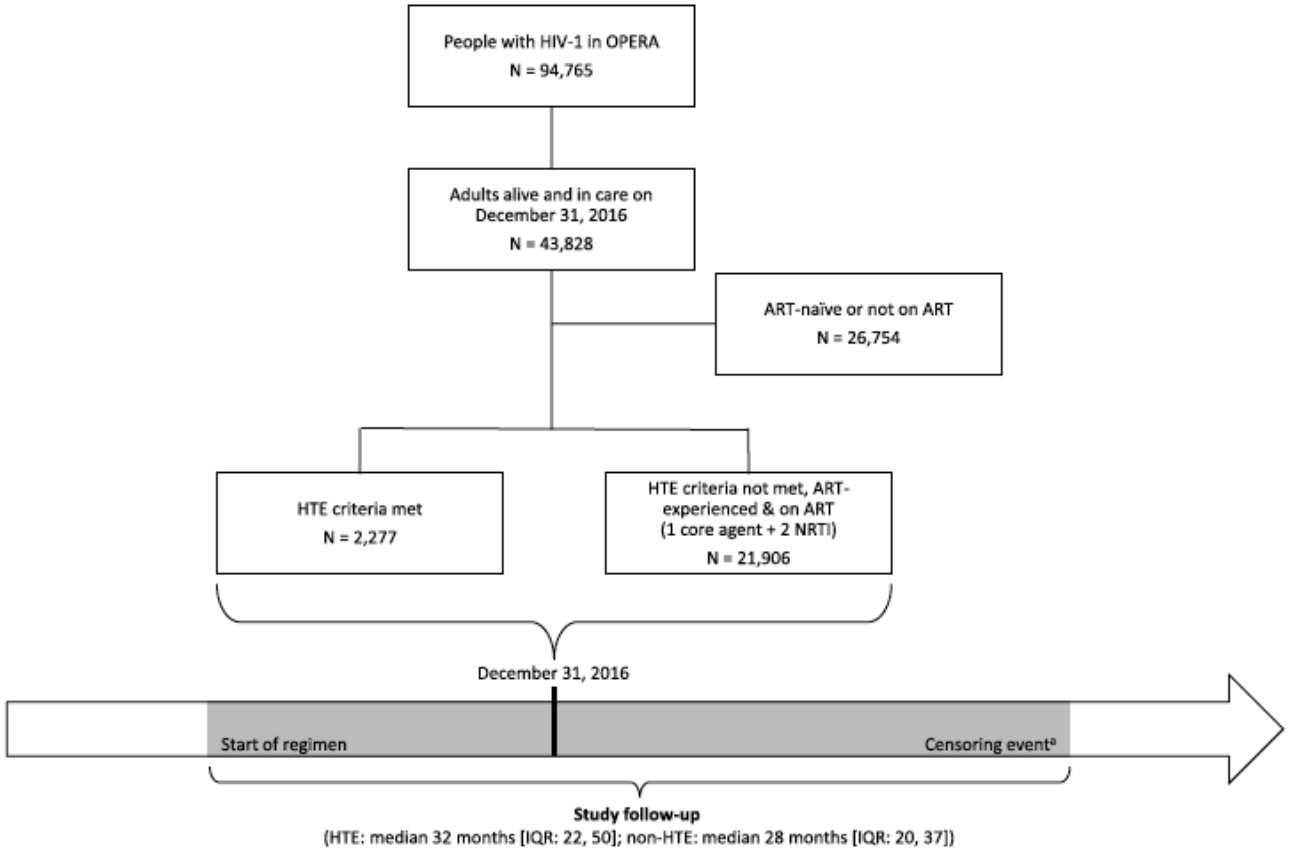
Table 3. Twelve-Month Follow-up All-Cause and HIV-Related Health Care Costs by Cohort

		Medical + Pharmacy Costs, US Dollars[a]					
		Mean 12-Month Costs			Adjusted for Demographics and Comorbidities[b]		
Costs	Cohort	Total	Medical	Pharmacy	Predicted Value	Cost Ratio (95% CI)	*P* Value
All-cause costs	HTE	66 845	17 776	49 068	60 027	Reference	
	Non-HTE	41 262	9235	32 028	42 831	0.714 (0.686–0.742)	<.001
	TN	44 368	13 763	30 605	44 310	0.738 (0.706–0.772)	<.001
HIV-related costs[c]	HTE	50 433	10 119	40 314	48 069	Reference	
	Non-HTE	32 344	4746	27 598	33 280	0.692 (0.673–0.712)	<.001
	TN	35 828	8680	27 148	34 876	0.726 (0.700–0.752)	<.001

Open Forum Infectious Diseases®2021

Heavily treatment-experienced people living with HIV in the OPERA® cohort: population characteristics and clinical outcomes

Ricky K. Hsu[1,2], Jennifer S. Fusco[3,8*], Cassidy E. Henegar[4], Vani Vannappagari[4], Andrew Clark[5], Laurence Brunet[3], Philip C. Lackey[6], Gerald Pierone Jr.[7] and Gregory P. Fusco[3]



[a] First of loss to follow-up, death, or study end (December 31, 2018), or changing status from non-HTE to HTE

Fig. 1 Inclusion into the study population and study timeline

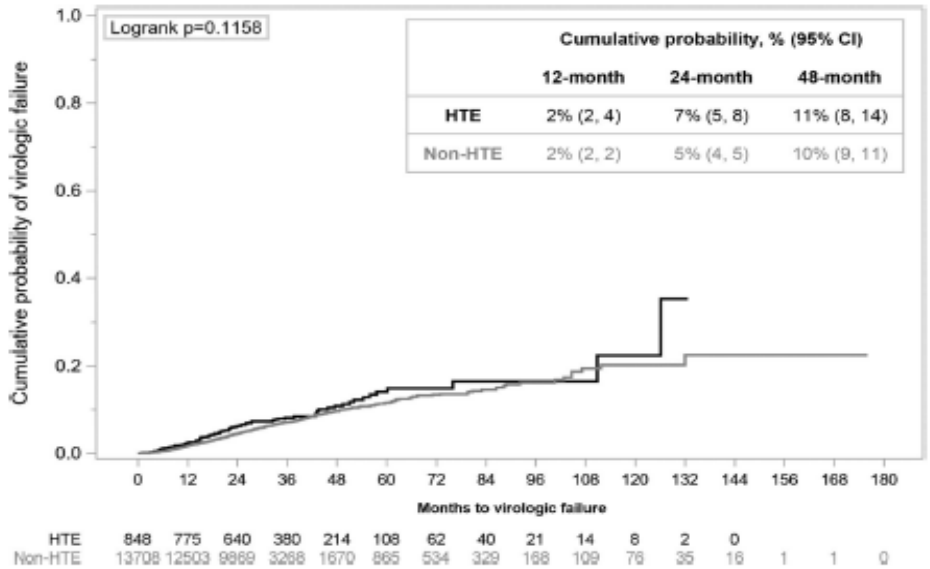


Fig. 3 Cumulative probability of virologic failure (two consecutive viral loads ≥ 200 copies/mL or discontinuation following a viral load ≥ 200 copies/mL) among people living with HIV with a viral load < 50 copies/mL at baseline

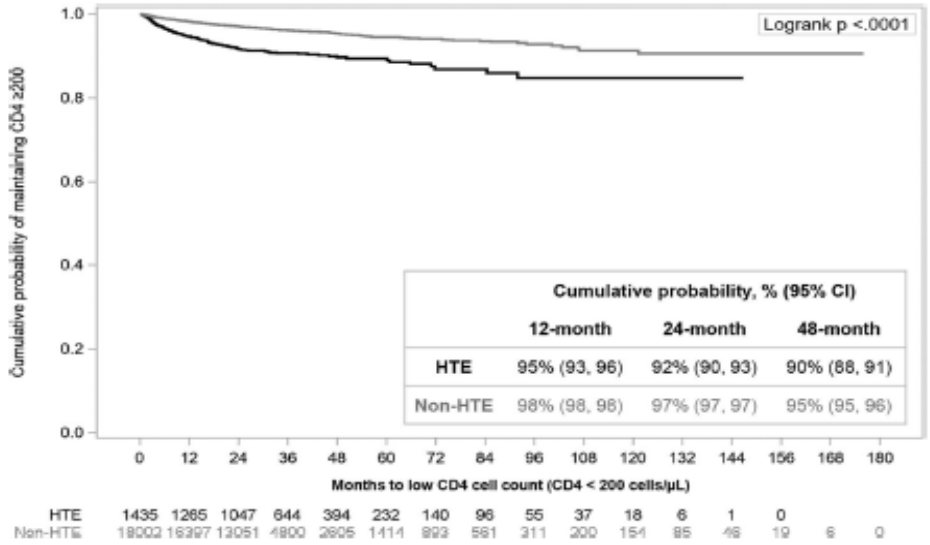


Fig. 4 Cumulative probability of maintaining CD4 cell count ≥ 200 cells/μL among people living with HIV with CD4 cell count ≥ 200 cells/μL at baseline

HTE PLWH Characteristics

Virological failure and/or poor CD4 recovery [1,2]

- Potential risk of HIV transmission
- Higher risk of disease progression
- High prevalence of low CD4 cell count

More frequent AIDS related comorbidities[1,2]

- More likely to have HIV-related emergency department visits
- Higher incidence of new AIDS events

Higher incidence of death [1,2]

AIDS or non-AIDS related

Complex HIV treatment[1,3,4,5]

- Higher daily pill burden
- Frequent treatment of or prophylaxis for opportunistic infections
- Frequent drug-drug interactions
- Limited remaining options due to multi-drug resistant HIV
- Need for treatment options without overlapping resistance such as experimental drugs with a new MOA

More frequent non-AIDS related comorbidities[1,2]

including

- Non–AIDS-defining malignancies [a]
- Chronic kidney disease
- Cardiovascular disease [b]
- Liver-related events [c]

All comparisons versus non-HTE PLWH

a) including any malignancies other than Kaposi sarcoma, non-Hodgkin lymphoma, or cervical cancer)

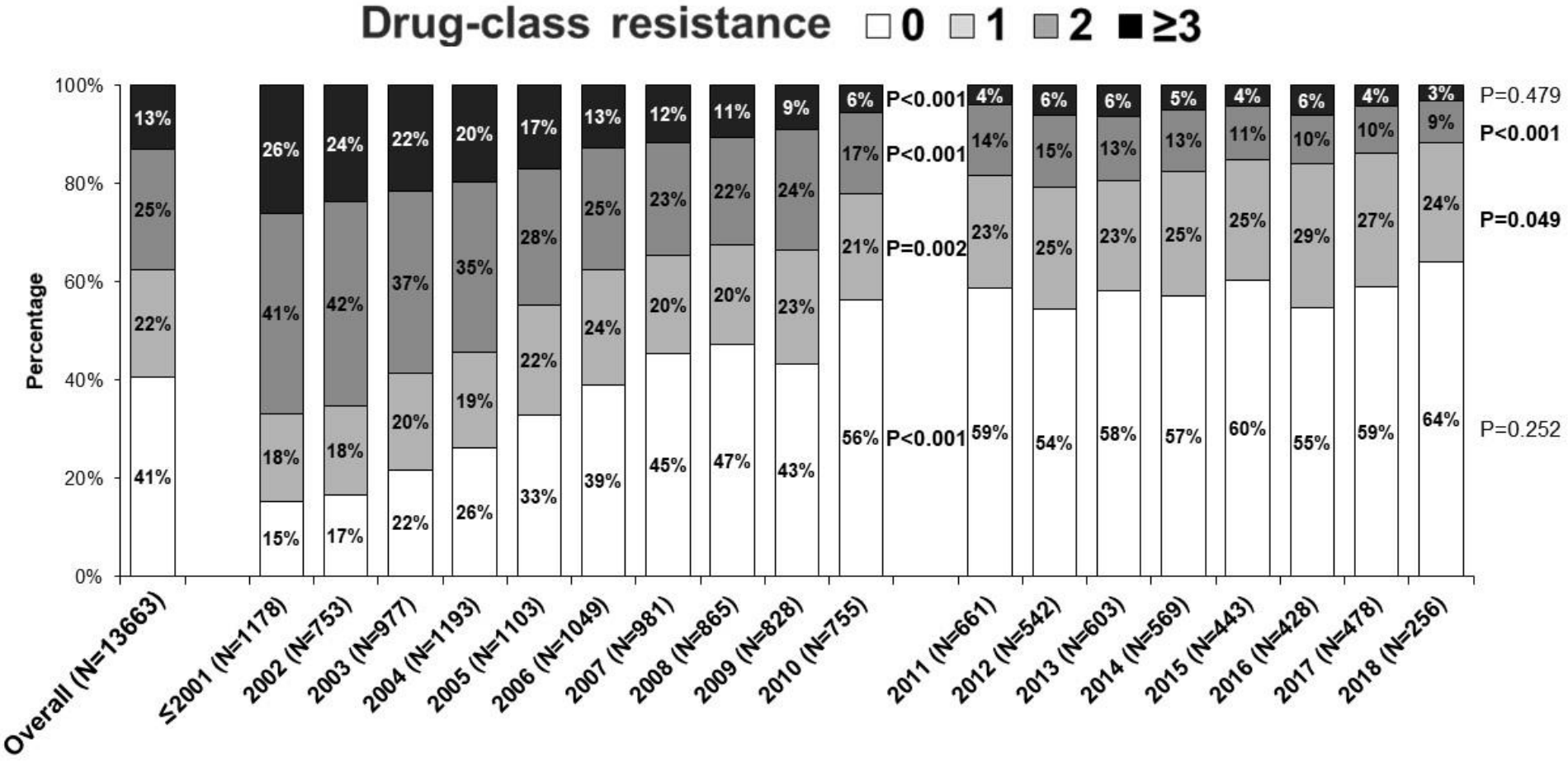
b) including myocardial infarction, stroke, or invasive cardiovascular procedures

c) including ascites, hepatic encephalopathy grade 3–4, hepatorenal syndrome, esophageal variceal bleeding, end-stage liver disease, and hepatocellular carcinoma

HTE is a broad definition, most commonly characterized as resistance to three main ARV classes (NRTIs, NNRTIs and PIs) based on genotypic resistance tests. HTE, Heavily Treatment Experienced; MOA, mechanism of action; PLWH, People Living With HIV.

1. Priest, J et al. Open Forum Infectious Diseases, Volume 8, Issue 12, December 2021, ofab562, https://doi.org/10.1093/ofid/ofab562
2. Pelche-Matthews A, et al. JAIDS Journal of Acquired Immune Deficiency Syndromes: June 1, 2021 - Volume 87 - Issue 2 - p 806-817 doi: 10.1097/QAI.0000000000002635
3. EACS Guidelines version 11.0 OCT 2021. Accessed October 2021.
4. DHHS. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, 2021. Accessed June 2021
5. Spivack S, et al. Drugs Context. 2022; 11: 2021-9-1. doi: 10.7573/dic.2021-9-1

Beyond 2010, prevalence of resistance in Italy remained stable around at 40% from 2011 to 2018.



Analysis performed on 13663 samples from 6739 ART-experienced HIV-1 infected patients, for whom GRTs for PR/RT (N=13663) and IN (N=2257) were performed for routine clinical purposes. P-values were calculated 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., JAC 2020

Characterization and outcomes of difficult-to-treat patients in Icona Cohort

International Journal of Antimicrobial Agents
Available online 29 October 2023, 107018
In Press, Journal Pre-proof What's this?

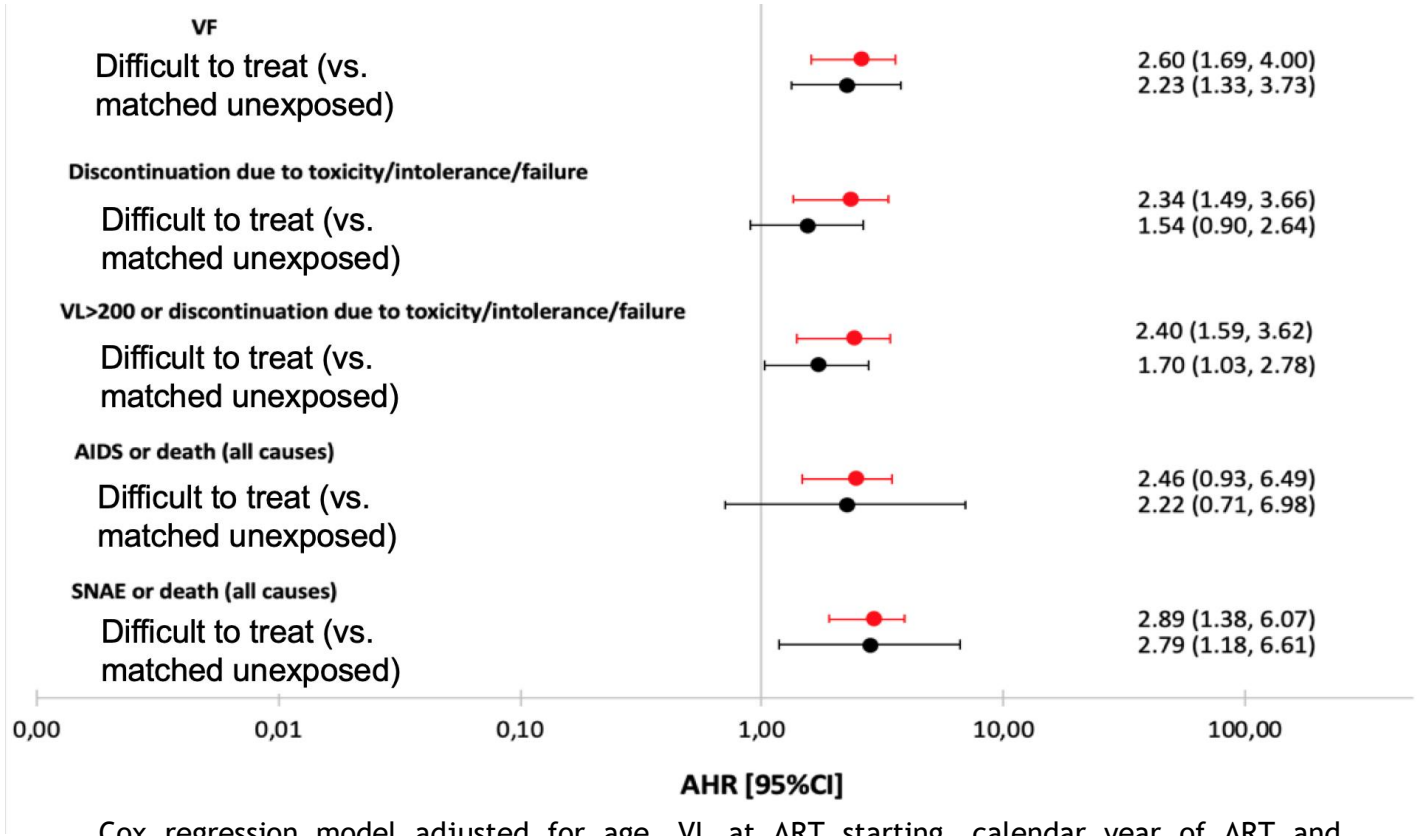
Characterization and outcomes of difficult-to-treat patients starting modern first-line ART regimens: data from the ICONA cohort

Roberta Gagliardini [1], Alessandro Tavelli [2], Stefano Rusconi [3 4], Sergio Lo Caputo [5],

PLWH as **"difficult to treat" (DTT)** if, after starting a modern ART, experienced ≥1 of the following events:

i) ≥2 VF (VF defined as 2 consecutive viral load, VL>50 copies/mL) with or without subsequent ART chang
ii) ≥2 treatment discontinuations due to toxicity/intolerance/failure on 2 different regimens;
iii) ≥1 VF followed by ART change plus ≥1 treatment discontinuation due to toxicity/intolerance/failure.

Among 8,061 PLWH included, **320 (4%)** experienced one of the **DTT**-defining

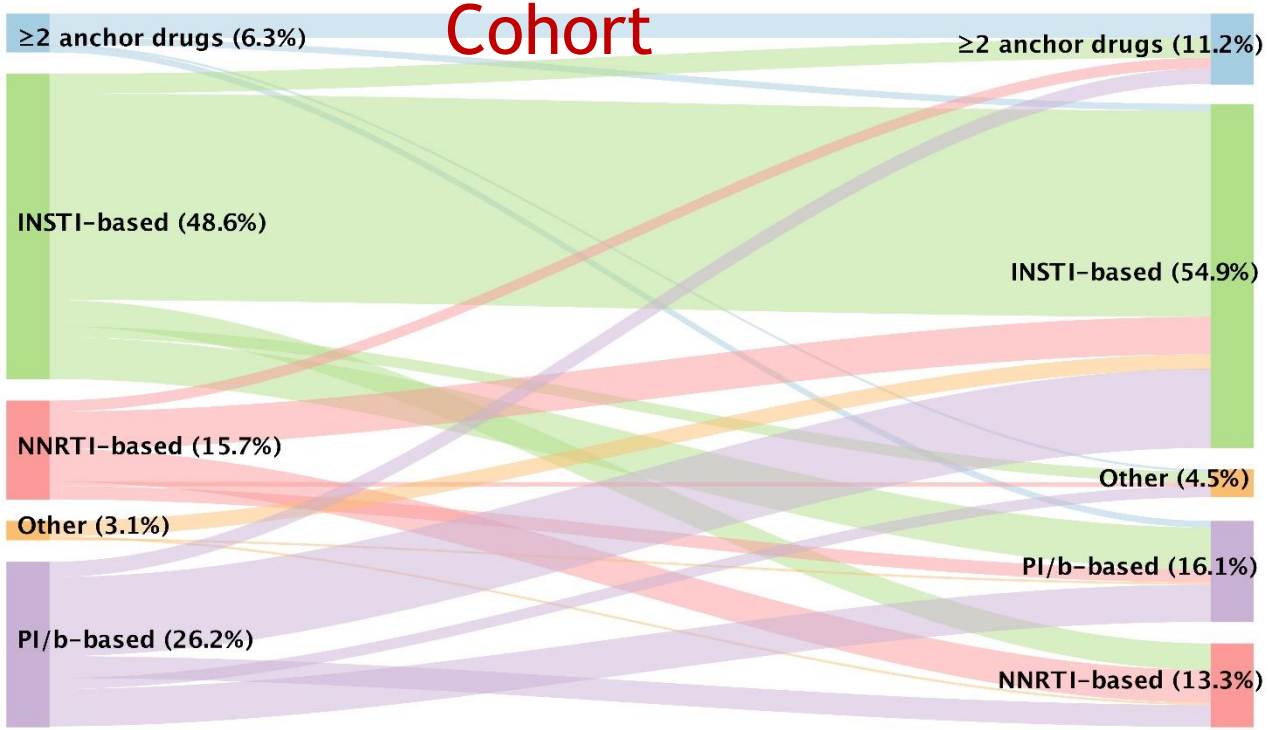


Cox regression model adjusted for age, VL at ART starting, calendar year of ART and nationality

- ✓ PLWH with advanced HIV disease had higher aHR of becoming DTT (aHR=1.30, 95% CI 0.98-1.74, p=0.072) when compared to PLWH without advanced HIV.
- ✓ In unadjusted analyses and compared to the matched unexposed group (286 DTT and 572 matched-unexposed), DTT showed higher probabilities of experiencing all the outcomes .After controlling for confounders, the associations remained significant for VF, treatment failure, SNAE/death.

Gagliardini R et al. IJAA 2023

Characterization and outcomes of difficult-to-treat patients in Icona Cohort



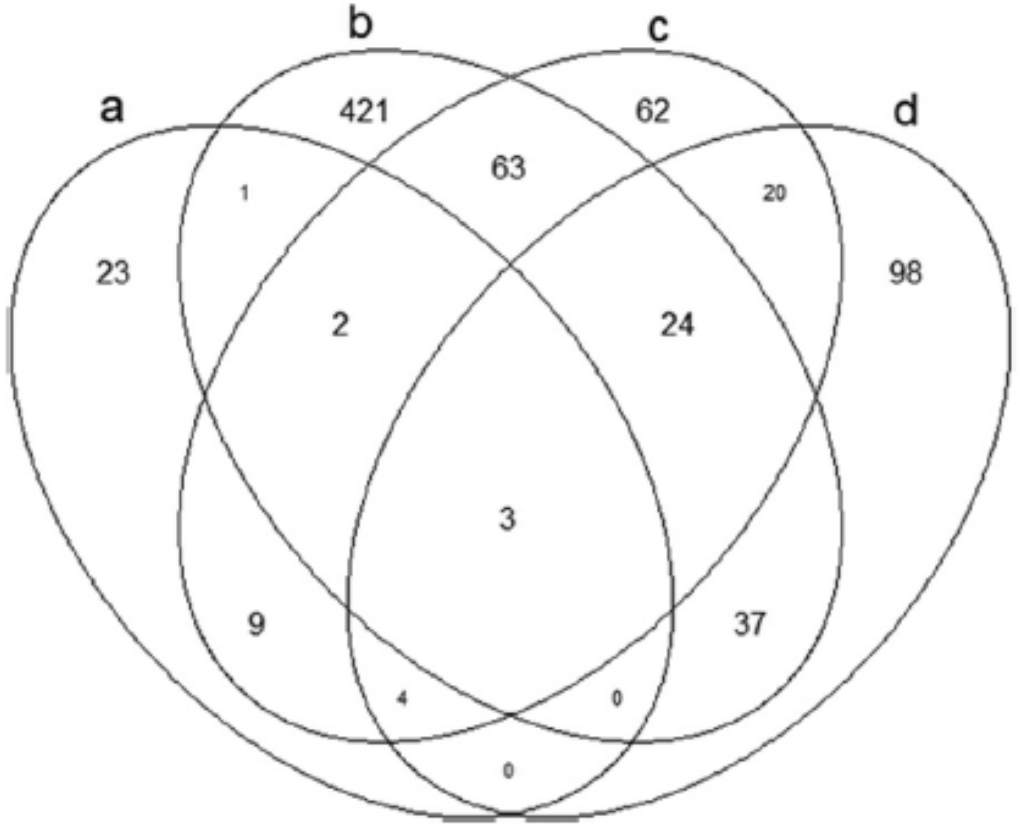
Most PWH who satisfied the DTT definition in our cohort, subsequently started a standardized regimen with 1 anchor drug + 1-2 NRTI, once daily, mainly INSTI-based, but more complex regimens (at least 2 anchor drugs) were prescribed in a higher proportion in comparison to non- DTT (11% of cases vs 7% of non-DTT), indicating potential lack of therapeutic options.

Gagliardini R et al. IJAA 2023

Heavily treatment-experienced persons living with HIV currently in care in Italy: characteristics, risk factors, and therapeutic options—the ICONA Foundation cohort study

Sergio Lo Caputo ,Mariacristina Poliseno, Alessandro Tavelli ,Roberta Gagliardini , Stefano Rusconi ,Giuseppe Lapadula , Andrea Antinori, Daniela Francisci , Loredana Sarmati ,Andrea Gori ,Vincenzo Spagnuolo, Francesca Ceccherini-Silberstein ,Antonella d'Arminio Monforte , Alessandro Cozzi-Lepri, the ICONA Foundation Study Group

Aim of the study: to investigate the prevalence and features of HTE individuals followed up in ICONA cohort as of December 31, 2021



Venn diagram to identify HTE subjects:

(a) current regimen indicative of HTE;
(b) at least three core ARV classes prior to cur- rent regimen;
(c) individuals who had at least four anchor drug switches at any previous time;
(d) ≥three virological failures followed by a treatment switch.

- **8758** PLWH actively followed in ICONA cohort,
- **163 HTE** (1.9%)

International Journal of Infectious Diseases 143 (2024) 106956

Heavily treatment-experienced persons living with HIV currently in care in Italy: characteristics, risk factors, and therapeutic options—the ICONA Foundation cohort study

Sergio Lo Caputo[1,§], Mariacristina Poliseno[2,§,*], Alessandro Tavelli[3], Roberta Gagliardini[4], Stefano Rusconi[5], Giuseppe Lapadula[6], Andrea Antinori[4], Daniela Francisci[7], Loredana Sarmati[8], Andrea Gori[9], Vincenzo Spagnuolo[10], Francesca Ceccherini-Silberstein[11], Antonella d'Arminio Monforte[12], Alessandro Cozzi-Lepri[13], the ICONA Foundation Study Group

International Journal of Infectious Diseases 143 (2024) 106956

mainly female, younger, Italian, and infected through heterosexual contact, met the HTE criteria. A lower CD4 count at ART initiation (odds ratio [OR] 1.60 per 100 cells/mmc lower CD4, 95% confidence interval [CI] 1.06-2.41, $P = 0.03$) and hepatitis C virus antibody positivity (OR 1.90, 95% CI 1.16-3.11, $P = 0.01$) were associated with higher HTE risk.

