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Initiation of antiretroviral therapy at high CD4⁺ cell counts is associated with positive treatment outcomes

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Abstract

Objective—There is limited research investigating the possible mechanisms of how starting combination antiretroviral therapy (cART) at a higher CD4⁺ cell count decreases mortality. This study investigated the association between initiating cART with short-term and long-term achievement of viral suppression; emergence of any drug resistance and of an AIDS-defining illness (ADI); long-term treatment adherence; and all-cause mortality.

Methods—This retrospective cohort study included 4120 naive patients who initiated cART between 2000 and 2012. Patients were followed until 2013, death or until the last contact date (varied by outcome). The main exposure was the interaction between period of cART initiation (2000–2006 and 2007–2012) and CD4⁺ cell count at cART initiation (<500 versus ≥500 cells/μl). We considered both baseline and longitudinal covariates. We fitted different multivariable models using cross-sectional and longitudinal statistical methods, depending on the outcome.

Results—Patients who initiated cART with a CD4⁺ cell count at least 500 cells/μl in 2007–2012 had an increased likelihood of achieving viral suppression at 9 months and of maintaining an adherence level of at least 95% overtime, and the lowest probability of developing any resistance and an ADI during follow-up. These patients were not the ones with the highest likelihood of maintaining viral suppression over time, most likely due to viral load blips experienced during the follow-up.

Conclusion—The outcomes in this study likely play an important role in explaining the positive impact of early cART initiation on mortality. These results should alleviate some of the concerns clinicians may have when initiating cART in patients with high CD4⁺s as recommended by current treatment guidelines.

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Keywords

adherence; AIDS-defining illness; antiretroviral therapy; combination antiretroviral therapy; CD4⁺ cell count; drug resistance; loss to follow-up; mortality; viral load; viral suppression

Introduction

With global estimates of around 35 million people living with HIV [1], the HIV/AIDS epidemic continues to be one of the world's most pressing public health challenges. In the last decade, there has been marked progress in combination antiretroviral treatment (cART), with more therapeutic options, safer and better-tolerated drugs, and simpler dosing regimens [2–8]. This has facilitated a shift towards earlier cART initiation to promote immune restoration [9,10] and prevent AIDS-related morbidity, as well as premature mortality [11]. More recently, the use of cART to prevent HIV transmission has fuelled enthusiasm for the implementation of HIV Treatment as Prevention programmes to control the HIV/AIDS pandemic [12–15]. In the summer of 2014, The Joint United Nations Programme on HIV/AIDS (UNAIDS) released a new target for antiretroviral cART roll out by 2020, calling for 90% of HIV-infected individuals to be diagnosed worldwide, 90% of diagnosed individuals to receive cART and 90% of those on cART to achieve sustained viral suppression [16]. The 90–90–90 target is expected to dramatically alter the course of the HIV/AIDS pandemic, transforming it into a sporadic endemic condition by 2030 [16].

Early initiation of cART has been shown to have a consistent beneficial impact on morbidity and mortality [17–24]. Conversely, there is limited research investigating the possible mechanisms of how starting cART at higher CD4⁺ cell counts (from this point forward referred to just as CD4⁺) decreases mortality. These mechanisms may include improved long-term treatment adherence and virologic suppression, and decreased incidence of viral resistance. In the existing literature, there are reports that have evaluated the association between CD4⁺ at cART initiation and loss to follow-up (LTFU). However, these results are conflicting [25–28] and are less relevant, as treatment guidelines have evolved substantially regarding cART initiation eligibility [17,29]. Some studies, although few, have looked at other mechanisms that may be related to mortality outcomes by CD4⁺ at cART initiation [30–36]. In 2007, Phillips *et al.* [33] found an increase in triple class failure among people who initiated cART at low a CD4⁺ (<200 cells/μl). More recently, Lodi *et al.* [34] reported a decrease in virologic failure and drug resistance in patients who initiated cART early. In 2008, Geretti *et al.* [30] found no association between CD4⁺ at cART initiation and risk of virologic failure. Therefore, we conducted this study aiming to investigate the association between initiating cART at different CD4⁺ cutoffs with short-term and long-term achievement of viral suppression; the emergence of drug resistance; long-term treatment adherence; LTFU; the emergence of an AIDS-defining illness (ADI); and all-cause mortality.

Materials and methods

Data

In British Columbia, Canada, cART, HIV medical care and laboratory monitoring are fully subsidized (free, without copayments or deductibles) by the provincial government since 1992 under the aegis of the BC Centre for Excellence in HIV/AIDS (BC-CfE)'s Drug Treatment Programme (DTP). cART is distributed to eligible patients on the basis of BC-CfE's HIV therapeutic guidelines, which have remained consistent with those put forward by the International Antiviral Society-USA (IAS-USA) since 1996 [17,29,37].

