"Inquadramento dei pazienti High Treatment Experienced"

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Disclosures

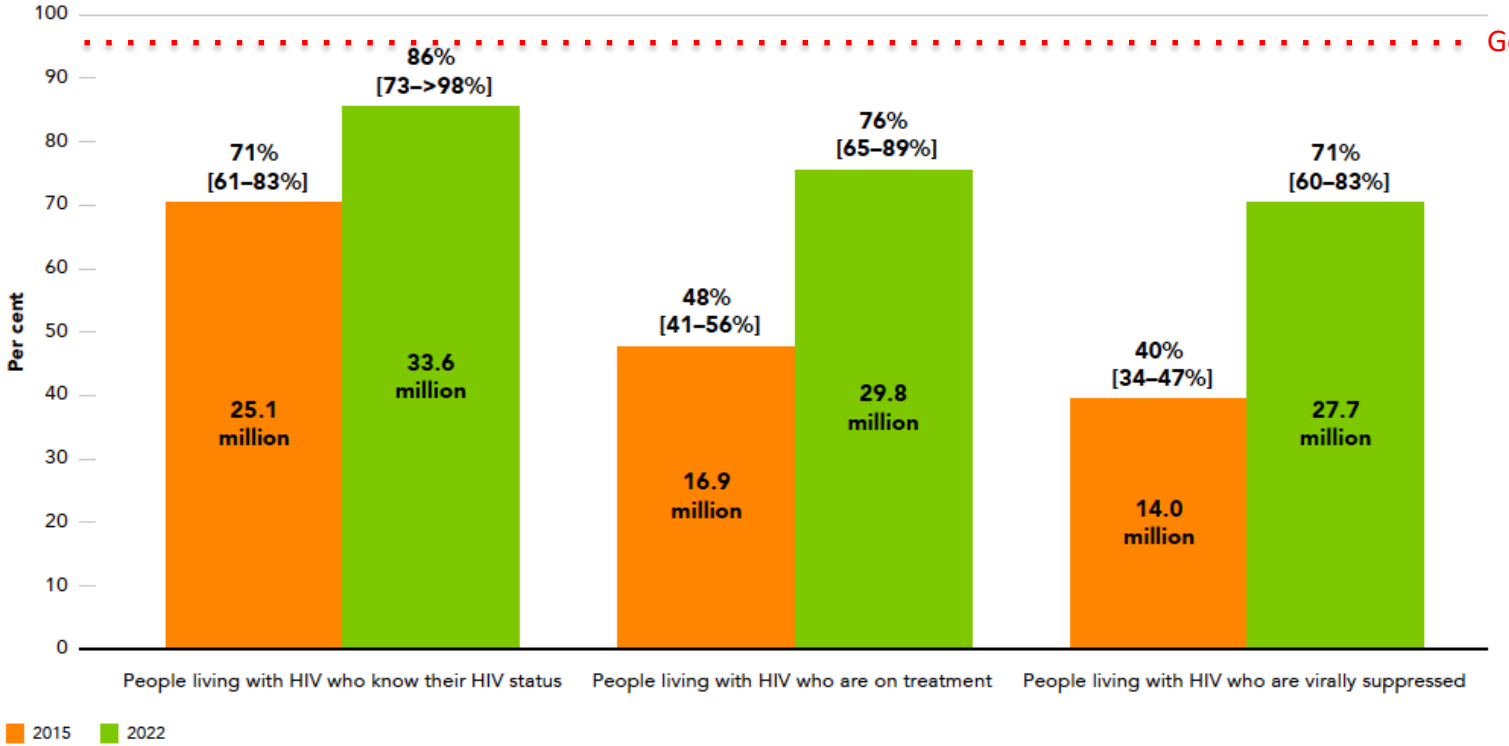
- Grants for research and educational activities

  Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme (MSD), ViiV Healthcare, Menarini

- Personal fees for advisory boards and speaker's bureau

  ViiV Healthcare, Janssen-Cilag, Merck Sharp & Dohme (MSD), Gilead Sciences, Bristol-Myers Squibb (BMS)

PLWH global statistics 2022

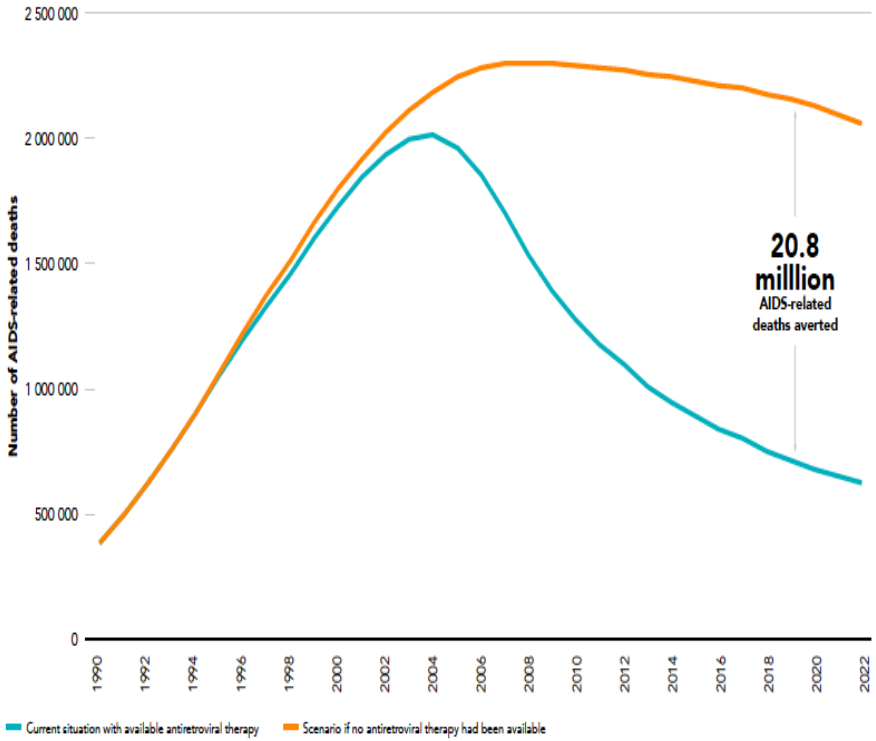


Source: UNAIDS special analysis of epidemiological estimates, 2023.

~39 million PLWH globally in 2022

UNAIDS Global AIDS Update, 2023 https://www.unaids.org/sites/default/files/media_asset/2023-unaids-global-aids-update_en.pdf (accessed Jan 2024)

Almost 21 million lives saved with antiretroviral therapy



Source: UNAIDS special analysis of epidemiological estimates, 2023.

Over 3 million children protected against HIV since 2000

Due to the availability of well-tolerated, efficacious and simplified regimens:

