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Heavy arv exposure and exhausted/limited arv options: predictors and clinical outcomes

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Abstract

Objectives: People with HIV and extensive antiretroviral (ARV) exposure may have limited/exhausted treatment options (LExTO) due to resistance, comorbidities or ARV-related toxicity. Predictors of LExTO were investigated in the RESPOND cohort.

Methods: Participants on ART for ≥5 years were defined as having LExTO when switched to ≥2 anchor agents+a third ARV (any class), a 2-drug regimen of 2 anchor agents (excluding rilpivirine with dolutegravir/cabotegravir), or ≥3 nucleoside reverse transcriptase inhibitors. Baseline was the latest of 1/1/2012, cohort enrolment or 5 years after starting ARVs. Poisson regression modelled LExTO rates and clinical events (all-cause mortality, non-AIDS malignancy, cardiovascular disease [CVD] and chronic kidney disease [CKD]).

Results: Of 23827 participants, 2164 progressed to LExTO (9.1%) during 130061 person-years follow-up (PYFU); incidence 1.66/100 PYFU (95% CI 1.59-1.73). Predictors of LExTO were HIV duration >15 years (vs. 7.5-15; adjusted incidence rate ratio [aIRR] 1.32; 95% CI 1.19-1.46), development of CKD (1.84; 1.59-2.13), CVD (1.64; 1.38-1.94), AIDS (1.18; 1.07-1.30) and current CD4≤350 (vs. 351-500 cells/μL, 1.51; 1.32-1.74). Those followed between 2018-2021 had lower rates of LExTO (vs. 2015-2017; 0.52; 0.47-0.59), as did those with baseline viral load ≤200 cp/mL (0.46; 0.40-0.53) and individuals under 40. Development of LExTO was not significantly associated with clinical events after adjustment for age and current CD4, except CKD (1.74; 1.48-2.05).

Conclusions: Despite an ageing and increasingly comorbid population we found declining LExTO rates by 2018-2021, reflecting recent developments in contemporary ART options and clinical management. Reassuringly, LExTO was not associated with a significantly increased incidence of serious clinical events apart from CKD

Introduction

Despite widespread availability of effective antiretroviral (ARV) therapy (ART), which allows persons with HIV to maintain suppressed viral load (VL) and to achieve a near-normal life expectancy(1), some individuals with more extensive prior treatment experience may have limited treatment options. Heavily treatment-experienced (HTE) individuals are usually defined as those with resistance to ARVs in ≥3 drug classes or having ≤2 classes with ≥1 fully active ARV (or ≤2 nucleoside reverse transcriptase inhibitors [NRTIs]) remaining which could be combined to form a viable new regimen(2-5). Having limited or exhausted treatment options may also arise from treatment-limiting drug toxicities, comorbidities or drug-drug interactions(6, 7). While the incidence of HIV-resistance to multiple ARV classes has been declining with the introduction of new ARV classes and novel ARVs with higher barriers to resistance(4), the absolute number of individuals with HTE status or limited and/or exhausted treatment options may be increasing as the population with HIV ages(6).

Although those with HTE or limited/ exhausted treatment options unrelated to ARV resistance may represent different populations(6), overlaps are likely common, and both represent individuals with more challenging management needs. A careful characterisation of individuals with such limited and/or exhausted treatment options or HTE (referred to as LExTO) is important in order to tailor the most viable and effective treatment regimen possible and clarify prognosis, monitoring and management needs. However, identifying individuals with LExTO in research or cohort settings where HIV resistance data are not available is complex. Various alternative definitions have been explored in both American and European cohorts, based on ART history or the use of specific ARVs or ARV combinations that are considered 'indicative of HTE' with LExTO prevalence relying heavily on the definition used and ranging widely from 2.1% to 16%(8-11).

Very narrow definitions, relying on extensive ARV resistance testing alone, will not capture individuals who may have limited options unrelated to resistance. The aims of this analysis were to estimate the incidence of LExTO (with or without HIV resistance/HTE) among individuals in the RESPOND cohort collaboration, to describe the characteristics and factors associated with developing LExTO and to examine potential clinical consequences.

Methods

Participants

The International Cohort Consortium of Infectious Diseases (RESPOND) is a collaboration among 17 cohorts from Europe and Australia, as described elsewhere(12). Standardised data on demographics, HIV-related factors and ARVs use are collected using the HIV Cohorts Data Exchange Protocol (HICDEP; (13)) and updated annually (details at https://www.chip.dk/Studies/RESPOND). Clinical events are reported on study-specific event forms and centrally validated.

Definitions

Baseline was defined as the latest of 01 January 2012, enrolment to local cohort, or the date 5 years after the first ARV use was reported.

