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Estimation of percentage of HIV-infected people with limited future drug options in a closed observational setting over the period 2007-2011 and beyond

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INTRODUCTION

Currently, few people receiving HIV care in resource rich settings are estimated to have limited future drug options (LFDO). It remains uncertain whether this is likely to change again and, if so, how quickly.

AIMS

- To estimate the prevalence of people in EuroSIDA with LFDO over the period 2007-201
- To predict the trend in the prevalence of people in EuroSIDA with LFDO over the following 5 years: 2012-2016

METHODS

We considered a total of 16 antivirals licensed before 2008 and currently used in the clinics: zidovudine (ZDV), lamivudine (3TC), emtricitabine (FTC), abacavir (ABC), tenofovir (TDF), efavirenz (EFV), nevirapine (NVP), etravirine (ETR), saquinavir (SQV/r), fos-amprenavir (FPV/r), lopinavir (LPV/r), atazanavir (ATV/r), tipranavir (TPV/r), darunavir (DRV/r), raltegravir (RAL) and maraviroc (MAR).

Stage 1

For each antiretroviral drug separately, we estimated the probability that the Rega v.8.0 IS would predict full activity if the drug had been previously virologically failed. Virological failure to a specific drug over follow-up was defined if a person experienced ≥4 months with a VL>500 copies/mL after starting and while still receiving the drug. We positioned the analysis at the time of the latest genotypic test available. At this time point for each person we calculated: i) whether there was evidence of virological failure before that time and ii) the Rega predictions using all tests available up to that point in time. An univariable logistic regression model with response full activity of drug according to Rega and history of virological failure as a covariate was used to obtain the predictions of full activity given previous failure. In a worst case scenario, we assumed that, for all drugs, previous failure to a drug meant that such a drug would be certainly non-active and therefore not an option regardless of the Rega predictions.

Stage 2

Similarly we estimated the probability, for each drug separately, that a person would re-start a drug after having first interrupted it because of an AE. We used the percentages of re-starting after a stop as predictions of the level of retained tolerance to a drug given a previous stop due to AE. In a worst case scenario we assumed that, for all drugs, previous interruption of a drug because of adverse events meant that such a drug would no longer be an option.

Stage 3

Our study population included participants in EuroSIDA who were enrolled and started cART (defined as at least 3 antiretroviral drugs) prior to 2007 and were still alive and under follow-up by the end of 2011. For each of these individuals, at August 31st of each year over 2007 and 2011, we identified their history of previous history of virological failure and of interruptions due to adverse events for each antiretrovirals.

If a person on August 31st 2007 had previously experienced virological failure to lamivudine and the Rega prediction for full activity of lamivudine given previous failure estimated in stage 1 was p% then lamivudine would be still an option for him/her with a p% chance. Similarly, if he/she had previously stopped lamivudine because of AE and the probability of re-starting it estimated in stage 2 was q% then lamivudine would be still an option for him/her with a q% chance. In addition, MAR was only an option in this analysis for people carrying CCR5-tropic viruses. We assumed that if people had a CD4 nadir of <200 cells/mm3 prior to August 31st of each year then it was likely that their HIV had already switched to a X4-tropic virus and therefore MAR was no longer an option for these individuals.

Two main definitions of LFDO were used. A participant was defined as having limited drug options (LFDO) at a given year if i) they did not have at least two nucleosides classified as 'O' and at least another 'O' drug from one of the other classes or ii) they have lost 3 of the total 5 drug classes.

Finally, for each year over the period 2007-2011, we calculated the proportion of participants with LFDO. Results beyond 2011 and up to 2016 were estimated by linear extrapolation of the proportions extending the trend observed up to 2011. The analysis was stratified by use of ART before initiation of cART and repeated using the data of the overall cohort.

RESULTS

Table 1 shows the estimeted probabilities calculated in Stage1/2 analyses

Table 2 shows a description of the study population (time-fixed characteristics are the same for each calendar year).

Table 3 shows the incidence of virological failure to the 16 antiretrovirals considered.

Figure 1 shows the estimated (2007-2011) and predicted (2011-2016) prevalence of LFDO over using definition i) of LFDO startified by ART use at cART initiation and under 4 different scenarios.

Estimated prevalence and predictions were similar when the whole cohort was used (data not shown) but lower when the LFDO definition ii) was used (max of 16% by 2016 in the worst case scenario C).

CONCLUSIONS

In conclusion, few participants in EuroSIDA were estimated to have LFDO at the end of 2011 (6% under scenario A). Our estimates are consistent with the prevalence of triple class virological failure estimated with great accuracy in single and collaborative European analyses. Also under scenario A, the proportion of people with LFDO in our cohort it is likely to remain below 10% by the end of 2016 (although this proportion may be as high as 16% under the worst case scenario C). Although this is still a relatively low proportion, it is not negligible and the issue of potential exhaustion of drug options should be carefully monitored again in the near future using both database-derived and simulated data analyses.