In this analysis, patients were cART naive, aged at least 19 years old, and enrolled in the DTP between 1 January 2000 and 31 December 2012. Within this cohort, cART was initiated with two nucleoside reverse transcriptase inhibitors as backbone, combined with either a non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine) or a ritonavir-boosted protease inhibitor (lopinavir or atazanavir), given that these were the most prescribed therapies during the study period. Participants must also have had a CD4⁺ and a viral load measurement within 6 months of the antiretroviral initiation date. CD4⁺s are measured by flow cytometry, followed by fluorescent mAb analysis (Beckman Coulter Canada, LP, Mississauga, Ontario, Canada). The CD4⁺ data come from different laboratories across British Columbia, and the DTP captures approximately 85% of all CD4⁺ tests done in the province, as these results are not automatically uploaded in our database. All viral load tests in British Columbia are performed at the virology laboratory at St Paul's hospital and are uploaded automatically in the DTP database. As the quantification range of viral load assays has evolved over time, for analytical purposes, we truncated our measurements to range from less than 50 (coded as 49) to more than 100000 (coded as 100010) copies/ml [38–41]. HIV drug resistance genotyping is routinely performed at the BC-CfE virology laboratory on samples with viral loads of at least 250 copies/ml upon physician request. Methods for HIV-1 RNA extraction and drug resistance analysis have been described in detail elsewhere [42]. Mortality data for all causes were provided by the BC Vital Statistics Agency and linked monthly to the DTP. ADI case reports were obtained from the BC-CfE, enriched with clinical records from St Paul's Hospital, the BC Cancer Agency and the BC Vital Statistics Agency.

Statistical analyses

In this study, the main exposure variable included the interaction between the period of cART initiation (2000–2006 and 2007–2012) and CD4⁺ at cART initiation categorized as less than 500 versus at least 500 cells/ μ l. In a subanalysis, we also categorized CD4⁺ as less than 350 versus at least 350 cells/ μ l. We decided to classify the years of cART initiation into these groups to ensure that we control for any differences that may exist regarding prescribing practices in those years.

The possible explanatory variables varied by study outcome and could include as measured at baseline: age (continuous), sex (male/female), history of injection drug use (no/yes/unknown) and viral load (\log_{10} transformed); measured at 6 or at 12 months since cART initiation: adherence level (0% to <40%, 40% to <80%, 80% to <95% and 95%); and

measured longitudinally at every 6 months until the end of study follow-up -adherence level (0% to <40%, 40% to <80%, 80% to <95% and 95%), viral load (\log_{10} transformed) and follow-up time (defined on the basis of each outcome). Adherence was assessed using a validated refill compliance measurement and defined as the number of days of antiretroviral drugs dispensed divided by the number of days between refills (expressed as a percentage) [43].

Patients LTFU were censored at the last contact date (i.e. the date for a laboratory test, a prescription refill or a physician visit) prior to any of the following events: if they moved outside of British Columbia; if the last contact date was longer than 18 months, if they started cART before 30 June 2012; if the last contact date was before 31 December 2013, if they started cART after 30 June 2012; if they enrolled in a blinded trial involving receiving placebo medication; or if they had a scheduled treatment interruption, given that information on the return date of the patient to the programme is unclear.

Longitudinal outcomes

All outcomes were assessed every 6 months from the date of cART initiation to the end of follow-up and modelled via a multivariable generalized estimating equations explanatory model assuming a binomial distribution, a logit link function and an autoregressive correlation structure of order one [44].

Combination antiretroviral therapy adherence

We modelled the probability of maintaining an adherence of at least 95% over time.

Explanatory variables included age, sex, history of injection drug use, longitudinal viral load and follow-up time. Follow-up time was measured from cART initiation until 31 December 2013 (if alive), to the last contact date (if LTFU), or to the death date.

Viral suppression

We modelled the probability of maintaining viral suppression (a viral load <50 copies/ml) over time.

Explanatory variables included age, sex, history of injection drug use, longitudinal adherence level and follow-up time defined the same way as per the adherence analysis.

HIV drug resistance

Resistant samples were assigned to one of the four classes on the basis of a modification of the 2014 IAS-USA list of mutations [45], as lamivudine/emtricitabine resistance (M184V/I); any other nucleoside reverse transcriptase inhibitor (NRTI) resistance (41L, 62V, 65R, 67N, 69D or insertion, 70E/R, 74V, 75I, 77L, 115F, 116Y, 151M, 210W, 215F/Y or 219E/Q); any nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance (100I, 101E/H/P, 103N, 106A/M, 108I, 138A/G/K/Q/R, 181C/I/V, 188C/H/L, 190A/S, 225H, 230L or 236L); and any protease inhibitor resistance (30N, 32I, 33F, 46I/L, 47A/V, 48V, 50L/V, 54V/L/M, 58E, 74P, 76V, 82A/F/L/S/T, 84V, 88S or 90M). We assumed that samples with a viral load less

than 250 copies/ml harboured no resistance. We restricted this analysis to include patients with no resistance prior to starting cART.

We modelled the probability of developing resistance to any class (yes/no) over time, defined by any combination of the above resistance classes.

Explanatory variables included age, sex, history of injection drug use, longitudinal adherence level and viral load, and follow-up time. Follow-up time was measured from cART initiation until 31 December 2013 (if no resistance was detected), to the last contact date (if LTFU before detecting any resistance), to the death date (if deceased before detecting any resistance), or to the date when any resistance was detected.

All-cause mortality

We modelled the probability of being dead by the end of follow-up.

Explanatory variables as per the resistance analysis and follow-up time were defined as per the adherence analysis.

Emergence of an AIDS-defining illness after combination antiretroviral therapy initiation

We modelled the probability of developing an ADI by the end of follow-up.

Explanatory variables are as per the resistance analysis. Follow-up time was measured from cART initiation to 31 December 2013 (if no ADI was reported), to the last contact date (if LTFU before any ADI was reported), to the death date (if deceased before an ADI was reported) or to the date when an ADI was reported.

Cross-sectional outcomes

All outcomes were modelled via a multivariable logistic regression explanatory model.

Loss to follow-up

Analysis was restricted to patients alive at the end of follow-up or those LTFU.

We modelled the probability of being LTFU (yes/no).