As the results of ART resistance testing was not available in RESPOND, individuals were defined as having LExTO based on ART use considered to be 'indicative of HTE' or indicative of treatment regimens offered to individuals with limited treatment options for other reasons, similar to the HTE proxy definitions described previously(8, 9, 11). LExTO comprised individuals who were ARV-experienced on ART for at least 5 years and who were not using more standard ART, composed of 2 backbone NRTIs with a 3rd ARV from a different class (referred to as an 'anchor' ARV). This would include individuals who are using any of the following regimen types:

i. ≥2 anchor agents together with a third ARV from any class
ii. exactly 2 anchor agents in a 2-drug regimen (excluding individuals on dual therapies recommended by EACS guidelines(7), i.e. dolutegravir/rilpivirine or cabotegravir/rilpivirine);

reflecting that during the follow-up period 2-drug regimens were largely used in treatment experienced individuals with a high prevalence of comorbidities(14)

iii. any regimen that includes enfuvirtide

iv. ≥3 NRTIs (with or without other ARVs)

The anchor ARVs were INSTIs (raltegravir, cobicistat boosted elvitegravir, dolutegravir, bictegravir, cabotegravir), protease inhibitors (PIs; boosted darunavir, any atazanavir, ritonavir boosted lopinavir), non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine, rilpivirine, doravirine), and others (enfuvirtide, maraviroc, fostemsavir, ibalizumab; note that there were no individuals using fostemsavir, ibalizumab or lenacapavir). The NRTIs included were abacavir, lamivudine, emtricitabine, tenofovir (disoproxil fumarate or alafenamide), and zidovudine. The date of LExTO was defined as the first date of starting any of these indicative regimens. LExTO status was considered to be irreversible, i.e. once an individual was identified as LExTO, they were assumed to remain LExTO.

We included all male and female individuals under follow-up in RESPOND who were ≥18 years old at baseline with a CD4 cell count and VL in the 12 months prior to or 3 months after baseline. Individuals with no prospective follow-up after baseline were excluded, as were those meeting the definition of LExTO prior to baseline. Persons were followed until last visit or the administrative censoring date of 31 December 2021; median date of last follow-up was April 2021.

Statistical analysis

Baseline characteristics of individuals, stratified by whether they developed LExTO, were described as numbers and percentages or medians with inter-quartile range (IQR) for continuous variables, with Chi^2 significance tests for proportions or Wilcoxon–Mann–Whitney U or Kruskal–Wallis significance tests for medians. Hypertension was defined as use of anti-hypertensives at any time before baseline and/or baseline systolic or diastolic blood pressure measurement higher than 140 or 90 mmHg, respectively. Diabetes mellitus (DM) was defined as a random blood glucose >11.1 mmol/L, HbA1c>6.5%, use of antidiabetic medication or site reported clinical diagnosis.

Poisson regression was used to assess factors associated with becoming LExTO. Confounding and effect modifying factors that were significant in univariate analyses ($p<0.1$) were included unless they were collinear with other variables or effect modifiers. Age and gender were included in models *a priori*. Poisson regression was also used to assess the relationship between LExTO and developing clinical events during follow-up by including LExTO as a time-updated covariate. Clinical events considered were all-cause mortality, cardiovascular disease (CVD, myocardial infarction, stroke and invasive cardiovascular procedure), non-AIDS defining malignancies (NADM), and chronic kidney disease (CKD), defined as a confirmed (>3 months apart) estimated glomerular filtration rate (eGFR) $\leq$60 mL/min/1.73m^2(15). Persons with baseline eGFR $\leq$60 mL/min/1.73m^2, <3 eGFRs or where the first and last eGFR were less than 3 months apart were excluded from the analysis with CKD as an endpoint. Persons with a prior event were included and allowed to progress to a new, unique, non-recurrent event. For analyses of clinical events, persons were followed from baseline until the event

of interest or last visit. Models were adjusted for gender, age, VL and baseline date as fixed covariates at study baseline, and LExTO, CD4 cell count, smoking status, DM, hypertension, AIDS, CVD, NADM and CKD as time-updated covariates. CVD, NADM and CKD were excluded from the adjustment when they were the endpoint of interest.

A sensitivity analysis considered a definition of LExTO where 2-drug regimens consisting of exactly 2 anchor ARVs were not considered sufficient for LExTO. A further sensitivity analysis considered a more stringent definition of LExTO. Persons were required to have started 2 or more qualifying LExTO regimens, either simultaneously or consecutively, with the date of LExTO defined as the date of the first regimen, and/or if they had ever experienced virologic failure (VL > 1000 copies/mL in the previous 12 months), had treatment failure reported as a reason for stopping ARVs prior to LExTO, or an ARV resistance test performed after starting ART (note that the results of such tests were not available), or if they had discontinued any previous regimen due to toxicities.

All analyses were performed using SAS (Statistical Analysis Software, Cary, NC, USA), version 9.4.