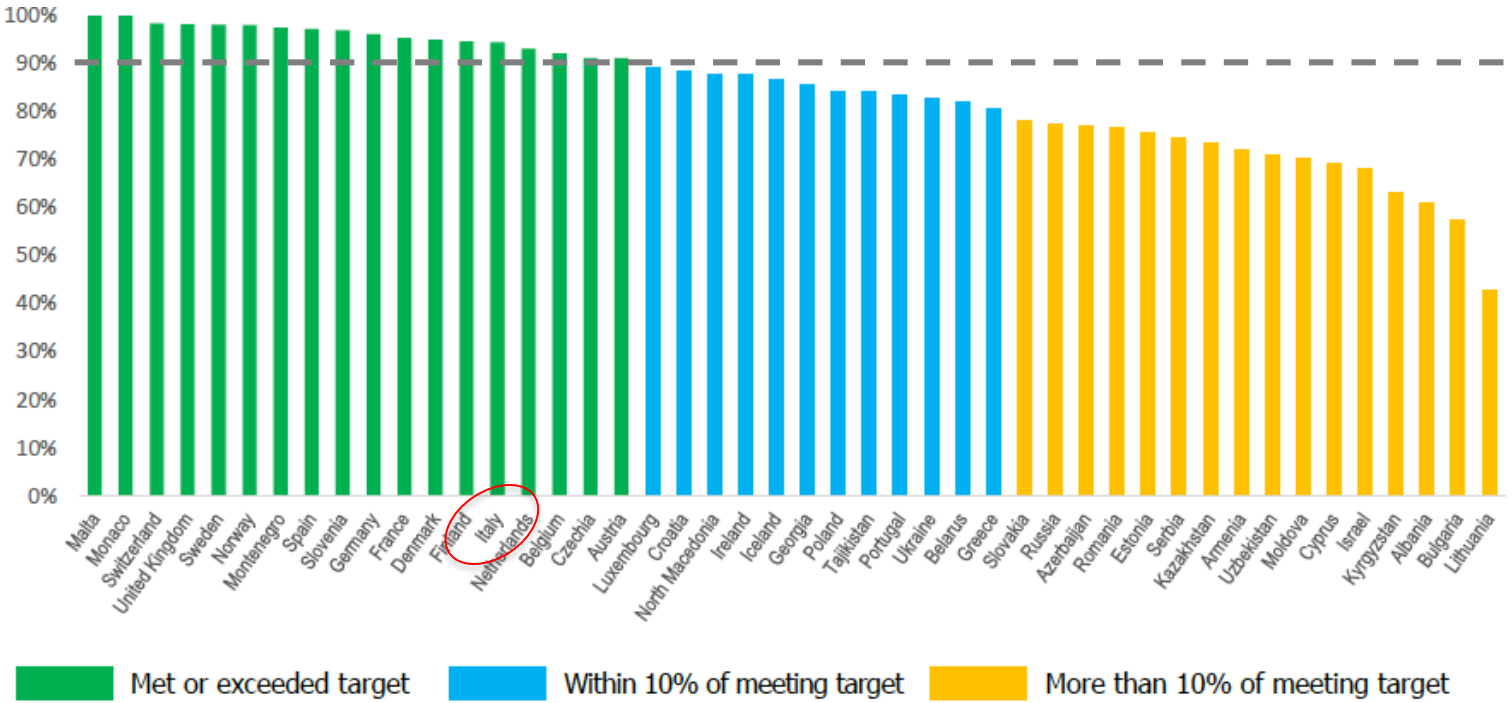
- The number of persons with long-term VS has **increased**
- The number of persons experiencing treatment failure, progression to AIDS and death has **decreased**

UNAIDS Global AIDS Update, 2023 https://www.unaids.org/sites/default/files/media_asset/2023-unaids-global-aids-update_en.pdf (accessed Jan 2024)

WHO. 2021. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach

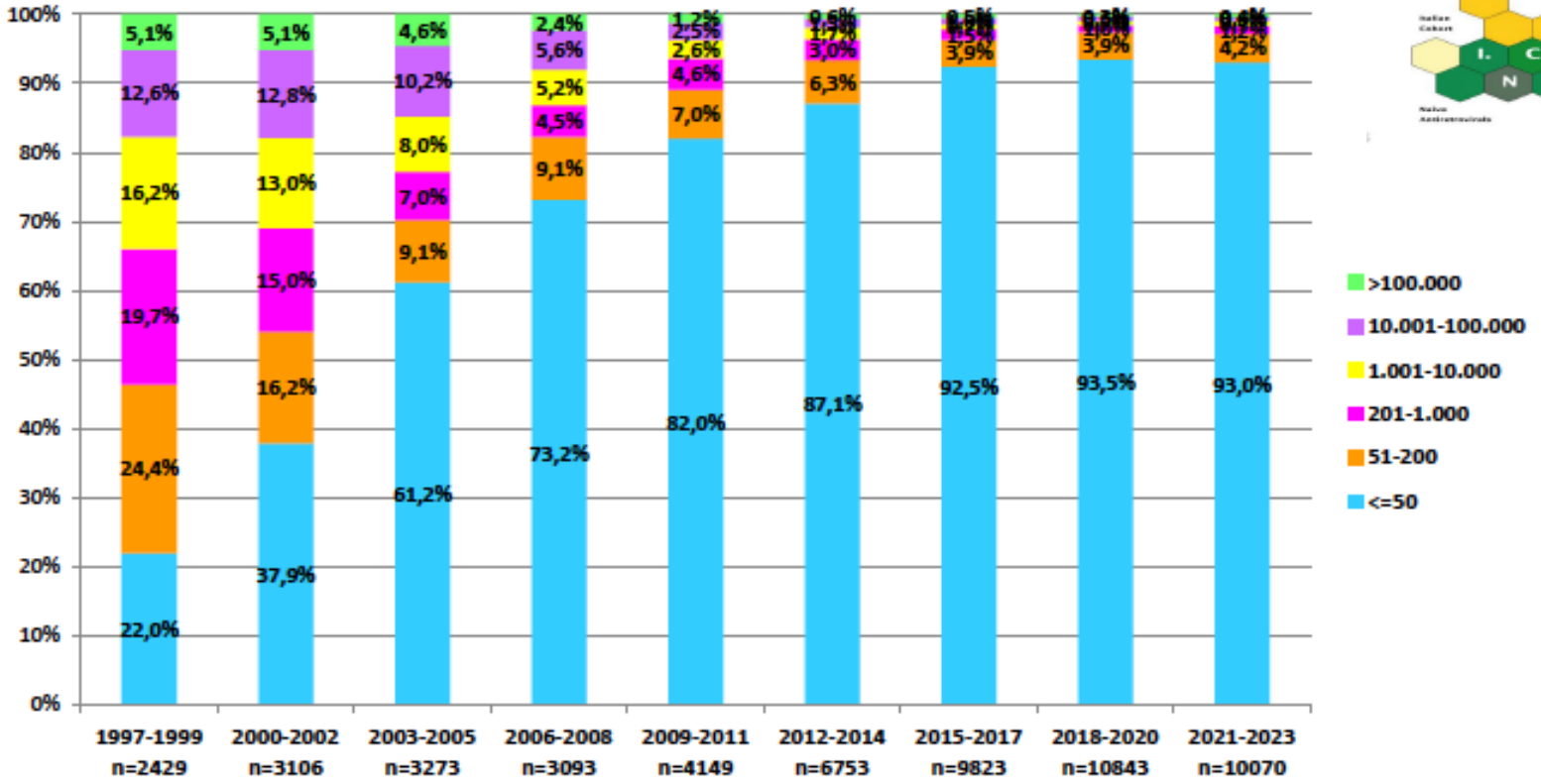
Did We Reach 90-90-90 Targets by 2020? Europe and Central Asia PLWH Receiving ART

Percentage of all PLWH who are on treatment for
46 countries of Europe and Central Asia, reported in 2021



https://www.ecdc.europa.eu/en/publications-data/continuum-hiv-care-monitoring-implementation-dublin-declaration-partnership-fight

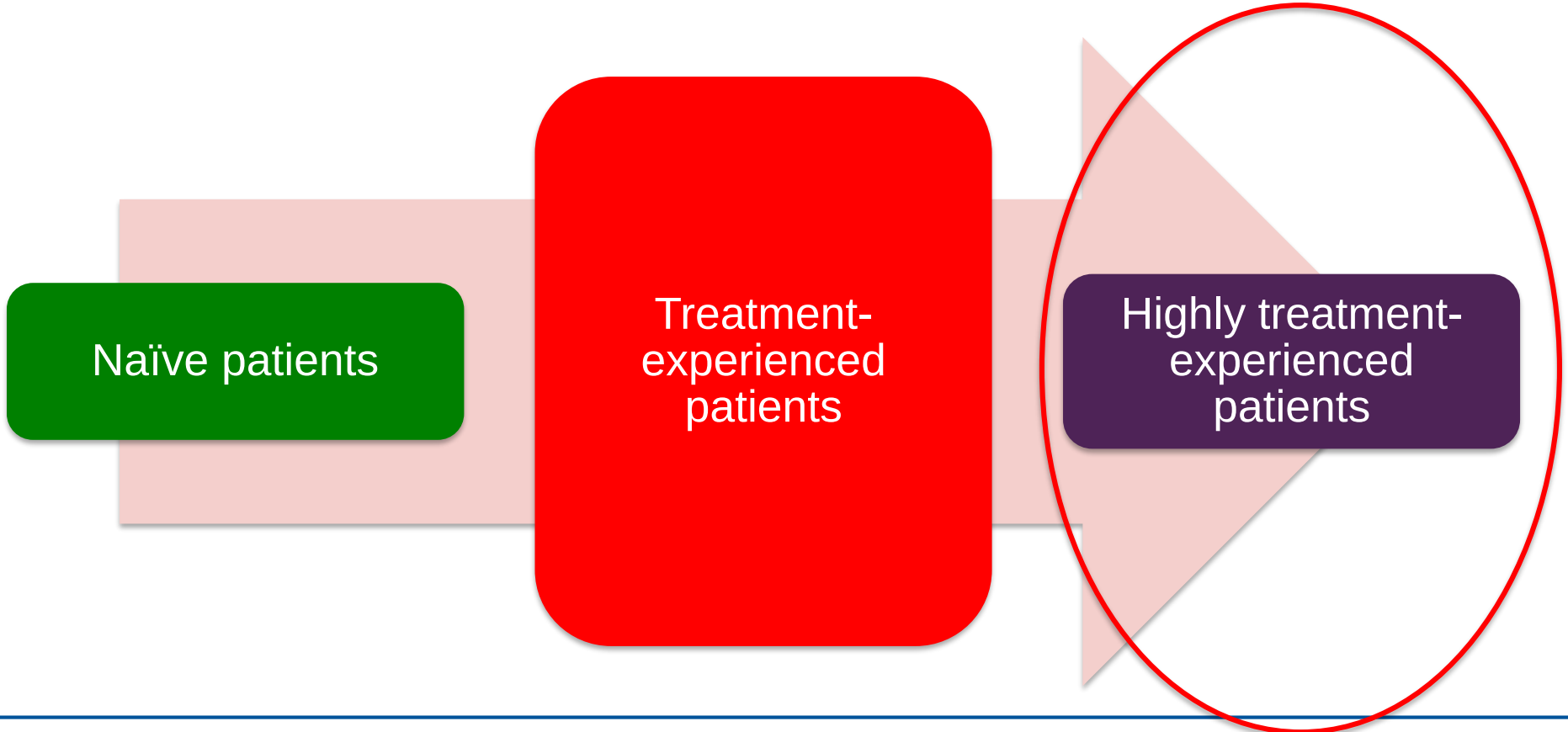
HIV-RNA strata in drug experienced PLWH, according to calendar period



