MDR/HTE: nuovi approcci terapeutici

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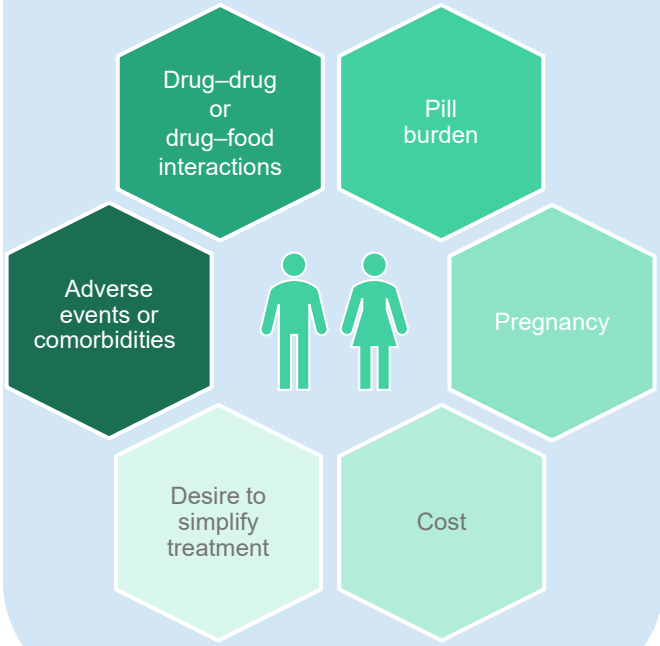
Disclosure of potential conflicts of interest

- 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

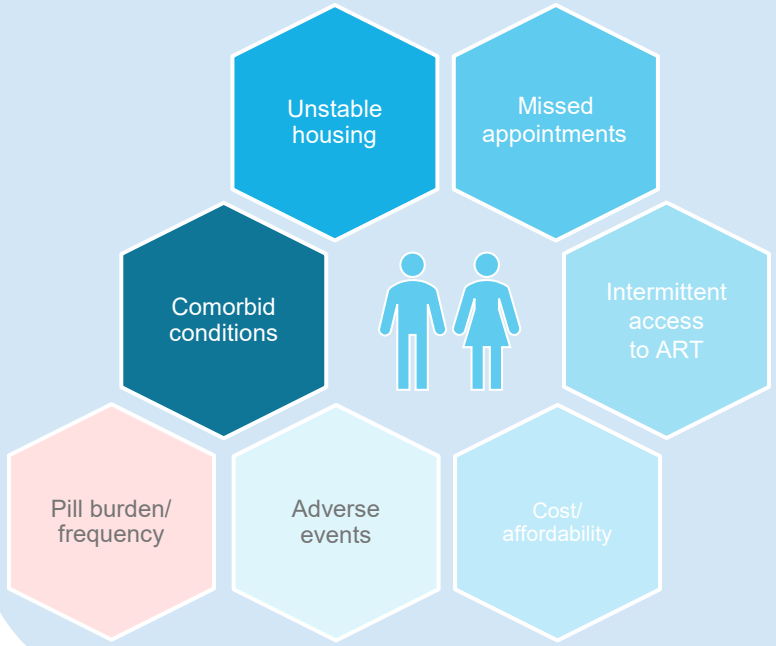
Understanding Treatment-Experienced PLWH

Suppressed PLWH
May still be dealing with:

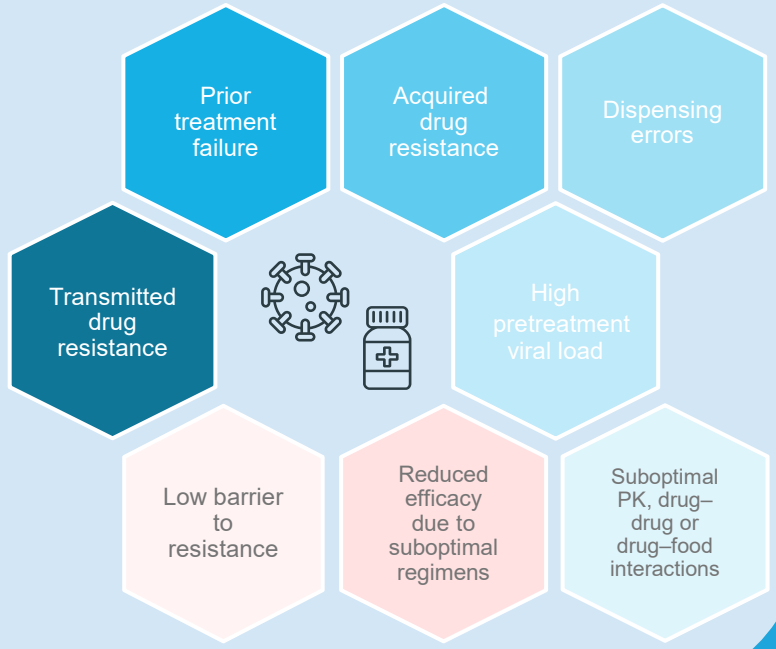


PLWH experiencing virologic failure
Virologic failure may be associated with a variety of factors, including:

Adherence/patient-related factors



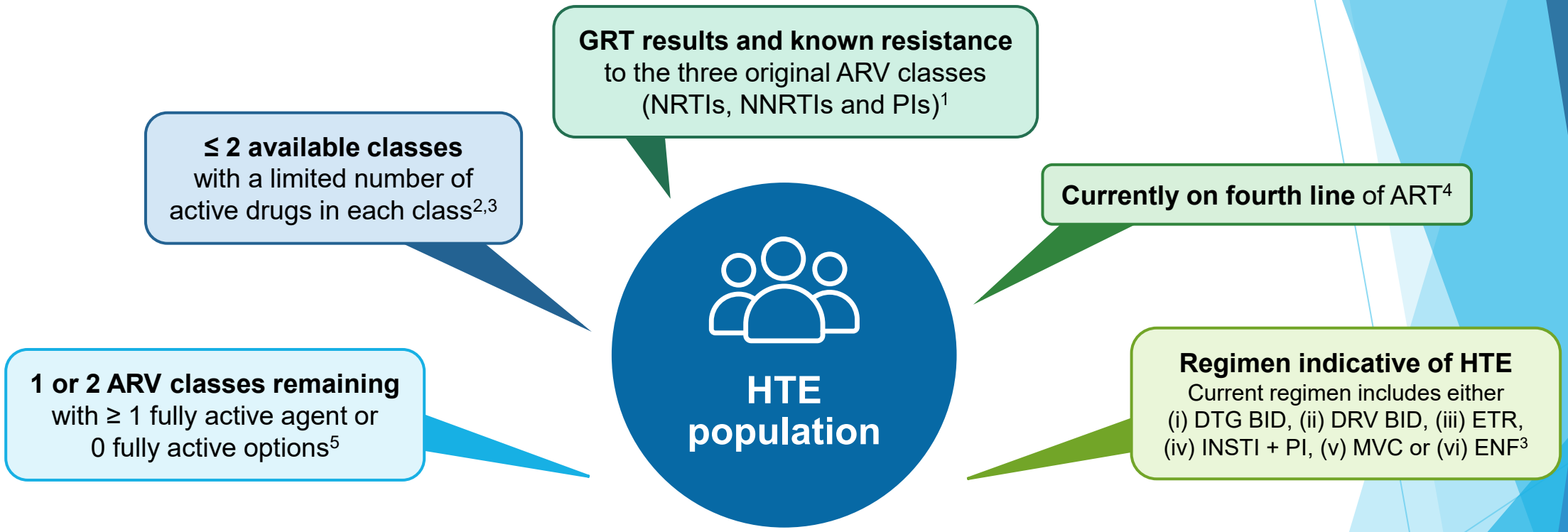
HIV- or ARV-related factors



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



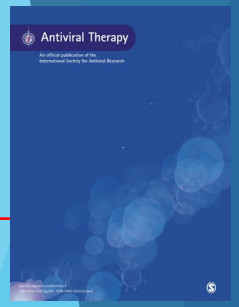
Various criteria have been used to define the HTE population across a range of studies

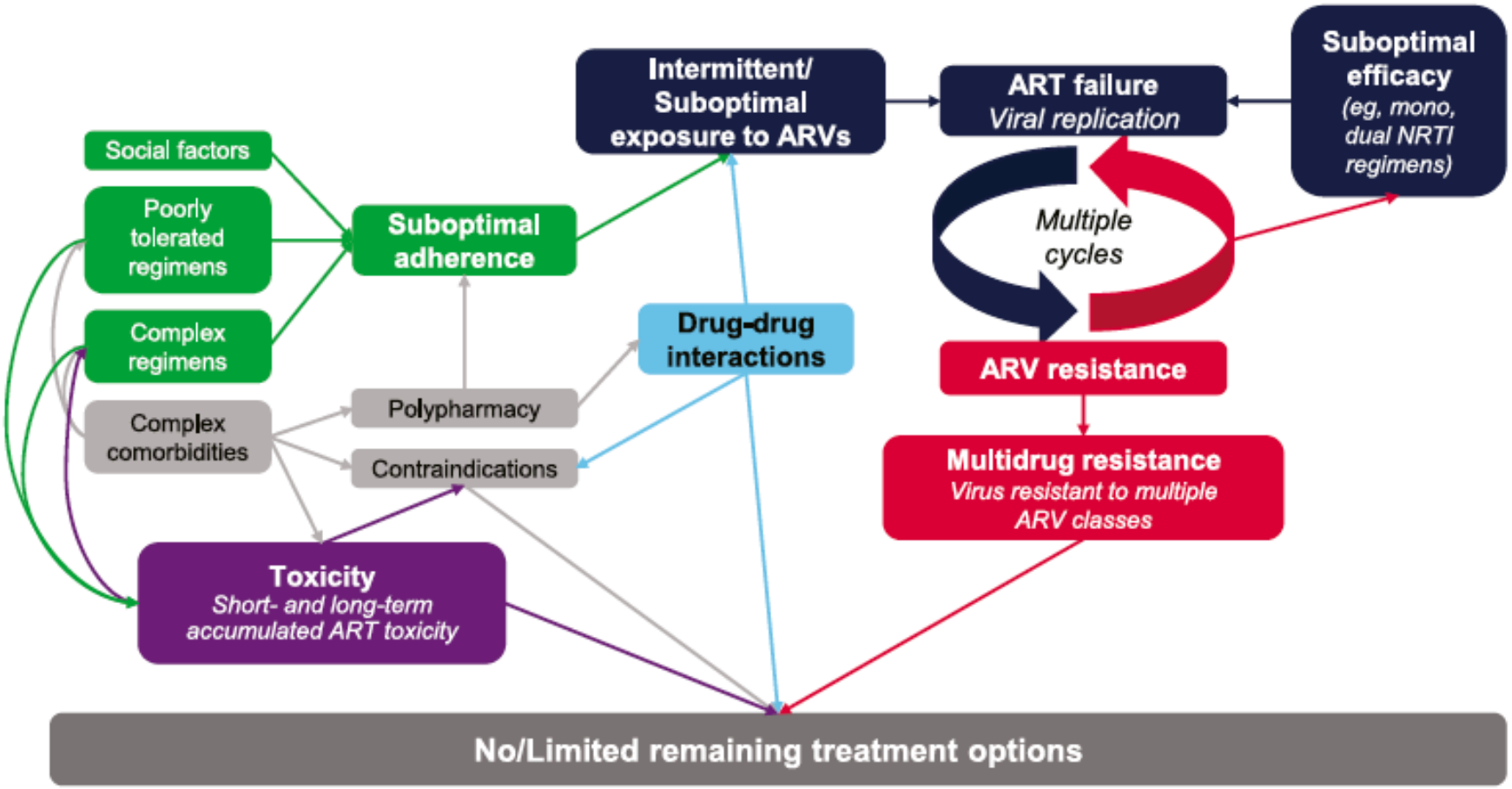
GRT, genotypic resistance testing; HTE, heavily treatment-experienced

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

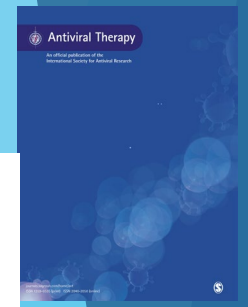




Clinical challenges to optimal ARV treatment in heavily treatment-experienced persons with HIV

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

Antiviral Therapy June 2023: 1–17



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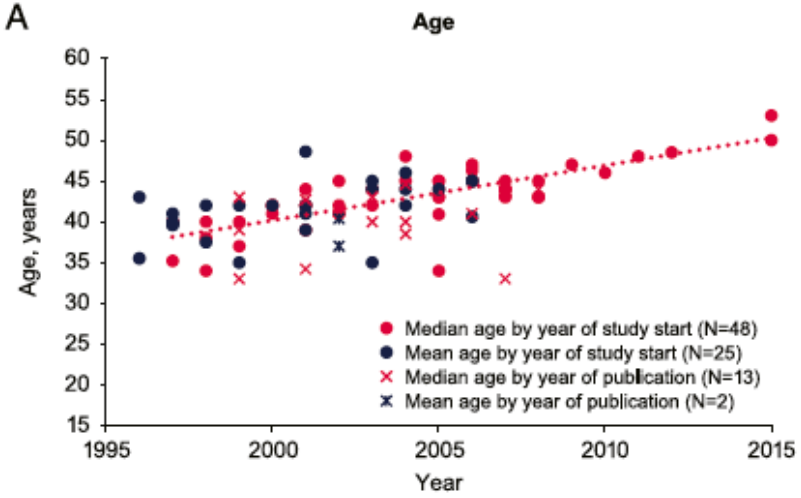
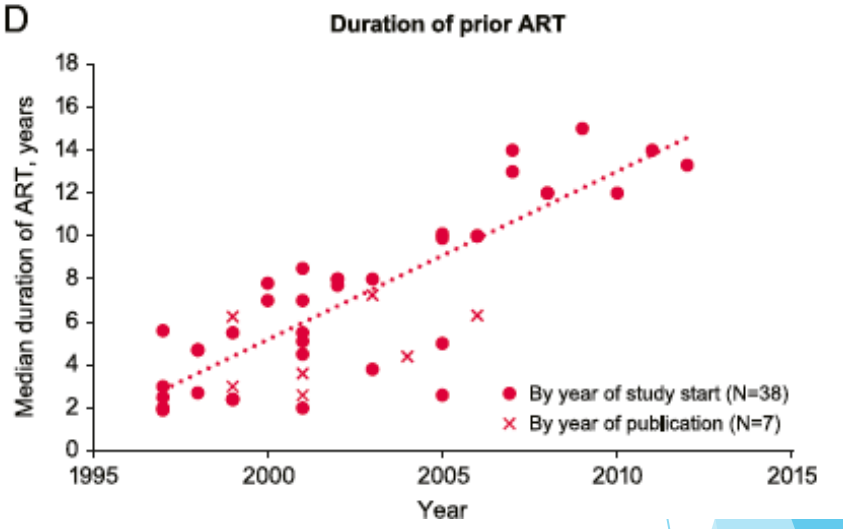