Explanatory variables included age, sex, history of injection drug use, baseline viral load, adherence level measured at 12 months since cART initiation and follow-up time. Follow-up time was measured from cART initiation until 31 December 2013 (if alive) or to the last contact date (if LTFU).

Viral suppression within 9 months after combination antiretroviral therapy initiation

We modelled the probability of achieving viral suppression within 9 months after initiating cART (yes/no), defined by two consecutive viral loads less than 50 copies/ml.

Explanatory variables included age, sex, history of injection drug use, baseline viral load, adherence level measured at 6 months since cART initiation and follow-up time. Follow-up time was measured from cART initiation until 31 December 2013 (if no viral suppression),

to the last contact date (if LTFU before viral suppression), to the death date (if deceased before viral suppression) or to the viral suppression date.

In both longitudinal and cross-sectional multivariable models, a modified backward stepwise technique, based on Akaike Information Criterion (AIC), or the quasi-AIC for the generalized estimating equation models (QIC), and Type III *P* values, was used in the selection of explanatory variables [43]. Categorical variables were compared using the Fisher's exact test (for 2×2 tables) or the Cochran–Mantel–Haenszel test (for other table sizes), and continuous variables were compared using the Wilcoxon rank-sum test [46]. All analyses were performed using SAS, version 9.3 (SAS, Cary North Carolina, USA).

Results

Table 1 presents the characteristics at cART initiation and treatment outcomes of 4120 patients included in our analyses. The median age was 42 years [25th–75th percentile (Q1–Q3): 35–49], 80% were male, 36% had a history of injection drug use and patients were followed for a median of 60 months (Q1–Q3: 34–95). By the end of the follow-up, we observed that 492 (12%; rate 1.77 per 1000 person-months) patients were deceased and 735 (18%; rate 2.65 per 1000 person-months) were LTFU (Table 1). The distribution of CD4⁺ at the start of cART based on the strata less than 200, 200–349, 350–499 and at least 500 cells/μl was 44%, 32%, 14% and 10%, respectively. The median viral load at the start of cART was 4.90 log₁₀copies/ml (Q1–Q3: 4.38–5.00); 78% of patients had at least 95% adherence during the first 6 months on cART, 71% achieved viral suppression at 9 months and 7% developed an ADI during follow-up. Baseline resistance was detected in 112 (3%) of patients. Of the 4008 patients without baseline resistance, 448 (11%) developed resistance to any drug class during follow-up.

The distribution of patients on the basis of the baseline CD4⁺ cell count strata was examined by adherence measured over time (Fig. 1a); achievement of viral suppression at 9 months (Fig. 1b); accumulation of drug resistance to any class during follow-up (Fig. 1c); their status at the end of follow-up (Fig. 1d); and by the emergence of an ADI during follow-up (Fig. 1e). The distribution of patients by adherence level over time did not differ significantly in CD4⁺ strata 350–499 and at least 500 cells/μl (Fig. 1a) ($P = 0.3665$ and $P = 0.0662$, respectively). For the other outcomes, we observed that patients in the stratum at least 500 cells/μl were more likely to achieve viral suppression at 9 months, to be alive at the end of follow-up and less likely to develop drug resistance and an ADI during follow-up ($P < 0.0001$). Interestingly, the proportion of patients LTFU in each CD4⁺ strata was very similar ($P = 0.1606$).

Focusing on our main exposure, the distribution of patients was 1628 (40%) for 2000–2006 and less than 500 cells/μl, 50 (1%) for 2000–2006 and at least 500 cells/μl, 2101 (51%) for 2007–2012 and less than 500 cells/μl, and 341 (8%) for 2007–2012 and at least 500 cells/μl (Table 2a). Although the number of patients in the CD4⁺ stratum at least 500 cells/μl was small for both periods of time, mostly due to the treatment guidelines in those years, we still obtained highly significant results. For example, we observed that young men, patients with an unknown history of injection drug use, those who initiated cART with a lower viral load

and maintained an adherence of at least 95% during the first 6 months on cART were more likely to be classified into stratum 2007–2012 and at least 500 cells/ μ l ($P < 0.0001$). In addition, patients who achieved suppression at 9 months, who did not develop an ADI or drug resistance during follow-up and were alive at the end of follow-up were also more likely to be classified into this stratum ($P < 0.0001$). Of note, there was no difference among exposure groups regarding drug resistance prior to the initiation of cART ($P = 0.1321$).

Next, we present the results of the predicted probabilities for each of the multivariable models in our cross-sectional (Table 3) and longitudinal analyses (Table 4). On the basis of our main exposure, we observed that the probability of achieving viral suppression at 9 months and of maintaining an adherence level of at least 95% over time was highest during 2007–2012 [median across patients 0.93: (Q1–Q3: 0.90–0.96) and 0.84 (Q1–Q3: 0.75–0.88), respectively]. Focusing on the outcomes, emergence of any resistance and of an ADI during follow-up and death, patients in the 2007–2012 had by far the lowest probabilities [0.01 (Q1–Q3: 0.01–0.02), 0.01 (Q1–Q3: 0.00–0.01) and 0.01 (Q1–Q3: 0.01–0.02), respectively]. It is important to mention that, for mortality, we run a subanalysis focusing only on the period 2007–2012 and comparing the less than 500 cells/ μ l and at least 500 cells/ μ l strata, as these were the strata with the smallest sample sizes. Patients with at least 500 cells/ μ l CD4⁺ had the lowest probability of dying [0.01 (Q1–Q3: 0.01–0.02) versus 0.03 (Q1–Q3: 0.01–0.07)] (results not shown in Tables 3 and 4). We also observed that patients in the CD4⁺ stratum at least 500 cells/ μ l, in both periods of time, had a higher probability of being LTFU and the lowest probability of maintaining viral suppression over time. However, if we focused on comparing these outcomes among patients in the CD4⁺ strata at least 500 cells/ μ l between periods 2000–2006 and 2007–2012, we observed that patients in 2007–2012 had the lowest probability of being LTFU [0.19 (Q1–Q3: 0.16–0.23) versus 0.28 (Q1–Q3: 0.23–0.34)] and the highest probability of maintaining viral suppression over time [0.69 (Q1–Q3: 0.58–0.76) versus 0.55 (Q1–Q3: 0.19–0.81)] (results not shown in Tables 3 and 4). Similar results were obtained when looking at the same outcomes for the exposure using the 350 cells/ μ l cut-off (Tables 2b–4).