Table 1

Estimated probabilities from stage 1 and stage 2 analyses

Antiretroviral	Stage 1*	Stage 2**
Zidovudine	41%	20%
Lamivudine	25%	43%
Emtricitabine	30%	21%
Tenofovir	44%	22%
Abacavir	30%	16%
Efavirenz	21%	13%
Nevirapine	25%	11%
Etravirine	8%	20%
Saquinavir	47%	12%
Nelfinavir	31%	6%
Amprenavir	25%	16%
Lopinavir	86%	16%
Atazanavir	85%	13%
Tipranavir	16%	0%
Darunavir	42%	12%

*Probability of having a sensitive virus to the drug given previous failure to the drug
**Probability of restarting the drug given previous discontinuation of the drug due to toxicity

Table 2

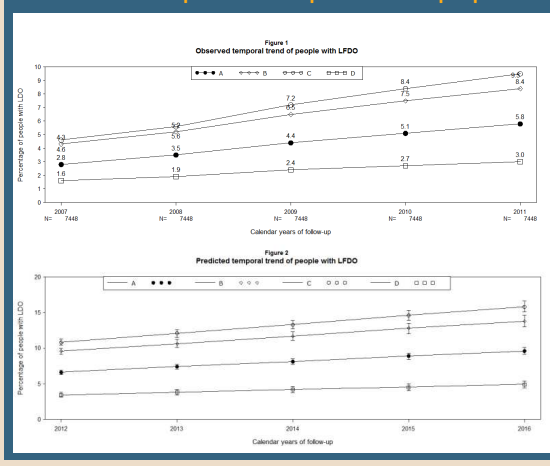
Main characteristics of participants

Characteristics	Calendar year of follow-up				
	2007	2008	2009	2010	2011
	N= 7448	N= 7448	N= 7448	N= 7448	N= 7448
Age, years					
Median (IQR)	37 (31, 44)	37 (31, 44)	37 (31, 44)	37 (31, 44)	37 (31, 44)
Gender, n(%)					
Female	2094 (28.1%)	2094 (28.1%)	2094 (28.1%)	2094 (28.1%)	2094 (28.1%)
Mode of HIV transmission, n(%)					
Homosexual contacts	2965 (39.8%)	2965 (39.8%)	2965 (39.8%)	2965 (39.8%)	2965 (39.8%)
IDU	1458 (19.6%)	1458 (19.6%)	1458 (19.6%)	1458 (19.6%)	1458 (19.6%)
Heterosexual contacts	2467 (33.1%)	2467 (33.1%)	2467 (33.1%)	2467 (33.1%)	2467 (33.1%)
Other/unknown	558 (7.5%)	558 (7.5%)	558 (7.5%)	558 (7.5%)	558 (7.5%)
Ethnicity, n(%)					
White	6555 (88.0%)	6555 (88.0%)	6555 (88.0%)	6555 (88.0%)	6555 (88.0%)
Asian	131 (1.8%)	131 (1.8%)	131 (1.8%)	131 (1.8%)	131 (1.8%)
Black	429 (5.8%)	429 (5.8%)	429 (5.8%)	429 (5.8%)	429 (5.8%)
Other/unknown	333 (4.5%)	333 (4.5%)	333 (4.5%)	333 (4.5%)	333 (4.5%)
ART naive when started cART, n(%)					
Yes	2043 (27.4%)	2043 (27.4%)	2043 (27.4%)	2043 (27.4%)	2043 (27.4%)
Type of cART started, n(%)					
PI	2648 (38.8%)	2648 (38.8%)	2648 (38.8%)	2648 (38.8%)	2648 (38.8%)
PI/r	808 (11.8%)	808 (11.8%)	808 (11.8%)	808 (11.8%)	808 (11.8%)
NNRTI	1246 (18.2%)	1246 (18.2%)	1246 (18.2%)	1246 (18.2%)	1246 (18.2%)
NRTI	923 (13.5%)	923 (13.5%)	923 (13.5%)	923 (13.5%)	923 (13.5%)
Year of cART					
Median (range)	2006 (2001, 2012)	2006 (2001, 2012)	2006 (2001, 2012)	2006 (2001, 2012)	2006 (2001, 2012)

Table 3 **History of viral failure/stop of single drugs according to year of follow-up**