for 2023, first 6 months

Jun 2023 Report

PLWH: 3 very different settings



Most common definitions of HTE

A changing landscape

GRT results and known resistance to the three original ARV classes (NRTIs, NNRTIs and PIs)[1]

Currently on fourth line of ART[4]

≤ 2 available classes with a limited number of active drugs in each class[2,3]

Regimen indicative of HTE
Current regimen includes either (i) DTG BID, (ii) DRV BID, (iii) ETR, (iv) INSTI + PI, (v) MVC or (vi) ENF[3]

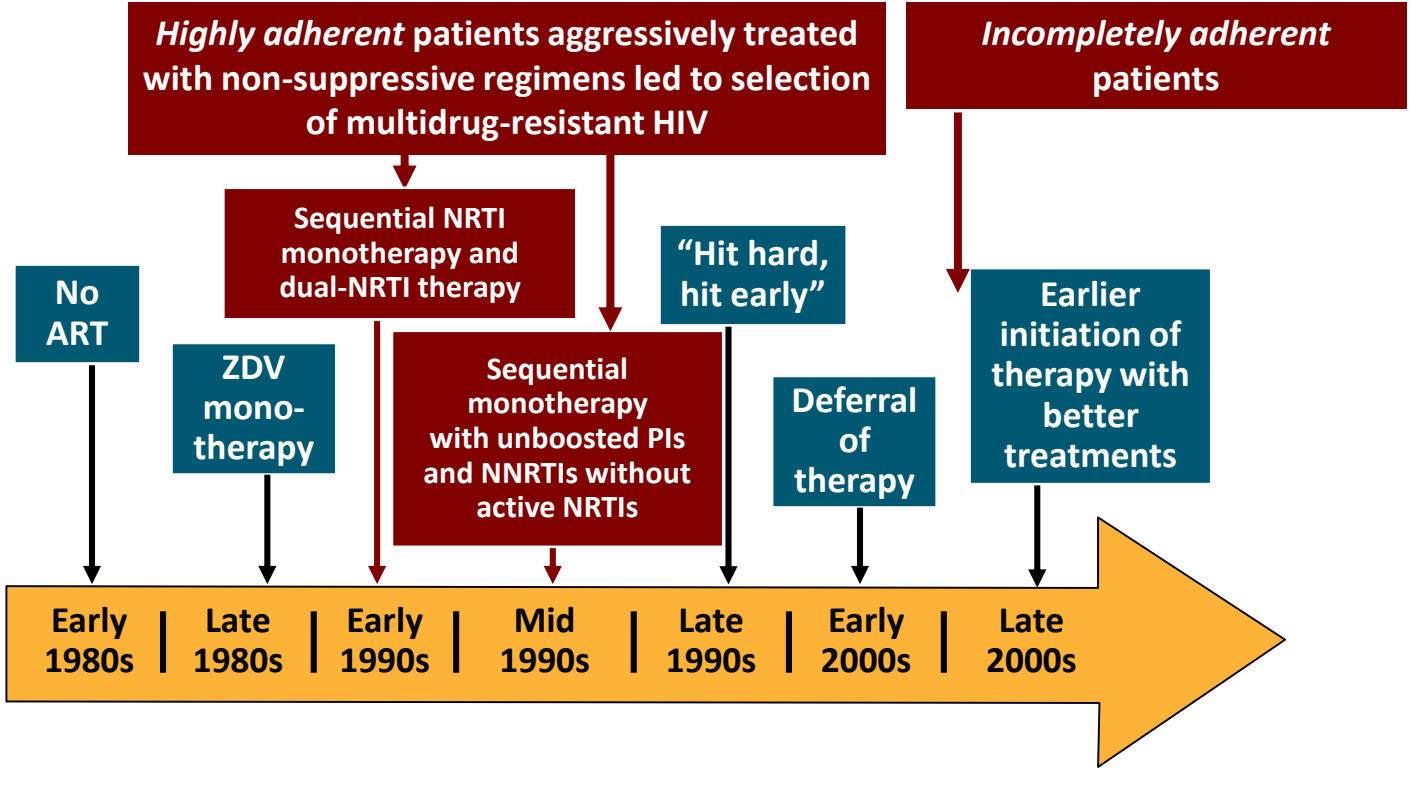
1 or 2 ARV classes remaining with ≥ 1 fully active agent or 0 fully active options[5]

Clinically oriented definitions
Inability to construct an effective antiretroviral regimen due to resistance, intolerance or safety considerations[6,7]

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

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;;6.Fostemsavir prescribing info. 7.Lo Caputo, et al. ICAR 2021, OC 56.

Who Are the People With Multidrug-Resistant HIV?

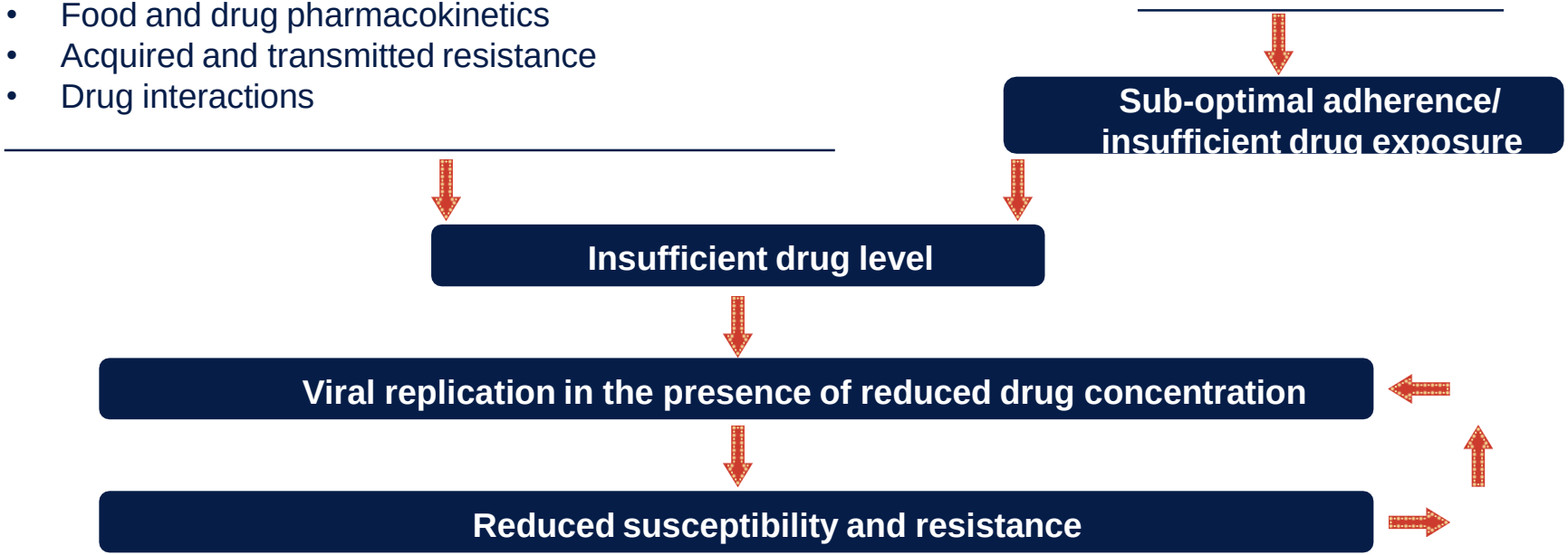


hiv.gov/hiv-basics/overview/history/hiv-and-aids-timeline.

