LATE PRESENTATION FOR HIV IMPAIRS IMMUNOLOGICAL BUT NOT VIROLOGICAL RESPONSE TO ANTIRETROVIRAL TREATMENT

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Abstract

Objectives:

To study the impact of late presentation (CD4 <350 cells/µL or an AIDS-defining event) on effectiveness and safety of initial ART and to evaluate whether treatment response depends on first-line ART regimen in late presenters (LP).

Design:

ART-naïve adults from the Cohort of the Spanish HIV/AIDS Research Network (CoRIS) starting triple ART between 2010 and 2018.

Methods:

We used multivariable models to assess differences in viral suppression (VS, viral load <50 copies/mL), immunological response (IR, change in CD4 count, CD4% (>29%) and CD4/CD8 normalization (>0.4 and >1) multiple T-cell marker recovery (MTMR): CD4+ >500 cells/µL plus CD4% >29% plus CD4/CD8 >1), and treatment discontinuation due to adverse events (TDAE) at 48 weeks from ART initiation.

Results:

Of 8,002 participants, 48.7% were LP. Of them 45.8% initiated ART with a NNRTI- (mostly TDF/FTC/EFV), 33.9% with a PI- (mostly TDF/FTC+boosted DRV) and 20.3% with an INI-based regimen (mostly ABC/3TC/DTG). At 48 weeks, LP had similar VS, but worse IR, than non-LP

with no difference on TDAE. LP initiating with NNRTI- based regimens were more likely to achieve VS than those starting with INI-based, due to the higher chance of achieving VS observed with TDF/FTC/RPV compared to ABC/3TC/DTG. Initial treatment with NNRTI- or PI-based showed similar IR than the INI-based regimens, which showed lower rates of TDAE than NNRTI- and PI-based regimens.

Conclusions

Despite safety and effectiveness of initial ART in terms of VS, LP may not experience complete IR. In LP, effectiveness and safety depends on both the class and the specific first-line ART regimen.

Key Words: Late presentation; clinical outcomes; AIDS events; serious non-AIDS events; mortality.

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Introduction

In 2011 a consensus definition was reached in the "HIV in Europe study group" to define late presenters (LP) as persons presenting for care either with a CD4 count <350 cells/μL or an AIDS defining event [1]. In Europe, prevalence of late presentation ranges from 47% to 57% [2,3] and in Spain is around 47%.[4,5].

Late presentation is associated with increased morbidity and mortality [2,6,7], as well as increased resource burden [8–11] and high risk of HIV transmission. [12,13]. Thus, late presentation may represent an important barrier in achieving the UNAIDS goals to end the AIDS epidemic by 2030. Individuals presenting late for care initiate treatment with low CD4 count, that may lead to an impaired virological response [14,15] and an increased risk of treatment failure [16]. Besides, immunosuppressed individuals at diagnosis may take longer to achieve CD4 count normalization (García et al., 2004) or not experience a complete immune restoration, even despite sustained virological response [17,18]. Most of the published studies consider effectiveness and safety of initial ART treatment in relation to initial CD4 count and only few of them compare response in late and non-late presenters (non-LP) according to the consensus definition that also includes presence of AIDS events.

Regimens based on integrase inhibitor (INI) are recommended as the preferred first-line ART [19–21] because they have shown both faster viral load decline and CD4 count recovery compared to protease inhibitor (PI)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens [22–26]. Despite the high prevalence of late presentation,

very little information exists on which ART regimen should be used first LP. In fact, individuals with an advanced HIV disease and mainly those with opportunistic infections are usually excluded from randomized clinical trials and no specific guidelines exist on how to treat them [27]. Therefore, it is important to characterise both effectiveness and safety of specific initial regimens among LP.

We aimed to study the impact of late presentation on the effectiveness and safety of initial ART, and to evaluate whether, among LP, treatment response depends on first-line ART regimens.

Methods

Study design

CoRIS is an open, prospective, multicentre cohort of subjects with confirmed HIV infection, naïve to ART at study entry. Participants are recruited in 46 centres from 13 of the 17 autonomous regions in Spain from 2004-onwards. Administrative censoring date for these analyses was 30 November 2018. A complete description of CoRIS has been published elsewhere [28]. Subjects agree to participate in the study by signing an informed consent form. Ethical approval for CoRIS was granted. Briefly, CoRIS collects a minimum dataset that includes baseline and follow-up socio-demographic, immunological and clinical data including ART medication. Data are highly standardized and are submitted for periodic quality control

procedures. Participants are followed periodically in accordance with routine clinical practice.

