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Prevalence and Outcomes for Heavily Treatment-Experienced (HTE) Individuals Living with HIV in a European Cohort

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BACKGROUND

The extent of limited treatment options due to extensive treatment history, drug resistance or intolerance to specific antiretrovirals (ARVs) is largely unknown, as are the clinical consequences. We estimated the prevalence, variation over time and potential clinical consequence of heavily treatment-experienced (HTE) individuals in the EuroSIDA study, a prospective observational cohort that has followed >22,000 HIV-1 positive individuals in Europe since 1994.

OBJECTIVES

- To derive a definition to identify individuals likely to be HTE
- To estimate the prevalence of HTE status among HIV-positive individuals in EuroSIDA between 2010 and 2016
- To describe the demographic characteristics of individuals classified as HTE compared to those not HTE
- To assess the viological and immunological outcomes of being HTE and the risk of developing new diagnoses of AIDS or non-AIDS-defining clinical conditions after becoming HTE

METHODS

- HTE status was defined as summarised in **Box 1**
- The annual prevalence at mid-year and regional distribution of HTE status were calculated during the study period between 01-Jan-2010 and 31-Dec-2016
- Outcomes were assessed for all individuals who became HTE on or after 01-Jan-2010 and with follow-up available before 31-Dec-2016. For each, three controls were randomly selected among individuals who were never HTE and under follow-up (FU) on the index date of the HTE individual, with the start of follow-up date (baseline) set to the index date of the HTE individual
- Incidence of clinical events per 1000 person-years of follow-up (PYFU) and incidence rate ratios (IRR) were calculated using Poisson regression. Multivariable models were constructed by including all possible common causes of becoming HTE and the risk of outcomes; the model assumptions were described using directed acyclic graphs (DAGs, not shown) [3]

RESULTS

- Of 15,570 individuals in EuroSIDA who were under follow-up between 2010 and 2016, 1617 were ever HTE (10.4%). Of these 479 (30%) were from South, 636 (40%) from West/Central, 378 (23%) from North Europe, 98 (6%) from Central East and 26 (2%) from East Europe. The prevalence of HTE at the start of the study and at each mid-year from 2010 to 2016 is shown in **Figure 1**. Overall HTE prevalence increased by 0.5% per year (95% CI 0.34-0.66% per year, P=0.0004)
- Of those who became HTE between 2010 and 2016, 1040 individuals had follow-up available. The baseline characteristics of these individuals and 3120 controls are shown in **Table 1**
- Outcomes after the index date (baseline) are summarised in **Figure 2**
- The proportion of individuals with high viral load (VL, ≥400 copies of RNA/ml) during FU was similar for HTE individuals and controls (**Figure 2A**). Compared to those not HTE, a larger proportion of HTE individuals had low CD4 cell counts (≤200 cells/µl, **Figure 2B**)
- Clinical outcomes. HTE individuals experienced 2.4 and 1.3-fold higher incidence rates of new AIDS and non-AIDS clinical events [unadjusted IR 10.9 (95% CI 7.6-15.5) and 33.6 (27.3-41.3) events/1000 PYFU, respectively] than those who were not HTE [IR 4.5 (3.3-6.2) and 26.4 (23.1-30.1) AIDS and non-AIDS events/1000 PYFU]
- Unadjusted and adjusted incidence rate ratios (IRR) are shown in **Figure 2C** and **Figure 2D**. After adjustment for baseline CD4 count, HTE status was no longer associated with the risk of AIDS (**Figure 2C**). The higher incidence of non-AIDS events was largely explained by older age, pre-existing comorbidities and CD4 cell counts (**Figure 2D**)

CONCLUSIONS

Around 10% of HIV-positive individuals in the EuroSIDA cohort were estimated to be HTE with limited treatment options. HTE prevalence increased over time and HTE individuals appeared to be at higher risk of developing new AIDS and non-AIDS events, which was largely explained by immunological parameters or by aging/comorbidities, respectively. Additional therapeutic options to ensure viral suppression and immune recovery as well as effective management of co-morbidities remain important to reduce clinical complications in the HTE population.

Box 1. Definition of heavily treatment-experienced (HTE) status

The composite definition of HTE status was based on genotypic resistance test (GRT) data and modelling of ARV resistance, as well as prior exposure to specific ARV regimens.