Discussion

Our results showed a strong association between CD4⁺ at cART initiation and all outcomes investigated in this study. Patients who initiated cART with a CD4⁺ at least 500 cells/ mm^3 in the most recent period (2007–2012) had an increased likelihood of achieving viral suppression at 9 months and of maintaining an adherence level of at least 95% over time than the other exposure groups. These individuals were also the ones with the lowest probability of developing any resistance and an ADI during follow-up. Interestingly, although these individuals had the lowest follow-up, comparing with patients in the same period with a CD4⁺ less than 500 cells/ μ l, they had the lowest probability of mortality. These analyses also indicated that, while patients with a CD4⁺ at least 500 cells/ μ l had a lower likelihood of being LTFU in 2007–2012 than in 2000–2006, they unfortunately did poorly regarding this outcome when compared with patients with a CD4⁺ less than 500 cells/ μ l in both periods. It is important to highlight that patients who initiated cART with a CD4⁺ at least 500 cells/ μ l in the most recent period were not the ones with the highest likelihood of maintaining viral suppression over time. On the basis of our definition for this

latest outcome, we believe that this result was influenced by viral load blips that have happened during the follow-up time. Despite these viral load blips resulting in a perceived lower probability of maintaining viral suppression over time, we showed that this outcome did not negatively influence the mortality of these patients.

One of the concerns often raised in the literature around early cART initiation is that people with a high CD4⁺ may be at risk of poor adherence because they are asymptomatic and, as such, less motivated to take cART [47]. In a Soweto cohort, Katz *et al.* [48] found that ‘feeling healthy’ was the number one reason why people stopped taking their treatment. In this context, our results regarding improved adherence and increased likelihood of viral suppression in the CD4⁺ at least 500 cells/μl stratum in recent years are noteworthy. Our results also suggest that this issue is evolving favourably over time probably due to enhanced programmatic features, including patient support and education, low threshold services and patient navigators, as well as the availability of simpler, more effective, safer and better tolerated regimens.

Our study has a number of strengths. Our cohort is unique in that it involves a large sample size within a population-based programme wherein all patients had access to the same facilitated free cART options, medical care and laboratory monitoring, with no copayments or deductibles. This minimizes treatment access issues as a possible confounding factor. Our database is also comprehensive, as it captures 100% of cART refills, 100% of viral loads and approximately 85% of CD4⁺s done in the province. Another strength was that we adjusted each of our models for a broad number of important cross-sectional and longitudinal variables. In addition, in the analysis looking at the emergence of any drug resistance, we excluded patients with primary viral resistance, which otherwise would have introduced a significant bias in our analyses.

Our study also has a number of potential limitations. As with every cohort study, causality cannot be established. Second, we controlled our analyses for history instead of ongoing injection drug use. Thus, our results did not capture changes in drug usage over time. Third, we used pharmacy refill as a measure of adherence, which may overestimate true adherence. However, we have previously validated this measurement against other commonly used adherence metrics and found it to be highly predictive of disease progression and death, among other key clinical outcomes [43,49]. Fourth, in collecting data for resistance, we assumed serum samples with a viral load less than 250 copies/ml to be nonresistant. Although resistance is possible at these low viral levels [35], its incidence in our setting is so low that it is unlikely that this could have had any effect on the direction or significance of our results. Fifth, our sample size in the 2000–2006 and CD4⁺ at least 500 cells/μl group was relatively small, while the more recent group 2007–2012 and CD4⁺ at least 500 cells/μl had a substantially larger number of patients. These sample sizes reflect the evolution of treatment guidelines under which, unlike current trends, patients were inclined to present for treatment only when they developed symptoms [17,29,50]. Nonetheless, it is noteworthy that, even with a smaller sample in 2000–2006, the differences described here were statistically significant. Sixth, it is possible that the data density between these periods has influenced our results (i.e. frequency of laboratory monitoring, follow-up visits and clinical assessment). However, it is hard to ascertain whether these activities have changed over

time, as they vary depending on each patient's response to antiretroviral therapy. Finally, it may be speculated that somehow patients entering treatment in recent years may be different than those in the earlier years. We have no evidence that this would represent a significant bias given the socioeconomic downdrift of the epidemic over time in this province. However, further analyses are necessary to explore this issue. On this note, it is important to mention that different trials are underway, which will provide additional insights on this issue: the Test and Link to Care-Plus (HPTN 065) trial in USA [51], the PopART Study (HPTN 071) in Zambia and South Africa [52], and the TasP (Treatment as Prevention) trial (ANRS 12249) in KwaZulu-Natal, South Africa [53].