Thirty PLWH exhibited ongoing immune-virological failure (18% of the HTE sub- group and 0.003% of the total population).

Factors associated with entering the HTE definition among patients features collected at the moment of ART initiation.

	Logistic regression estimates of factors associated with HTE status					
	Unadjusted		Adjusted[a]		Adjusted[b]	
Factor	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Nationality						
Not Italian vs Italian	0,43 (0,25, 0,73)	***0.002***	0,34 (0,20, 0,59)	***<.001***		
Mode of transmission						
PWID vs not	4,81 (3,42, 6,77)	***<.001***	4,71 (3,34, 6,65)	***<.001***		
AIDS						
Yes vs not	1,78 (1,14, 2,78)	***0.012***	1,77 (1,13, 2,79)	0,013	1,43 (0,87, 2,34)	0,153
HCVAb						
Positive vs negative	4,63 (3,23, 6,63)	***<.001***	4,14 (2,87, 5,98)	***<.001***	1,90 (1,16, 3,11)	***0.011***
Year of ART initiation						
per more recent	0,80 (0,77, 0,82)	***<.001***	0,80 (0,78, 0,82)	***<.001***		
CD4 count nadir						
below 200 vs >200 cells/mmc	1,51 (1,10, 2,07)	***0.012***	1,72 (1,24, 2,38)	***0.001***	1,60 (1,06, 2,41)	***0.026***
HIV-RNA						
>100,000 vs below 100,000 copies/ml	1,13 (0,78, 1,63)	0,528	1,29 (0,89, 1,87)	0,179		
2NNRTIas 1st line						
Yes vs no	9,70 (6,70, 14,03)	***<.001***	7,45 (5,11, 10,86)	<,001	1,05 (0,69, 1,60)	0,809

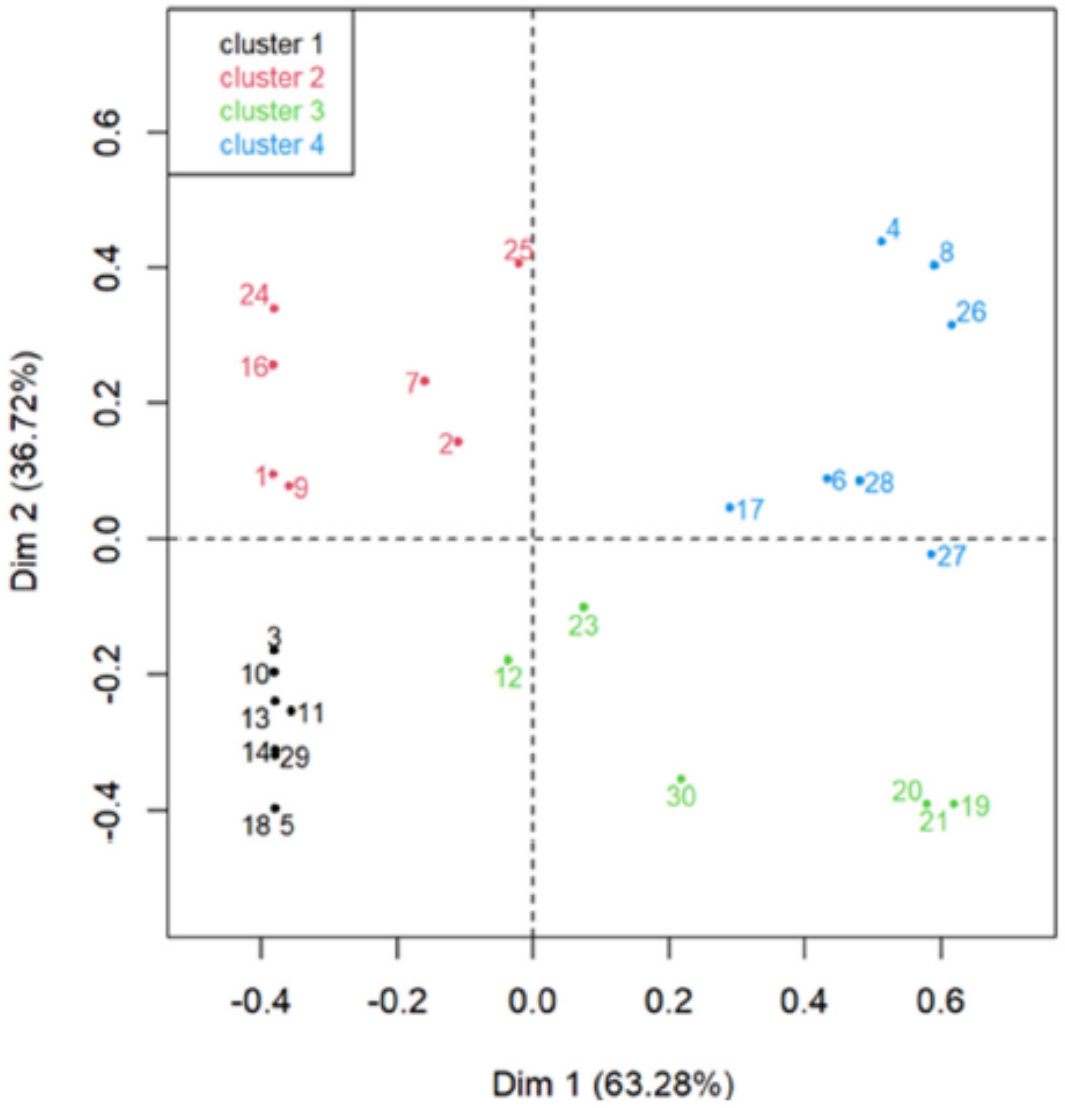
Factors associated with transitioning to HTE status with immune-virological failure among the features collected at the moment of ART initiation.

	Logistic regression estimates of factors associated with immune-virological failure					
	Unadjusted		Adjusted[a]		Adjusted[b]	
Factor	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Nationality						
Not Italian vs Italian	0,85 (0,32, 2,21)	0,734	0,72 (0,27, 1,95)	0,523		
Mode of transmission						
PWID vs not	3,95 (1,75, 8,91)	***<.001***	3,84 (1,70, 8,66)	***0.001***		
AIDS						
Yes vs not	0,77 (0,18, 3,25)	0,724	0,74 (0,17, 3,12)	0,678	0,53 (0,12, 2,36)	0,404
HCVAb						
Positive vs negative	4,85 (2,15, 10,93)	***<.001***	4,27 (1,88, 9,70)	***<.001***	2,61 (0,85, 8,00)	0,092
Year of ART initiation						
per more recent	0,83 (0,79, 0,87)	***<.001***	0,83 (0,79, 0,88)	***<.001***		
CD4 count nadir						
below 200 vs >200 cells/mmc	1,59 (0,77, 3,31)	0,212	1,75 (0,83, 3,70)	0,140	1,62 (0,67, 3,93)	0,284
HIV-RNA						
>100,000 vs below 100,000 copies/ml	0,95 (0,42, 2,14)	0,903	1,09 (0,48, 2,46)	0,838		
NNRTI as 1st line						
Yes vs no	10,16 (4,49, 23,00)	***<.001***	8,00 (3,48, 18,37)	***<.001***	1,56 (0,61, 3,99)	0,350

Heavily treatment-experienced persons living with HIV currently in care in Italy: characteristics, risk factors, and therapeutic options—the ICONA Foundation cohort study

Sergio Lo Caputo[1,§], Mariacristina Poliseno[2,§,*], Alessandro Tavelli[3], Roberta Gagliardini[4], Stefano Rusconi[5], Giuseppe Lapadula[6], Andrea Antinori[4], Daniela Francisci[7], Loredana Sarmati[8], Andrea Gori[9], Vincenzo Spagnuolo[10], Francesca Ceccherini-Silberstein[11], Antonella d'Arminio Monforte[12], Alessandro Cozzi-Lepri[13], the ICONA Foundation Study Group

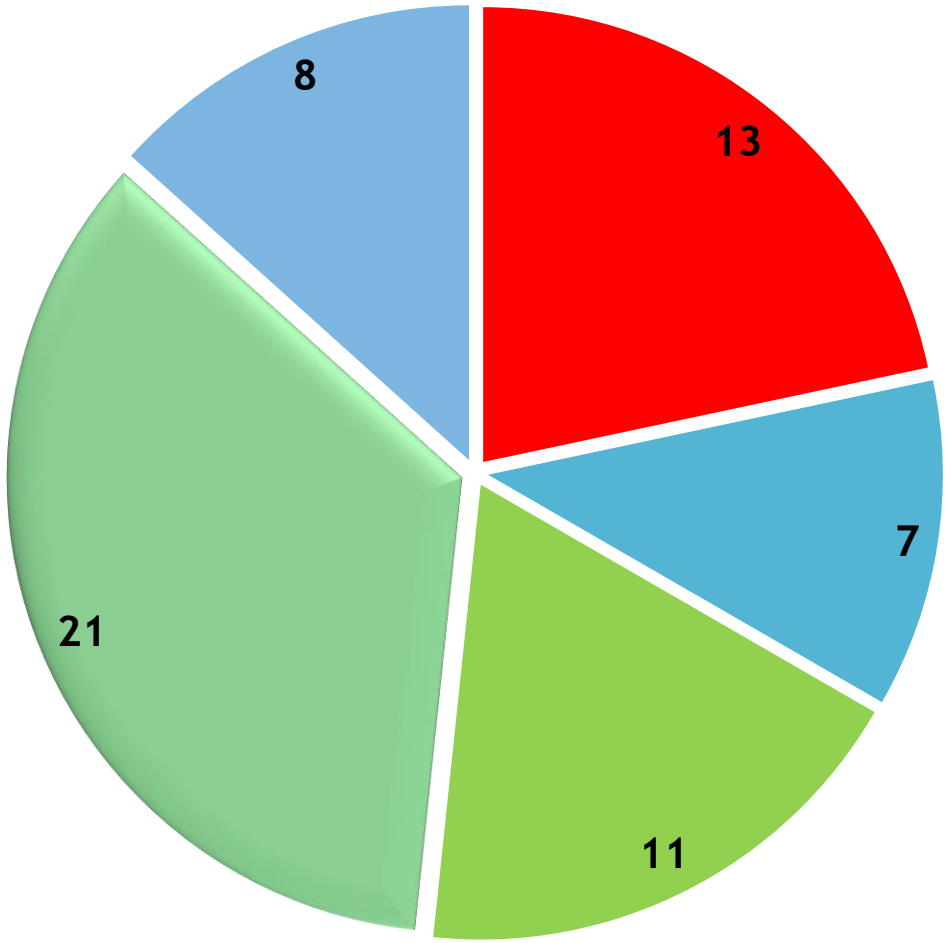
Cluster 1: n = 8 patients with low viral loads and CD4 counts above 200 cells/mm3
Cluster 2: n = 9 patients with viral loads above 200 cp/ml but good CD4 counts > 200 cells/mm3
Cluster 3: n = 6 subjects with CD4 counts < 200 cells/mm3 despite low viral loads,
Cluster 4: n = 7 patients with CD4 count con- stantly < 200 cells/mm3 regardless of viral load



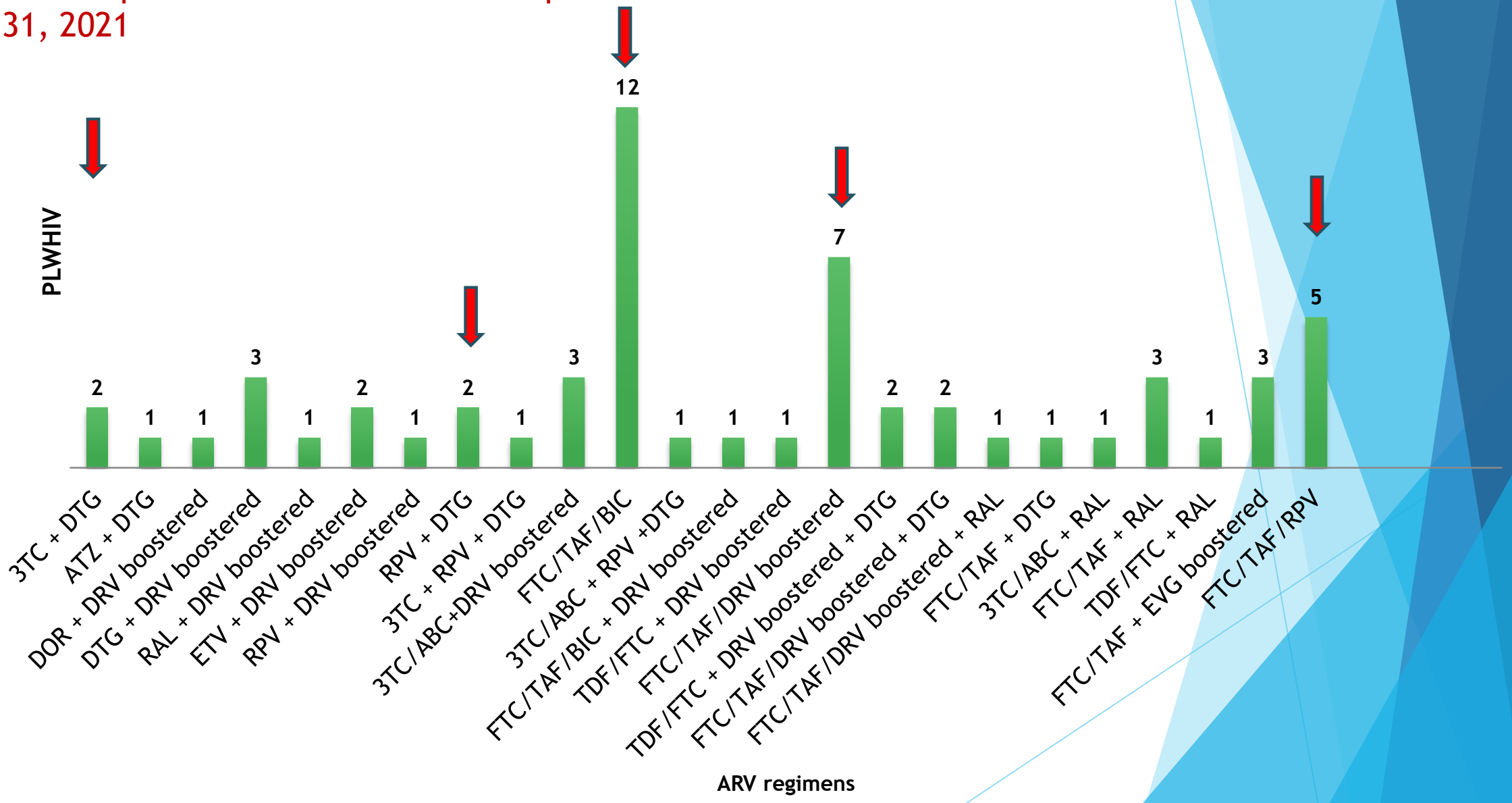
Thirty PLWH exhibited ongoing immune-virological failure (i.e., with a current CD4 count < 200 cells/mmc or VL > 200 copies/mL). A cluster analysis identified 13 (43%) with a current CD4 count < 200 cells/mmc. Also, notably, 19/30 (63%) had major acquired resistance- associated mutations to at least one antiretroviral drug class.

International Journal of Infectious Diseases 143 (2024) 106956

Proportion of ARV regimes prescribed in 60 stable, compromised HTE patients in ICONA cohort – Update December 31, 2021



Types of ARV regimes prescribed in 60 stable, compromised HTE patients in ICONA cohort – Update December 31, 2021



BMJ Open

Cohort profile: PRESTIGIO, an Italian prospective registry-based cohort of people with HIV-1 resistant to reverse transcriptase, protease and integrase inhibitors

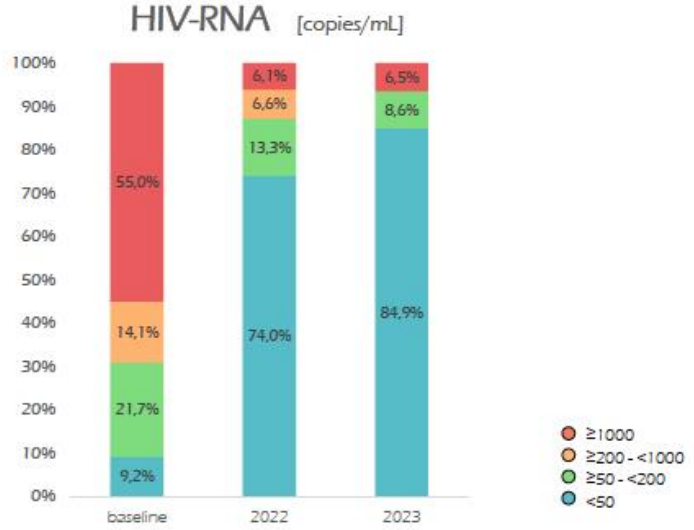
Clemente T, 2024

Table 2 Continued

Characteristics	Overall (n=229)
Number of antiretrovirals in the current regimen	
≤3	134 (58.5%)
4–5	89 (38.9%)
6–7	6 (2.6%)
NRTI-containing regimens	167 (72.9%)
NNRTI-containing regimens	71 (31%)
PI-containing regimens	168 (73.4%)
INSTI-containing regimens	195 (85.2%)
Maraviroc-containing regimens	48 (21%)
Enfuvirtide-containing regimens	6 (2.6%)
Fostemsavir-containing regimens	17 (7.4%)
Ibalizumab-containing regimens	7 (3.1%)
Lenacapavir-containing regimens	9 (3.9%)

Data are reported as frequency (percentage) or median (IQR), as appropriate.
ART, antiretroviral therapy; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

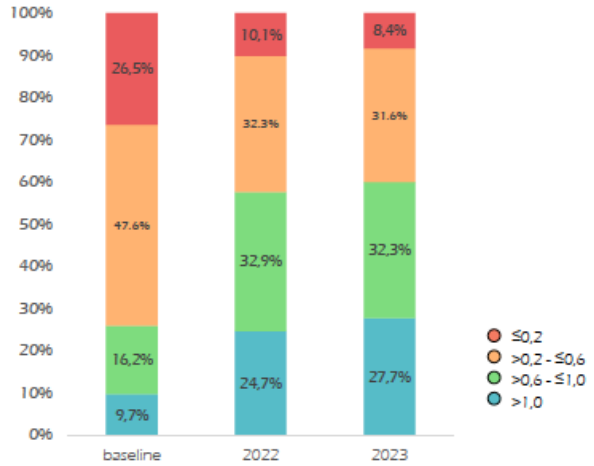
VIRAL LOAD



PRESTIGIO Registry meetING on HIV multidrug resistance

Data updated to March 1st, 2024

IMMUNOLOGICAL PROFILE



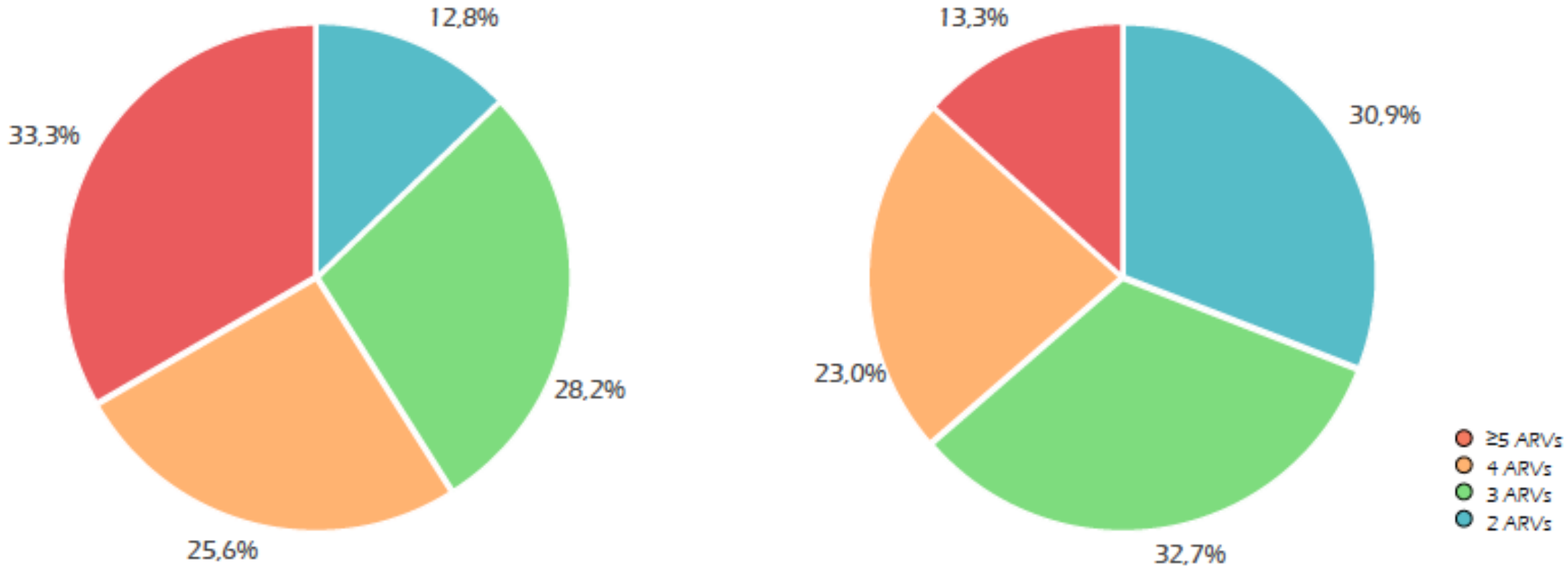
PRESTIGIO Registry meetING on HIV multidrug resistance

Data updated to March 1st, 2024

Antiretroviral drugs

		2021 (n=205)	2022 (n=206)	2023 (n=205)
Drugs	DTG	159 (77,6%)	154 (74,8%)	153 (74,6%)
	DRV/r	87 (42,4%)	74 (35,9%)	74 (36,1%)
	DRV/c	55 (26,8%)	61 (29,6%)	58 (28,3%)
	XTC	102 (49,8%)	108 (52,4%)	110 (53,7%)
	TAF	74 (36,1%)	79 (38,3%)	83 (40,5%)
	TDF	15 (7,3%)	15 (7,3%)	12 (5,9%)
	DOR	27 (13,2%)	32 (15,5%)	36 (17,6%)
	ETV	29 (14,1%)	24 (11,7%)	20 (9,8%)
	RPV	12 (5,9%)	11 (5,3%)	10 (4,9%)
	MVC	40 (19,5%)	43 (20,9%)	41 (20,0%)
	FTR	11 (5,4%)	24 (11,7%)	34 (16,6%)
	LEN	8 (3,9%)	8 (3,9%)	9 (5,3%)
	IBA	5 (2,4%)	8 (3,9%)	5 (2,5%)
	ISL	3 (1,5%)	3 (1,5%)	3 (1,5%)
	ENF	2 (1,0%)	4 (1,9%)	2 (1,0%)

Current antiretroviral regimen

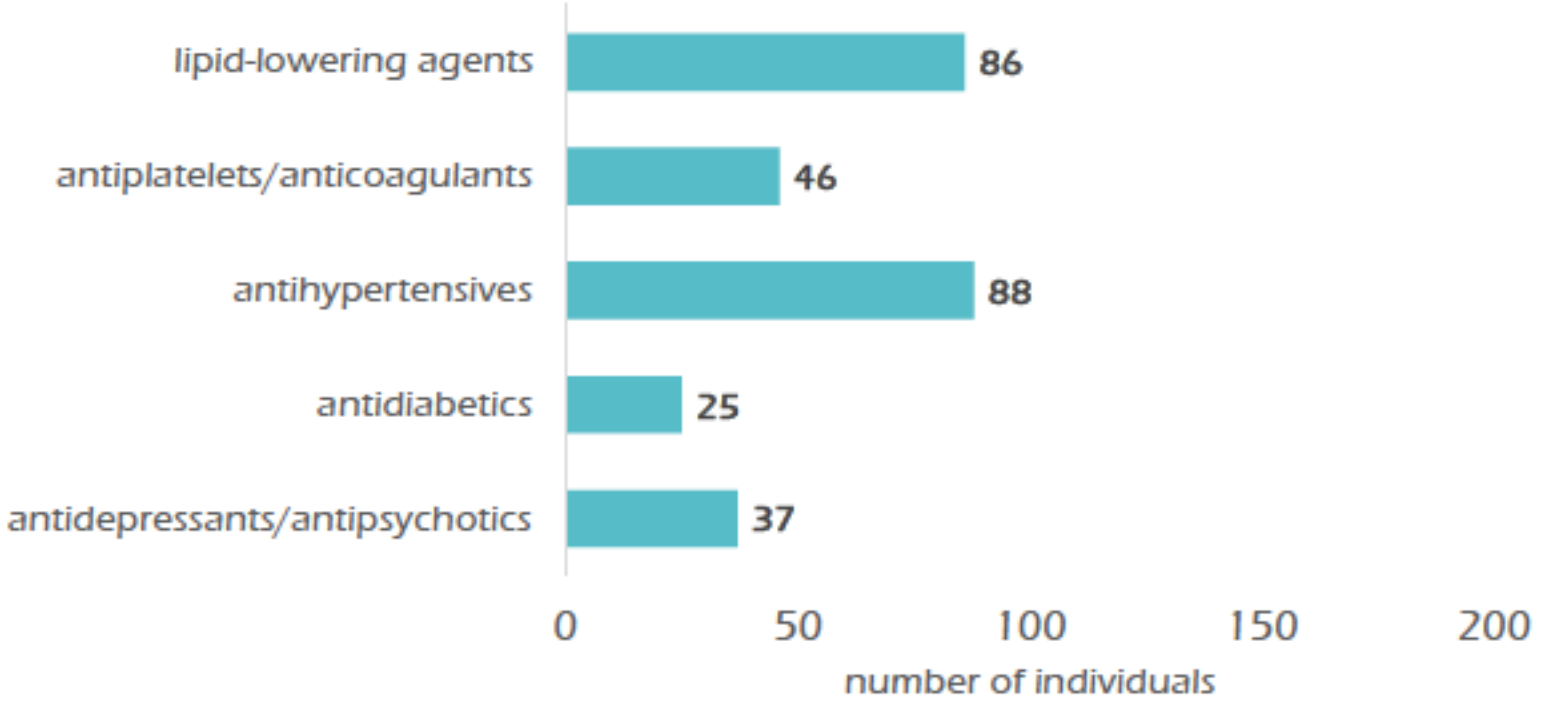


PRESTIGIO Registry meetING on HIV multidrug resistance

Data updated to March 1st, 2024

CONCOMITANT THERAPIES

last available



NEW DRUGS FOR HTE MANAGEMENT

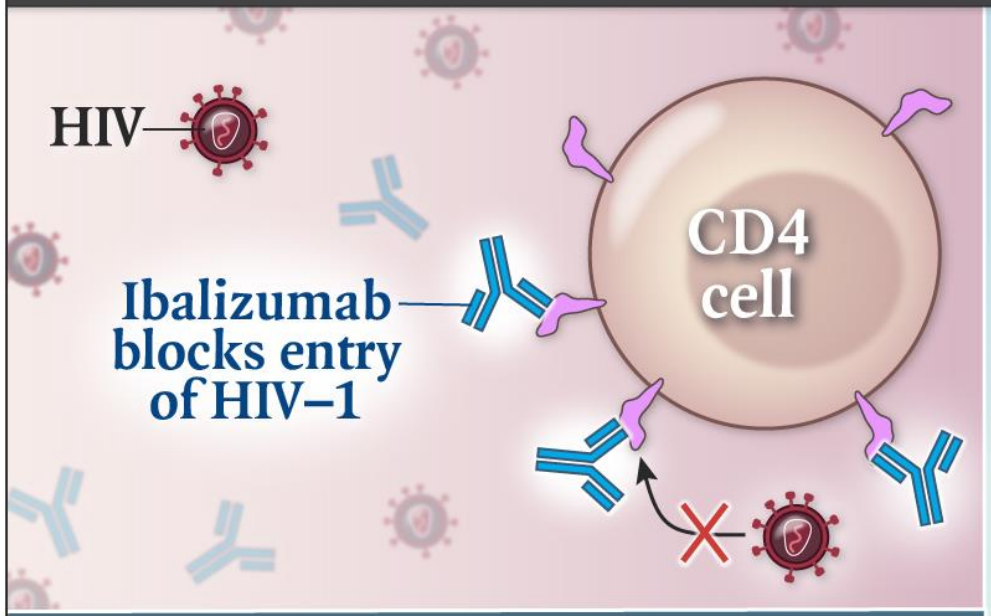
IBALIZUMAB

FOSTEMSAVIR

LENACAPAVIR

Ibalizumab for Multidrug-Resistant HIV-1 (n=40)

SINGLE-GROUP, OPEN-LABEL, MULTICENTER, PHASE 3 TRIAL



Patients with viral load decrease ≥0.5 $\log_{10}$ copies per milliliter from baseline