D



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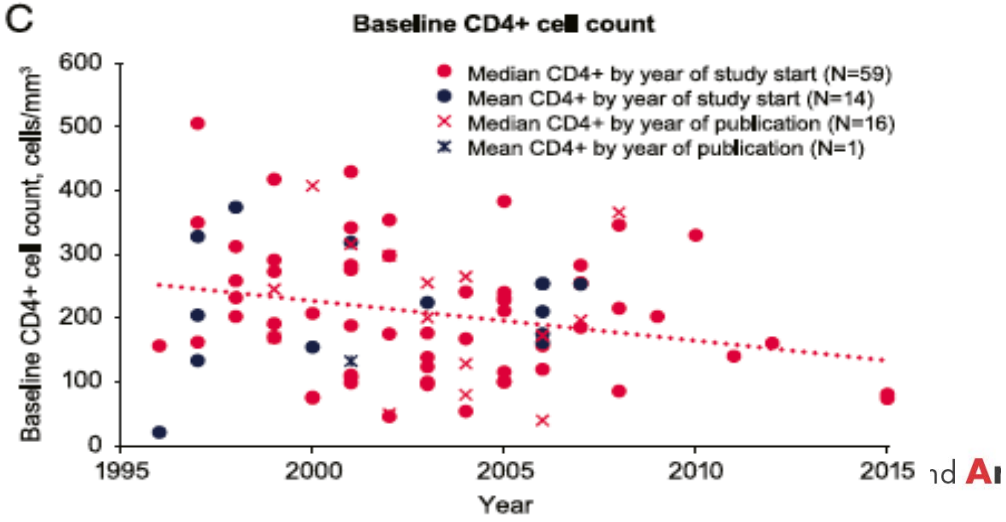

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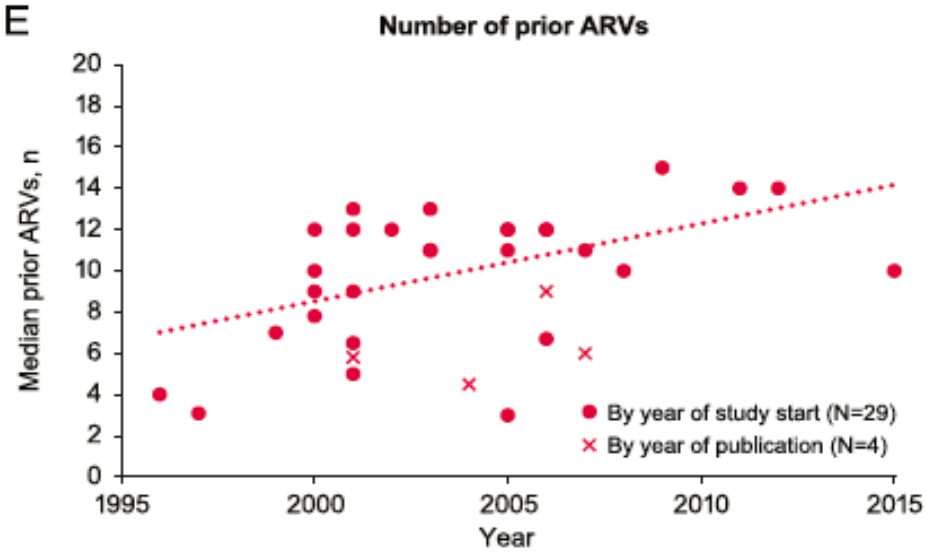


Characterization of Heavily Treatment-Experienced People With HIV and Impact on Health Care Resource Utilization in US Commercial and Medicare Advantage Health Plans

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***

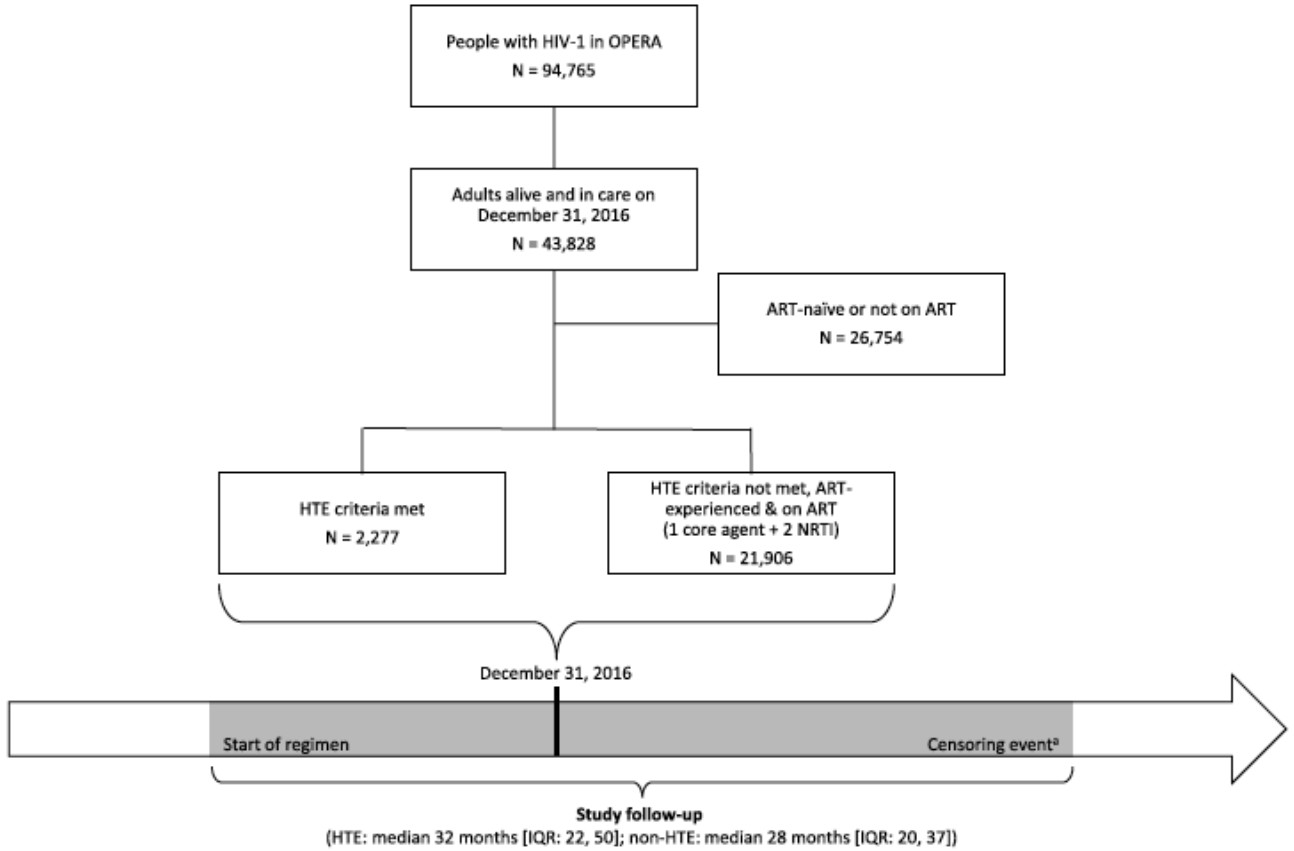
Table 3. Twelve-Month Follow-up All-Cause and HIV-Related Health Care Costs by Cohort

		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

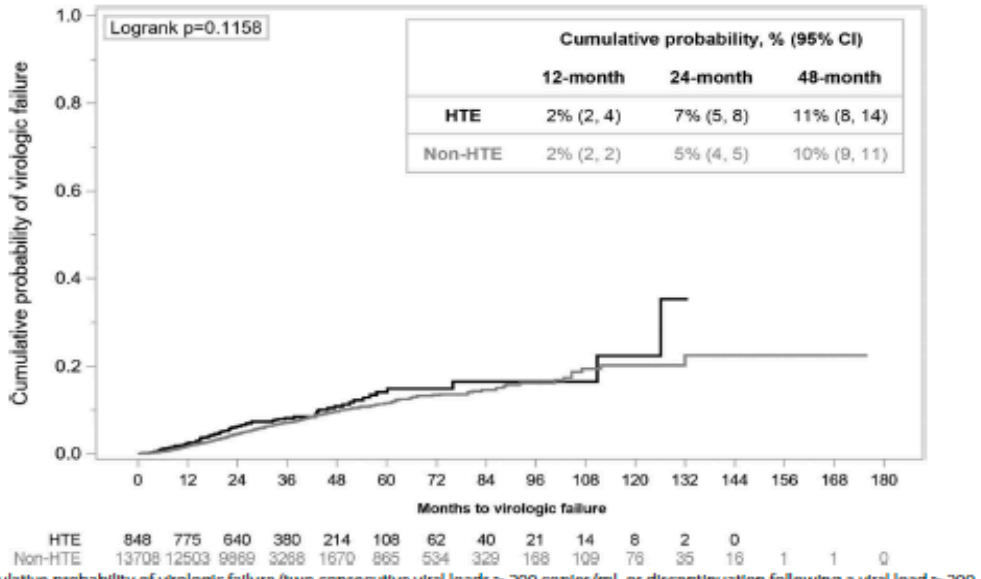


Fig. 3 Cumulative probability of virologic failure (two consecutive viral loads ≥ 200 copies/mL or discontinuation following a viral load ≥ 200 copies/mL) among people living with HIV with a viral load < 50 copies/mL at baseline

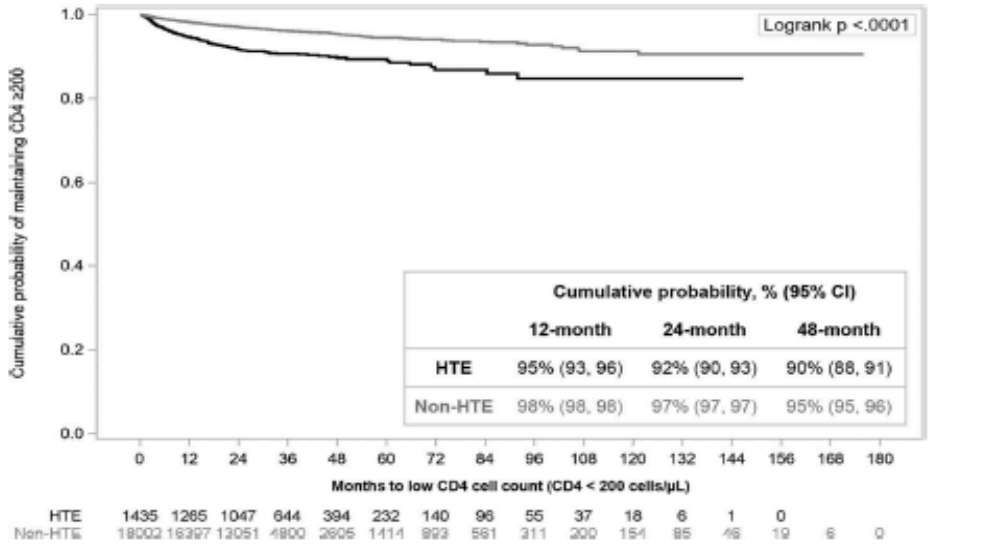


Fig. 4 Cumulative probability of maintaining CD4 cell count ≥ 200 cells/µL among people living with HIV with CD4 cell count ≥ 200 cells/µL at baseline

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. Eries J, et al. Open Forum Infectious Diseases, Volume 8, Issue 12, December 2021, ofab562, https://doi.org/10.1093/ofid/ofab562
2. Pelchen-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

Epidemiology of HTE PWH

CNICS cohort (2000–2017)[1]

Definition: ≤ 2 available classes with a limited number of active drugs in each class

Estimated prevalence by 2017:

< 1% (N = 27,133)

EuroSIDA cohort (2010–2016)[2]

Definition: Positive GRT results and known resistance to the three original ARV classes (NRTIs, NNRTIs and PIs)

Estimated prevalence by 2016:

10.4% (N = 15,570)

Despite the use of different definitions between cohorts, the number of HTE PWH among the global population of PWH is generally low

CNICS, Centers for AIDS Research Network of Integrated Clinical Systems; GRT, genotypic resistance testing; HAART, highly active antiretroviral therapy; HTE, heavily treatment-experienced

1. Bajema K, et al. AIDS 2020;34:2051-2059; 2. Pelchen-Matthews A, et al. JADIS 2021;87:806-817

AIDS 2020, 34:2051–2059

Substantial decline in heavily treated therapy-experienced persons with HIV with limited antiretroviral treatment options