➢ Where GRT data were available (5502 individuals in EuroSIDA had at least one GRT), ARV resistance for nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs, NNRTIs) and protease inhibitors (PIs) was defined using the Stanford HIV DB 2017 [1].

➢ Factors associated with the risk of detecting resistance to each of these ARVs were identified by logistic regression modelling, and the models used to predict ARV resistance for individuals who had no recent GRT available.

➢ Predictions of resistance to integrase strand transfer inhibitors (INSTIs), maraviroc (MVC) or enfuvirtide (ENF) were based on the peak viral load experienced by participants while on the drug and probabilities of resistance.

HTE definition 1 was based on GRT and modelled resistance data and classifies as HTE all individuals with ≤2 drug classes available to use from NRTIs, NNRTIs, PIs or other ARVs (INSTIs, MVC or ENF); for NRTIs and PIs we considered only those ARVs recommended in the current EACS guidelines [2].

HTE definition 2: Individuals who previously had ≥4 combination ARV therapy (cART) anchor agent switches and for whom the 4th or any subsequent anchor agent was one of the following: ENF, darunavir (DRV), etravirine (ETR), MVC, tipranavir (TPV), dolutegravir (DTG) or raltegravir (RAL).

HTE definition 3: Multiple drug ARV regimens: Individuals who had ever used a regimen consisting of ≥4 ARVs including one or more of the following drugs: DTG, DRV, ETR, RAL together with a PI component, MVC or ENF.

The composite definition for HTE included everyone who had GRT results available and was known to have resistance to the three main ARV classes (NRTIs, NNRTIs and PIs), or else who fulfilled the criteria of at least two of the three HTE definitions.

The HTE index date was defined as the earliest date at which the composite definition was satisfied.

Contributions to the composite definition for HTE

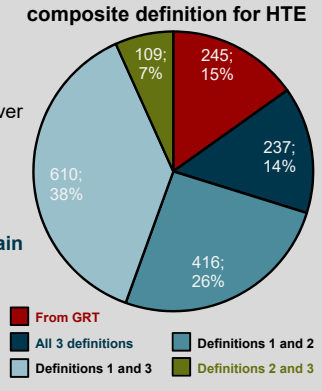
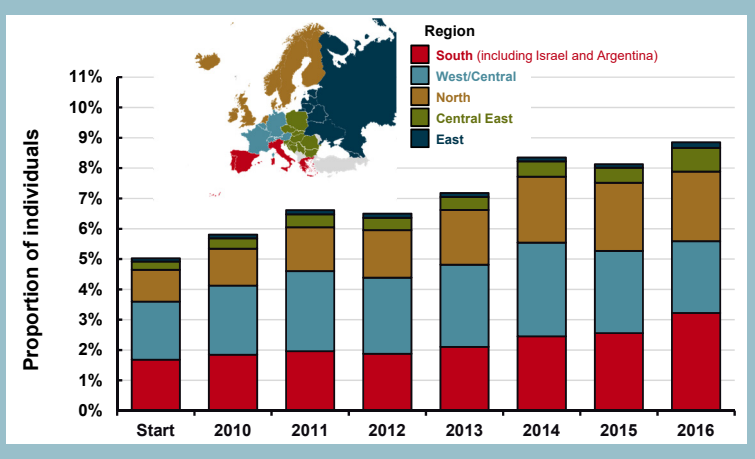