Results

Of 37666 enrolled in RESPOND, 2794 had LExTO at RESPOND enrolment and were excluded, as were 9608 with <5 years ART and/or no prospective follow-up. A further 1437 were excluded with missing CD4 cell count and/or VL at baseline, or were aged <18 years, and were less likely to be older, from Southern Europe and have an earlier study baseline. A total of 23827 were included; persons with injecting drug usage as HIV acquisition risk were more likely to be excluded versus men-having-sex-with-men, as were those hepatitis C antibody positive versus negative. The incidence rate of LExTO in excluded persons was 2.64 (95% confidence interval [CI] 2.20–3.07)/100 person-years of follow-up (PYFU).

A total of 2164 persons developed LExTO (9.1%) during 130061 PYFU, a median follow-up of 5.5 years per person (IQR 2.5- 8.8) with an incidence rate of 1.66/100 PYFU (95% CI 1.59-1.73). Persons developing LExTO tended to be older, have been living with HIV for longer, have lower baseline CD4 cell counts, and a lower CD4 nadir, as shown in Table 1. Individuals were also more likely to have a baseline VL >200 copies/mL, and a higher prevalence of comorbidities, including DM, hypertension, prior CKD, CVD, AIDS and NADM. Those with LExTO had more extensive prior exposure to ARVs (Figure 1a). The median number of ARVs individuals developing LExTO had been exposed to prior to LExTO was 7 (IQR 5-9) and median time since first starting ARVs at LExTO was 13.5 years (IQR 8.7-18.0). In contrast, among those that did not develop LExTO, the median number of ARVs exposed to by last follow-up was 6 (IQR 5-8) and a median time since first starting ARVs of 12.8 years (IQR 8.6-18.7). In terms of specific ARVs, exposure to both older and newer PIs was higher in those with LExTO, while exposure to INSTIs was lower (Figure 1b; only showing ARVs used in >500 individuals).

Comparison of types of LExTO

Of the 2164 who developed LExTO, 1041 (48.1%) developed LExTO with ≥2 anchor agents plus a third ARV, 689 (31.8%) with a 2-drug regimen, 322 (14.9%) including ≥3 NRTIs and 112 (5.2%) started both a regimen including ≥2 anchor agents plus a third ARV and ≥3 NRTIs. Darunavir was used in 429/689 (62.3%) of 2-drug LExTO regimens. The use of lamivudine, emtricitabine and/or tenofovir (disoproxil or fumarate) approached 100% of all LExTO regimens except the 2-drug LExTO regimens. Dolutegravir was used in 80/112 (71.4%) of those starting a regimen including ≥2 anchor agents plus a third ARV and ≥3 NRTIs.

While overall, 343 (15.9%) became LExTO with a VL>200 copies/mL, this proportion was highest for those starting an LExTO regimen with ≥2 anchor agents plus a third ARV (190/1041; 18.3%) versus 33/322 (10.2%) starting ≥3 NRTIs (global p=0.0011). Individuals starting an LExTO regimen including ≥2 anchor agents plus a third ARV and ≥3 NRTIs had the shortest time since first starting ART (median 11 years; IQR 7-15 vs overall median 13; IQR 9-18; global p=0.0018). Figure 2 summarises the reported reason for stopping any ARV in any regimen prior to LExTO, stratified by type of LExTO regimen. Treatment failure was reported as a reason for prior discontinuation of any previous ARV in 587/2164 (27.1%) and was highest in those with a 2-drug LExTO regimen (224/689; 32.5%). ARV-related toxicities were a major reported cause of prior ARV discontinuation in those with LExTO (1189/2164; 54.9%) and more commonly reported in those with a 2-drug LExTO regimen (422/689; 61.2%).

In total, 1239 of those with LExTO started a new ARV regimen during follow-up after LExTO (57.3%), and of these, 647 (52.2%) started a new regimen that remained indicative of LExTO.

Factors associated with becoming LExTO

Factors associated with developing LExTO during prospective follow-up are shown in Figure 3. After adjustment, compared to those under follow-up in 2015-2017, those under follow-up in 2018-2021 had a significantly lower incidence of LExTO, indicating LExTO has become less common over time. Those with higher CD4 counts >500 cells/mm^3 were less likely to develop LExTO compared to those with CD4 counts 351-500 cells/mm^3, as were those with VL less than 200 copies/mL. Persons aged over 40 and those living with HIV for >15 years were more likely to develop LExTO. Compared to Central Europe, those from Southern Europe and Argentina were more likely to develop LExTO, while other regions were less likely. Experience of AIDS, CKD, and CVD were all associated with a significantly increased incidence of LExTO, as were current and past smokers, while there was no association with NADM, ESLD, DM and hypertension. Of note, there was no difference between males and females in incidence of LExTO (aIRR 0.93; 95% CI 0.83-1.04

New clinical events following development of LExTO

There were 1332 deaths during follow-up, and a crude 54% increased mortality rate among those with LExTO (IRR 1.54; 95% CI 1.30-1.85). However, after adjustment, primarily for age and CD4 cell count, no significant differences in mortality were seen (aIRR 0.87; 95% CI 0.72-1.04; Figure 4).