Kristina L. Bajema[a], Robin M. Nance[a], Joseph A.C. Delaney[a], Ellen Eaton[b], Thibaut Davy-Mendez[c], Maile Y. Karris[d], Richard D. Moore[e], Joseph J. Eron[c], Benigno Rodriguez[f], Kenneth H. Mayer[g], Elvin Geng[h], Cindy Garris[i], Michael S. Saag[b], Heidi M. Crane[a], Mari M. Kitahata[a], Centers for AIDS Research Clinical Network of Integrated Systems (CNICS)

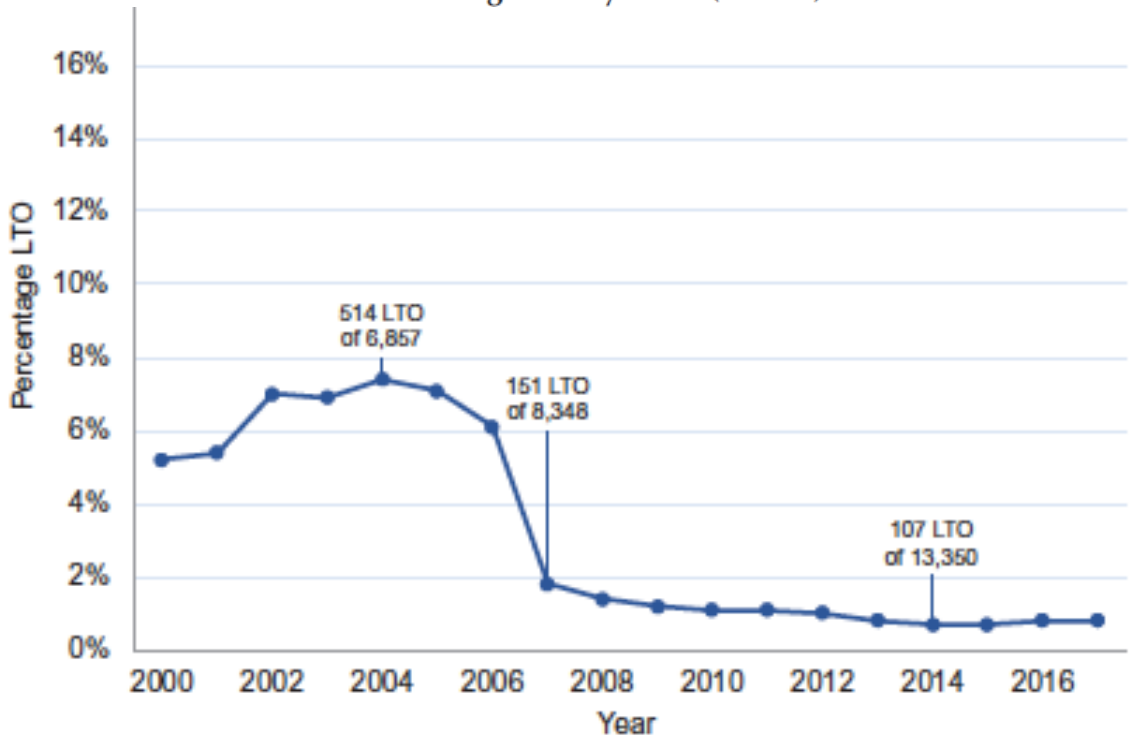
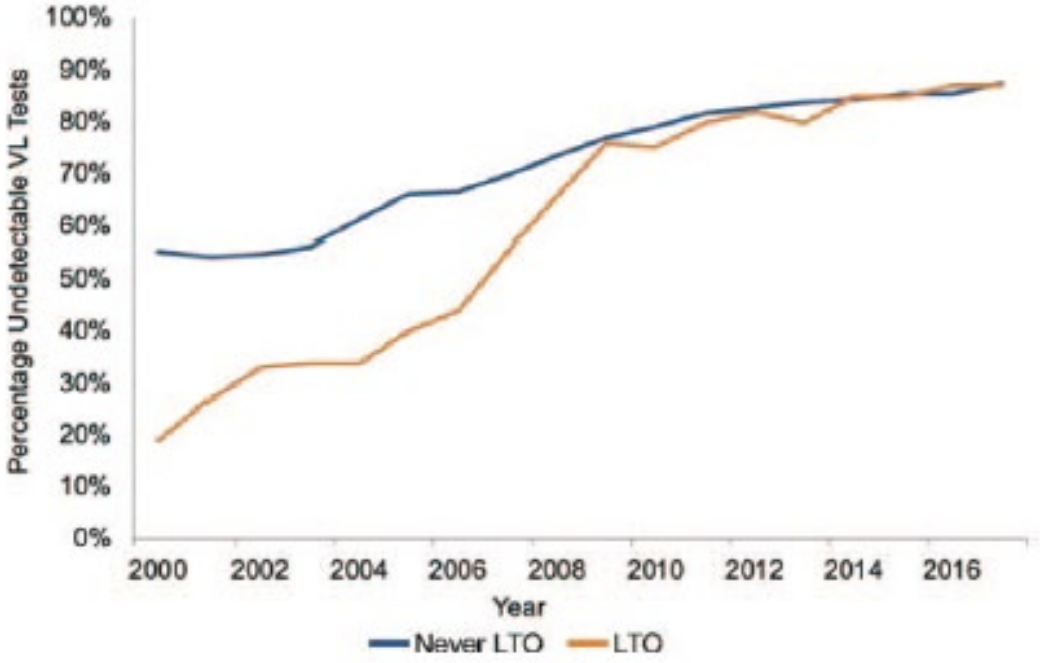


Fig. 1. Annual prevalence of persons with HIV with limited treatment options among antiretroviral therapy-experienced persons in care by year (2000–2017).



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

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

Prevalence and Outcomes for Heavily Treatment-Experienced Individuals Living With Human Immunodeficiency Virus in a European Cohort

Annegret Pelchen-Matthews, PhD,[a] Álvaro H. Borges, MD, PhD,[b] Joanne Reekie, PhD,[c] Line D. Rasmussen, MD, PhD,[d] Lothar Wiese, MD, PhD,[e] Jonathan Weber, MD, PhD,[f] Christian Pradier, MD, PhD,[g] Olaf Degen, MD,[h] Roger Paredes, MD, PhD,[i] Luba Tau, MD,[j] Leo Flamholc, MD,[k] Magnus Gottfredsson, MD, PhD,[l] Justyna Kowalska, MD, PhD,[m] Elzbieta Jablonowska, MD, PhD,[n] Iwona Mozer-Lisewska, MD, PhD,[o] Roxana Radoi, MD,[p] Marta Vasylyev, MD,[q] Anastasiia Kuznetsova, MD,[r] Josip Begovac, MD, PhD,[s] Veronica Svedhem, MD, PhD,[t] Andrew Clark, MD,[u] and Alessandro Cozzi-Lepri, PhD,[a] for the EuroSIDA study

Conclusions: HTE prevalence increased with time. After adjusting for key confounding factors, there was no evidence for an increased risk of new AIDS or non-AIDS clinical events in HTE. Additional therapeutic options and effective management of comorbidities remain important to reduce clinical complications in HTE individuals.

Methods: A composite definition for HTE was developed, based on estimates of antiretroviral resistance and prior exposure to specificantiretroviral regimens.

Results: Of 15,570 individuals under follow-up in 2010–2016, 1617 (10.4%) were classified as HTE. 1093 individuals became HTE during prospective follow-up (HTE incidence rate 1.76, per 100 person-years of follow-up).

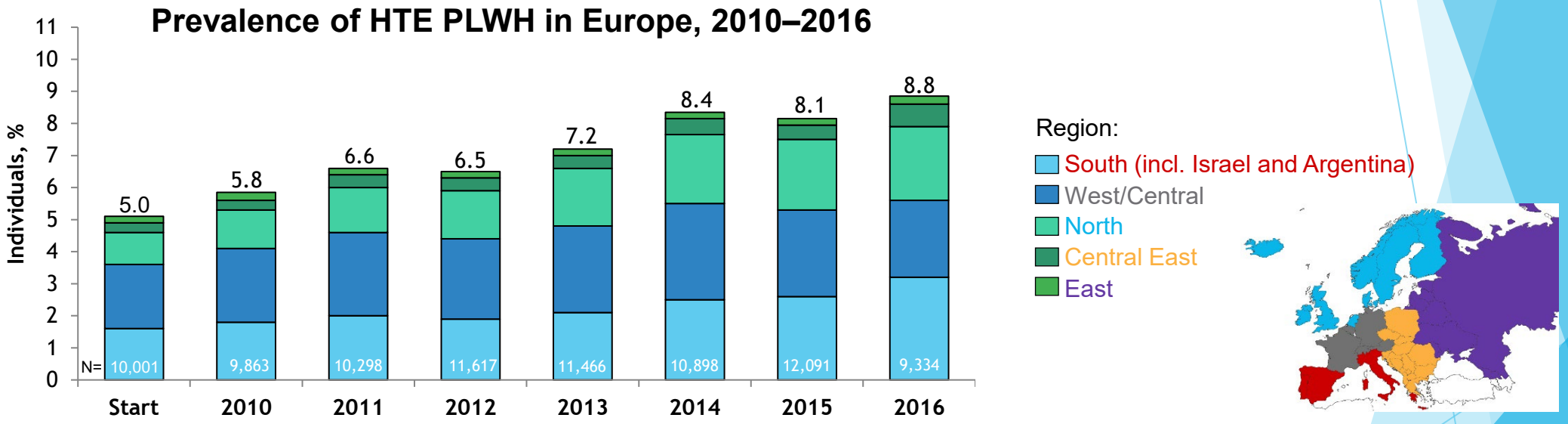
The number of HTE individuals was highest in West/Central Europe (636/4019 persons, 15.7%) and lowest in East Europe (26/2279 persons, 1.1%).

After controlling for age, immunological parameters and pre-existing comorbidities, HTE status was not associated with the risk of new AIDS (adjusted incidence rate ratio, aIRR 1.44, CI: 0.86 to 2.40, P = 0.16) or non-AIDS clinical events (aIRR 0.96, CI: 0.74 to 1.25, P = 0.77).

Prevalence of HTE PLWH in Europe

HTE composite definition includes resistance to NRTIs, NNRTIs and PIs, or at least two of the following:

- **Definition 1**: ≤ 2 drug classes available
- **Definition 2**: ≥ 4 anchor agent switches and the fourth anchor agent was ENF (T20), DRV, ETR, MVC, TPV, DTG or RAL
- **Definition 3**: Use of ≥ 4 of the following ARVs (DTG, DRV, ETR, RAL) together with a PI, MVC or ENF (T20)

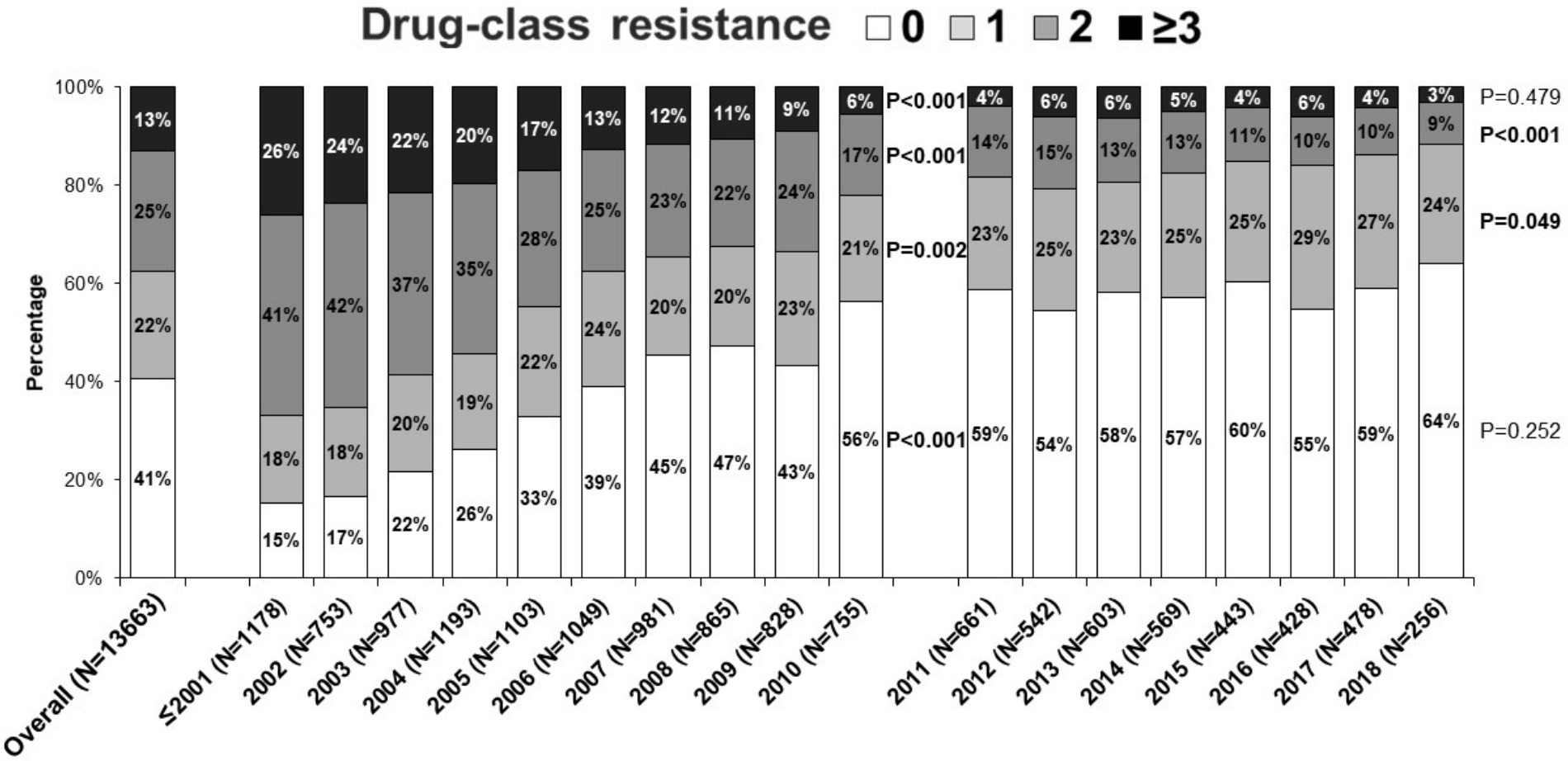


HTE PLWH had a 2.4-fold and 1.3-fold higher incidence of new AIDS and non-AIDS clinical events than non-HTE PLWH, respectively

HTE, heavily treatment-experienced

Pelchen-Matthews A, et al. JAIDS 2021;87(2):806-817, figure adapted with permission from Wolters Kluwer Health, Inc.

