Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies.

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When should AIDS-free HIV-1 infected persons initiate antiretroviral therapy? Collaborative analysis of HIV cohort studies

When To Start Consortium*

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Abstract

Background: The CD4 count at which combination antiretroviral therapy (cART) should be initiated is a central, unresolved issue in the care of HIV-1 infected patients. In the absence of randomized trials, we examined this question in prospective cohort studies.

Methods: Antiretroviral-naïve patients from 15 cohort studies, who started cART after 1997 with CD4 <550 cells/mm^3, AIDS-free and without a history of injection drug use, were eligible. We estimated distributions of lead times (from the first CD4 count measurement in an upper range to the upper threshold of a lower range) and unseen AIDS and death events (occurring before reaching the upper threshold of a lower CD4 count range) in the absence of treatment using data on patients followed during the pre-cART era, and used these to impute completed datasets including lead times and unseen events. We compared the effect of deferred with immediate initiation of cART on rates of AIDS and death, and death, in adjacent CD4 ranges of width 100 cells/mm^3.

Findings: Deferring cART until CD4 count range 251-350 cells/mm^3 was associated with higher rates of AIDS and death, compared with starting in the range 351-450 cells/mm^3 (hazard ratio 1.28; 95% CI: 1.04, 1.57). The adverse effect of deferring cART increased with decreasing CD4 threshold. Deferring cART was associated with higher mortality rates, although effects on mortality were less marked than effects on AIDS and death.

Interpretation: These findings should help guide physicians and patients in deciding when to initiate antiretroviral treatment. Our results support the minimum threshold for initiation of antiretroviral therapy being 350 cells/mm^3.

Introduction

Combination antiretroviral therapy (cART) has dramatically reduced morbidity and mortality in HIV-1 infected individuals since its introduction in 1996.[1,2] Short-term randomized controlled trials (RCTs) conducted in immunodeficient patients demonstrated that rates of AIDS or death were halved after approximately one year of cART, compared with rates in patients treated with drugs from only one antiretroviral therapy class.[3] There has been no long-term trial examining the clinical effect of cART, but observational data indicate that cART reduces rates of AIDS or death over several years, both in immunodeficient patients and those with higher CD4 cell counts.[4,5]

A central, unresolved issue is the CD4 cell count at which cART should be initiated, in patients who have not yet experienced an AIDS-defining event. The best way to address this question is to randomize AIDS-free HIV-1 infected patients to either initiate cART while in an upper CD4 cell count range or defer initiation until the upper threshold of a lower CD4 count range is reached. No such RCT has been conducted: the randomized evidence is limited to a sub-study in the Strategies for Management of Anti-Retroviral Therapy (SMART) trial,[6] suggesting that deferring cART initiation to CD4 <250 cells/mm^3, compared with starting at CD4 >350 cells/mm^3, more than triples the hazard of AIDS or death and, unexpectedly, increases other serious adverse events.[7]

In the absence of randomized evidence, the question of when to start cART is best addressed in prospective observational studies of HIV-1 infected individuals. Most analyses of such data have, however, compared rates of AIDS and death from the time that patients started treatment[8-10] (upper panel of Figure 1). Such comparisons are problematic because they do not account for AIDS events or deaths that occur during the so called 'lead time', before the upper threshold of the lower CD4 range is reached (lower panel of Figure 1). These 'unseen events', as well as lead times, will be ignored in analyses where patients' follow up time is measured from the start of treatment, introducing lead-time bias.[11,12]

We analyzed data from a collaboration of cohort studies, employing novel methods to estimate the effect of initiating cART at different CD4 thresholds.

Methods

We used data from seven cohort studies with patients followed up during the pre-cART era, and data from the Antiretroviral Therapy (ART) Cohort Collaboration of patients starting cART, to estimate rates of AIDS or death in patients starting cART in different CD4 ranges, taking into account the probability of progression before reaching the upper threshold of the lower CD4 count range. Patients whose presumed HIV transmission was by injection drug use (IDU) were analysed separately, because they have a high prevalence of comorbidities including chronic hepatitis C[13] and worse prognosis on cART.[14,15]

Cohorts and patients included in analyses

Pre-cART data: Analyses of progression before starting cART included patients followed during the pre-cART era (July 1, 1989 to December 31, 1995) with a CD4 count in the range 0 to 550 cells/mm^3 in one of the following cohort studies: the Multicenter AIDS Cohort Study (MACS),[16] the Swiss HIV Cohort Study (SHCS),[17] the French Hospital Database on HIV (FHDH) ANRS CO4,[18] the Aquitaine Cohort ANRS CO3,[19] the Amsterdam Cohort Studies,[20] the South Alberta Clinic,[21] and the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) collaboration[22] (excluding patients who were also included in the other cohorts). Patients had regular CD4 cell count measurements at scheduled clinics and were followed for clinical AIDS events and death. A small number of patients who started cART before 1st January 1996 were excluded.