A similar pattern was seen for both CVD and NADM, with increased crude incidence rates of 1.50 (95% CI 1.13-1.98) and 1.28 (95% CI 1.00-1.66) respectively; however, after adjustment these were no longer significant. CKD was the exception to his finding, with a significantly increased incidence of CKD among those with LExTO after adjustment (aIRR 1.74; 95% CI 1.48-2.05).

Sensitivity Analyses

We performed two sensitivity analyses. The first excluded all LExTO regimens based on exactly 2-drug regimens and included 24133 individuals, of whom 1609 (6.7%) developed LExTO during 134908 PYFU, an incidence rate of 1.19/100 PYFU (95% CI 1.13-1.25). The results for predictors of LExTO were highly consistent with the primary analysis, except for region, where compared to Central Europe, Southern Europe and Argentina had a marginally significantly lower rate of LExTO (aIRR 0.85; 95% CI 0.71-1.01). The second sensitivity analysis used a more stringent definition of LExTO, as defined in the methods. In this analysis, 1713 developed LExTO during 131524 PYFU, incidence rate 1.30/100 PYFU (95% CI 1.24-1.36). Of note, of those with LExTO, 668 (39.0%) were defined as LExTO with 2 qualifying regimens and 774 (54.3%) had prior treatment failure. Results for predictors of LExTO were again highly consistent (Supplementary Figure 1, http://links.lww.com/QAD/D79), except that females had a significantly lower incidence of LExTO compared to men (aIRR 0.87; 95% CI 0.76-0.99).

Results from these two sensitivity analyses were also highly consistent when analysing clinical events following LExTO (data not shown).

Discussion

This study included data from >23000 individuals contributing over 130000 PYFU, and shows the incidence and predictors of LExTO in a real-world, heterogeneous cohort, as well as clinical outcomes following LExTO. The incidence rate of LExTO decreased over time with a prevalence of LExTO of just over 9%; estimates from other studies vary widely, depending on the definition alone, but the prevalence we found is consistent with studies relying on ARV history (8, 11). The population with LExTO is difficult to identify accurately, but nonetheless, an important group to understand regardless of whether the limited treatment options are based upon resistance, comorbidities or polypharmacy, in order to better tailor clinical management to fit individual needs. Continued development of new ARVs targeted at this group will remain a key component of management(6).

In this study, individuals with LExTO had extensive ARV experience with exposure to a median of 7 ARVs prior to LExTO, and a median time since first starting ARVs of 13.5 years. The reasons for stopping any prior ARV before LExTO varied. Treatment failure was reported as a reason for prior discontinuation of any previous ARV in approximately one-quarter of individuals and was highest in those with a 2-drug LExTO regimen. ARV-related toxicities and patient/physician choice were common reasons for prior ARV discontinuation for all with h LExTO and particularly for those with a 2-drug LExTO regimen. This could suggest a move to a simpler regimen and/or wanting to reduce potential ongoing risks associated with use of some ARVs in an aging population(16, 17).

We found a number of factors associated with LExTO. Southern Europe/Argentina had the highest incidence rate of LExTO, significantly higher than in Central Europe. However, in the sensitivity analysis where we excluded those on exactly 2-drug LExTO regimens, we found no differences between regions. This suggests our findings were driven by a higher use of 2-drug regimens in Southern Europe compared to other regions, reflecting that many of the early strategy studies for 2-drug regimens were from Southern Europe(18, 19). As expected, individuals with ongoing comorbidities, including CVD and CKD also had higher rates of LExTO. This is consistent with other pharmacoepidemiology studies which have shown an association between use of certain individual ARVs and selected comorbidities(20, 21), leading to changes in management and switching away from some ARVs such as tenofovir disoproxil fumarate in those with renal risks(22, 23) and abacavir in those with cardiovascular risks. Persons with detectable viremia and low CD4 cell counts had higher rates of LExTO, consistent with other studies using alternative definitions(4). Persons with detectable viremia and/or lower CD4 cell count reflect those who were failing previous regimens, with the greatest chance of drug resistance(24). Of particular interest, we observed a decrease in LExTO in later calendar years, confirming an earlier study(4). There are several possible explanations for this finding, notably the introduction of second generation INSTIs with a high barrier for resistance development and lower rates of treatment failure(25-29). These lower recent rates of LExTO in an aging population with an increasing prevalence of comorbidities and extensive ART history is a positive finding and potentially reflects more individualised clinical management with increased awareness of potential ART-related toxicities, comorbidities, and drug-drug interactions.