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.

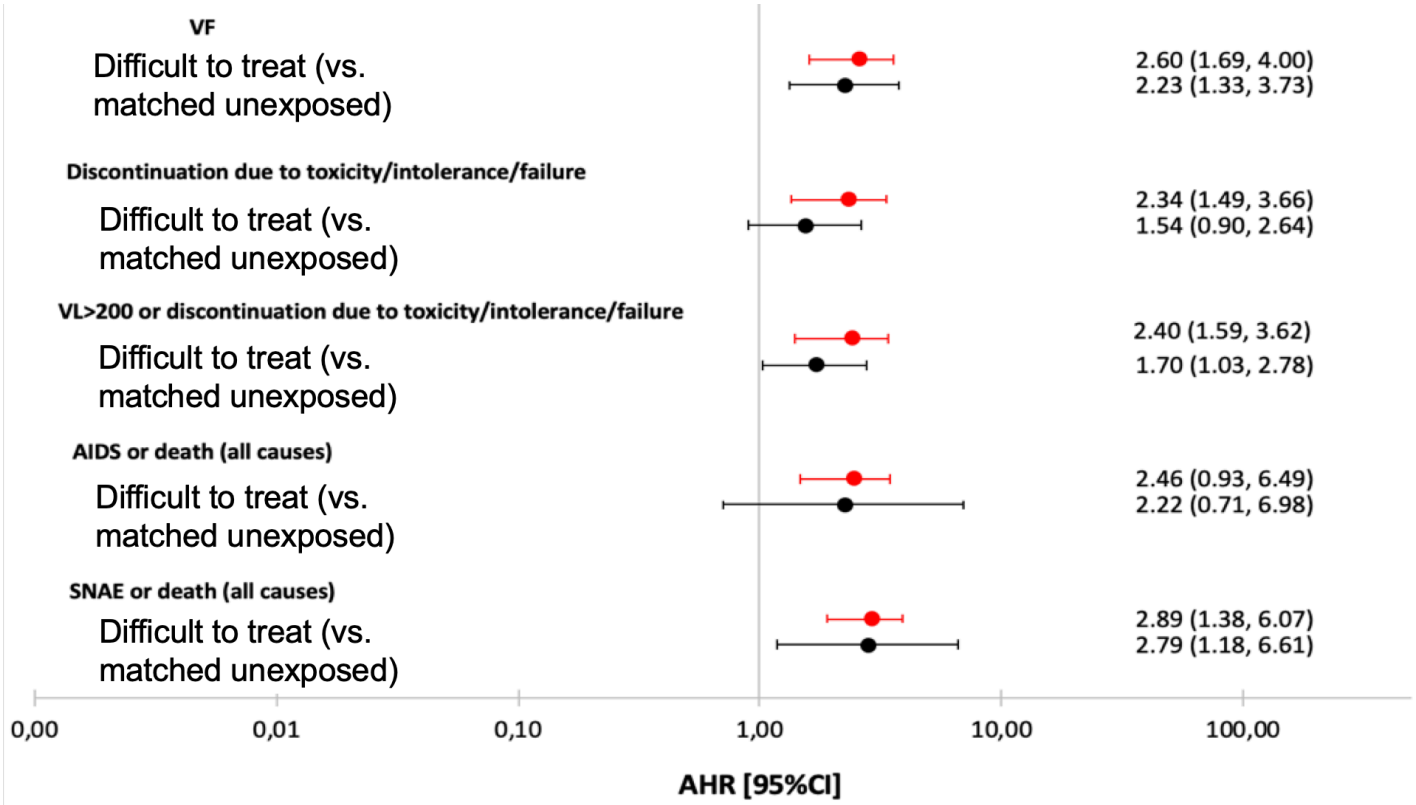
Armenia et al., JAC 2020

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

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

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

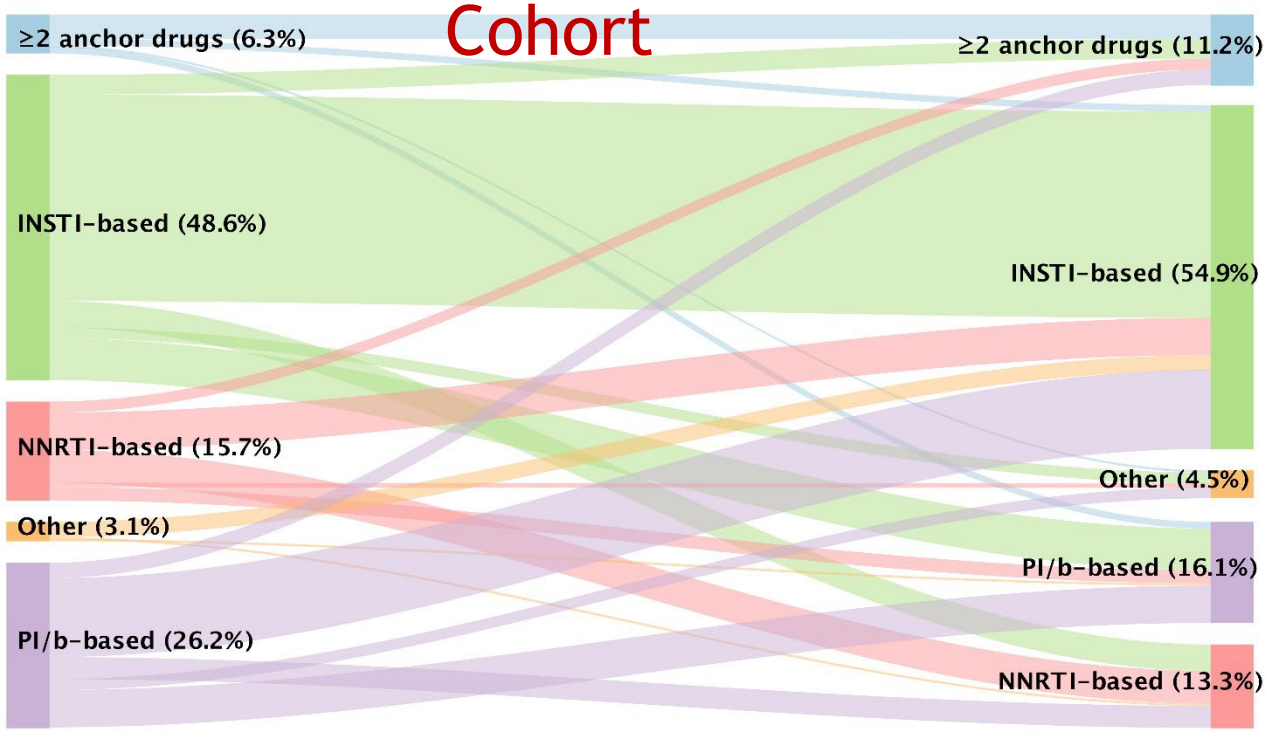
Characterization and outcomes of difficult-to-treat patients starting modern first-line ART regimens: data from the ICONA cohort

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

- ✓ PLWH 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



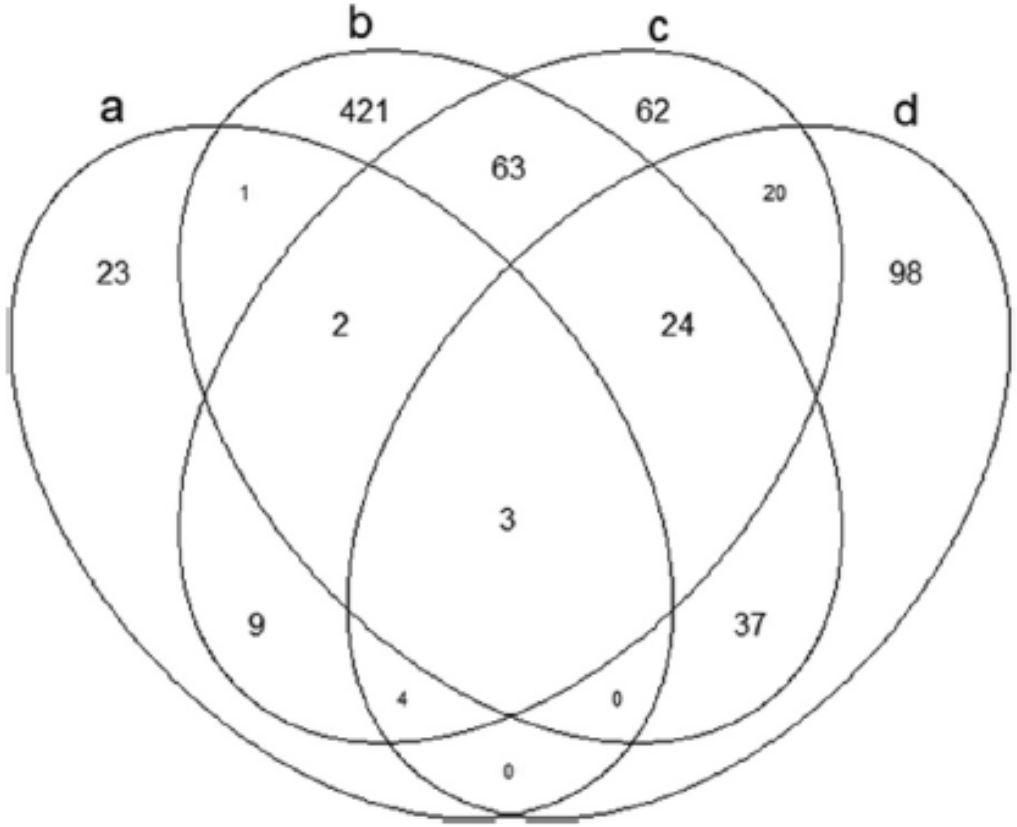
Most PWH who satisfied the DTT definition in our cohort, subsequently started a standardized regimen with 1 anchor drug + 1-2 NRTI, once daily, mainly INSTI-based, but more complex regimens (at least 2 anchor drugs) were prescribed in a higher proportion in comparison to non- DTT (11% of cases vs 7%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

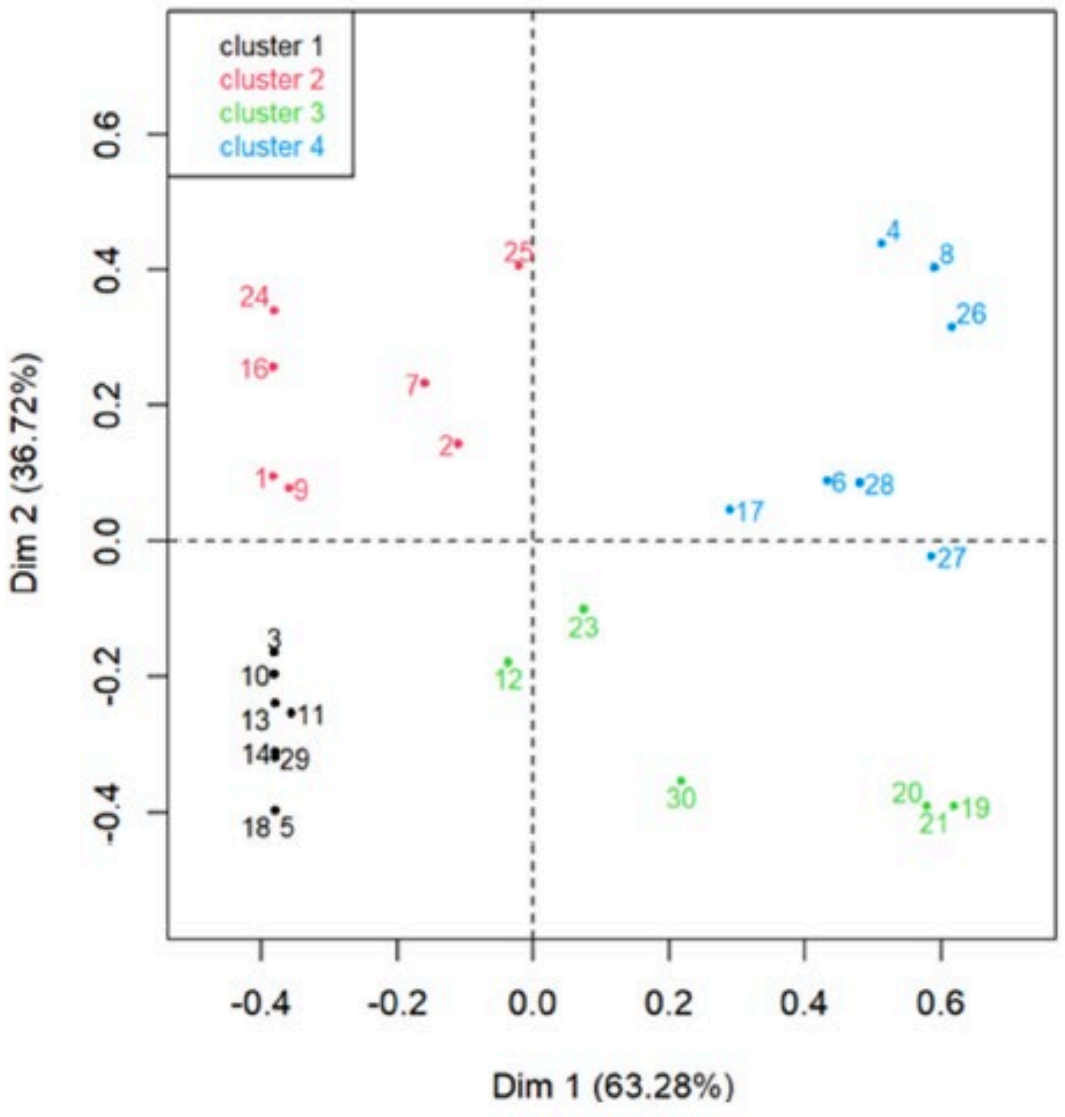
Factors associated with transitioning to HTE status with immune-virological failure among the features collected at the moment of ART initiation.