In summary, we demonstrated that initiation of cART at a high CD4⁺ was positively associated with several treatment outcomes, suggesting that these outcomes are likely to play an important role in explaining the positive impact of early cART initiation on mortality. Therefore, our results should alleviate some of the concerns clinicians may have when initiating cART in people with CD4⁺ at least 500 cells/ μ l, as recommended by current guidelines [17], particularly where free access to modern cART and related monitoring is available. Furthermore, our results support the shift to immediate cART initiation upon testing positive for HIV, consistent with the new UNAIDS 90–90–90 target for cART rollout by 2020 [16].

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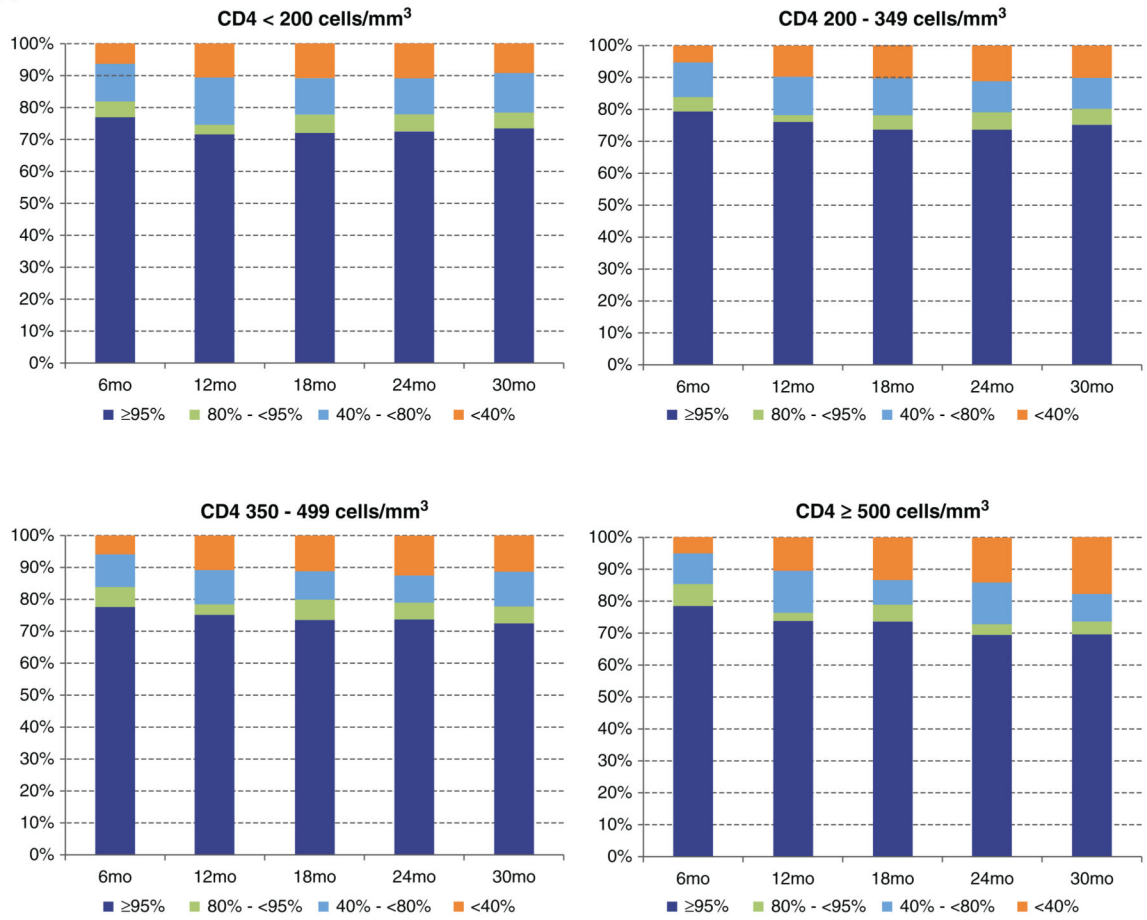
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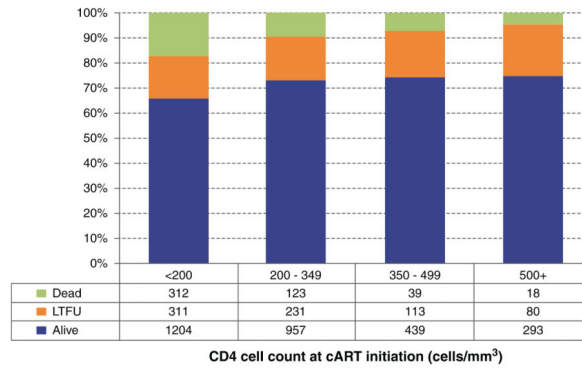
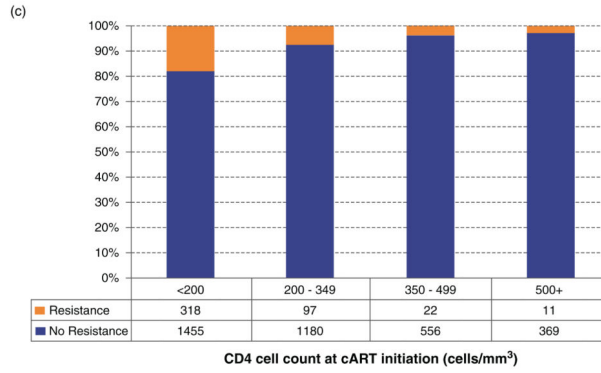
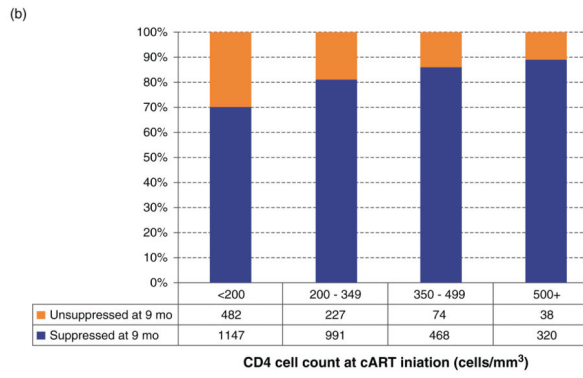
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(a)