Characteristics	Calendar year of follow-up				
	2007	2008	2009	2010	2011
	N= 7448	N= 7448	N= 7448	N= 7448	N= 7448
Drugs previously failed, n(%)					
Zidovudine	2324 (31.2%)	2406 (32.3%)	2522 (33.9%)	2596 (34.9%)	2621 (35.2%)
Lamivudine	2953 (39.6%)	3060 (41.1%)	3234 (43.4%)	3332 (44.7%)	3376 (45.3%)
Emtricitabine	128 (1.7%)	212 (2.8%)	369 (5.0%)	428 (5.7%)	487 (6.5%)
Abacavir	821 (11.0%)	870 (11.7%)	976 (13.1%)	1013 (13.6%)	1059 (14.2%)
Tenofovir	639 (8.6%)	738 (9.9%)	900 (12.1%)	992 (13.3%)	1066 (14.3%)
Efavirenz	824 (11.1%)	896 (12.0%)	995 (13.4%)	1036 (13.9%)	1064 (14.3%)
Nevirapine	787 (10.6%)	813 (10.9%)	868 (11.7%)	892 (12.0%)	903 (12.1%)
Etravirine	9 (0.1%)	14 (0.2%)	38 (0.5%)	56 (0.8%)	70 (0.9%)
Saquinavir/r	699 (9.4%)	715 (9.6%)	735 (9.9%)	742 (10.0%)	746 (10.0%)
Fos-amprenavir/r	198 (2.7%)	215 (2.9%)	242 (3.2%)	251 (3.4%)	258 (3.5%)
Lopinavir/r	608 (8.2%)	696 (9.3%)	804 (10.8%)	875 (11.7%)	906 (12.2%)
Atazanavir/r	269 (3.6%)	323 (4.3%)	405 (5.4%)	439 (5.9%)	469 (6.3%)
Tipranavir/r	68 (0.9%)	75 (1.0%)	82 (1.1%)	82 (1.1%)	83 (1.1%)
Darunavir/r	25 (0.3%)	40 (0.5%)	93 (1.2%)	129 (1.7%)	173 (2.3%)
Raltegravir	3 (0.0%)	9 (0.1%)	29 (0.4%)	52 (0.7%)	83 (1.1%)
Maraviroc	3 (0.0%)	5 (0.1%)	9 (0.1%)	9 (0.1%)	14 (0.2%)
Drugs previously interrupted due to AE, n(%)					
Zidovudine	1047 (14.1%)	1173 (15.7%)	1275 (17.1%)	1344 (18.0%)	1399 (18.8%)
Lamivudine	1089 (14.6%)	1250 (16.8%)	1388 (18.6%)	1500 (20.1%)	1583 (21.3%)
Emtricitabine	63 (0.8%)	110 (1.5%)	155 (2.1%)	211 (2.8%)	295 (4.0%)
Abacavir	474 (6.4%)	556 (7.5%)	652 (8.8%)	723 (9.7%)	775 (10.4%)
Tenofovir	247 (3.3%)	313 (4.2%)	384 (5.2%)	471 (6.3%)	579 (7.8%)
Efavirenz	684 (9.2%)	764 (10.3%)	826 (11.1%)	883 (11.9%)	913 (12.3%)
Nevirapine	409 (5.5%)	433 (5.8%)	454 (6.1%)	471 (6.3%)	486 (6.5%)
Etravirine	2 (0.0%)	7 (0.1%)	12 (0.2%)	19 (0.3%)	23 (0.3%)
Saquinavir/r	379 (5.1%)	393 (5.3%)	408 (5.5%)	423 (5.7%)	437 (5.9%)
Fos-amprenavir/r	110 (1.5%)	125 (1.7%)	137 (1.8%)	143 (1.9%)	152 (2.0%)
Lopinavir/r	451 (6.1%)	536 (7.2%)	612 (8.2%)	690 (9.3%)	761 (10.2%)
Atazanavir/r	130 (1.7%)	175 (2.3%)	209 (2.8%)	258 (3.5%)	305 (4.1%)
Tipranavir/r	18 (0.2%)	21 (0.3%)	27 (0.4%)	30 (0.4%)	32 (0.4%)
Darunavir/r	5 (0.1%)	17 (0.2%)	27 (0.4%)	45 (0.6%)	61 (0.8%)
Raltegravir	0 (0.0%)	5 (0.1%)	7 (0.1%)	20 (0.3%)	29 (0.4%)
Maraviroc	2 (0.0%)	4 (0.1%)	6 (0.1%)	8 (0.1%)	8 (0.1%)

Figure 1 **Observed and predicted temporal trend of people with LFDO**



A – Predicted viral activity and predicted intolerance

B – failure = loss of option (=0% FA) and predicted intolerance

C – failure = loss of option (0% FA) and stop due to TLT= loss of option (worst case)

D – predicted viral activity only (best case)

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