	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

Ascending Hierarchical classification of HTE according to cluster dendro- gram analysis. Each dot in the plot is a participant included in the subgroup of HTE with evidence of immune-virological failure, indicated by their patient ID, and specifically: 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

4-DRUG CLASSES RESISTANCE

PLWH, heavily treatment-experienced with resistance to all the 4 standard antiretroviral drug classes (NRTI, NNRTI, PI, INSTI) represent a rare subset of PLWH with:

- **very limited treatment options**
- **low chances of treatment success**
- **elevated risk** of **disease progression** and **death** with rates ranging from 27% to 33% at 4 years.

Data on true incidence and prevalence of PLWH-4DR in Europe are limited; Italian prevalence estimated at 1-3%

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

Lombardi F. et al. 10th Italian Conference on AIDS and Antiviral Research, OC 60. June 5-7, 2019, Milan, Italy.
Multiple drug class-wide resistance associated with poorer survival after treatment failure in a cohort of HIV-infected patients. Zaccarelli M. et al. AIDS, 2005 Jul 1;19 (10):1081-9
Trends in virological and clinical outcomes in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: a cohort study. Pursuing Later Treatment Option II (PLATO II) project team; Observational HIV Epidemiological Research Europe (COHERE) Group. Lancet Infect Dis. 2012 Feb;12(2):119-27.

NEW DRUGS FOR HTE MANAGEMENT

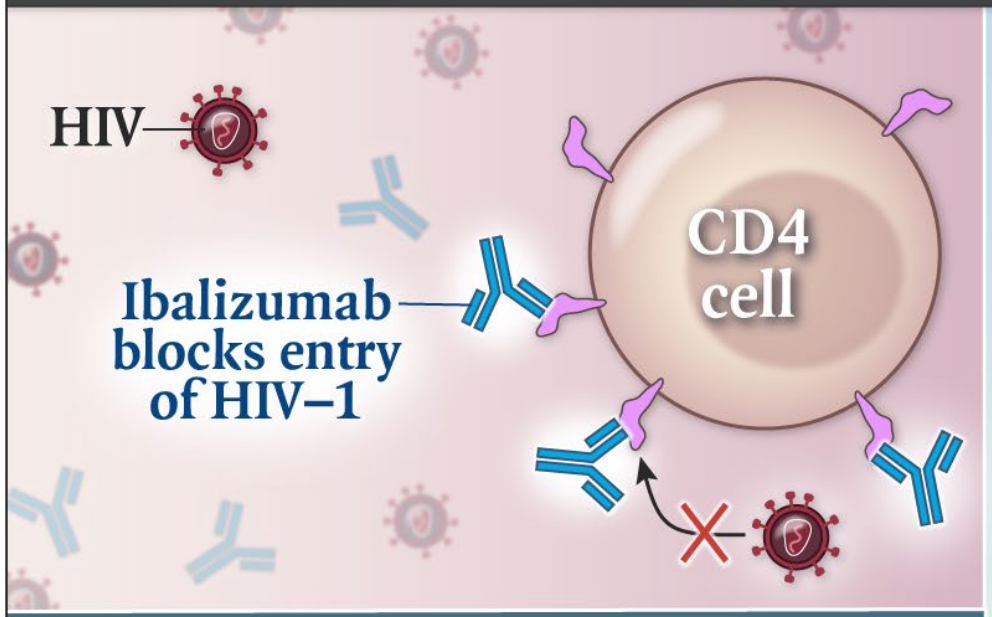
IBALIZUMAB

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)

Current therapy

3% (1/40)

Functional Monotherapy (Days 7–13)

Current therapy + Ibalizumab (Day 7, 2000 mg)

P < 0.001

83% (33/40)

Maintenance Period (Day 14–wk 25)

Optimized background regimen + Ibalizumab (800 mg every 14 days)

HIV-RNA <50 cp/ml

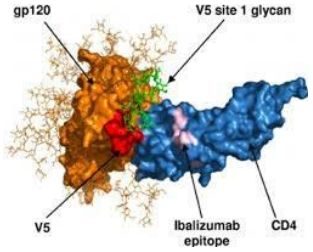
43% (17/40)

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

The NEW ENGLAND JOURNAL of MEDICINE

Emu et al. 2018

PHASE 3 STUDY OF IBALIZUMAB FOR MULTIDRUG-RESISTANT HIV-1: VIROLOGICAL FAILURE



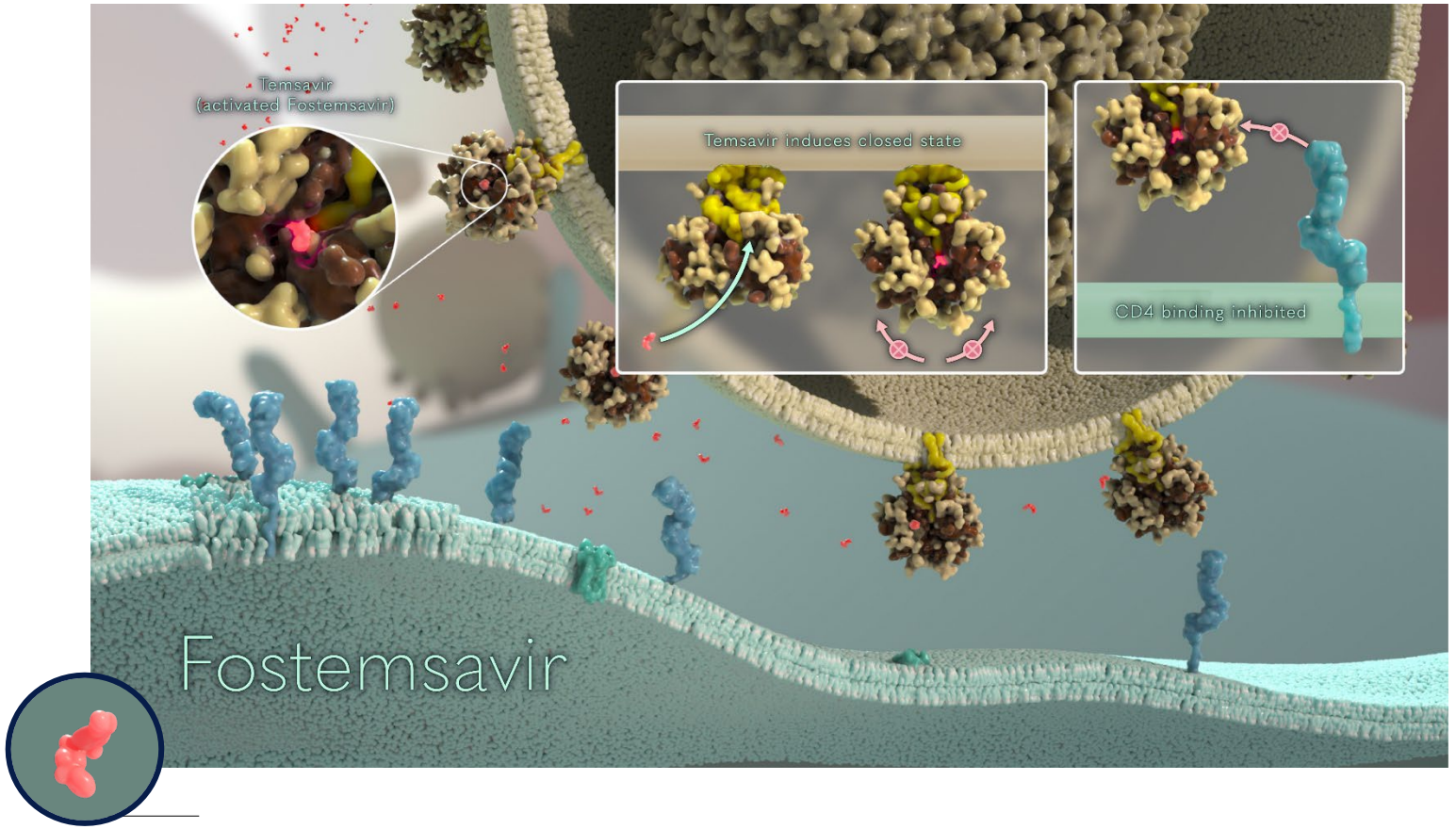
At week 25, 7 patients (18%) had virologic failure; of these patients, 1 also had virologic breakthrough. Three other patients had viral rebound.

Among the 10 patients with virologic failure or rebound, **9 showed a lower degree of susceptibility to ibalizumab** than at baseline, as measured by maximum percent inhibition. In 8 of the 9 patients, the **loss** of predicted **N-linked glycosylation sites** in the V5 loop of HIV-1 gp120 was the primary genetic change associated with reduced susceptibility to ibalizumab

N Engl J Med 379;7

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

FTR Virology Profile: *In vitro* Data

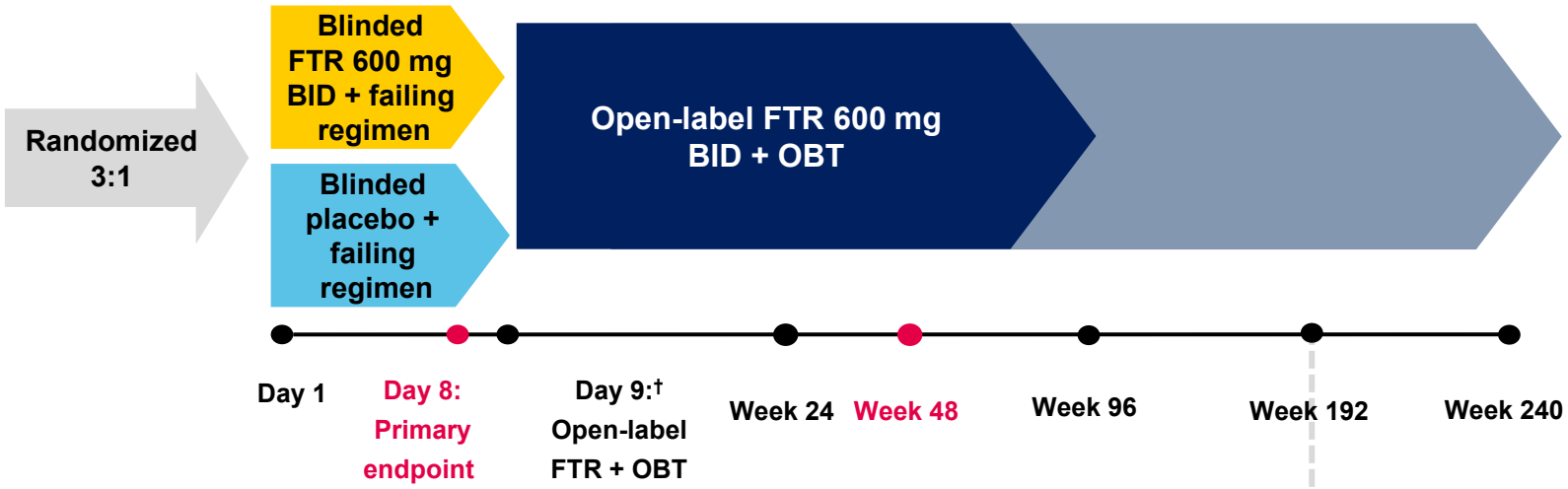
- FTR has a unique resistance profile, and no *in vitro* cross-resistance has been observed with other classes of ARVs, including NRTIs, non-NRTIs, PIs, INIs and entry inhibitors (CCR5 antagonists, attachment inhibitors and fusion inhibitors)[1–3]
- *In vitro* studies also showed that against the majority of viruses, including CCR5, CXCR4, and dual-tropic viruses, and all HIV-1 subtypes tested, apart from CRF01AE and group O[2]
- Previous studies have identified amino acid substitutions at four gp120 positions that may influence HIV-1 susceptibility to TMR: S375H/I/M/N/T, M426L/P, M434I/K, and M475I[4–7]