Study population

We included CoRIS participants, aged ≥18 years at enrolment, with available information on late presentation, who received triple therapy (2NRTI+1INI, 2NRTI+1NNRTI or 2NRTI+1PI) as first-line regimen from 1 January 2004 to 30 November 2018, and who had CD4 count and viral load measurements available during both 24 weeks before and 48 weeks after ART initiation.

Definition of late presentation

LP were participants with CD4 count below 350 cells/µL between 4 weeks before and 24 weeks after enrolment and/or with an AIDS-defining event occurred before the 24 weeks after enrolment, both conditions met before ART initiation.

Outcomes

Primary endpoint was ART effectiveness, evaluated through viral suppression (VS) and immunological response at 48 weeks (±24) from ART initiation. VS was defined as achieving a viral load <50 copies/mL, and immunological response was based on different markers: change in CD4 count, CD4% normalization at a cut-off of 29%, CD4+/CD8+ cell ratio

(CD4/CD8) normalization at cut-off of 0.4 and 1, and achievement of multiple T-cell marker recovery (MTMR: CD4 >500 cells/μL plus CD4% >29% plus CD4/CD8 >1).

Safety outcomes included incidence and proportion of participants who discontinued treatment due to adverse events (AE) during the first 48 weeks after ART initiation. We classified AE as neuropsychiatric (headache, dizziness, fatigue, insomnia, sleep disturbance, anxiety/depression, emotional instability), renal, gastrointestinal (nauseas/vomiting, diarrhoea, abdominal pain), skin, liver, other or unknown.

We performed an intention-to-treat analysis: all outcomes were analysed by initial regimen and later changes in the regimen were ignored; therefore, once a participant started a regimen, he/she was assumed to remain on it.

Statistical methods

Variables were summarized as medians and interquartile ranges (IQR) when continuous, and as percentages when categorical. We first assessed the impact of late presentation on treatment effectiveness and safety and, secondly, we focused on LP to assess differences on treatment response according to the first-line ART regimen. For these latter analyses, we used two different approaches: (i) we classified first-line ART regimens as INI-, PI- and NNRTI-based regimens, and (ii) we restricted the analyses to the most frequently prescribed first-line ART among this population: TDF/FTC/EFV, TDF/FTC+boosted DRV, TDF/FTC+LPV/r, ABC/3TC/DTG, TDF/FTC+RAL, TDF/FTC/RPV, TDF/FTC/EVG/COBI and TAF/FTC/EVG/COBI.

We used linear regression to assess differences in mean changes in CD4 count, logistic regression for VS and all other immunological markers, and Poisson regression to assess differences in the incidence of treatment discontinuation due to AE.

All multivariable models were adjusted for a combined variable of gender and HIV transmission category (men having sex with men [MSM]), injection drug users [IDU], heterosexual women, heterosexual men, other/unknown), educational level (none or primary education only, secondary education, university, other/unknown), region of origin (Europe, Sub-Saharan Africa, Latin America, other/unknown), age at starting ART (<30, 30-49, ≥50 years), presence of HCV antibodies (no, yes, unknown), presence of HBV surface antigen (no, yes, unknown) and viral load (<10,000, 10,000-100,000, ≥100,000 copies/mL, unknown) during 24 weeks before ART initiation, and year of ART initiation (2004-2008, 2009-2012, 2013-2018). For analyses on comparison between LP and non-LP, we additionally adjusted for initial ART regimen categorized as INI-, PI- and NNRTI-based. Furthermore, as CD4 count at ART initiation is known to be a predictor of immunological response and is low in LP, we further adjusted for CD4 count during 24 weeks before ART initiation (<200, 200-499, ≥500 cells/μL) to compare LP and non-LP with the same CD4 count at start of ART. Analyses focused on LP were additionally adjusted for CD4 count during 24 weeks before ART initiation with a different categorization (<24, 25-49, 50-99, 100-199, 200-349, ≥350 cells/μL).