Control Period (Days 0–6)	Functional Monotherapy (Days 7–13)	Maintenance Period (Day 14–wk 25)
Current therapy	Current therapy + Ibalizumab (Day 7, 2000 mg)	Optimized background regimen + Ibalizumab (800 mg every 14 days)
3% (1/40)	83% (33/40)	HIV-RNA <50 cp/ml: 43% (17/40)

P < 0.001

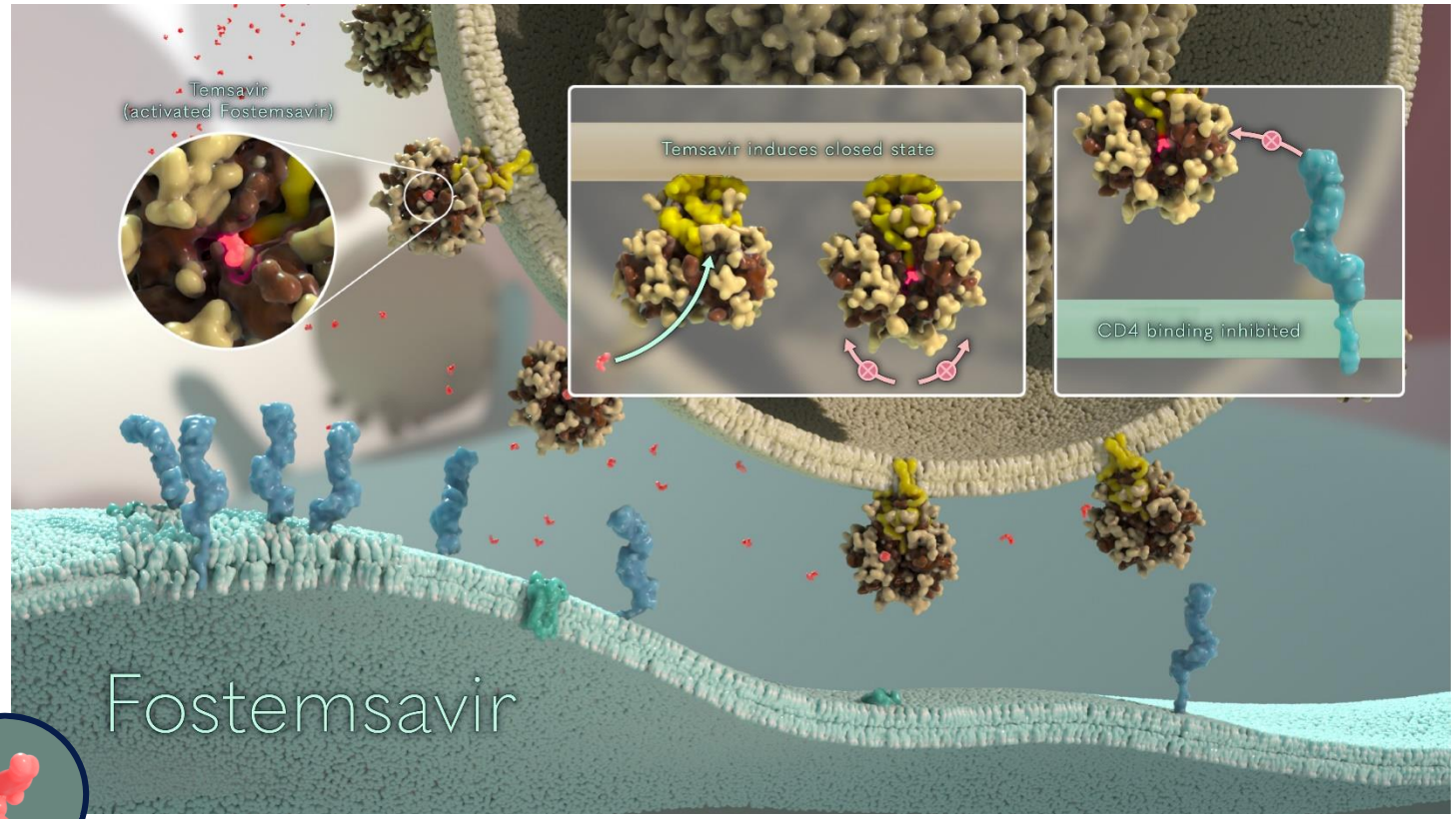
Ibalizumab had significant antiviral activity, reducing viral load over 24 weeks

The NEW ENGLAND JOURNAL of MEDICINE

Emu et al. 2018

Fostemsavir

- Fostemsavir (FTR) is a prodrug of temsavir, a first-in-class and only **attachment inhibitor** that binds to the **HIV-1 envelope gp120**, preventing attachment to CD4+ cell-surface receptors[1]



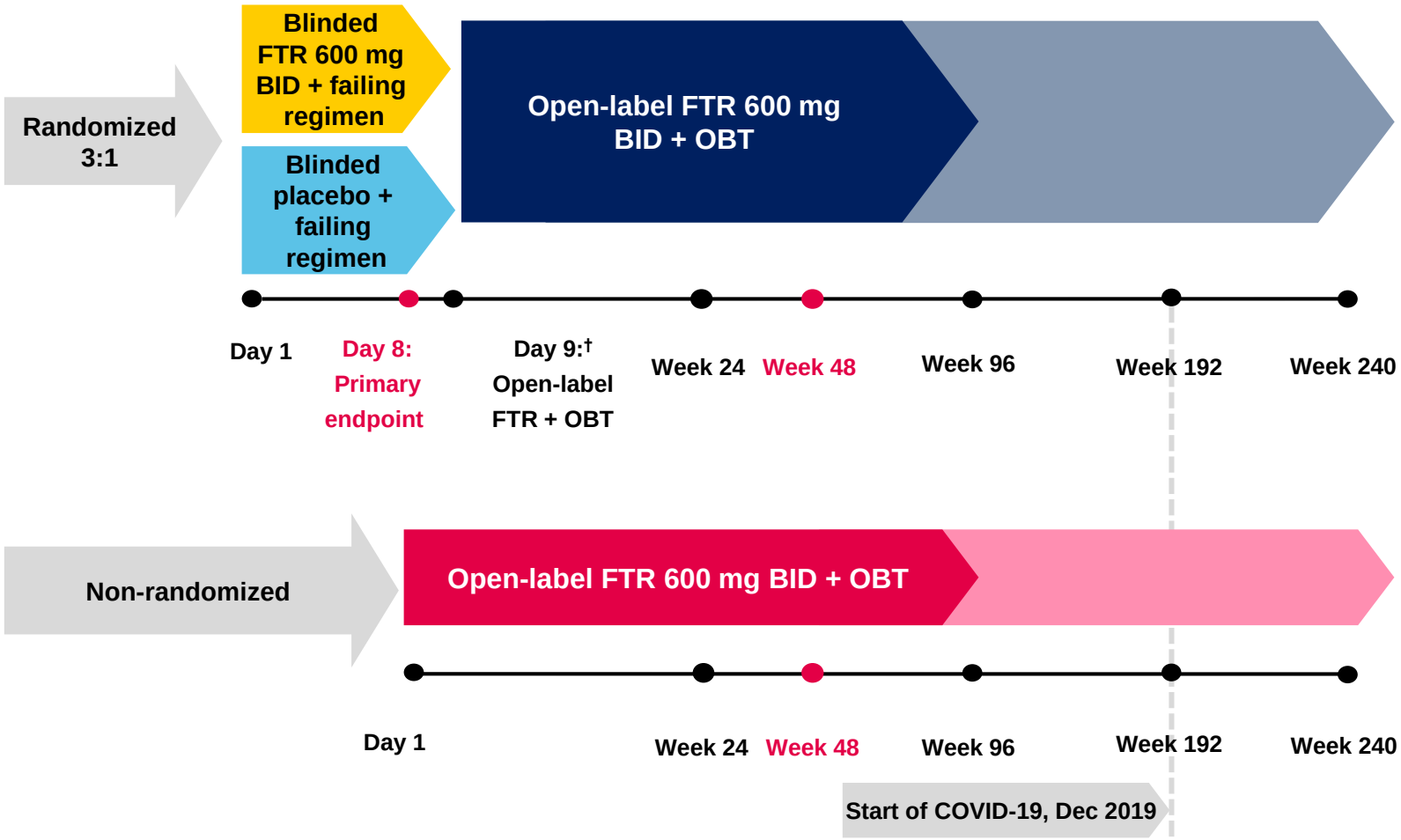
- Attachment and inhibition by TMR occurs **regardless of R5/X4 tropism** and is therefore not affected by tropism[1,2]
  - The unique MoA of TMR means there is no cross-resistance with other entry inhibitors or other ARVs
- TMR binding causes the locking of gp120 into a 'closed state' which does not permit any CD4 binding[1]
- By inhibiting attachment to CD4, TMR prevents targeT-cell infection. HIV-1 is subsequently cleared from the extracellular space by immune processes[1]
- The closed conformation of TMR bound gp120 precludes CD4 binding, thereby preventing gp120 structural rearrangements and intracellular signaling cascades[1]

1. Lataillade M, et al. Lancet HIV 2020;7:e740–51
2. Kozal M, et al. N Engl J Med 2020;382:1232–43

BRIGHTE: Study Design

Randomized cohort:*
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and:
- One or two ARV classes remaining with ≥1 approved fully active agent per class
- Unable to construct viable regimen from remaining approved agents

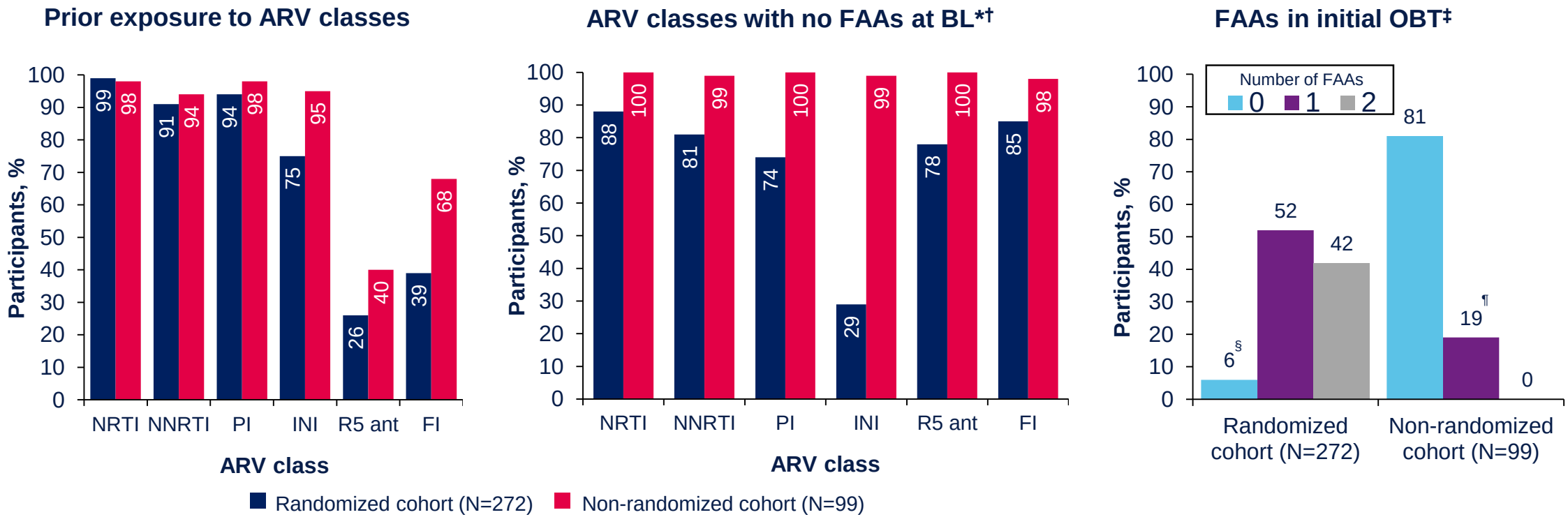
Non-randomized cohort:*
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and:
- Zero ARV classes remaining and no remaining approved fully active agents†



*There were no screening of TMR susceptibility criteria
†Measured from the start of open-label FTR 600 mg BID + OBT
‡ Use of investigational agents as part of OBT was permitted in the non-randomized cohort only
§The study is expected to be conducted until participants can access FTR through other means (e.g. marketing ap

1. Kozal M, et al. N Engl J Med 2020;382:1232–43
2. Aberg J, et al. IAC 2022. Poster EPB160

BRIGHTE: Baseline Prior ARV Experience and Resistance



*Ibalizumab was not approved when this study was initiated; †Proportions of participants for whom there were no remaining fully active and approved antiretroviral agents within the indicated class based on the screening criteria of activity (per screening and historical resistance measures) and availability (tolerability, contraindications, and, in the case of enfuvirtide only, willingness to receive an injectable) ‡Including investigational ARVs; §These included participants who discontinued from the study during the double-blind period and never initiated OBT, had no active antiretroviral available at screening and were incorrectly assigned to the randomized cohort, or had one or more active antiretrovirals available at screening but did not use these as part of the initial OBT; ¶15 of these 19 participants received the investigational antiretroviral ibalizumab and four received an approved antiretroviral (n=2 enfuvirtide, n=1 etravirine, and n=1 dolutegravir) and were classified as protocol deviations

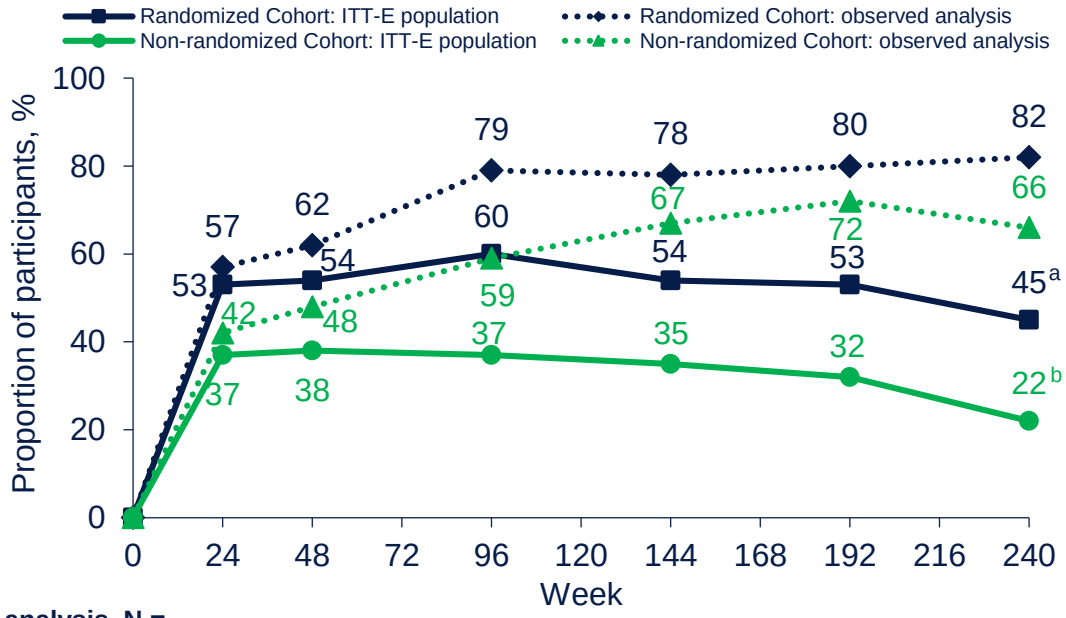
FAAs, fully active and approved

Lataillade M, et al. Lancet HIV 2020;7:e740–51 (and suppl. appendix)

BRIGHTE: Virologic Response

- In the Randomized Cohort, virologic response rates (HIV-1 RNA <40 c/mL) generally remained consistent through Week 240
  - Reduced virologic response rates by Snapshot at Week 192 and beyond were partially confounded by missing data due to COVID-19: at Week 240, 19 (7%) participants in the Randomized Cohort and 5 (5%) in the Non-randomized Cohort were counted as virologic failures for this reason

HIV-1 RNA <40 c/mL Through Week 240 by Snapshot Analysis (ITT-E) and Observed Analysis



Observed analysis, N =						
Randomized Cohort	247	233	214	206	195	164
Non-randomized Cohort	89	83	66	57	50	35

ITT-E participants without an HIV-1 RNA value at the relevant time point or those who changed OBT due to lack of efficacy up to each time point counted as failures.

[a]ITT-E population, N=267. [b]ITT-E population, N=92.

Aberg et al. HIV Drug Therapy Glasgow 2022; Virtual and Glasgow, Scotland. Poster P061.

BRIGHTE: Virologic Response

- By observed analysis at Weeks 96, 192, and **240**
  - **HIV-1 RNA was <200 c/mL** for 187/214 (87%), 181/195 (93%), and **151/164 (92%)** participants, respectively, in the Randomized Cohort and 43/66 (65%), 40/50 (80%), and 27/35 **(77%)** participants, respectively, in the Non-randomized Cohort
  - **HIV-1 RNA was <400 c/mL** for 189/214 (88%), 182/195 (93%), and 155/164 (**95%**) participants, respectively, in the Randomized Cohort and 45/66 (68%), 40/50 (80%), and 28/35 (**80**%) participants, respectively, in the Non-randomized Cohort

Virologic Outcomes and Protocol-Defined Virologic Failure Through Week 240 by Snapshot Analysis (ITT-E)

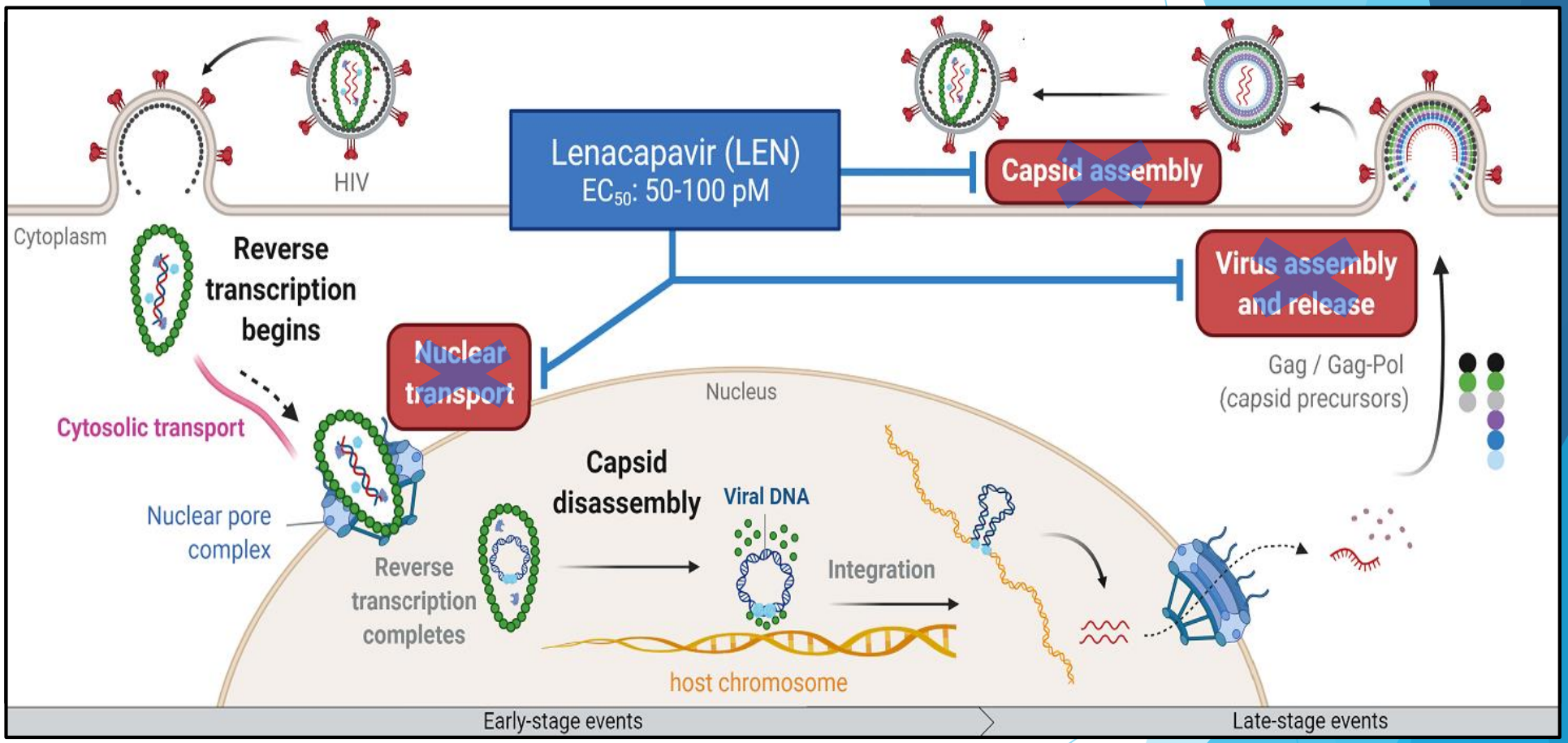
	Randomized Cohort			Non-randomized Cohort		
Outcome, n (%)	Week 96	Week 192[a]	Week 240[b]	Week 96	Week 192[a]	Week 240[b]
Number of participants	**272**	**272**	**267**	**99**	**99**	**92**
HIV-1 RNA <40 c/mL	**164 (60)**	**145 (53)**	**120 (45)**	**37 (37)**	**32 (32)**	**20 (22)**
HIV-1 RNA ≥40 c/mL	**80 (29)**	**90 (33)**	**89 (33)**	**43 (43)**	**43 (43)**	**43 (47)**
Data in window not <40 c/mL	32 (12)	27 (10)	20 (7)	15 (15)	5 (5)	5 (5)
D/C for lack of efficacy	9 (3)	12 (4)	14 (5)	3 (3)	6 (6)	6 (7)
D/C for other reason while not <40 c/mL	17 (6)	21 (8)	24 (9)	6 (6)	10 (10)	10 (11)
Change in background ART	22 (8)	30 (11)	31 (12)[c]	19 (19)	22 (22)	22 (24)[d]
No virologic data	**28 (10)**	**37 (14)**	**58 (22)**	**19 (19)**	**24 (24)**	**29 (32)**
D/C study due to AE or death	15 (6)	16 (6)	17 (6)	14 (14)	18 (8)	18 (20)
D/C study for other reasons	8 (3)	15 (6)	19 (7)	4 (4)	4 (4)	4 (4)
Missing data during window but on study						
Not COVID-19 related	5 (2)	2 (<1)	3 (1)	1 (1)	0	2 (2)
COVID-19 related	—	4 (1)	19 (7)	—	2 (2)	5 (5)
Protocol-defined virologic failure	63 (23)	75 (28)	80 (29)	49 (49)	52 (53)	53 (54)

D/C, discontinuation. [a]Week 192 was the last study time point that included all participants from the original ITT-E population (no participants had completed the study). [b]At Week 240, 12 participants had completed the study by transitioning to locally approved fostemsavir (the first fostemsavir approval was in the US in July 2020). [c]Week 240 HIV-1 RNA was <40 c/mL for 17 of these 31 participants. [d]Week 240 HIV-1 RNA was <40 c/mL for 4 of these 22 participants. [e]Protocol-defined virologic failure was defined as the following: before Week 24, confirmed HIV-1 RNA ≥400 c/mL after confirmed suppression to <400 c/mL or confirmed >1 $\log_{10}$ nadir where nadir is ≥40 c/mL; at or after Week 24, confirmed HIV-1 RNA ≥400 c/mL.

LEN Targets Multiple Stages of the HIV Replication Cycle

LEN binding directly between capsid protein subunits and inhibits 3 essential steps of the viral lifecycle:

1. Capsid-mediated nuclear uptake of HIV proviral DNA
2. Virus assembly and release
3. Capsid core formation



LEN modulates the stability and/or transport of capsid complexes, leading to inhibition of multiple processes in the HIV lifecycle[31]

Figure generated based on the following references: Link J, et al. Nature 2020;584:614-618; Bester SM, et al. Science 2020;370:360-364; Cihlar T. vCROI 2021. Oral #22; Muller B. vCROI 2021. Oral #19; Pathak VK. vCROI 2021. Oral #20; Ganser-Pornillos B. vCROI 2021. Oral #21

SERIE GENERALE

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 164° - Numero 193

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA — Roma - Sabato, 19 agosto 2023 — SI PUBBLICA TUTTI I GIORNI NON FESTIVI

DIREZIONE E REDAZIONE PRESSO IL MINISTERO DELLA GIUSTIZIA - UFFICIO PUBBLICAZIONE LEGGI E DECRETI - VIA ARENULA, 70 - 00186 ROMA
AMMINISTRAZIONE PRESSO L'ISTITUTO POLIGRAFICO E ZECCA DELLO STATO - VIA SALARIA, 691 - 00138 ROMA - CENTRALINO 06-85081 - LIBRERIA DELLO STATO
PIAZZA G. VERDI, 1 - 00198 ROMA

La **Gazzetta Ufficiale, Parte Prima,** *oltre alla* **Serie Generale**, *pubblica cinque Serie speciali, ciascuna contraddistinta da autonoma numerazione:*

1ª Serie speciale: *Corte costituzionale (pubblicata il mercoledì)*
2ª Serie speciale: *Unione europea (pubblicata il lunedì e il giovedì)*
3ª Serie speciale: *Regioni (pubblicata il sabato)*
4ª Serie speciale: *Concorsi ed esami (pubblicata il martedì e il venerdì)*
5ª Serie speciale: *Contratti pubblici (pubblicata il lunedì, il mercoledì e il venerdì)*

La **Gazzetta Ufficiale, Parte Seconda,** "Foglio delle inserzioni", *è pubblicata il martedì, il giovedì e il sabato*

Lenacapavir

- **CAPELLA**
- **CALIBRATE**

Sunlenca® (lenacapavir)

Lenacapavir in Heavily Treatment-Experienced PWH

Capella

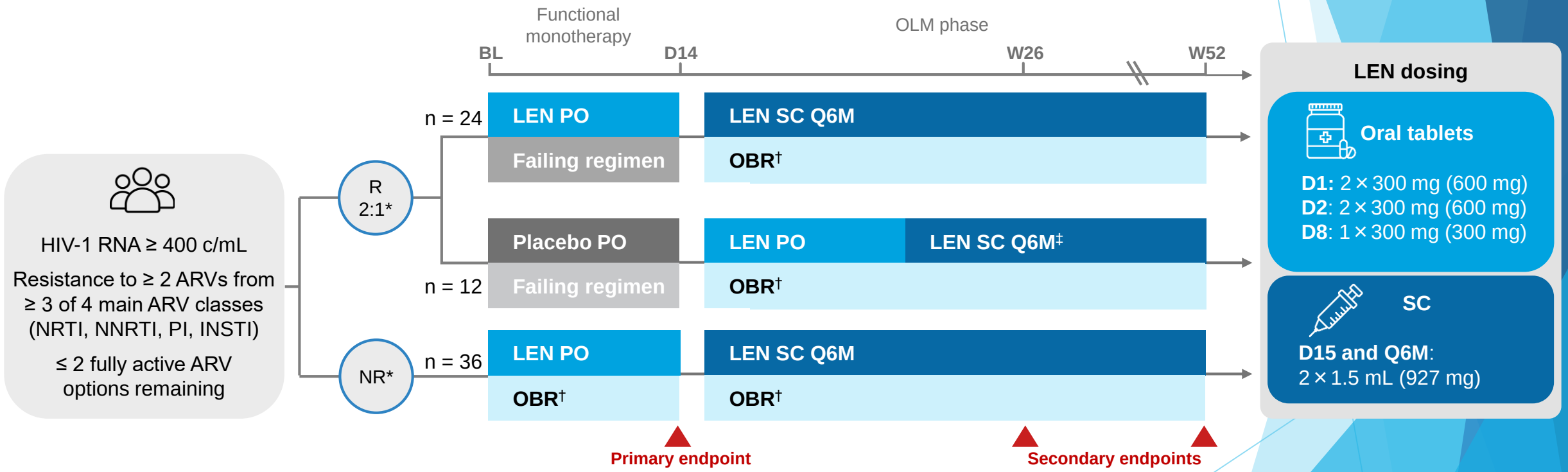
N = 72

HTE PLWH with MDR, aged ≥ 12 years and weighing ≥ 35 kg

Outcomes (randomized cohort)

Primary: ≥ 0.5 $\log_{10}$ c/mL reduction in HIV-1 RNA from BL at D15
Secondary: HIV-1 RNA < 50 c/mL and < 200 c/mL at W26 and W52 (FDA Snapshot)

2019–present (ongoing)



LEN dosing

Oral tablets

D1: 2 × 300 mg (600 mg)
D2: 2 × 300 mg (600 mg)
D8: 1 × 300 mg (300 mg)

SC

D15 and Q6M:
2 × 1.5 mL (927 mg)

*Participants with < 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the randomized cohort; participants with ≥ 0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening entered the nonrandomized cohort; †Investigational agents (e.g., FTR) permitted; atazanavir (ATV), ATV/cobicistat, ATV/ritonavir, efavirenz (EFV), entecavir (ETR), nevirapine (NVP), tipranavir (TPV) not permitted

BL, baseline; D, day; FDA, U.S. Food and Drug Administration; HTE, heavily treatment-experienced; MDR, multidrug resistance; NR, nonrandomized, OBR, optimized background regimen; OLM, open-label maintenance; PLWH: people living with HIV; PO, by mouth; Q6M, every 6 months; R, randomization; SC, subcutaneous

Ogbuagu O, et al. CROI 2023, Poster 523

Table 1 Recommended Treatment Regimen for SUNLENCA Initiation and Maintenance, Option 1

Treatment Time	
	Dosage of SUNLENCA: Initiation
Day 1	927 mg by subcutaneous injection (2 x 1.5 mL injections) 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
	Dosage of SUNLENCA: Maintenance
Every 6 months (26 weeks)[a] +/-2 weeks	927 mg by subcutaneous injection (2 x 1.5 mL injections)

a. From the date of the last injection.