EC_{50}, half maximal effective concentration

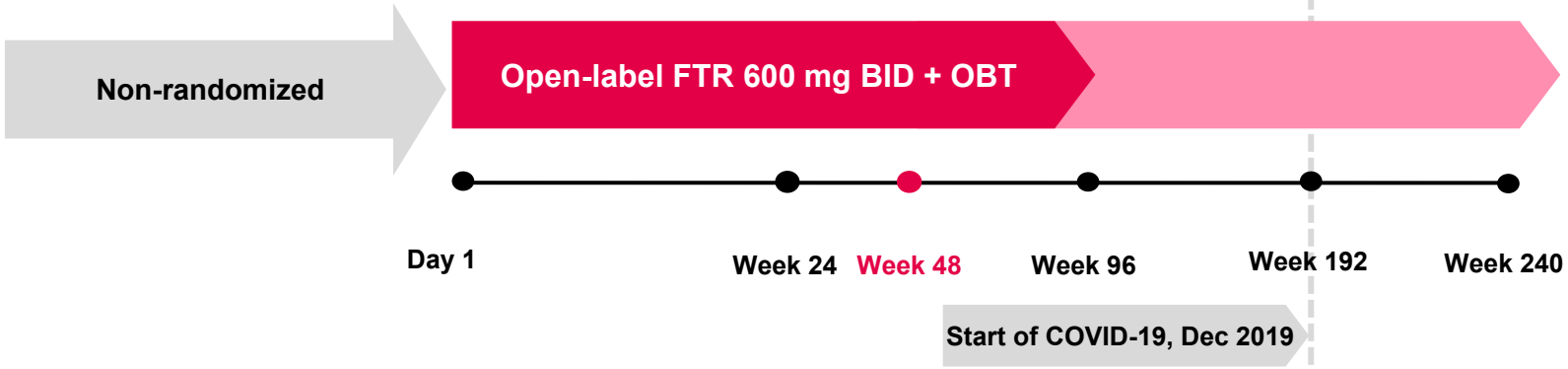
1. Li Z, et al. Antimicrob Agents Chemother 2013;57:4172–80
2. Nowicka-Sans B, et al. Antimicrob Agents Chemother 2012;56:3498–507
3. ViiV Healthcare. Fostemsavir Investigator's Brochure March 2019. REF-147248
4. Kozal, et al. N Engl J Med. 2020;382:1232–43; **5.** Zhou N, et al. J Antimicrob Chemother. 2014;69:573–81
6. Ray N, et al. J Acquir Immune Defic Syndr. 2013;64:7–15; **7.** Lataillade M, et al. J Acquir Immune Defic Syndr. 2018;77:299–307

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



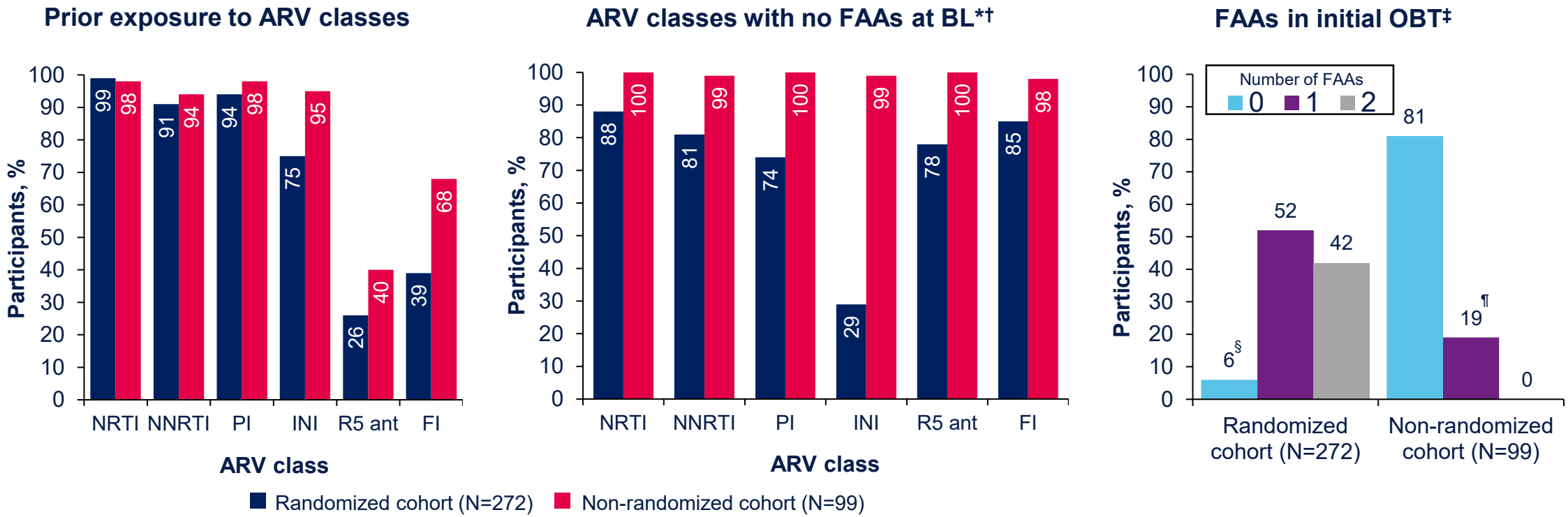
Non-randomized cohort:*
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and:
- Zero ARV classes remaining and no remaining approved fully active agents†



*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



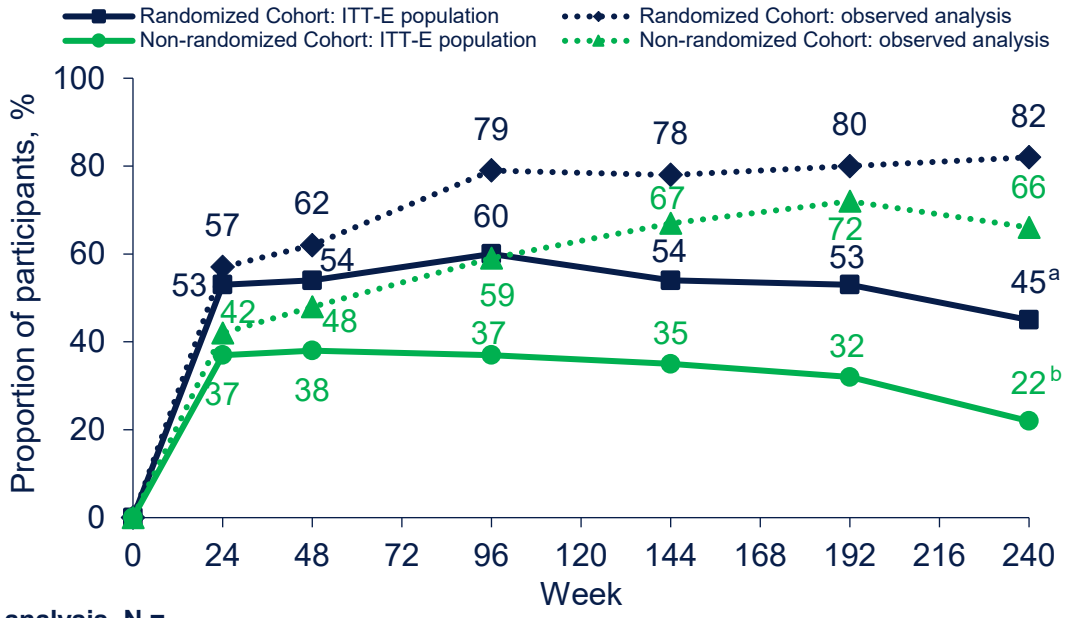
*Ibalizumab was not approved when this study was initiated; †Proportions of participants for whom there were no remaining fully active and approved antiretroviral agents within the indicated class based on the screening criteria of activity (per screening and historical resistance measures) and availability (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)

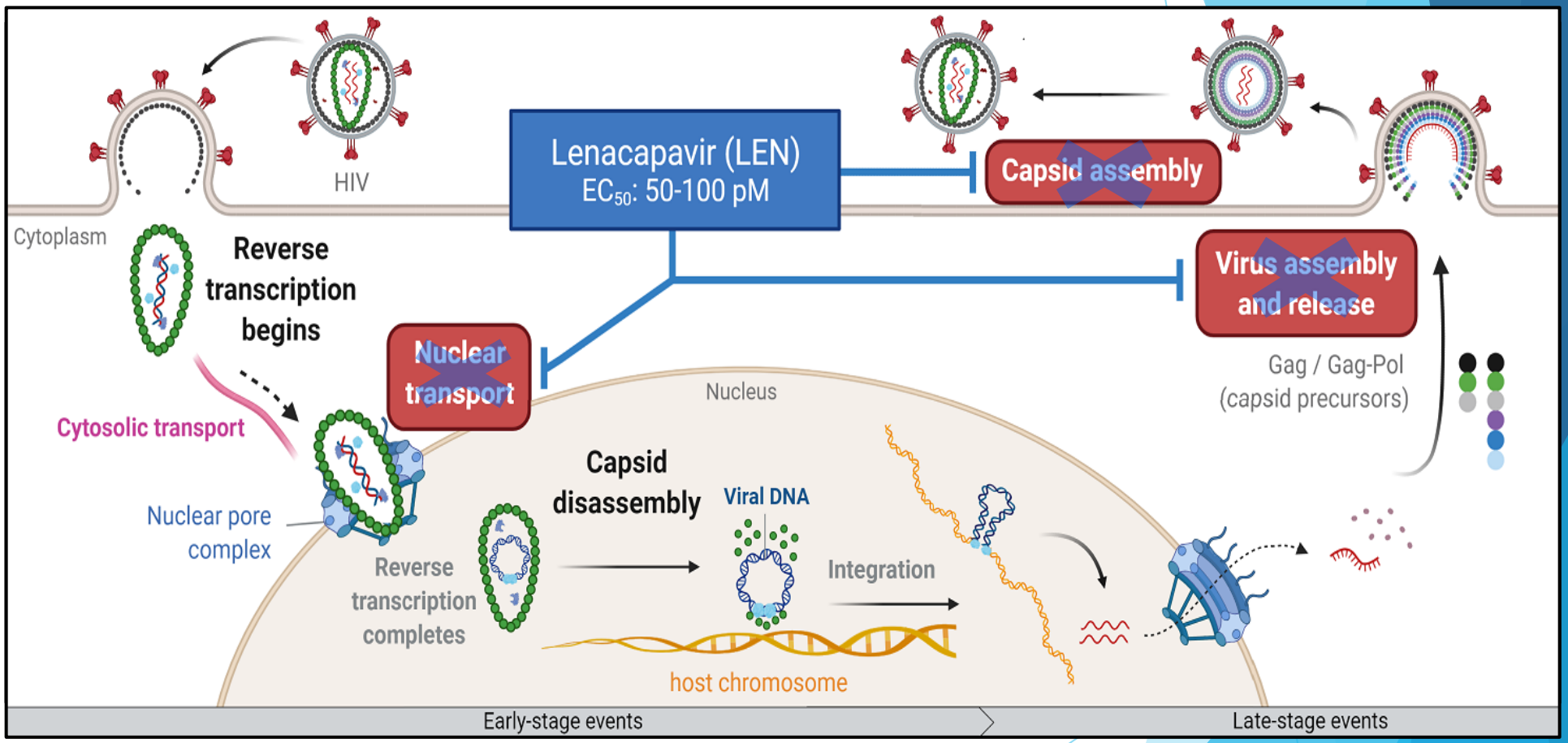
	Randomized Cohort			Non-randomized Cohort		
Outcome, n (%)	Week 96	Week 192[a]	Week 240[b]	Week 96	Week 192[a]	Week 240[b]
Number of participants	**272**	**272**	**267**	**99**	**99**	**92**
HIV-1 RNA <40 c/mL	**164 (60)**	**145 (53)**	**120 (45)**	**37 (37)**	**32 (32)**	**20 (22)**
HIV-1 RNA ≥40 c/mL	**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

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

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Lenacapavir

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

Sunlenca® (lenacapavir)

Lenacapavir in Heavily Treatment-Experienced PWH

LEN in HTE

Capella

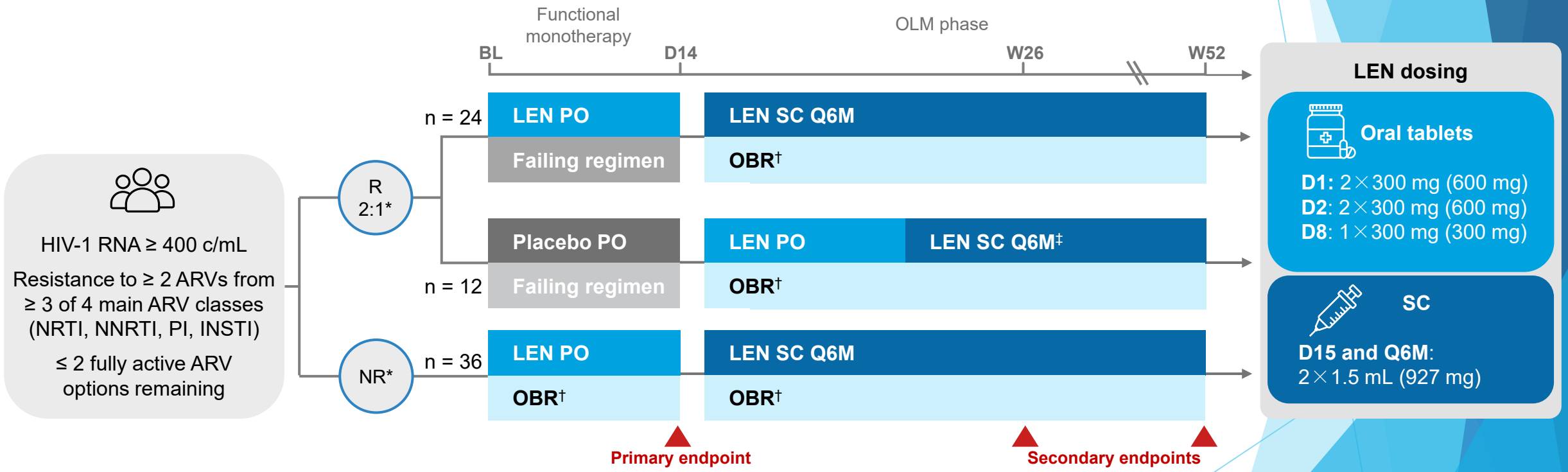
N = 72

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.