While previous research has suggested higher rates of clinical events following triple class failure and more extensive treatment(11, 24, 30), apart from CKD, we found similar rates of clinical outcomes in those with and without LExTO after adjustment for relevant confounders, most notably age and CD4 cell count. One possible rationale for the higher rates of CKD in those with LExTO could be extensive exposure to tenofovir disoproxil fumarate and several older ritonavir-boosted PIs, given the association with CKD (31). The number of effective ARVs has expanded in recent years, with ibalizumab, fostemsavir and lenacapavir available to those with limited treatment options; there were no individuals from RESPOND who had started these ARVs. Nonetheless, those with LExTO now have a wider range of options including more potent salvage regimens, ARVs from entirely new classes being introduced, regimens constructed based on knowledge of HIV resistance and use of ARVs with fewer severe adverse events and less potential for drug-drug interactions(32-35). These factors may all potentially reduce the incidence of serious clinical events following LExTO to the level seen in our analysis. Crude mortality rates from studies which have considered clinical outcomes are 1.5-2-fold higher in those with HTE(9-11), consistent with our unadjusted analysis of LExTO, although adjusted rates were not presented in these studies(9, 11).

There are a number of limitations to this research. Of note, while for some cohorts we knew resistance testing had been done for some individuals, we did not have the results of those resistance tests. We have used a comprehensive definition of LExTO, and those excluded had a higher ncidence of LExTO, suggesting we could have underestimated the prevalence, as could the exclusion of dolutegravir/rilpivirine as a regimen indicative of LExTO in ART-experienced individuals. RESPOND is predominantly a cohort of white males and of cohorts from developed countries. Both factors limit the generalisability of our findings; particularly for individuals with LExTO from

regions with more limited resources where more expensive, newer ARVs may not be available. definition encompasses a wider group of individuals where clinicians face a potential challenge of constructing an ARV regimen due to previous toxicities, virological failure or where many ARVs have already been used. This limitation is also one of key advantages of this analysis, as we identify individuals who may be in need of new regimens as they are developed, as well as personalised clinical management. We assumed that LExTO was not reversible, and a sensitivity analysis showed that over half started a new ART regimen after LExTO, and of these, approximately one half started a new regimen which remained indicative of LExTO. This suggests for some individuals it became possible to construct a subsequent regimen not indicative of LExTO likely reflecting a more contemporary ART era, such as second generation INSTIs, with broad availability of ARVs with high genetic barrier for resistance, fewer drug-interactions and less treatment-limiting toxicities. We used several sensitivity analyses to define LExTO more conservatively with consistent results.

To conclude, the prevalence of LExTO in a contemporarily treated and heterogenous population of people with HIV in Europe and Australia was 9% using a fairly broad definition. Despite dealing with an ageing and increasingly comorbid population we found evidence of declining LExTO rates by 2018-2021 suggesting effective recent developments in contemporary ART options and clinical management. LExTO was associated with longer duration of HIV infection, older age, low CD4 cell count, ongoing viremia and comorbidities such as CVD and CKD, but not with gender. After adjustment for age and CD4, it was reassuring to note that LExTO was not associated with a significantly increased incidence of serious clinical events apart from CKD. Continued long-term follow-up with monitoring of the prevalence and outcomes of LExTO remains important to identify trends going forwards as the population with HIV continues to age and new ARVs are developed.

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Figure 1 a. ARVs exposed to before LExTO / last follow-up.

ARV, antiretroviral; N, number; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase inhibitor. b. Specific ARVs used before LExTO / last follow-up. ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase inhibitor; 3TC, lamivudine; ABC, abacavir; D4T, stavudine; DDC, zalcitabine; DDI, didanosine; FTC, emtricitabine; TAF, tenofovir alafenamide, TDF, tenofovir disoproxil fumarate; ZDV, zidovudine; EFV, efavirenz; ETR, etravirine; NVP, nevirapine; RPV, rilpavirine; APV, amprenavir; ATV, atazanavir; DRV, darunavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; SQV, saquinavir; BIC, bictegravir; DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir.