On cART data: Analyses of progression after starting cART included all patients enrolled in one of 15 cohorts participating in the ART Cohort Collaboration who started cART on or after 1st January 1998 with a CD4 count between 0 and 550 cells/mm^3 and did not have an AIDS diagnosis prior to starting cART. The ART Cohort Collaboration is a collaboration of cohort studies from Europe and North America, established with the aim of describing the prognosis of antiretroviral-naïve patients starting cART. The study design has been described in detail elsewhere.[23-25] Prospective cohort studies were eligible if they had enrolled at least 100 patients with HIV-1 infection aged 16 years or older who had not previously received antiretroviral treatment and who had started antiretroviral therapy with a combination of at least three drugs, including nucleoside reverse transcriptase inhibitors, protease inhibitors, and/or non-nucleoside reverse transcriptase inhibitors, with a median duration of follow-up of at least one year. All

cohorts provided anonymized data on a predefined set of demographic, laboratory and clinical variables.

Fifteen cohorts contributed on cART data to the present analysis, including the French Hospital Database on HIV (FHDH) ANRS CO4,[18] the Aquitaine Cohort ANRS CO3,[19] the AIDS Therapy Evaluation Netherlands project (ATHENA),[26] the Italian Cohort of Antiretroviral-Naive Patients (ICONA)[27], the Swiss HIV Cohort Study (SHCS),[17] the Frankfurt HIV Cohort,[28] the Köln-Bonn Cohort,[29] the Collaborations in HIV Outcomes Research United States (CHORUS),[30] the 1917 Clinic Cohort University of Birmingham, Alabama,[31] the Veterans Aging Cohort Study (VACS),[32] the London Royal Free Hospital Cohort,[33] the British Columbia Centre for Excellence in HIV/AIDS,[34] the South Alberta Clinic,[21] the Proyecto para la Informatizacion del Seguimiento Clinico epidemiologico de los pacientes con Infección por VIH/SIDA (PISCIS),[35] and the EuroSIDA study,[36] which collects data from 20 countries in Europe and Argentina, (excluding patients who were also included in other ART-CC cohorts).

Censoring and statistical analysis

Patients who remained alive were censored at their last visit, plus 50% of the average time between visits for each cohort. For example, if a cohort had, on average, 6 months between follow-up visits, patients were censored at last visit plus 3 months. Patients with a gap of more than one year between clinic visits were considered lost to follow up and were censored at the beginning of the gap plus 50% of the average time between visits. Follow up of patients in the pre-cART era was administratively censored on 31st December 1995 and, in patients starting cART, at 6 years after starting cART or at the (cohort-specific) date of the close of the database.

Using on cART data, we derived Kaplan-Meier estimates of cumulative probabilities of progression to AIDS and death from the time of starting cART, according to CD4 cell count at initiation. We used Cox regression to estimate "naïve" hazard ratios (HRs) for AIDS or death (based on analyses ignoring lead-time and unseen AIDS and death events) comparing individuals with differing CD4 cell count category at initiation of cART. In sensitivity analyses, we examined whether adjusting for patient characteristics at the time of starting cART altered these naïve HRs.

To account for lead-time and unseen AIDS and death events, we used a method described by Cole et al.,[12] whereby missing data on lead-time and unseen events in the deferred arm are

recovered using multiple imputation[37]. Full details are given in the Web Appendix (available at http.//www. …). Using pre cART data, we modelled the distribution of times from the first CD4 measurement in the upper CD4 range to the upper threshold of the lower CD4 range (i.e., lead-time) and the probability of progression to AIDS or death before reaching the upper threshold of the lower CD4 range (i.e., unseen events). We repeated all comparisons using death alone as the endpoint, assuming that cART has no effect on deaths for two weeks and that an AIDS diagnosis will lead to immediate initiation of cART. Therefore in patients on cART deaths within two weeks of initiation were excluded, while in pre-cART data deaths included in analyses were those before reaching the upper threshold of the lower CD4 range, or within 2 weeks of an AIDS diagnosis. We examined whether progression rates differed between the earlier (1989-91) and later (1992-95) years of the pre-cART era, by splitting follow up time and including interaction terms in Cox regression models. We used random-effects regression models for log-transformed CD4 counts to estimate the average rate of decline in CD4 counts during the pre-cART era.