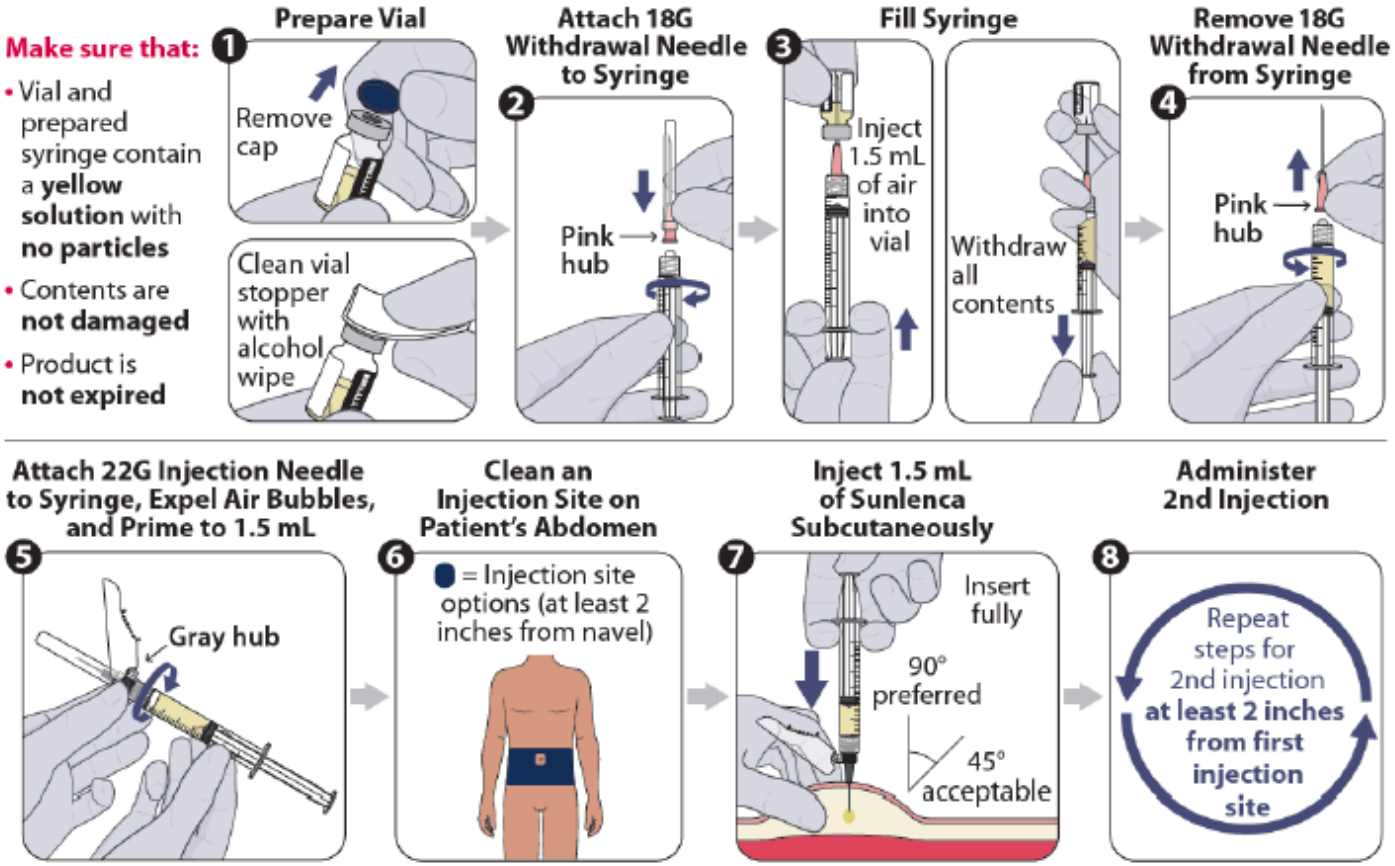
Table 2 Recommended Treatment Regimen for SUNLENCA Initiation and Maintenance, Option 2

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

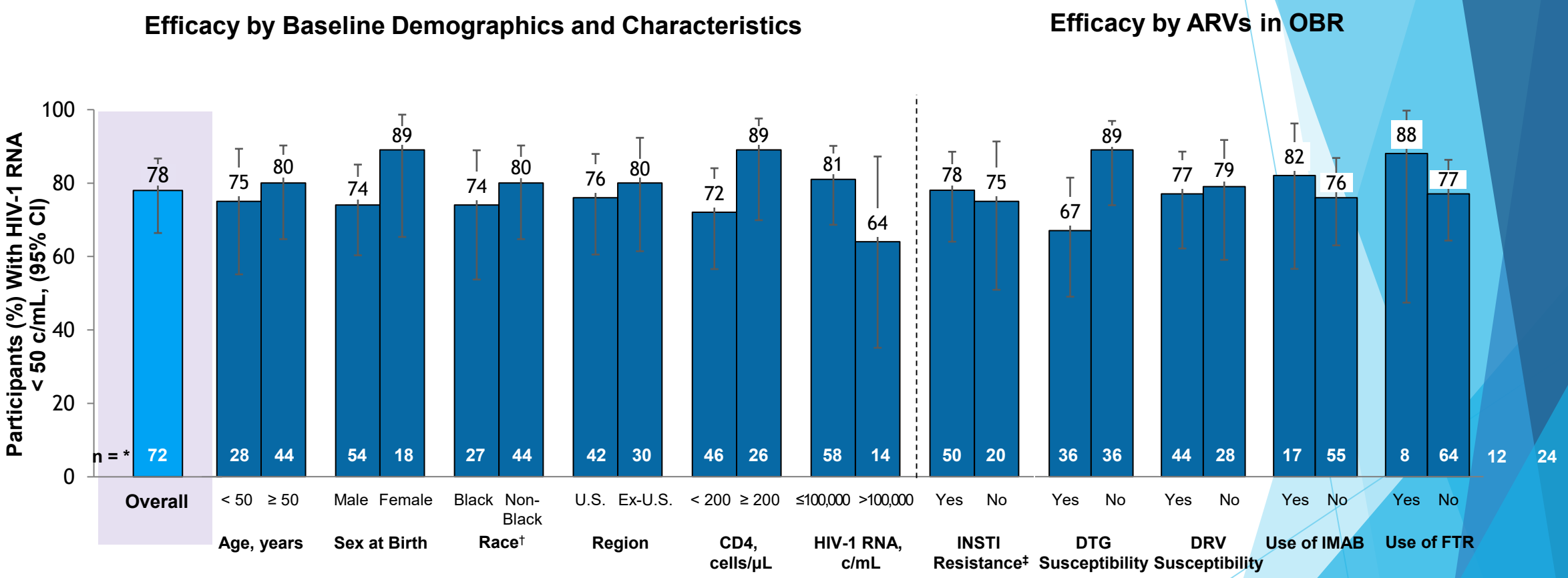
Characteristic	Randomized		Nonrandomized	Total N = 72
	LEN n = 24	Placebo n = 12	LEN n = 36	
Age, years, median (range)	55 (24-71)	54 (27-59)	49 (23-78)	52 (23-78)
Female at birth, %	29	25	22	25
Black race, %	42	55	31	38
Hispanic/Latinx %	25	36	14	21
HIV-1 RNA, $\log_{10}$ c/mL, median (range)	4.2 (2.3-5.4)	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

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

	No. of Participants (%)		
Resistance Categories	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)

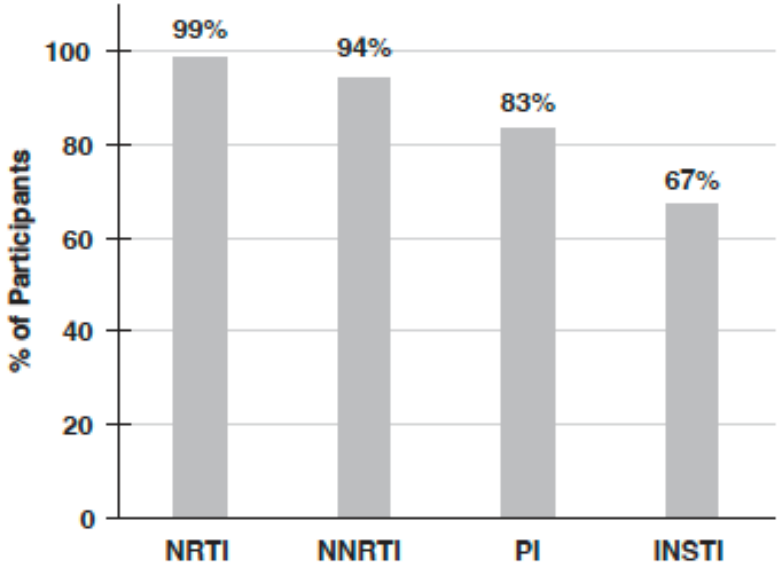


Figure 1. Proportion (%) of participants with resistance-associated mutations (RAMs) to the 4 main antiretroviral drug classes and mean number of RAMs per participant at baseline. The lists of RAMs per class are detailed in th- e Materials and Methods ("Definitions of Resistance Mutations"). Abbreviations: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

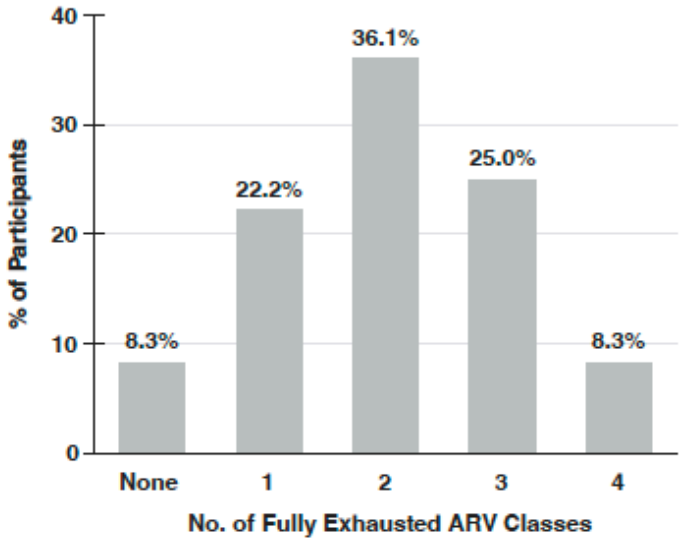


Figure 2. Exhaustion of antiretroviral (ARV) classes at baseline. The proportion of participants with no fully active ARV option remaining within the 4 main ARV drug classes is shown.

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

	No. of Participants (%)		
Resistance Classes	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.

Efficacy and Safety of LEN in HTE PLWH: Study Design[1]

N=72[1]

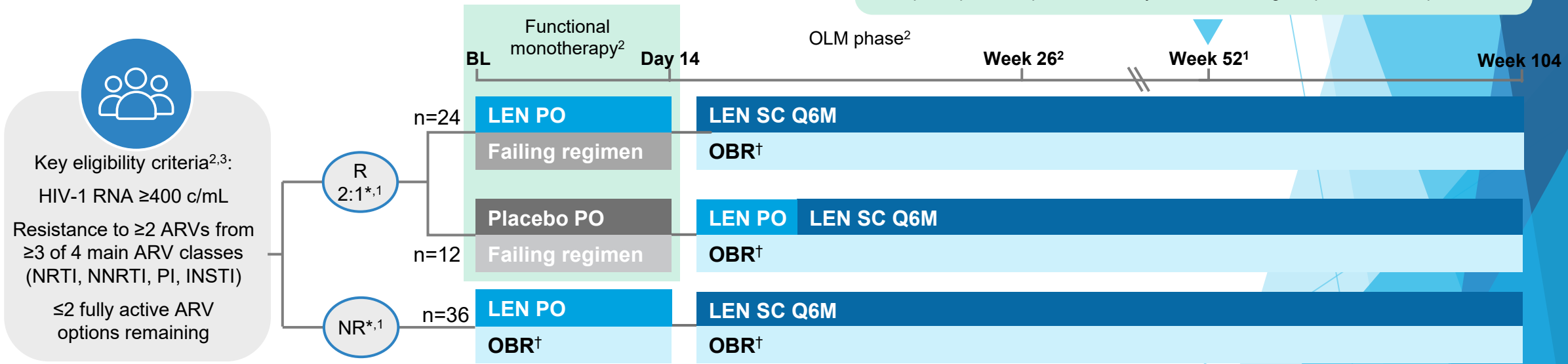
HTE PLWH with MDR HIV-1,[1] aged ≥12 years and weighing ≥35 kg [2]

Outcomes

Virologic outcomes, CD4 cell count, resistance emergence, and safety of LEN through Week 104[1]