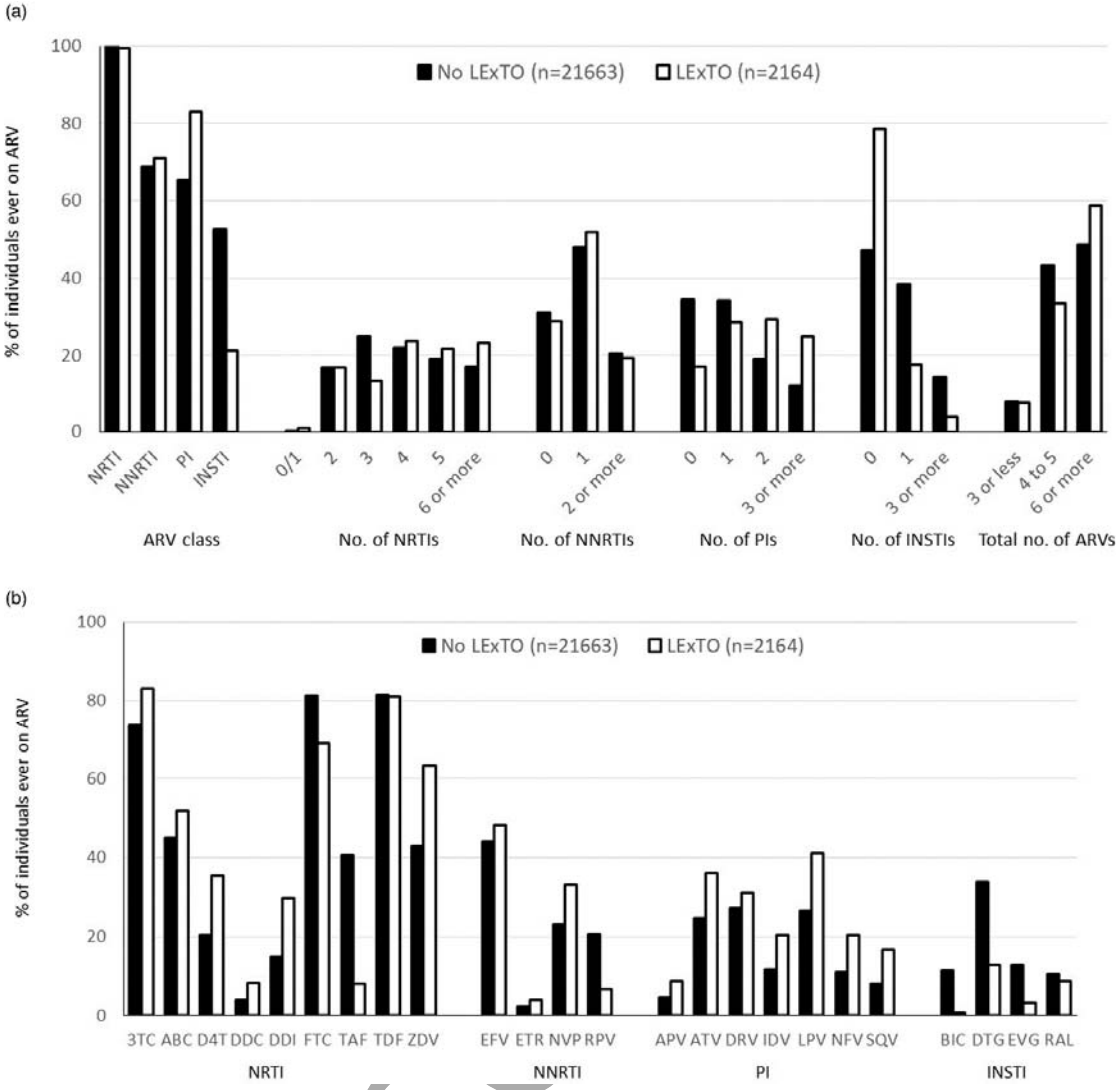

Figure 2 Reported reasons for discontinuation of any ARV before LExTO. ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor.