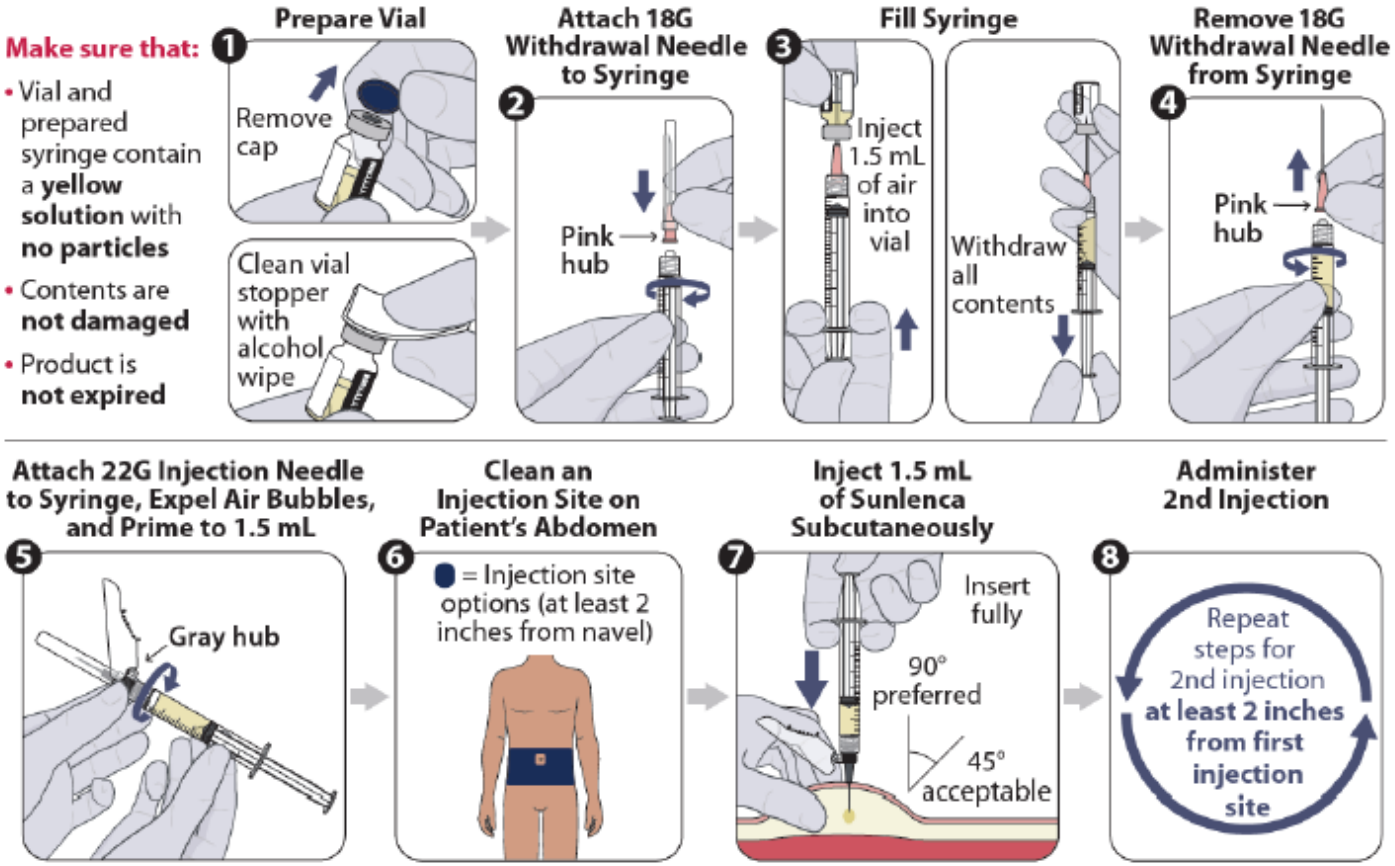
Table 2 Recommended Treatment Regimen for SUNLENCA Initiation and Maintenance, Option 2

Treatment Time	
	Dosage of SUNLENCA: Initiation
Day 1	600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
Day 8	300 mg orally (1 x 300 mg tablet)
Day 15	927 mg by subcutaneous injection (2 x 1.5 mL injections)
	Dosage of SUNLENCA: Maintenance
Every 6 months (26 weeks)[a] +/-2 weeks	927 mg by subcutaneous injection (2 x 1.5 mL injections)

a. From the date of the last injection.

Figure 3 SUNLENCA Withdrawal Needle Injection Kit Components

Figure 4 SUNLENCA Injection Steps for Withdrawal Needle Injection Kit



Baseline Characteristics

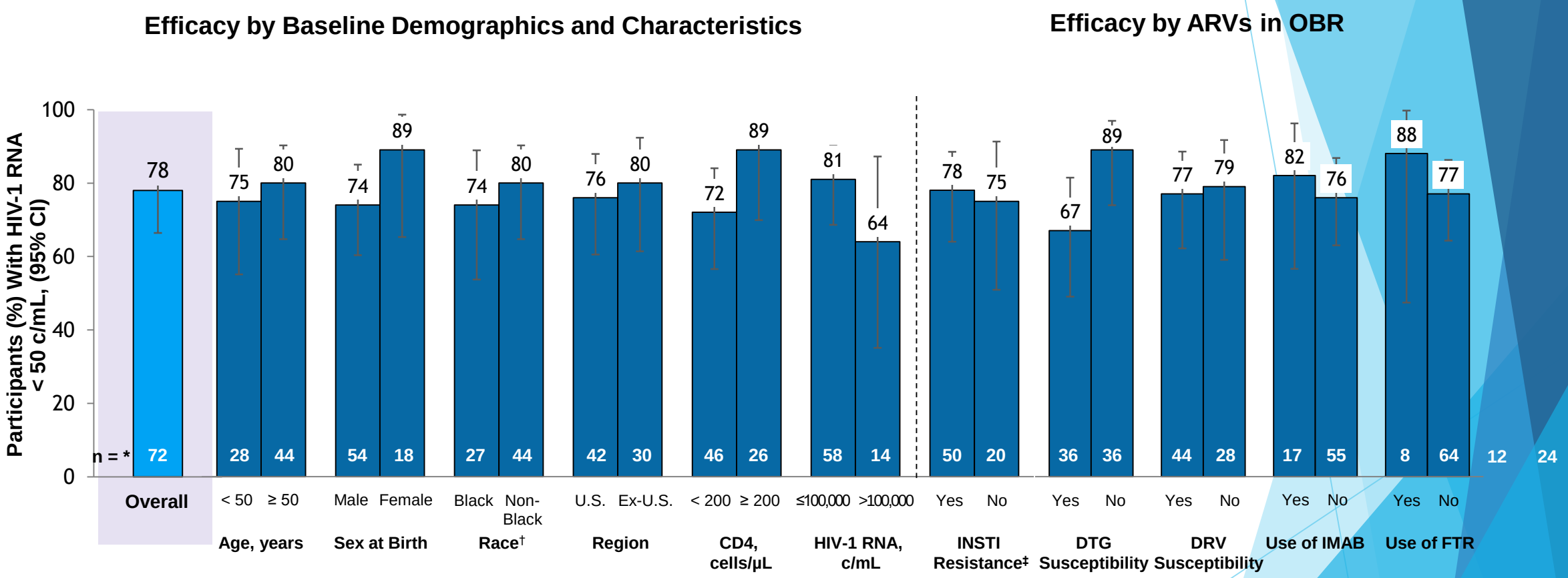
Characteristic	Randomized		Nonrandomized	Total N = 72
	LEN n = 24	Placebo n = 12	LEN n = 36	
Age, years, median (range)	55 (24-71)	54 (27-59)	49 (23-78)	52 (23-78)
Female at birth, %	29	25	22	25
Black race, %	42	55	31	38
Hispanic/Latinx %	25	36	14	21
HIV-1 RNA, $\log_{10}$ c/mL, median (range)	4.2 (2.3-5.4)	4.9 (4.3-5.3)	4.5 (1.3-5.7)	4.5 (1.3-5.7)
HIV-1 RNA > 75,000 c/mL, %	17	50	28	28
CD4 count, cells/μL, median (range)	172 (16-827)	85 (6-237)	195 (3-1,296)	150 (3-1,296)
CD4 count ≤ 200 cells/μL, %	67	92	53	64
Years since HIV diagnosis, median (range)	27 (13-39)	26 (14-35)	23 (9-44)	24 (9-44)
Number of prior ARV agents, median (range)	9 (2-24)	9 (3-22)	13 (3-25)	11 (2-25)
Number of ARV agents in failing regimen, median (range)	3 (1-7)	3 (2-6)	4 (2-7)	3 (1-7)
Known resistance to ≥ 2 drugs in class, %				
NRTI	96	100	100	99
NNRTI	92	100	100	97
PI	83	67	83	81
INSTI	83	58	64	69

HTE, heavily treatment-experienced

1. Ogbuagu O, et al. CROI 2023, Poster 523; 2. Segal-Maurer S, et al. vCROI 2021, Oral 127; 3. Molina JM, et al. vIAS 2021, Oral OALX01LB02; 4. Segal-Maurer S, et al. N Engl J Med 2022;386:1793-803

Post Hoc Subgroup Analysis at Week 52 of HIV-1 RNA < 50 c/mL

Randomized and Non-Randomized Cohorts



The efficacy of LEN in combination with an OBR was consistent across diverse subgroups

*Total n in each subgroup; †Reported as "not permitted" for one participant; ‡Included phenotypic and genotypic resistance to bictegravir, cabotegravir, dolutegravir, elvitegravir and raltegravir; data missing for two participants. FTR, fostemsavir; HTE, heavily treatment-experienced; IMAB, ibalizumab; OBR, optimized background regimen

Ogbuagu O, et al. CROI 2023, Poster 523

The Journal of Infectious Diseases
MAJOR ARTICLE

Resistance Analyses in Highly Treatment-Experienced People With Human Immunodeficiency Virus (HIV) Treated With the Novel Capsid HIV Inhibitor Lenacapavir

Nicolas A. Margot,[1] Vidula Naik,[1] Laurie VanderVeen,[1] Olena Anoshchenko,[2] Renu Singh,[2] Hadas Dvory-Sobol,[3] Martin S. Rhee,[3] and Christian Callebaut[1]

[1]Clinical Virology, Gilead Sciences, Inc, Foster City, California, USA; [2]Clinical Pharmacology, Gilead Sciences, Inc, Foster City, California, USA; and [3]Clinical Research, Gilead Sciences, Inc, Foster City, California, USA

LEN added to OBR led to high efficacy in this HTE patient population with MDR but could select for resistance when used unintentionally as functional monotherapy

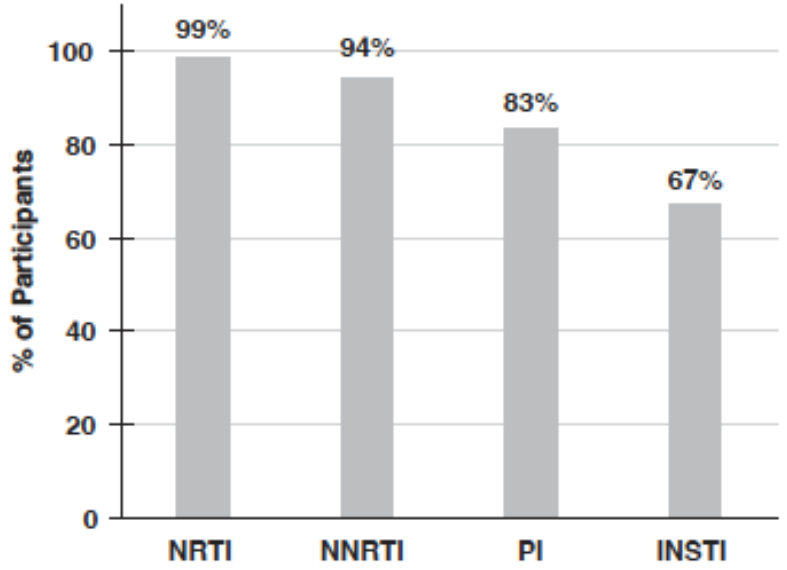


Figure 1. Proportion (%) of participants with resistance-associated mutations (RAMs) to the 4 main antiretroviral drug classes and mean number of RAMs per participant at baseline. The lists of RAMs per class are detailed in th-e Materials and Methods ("Definitions of Resistance Mutations"). Abbreviations: INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2. Resistance Analysis Population and Selection of Lenacapavir Resistance Mutations by Week 26

Resistance Categories	No. of Participants (%)		
	Cohort 1 (n = 36)	Cohort 2 (n = 36)	All (N = 72)
RAP	11 (31)	9 (25)	20 (28)
With data	11 (31)	9 (25)	20 (28)
With LEN resistance	4 (11)	4 (11)	8 (11)
M66I[a]	4 (11)	2 (6)	6 (8)
Q67H + K70R	0	1 (3)	1 (1)
K70H[b]	0	1 (3)	1 (1)
No LEN resistance	7 (19)	5 (14)	12 (17)

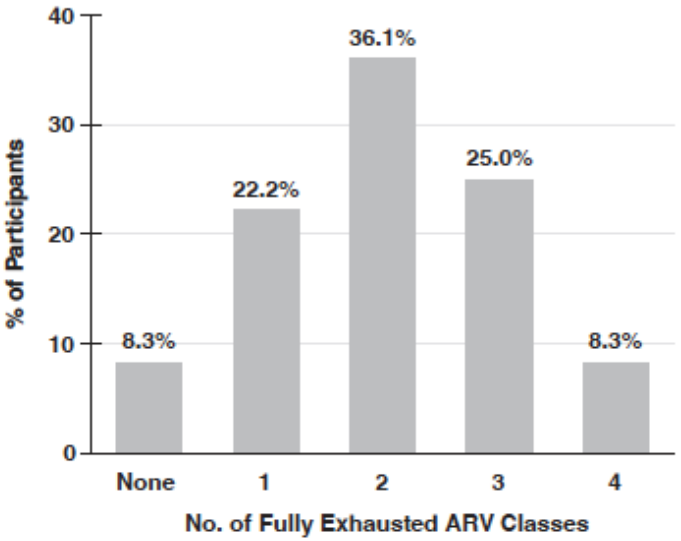


Figure 2. Exhaustion of antiretroviral (ARV) classes at baseline. The proportion of participants with no fully active ARV option remaining within the 4 main ARV drug classes is shown.

Table 1. Baseline Resistance to the 4 Main Classes of Antiretroviral Drugs[a]

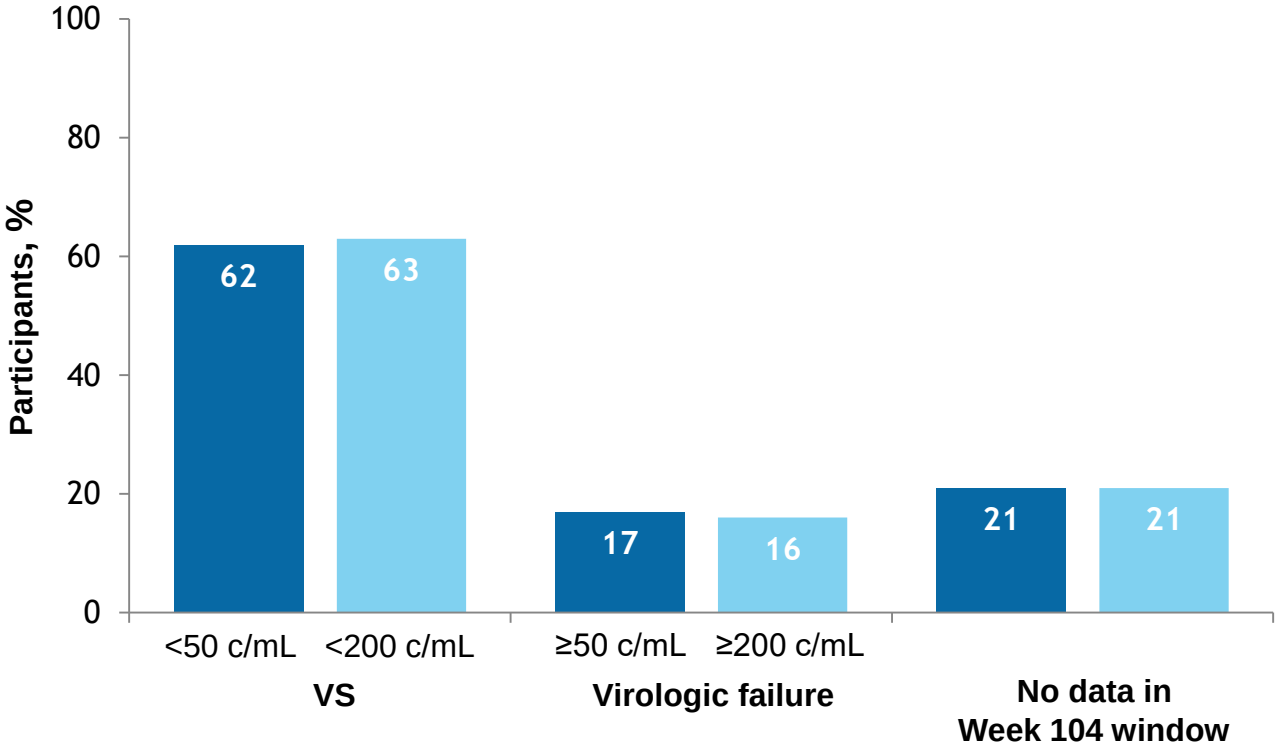
Resistance Classes	No. of Participants (%)		
	Cohort 1 (n = 36)	Cohort 2 (n = 36)	All (N = 72)
NRTI, NNRTI, PI, INSTI	17 (47)	16 (44)	33 (46)
NRTI, NNRTI, PI	9 (25)	13 (36)	22 (18)
NRTI, NNRTI, INSTI	8 (22)	5 (14)	13 (18)
NRTI, PI, INSTI	2 (6)	0	2 (3)
NNRTI, PI, INSTI	0	1 (3)	1 (1)
NNRTI, INSTI	0	1 (3)[b]	1 (1)

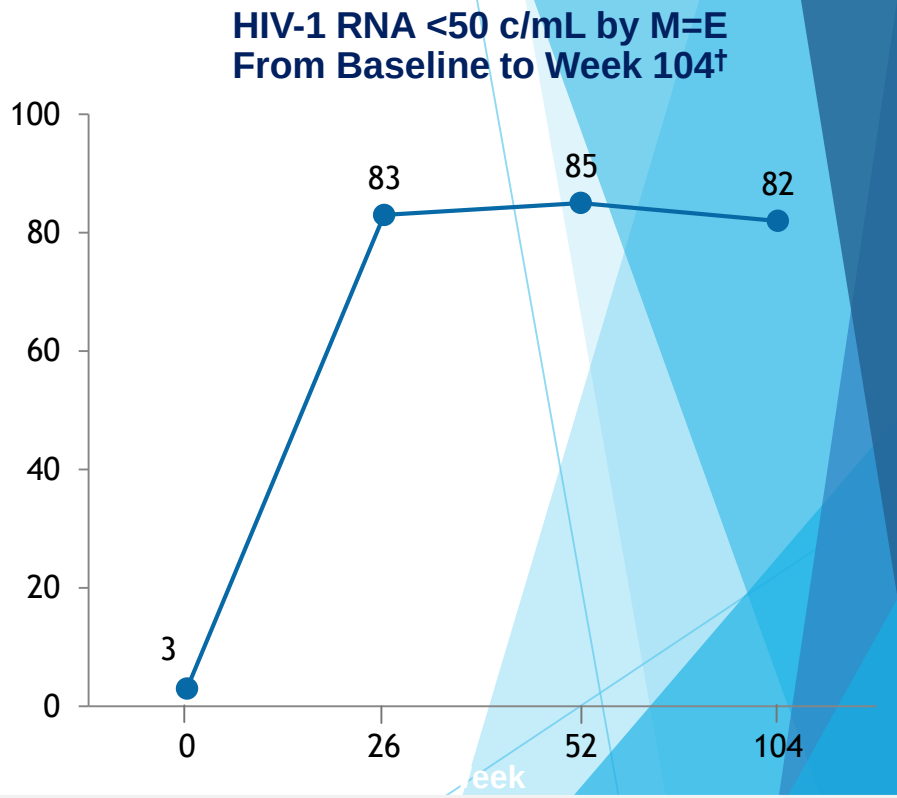
Abbreviations: INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Entry into the study required that participants have resistance to at least 2 antiretrovirals (ARVs) from at least 3 of the 4 main ARV classes (NRTI, NNRTI, PI, INSTI).

[b]One participant in the nonrandomized cohort had 3-class resistance in the presence of the NRTI mutation M184V/I only. Due to its high prevalence upon treatment failure, the presence of that mutation alone was not sufficient to fulfill the NRTI resistance criteria in the study.

Virologic Outcomes
(Combined Randomized and Non-Randomized Cohorts)

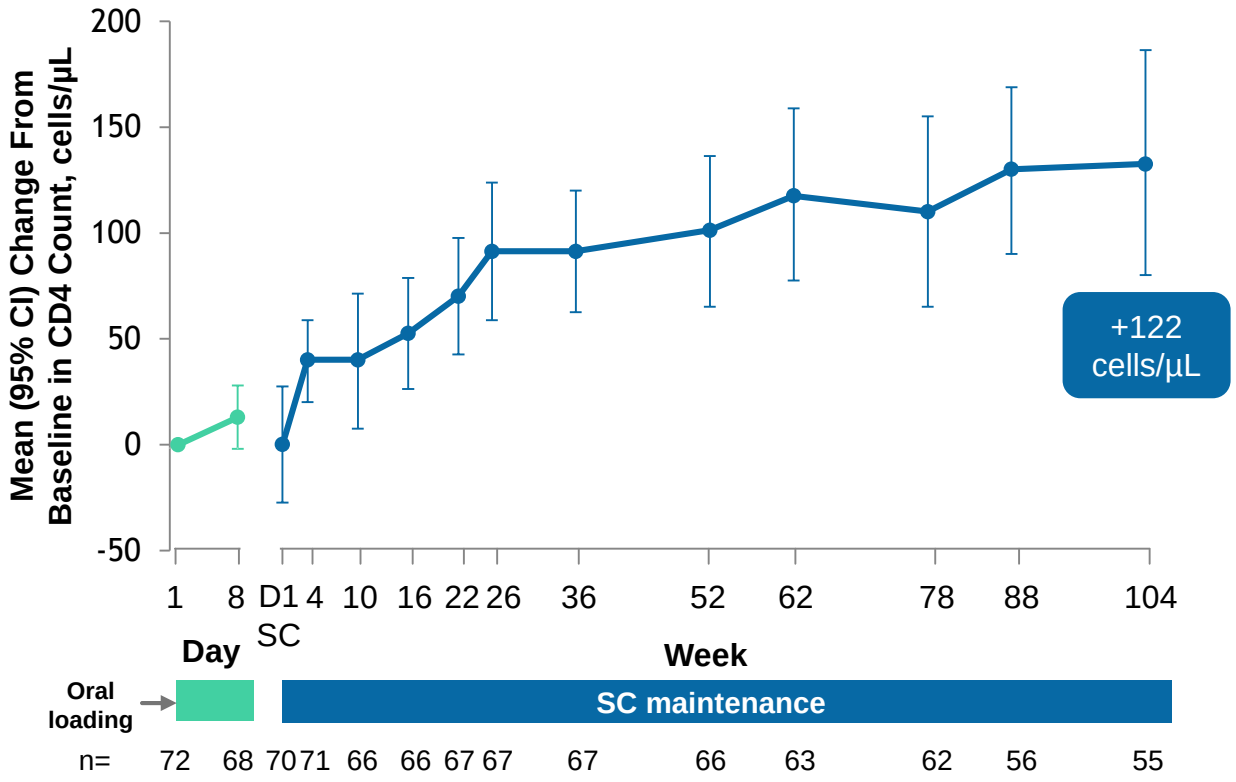


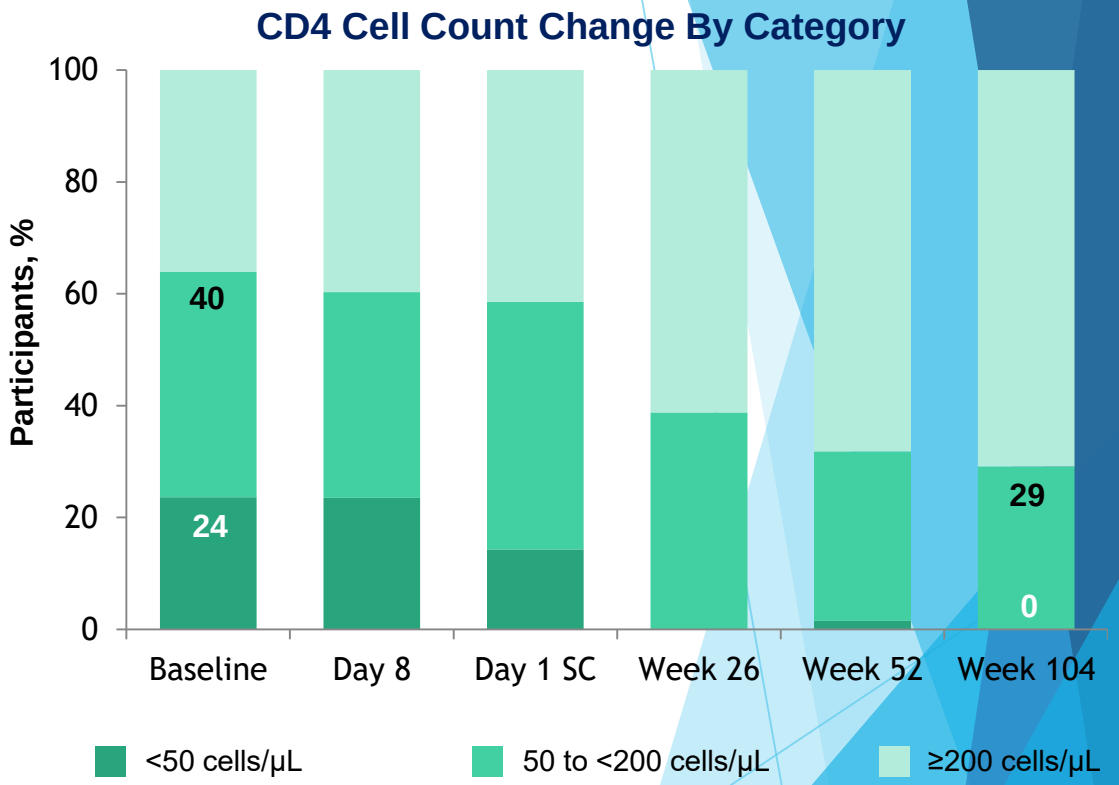


CAPELLA participants continued to maintain high rates of VS (82% by M=E analysis at Week 104)

*The Week 104 window is Day 688 to Day 778 (inclusive); participants who had missing HIV-1 RNA at Week 104 and had completed the study before reaching the upper limit of the analysis window for Week 104 were excluded (n=1); †The denominator for percentages is the number of participants with non-missing HIV-1 RNA values at each time point
M=E, missing=excluded; VS, virologic suppression
Ogbuagu O, et al. IDWeek 2023, Poster 1596

CD4 Cell Count Changes





Consistent with earlier analyses, clinically meaningful increases in CD4 cell count were achieved after starting LEN and maintained through Week 104, with a majority achieving CD4 counts ≥200 cells/µL