Causes of ART Failure

- Lack of potency
- Inadequate dosing
- Host genetics
- Sub-optimal absorption and tissue compartment distribution
- Food and drug pharmacokinetics
- Acquired and transmitted resistance
- Drug interactions

- Social/personal issues
- Regimen issues
- Toxicities



1.DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, January 2024
2.Anderson SJ, et al. Patient 2022;15:131–43
3.Cutrell J, et al Ther Adv Infectious Dis 2020;7:1–15

General Characteristics of the HTE Population

Sequential ART Failure[1]

Multiple past ART failures due to the development of ARV resistance, intolerance/toxicity, DDIs or complex regimens

Multiple Drug Resistance[1,2]

Resistance to multiple ART classes due to suboptimal exposure, poor adherence,[2] suboptimal efficacy (e.g. single, dual NRTI regimens)

Toxicity[1]

Short- and long-term accumulated ART toxicity resulting in treatment-limiting adverse drug reactions

Drug–drug Interactions[1,2]

Unfavorable DDIs limit treatment options due to safety (contraindications and precautions) or efficacy (reduced exposure) considerations

Suboptimal Exposure[1–3]

Intermittent /suboptimal exposure to ARVs leads to ART resistance. Complex or poorly tolerated regimens, or complex social factors contribute to suboptimal adherence

Complex Comorbidities[1,2]

Multiple concomitant comorbidities resulting in polypharmacy and ART-limiting DDIs

1.Anderson SJ, et al. Patient 2022;15:131–43
2.Cutrell J, et al Ther Adv Infectious Dis 2020;7:1–15
3.Lataillade M, et al. Lancet HIV 2020;7:e740–51

Trends and characteristics of HIV-1 Drug Resistance in the US (2012–2018)

Samples from HIV-1-infected individuals in the United States submitted for genotypic resistance testing to four ARV classes (PIs, NRTIs, NNRTIs, and INIs) between July 1, 2012 and June 30, 2018 were analyzed

Decreasing prevalence of multiclass ARV resistance, in addition to declines in NRTI, PI, and INSTI resistance

Figure 1. Prevalence of class resistance among samples with resistance, 2012-2018

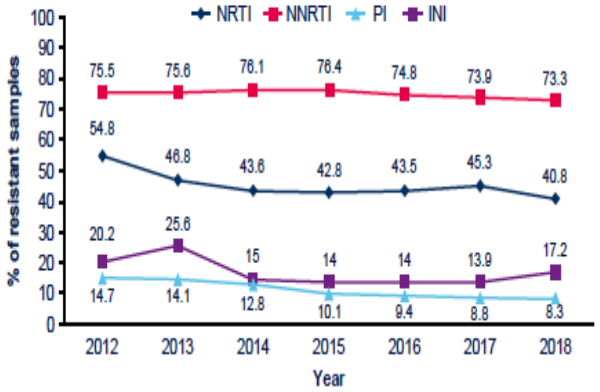


Figure 2. Prevalence of multi-class resistance among samples with resistance, 2012-2018

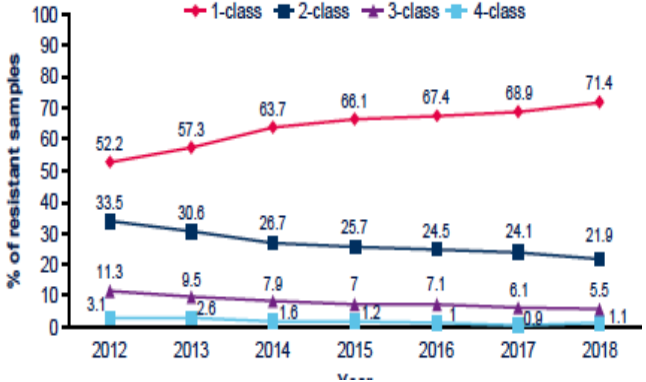
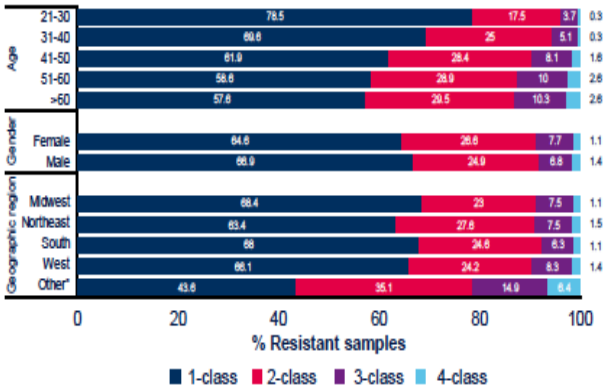


Figure 3. 1-, 2-, 3-, and 4-class resistance by demographic characteristics



Henegar C, et al. CROI 2020. Poster 521

Epidemiology of HTE PLWH

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)

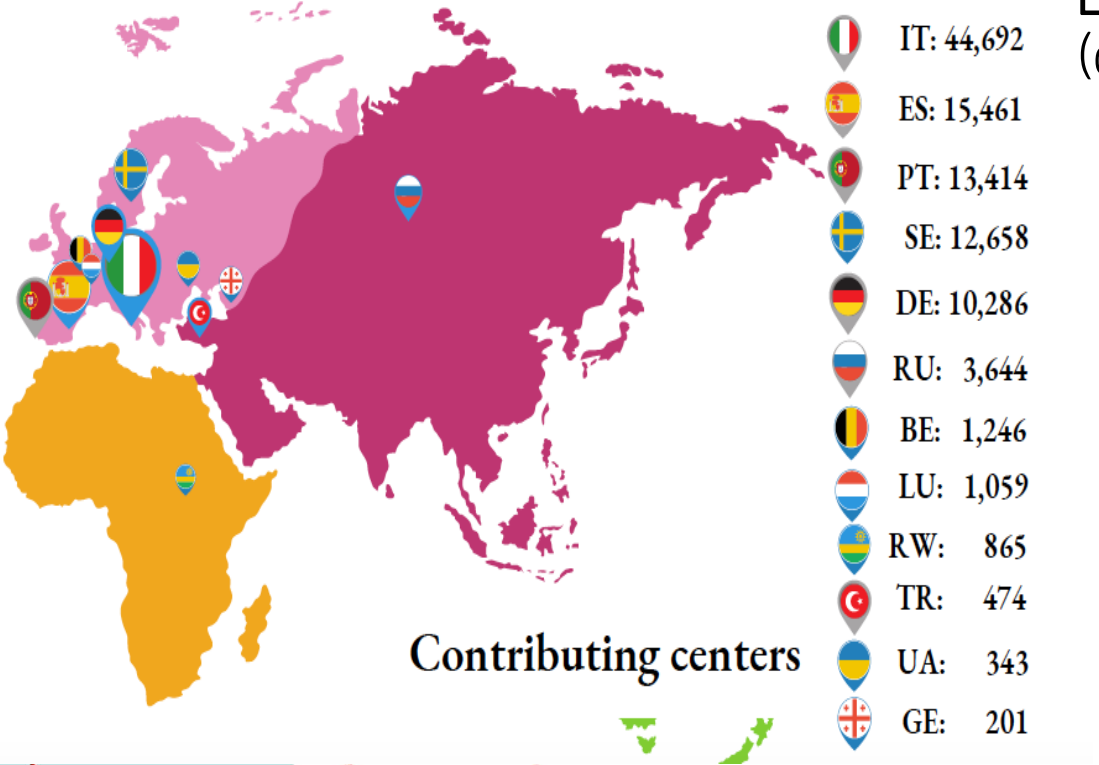
Estimated prevalence by 2016:

10.4% (N = 15,570)