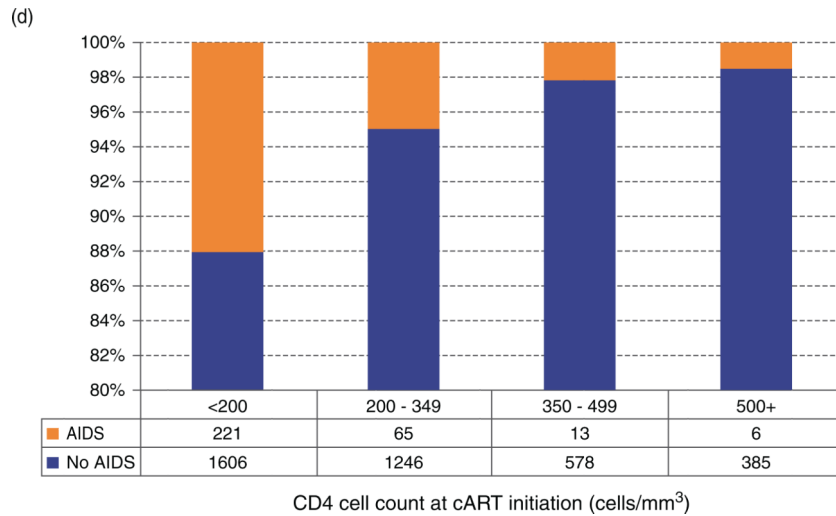


Fig. 1. Distribution of CD4⁺ at the start of combination antiretroviral therapy by different outcomes

Stratified by: (a) adherence level over time; (b) achievement of suppression in 9 months after combination antiretroviral therapy initiation; (c) the emergence of resistance to any antiretroviral class during follow-up; (d) LTFU: lost to follow-up; (e) The emergence of an AIDS-defining illness during follow-up.

Table 1
Distribution of patient characteristics and outcomes

Covariates and outcomes	<i>n</i> (%) or Median (Q1–Q3)
CD4 ⁺ cell count (cells/ml) at cART initiation	
<200	1827 (44%)
200–349	1311 (32%)
350–499	591 (14%)
More than 500	391 (10%)
Sex	
Male	3328 (80%)
Female	792 (20%)
Age (years)	42 (35–49)
Viral load (log ₁₀ copies/ml) at cART initiation, median (Q1–Q3)	4.90 (4.38–5.00)
History of injection drug use	
No	1839 (45%)
Yes	1501 (36%)
Unknown	780 (19%)
Follow-up (months)	60 (34–95)
Adherence to therapy during the first 6 months on cART	
95%	3219 (78%)
80 to <95%	213 (5%)
40 to <80%	455 (11%)
0 to <40%	233 (6%)
Suppression at 9 months	
Yes	2926 (71%)
No	1194 (29%)
Drug resistance at cART initiation	
No	4008 (97%)
Yes	112 (3%)
Developing resistance to any class during follow-up ^a	
No	3560 (89%)
Yes	448 (11%)
Developing an AIDS-defining illness during follow-up	
No	3815 (93%)
Yes	305 (7%)
Status at the end of follow-up	
Alive	2893 (70%)
Death	492 (12%)
Loss to follow-up	735 (18%)

Q1: 25th percentile, Q3: 75th percentile. cART, combination antiretroviral therapy.

^aDenominator is the number of patients without baseline resistance.

Table 2

Bivariable associations between covariates and outcomes, stratified by the period of combination antiretroviral therapy initiation (2000–2006 and 2007–2012) and CD4⁺ cell count level at combination antiretroviral therapy initiation

Covariate	Period (years) and CD4 ⁺ cell count (cells/ μ l)				P
	2000–2006 and <500	2000–2006 and 500	2007–2012 and <500	2007–2012 and 500	
(a) Using the CD4⁺ cell count cut-off of 500 cells/ml at cART initiation					
Sex, n (%)					
Male	1309 (80%)	38 (76%)	1683 (80%)	298 (87%)	0.0073
Female	319 (20%)	12 (24%)	418 (20%)	43 (13%)	
Age (years), median (Q1–Q3)	42 (36–48)	39 (33–45)	42 (35–49)	39 (32–47)	<0.0001
Viral load (log ₁₀ copies/ml) at cART initiation, median (Q1–Q3)	5.00 (4.69–5.00)	4.88 (4.32–5.00)	4.80 (4.27–5.00)	4.46 (4.02–5.00)	<0.0001
History of injection drug use, n (%)					
No	710 (44%)	25 (50%)	948 (45%)	156 (46%)	<0.0001
Yes	674 (41%)	16 (32%)	735 (35%)	76 (22%)	
Unknown	244 (15%)	9 (18%)	418 (20%)	109 (32%)	
Follow-up (months), median (Q1–Q3)	104 (84–129)	103 (77–127)	47 (29–65)	30 (20–42)	<0.0001
Adherence to therapy during the first 6 months on cART, n (%)					
95%	1241 (76%)	29 (58%)	1670 (80%)	279 (82%)	<0.0001
80 to <95%	74 (5%)	6 (12%)	111 (5%)	22 (6%)	
40 to <80%	195 (12%)	10 (20%)	223 (11%)	27 (8%)	
0 to <40%	118 (7%)	5 (10%)	97 (5%)	13 (4%)	
Suppression at 9 months, n (%)					
Yes	1075 (66%)	31 (62%)	1531 (73%)	289 (85%)	<0.0001
No	553 (34%)	19 (38%)	570 (27%)	52 (15%)	
Drug resistance at cART initiation, n (%)					
No	1581 (97%)	46 (92%)	2047 (97%)	334 (98%)	0.1321
Yes	47 (3%)	4 (8%)	54 (3%)	7 (2%)	
Developing resistance to any class during follow-up, n (%) ^d					
No	1278 (81%)	42 (91%)	1913 (94%)	327 (98%)	<0.0001
Yes	303 (19%)	4 (9%)	134 (6%)	7 (2%)	