Ogbuagu O, et al. IDWeek 2023, Poster 1596

Safety Profile of LEN-Based Regimens Through Week 104

Safety Summary

TEAEs, n (%)	Total (N=72)
Most common TEAEs (occurring in ≥15% of participants, excluding ISRs and COVID-19)	
Diarrhea	14 (19.4)
Nausea	14 (19.4)
Urinary tract infection	12 (16.7)
Cough	11 (15.3)
TEAEs	71 (98.6)
Grade ≥3	24 (33.3)
TRAEs	57 (79.2)
Grade 3	6 (8.3)*
Serious TEAEs	15 (20.8)
TEAEs leading to premature study drug discontinuation	1 (1.4)†
All deaths	3 (4.2)§

- Median (IQR) duration of follow-up on LEN was 125 (111–140) weeks
- No serious TRAEs or Grade ≥4 TRAEs were reported
- There were 3 deaths during the study:
  - 2 previously reported (malignant neoplasm, acute respiratory failure)[1,2]
  - 1 of unknown cause[1] (occurred after Week 52[3])

The safety profile of LEN was consistent with that in previous analyses; no participants discontinued LEN due to TEAEs after Week 52, and no participants experienced a serious TRAE

*ISR, n=4; immune reconstitution inflammatory syndrome, n=1; abdominal abscess, n=1; rash, n=1; †Due to Grade 1 injection-site nodule (prior to Week 52); §Due to: malignant neoplasm, n=1; acute respiratory failure, n=1; unknown cause, n=1

ISR, injection-site reaction; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

1. Ogbuagu O, et al. IDWeek 2023, Poster 1596; 2. Ogbuagu O, et al. Lancet 2023;10:E497-E505; 3. Data on file. Gilead Sciences, Inc

Emergent LEN Resistance Through Week 104

LEN Resistance Summary[1]

LEN Resistance	Total (N=72)
Emergent LEN resistance	**14**
No fully active agents in OBR	4
Inadequate adherence to OBR	10
Resuppressed after LEN resistance emergence while remaining on LEN	
Yes*	7
With OBR change	2
Without OBR change	5
No†	7
Continued study treatment§	4
Discontinued study treatment¶	3

- 5 additional participants developed emergent LEN resistance in the second year of CAPELLA, bringing the total number to 14[1]
- All 14 participants had high risk of emergent LEN resistance (no fully active ARV in OBR or inadequate OBR adherence)[1]
- 7/14 participants resuppressed after LEN resistance emergence while remaining on LEN[1]

All 14 cases of LEN emergent resistance occurred in the setting of inadequate adherence to OBR or absence of fully active ARVs in the OBR[1,2]

*Pharmacokinetic analysis of 2 participants indicated improved adherence (analysis ongoing, n=5); †All 7 participants had CD4 count <200 cells/μL at baseline; whilst these participants had some increase in CD4 count during the study, CD4 count returned to baseline in 3 participants; §Returned to baseline VL, n=2; >1 log reduction in HIV-1 RNA, n=2 (1.1 and 1.8 log); ¶Due to: death (n=1); investigator's discretion due to non-compliance (n=1); lost to follow-up (n=1)
OBR, optimized background regimen; VL, viral load

1. Ogbuagu O, et al. IDWeek 2023, Poster 1596; 2. Margot N, et al. EACS 2023, Oral PS8 O4

CAPELLA: Phase 2/3 multicenter study

LEN SC in People With Multidrug-Resistant HIV-1: 3-Year Results[1]

N=72

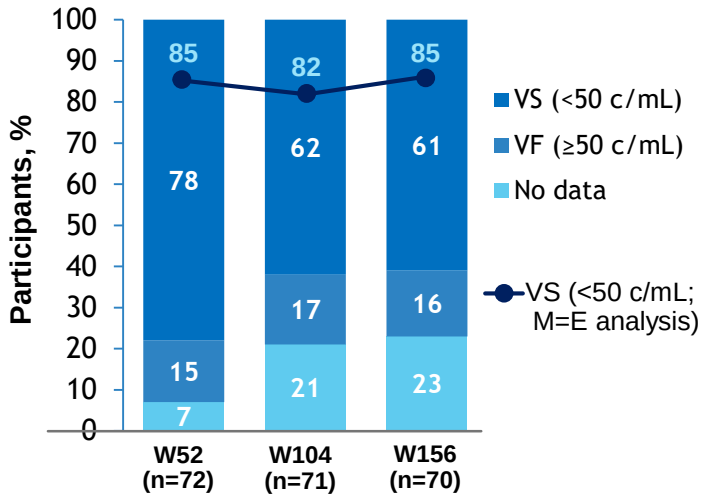
HTE PWH with MDR HIV-1 received 2-week oral LEN lead-in followed by SC LEN Q6M + OBR

Outcomes

VS, CD4 count, LEN resistance and TEAEs at Week 156

Enrollment November 2019–January 2021[2]

Virologic Outcomes: FDA Snapshot Analysis[1,3,4]



- From baseline to Week 156, the proportion of participants with CD4 count:
  - ≥200 cells/μL increased from 36% to 78%
  - ≥50 cells/μL increased from 76% to 98%

- No new cases of LEN resistance emerged between 104 and 156 weeks
- 14 cases of emergent LEN resistance (4 with no fully active agents in OBR and 10 with inadequate adherence to OBR) were previously reported

- No participant discontinued due to non-ISR AEs

- ISRs were mostly Grade 1 or 2 (93%) and decreased over time
- Up to Week 156, only 2 participants (3%) discontinued LEN due to ISRs (nodules)
- Only 11% of participants reported nodules (all grade 1) after the 5th injection, versus 26% after the first

In HTE PWH, LEN combined with an optimized background regimen achieved and sustained VS through week 156. ISRs were mostly mild and decreased over time

events; VF, virologic failure; VS, virologic suppression

1. Ogbuagu O, et al. IDWeek 2024, Oral 155; 2. Segal-Maurer S, et al. *N Engl J Med*. 2022;386:1793-1803; 3. Ogbuagu O et al. IDWeek 2022, Oral 1585; 4. Ogbuagu O et al. IDWeek 2023, Poster 1596

DRUGS IN CONTEXT
RIGOROUS • RAPID • RESPONSIVE

Table 1. Summary of medications that may be implemented in regimens for heavily treatment-experienced patients with HIV.

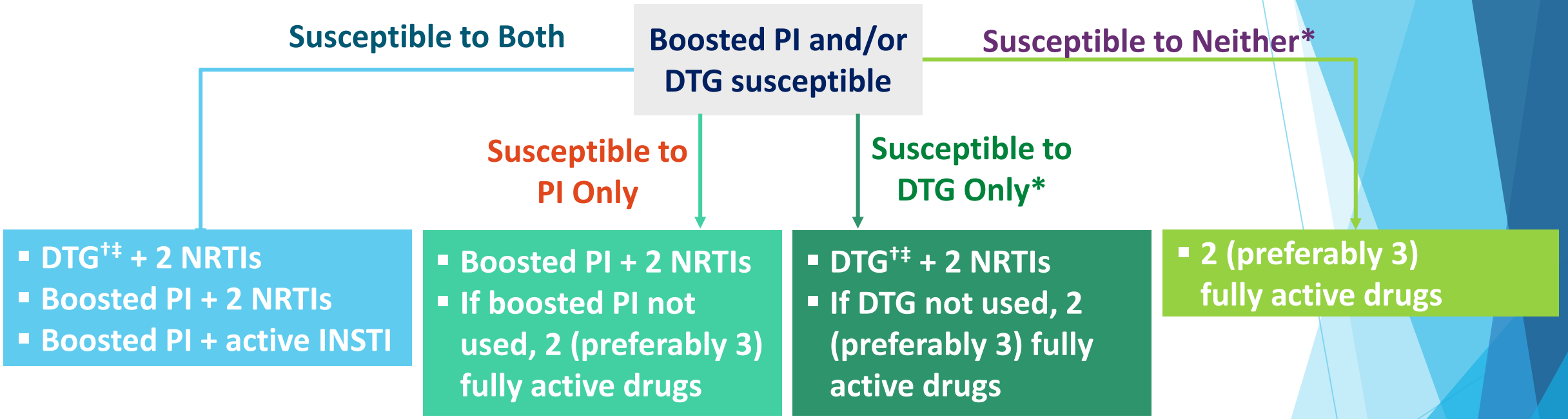
Medication	Class	Mechanism of action	Key resistance mutations	Administration route	Trials of note
Tenofovir alafenamide (TAF)	Nucleotide reverse transcriptase inhibitor	Inhibits reverse transcription by incorporating into HIV DNA and causing chain termination	K65R	Oral	
Etravirine (ETR)	Non-nucleoside reverse transcriptase inhibitor	Inhibits reverse transcription by binding reverse transcriptase	L100I, K101P, V106A, E138A, V179F, Y181I/C/V, G190C, M230L	Oral	DUET 1 and 2
Doravirine (DOR)	Non-nucleoside reverse transcriptase inhibitor	Inhibits reverse transcription by binding reverse transcriptase	V106A, E138K, P225H F227C	Oral	DRIVE FORWARD; DRIVE AHEAD; ILLUMINATE
Darunavir/ritonavir (DRV/r)	Protease inhibitor	Prevents cleavage of proteins after transcription by binding protease	V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, L89V	Oral	POWER 1, 2, 3
Dolutegravir (DTG)	Integrase strand inhibitor	Prevents viral DNA from incorporating with host DNA by blocking integrase	G118R, Q148H/K/R, R263K	Oral	SAILING; VIKING-3
Fostemsavir (FTR)	Attachment inhibitor	Prevents HIV attachment to CD4 cells by binding to glycoprotein 120 on viral envelope	No commercially available resistance test	Oral	BRIGHTE

Table 1. *(Continued)*

Medication	Class	Mechanism of action	Key resistance mutations	Administration route	Trials of note
Ibalizumab (IBA)	Post-attachment inhibitor	Monoclonal antibody; binds CD4 receptor after HIV attachment and prevents fusion	No commercially available resistance test	Intravenous	TMB-301
Enfuvurtide (T-20)	Fusion inhibitor	Prevents viral fusion by binding glycoprotein 41 on viral envelope	G36D/E/S, I37T/N/V, V38A/E/M, Q39R, Q40H, N42T, N43D/K/S	Subcutaneous	TORO 1 and 2
Maraviroc (MVC)	CCR5 coreceptor antagonist	Binds CCR5 coreceptor on CD4 cells and prevents viral entry	CXCR4 or dual tropic virus	Oral	MOTIVATE 1 and 2
Islatravir (ISL)[a]	Nucleoside reverse transcriptase translocation inhibitor	Inhibits translocation of viral RNA into DNA via multiple mechanisms	Data under development	Oral	Protocol 011; ILLUMINATE
Lenacapavir (LEN)[a]	Capsid inhibitor	Inhibits viral assembly, disassembly and transport through p24 protein binding	No commercially available resistance test	Subcutaneous/ oral	CALIBRATE; CAPELLA

Drugs Context. 2022;11:2021-9-1.

Management of ARV Failure: Second Line and Beyond



*Rare in patients never exposed to unboosted PIs (eg, NFV, DHHS alternative since 2003 and not recommended since 2008).
†If INSTI naive or experienced with no resistance (limited data in patients with resistance to RAL or EVG but susceptibility to DTG).
‡Data limited to DTG, but similar results might be seen with BIC.

Adapted from DHHS ART Guidelines. September 2022.

IAS-USA Guideline Updates: HIV Treatment (2 of 2)

ART for Individuals With HIV[a,b]

Switching ART

- Switching from older ART regimens to one of the recommended initial ART regimens is recommended, provided VS can be maintained
- Individuals with VS receiving regimens that contain a boosted PI and 2 NRTIs can be switched to DTG + TXF/XTC or B/F/TAF regardless of known or likely prior resistance to the NRTI pair and provided there is no history of INSTI resistance

Switching Therapy With Blips, Low-Level Viremia or Virologic Failure

- Intermittent detection of HIV RNA at levels between 20 and 200 c/mL and persistent low-level viremia at this level should not prompt changing treatment
- Virologic failure with multiclass resistance should prompt consideration of agents with novel MoAs, such as ibalizumab, fostemsavir or LEN, ideally in combination
- For people who have stopped ART, resuming the most recent DTG- or BIC-based regimen is recommended even before the results of the resistance genotype test have been returned, provided adherence is good and the individual is amenable
- For PWH with advanced disease who are unable to take oral ART long-acting CAB + long-acting RPV, in conjunction with adherence support, may be considered

Weight Gain and Cardiometabolic Comorbidities

- Documentation of weight and BMI at baseline and every 6 months is recommended for individuals initiating or switching to an INSTI- or TAF-based regimen, to identify those with excessive weight gain
- Monitoring blood pressure at each clinical visit is recommended to diagnose and treat incident hypertension
- Changing regimens because of weight gain, hypertension or insulin resistance is not recommended
- People with or at high risk of CVD who are receiving an ABD-containing regimen should switch to a non–ABC-containing regimen if an active regimen is available
- Counseling about potential cardiometabolic complications and the importance of lifestyle changes is recommended for all persons beginning ART

Laboratory Monitoring

- Before initiating ART, recommended laboratory tests should assess HIV RNA levels, CD4+ cell counts, general health, ART resistance and potential coinfections
- 4 to 6 weeks after starting ART, HIV RNA levels should be measured, and adherence and tolerability of ART assessed
- If, after 12 to 24 weeks of therapy, HIV RNA levels have not decreased to <200 c/mL with adequate adherence, regimen-based genotyping is recommended
- If an HIV RNA level above 50 c/mL is detected during ART following previous suppression (<50 c/mL), a repeat measurement is recommended in 2 to 4 weeks, and adherence to medication and tolerability should be assessed
- If HIV RNA levels are >200 c/mL on 2 consecutive measurements, then an HIV RNA RT-PI genotype should be obtained, and if the person is receiving an INSTI, an INSTI genotype assay should be ordered

[a]For a comprehensive list of updates, please refer to the IAS-USA guidelines; [b]The data presented on this slide were not part of the CROI 2024 program
MoA, mechanism of action; VS, virologic suppression

Gandhi RT, et al. *JAMA.* December 2024 [ePub]. doi: 10.1001/jama.2024.24543

Guideline-Based Definitions and Management of Treatment Experienced PWH

EACS[1]

When a 2–3-drug active regimen cannot be constructed, a drug with a new mechanism of action, such as LEN, FTR or IBA, can be added to obtain a 2-3 drug active regimen

IAS-USA[2]

In the setting of multiclass resistance (3-class resistance), the next regimen should be constructed using drugs from new classes, if available (evidence rating: BIII); e.g., FTR (AIb) or IBA (BII), with at least one additional active drug in an optimized ART regimen

DHHS[3]

Failing regimen	Resistance considerations	New regimen options	Goal
Drug resistance **with fully active treatment** options	• Use past and current genotypic +/- phenotypic resistance testing and ART history when designing new regimen	• Two fully active agents, at least one of which has a high barrier to resistance; otherwise, three fully active agents are preferred • Partially active drugs may be used when no other options are available • Consider using an ARV drug with a different mechanism of action	• Resuppression
Multiple or extensive drug resistance **with few treatment** options	• Use past and current genotypic and phenotypic resistance testing to guide ART • Confirm with viral tropism assay when use of MVC is considered • Consult an expert in drug resistance, if needed	• Identify as many active or partially active drugs as possible based on resistance test results • Consider using an ARV drug with a different mechanism of action (i.e., LEN, IBA, FTR) • Clinical trials or expanded access programs for investigational agents may be available • Discontinuation of ARV drugs **is not recommended**	• Resuppression, if possible • Otherwise, keeping viral load as low as possible and CD4 count as high as possible

DHHS; the US Department of Health and Human Services; EACS, European AIDS Clinical Society; FTR, fostemsavir; IAS-USA, International Antiviral Society–USA; IBA, ibalizumab

1. EACS Guidelines version 12, Oct 2023. https://www.eacsociety.org/media/guidelines-12.0.pdf (accessed Nov. 29, 2023); 2. Saag MS, et al. JAMA 2020;324(16):1651-1669;
3. DHHS. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, May 2023. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf (accessed August 2023)

Management of Multidrug Resistance Without Fully Active Boosted PIs and Second-Generation INSTIs

- **Construct an ART regimen with 2, preferably 3, active drugs or sum up equivalent with partially active drugs[1]**
  - Precise estimation of residual activity can be challenging (phenotype)
  - Choose best OBR
    - Avoid using a drug if full resistance:
      >60 points in Stanford HIV Drug Resistance Database or history of treatment-limiting toxicity

- **Potential fully active drugs may be those with novel MoA:**
  - Ibalizumab: 800 mg IV every 14 days[2]
  - Fostemsavir: 600 mg PO BID[3]
  - Lenacapavir (investigational): 600 mg PO Days 1 and 2, 300 mg Days 8, then 927 mg SC Day 15 and every 6 mo[4]
  - Enfuvirtide: 90 mg SC BID[1]
  - Maraviroc (CCR5 tropic): 300 mg PO BID[1]

1. DHHS ART Guidelines. September 2022. 2. Ibalizumab PI. 3. Fostemsavir PI. 4. NCT04150068.

DELFINO Study

Doravirine + Lenacapavir + Fostemsavir
in PWH enrolled in the Prestigio Registry

A bPI, INSTI (and NRTI) sparing strategy to improve QOL

40 People with HIV-1:

- age ≥18 years
- Enrolled in PRESTIGIO Registry
- Need to change ART
- non-CRF_01AE strain
- no previous exposure to LEN- and/or FTR-containing regimens
- Susceptibility to DOR
- HbABs pos

→ DOR + LEN + FTR

Primary endpoint HIV-RNA < 50 copies/mL at 26 weeks

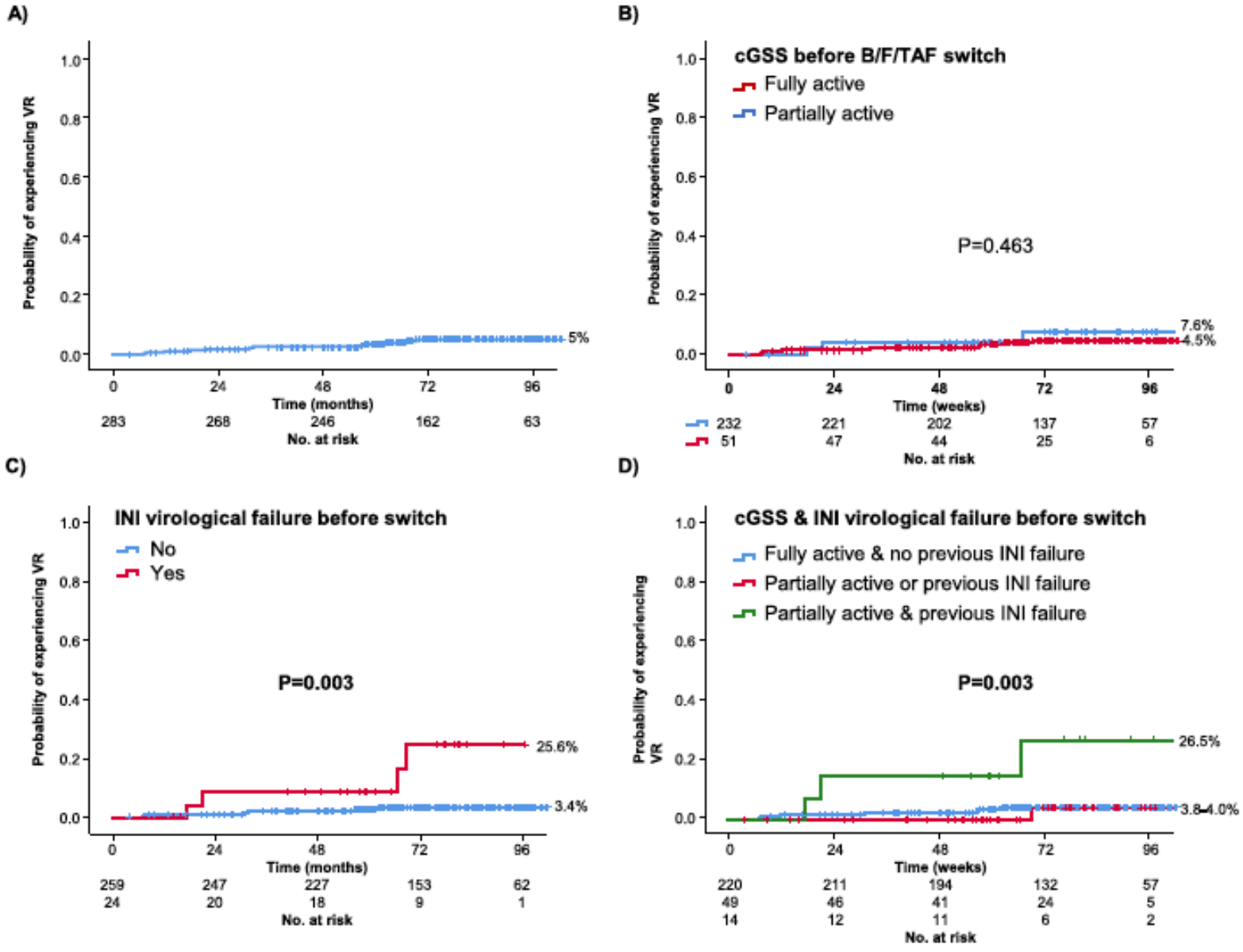
Bictegravir/emtricitabine/tenofovir alafenamide plus doravirine in highly treatment-experienced men with multidrug-resistant HIV

- Open-label switch trial enrolled HTE PWH
- Eligible participants were male, aged ≥45 years, with documented viral resistance to protease inhibitors, nucleoside reverse transcriptase inhibitors, and/or nonnucleoside reverse transcriptase inhibitors but no resistance to RPV or DOR, and no K65R or T69 insertion mutations.
- Virologic suppression (≤50 copies/ml) while on RPV/FTC/TAF plus DTG for ≥6 months was required prior to enrollment.
- The primary endpoint of the study was virologic suppression (<50 and <200 copies/ml) at 48 weeks..
- Twenty males completed the study. **BIC/FTC/TAF plus DOR was well tolerated At Week 48, 100% of participants had <50 viral copies/ml.**

AIDS 37(7):p 1057-1064, June 1, 2023.

Bictegravir/emtricitabine/tenofovir alafenamide ensures high rates of virological suppression maintenance despite previous resistance in PLWH who optimize treatment in clinical practice☆

Daniele Armenia[a], Federica Forbici[b], Ada Bertoli[c,d], Giulia Berno[b], Vincenzo Malagnino[d], Roberta Gagliardini[b], Vanni Borghi[e], William Gennari[e], Stefania Cicalini[b], Annarita Buonomini[f], Elisabetta Teti[d], Simone Lanini[b], Alessandra Latini[f], Loredana Sarmati[d], Cristina Mussini[e], Massimo Andreoni[d], Andrea Antinori[b], Carlo F. Perno[g], Francesca Ceccherini-Silberstein[c], Maria M. Santoro[c,*]



Kaplan-Meir estimates of the probability of experiencing virological rebound at 24 mo under B/F/TAF treatment stratified according to genotypic susceptibility and previous INI failure experience. A) Virological rebound stratified in overall population. B) Virological rebound stratified according to B/F/TAF genotypic susceptibility. C) Virological rebound stratified according to previous INI failure experience D) Virological rebound stratified according to B/F/TAF genotypic susceptibility and previous INI failure experience.

Journal of Global Antimicrobial Resistance 30 (2022) 326–334

Case Series of People With HIV on the Long-Acting Combination of Lenacapavir and Cabotegravir: Call for a Trial

Monica Gandhi,[1] Lucas Hill,[2] Janet Grochowski,[1] Alexander Nelson,[3] Catherine A. Koss,[1] Francis Mayorga-Munoz,[1] Jon Oskarsson,[1] Mary Shiels,[1] Ann Avery,[4] Laura Bamford,[2] Jillian Baron,[5] William R. Short,[5] and Corrilynn O. Hileman[4]

[1]Division of HIV, Infectious Diseases and Global Medicine, University of California, San Francisco (UCSF), San Francisco, California, USA, [2]Division of Infectious Diseases and Global Public Health, University of California San Diego (UCSD), San Diego, California, USA, [3]Department of Specialty Pharmacy, MetroHealth Medical Center, Cleveland, Ohio, USA, [4]Division of Infectious Diseases, MetroHealth Medical Center, and Case Western Reserve University (CWRU), Cleveland, Ohio, USA, and [5]Division of Infectious Diseases, Hospital of the University of Pennsylvania (UPenn), Philadelphia, Pennsylvania, USA

Background. Injectable cabotegravir (CAB)/rilpivirine (RPV) is the only combination long-acting (LA) antiretroviral regimen approved for HIV. RPV may not be effective among individuals with non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance, which has >10% prevalence in many countries. Lenacapavir (LEN) is an LA capsid inhibitor given every 6 months, but has not been studied in combination with other LA agents.

Methods. We assembled a case series from 4 US academic medical centers where patients with adherence challenges were prescribed LEN subcutaneously every 26 weeks/CAB (+/− RPV) intramuscularly every 4 or 8 weeks. Descriptive statistics, including viral load (VL) outcomes, were summarized.

Results. All patients (n = 34: 76% male; 24% cis/trans female; 41% Black; 38% Latino/a; median age [range], 47 [28–75] years; 29% and 71% on CAB every 4 or 8 weeks) reported challenges adhering to oral ART. The reasons for using LEN/CAB with or without RPV were documented or suspected NNRTI mutations (n = 21, 59%), integrase mutations (n = 5, 15%), high VL (n = 6, 18%), or continued viremia on CAB/RPV alone (n = 4, 12%). Injection site reactions on LA LEN were reported in 44% (32% grade I, 12% grade 2). All patients but 2 (32/34; 94%) were suppressed (VL <75 copies/mL) after starting LEN at a median (range) of 8 (4–16) weeks, with 16/34 (47%) suppressed at baseline.

Conclusions. In this case series of 34 patients on LEN/CAB, high rates of virologic suppression (94%) were observed. Reasons for using LEN/CAB included adherence challenges and underlying resistance, mostly to NNRTIs. These data support a clinical trial of LEN/CAB among persons with NNRTI resistance.