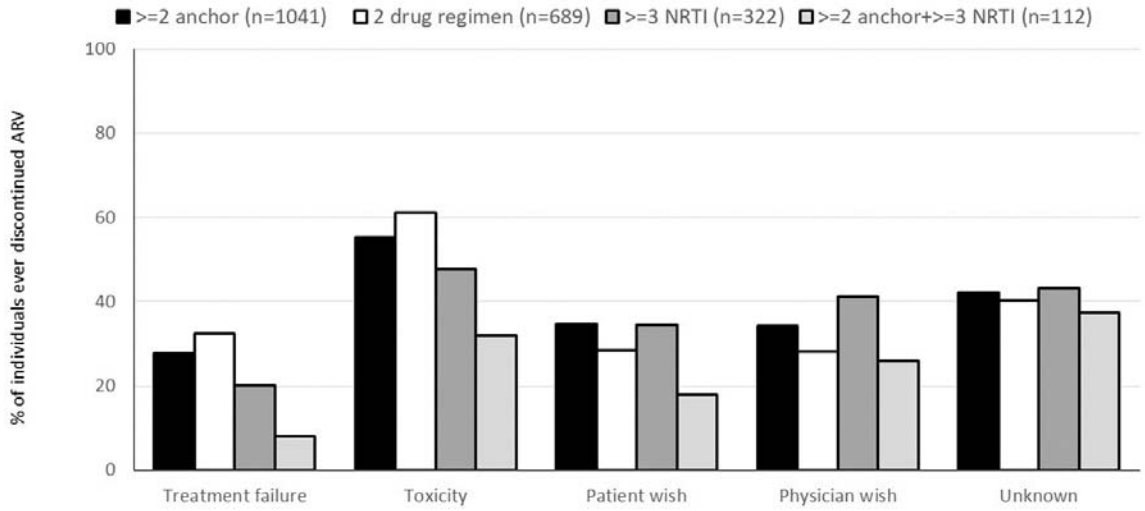

Figure 3 Predictors of LExTO: Adjusted incidence rate ratios (95% CI). *Included as time-updated. Additionally adjusted for (all ns) HIV risk, ethnicity, HBV, HCV status, gender, CD4 nadir (fixed at baseline), and BMI, HTN, DM, NADM, ESLD (time-updated)

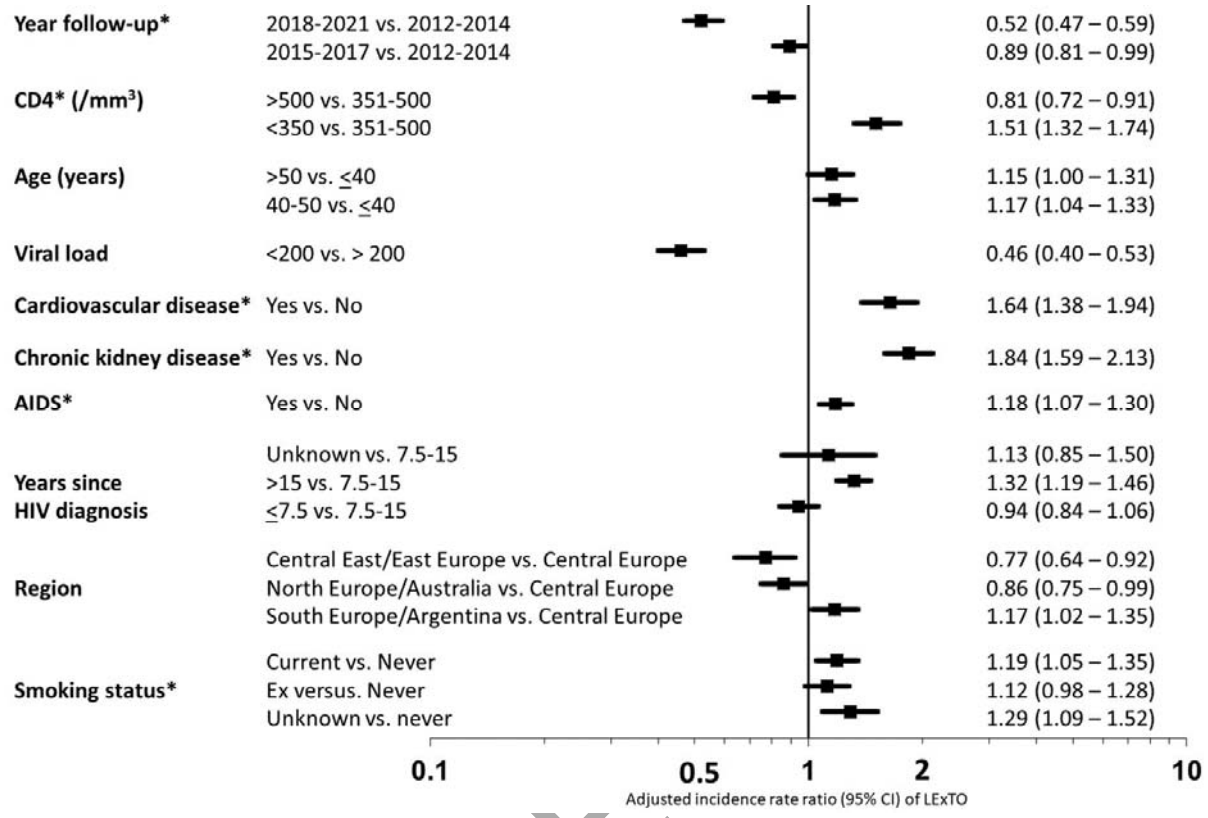

Figure 4 Adjusted incidence rate ratio (95% CI) of clinical events following LExTO Adjusted for sex, age, CD4 nadir, region, HIV VL, ethnicity, HBV/HCV status, years HIV+, smoking*, BMI*, DM*, hypertension*, CKD*, AIDS*[1], NADM*[1], CVD*[1], ESLD*[1], CD4*, calendar year of follow-up*. *time-updated. [1]Variable not adjusted for when variable is the endpoint.