We used robust standard errors to account for clustering of participants within centres and estimated p-values using Wald test.

All statistical analyses were performed using R version 4.0 [29].

Sensitivity analysis

We evaluated the impact of late presentation on treatment effectiveness and safety considering LP as participants with a CD4 count <350/µL and/or an AIDS-defining event considering 12 instead of 24 weeks after enrolment.

Results

During the study period 11,991 adults with information on late presentation at enrolment started treatment with a triple regimen. Of them, 1,239 were excluded because they had no information on CD4 count at starting ART or on CD4 count or viral load 48 weeks after ART initiation. Finally, 8,002 participants were included in the analyses, of whom 3,900 (48.7%) were LP. A 75.7% participants were from Europe, mostly from Spain (59.9%). The most frequent transmission route was MSM (61.4%) followed by male (15.5%) and female heterosexual contact (13.7%). At treatment initiation, median age was 37 years (interquartile range [IQR]: 31; 44), median CD4 count was 308 cells/µL (IQR: 180.0, 452.0) , and 40.1% had a viral load >100,000 copies/mL.

LP were more likely than non-LP to have acquired HIV infection through heterosexual contact or IDU, to be from Sub-Saharan Africa or Latin America, and to have started ART at an older age and with a higher viral load (Table 1). LP received more likely PI-based regimens as initial treatment (33.9%) than non-LP (20.2%). A complete description of first-line ART regimens in LP and non-LP is shown in Table S1.

Impact of late presentation on effectiveness and safety of initial ART

At 48 weeks from ART initiation, 83.4% LP and 89.4% non-LP achieved VS. Although in the univariable model late presentation was associated with a lower chance to achieve VS (unadjusted OR: 0.59, 95%CI 0.50, 0.70), this result was not confirmed in the multivariable analysis (adjusted OR: 0.90, 95% CI 0.73, 1.11). The CD4 count increased on average 219.0 cells/µL in LP and 245.9 cells/µL in non-LP. Estimates from the multivariable analysis suggested that late presentation was associated with a lower mean increase in CD4 count (adjusted mean difference: -20.8, 95% CI -30.6, -11.3 cells/µL) than non-late presentation. We further observed lower chance of LP to achieve CD4% normalization (adjusted OR: 0.22, 95% CI 0.19, 0.24), CD4/CD8 normalization for both the cut-offs of 0.4 (adjusted OR: 0.17, 95% CI 0.14, 0.21) and 1 (adjusted OR: 0.26, 95% CI 0.22, 0.30) and the MTMR (adjusted OR: 0.18, 95% CI 0.14, 0.24) with respect to non-LP (Figure 1).

During the first 48 weeks after ART initiation, the proportion of treatment discontinuations due to AE was similar and around 9% in both LP and non-LP, as confirmed in the multivariable analysis (adjusted RR: 0.91, 95% CI 0.78, 1.07, Table 2).

Additional adjustment for CD4 count during 24 weeks before ART initiation supported the results although the magnitude of the association between late presentation and immune response was slightly decreased.

Impact of first-line regimen on effectiveness and safety of treatment among late presenters

At 48 weeks from starting ART, LP initiating with a NNRTI-based regimen appeared to have a 36% higher odds of achieving VS, than those initiating with an INI-based regimen (adjusted OR: 1.36, 95%CI 1.00, 1.85) while no differences were observed between LP initiating with a PI- or an INI-based regimen (OR: 1.03, 95%CI 0.75, 1.43) (Figure 2). Analyses restricting to the most frequently prescribed initial regimens (N=2574) showed that, compared to LP starting with ABC/3TC/DTG, those initially treated with TDF/FTC/RPV were more likely to achieve VS at 48 weeks from starting treatment, even after adjustment for viral load at ART initiation (Table S2). Initial treatment with NNRTI- or PI-based regimens showed similar immunological response as the INI-based regimens, not only in terms of increase of CD4 count but also in CD4% and CD4/CD8 normalization and achievement of MTMR.

When we restricted the analyses to the most frequently prescribed initial regimens, we found that, compared to ABC/3TC/DTG, initial treatment with TDF/FTC+boosted DRV, TDF/FTC/EVG/COBI or TAF/FTC/EVG/COBI were associated with lower chances to achieve the CD4/CD8>0.4.