Covariate	Period (years) and CD4 ⁺ cell count (cells/ μ l)				P
	2000–2006 and <500	2000–2006 and 500	2007–2012 and <500	2007–2012 and 500	
(a) Using the CD4⁺ cell count cut-off of 500 cells/ml at cART initiation					
Developing an AIDS-defining illness during follow-up, <i>n</i> (%)					
No	1432 (88%)	48 (96%)	1998 (95%)	337 (99%)	<0.0001
Yes	196 (12%)	2 (4%)	103 (5%)	4 (1%)	
Status at the end of follow-up, <i>n</i> (%)					
Alive	982 (60%)	26 (52%)	1618 (77%)	267 (78%)	<0.0001
Death	339 (21%)	11 (22%)	135 (6%)	7 (2%)	
Loss to follow-up	307 (19%)	13 (26%)	348 (17%)	67 (20%)	
Overall	1628 (40%)	50 (1%)	2101 (51%)	341 (8%)	
(b) Using the CD4⁺ cell cut-off 350 cells/μl at cART initiation					
Period (years) and CD4 ⁺ cell count (cells/ml)					
Covariate	2000–2006 and <350	2000–2006 and 350	2007–2012 and <350	2007–2012 and 350	P
Sex, <i>n</i> (%)					
Male	1221 (80%)	126 (78%)	1292 (80%)	689 (84%)	0.0436
Female	295 (20%)	36 (22%)	330 (20%)	131 (16%)	
Age (years), median (Q1–Q3)	42 (36–48)	41 (33–48)	43 (35–50)	41 (32–47)	<0.0001
Viral load (log ₁₀ copies/ml) at cART initiation, median (Q1–Q3)	5.00 (4.72–5.00)	4.85 (4.20–5.00)	4.88 (4.36–5.00)	4.48 (3.98–4.96)	<0.0001
History of injection drug use, <i>n</i> (%)					
No	658 (43%)	77 (48%)	721 (44%)	383 (47%)	<0.0001
Yes	633 (42%)	57 (35%)	613 (38%)	198 (24%)	
Unknown	225 (15%)	28 (17%)	288 (18%)	239 (29%)	
Follow-up (months), median (Q1–Q3)	104 (84–128)	109 (86–140)	51 (33–67)	33 (22–49)	<0.0001
Adherence to therapy during the first 6 months on cART, <i>n</i> (%)					
95%	1157 (76%)	113 (70%)	1294 (80%)	655 (80%)	<0.0001
80 to <95%	70 (5%)	10 (6%)	79 (5%)	54 (7%)	
40 to <80%	183 (12%)	22 (14%)	173 (11%)	77 (9%)	
0 to <40%	106 (7%)	17 (10%)	76 (4%)	34 (4%)	
Suppression at 9 months, <i>n</i> (%)					

(a) Using the CD4⁺ cell count cut-off of 500 cells/ml at cART initiation

Covariate	Period (years) and CD4 ⁺ cell count (cells/ μ l)				<i>P</i>
	2000–2006 and <500	2000–2006 and \geq 500	2007–2012 and <500	2007–2012 and \geq 500	
Yes	1000 (66%)	106 (65%)	1138 (70%)	682 (83%)	<0.0001
No	516 (34%)	56 (35%)	484 (30%)	138 (17%)	
Drug resistance at cART initiation, <i>n</i> (%)					
No	1472 (97%)	155 (96%)	1578 (97%)	803 (98%)	0.3560
Yes	44 (3%)	7 (4%)	44 (3%)	17 (2%)	
Developing resistance to any class during follow-up, <i>n</i> (%) ^d					
No	1178 (80%)	142 (92%)	1457 (92%)	783 (98%)	<0.0001
Yes	294 (20%)	13 (8%)	121 (8%)	20 (2%)	
Developing an AIDS-defining illness during follow-up, <i>n</i> (%)					
No	1329 (88%)	151 (93%)	1523 (94%)	812 (99%)	<0.0001
Yes	187 (12%)	11 (7%)	99 (6%)	8 (1%)	
Status at the end of follow-up, <i>n</i> (%)					
Alive	916 (60%)	92 (57%)	1245 (77%)	640 (78%)	<0.0001
Death	316 (21%)	34 (21%)	119 (7%)	23 (3%)	
Loss to follow-up	284 (19%)	36 (22%)	258 (16%)	157 (19%)	
Overall	1516 (37%)	162 (4%)	1622 (39%)	820 (20%)	

Q1: 25th percentile, Q3: 75th percentile.

^dDenominator is the number of patients without baseline resistance. *P* values should be used to compare across categories of our main exposure. Number in parenthesis for *n* (%) refers to column percentages.