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

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

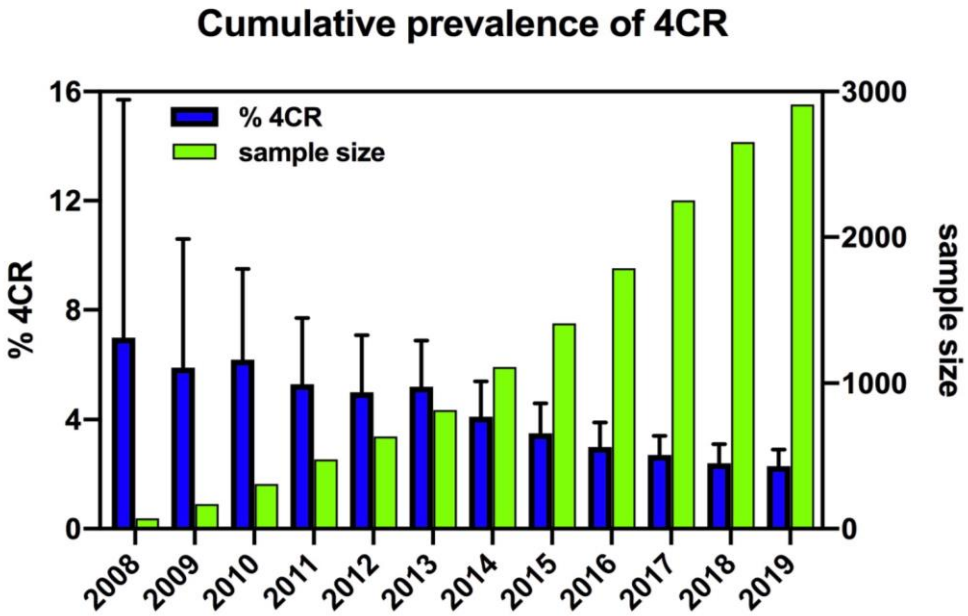
From EuResist multicohort



EuResist Integrated Database
(current release)

- 115,800 PLWH
- 112,257 viral sequences
- 267,112 treatments
- 1,562,581 VL data
- 1,628,138 CD4 cell data

Four-class resistance is rare in treatment-experienced PLWH across Europe



3,414 PLWH with **PR, RT, IN genotype information available** at one or more time points in 2008-2019

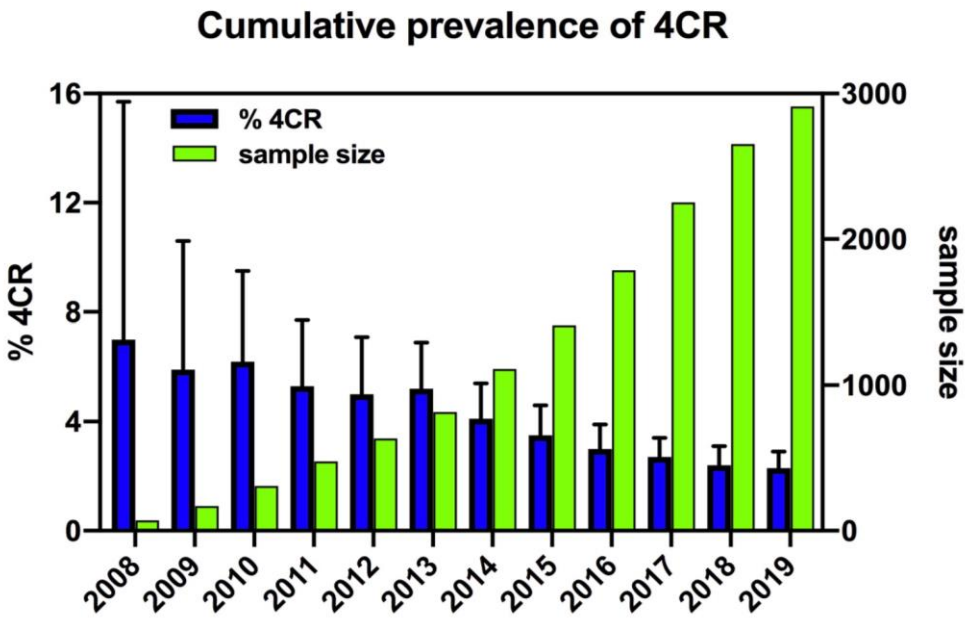
Four-class resistance (4CR) defined as at least intermediate resistance to at least one NRTI, NNRTI, PI and INSTI

Over time, the 4CR status was reached by 85 (**2.5%**) PLWH

Significant decrease in prevalence over time

Vercauteren et al. (EuResist), CROI 2020

Four-class resistance is rare in treatment-experienced PLWH across Europe

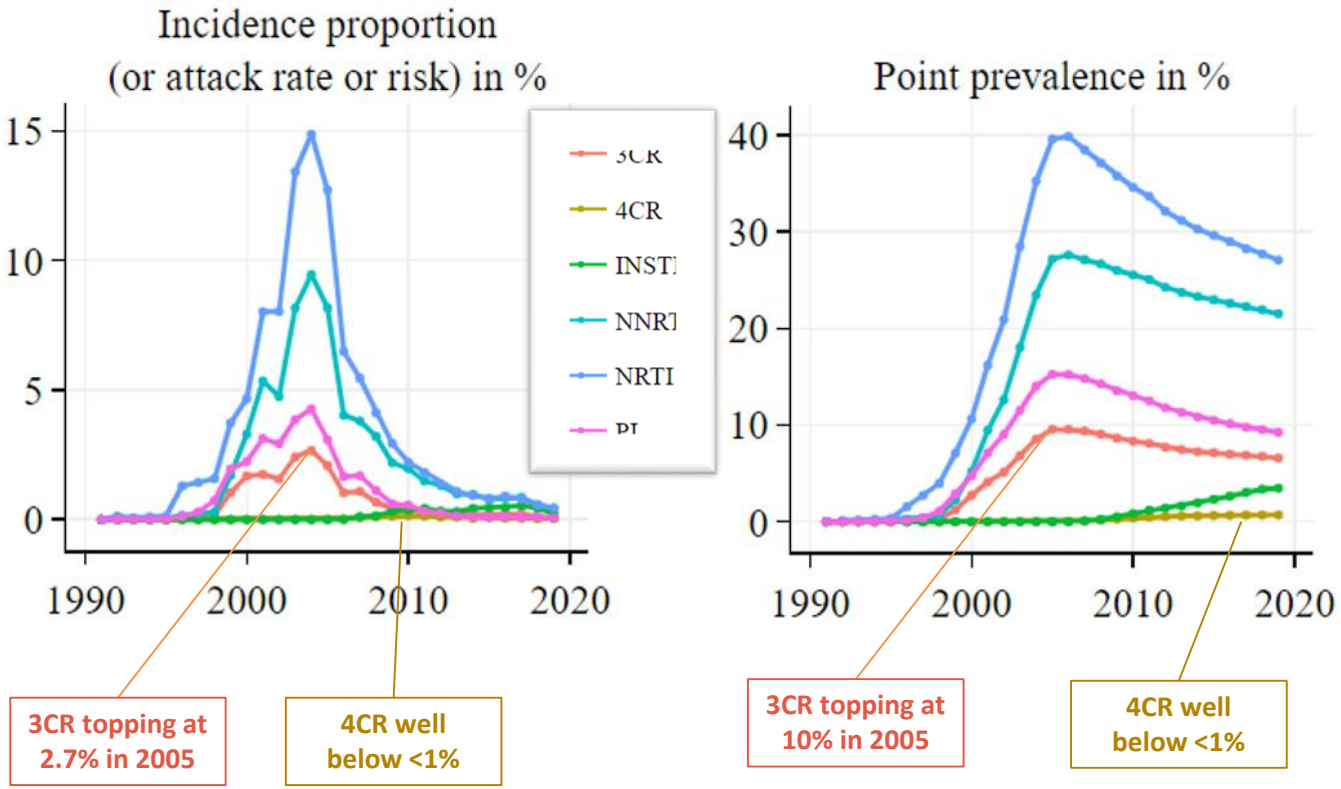


This analysis focused on cases with PR, RT and IN sequences, showing that 4CR has been consistently declining since 2014 *in this setting*

What is true prevalence of 4CR when considering *all* PLWH under treatment?