During the first 48 weeks after ART initiation, the proportion of treatment discontinuation due to AE was higher among participants starting with either NNRTI-based (10.8%) or PI-based regimens (11.4%) than in those starting with INI-based regimens (5.6%).

The description of the most frequent reasons for discontinuation due to AE by initial regimen are reported in Table 3. The multivariable analysis confirmed that the rate of treatment discontinuation due to AEs was higher in participants initiating with NNRTI- (adjusted RR: 1.63, 95%CI: 1.12, 2.36) and PI-based regimens (adjusted RR: 1.77, 95%CI: 1.22, 2.59) than in those starting with INI-based regimens (Table 3). When we considered only the most frequently prescribed initial regimens, we observed higher discontinuation rates due to AE in LP treated with TDF/FTC/EFV, TDF/FTC+boosted, TDF/FTC+LPV/r or TDF/FTC/EVG/COBI compared to those starting with ABC/3TC/DTG (Table S3).

Sensitivity analysis

When LP were defined as having a CD4 < 350/μL and/or an AIDS-defining event within the 12 weeks after enrolment, we observed that the impact of late presentation on both treatment effectiveness and safety was similar to the one observed when a 24-weeks interval was used to define LP (Tables S4 and S5).

Discussion

We observed that LP had similar virological but worse immunological response than non-LP at 48 weeks from ART initiation and that impaired immune recovery in LP was con-

sistent across all the immune markers considered. These findings were confirmed after additionally controlling for CD4 count at ART initiation. We further observed that late presentation was unrelated with treatment safety. These results underline that ART therapy effectively reduces viral load but may not restore the immune system in participants presenting for late for care.

Focusing on LP, we observed that initial treatment with an NNRTI-based regimen appeared to have a higher odd of achieving VS than an INI-based regimen, though the estimate need further confirmation as the confidence interval include 1. These differences were mainly due to the higher chance of VS observed in TDF/FTC/RPV compared to ABC/3TC/DTG.

Initial treatment with NNRTI- or PI-based regimens showed similar immunological response as the INI-based regimens, not only in terms of CD4 count increase but also in CD4% and CD4/CD8 normalization and achievement of MTMR. These results agree with what observed comparing the initial treatment with ABC/3TC/DTG with the other specific regimens, with the exception of CD4/CD8 normalization at a cut-off of 0.4. Finally, in LP, INI-based regimens were safer than NNRTI- and PI-based regimens and ABC/3TC/DTG showed lower discontinuation rates due to AE with respect to TDF/FTC/EFV, TDF/FTC+boosted DRV, TDF/FTC+LPV/r and TDF/FTC/EVG/COBI.

To the best of our knowledge, this is the first study focused on the impact of late presentation on effectiveness and safety of initial ART according to the consensus definition

of LP and it is one of the few studies investigating effectiveness and safety of the initial treatment specifically in LP.

In our study more than 80% of the participants achieved VS after 48 weeks of treatment initiation regardless of late presentation status. This result is in line with findings from other studies on the effectiveness of ART therapy independently of the initial CD4 count [30,31]. Conversely, JA Pérez-Molina et al. [15], in a meta-analysis of randomized clinical trials found that ART initiation with very low CD4 count (≤50 CD4 cells/μL or ≤200 CD4 cells/μL) was consistent associated with poorer virological response. Further D'Almeida et al. [14] showed that both LP and late starters had lower chance to achieve sustained virological response than the ideal starters (CD4 count >350 cells/μL at starting ART). We observed worse immune response in LP than in non-LP that was consistent across several markers of immune restoration. We found that LP had slightly lower mean CD4 count increase than non-LP. Multiple studies indicate that highly immunosuppressed participants at diagnosis have poorer immune recovery in terms of CD4 count recuperation, despite even effective ART. This occurs both in the short term [30,32–34], consistent with our results, as well as in the long term [17]. The lack of immune restoration during the first year of treatment agrees with data from CoRIS that showed the highest impact of late presentation on mortality during the first year after diagnosis. [35,36]. Taken together these findings suggest that ART therapy may be not effective enough to reduce the excess morbidity and mortality related with late presentation, at least not during the first-year post-diagnosis. Patients' clinical course is determined by the complex interplay between their immune and