OFID 2024

ARTISTRY-1: Phase 2/3, randomized, open-label study

BIC + LEN in PWH Switching From a Complex ART Regimen: Phase 2 Study Design[1]

N=128

VSTE PWH on complex ART regimen[a]

Outcome

- **Primary endpoint:** HIV-1 RNA ≥50 c/mL (FDA Snapshot algorithm) at Week 24
- **Secondary endpoints:** HIV-1 RNA <50 c/mL, CD4 cell count and treatment-emergent AEs at Week 24, and pharmacokinetics

Aug. 2022–ongoing[2]

Adults ≥18 years of age on a complex ART regimen[b]

- HIV-1 RNA <50 c/mL on SBR for ≥6 months prior to screening
- No prior exposure to LEN or resistance to BIC
- No history of chronic HBV infection
- eGFR ≥15 mL/min; not on renal replacement therapy

2:2:1

Week 0 — **Primary endpoint Week 24** — **End of randomization visit**

- **BIC 75 mg + LEN 25 mg QD[c] (n=51)**
- **BIC 75 mg + LEN 50 mg QD[c] (n=52)**
- **SBR (n=25)**

Phase 2 extension

BIC/LEN STR QD 75 mg/50 mg

ARTISTRY-1 is an ongoing, randomized, open-label, multicenter Phase 2/3 study

[a]Containing bPI or NNRTI plus ≥1 other third agent from a class other than NRTIs; or consisting of ≥2 pills/day, or requiring dosing more than once daily; or containing parenteral ART (excluding a complete long-acting injectable regimen) plus oral ART; [b]Due to viral resistance, intolerance or contraindication to existing STRs; [c]All participants receiving BIC + LEN received an oral loading dose of LEN 600 mg on Days 1 and 2. SBR, stable baseline regimen; STR, single tablet regimen; VSTE, virologically suppressed treatment-experienced

1. Mounzer K, et al. CROI 2024, Poster 642; 2. NCT05502341. https://classic.clinicaltrials.gov/ct2/show/NCT05502341 (accessed Feb. 26, 2024)

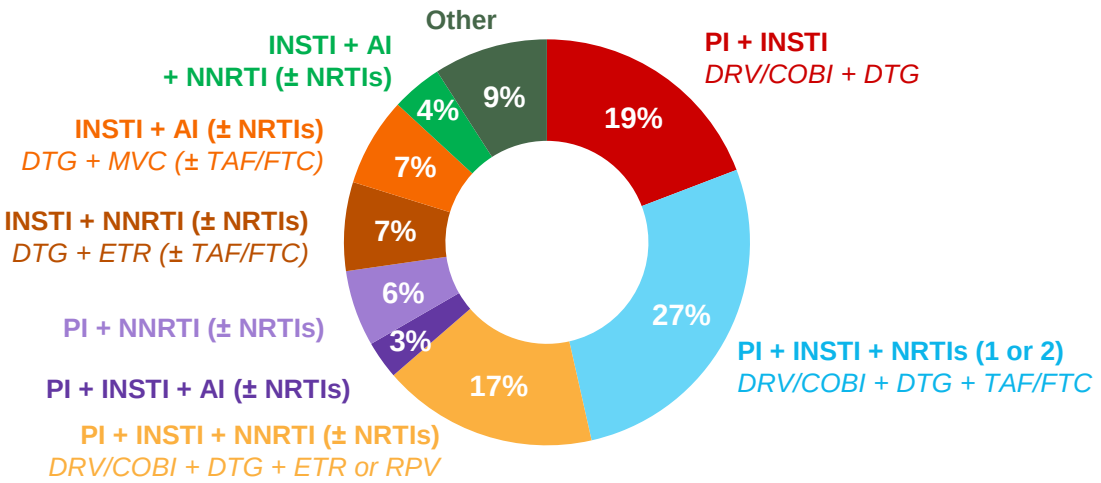
ARTISTRY-1: Phase 2/3, randomized, open-label study

BIC + LEN in PWH Switching From a Complex ART Regimen: Phase 2 Baseline Characteristics

Baseline Characteristics

	BIC 75 mg + LEN 25 mg n=51	BIC 75 mg + LEN 50 mg n=52	SBR n=25
Duration of HIV treatment, years, median (Q1, Q3)[a]	27.8 (22.7, 32.4)	27.0 (18.9, 31.5)	26.9 (19.8, 31.9)
Number of pills/day, median (range)	2.0 (2.0, 8.0)	3.0 (2.0, 9.0)	3.0 (2.0, 8.0)
Dosing frequency of ARTs, n (%)			
Daily	47 (93)	46 (89)	22 (88)
Twice per day	18 (35)	22 (42)	13 (52)
Other	1 (2)	0	0
Reasons for complex ART, n (%)			
History of resistance	44 (86)	40 (77)	20 (80)
Intolerance to components of STRs	20 (39)	11 (21)	7 (28)
Contraindication to STRs	7 (14)	4 (8)	1 (4)
Resistance mutations, n (%)			
INSTI	0	0	0
NNRTI	25 (49)	28 (54)	14 (56)
NRTI	31 (61)	35 (67)	16 (64)
PI	18 (35)	17 (33)	11 (44)

Diversity of Complex ART Regimens[b]



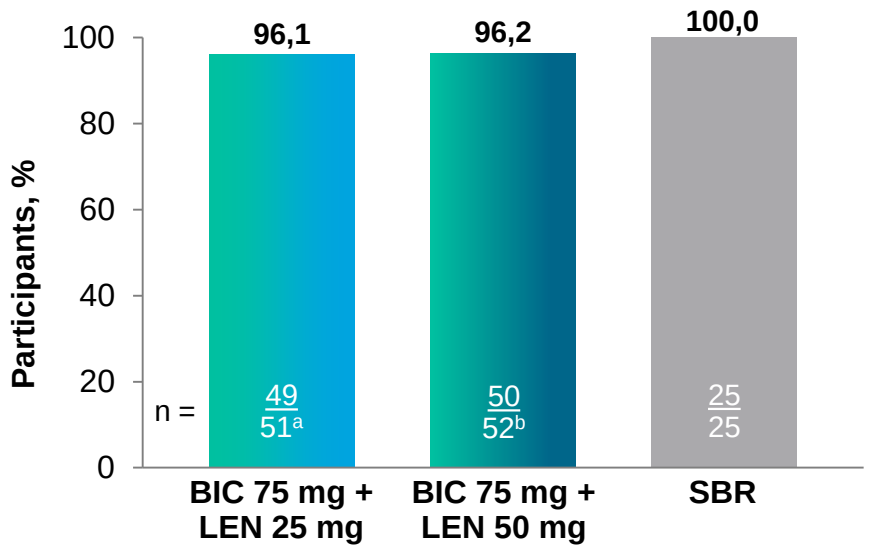
Participants enrolled in ARTISTRY-1 were VSTE PWH receiving complex ART regimen, primarily due to a history of resistance

[a]N=50 for BIC 75 mg + LEN 25 mg group; [b]Most common regimen(s) in each category shown in italics; percentages do not sum to 100% due to rounding
AI, attachment inhibitor; SBR, stable baseline regimen; STR, single tablet regimen; VSTE, virologically suppressed treatment-experienced
Mounzer K, et al. CROI 2024, Poster 642

ARTISTRY-1: Phase 2/3, randomized, open-label study

Efficacy and Safety Results of Switch to BIC + LEN from a Complex ART Regimen: Phase 2 Results

VS (HIV-1 RNA <50 c/mL) at Week 24 (FDA Snapshot Algorithm)



1 participant in the BIC 75 mg + LEN 50 mg arm had **HIV-1 RNA ≥50 c/mL** in Week 24 window (later suppressed to <50 c/mL without regimen change)

TEAEs up to Week 24

	BIC 75 mg + LEN 25 mg n=51	BIC 75 mg + LEN 50 mg n=52	SBR n=25
Any TEAE, n (%)	39 (76)	33 (63)	17 (68)
Related to study drug or SBR	9 (18)	3 (6)	0
Grade 3 or higher	4 (8)	2 (4)	1 (4)
SAEs	2 (4)	1 (2)	2 (8)
Leading to discontinuation[c]	1 (2)	1 (2)	0
TEAEs with frequency ≥5%, n (%)			
COVID-19	4 (8)	2 (4)	2 (8)
Diarrhea	5 (10)	2 (4)	1 (4)
Hypertension	0	4 (8)	1 (4)
Constipation	3 (6)	2 (4)	0
Cough	3 (6)	1 (2)	0
Nasopharyngitis	4 (8)	0	0

All TEAEs with frequency ≥5% were **Grade 1 or 2** apart from 1 occurrence of Grade 3 diarrhea (unrelated to study drug)

BIC + LEN maintained high rates of VS in TE participants on a complex ART regimen and was generally well tolerated. Based on these data, a BIC 75 mg/LEN 50 mg STR will be assessed in the Phase 3 part of the study

[a]Data missing for 2 participants; [b]Data missing for 1 participant, and 1 participant had HIV-1 RNA ≥50 c/mL; [c]Grade 1 nausea (BIC 75 mg + LEN 25 mg group, n=1) and Grade 3 worsening of vomiting (BIC 75 mg + LEN 50 mg group, n=1)

SBR, stable baseline regimen; STR, single tablet regimen; TE, treatment-experienced; TEAE, treatment-emergent adverse event; VS, virologic suppression

Mounzer K, et al. CROI 2024, Poster 642

Key points on HTE patients:

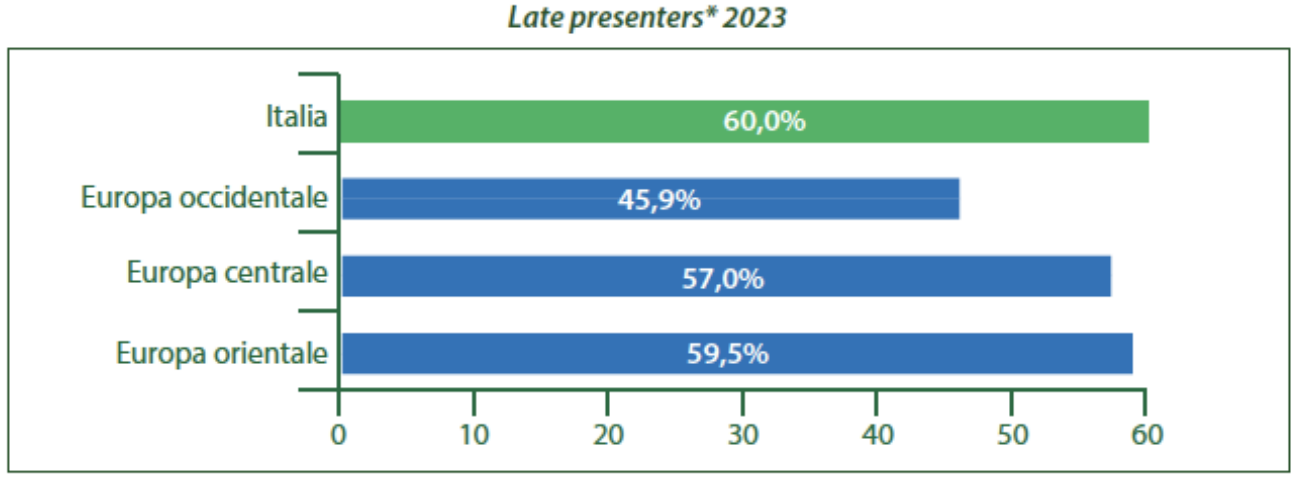
- HTE definition: from MDR to difficolt to treat
- Management of HTE patient: «tailoring»
- New therapeutic options for HTE patients available
- Avoid functional monotherapies
- Possible simplification of therapy even in these patients

Take home message

A new era for HTE patients is coming:
HIV-RNA undetectable for all is not a mirage

HIV: Late presenter

Università di Foggia



(*) *Late presenters*: nuove diagnosi di infezione da HIV con numero di linfociti CD4 <350 cell/µl.
Fonti: Sistema di Sorveglianza HIV nazionale, *ECDC/WHO. HIV/AIDS Surveillance in Europe 2024-2023 data (1)*

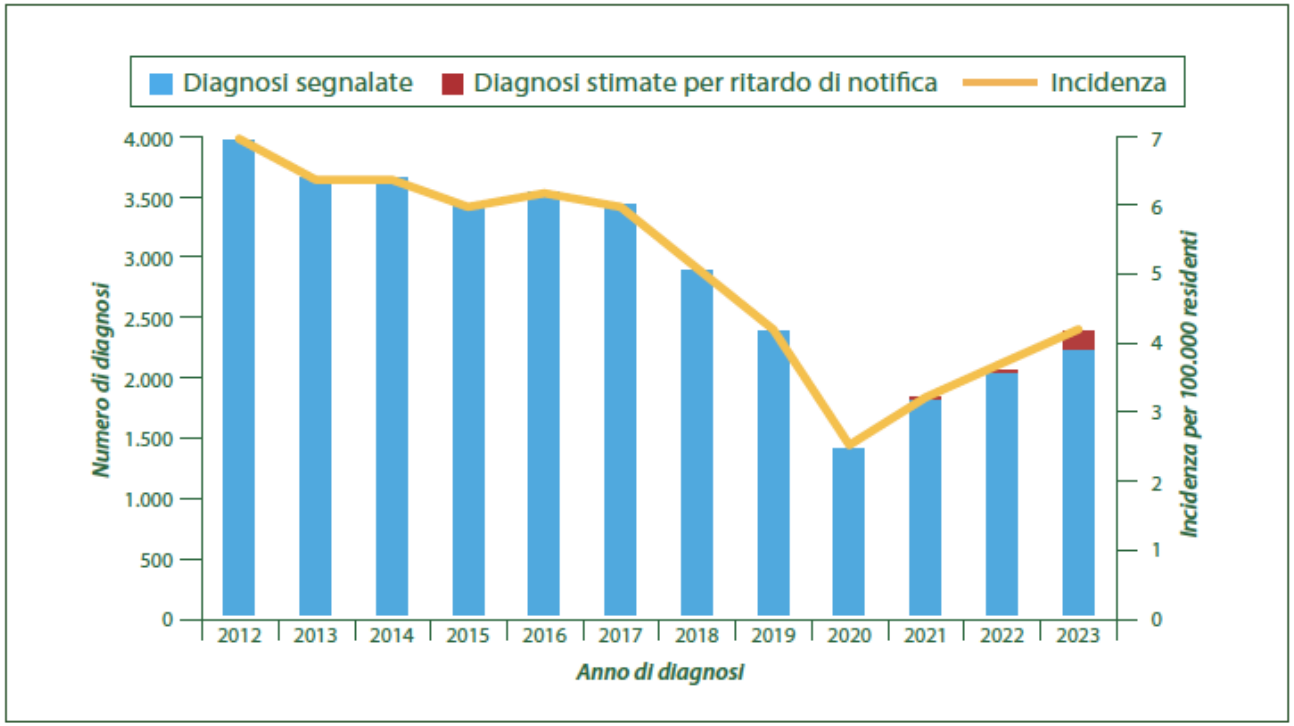


Figura 1 - Nuove diagnosi di infezione da HIV e incidenze corrette per ritardo di notifica (2012-2023)

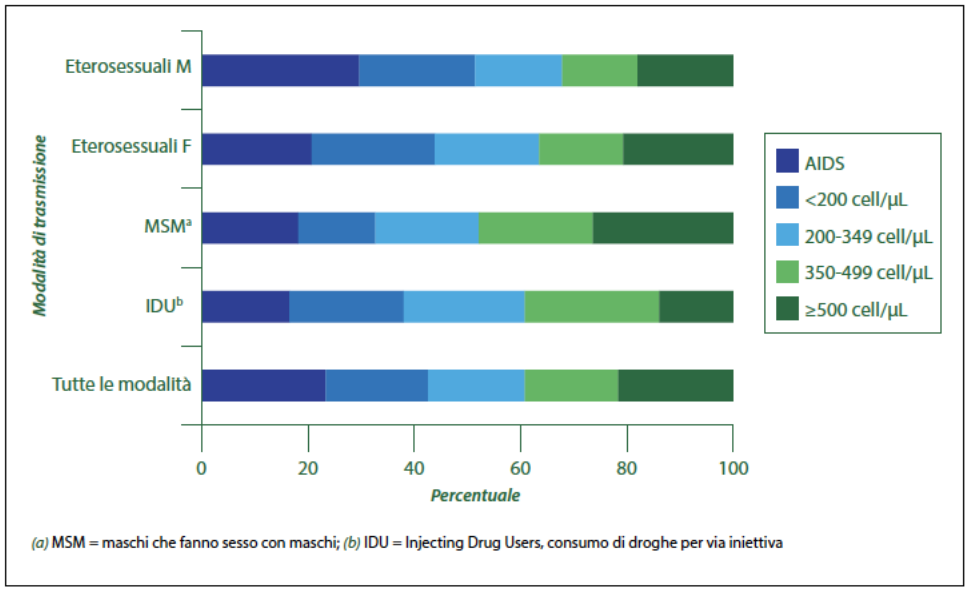


Figura 13 - Nuove diagnosi di infezione da HIV per classi di CD4, diagnosi di AIDS e modalità di trasmissione (2023)

Fattori significativamente associati alla diagnosi tardive

- ***età avanzata***
- ***maschio eterosessuale***
- ***nazionalità straniera***

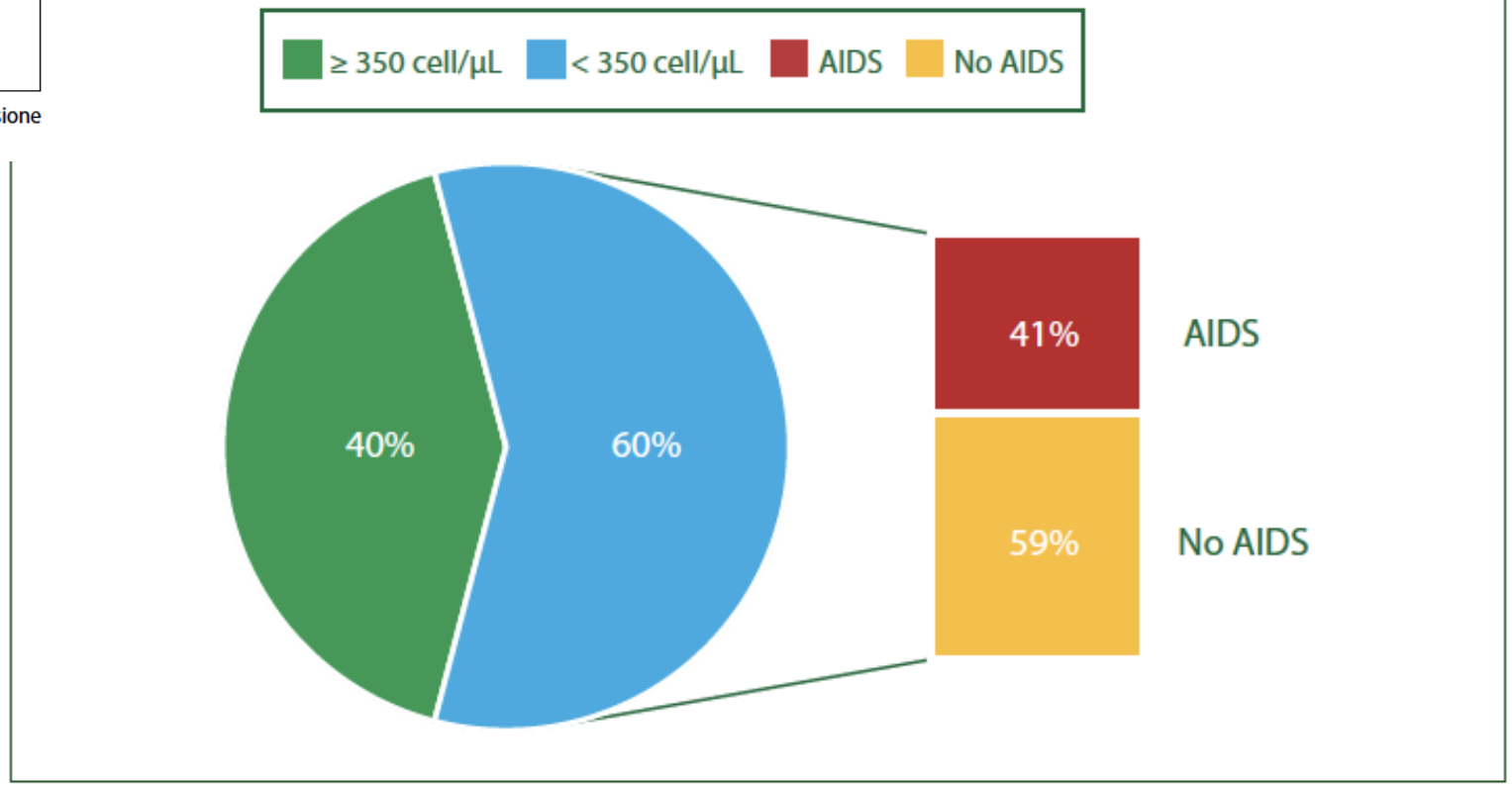
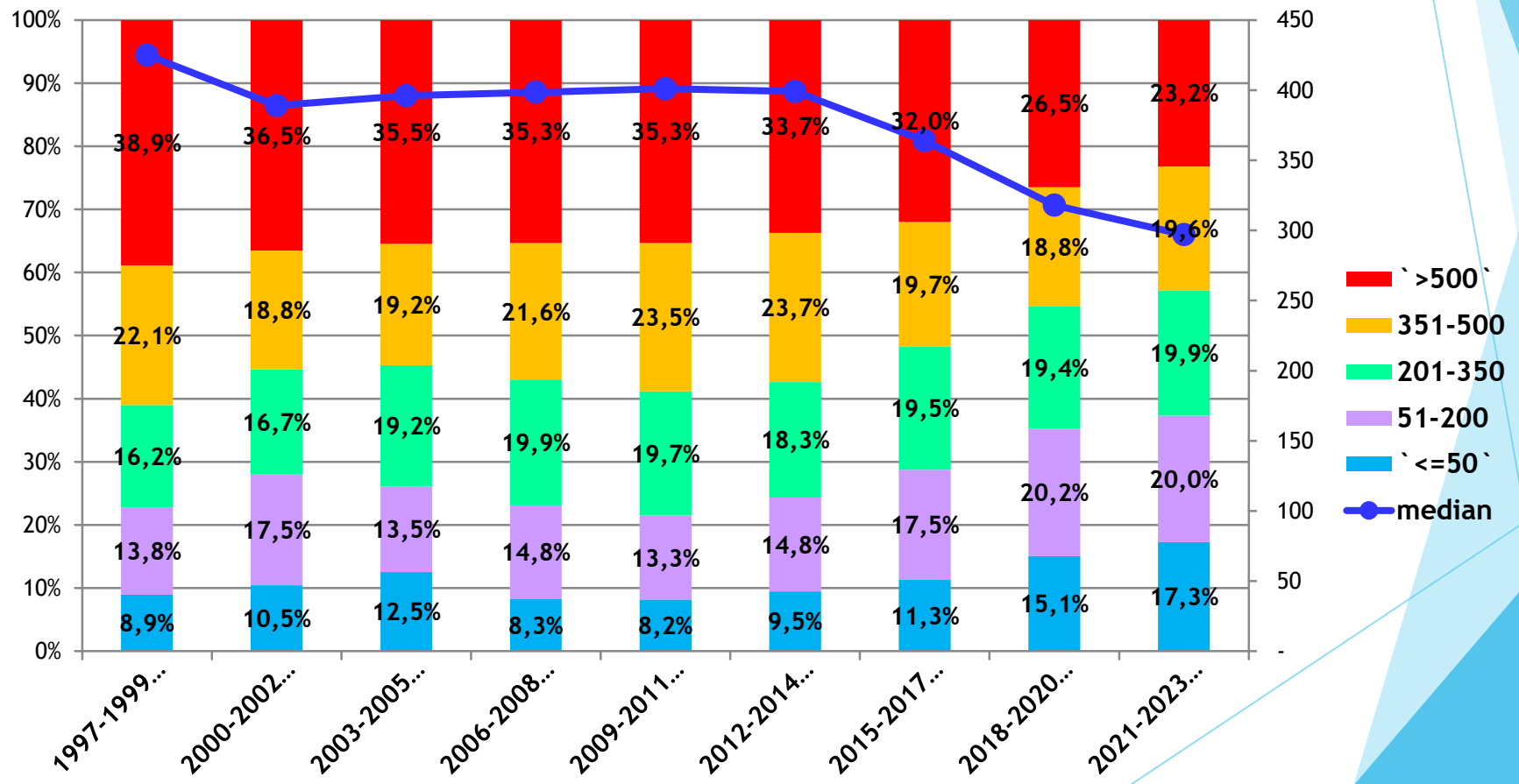


Figura 12 - Proporzione delle nuove diagnosi di infezione da HIV per numero di linfociti CD4 e diagnosi di AIDS (2023)

Not Ist Super Sanità 2024;37(11):3-59

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

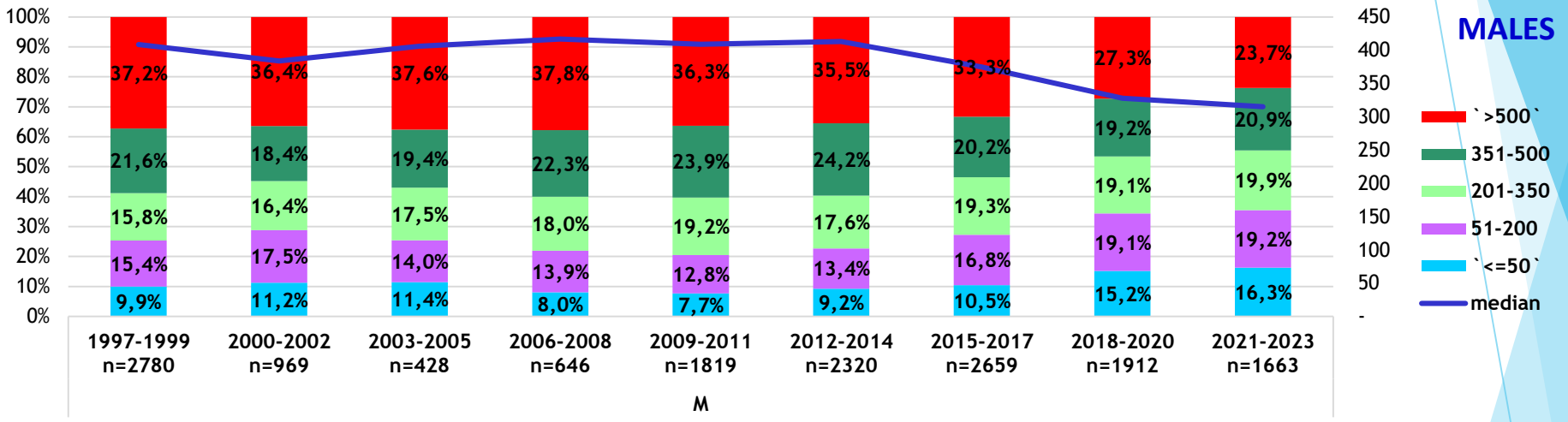
CD4 cells/mmc strata and median values at enrolment according to calendar period

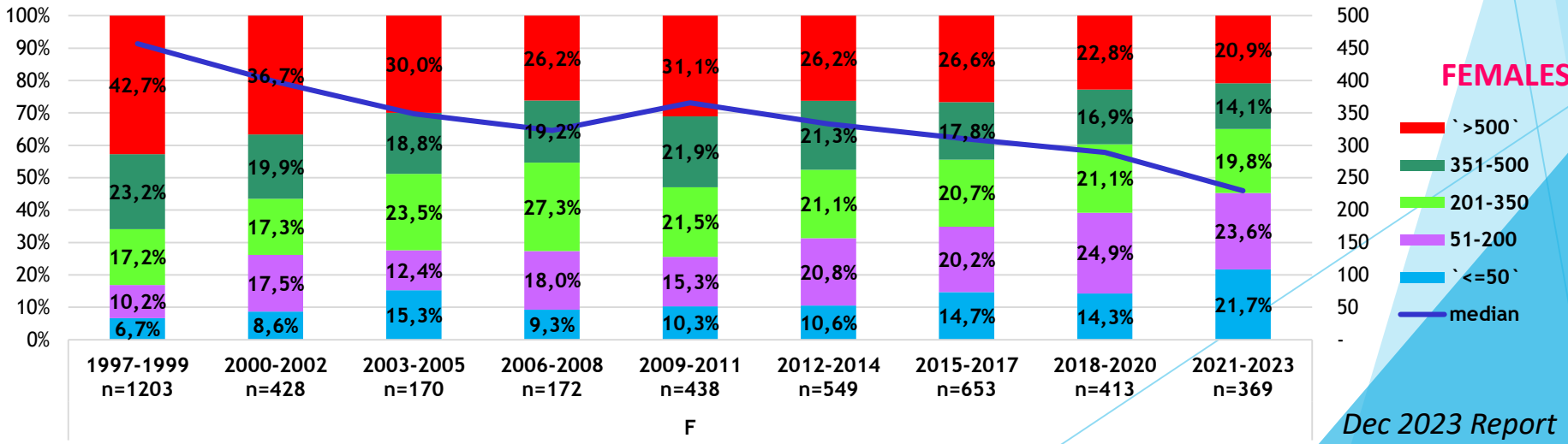


Dec 2023 Report

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

CD4 cells/mmc strata and median values at enrolment according to calendar period and sex