Based on the fitted distributions, imputation was used to create completed datasets, in which lead-times and unseen AIDS and death events were added to the on cART data, for patients in the deferred initiation group. We used Cox regression to estimate HRs comparing deferred with immediate initiation of cART for each completed dataset, then combined these using Rubin's formula.[37] We used generalized gamma distributions for the lead times and unseen events, after redistributing censored patients according to the proportions progressing to AIDS or death and reaching the upper threshold of the lower CD4 range to estimate the probability of progression before reaching the threshold. We examined the proportional hazards assumption by comparing progression rates in the first 2 years with rates from 2 years to the end of follow up (6 years).

We compared deferred with immediate initiation of cART in adjacent ranges of width 100 cells/mm^3. We started with a comparison of initiation at 101-200 compared with deferring to 0-100 cells/mm^3, then compared initiation at 126-225 with deferring to 25-125 cells/mm^3 and, using successive increments of 25 cells/mm^3, made similar comparisons ending with a comparison of initiation at 451-550 with deferring to 351-450 cells/mm^3. We conducted sensitivity analyses restricted to patients included in four cohorts that provided both pre-cART and on-cART data (the French Hospital Database on HIV, Aquitaine Cohort, Swiss HIV Cohort Study and the South Alberta Clinic Cohort). We also plotted the hazard ratios for the cumulative

effects of delayed initiation, compared with starting in the range 351-450 cells/mm^3, by multiplying hazard ratios for successive non-overlapping CD4 ranges: 250-350, 150-250 and 50-150 cells/mm^3. Confidence intervals for the plotted cumulative effects were obtained using a Poisson approximation after decomposing the variance into contributions from each of the CD4 groups. All analyses were conducted using SAS™ version 9 (Cary, NC, USA) and Stata™ version 10.0 (College Station, TX, USA).

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Our sponsors had no role in the design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 21,247 AIDS-free patients with presumed transmission not by IDU who were followed up during the pre-cART era, and 24,444 such patients followed from the start of cART within the ART Cohort Collaboration were included in the main analyses. A total of 4159 patients (17%) were followed for more than six years (at which time follow-up was censored) after starting cART. Patient characteristics are shown in Table 1. Compared with patients starting cART, those followed up in the pre-cART era were younger, more likely to be men who have sex with men and more likely to develop AIDS or die during follow up. We found little evidence that progression rates differed between the earlier (1989-91) and later (1992-95) years of the pre-cART era (Web Table 1). The average annual decline in CD4 counts during the pre-cART era was 77 (95% CI 76, 78) cells/mm^3 per year. Among those starting cART, 9103 (37%) patients started with CD4 below 350 but above 200 cells/mm^3, with a further 23% of patients starting in the range 101-200 cells/mm^3, and 21% in the range 350-550 cells/mm^3. A total of 1860 (7.6%) patients experienced AIDS-defining events after starting treatment and 808 (3.3%) died. Half of the patients initiated cART with a regimen including a protease inhibitor.

Figure 2 shows cumulative probabilities of AIDS or death (upper panel) and death (lower panel) up to 6 years after starting cART, according to the range of CD4 count at the time of starting cART (0-50, 51-150, 151-250, 251-350, 351-450 and 451-550 cells/mm^3). As reported previously,[10,38] the cumulative probability of AIDS and death increased dramatically with decreasing CD4 at the time of starting cART. However, this does not necessarily imply that

cART should be initiated in the higher CD4 count range, because this comparison does not account for lead-time or unseen AIDS and death events (see Figure 1).

Table 2 compares rates of progressing to AIDS or death, in adjacent CD4 ranges of width 100 cells/mm^3, with successive increments of 25 cells/mm^3. Note that results in overlapping ranges are not statistically independent of each other. The mean decline in CD4 count from the first measurement in the upper range to the upper threshold of the lower range varied from 48 cells/mm^3 for upper range 451-550 cells/mm^3 to 61 cells/mm^3 for upper range 101-200 cells/mm^3. Estimated lead-times increase with decreasing CD4 cell count. This is at least partly because the variability of CD4 counts is greater at higher CD4 ranges, so that observed declines of more than 100 cells/mm^3 are more rapid. As expected, the estimated percent of patients progressing to AIDS or death before reaching the upper theshold of the lower CD4 range (the percentage experiencing unseen AIDS and death events) increases with decreasing CD4 count. The right-hand columns of Table 2 show naive HRs comparing the effects of deferring cART to a lower CD4 range, compared with starting in a higher CD4 range, and HRs after adjusting for lead-time and unseen events. Adjusting for age at initiation, sex and risk group (men who have sex with men versus other) did not materially alter naïve HRs (Web Table 2).