inflammatory status, even despite CD4 restoration: for this reason we considered other markers of immune recovery, such as the CD4/CD8 and the CD4% normalization and the MTMR. Although both markers of immunity, variation of CD4 and CD4/CD8 are not necessarily correlated and may provide different information on immune restoration [37,38]. CD4/CD8 is candidate prognostic marker for comorbidities and mortality: low CD4/CD8 ratio is associated with higher risk of non-AIDS-related morbi-mortality despite long-term VS [39–41]. Albeit in the long term CD4 count may reach levels of HIV-negative individuals, the CD4/CD8 ratio may not because of persisting high CD8 count [42]. We further observed a negative impact of late presentation also on the CD4% normalization and the MTMR. Only around 5% of LP compared to 25% of non-LP achieved immune response according to the MTMR, which can be viewed as a broad indicator of immune restoration [43,44]. For all the markers considered, we observed that adjustment for CD4 count at starting ART decreased the impact of late presentation on the chance to achieve immune restoration. Since higher initial CD4 count is associated with better immune response, the adjustment for CD4 count accounts for its impact downplaying the effect of late presentation.

In our study we observed that late presentation is not related with treatment discontinuation due to AE. Similarly, two studies observed an association between late ART initiation and treatment discontinuation due to virological failure but not to AE [45,46]. Conversely, other studies showed decreased ART durability due to any reason in LP older than 50 years [47] and in individuals with CD4 count<200 cells/μL [48]

In the whole period (2004-2018), LP were more likely prescribed NNRTI-based regimens as initial ART, followed by PI-based and INI-based regimens. Non-LP were more frequently treated with NNRTI -based, followed by INI-based and PI-based regimens. LP initially treated with an NNRTI-based regimen appeared to have a better virological response than those initially treated with INI-based regimens, though the estimate needs further confirmation as the confidence interval include 1, but similar immunological response was found among INI, NNRTI- and PI-based regimens. Previous findings from both clinical trials [23,49–53] and observational studies [54–56] showed that specific initial INI-based were more effective than other PI- or NRTI-based regimens, although, to the best of our knowledge, no study has been performed considering INI-based regimen as a whole. We further observed that LP who started INI-based regimens experienced lower treatment discontinuation due to AE than those starting with NNRTI- and PI-based regimens.

Little evidence exists on effectiveness and safety of specific ART regimens in LP. A systematic review of phase 3/4 randomized clinical trials found that the odds of achieving VS with dolutegravir was superior to other core agents [57]. We observed similar or worse effectiveness of specific treatment when compared to ABC/3TC/DTG, with the exception of TDF/FTC/RPV which showed better virological effectiveness, similarly to what observed in CoRIS by Alejos et al. [26]. TDF/FTC/RPV is indicated only in patients with basal viral load below 100,000 copies/mL but its association with a better virological effectiveness with respect to ABC/3TC/DTG was confirmed in the multivariate models adjusted also for baseline viral load. This result may be related with better tolerance and durability of this regimen, as

supported by the low number of AE observed, but it may also be due to a prescription bias as this low genetic barrier ART-regimen was prescribed to LP with more favourable clinical outcomes than others.

Our findings must be interpreted with caution. It is possible that we are misclassifying LP including patients with recent infection characterized by low and transient CD4 count [58]. Our results might be affected by selection bias because we excluded individuals that did not survive long enough to have CD4 count measurements after 48 weeks of treatment [59]. We further could not classify as LP or non-LP those who did not have CD4 count or AIDS events available before starting treatment, although this proportion account only for the 3% of the CoRIS participants. Only half participants had available data to estimate the MTMR: this percentage was lower in LP vs. non-LP and was not homogeneous across ART treatments. In CoRIS the availability of CD8 count has improved over the past few years and coincided with an increased prescription of INI-based as first-line regimen, and this fact may lead to spurious results. Other factors potentially associated with the outcomes of interest, such as adherence to treatment or presence of an acute infection, are not collected in Co-RIS. To overcome this potential bias, we adjusted for patients' characteristics such as age or region of origin, educational level and mode of transmission that have been associated with treatment adherence [60].

The main strength of our study lies in being based on CoRIS, a large national cohort representative of the epidemiological situation of HIV-infected individuals in Spain. We can

count on detailed information on immunological recovery and complete information on treatment initiation and modification.