Table 1. Characteristics of HTE individuals and controls on the index date

		HTE N (%)	Not HTE N (%)	P-value*
Number included		**1040**	**3120**	
Age (years)	(Median, IQR)	51.6 (47.0, 57.5)	48.1 (41.0, 54.7)	<0.0001
Gender	Male	799 (76.8)	2218 (71.1)	0.0004
Ethnic group	White/Caucasian	830 (79.8)	2692 (86.3)	<0.0001
CD4 counts (cells/µl)	≤200	138 (13.3)	160 (5.1)	<0.0001
	201 - 500	404 (38.8)	1023 (32.8)	
	>500	498 (47.9)	1937 (62.1)	
CD4 nadir (cells/µl)	≤200	794 (76.3)	1551 (49.7)	<0.0001
Viral load (RNA copies/ml)	controlled (<400)	835 (80.3)	2850 (91.3)	<0.0001
Time since HIV diagnosis	≥10 years	956 (91.9)	2085 (66.8)	<0.0001
Previously exposed to	NRTI	1040 (100)	3108 (99.6)	0.0453
	NNRTI	963 (92.6)	2260 (72.4)	<0.0001
	PI	1031 (99.1)	2399 (76.9)	<0.0001
	INSTI	500 (48.1)	478 (15.3)	<0.0001
	Fusion inhibitor (ENF)	132 (12.7)	14 (0.4)	<0.0001
	CCR5 inhibitor (MVC)	87 (8.4)	40 (1.3)	<0.0001
Total number of ARV drugs previously exposed to	(Median, IQR)	13 (11, 15)	7 (5, 9)	<0.0001
Prior Clinical conditions	Any AIDS-defining event	452 (43.5)	874 (28.0)	<0.0001
	Hepatitis C virus positive	368 (35.4)	1158 (37.1)	0.1704
	Cardiovascular disease	94 (9.0)	154 (4.9)	<0.0001
	Non-AIDS cancer	75 (7.2)	117 (3.8)	<0.0001
	Liver disease	35 (3.4)	52 (1.7)	0.0049
	Chronic kidney disease	100 (9.6)	175 (5.6)	<0.0001

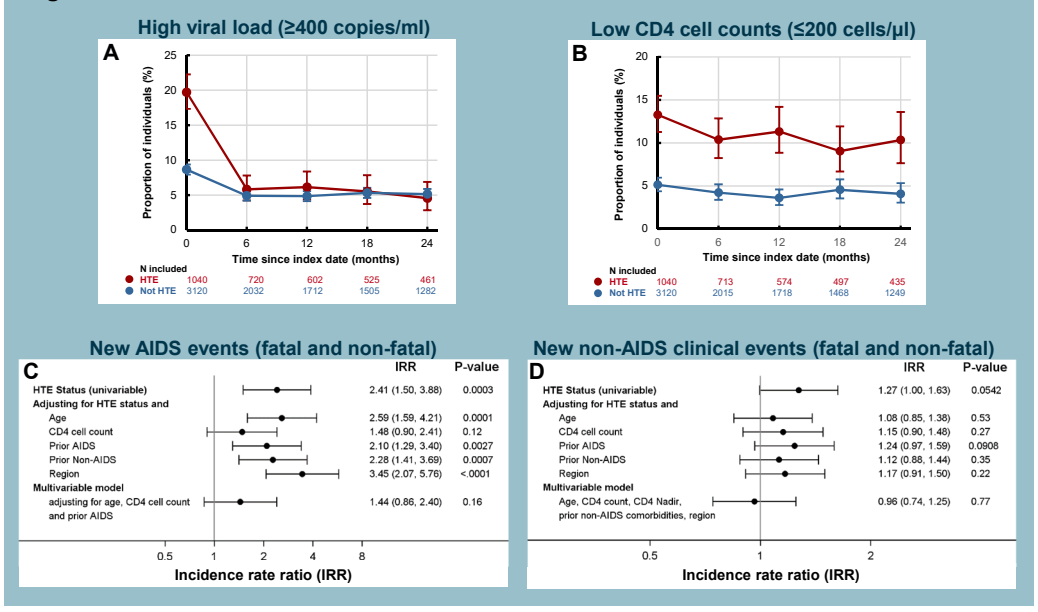
* P-values from the chi square test for categorical variables or Wilcoxon signed rank test for continuous variables.

Figure 1. Prevalence of HTE in Europe, 2010-2016



Reference date	01-Jan-10	01-Jul-10	01-Jul-11	01-Jul-12	01-Jul-13	01-Jul-14	01-Jul-15	01-Jul-16
Number under FU	10001	9863	10298	11617	11466	10898	12091	9334
Number HTE	503	573	681	755	823	910	983	826
HTE prevalence	**5.0%**	**5.8%**	**6.6%**	**6.5%**	**7.2%**	**8.4%**	**8.1%**	**8.8%**

Figure 2. Outcomes after the HTE index date



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3. DAGitty: http://dagitty.net/.

The EuroSIDA Study Group: https://chip.dk/Studies/EuroSIDA

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EuroSIDA

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