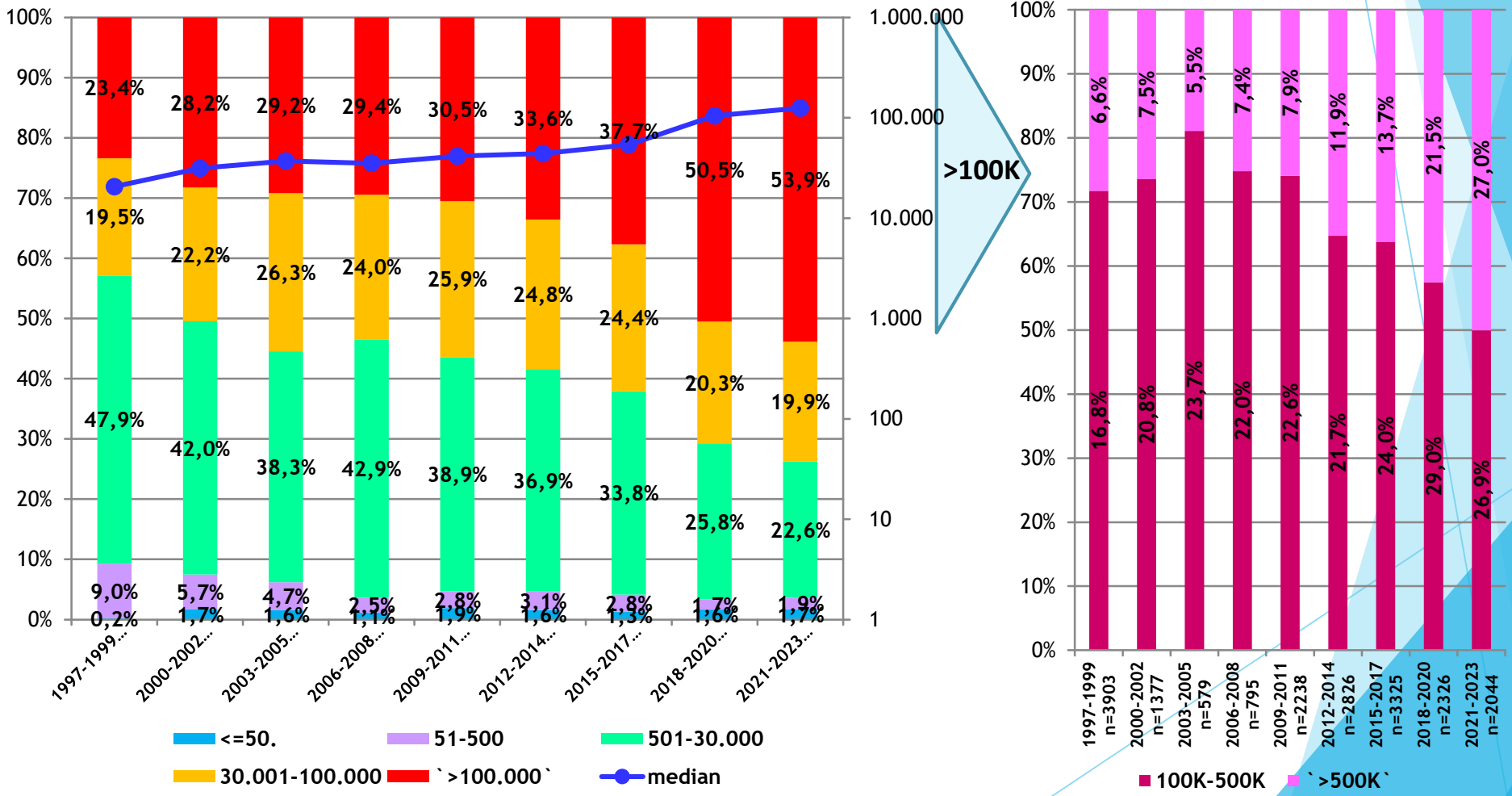




Dec 2023 Report

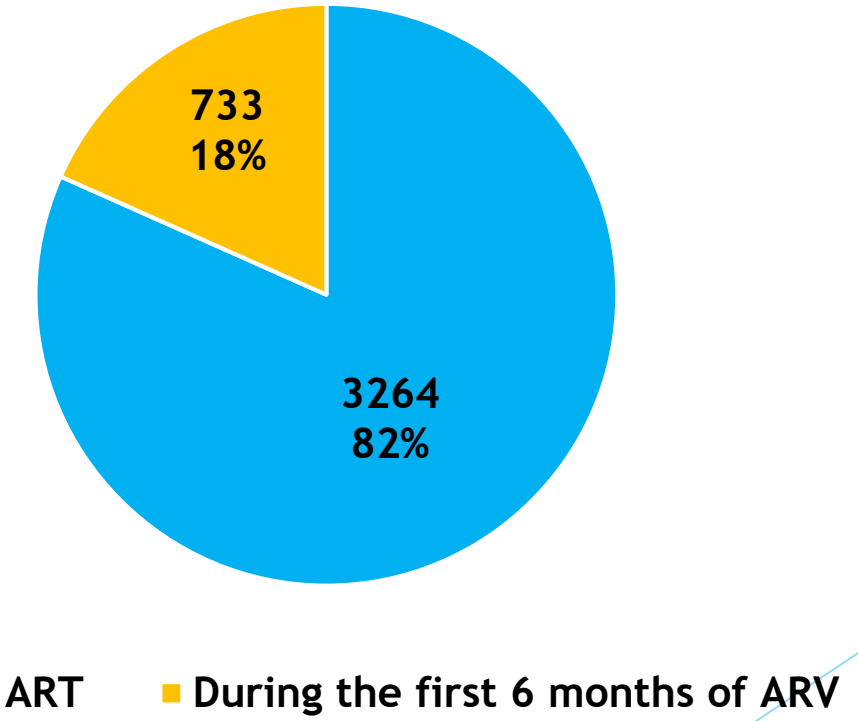
Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

HIV-RNA strata and median values at enrolment according to calendar period



Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

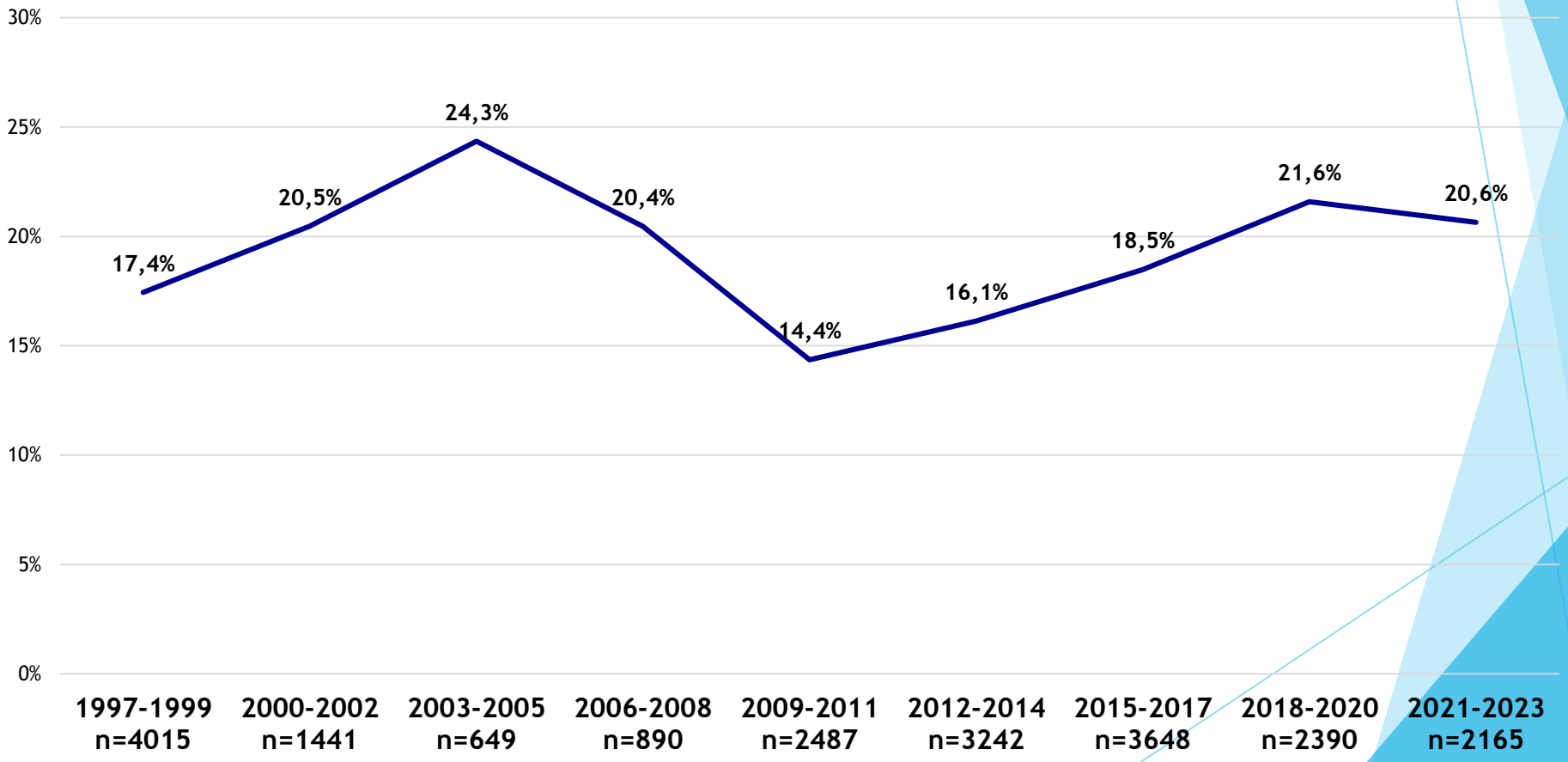
Distribution of AIDS defining diseases (n=3.997) recorded before starting ART and during the first 6 months of ART in 3.480 PWH with AIDS



Dec 2023 Report

Fondazione Icona
ITALIAN COHORT NAIVE ANTIRETROVIRALS

Prevalence of AIDS presenters (n=3.847) according to calendar period at enrolment (total PWH n=20.927)



Advanced HIV as a Neglected Disease

Nathan Ford, D.Sc., Peter Ehrenkranz, M.D., and Joseph Jarvis, M.B., B.S.

The NEW ENGLAND JOURNAL of MEDICINE

*The proportion of people with **advanced HIV disease** (CD4 <200 cells/mmc) remains high: it is estimated that **more than 4 million** people have advanced HIV disease, and each year more than **600,000 of them are expected to die**.*

Until recently, advanced HIV was viewed as a problem of late presentation, so the solution was thought to be testing more people and diagnosing the disease earlier.
*Advanced HIV is now predominantly seen among **people who started care but were not effectively engaged or have disengaged,** returning only when they're ill.*

The leading causes of HIV-related deaths appear to have changed little over time: they include tuberculosis, cryptococcal meningitis, and pneumocystis pneumonia. But there have been few recent attempts to confirm empirically whether these infections are still the major killers of people with HIV in the highest burden countries.

n engl j med 390;6 February 8, 2024

Advanced HIV as a Neglected Disease

Nathan Ford, D.Sc., Peter Ehrenkranz, M.D., and Joseph Jarvis, M.B., B.S.

The NEW ENGLAND JOURNAL of MEDICINE

Neglect of advanced HIV disease is an unintended consequence of the global shift in objectives from treating the sickest people to treating all who are infected

Once HIV disease becomes advanced,
there are few tools for preventing
and treating the resulting opportunistic infections.

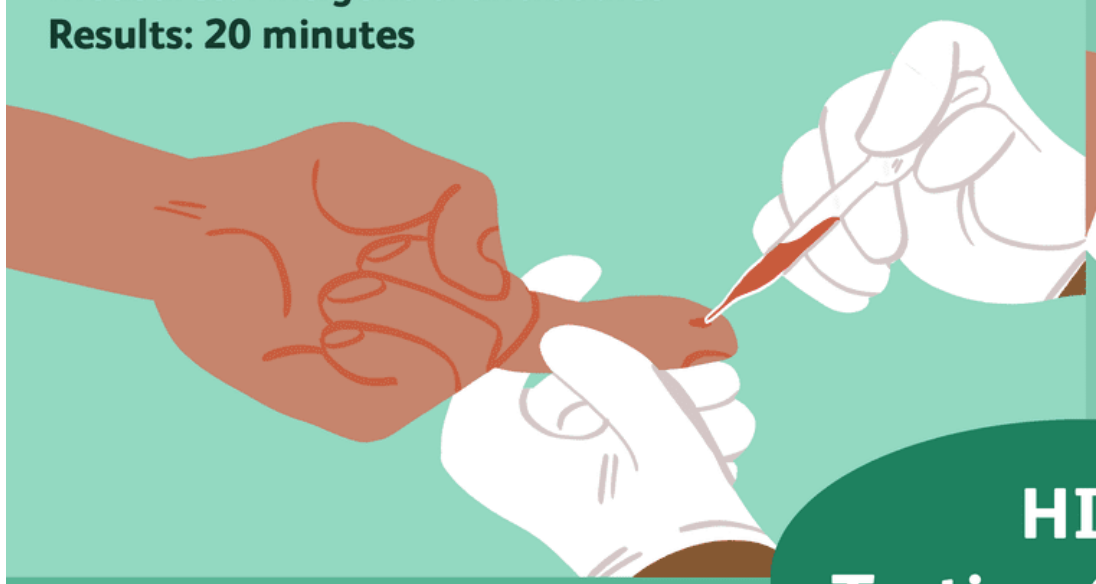
n engl j med 390;6 February 8, 2024

FIGURE 1: FACILITATING THE HIV CARE CONTINUUM THROUGH SOCIAL WORK PRACTICE

HIV Testing Options

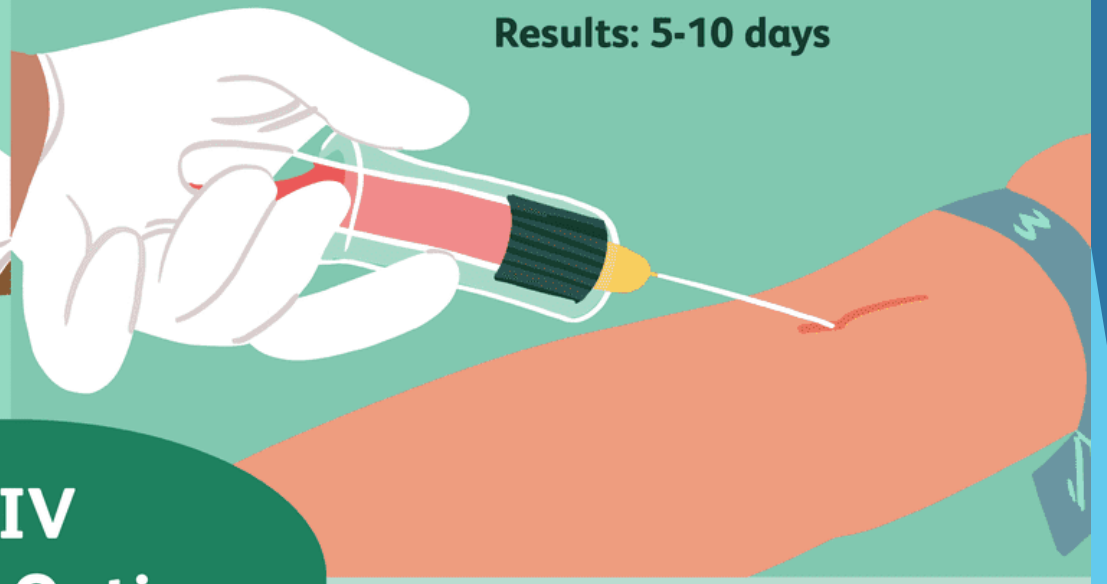
Rapid Point-of-Care

Measures: Antigens & antibodies
Results: 20 minutes



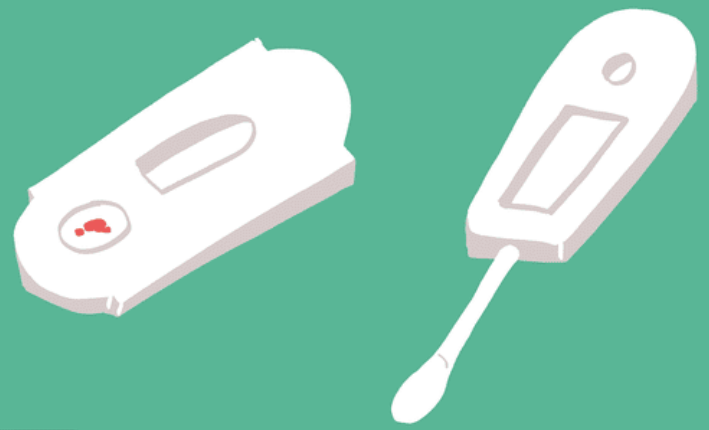
Standard Point-of-Care

Measures: Antibodies
Results: 5-10 days



At-Home Tests

Measures: Antibodies
Results: 20 minutes-1 day



Nucleic Acid Test*

Measures: HIV RNA
Results: A few days

*For people with high-risk exposure/early symptoms

verywell

What Is Opt-Out HIV Screening?

- Opt-out screening is an approach whereby an HIV test performed after notifying the patient of the following:
  - The test will be performed
  - The patient may elect to decline or defer testing
- Consent is inferred unless the patient declines testing.
- Opt-out screening:
  - Removes separate consent requirements
  - Removes prevention counseling requirements
  - Makes screening routine and systematized
  - Destigmatizes HIV testing
  - Has been used successfully in prenatal care settings

Branson BM, et al. *MMWR Recomm Rep.* 2006;55:1-17.[2]

life

MDPI

Article

HIV-Indicator Condition Guided Testing in a Hospital Setting

Diletta Barbanotti *, Camilla Tincati, Alessandro Tavelli, Andrea Santoro, Matteo Sala, Teresa Bini, Anna De Bona, Antonella d'Arminio Monforte and Giulia Carla Marchetti

Table 3. Newly diagnosed HIV infections.

Patient	Age	Gender	Nationality	HIV Indicator Conditions	Transmission Route	CD4 Cells/mm^3	CD4%	HIVRNA Copies/mL
1	32	F	Nigeria	Pneumonia (<50 yo)	Heterosexual	176	9	24.703
2	47	M	Italy	*P. jirovecii* pneumonia	Heterosexual	1	5	16.605
3	23	M	Morocco	Pneumonia (<50 yo); HBV and HCV infection	IDU	1100	25	5.472
4	45	F	Ethiopia	Dementia (<60 yo)	Heterosexual	31	5	130.721
5	40	M	Italy	Gonorrhea; Syphilis	n.a.	n.a.	n.a.	n.a.
6	36	M	Perù	Mononucleosis-like syndrome (acute HIV infection)	MSM	119	5	13,000.000
7	42	M	Italy	HBV infection	IDU	21	8	1146.543
8	54	F	Italy	Herpes zoster (<60 yo)	Heterosexual	224	20	1.333
9	34	F	Italy	Mononucleosis-like syndrome	Heterosexual	27	8	320.323
10	42	M	Italy	Mononucleosis-like syndrome; HCV infection; Syphilis	n.a.	117	16	186.988
11	67	M	Italy	Esophageal candidiasis; HBV infection; Syphilis	Heterosexual	18	1	160.831
12	40	M	Italy	HBV infection; Kaposi's sarcoma; Mononucleosis-like syndrome	MSM	49	4	167.638
13	32	F	Italy	HBV infection (pregnant patient)	Heterosexual	361	29	25.329
14	32	M	Italy	Mononucleosis-like syndrome	MSM	6	3	69.517
15	27	M	Italy	Mononucleosis-like syndrome	n.a.	1706	34	544.599
16	51	M	Italy	Esophageal candidiasis; HCV infection; *P. jirovecii* pneumonia	IDU	3	1	39.759
17	24	M	Italy	Mononucleosis-like syndrome; Syphilis	MSM	367	15	4607.623
18	40	M	Sierra Leone	Tuberculosis; HBV infection	Heterosexual	202	18	4047.851
19	31	M	Perù	Syphilis; Mononucleosis-like syndrome; disseminated CMV infection	MSM	19	4	398.424
20	31	M	Italy	*P. jirovecii* pneumonia	Heterosexual	11	2	118.494

ICEBERG: in-hospital HIVICs guided screening campaign in Milan between 2019 and 2021. Among the 520 subjects enrolled, mainly presenting with viral hepatitis or mononucleosis-like syndrome, 20 resulted HIV positive (3.8% prevalence). A significant proportion of them had multiple conditions and advanced immunosuppression, with 40% being AIDS-presenters

Table 6. Factors associated with HIV positivity by univariate and multivariate logistic regression analysis.

		Univariate Analysis		Multivariate Analysis	
		OR	*p*	aOR	*p*
HIV-ICs number (vs. 1)	2	1.4 (0.4–5.2)	0.590	1.9 (0.5–7.2)	0.359
	3	32.3 (9.3–111.9)	<0.001	51.5 (12.2–217.3)	<0.001
Male gender (vs. female)		1.2 (0.4–3.3)	0.741	0.8 (0.2–2.4)	0.635
Ethnicity (vs. Caucasian)	African	3.1 (0.8–11.6)	0.087	2.6 (0.6–11)	0.190
	Hispanic	1.9 (0.4–9)	0.396	1.4 (0.3–3.5)	0.710
	Asian	-	-	-	-
	Maghrebi	0.6 (0.1–5)	0.670	0.3 (0.03–3.5)	0.355
Age (10 years increment)		0.7 (0.6–1)	0.051	0.7 (0.5–0.9)	0.015

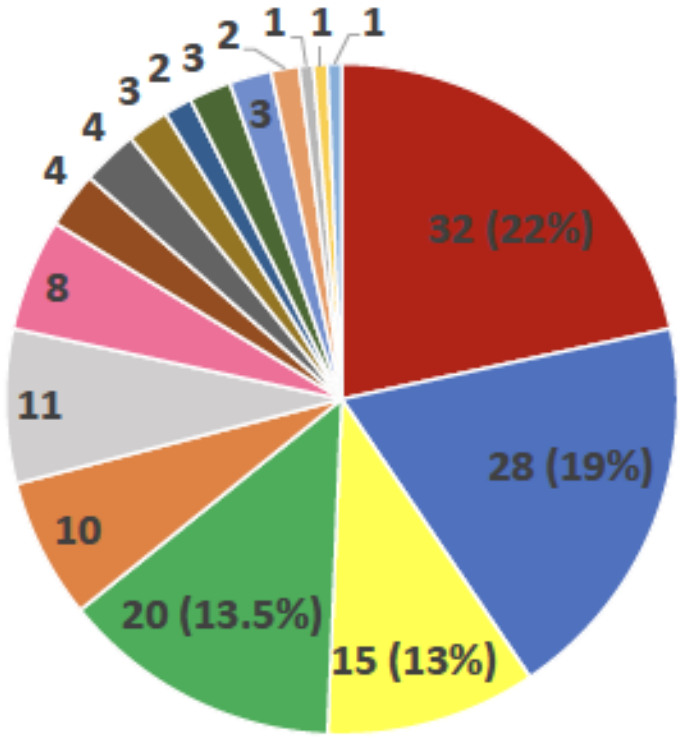
Studio INDI: verificare la fattibilità e l'utilità dell'offerta del test HIV a pazienti con una o più HIV Indicator Condition che accedono presso il Pronto Soccorso al fine di una diagnosi di HIV (più) precoce

Caratteristiche dei partecipanti allo studio

Caratteristica	Popolazione in studio N=119 *
Sesso maschile	81 (68%)
Nazionalità italiana	68 (57%)
Età, mediana (IQR)	46 (34-60)

* HIV-IC totali: 148

HIV-IC dello studio INDI



- Tubercolosi
- HBV
- Sindrome simil-mononucleosica
- Sifilide
- Polmonite < 50 anni
- HCV
- HAV
- Herpes Zoster < 60 anni
- Infezione invasiva da CMV
- Micobatteriosi atipica
- Candidosi esofagea
- Lesioni cerebrali occupanti spazio
- Gonorrea
- NHL
- PJP
- Polmonite ricorrente
- Piastrinopenia

Nuove diagnosi studio INDI: 8/119 (prevalenza 6.7%)

Sesso	Età	Nazionalità	HIV-IC 1	HIV-IC 2	HIV-IC 3	CD4/ul	FDR
M	35	Marocco	Polmonite < 50 aa			48 (4%)	Eterosessuale
M	46	Italia	Candidosi esofagea	Polmonite < 50 aa	S. simil-mononucleosica	33 (9%)	Eterosessuale
M	33	Cina	HBV	S. simil-mononucleosica	Micobatteriosi atipica	34 (7%)	Non riferito
F	64	Italia	CMV	S. simil-mononucleosica		7 (3%)	Non riferito
F	48	Perù	PJP	CMV		17 (5%)	Eterosessuale
M	76	Italia	Candidosi esofagea	TB		194 (9%)	Eterosessuale
M	61	Italia	Polmonite recidivante	HAV		467 (38%)	Omosessuale
M	23	Italia	HCV			28 (2%)	TD

Caratteristiche viro-immunologiche	Nuove diagnosi HIV N=8
Conta CD4+ (assoluta)	33 (20- 157)/mmc
Conta CD4+ (percentuale)	6 (3-9)%
HIV-RNA (mediana)	163800 cp/mL
Late presenter (%)	87%
Patologie AIDS-definenti	62%

1. Conditions which are AIDS defining among PLHIV*

Strongly recommend testing:

Neoplasms:
- Cervical cancer
- Non-Hodgkin lymphoma
- Kaposi's sarcoma

Bacterial infections
- Mycobacterium Tuberculosis, pulmonary or extrapulmunary
- Mycobacterium avium complex (MAC) or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmunary
- Pneumonia, recurrent (2 or more episodes in 12 months)
- Salmonella septicaemia, recurrent

Viral infections
- Cytomegalovirus retinitis
- Cytomegalovirus, other (except liver, spleen, glands)
- Herpes simplex, ulcer(s) >1 month/bronchitis/pneumonitis
- Progressive multifocal leucoencephalopathy

Parasitic infections
- Cerebral toxoplasmosis
- Cryptosporidiosis diarrhoea, >1 month
- Isosporiasis, >1 month
- Atypical disseminated leismaniasis
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

Fungal infections
- Pneumocystis carinii pneumonia
- Candidiasis, oesophageal
- Candidiasis, bronchial/ tracheal/ lungs
- Cryptococcosis, extra-pulmonary
- Histoplasmosis, disseminated/ extra pulmonary
- Coccidiodomycosis, disseminated/ extra pulmonary
- Penicilliosis, disseminated

2a. Conditions associated with an undiagnosed HIV prevalence of >0.1 %**

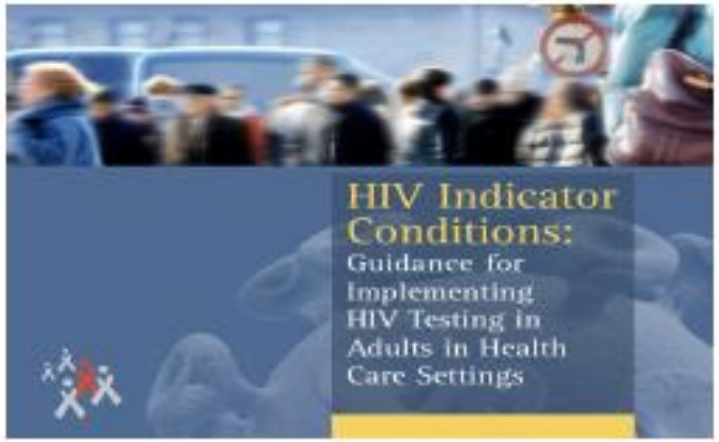
Strongly recommend testing:
- Sexually transmitted infections
- Malignant lymphoma
- Anal cancer/dysplasia
- Cervical dysplasia
- Herpes zoster
- Hepatitis B or C (acute or chronic)
- Mononucleosis-like illness
- Unexplained leukocytopenia/ thrombocytopenia lasting >4 weeks
- Seborrheic dermatitis/exanthema
- Invasive pneumococcal disease
- Unexplained fever
- Candidaemia
- Visceral leishmaniasis
- Pregnancy (implications for the unborn child)

2b. Other conditions considered likely to have an undiagnosed HIV prevalence of >0.1%

Offer testing:
- Primary lung cancer
- Lymphocytic meningitis
- Oral hairy leukoplakia
- Severe or atypical psoriasis
- Guillain–Barré syndrome
- Mononeuritis
- Subcortical dementia
- Multiplesclerosis-like disease
- Peripheral neuropathy
- Unexplained weightloss
- Unexplained lymphadenopathy
- Unexplained oral candidiasis
- Unexplained chronic diarrhoea
- Unexplained chronic renal impairment
- Hepatitis A
- Community-acquired pneumonia
- Candidiasis

3. Conditions where not identifying the presence of HIV infection may have significant adverse implications for the individual's clinical management despite that the estimated prevalence of HIV is most likely lower than 0.1%

Offer testing:
- Conditions requiring aggressive immuno-suppressive therapy:
  - Cancer
  - Transplantation
  - Auto-immune disease treated with immunosuppressive therapy
- Primary space occupying lesion of the brain.
- Idiopatic/Thrombotic thrombocytopenic purpura



Condizioni indicative di HIV riportate nel documento "HIV Indicator Conditions" promosso da HIV in Europe

Rapid ART initiation with bictegravir/emtricitabine/tenofovir alafenamide in individuals presenting with advanced HIV disease (Rainbow study)

Marta Camici[a,§,*], Roberta Gagliardini[a,§], Simone Lanini[a], Giulia Del Duca[a], Annalisa Mondi[a], Sandrine Ottou[a], Maria M. Plazzi[a], Federico De Zottis[a], Carmela Pinnetti[a], Alessandra Vergori[a], Elisabetta Grilli[a], Ilaria Mastrorosa[a], Valentina Mazzotta[a], Jessica Paulicelli[a], Rita Bellagamba[a], Eleonora Cimini[c], Eleonora Tartaglia[c], Stefania Notari[c], Massimo Tempestilli[c], Stefania Cicalini[a], Alessandra Amendola[b], Isabella Abbate[b], Federica Forbici[b], Lavinia Fabeni[b], Enrico Girardi[d], Francesco Vaia[e,#], Fabrizio Maggi[b], Andrea Antinori[a]

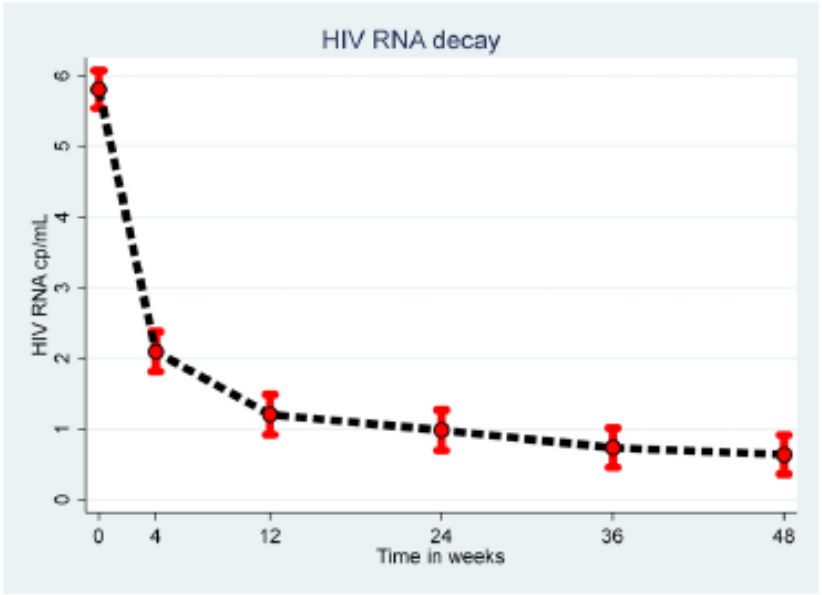


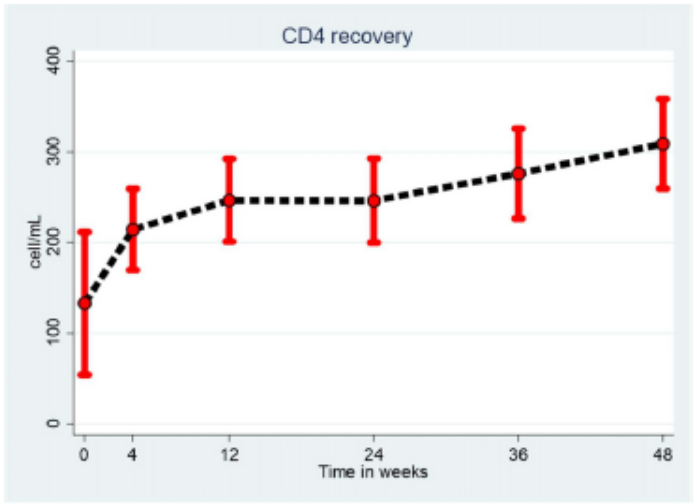
Fig. 1. HIV-RNA decay during study period.