We focused only on treatment response and safety at 48 weeks after initial treatment. Results on the longer term, e.g. in 96 weeks, are warranted to confirm previous findings on effective immune recovery on the long term. Besides we did not distinguish LP from those with advanced HIV disease (initial CD4 count <200 cells/μL): further studies may highlight specificities in this subgroup.

Taken together, our findings demonstrate that, although ART treatment is successful in terms of VS and it is safe in terms of treatment discontinuation due to AE, LP may not experience complete immune restoration, at least during the first year of treatment, with possible consequences in terms of clinical progression and mortality. Our results further show that in LP effectiveness and safety depend on the class as well as the specific first-line ART regimen.

This study underlines the importance to improve diagnosis of HIV at an earlier stage of disease progression and to start treatment with specific drug regimens and at higher CD4 count to enable a complete immune recovery.

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TABLES

Table 1 Sociodemographic and clinical characteristics at ART initiation according to late presentation

	Non-late present-ers N=4102 (51.3%)	**Late presenters N= 3900 (48.7%)**	**Total N=8002**
Age (year)			
Median (1st, 3rd quartile)	35.7 (29.8, 42.7)	38.5 (31.7, 46.0)	36.9 (30.6, 44.3)
<30	908 (22.1%)	633 (16.2%)	1541 (19.3%)
30-49	2745 (66.9%)	2557 (65.6%)	5302 (66.3%)
≥50	449 (10.9%)	710 (18.2%)	1159 (14.5%)
Transmission group (n (%))			
MSM	2915 (71.1%)	2000 (51.3%)	4915 (61.4%)
IDU	166 (4.0%)	329 (8.4%)	495 (6.2%)
Heterosexual women	472 (11.5%)	628 (16.1%)	1100 (13.7%)
Heterosexual men	459 (11.2%)	778 (19.9%)	1237 (15.5%)
Other/unknown	90 (2.2%)	165 (4.2%)	255 (3.2%)
Educational level (n (%))			
None or primary education only	383 (9.3%)	653 (16.7%)	1036 (12.9%)

	Non-late present-ers N=4102 (51.3%)	**Late presenters N= 3900 (48.7%)**	**Total N=8002**
Secondary education	1915 (46.7%)	1769 (45.4%)	3684 (46.0%)
University	1234 (30.1%)	814 (20.9%)	2048 (25.6%)
Other/unknown	570 (13.9%)	664 (17.0%)	1234 (15.4%)
Region of origin (n (%))			
Europe	3245 (79.1%)	2809 (72.0%)	6054 (75.7%)
Sub-Saharan Africa	104 (2.5%)	206 (5.3%)	310 (3.9%)
Latin America	683 (16.7%)	798 (20.5%)	1481 (18.5%)
Other/unknown	70 (1.7%)	87 (2.2%)	157 (2.0%)
Aids diagnosis	46 (1.1%)	972 (24.9%)	1018 (12.7%)
CD4 count, cells/µL			
Median (1^{st}; 3^{rd} quartile)	440.0 (348.0, 575.8)	186.0 (76.0, 270.0)	308.0 (180.0, 452.0)
<200	146 (3.6%)	2118 (54.3%)	2264 (28.3%)
200-499	2453 (59.8%)	1727 (44.3%)	4180 (52.2%)
≥500	1503 (36.6%)	55 (1.4%)	1558 (19.5%)
CD4/CD8			
<0.4	1251 (41.7%)	2206 (81.9%)	3457 (60.7%)
0.4-1	1567 (52.2%)	453 (16.8%)	2020 (35.5%)
≥1	185 (6.2%)	34 (1.3%)	219 (3.8%)