Vercauteren et al. (EuResist), CROI 2020

Declining incidence of HIV multidrug resistance in Europe



- 39,956 PLWH in 3-class resistance (**3CR**) analysis
  - Overall, 2,768 (6.9%) PLWH developed 3CR
- 16,019 PLWH in 4-class resistance (**4CR**) analysis
  - Overall, 291 (1.8%) PLWH developed 4CR

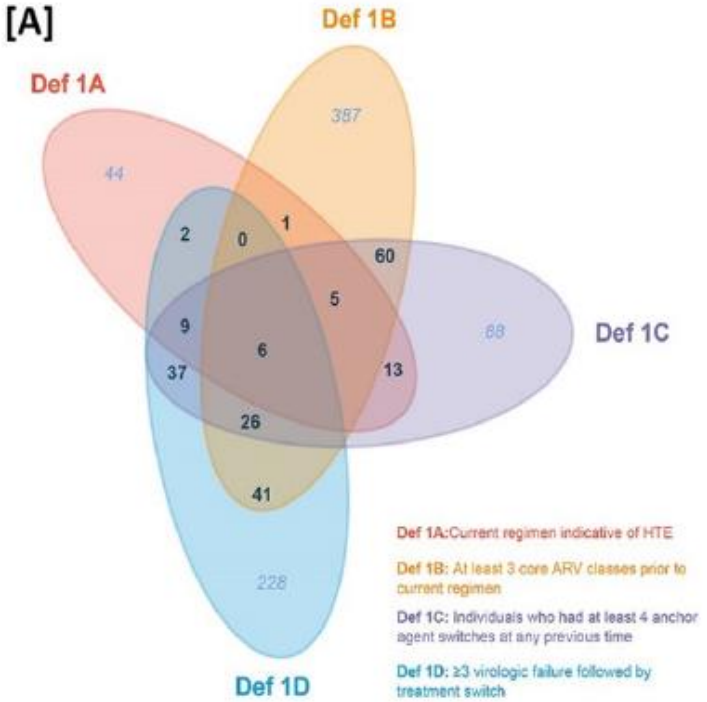
Dewandre et al. Declining incidence of HIV multidrug resistance in Europe, EACS 2021

Factors associated with **3CR** and **4CR** in multivariable analysis

Factor	3CR			4CR		
	aOR	95% CI	P value	aOR	95% CI	P value
Subtype B	1.38	1.04, 1.85	0.030	2.18	1.06, 4.74	0.041
Male gender	1.52	1.27, 1.83	<0.001			
Zenith HIV-1 RNA Log_{10}	1.08	1.04, 1.11	<0.001	1.12	1.03, 1.23	0.012
Nadir CD4 count				1.00	1.00, 1.00	0.033
No. of virological failures	1.24	1.18, 1.32	<0.001	1.23	1.11, 1.36	<0.001
No. of therapies	1.02	1.02, 1.02	<0.001	1.01	1.01, 1.01	<0.001
Year of first treatment	0.97	0.95, 1.00	0.037	1.06	1.00, 1.13	0.042
No. of years since HIV diagnosis				1.05	1.02, 1.09	0.005

- Subtype B associated with a higher prevalence of MDR
- Likely to be a proxy of more extensive exposure to ART, hence also to suboptimal treatment and chances of emergent resistance

Prevalence and characteristics of HTE PLWH: data from the Italian ICONA Cohort



All participants of the Icona cohort with ≥1 clinical visit in 2009-2019

- 200/13,285 (1.5%) PLWH defined as HTE
- prevalence of HTE was 0.64% (95% CI 0.51-0.69), declining from 1.15% (95% CI 0.82-1.56) in 2009 to 0.68% (95% CI 0.52-0.87) in 2019

Lo Caputo et al, abs OC 56, ICAR 2021

Prevalence and characteristics of HTE PLWH: data from the Italian ICONA Cohort

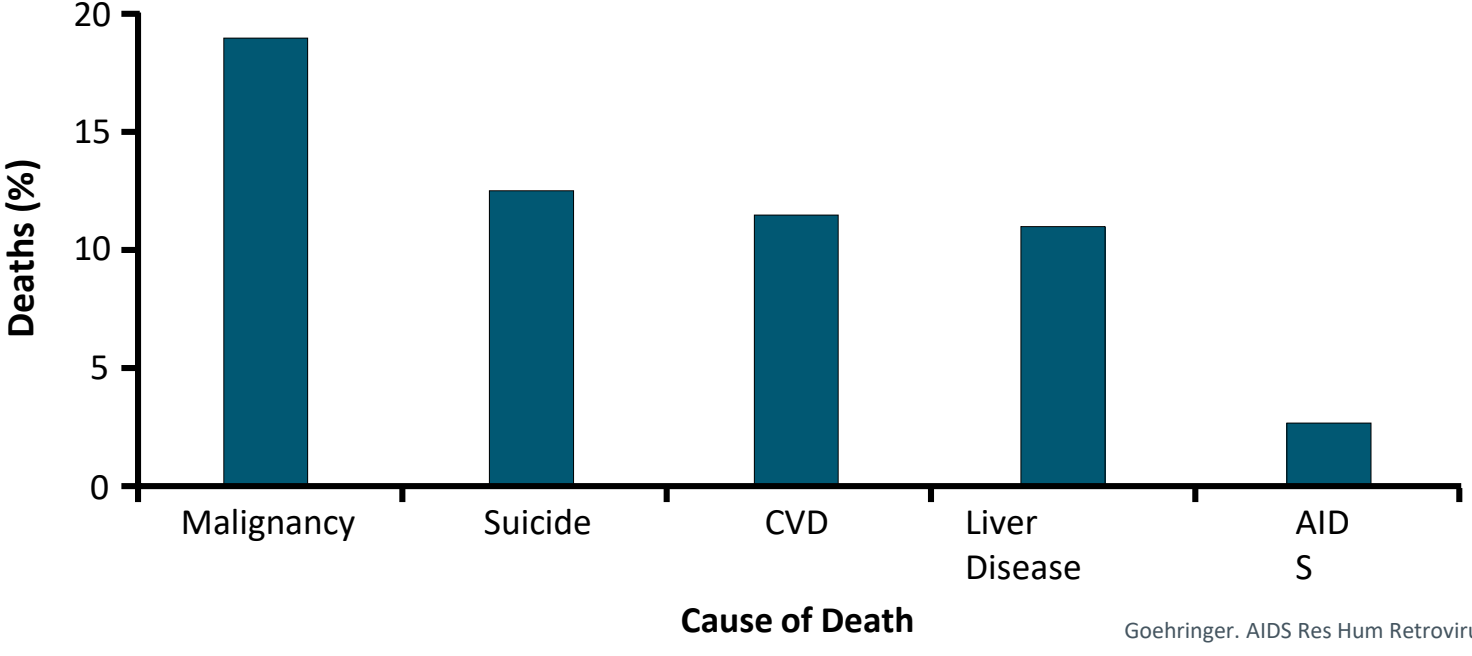
Table 1 – Characteristics of patients according to eligibility for FTV

Characteristics	HTE eligible for FTV (N=85)	Non-HTE / non eligible for FTV (N=13200)	p-value*	Total
Gender, Female, n(%)	37 (43.5%)	2817 (21.3%)	<.001	2854 (21.5%)
Mode of HIV Transmission, n(%)				
PWIDU	29 (34.1%)	1374 (10.4%)	<.001	1403 (10.6%)
MSM	20 (23.5%)	5806 (44.0%)		5826 (43.9%)
Heterosexual contacts	33 (38.8%)	5231 (39.6%)		5264 (39.6%)
Other/Unknown	3 (3.5%)	789 (6.0%)		792 (6.0%)
Nationality, Not Italian, n(%)	6 (7.1%)	2684 (20.3%)	0.002	2690 (20.2%)
Hepatitis B/C coinfection[&], n(%)				
No	47 (55.3%)	9287 (70.4%)	<.001	9334 (70.3%)
Yes	35 (41.2%)	1801 (13.6%)		1836 (13.8%)
Not tested	3 (3.5%)	2112 (16.0%)		2115 (15.9%)
Calendar year of HTE, median (IQR)	2010 (2009, 2015)	.	.	2010 (2009, 2015)
Age, years, median (IQR)	44 (38, 48)	37 (28, 45)	<.001	37 (28, 45)
CD4 count, cells/mmc, median (IQR)	432 (260, 528)	540 (382, 735)	<.001	534 (381, 731)
CD4 count nadir, cells/mmc, median (IQR)	194 (67, 307)	324 (162, 504)	<.001	323 (160, 503)
CD8 count, cells/mmc, median (IQR)	881 (628, 1215)	887 (645, 1207)	0.788	886 (644, 1208)
HIV-RNA, log10 copies/mL, median (IQR)	1.70 (1.70, 3.78)	1.70 (1.69, 3.11)	0.053	1.70 (1.69, 3.13)
Time from HIV diagnosis[&], months, median (IQR)	257 (169, 328)	76 (33, 139)	<.001	77 (33, 140)
[*]Chi-square or Kruskal-Wallis test as appropriate				
All variables measured at baseline (2009) apart when noted (2019)[&]				

Lo Caputo et al, abs OC 56, ICAR 2021

Leading Causes of Death for People Living With HIV With Immunovirologic Success

Prospective, multicenter, observational survey evaluating causes of death among 120 persons living with HIV with immunovirologic success (ie, CD4 cell count >500 c/mL and HIV-1 RNA <50 c/mL) in France in 2010



Goehringer. AIDS Res Hum Retroviruses. 2017;33:187.