Table 2a
Proportion of participants with HIV-RNA <50 cp/mL (per-protocol analysis).

Time (week)	HIV-RNA < 50 cp/mL	Assessed (N)	*P*-value
0	0%	30	<0.001
4	32%	28	
12	63%	30	
24	80%	30	
36	76%	29	
48	90%	30	

Table 2b
Proportion of participants with HIV-RNA < 50 cp/mL (ITT analysis).

Time (week)	HIV-RNA < 50 cp/mL	Assessed (N)	*P*-value
0	0%	30	<0.001
4	30%	30	
12	63%	30	
24	80%	30	
36	73%	30	
48	90%	30	



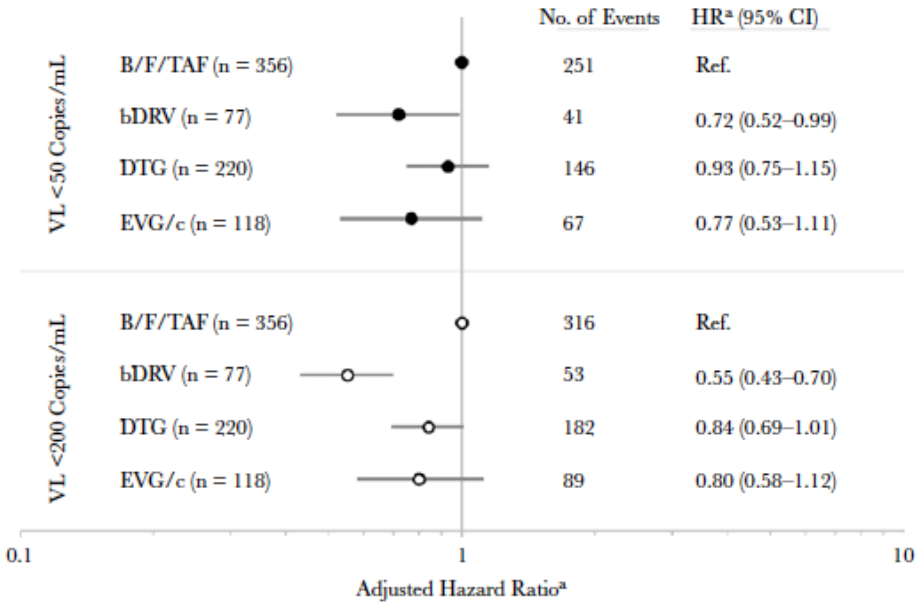
Time	obs	Mean CD4			CD4 variation			P-value	P-joint
		est.	95% CI		difference	95% CI			
0	30	132,95	54,30	211,61	base	-	-		
4	26	214,38	169,41	259,34	81,43	10,20	152,65	0,025	
12	29	246,58	200,97	292,20	113,63	30,92	196,34	<0.001	<0.001
24	29	246,16	199,76	292,57	113,21	27,86	198,57	<0.001	
36	28	276,06	226,45	325,64	143,10	50,61	235,58	<0.001	
48	29	308,97	259,48	358,46	176,02	83,06	268,98	<0.001	

Fig. 3. CD4+ cells recovery during study period.

Open Forum Infectious Diseases
MAJOR ARTICLE

Advanced HIV Infection in Treatment-Naïve Individuals: Effectiveness and Persistence of Recommended 3-Drug Regimens

Karam Mounzer,[1] Laurence Brunet,[2] Jennifer S. Fusco,[2] Ian R. Mcnicholl,[3] Helena Diaz Cuervo,[4] MichaelEnsion,[5] Lewis Mccurdy,[6] and Gregory P. Fusco[2]



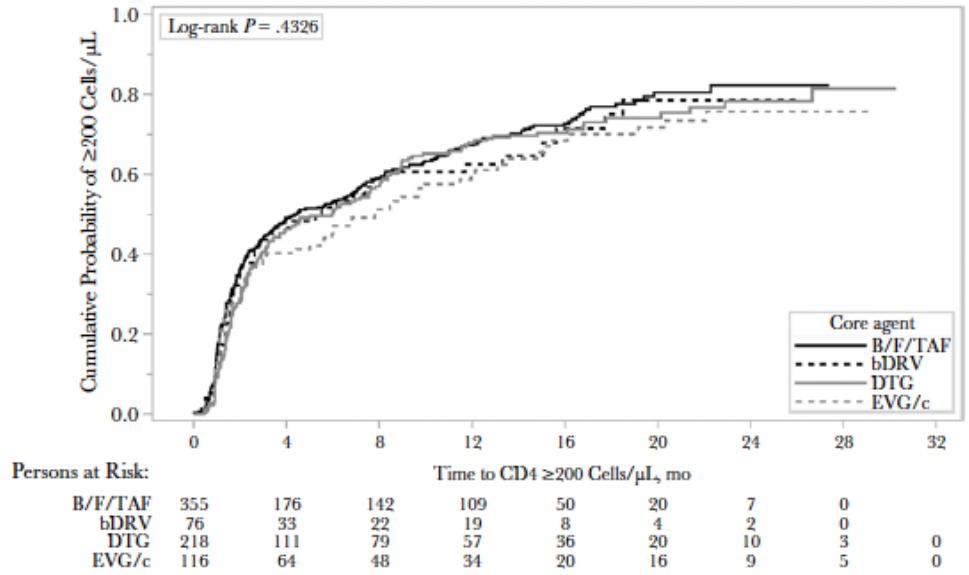
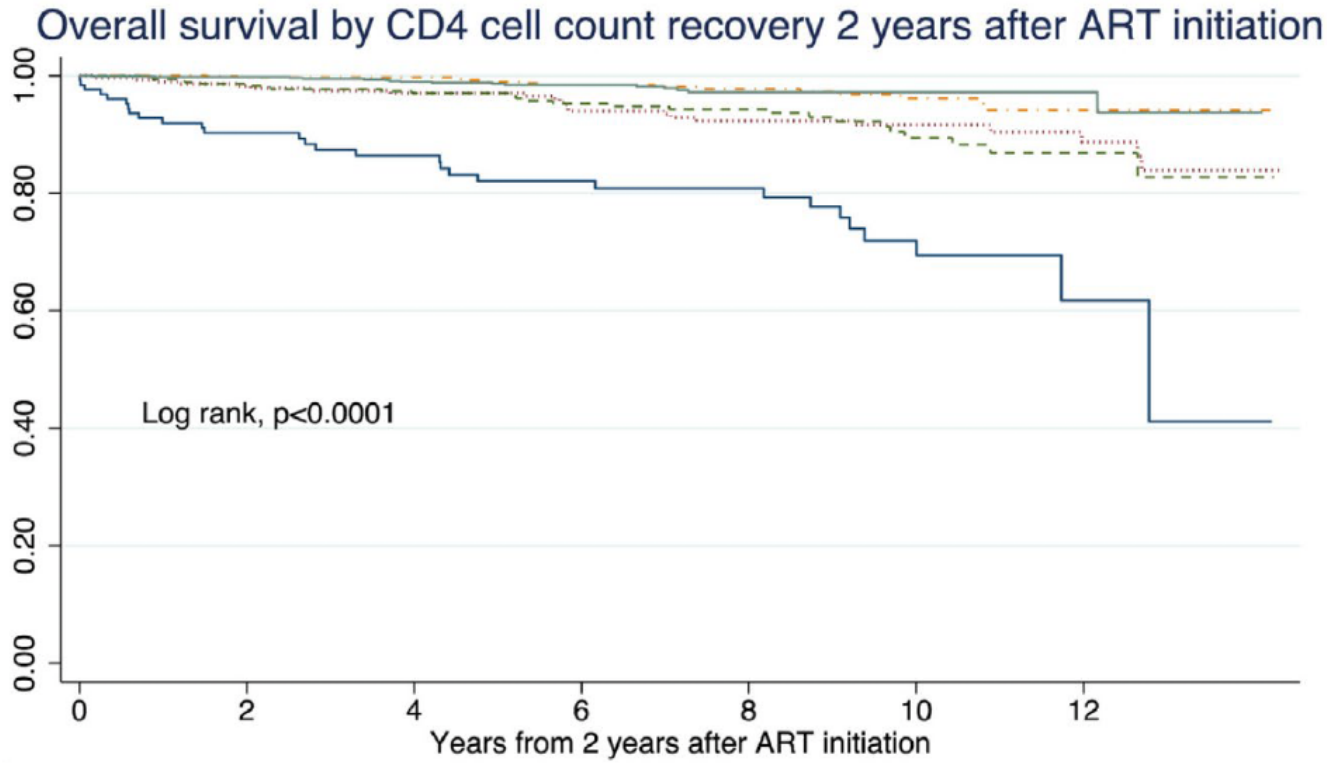


Figure 3. Cumulative probability of achieving a CD4 cell count ≥200 cells/μL. Abbreviations: B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; bDRV, boosted darunavir; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat.

- *961 PWH (416 B/F/TAF, 106 bDRV, 271 DTG, 168 EVG/c); 70% achieved a CD4 cell count ≥200cells/μL*
- *16-month median follow-up.*
- *discontinuation B/F/TAF vs all regimens (bDRV [aHR], 2.65; DTG: aHR, 2.42; EVG/c: aHR, 3.52).*

Among people with advanced HIV infection, those initiating B/F/TAF were less likely to discontinue/modify their regimen than those on any other regimen, and more likely to achieve viral suppression compared with those on bDRV but not compared with those on other integrase inhibitors



Number at risk							
LP, CD4<200	126	101	83	70	54	29	7
LP, CD4 200–350	304	253	220	185	153	98	52
LP, CD4>350–500	374	328	273	205	161	90	33
LP, CD4>500	637	572	460	354	244	137	48
Non–LP, CD4>500	1145	959	689	438	218	86	31

2719 PLWH, >50%LP

Outcome: all-cause mortality according to the two-year CD4 count

Martin-Iguacel eClinicalMedicine 2022

2024
ROMA
19-21 GIUGNO
UNIVERSITA' CATTOLICA
DEL SACRO CUORE
CENTRO CONGRESSI
EUROPA

16° CONGRESSO NAZIONALE
ICAR
Italian Conference on AIDS and Antiviral Research

Presidenza del Congresso
A. Cingolani, A. Di Biagio,
M. Farinella, G. C. Marchetti

Promosso da SIMIT Società Italiana di Malattie Infettive e Tropicali

RESEARCH and CARE: FROM BENCH, TO BEDSIDE, TO COMMUNITY

HIV ADVANCED NAIVE: THE FORGOTTEN TEST

A. Narducci [1], R. Simac [1], I.F. Bottalico [1], S. Ferrara [1], T. Santantonio [1], C. Santoro [2], A. Saracino [2], A. Dargenio[2], R. Schiavoni [3], L. Mezzogori [3], A. Di Biagio [3], A. Santoro [4],
G. C. Marchetti [4], C. Tincati [4], S. Lo Caputo

Presenting Author: **Arianna Narducci, MD**

Infectious Disease Unit Policlinico Foggia - University of Foggia

Material and methods

Aim of the study is to evaluate the viroimmunological features and outcome of a cohort of PLWH with advanced HIV infection and to investigate ***symptoms and hospitalization before the diagnosis***

- All PLWH diagnosed with advanced HIV infection since **1 January 2019 to 31 December 2023** from four Italian infectious diseases units (Foggia, Bari, Milano, Genova) were enrolled
- Data collected:
  - Demographic, clinical, therapeutical and viroimmunological data at baseline
  - Viroimmunological and therapeutical data one year from the start of antiretroviral treatment (cART)
  - Medical histories, symptoms, medical examinations, hospitalizations and surgery in the last two years prior to diagnosis and about HIV testing.

- The study population was stratified according to groups presenting AIDS and no AIDS at diagnosis. The chi-square test was used as appropriate to compare the groups.
- Survival analysis with Kaplan-Maier (KM) curves was used to access 5-year survival rate after infection

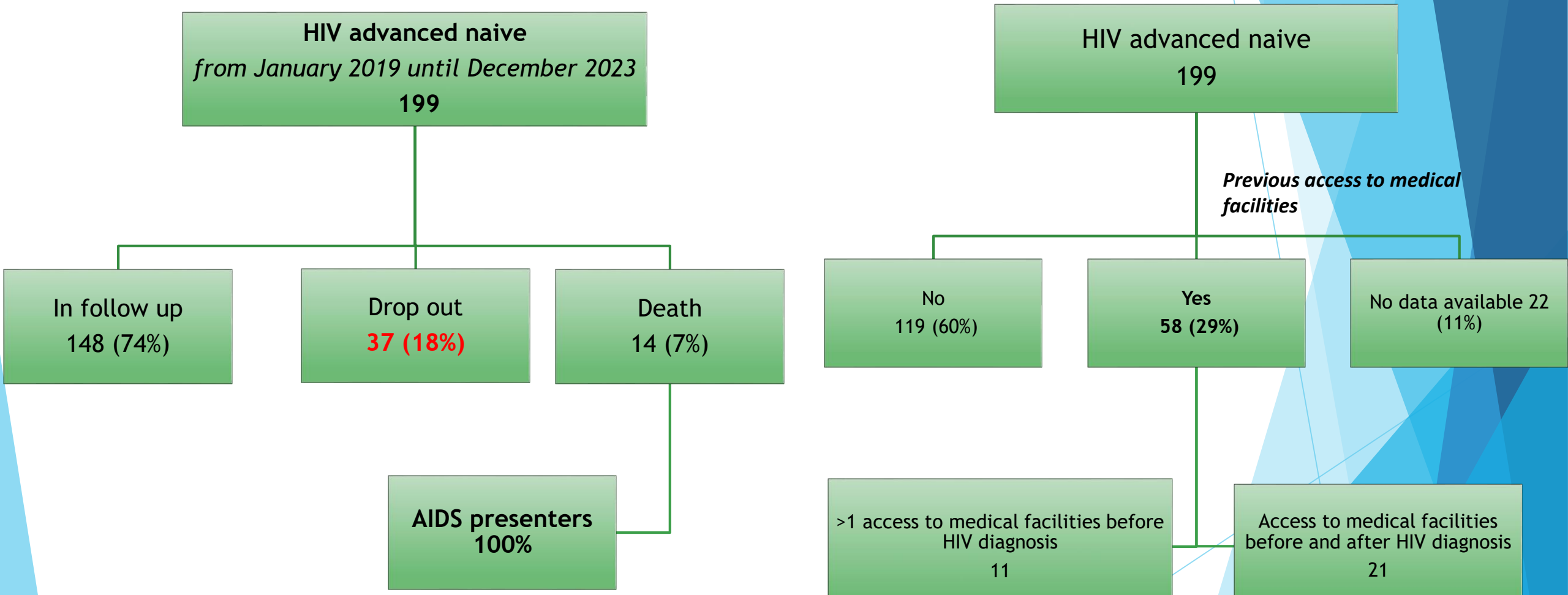
Demographic and viroimmunological characteristics

Advanced naive of total diagnosis, n (%)	199/575 (35%)
Sex, n (%)	
Male	150 (75%)
Female	46 (23%)
Transgender people	3 (2%)
Age, years, mean (-/+ sd)	
45 (33-57)	
Mode of transmission, n (%)	
Heterosexual	**115 (58%)**
MSM	65 (33%)
IDU	13 (7%)
Other	6 (3%)

Years of diagnosis, n (%)	
2019	44 (22%)
2020	35 (18%)
2021	33 (17%)
2022	38 (19%)
2023	49 (25%)
AIDS presenters baseline, n, (%)	
108 (54%)	
CD4 baseline	
Median (IQR)	52 (22,5-117)
CD4 < 50 cell/mm^3	**96 (48)**
VL baseline	
Median (IQR)	267600 (82758-980000)
> 100.000 cp/ml, n (%)	**141 (71%)**

OI prophylaxis, n (%)
147 (60%)
Previous HIV test, n (%)
23 (12%)

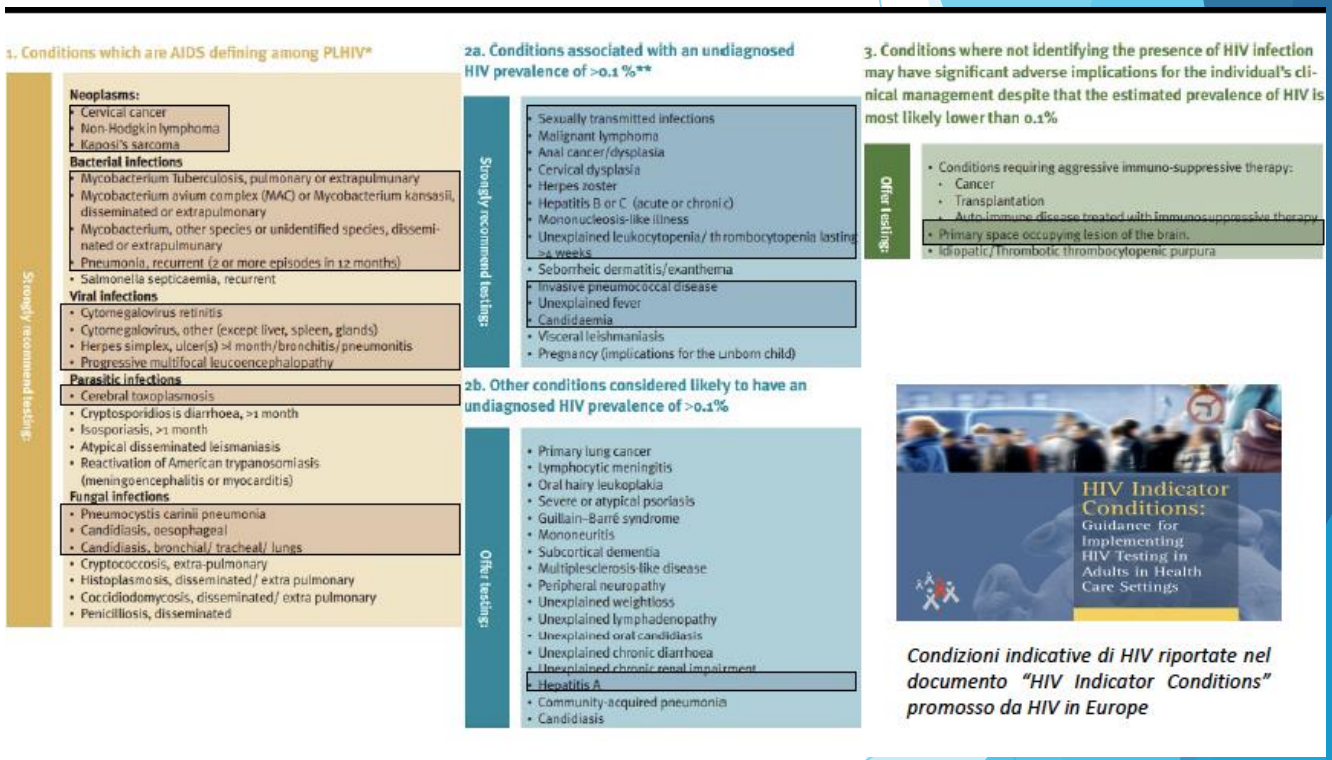
Result


HIV advanced naive
from January 2019 until December 2023
199
In follow up
148 (74%)
Drop out
37 (18%)
Death
14 (7%)
AIDS presenters
100%
HIV advanced naive
199
Previous access to medical facilities
No
119 (60%)
Yes
58 (29%)
No data available 22
(11%)
>1 access to medical facilities before HIV diagnosis
11
Access to medical facilities before and after HIV diagnosis
21

Symptoms and hospitalizations before the diagnosis

58/199 (29%) advanced naive were admitted two years before HIV diagnosis:

- Mononucleosis-like illness (44%)
- Leukocytopenia/thrombocytopenia, anemia (7%)
- Lymphadenopathy (7%)
- Cutaneous lesion (7%)
- Pneumonia (5%)
- Gastroenteritis (5%)
- Oral candidiasis
- Genital herpes
- Seborrheic dermatitis
- Leishmania
- Other (20%)

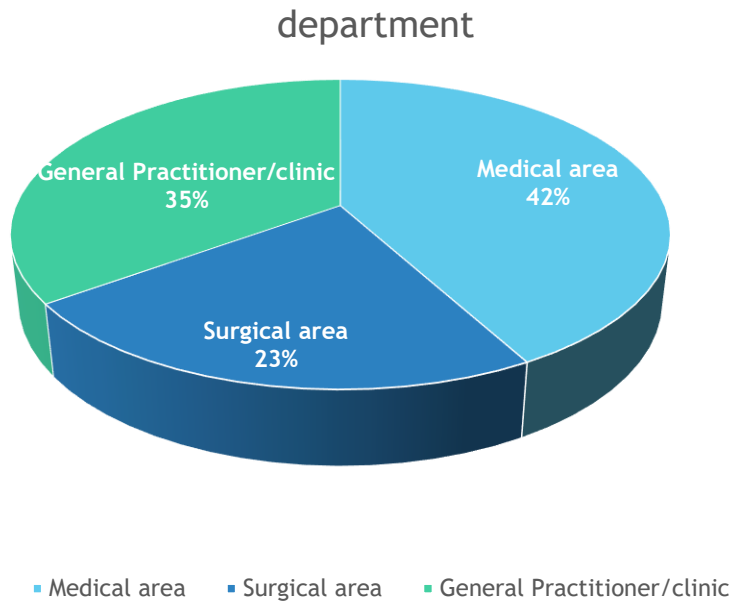


Condizioni indicative di HIV riportate nel documento "HIV Indicator Conditions" promosso da HIV in Europe

Symptoms and hospitalizations before the diagnosis

58/199 (29%) advanced naive were admitted two years before HIV diagnosis:

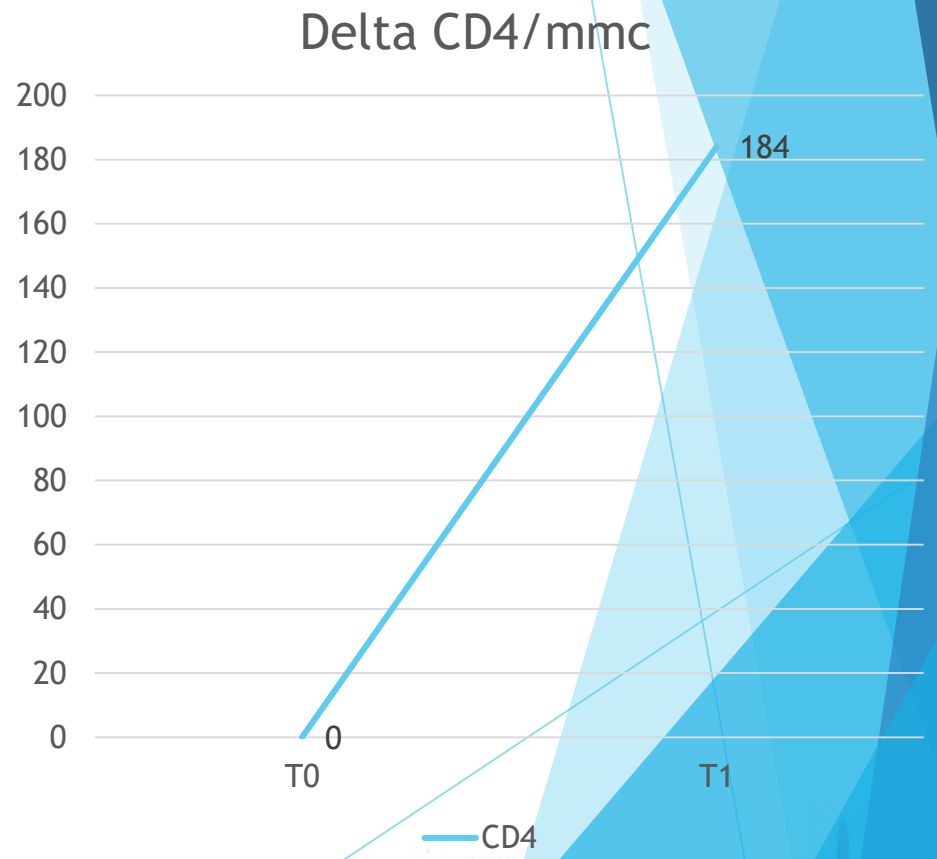
- General practitioner
- Internal medicine
- Emergency room
- General surgery



But also: Urology, Ematology, Intensive Care Unit, Infectious Disease, Cardiology, Gastroenterology, Ob/Gyn, Dermatology, Ophthalmology, Oncology, Reumtology, Otolaryngology

Follow-up immuno-virological data

Follow up	
CD4 after one year	
Median (IQR)	254 (170.5-348)
CD4 < 50 cell/mm^3, n (%)	2 (1%)
CD4 > 200 cell/mm^3, n (%)	102 (68%)
HIV-RNA after one year	
< 50 cp/ml, n (%)	**140 (93%)**
50 -200 cp/ml, n (%)	8 (5%)



Antiretroviral switch

cART baseline, n (%)	
BIC/FTC/TAF	**114 (59%)**
DTG/FTC/TAF	**31 (16%)**
DRV/c/FTC/TAF	**21 (11%)**
Other	**26 (14%)**

Follow up

Switch one year after diagnosis, n (%)		
Yes 25 (13%)	No 140 (70%)	ND 34 (17%)

BIC/FTC/TAF (73%)
DTG/FTC/TAF (41%)
DRV/c/FTC/TAF(86%)
RAL/FTC/TAF (57%)
EVG/TAF/FTC (50%)
DTG/3TC (80%)

- DTG/TAF/FTC to: BIC/TAF/FTC (7) DRV/c/TAF/FTC (1)

  DTG/3TC (2), RPV/TAF/FTC (1)
- DRV/c/TAF/FTC to BIC/FTC/TAF (2)
- RAL/TAF/FTC to BIC/TAF/FTC (1)
- EVG/TAF/FTC to BIC/TAF/FTC (1)
- BIC/FTC/TAF to: DTG/3TC (1), CAB/RPV (1)

Acknowledgement

R. Simac
I.F. Bottalico
S. Ferrara
T. Santantonio
S. Lo Caputo

Infectious Diseases Unit, A.O.U. Policlinico Foggia, University of Foggia

R. Schiavoni
L. Mezzogori
A. Di Biagio

Infectious Diseases Unit, IRCCS San Martino, University of Genova

A. Santoro
C. Tincati
G.C. Marchetti

Infectious Diseases Unit, ASST Santi Paolo e Carlo, University of Milano

A. Dargenio
C. Santoro
A. Saracino

Infectious Diseases Unit, A.O.U Consorziale Policlinico Bari, University of Bari

This publication was partially founded by an unconditional Grant of Gilead Sciences