Table 3
Results of the cross-sectional analyses focusing on the interaction between the period of combination antiretroviral therapy initiation (2000–2006 and 2007–2012) and CD4⁺ cell count level at combination antiretroviral therapy initiation (<350 versus 350 cells/μl and <500 versus 500 cells/ml)

Variable	Predicted probability of achieving viral suppression in 9 months	Predicted probability of being lost to follow-up
Period and CD4 ⁺ cell count (cells/μl), median (Q1–Q3)		
2000–2006 and <350	0.83 (0.70–0.84)	0.18 (0.11–0.27)
2000–2006 and 350	0.83 (0.62–0.87)	0.23 (0.14–0.37)
2007–2012 and <350	0.83 (0.70–0.87)	0.14 (0.09–0.22)
2007–2012 and 350	0.93 (0.90–0.96)	0.19 (0.12–0.26)
Period and CD4 ⁺ cell count (cells/μl), median (Q1–Q3)		
2000–2006 and <500	0.78 (0.60–0.81)	0.11 (0.18–0.28)
2000–2006 and 500	0.70 (0.40–0.82)	0.16 (0.22–0.41)
2007–2012 and <500	0.82 (0.66–0.87)	0.09 (0.15–0.23)
2007–2012 and 500	0.90 (0.86–0.94)	0.13 (0.19–0.25)

Q1: 25th percentile, Q3: 75th percentile. Models were adjusted for predicted probability of achieving viral suppression in 9 months (for CD4⁺ cell count cut-off 350 cells/μl) – adherence to therapy during the first 6 months on cART, viral load at cART initiation and history of injection drug use; predicted probability of achieving viral suppression in 9 months (for CD4⁺ cell count cut-off 500 cells/μl) – sex, adherence to therapy during the first 6 months on cART, viral load at cART initiation and history of injection drug use; predicted probability of being lost to follow-up (for CD4⁺ cell count cut-off 350 cells/μl) – age, adherence to therapy during the first 12 months on cART, history of injection drug use, viral load at cART initiation and follow-up time; predicted probability of being lost to follow-up (for CD4⁺ cell count cut-off 500 cells/μl) – age, adherence to therapy during the first 12 months on cART, history of injection drug use and follow-up time.

Table 4
Results of the longitudinal analyses focusing on the interaction between the period of combination antiretroviral therapy initiation (2000–2006 and 2007–2012) and CD4⁺ cell count level at combination antiretroviral therapy initiation (<350 versus 350 cells/ml and <500 versus 500 cells/ml)

Variable	Predicted probability of maintaining adherence 95% over time	Predicted probability of maintaining viral suppression over time	Predicted probability of developing resistance to any drug class over time	Predicted probability of developing an AIDS-defining illness by the end of follow-up	Predicted probability of being dead by the end of follow-up
Period and CD4 ⁺ cell count (cells/ μ l), median (Q1–Q3)					
2000–2006 and <350	0.79 (0.67–0.86)	0.77 (0.58–0.90)	0.11 (0.07–0.18)	0.14 (0.08–0.22)	0.14 (0.08–0.22)
2000–2006 and 350	0.72 (0.56–0.81)	0.70 (0.45–0.88)	0.04 (0.03–0.08)	0.13 (0.08–0.22)	0.14 (0.09–0.22)
2007–2012 and <350	0.83 (0.73–0.88)	0.68 (0.57–0.79)	0.05 (0.03–0.08)	0.05 (0.03–0.08)	0.05 (0.03–0.08)
2007–2012 and 350	0.83 (0.74–0.87)	0.68 (0.58–0.77)	0.02 (0.01–0.02)	0.03 (0.01–0.05)	0.02 (0.01–0.04)
Period and CD4 ⁺ cell count (cells/ μ l), median (Q1–Q3)					
2000–2006 and <500	0.75 (0.62–0.84)	0.77 (0.58–0.90)	0.11 (0.07–0.18)	0.04 (0.02–0.08)	0.13 (0.08–0.22)
2000–2006 and 500	0.55 (0.36–0.70)	0.51 (0.23–0.79)	0.04 (0.03–0.08)	0.02 (0.01–0.03)	0.16 (0.10–0.24)
2007–2012 and <500	0.82 (0.73–0.87)	0.68 (0.58–0.78)	0.04 (0.03–0.07)	0.03 (0.01–0.04)	0.05 (0.03–0.08)
2007–2012 and 500	0.84 (0.75–0.88)	0.65 (0.55–0.74)	0.01 (0.01–0.02)	0.01 (0.00–0.01)	0.01 (0.01–0.02)

Q1: 25th percentile, Q3: 75th percentile. Models were adjusted for predicted probability of maintaining adherence 95% over time (for both CD4⁺ cell count cut-offs) – age, sex, history of injection drug use, longitudinal viral load and follow-up time; predicted probability of maintaining viral suppression over time (for both CD4⁺ cell count cut-offs) – age, sex, history of injection drug use, longitudinal adherence to cART and follow-up time; predicted probability of developing resistance to any drug class over time (for both CD4⁺ cell count cut-offs) – age, sex, history of injection drug use, longitudinal adherence to cART, longitudinal viral load and follow-up time; predicted probability of developing an AIDS-defining illness by the end of follow-up (for both CD4⁺ cell count cut-offs) – history of injection drug use, longitudinal adherence to cART, longitudinal viral load and follow-up time; predicted probability of being dead by the end of follow-up (for both CD4⁺ cell count cut-offs) – age, sex, history of injection drug use, longitudinal adherence to cART, longitudinal viral load and follow-up time.