HTE PLWH were at greater risk of unfavorable treatment outcomes than non-HTE PLWH

	HTE population N = 2277	Non-HTE population N = 21,906
Demographic characteristics		
Age (yrs), median (IQR)	50 (42, 56)	44 (33, 52)
Sex, n (%)		
Female	431 (19)	3615 (17)
Male	1844 (81)	18,280 (83)
Unknown	2 (0)	11 (0)
Race, n (%)		
Black	906 (40)	8612 (39)
White	1239 (54)	11,693 (53)
Other	58 (3)	776 (4)
Unknown	74 (3)	825 (4)
Ethnicity, n (%)		
Hispanic	572 (25)	5626 (26)
Non-Hispanic	1644 (72)	15,813 (72)
Unknown	61 (3)	467 (2)
MSM, n (%)	1190 (52)	12,798 (58)
US geographic region, n (%)		
Northeast	109 (5)	2039 (9)
South	1189 (52)	11,267 (51)
Midwest	37 (2)	845 (4)
West	940 (41)	7755 (35)
US territories	≤ 5[b]	0 (0)
Clinical characteristics		
VL (copies/mL), n (%)		
Median (IQR)	82 (19, 15,650)	19 (19, 100)
< 50	900 (40)	14,645 (67)
50 to < 200	209 (9)	1729 (8)
≥ 200 to < 10,000	331 (15)	1856 (9)
≥ 10,000 to < 100,000	345 (15)	1957 (9)
≥ 100,000	202 (9)	818 (4)
Missing	290 (13)	901 (4)
CD4 cell count (cells/μL), n (%)		
Median (IQR)	412 (209, 636)	587 (396, 801)
> 500	761 (33)	13,007 (59)
> 350 to ≤ 500	402 (18)	3833 (18)
> 200 to ≤ 350	345 (15)	2505 (11)
> 50 to ≤ 200	337 (15)	1299 (6)
≤ 50	146 (6)	355 (2)
Missing	286 (13)	907 (4)
Years since HIV diagnosis, median (IQR)	15 (7, 22)	7 (3, 15)
Year of ART initiation, median (IQR)	2012 (2005, 2015)	2013 (2011, 2015)
History of ADE[c], n (%)	1221 (54)	6294 (29)
Morbid conditions[d]	1823 (80)	15,132 (69)
VACS mortality risk[e], median (IQR)	24 (13, 41)	12 (6, 23)
Concomitant medications[f]	1477 (65)	11,071 (51)

24,183 ART-experienced PLWH in OPERA cohort (USA and Puerto Rico)

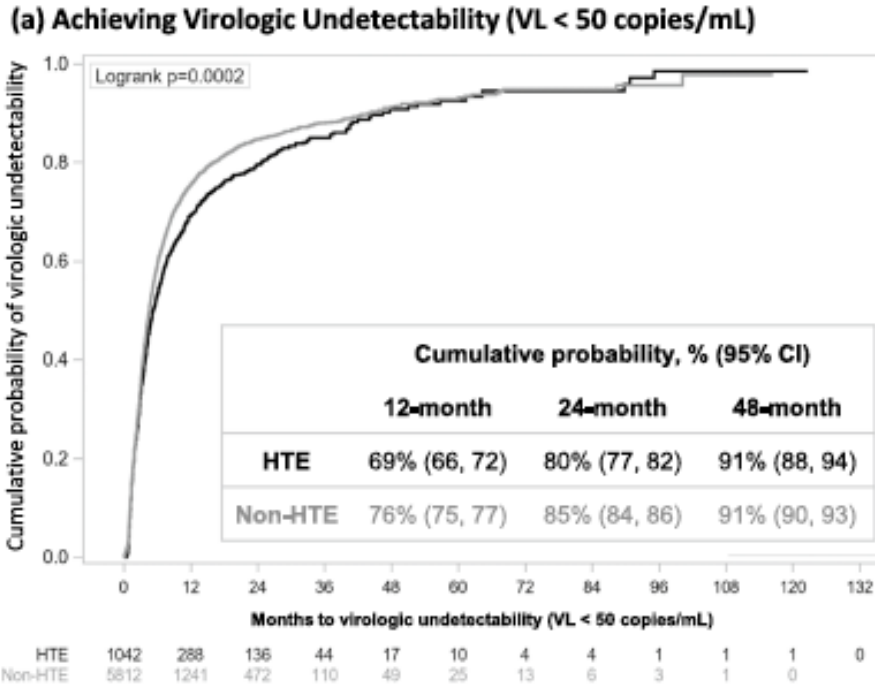
Cross-sectional analysis on Dec, 31, 2016

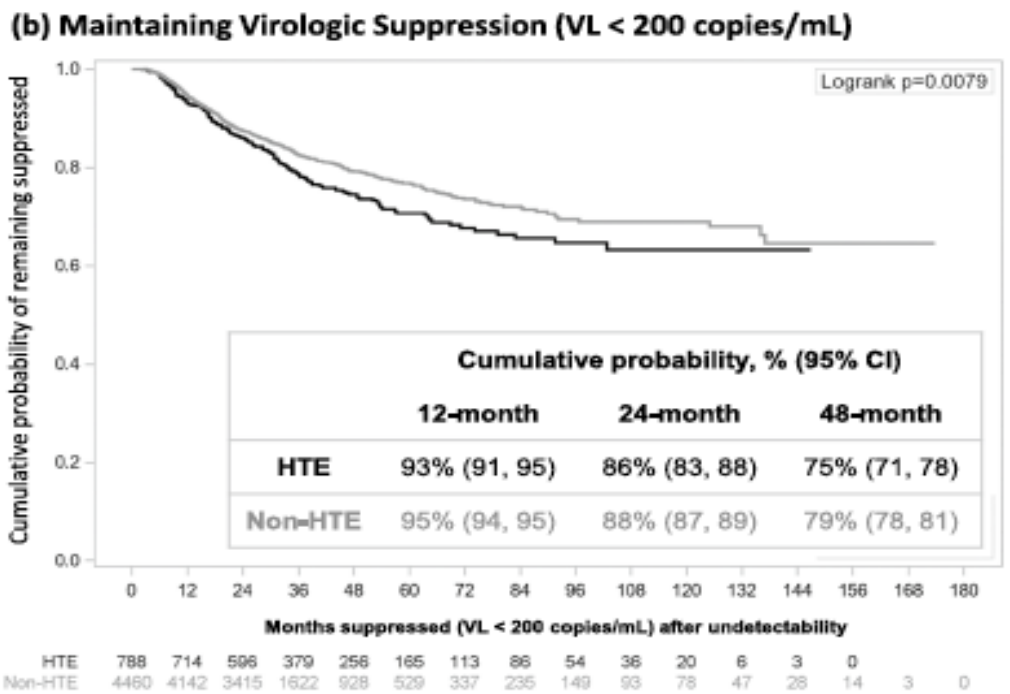
No data on GRT

- Incident ADEs were uncommon, but more frequent among HTE PLWH (n = 108, 5%) than
- non-HTE PLWH (n = 506, 2%).
- Incident non-ADE morbidities were among HTE PLWH (n = 1026, 45%; median 10 months, IQR 3, 22) and among non-HTE PLWH (n = 7608, 35%; median 11 months, IQR 5, 22).
- Deaths were uncommon among HTE (n = 36, 2%) and non-HTE (n = 163, 1%) PLWH.