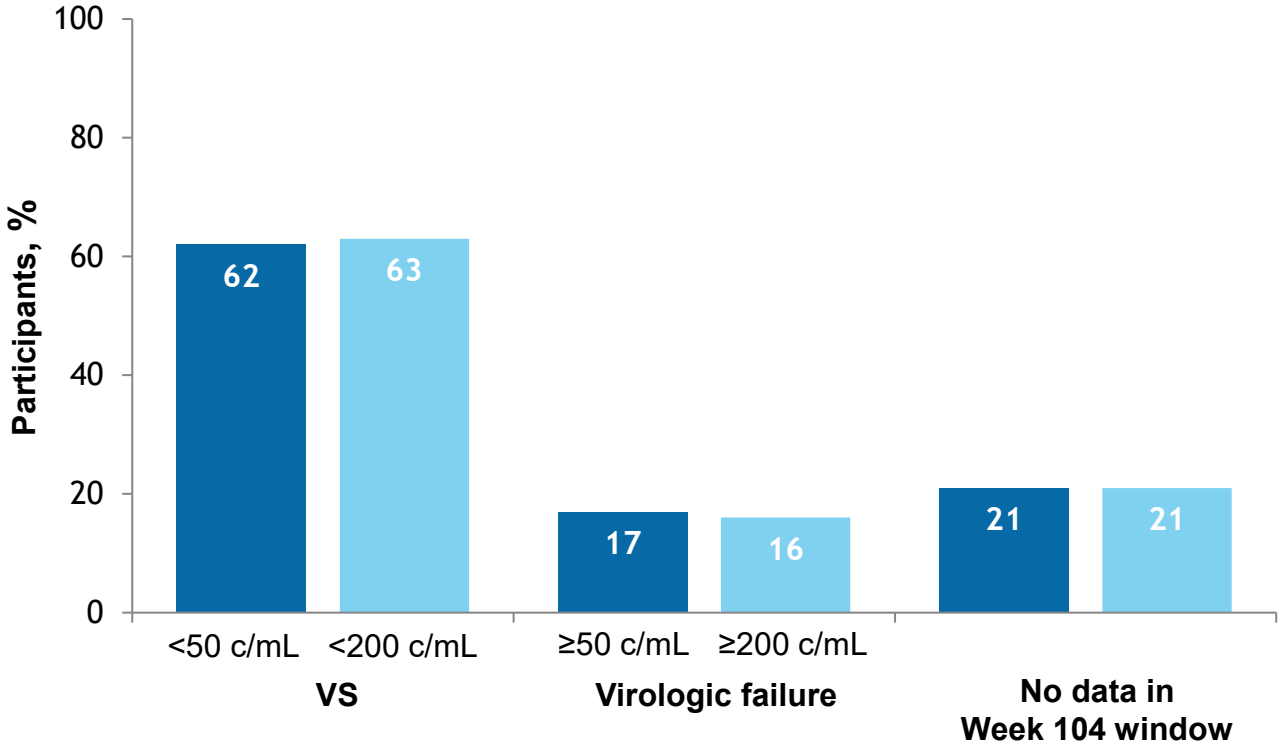
2019–present (ongoing)[2]

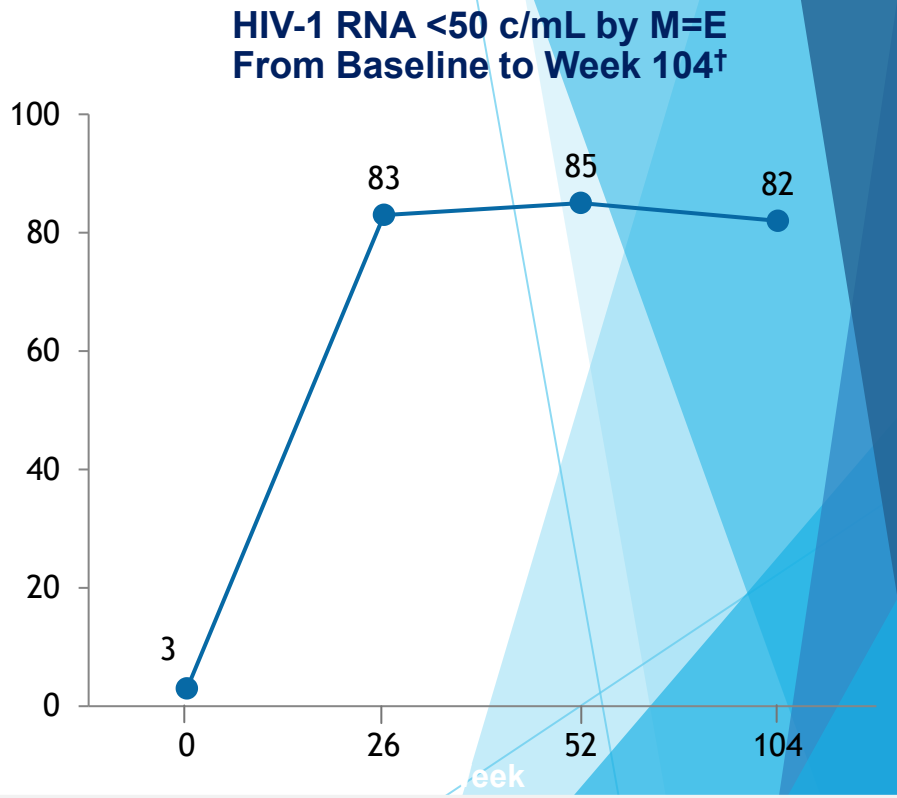
Most participants (66/72; 92%) remained on study drug beyond Week 52[1]
- 5 participants discontinued study drug prior to Week 52[§]
- 1 participant completed the study without entering the post-Week 52 phase



LEN oral tablets were taken on Day 1 and Day 2 (2 × 300 mg) and Day 8 (1 × 300 mg), and LEN SC injections (2 × 1.5 mL [927 mg]) were administered in the abdomen on Day 15 and then Q6M[1,2]; *Participants with <0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening and HIV-1 RNA ≥400 c/mL entered the randomized cohort; participants with ≥0.5 $\log_{10}$ c/mL decline in HIV-1 RNA during screening and/or HIV-1 RNA <400 c/mL entered the non-randomized cohort;[1,2] †Investigational agents (e.g., FTR) permitted; ATV, ATV/c, ATV/r, EFV, ETR, NVP, TPV not permitted[2,3]; §Lost to follow-up (n=3), investigator's discretion (n=1), death (n=1). BL, baseline; HTE, heavily treatment-experienced; MDR, multidrug-resistant; NR, non-randomized; OBR, optimized background regimen; OLM, open-label maintenance; PO, orally; Q6M, every 6 months

Virologic Outcomes
(Combined Randomized and Non-Randomized Cohorts)

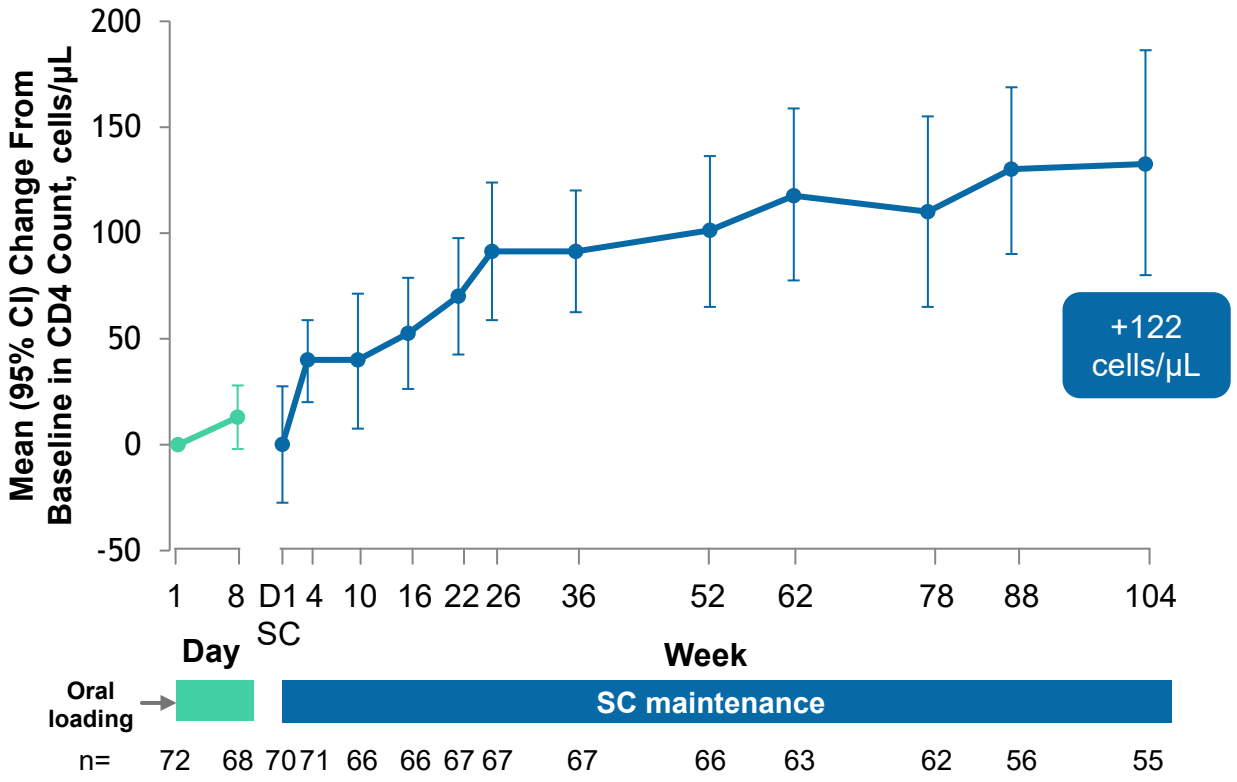


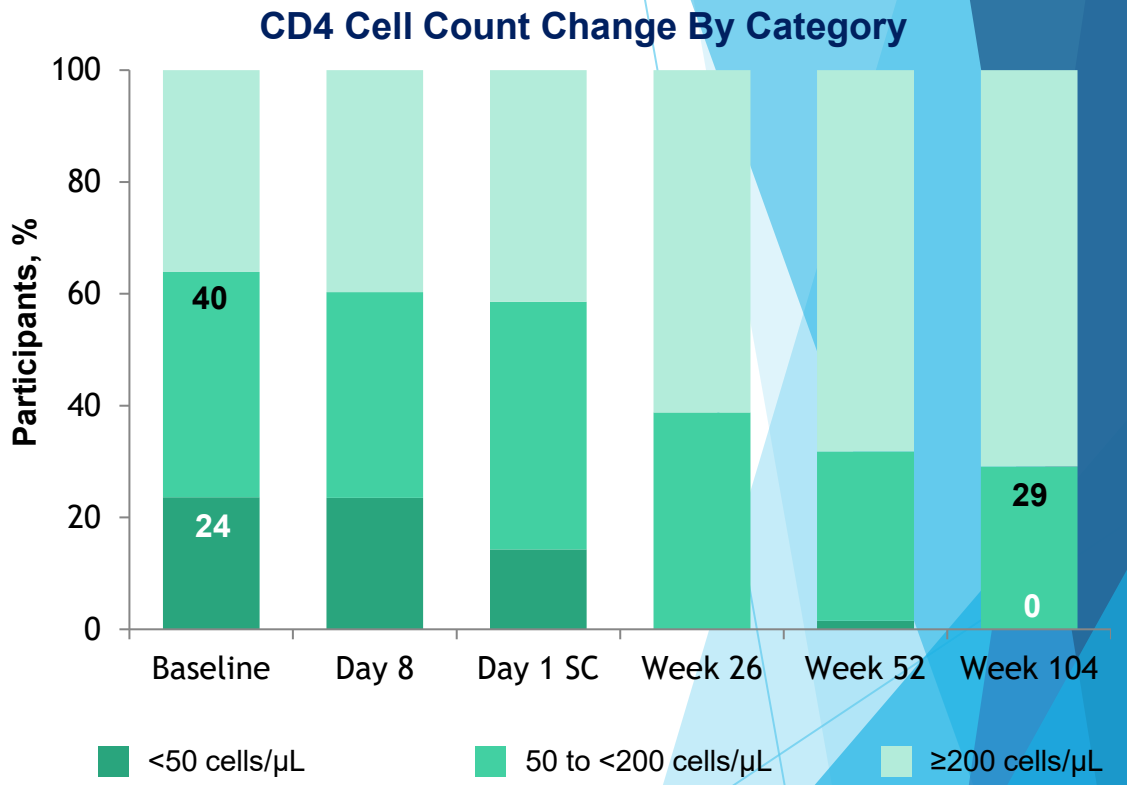


CAPELLA participants continued to maintain high rates of VS (82% by M=E analysis at Week 104)

*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

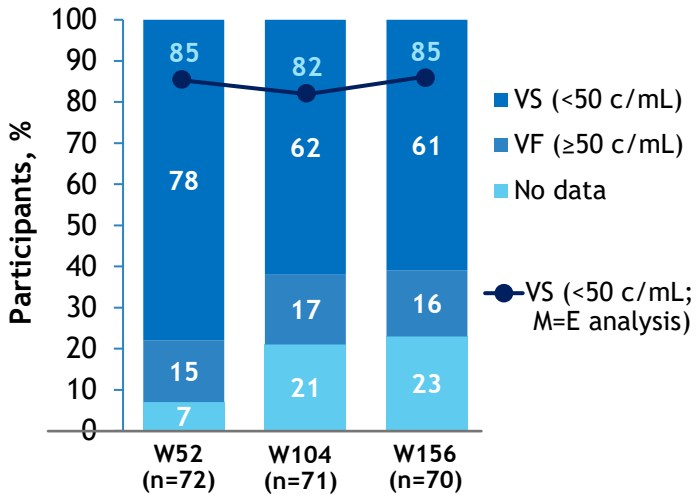
HTE PWH with MDR HIV-1 received 2-week oral LEN lead-in followed by SC LEN Q6M + OBR

Outcomes

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

Enrollment Nov 2019–Jan 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 decreased from 64% to 22%
  - <50 cells/μL decreased from 24% to 2%

- 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.

HTE, heavily treatment experienced; ISR, injection-site reaction; M=E, missing=excluded; MRD, multidrug-resistant; OBR, optimized background regimen; Q6M, every 6 months; TEAE, treatment-emergent adverse 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;386:1793-180; 2. Ogbuagu O et al., IDWeek 2022, Oral 1585; 3. Ogbuagu O et al., IDWeek 2023, Poster 1596

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