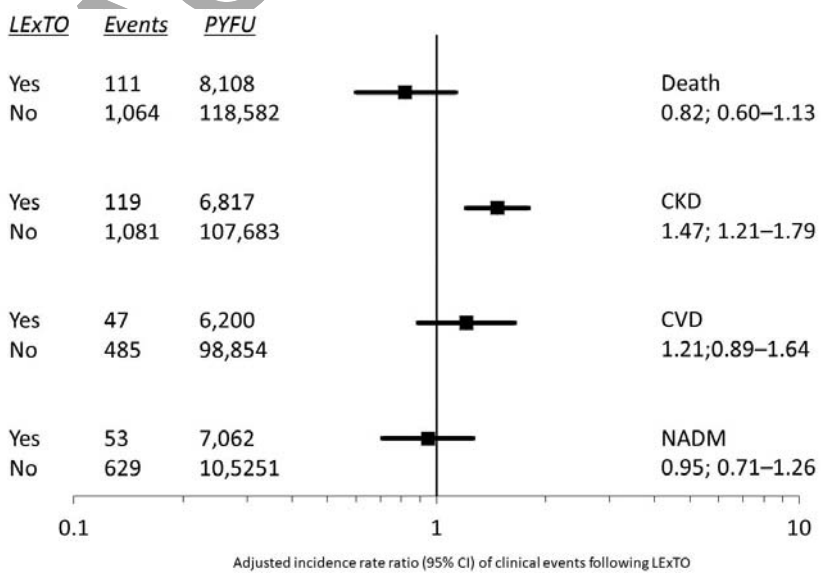

Table 1 Baseline characteristics of persons with and without LExTO

		All		No LExTO		LExTO		P
		N	%	N	%	N	%	
All		23827	100.0	21663	90.9	2164	9.1	
Gender	Male	17609	73.9	16017	73.9	1592	73.6	0.70
	Female	6218	26.1	5646	26.1	572	26.4	
Region(1)	South Europe/Argentina	4710	19.8	4299	19.8	411	19.0	<0.0001
	Central Europe	10691	44.9	9693	44.7	998	46.1	
	North Europe/Australia	5790	24.3	5215	24.1	575	26.6	
	East/Central East Europe	2636	11.1	2456	11.3	180	8.3	
HIV risk	Men having sex with men	10639	44.7	9749	45.0	890	41.1	0.010
	Intravenous drug users	3167	13.3	2823	13.0	344	15.9	
	Heterosexual	8606	36.1	7809	36.0	797	36.8	
	Other	1415	5.9	1282	5.9	133	6.1	
Ethnicity	White	16636	69.8	15096	69.7	1540	71.2	0.61
	Other	3925	16.5	3579	16.5	346	16.0	
	Unknown	3266	13.7	2988	13.8	278	12.8	
Years since HIV diagnosis	≤7.5	8807	37.0	8324	38.4	483	22.3	<0.0001
	7.5-15	8456	35.5	7684	35.5	772	35.7	
	>15	6040	25.3	5182	23.9	858	39.6	
	unknown	524	2.2	473	2.2	51	2.4	
Smoking Status	Never	6652	27.9	6148	28.4	504	23.3	<0.0001
	Current	8068	33.9	7340	33.9	728	33.6	
	Past	3715	15.6	3340	15.4	375	17.3	
	Unknown	5392	22.6	4835	22.3	557	25.7	
Diabetes		1255	5.3	1097	5.1	158	7.3	<0.0001
Hypertension[1]		8250	34.6	7382	34.1	868	40.1	<0.0001
CKD[2]		700	2.9	578	2.7	122	5.6	<0.0001
AIDS		4679	19.6	4054	18.7	625	28.9	<0.0001
NADM[3]		735	3.1	640	3.0	95	4.4	<0.0001
ESLD[4]		170	0.7	150	0.7	20	0.9	<0.0001
CVD[5]		611	2.6	506	2.3	105	4.9	<0.0001
HIV viral load	>200/limit of detection	1256	5.3	1026	4.7	230	10.6	<0.0001
	≤200/limit of detection	22571	94.7	20637	95.3	1934	89.4	
		Median	IQR	Median	IQR	Median	IQR	P
Age	Years	46	39-53	46	39-52	48	42-54	<0.0001
CD4	cells/mm^3	614	449-813	618	452-817	572	400-761	<0.0001
Nadir CD4	cells/mm^3	230	119-348	236	123-355	185	80-286	<0.0001
Baseline date	Month/year	Nov12	Jan12-Aug16	Mar13	Jan12-Nov16	Jan12	Jan12-Sep13	<0.0001

Unknown for [1]2722, [2]819, [3]1399, [4]1230, [5]4084 persons. CKD; chronic kidney disease. NADM; non-AIDS defining malignancy. ESLD; end-stage liver disease. CVD; cardiovascular disease. IQR; interquartile range.