	Non-late present-ers N=4102 (51.3%)	**Late presenters N= 3900 (48.7%)**	**Total N=8002**
CD4 % (n (%))			
≤29%	2596 (63.3%)	3105 (79.6%)	5701 (71.2%)
>29%	811 (19.8%)	98 (2.5%)	909 (11.4%)
Unknown	695 (16.9%)	697 (17.9%)	1392 (17.4%)
Viral load (n (%)), copies/mL			
<10,000	787 (19.2%)	425 (10.9%)	1212 (15.1%)
10,000-100,000	2051 (50.0%)	1387 (35.6%)	3438 (43.0%)
≥100,000	1223 (29.8%)	1985 (50.9%)	3208 (40.1%)
Unknown	41 (1.0%)	103 (2.6%)	144 (1.8%)
Hepatitis C virus antibodies			
No	3375 (82.3%)	3061 (78.5%)	6436 (80.4%)
Yes	278 (6.8%)	441 (11.3%)	719 (9.0%)
Unknown	449 (10.9%)	398 (10.2%)	847 (10.6%)
Hepatitis B virus surface antigen			
No	2665 (65.0%)	2324 (59.6%)	4989 (62.3%)
Yes	978 (23.8%)	1165 (29.9%)	2143 (26.8%)
Unknown	459 (11.2%)	411 (10.5%)	870 (10.9%)
Year of starting ART			
2004-2009	546 (13.3%)	1418 (36.4%)	1964 (24.5%)

	Non-late present-ers N=4102 (51.3%)	Late presenters N= 3900 (48.7%)	Total N=8002
2010-2014	1380 (33.6%)	1158 (29.7%)	2538 (31.7%)
2014-2018	2176 (53.0%)	1324 (33.9%)	3500 (43.7%)
Initial ART regimen			
2NRTI+1INI	1198 (29.2%)	792 (20.3%)	1990 (24.9%)
2NRTI+1NNRTI	2077 (50.6%)	1786 (45.8%)	3863 (48.3%)
2NRTI+1PI	827 (20.2%)	1322 (33.9%)	2149 (26.9%)

For all the participants' characteristics reported in the table, p-values for the difference between non-LP and LP were <0.001.

ART, antiretroviral therapy; CI, confidence interval; IDU, injection drug use; INI, integrase inhibitor; IQR, interquartile range; MSM, men having sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Table 2. Impact of late presentation on treatment discontinuation due to AE during the first 48 weeks after ART initiation

	Non-late presenters N=4102	**Late presenters N= 3900**	**p-value**
Treatment discontinuation due to AE [n (%)]	393 (9.6%)	387 (9.9%)	0.606 [a]
Type of AE:			0.165 [a]
Osteoarticular	10 (0.2%)	9 (0.2%)	
Gastrointestinal	33 (0.8%)	41 (1.1%)	
Hepatic	12 (0.3%)	11 (0.3%)	
Neuropsychiatric	64 (1.6%)	37 (0.9%)	
Renal	25 (0.6%)	31 (0.8%)	
Cutaneous	44 (1.1%)	42 (1.1%)	
Other	30 (0.7%)	27 (0.7%)	
Unknown	175 (4.2%)	189 (4.8%)	
Discontinuation rate due to AE, per 100 PY **(95% CI)**	12.0 (10.9, 13.3)	13.1 (11.8, 14.4)	
Unadjusted Rate Ratio (95% CI) [b]	1.00	1.09 (0.94, 1.25)	0.246
Adjusted Rate Ratio (95% CI) [b,c]	1.00	0.91 (0.78, 1.07)	0.237
Adjusted Rate Ratio (95% CI) [b,c,d]	1.00	0.91 (0.76, 1.10)	0.320

CI: confidence interval; AE: adverse event; PY persons-year

[a] Pearson's Chi-squared test

[b] Rate ratios were obtained with Poisson regression models

[c] Rate ratios were adjusted for a combined variable of gender and HIV transmission category (MSM, IDU, heterosexual women, heterosexual men, other/unknown, educational level (None or primary education only,

secondary education, university, other/unknown), region of origin (Europe, Sub-Saharan Africa, Latin America, other/unknown), age at starting ART (<30, 30-49, ≥50 years), initial regimen (2NRTI+1INI, 2NRTI+1NNRTI, 2NRTI+1PI), HIV-RNA (<10,000, 10,000-100,000, ≥100,000, Unknown copies/mL), presence of HCV antibodies (no, yes or unknown), presence of HBV surface antigen (no, yes or unknown) during 24 weeks before ART initiation

[d] Rate ratios were further adjusted for CD4 count (<200, 200-499, ≥500 cells/µL) during 24 weeks before ART initiation