Hsu et al. BMC Infectious Diseases (2023)

HTE PLWH were at greater risk of unfavorable treatment outcomes than non-HTE PLWH

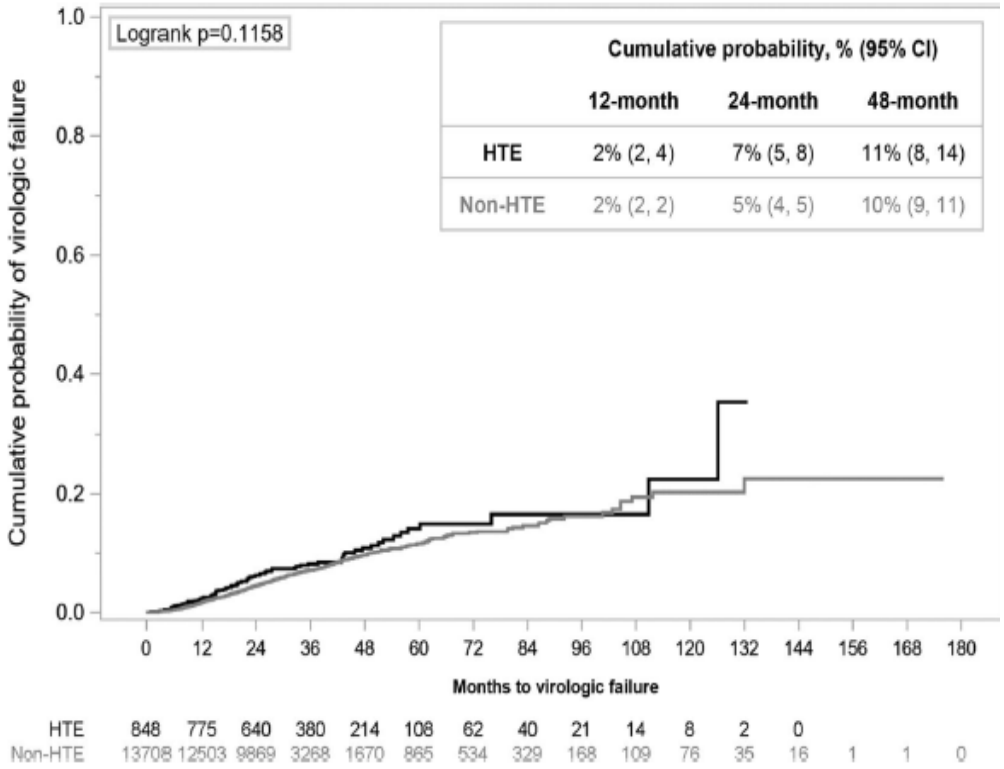




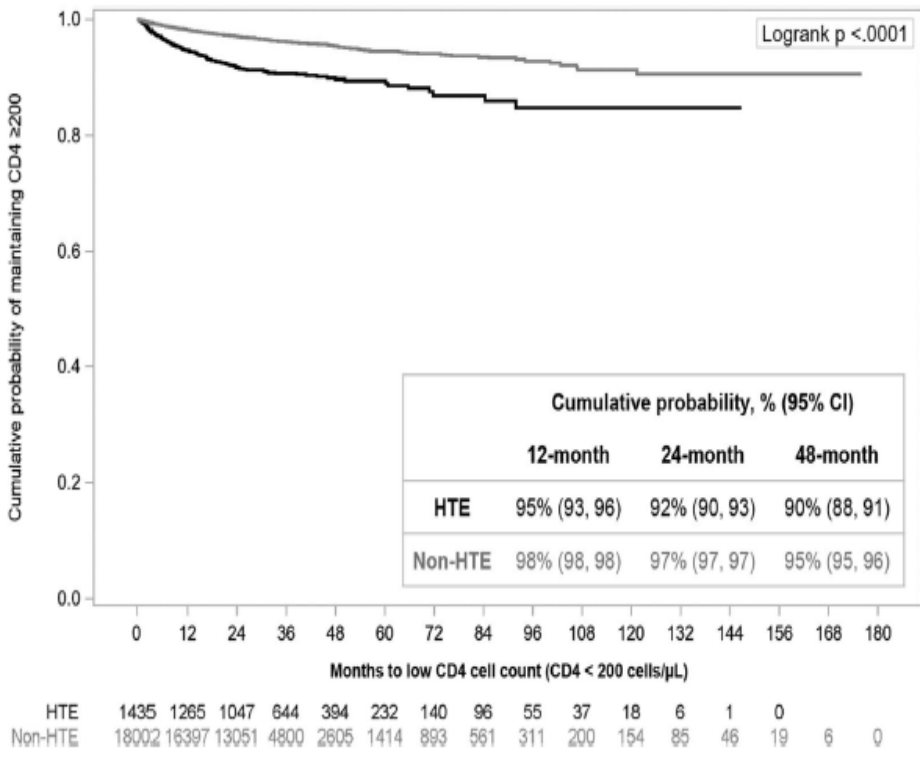
Hsu et al. BMC Infectious Diseases (2023)

HTE PLWH were at greater risk of unfavorable treatment outcomes than non-HTE PLWH

Cumulative probability of VF or TD following a VL≥ 200 cps/mL) among PLWH with a VL< 50 cps/mL at baseline



Cumulative probability of maintaining CD4 cell count ≥ 200 cells/µL among PLWH with CD4 cell count ≥ 200 cells/µL at baseline



Hsu et al. BMC Infectious Diseases (2023)

Risk of more unfavorable treatment outcomes in HTE than non-HTE PLWH?

EuroSIDA cohort (2010–2016)

Among 15,570 PLWH, HTE PLWH experienced higher incidence rates of new ADEs and non-ADE morbidities than non-HTE PLWH.

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).

Pelchen-Matthews A, et al. JADIS 2021;87:806-817

DHHS and EACS: Drug Resistance Testing

- Perform drug resistance testing, preferably **while patient is taking failing regimen under drug pressure**
- ***Do not* discontinue or briefly interrupt therapy** in patients with overt or low-level viremia because of risk of rapid HIV-1 RNA increase, CD4+ T-cell count decrease, and clinical progression[1,2]
- Drug resistance is cumulative, so consider **previous ART history** and **all previous genotypic or phenotypic resistance test results (CUMULATIVE GENOTYPE)**[1,2]
- Archived drug resistance mutations **may not be detected** by standard genotype tests, particularly if performed when patient is not taking drug in question[1]
  - Drug-resistant viruses that constitute <10% to 20% of circulating virus population are likely not detected by commercially available assays
- **Genotypic plus phenotypic testing** is recommended in some PLWH with known or suspected complex drug resistance mutation patterns
- **Genotypic sequencing assay** that analyzes **HIV-1 proviral DNA** may provide additional information on drug resistance especially in some PLWH with low plasma HIV-1 RNA levels
  - Interpreted with caution: might still miss some/all previous drug resistance mutations

1. DHHS guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2023. 2. EACS guidelines. Version 12.0 October 2023.

Managing ART in PLWH
General aim of antiretroviral regimen: viral suppression

Characteristics to consider in all people with HIV

- **Review treatment history**
- **HIV genotype results**
- HLA-B 5701 status
- Individual preferences
- Anticipated adherence

Regimen-specific considerations

- Regimen's barrier to resistance
- DDI
- Potential AEs and drug toxicities
- Convenience
- Cost and access

Presence of specific conditions/ factors

- Comorbid conditions
- Pregnancy or wish to become pregnant
- Coinfections: **HBV**, HCV, TB

ADDRESS THE NEEDS OF HTE POPULATION WITH MULTIPLE DRUG RESISTANCE

The goal of treatment for ART-experienced individuals is to establish and to mantain virologic suppression[1]

Regimens* for HTE individuals should be designed to:[1,2]

- Minimize toxicity[1]
- Preserve CD4+ T-cell counts[1]
- Delay clinical progression[1]
- Be well tolerated, with a favorable short- and long-term safety profile[2]
- Have no cross-resistance to available therapies

1.DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Dec 2023
2.Lataillade M, et al. Lancet HIV 2020;7:e740–51

Key Points for PLWH HTE

- PLWH HTE are relatively uncommon in the current era
- HTE population is complex and there is no clearly defined standard definition of HTE, resulting in difficulties characterizing the HTE population
- Existing cohorts often have incomplete data to accurately characterize the prevalence and incidence of HTE
- Clinical studies in this population have evolved over time with very different study designs and endpoints
- These individuals typically have multiclass-resistant virus and do not have fully active high barrier drugs to include in their regimen
- This setting calls for careful review of measured or inferred viral resistance and establishing which available drugs are likely to be fully and partially active for tailoring regimen
- There are no guidelines or standard regulatory definitions specifically for the HTE population at present
- Management of such patients often requires consultation with expert clinicians and virologists


THE
WALK
TO
STOP
HIV