Table 3 Impact of initial ART treatment on treatment discontinuation due to AE during the first 48 weeks after ART initiation in late presenters

	2NRTI+1INI N=792	**2NRTI+1NNRTI N=1786**	**2NRTI+1PI N=1322**	**p-value**
Treatment discontinuation due to AE [n (%)]	44 (5.6%)	192 (10.8%)	151 (11.4%)	<0.001[a]
Type of AE:				<0.001[a]
Osteoarticular	4 (0.5%)	3 (0.2%)	2 (0.2%)	
Gastrointestinal	2 (0.3%)	6 (0.3%)	33 (2.5%)	
Hepatic	2 (0.3%)	3 (0.2%)	6 (0.5%)	
Neuropsychiatric	8 (1.0%)	25 (1.4%)	3 (0.2%)	
Renal	15 (1.9%)	4 (0.2%)	12 (0.9%)	
Cutaneous	3 (0.4%)	27 (1.5%)	12 (0.9%)	
Other	1 (0.1%)	9 (0.5%)	16 (1.2%)	
Unknown	9 (1.1%)	115 (6.4%)	67 (5.1%)	
Discontinuation rate due to AE, per 100 PY (95% CI)	7.4 (5.4, 10.0)	13.8 (11.9, 15.9)	15.5 (13.1, 18.1)	
Unadjusted Rate Ratio (95% CI) [b]	1.00	1.86 (1.34, 2.59)	2.09 (1.49, 2.93)	<0.001
Adjusted Rate Ratio (95% CI) [b,c]	1.00	1.63 (1.12, 2.36)	1.77 (1.22, 2.59)	0.011

AE, adverse events; CI, confidence interval; INI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PY persons-year.

[a] Pearson's Chi-squared test

[b] Estimates were obtained with Poisson regression models

[c] Multivariable models were adjusted for a combined variable of gender and HIV transmission category (MSM, IDU, Heterosexual women, Heterosexual men, Other/unknown, educational level (None or primary education only, secondary education, university, other/unknown), region of origin (Europe, Sub-Saharan Africa, Latin America, other/unknown), age at ART initiation (<30, 30-49, ≥50 years) HIV-RNA (<10,000, 10,000-100,000, ≥100,000, Unknown copies/mL) and CD4 count (<24, 25-49, 50-99, 100-199, 200-349, ≥350 cells/µL), presence of HCV antibodies (no, yes or unknown), presence of HBV surface antigen (no, yes or unknown) during 24 weeks before ART initiation.

Figure 1. Impact of late presentation on viral suppression and immunologic response at 48 weeks from ART initiation

Estimates were obtained with linear (mean changes in CD4 count) or logistic (viral suppression and all other immunologic markers) regression, with robust standard error estimates.

Estimates were adjusted for (1) a combined variable of gender and HIV transmission category (MSM, IDU, Heterosexual women, Heterosexual men, Other/unknown, educational level (None or primary education only, secondary education, university, other/unknown), region of origin (Europe, Sub-Saharan Africa, Latin America, other/unknown), age at starting ART (<30, 30-49, ≥50 years), initial regimen (2NRTI+1INI, 2NRTI+1NNRTI, 2NRTI+1PI), HIV-RNA (<10,000, 10,000-100,000, ≥100,000, Unknown copies/mL), presence of HCV antibodies (no, yes or unknown), presence of HBV surface antigen (no, yes or unknown) during 24 weeks before ART initiation, and (2) for CD4 count (<200, 200-499, ≥500 cells/μL) during 24 weeks before ART initiation.

Figure 2: Viral suppression and immunological response in late presenters by initial ART regimen

Multivariable models were adjusted for a combined variable of gender and HIV transmission category (MSM, IDU, heterosexual women, heterosexual men, other/unknown, educational level (none or primary education only, secondary education, university, other/unknown), region of origin (Europe, Sub-Saharan Africa, Latin America, other/unknown), age at ART initiation (<30, 30-49, ≥50 years) HIV-RNA (<10,000, 10,000-100,000, ≥100,000, Unknown copies/mL), CD4 count (<24, 25-49, 50-99, 100-199, 200-349, ≥350 cells/µL), presence of HCV antibodies (no, yes or unknown), presence of HBV surface antigen (no, yes or unknown) during 24 weeks before ART initiation.