The adjusted results suggest that deferring cART until CD4 counts are in the range 251-350 cells/mm^3 leads to increased rates of AIDS or death, compared with starting in the range 351-450 cells/mm^3 (HR 1.28, 95% CI 1.04-1.57). At the higher CD4 cell count ranges there is little evidence that deferred initiation of cART leads to higher rates of AIDS and death (HR 0.99; 95% CI: 0.76, 1.43 for the comparison of deferring to 351-450 compared with starting at 451-550 cells/mm^3). Comparing adjusted and naïve results, the effect of accounting for unseen AIDS and death events outweighs the effect of lead-time in lower CD4 ranges, so that adjusted HRs exceed naïve HRs. In contrast, in higher CD4 ranges rates of unseen events are lower, and approximately balance the effect of lead-time, so that the naïve and adjusted HRs are similar. The upper panel of Figure 3 illustrates the successive increase in the rates of AIDS or death as cART is deferred to lower CD cell count thresholds.

Table 3 compares mortality rates resulting from deferring cART to lower compared with starting at higher CD4 ranges. As expected, mortality rates increase with declining CD4 cell count. Compared with Table 2, confidence intervals for HRs are wider, because the number of

deaths is smaller than the number of combined AIDS and death endpoints. Because the proportions of patients with "unseen" deaths are smaller than the proportions with unseen AIDS and death events, the adjusted mortality hazard ratios are more similar to the naïve mortality hazard ratios than in the analyses of AIDS and death presented in Table 2. The adjusted HRs suggest that there is no adverse effect on mortality rates of deferring cART to the range 276-375 cells/mm^3 (HR 0.99, 95% CI 0.68-1.43, compared with starting in the range 376-475 cells/mm^3). As illustrated in the lower panel of Figure 3, below these ranges, mortality increases as cART is deferred to lower CD4 ranges. Except in the highest CD4 ranges, the beneficial effects of earlier initiation were greater in the first two years' follow up than in the period from 2 to 6 years' follow up (Web Table 3).

We repeated analyses in patients with presumed transmission by IDU. A total of 4605 such patients were included in on-cART data: they experienced 653 AIDS or death events (334 deaths) during 15,141 years of follow up. There were 9,860 such patients followed during the pre-cART era: they experienced 905 AIDS or death events (823 deaths) during 27,182 years of follow up. Web Table 4 shows estimated HRs for deferring compared with initiating cART in different CD4 ranges. For comparisons in which the threshold CD4 was low, estimated benefits of earlier initiation were less for patients whose presumed transmission was by IDU, than for other patients. At higher CD4 thresholds the estimated benefits of earlier initiation were broadly consistent with those in the main analyses presented in Tables 2 and 3, though as expected (given that the numbers of patients with transmission by IDU were smaller than in the main analyses), confidence intervals were wide. A total of 13084 (54%) patients on cART and 17993 (85%) patients followed during the pre-cART era were included in the four cohorts that contributed both on-cART and pre-cART data. Web Table 5 shows the results of sensitivity analyses for the combined AIDS and death endpoint, restricted to these patients. Results were consistent with the main analyses: most hazard ratios for the adverse effect of deferring treatment were somewhat larger, particularly for low CD4 ranges.

Figure 4 shows the cumulative effect of delayed initiation of cART, compared with starting in the range 350-450 cells/mm^3. Deferring cART to CD4 cell counts of between 50 and 150 cells/mm^3 was associated with a hazard ratio of 5.67 (95% CI 4.83-6.65) for the combined endpoint AIDS and death, and a hazard ratio of 2.24 (95% CI 1.72-2.92) for mortality. In the ART Cohort Collaboration 37% of patients started cART below 150 cells/mm^3.

Discussion

This collaborative analysis of over 45,000 patients who were followed up in cohort studies in Europe and North America suggests that in AIDS-free HIV-1-infected individuals, deferring cART until CD4 cell counts are in the range 251-350 cells/mm^3 leads to increased rates of the combined endpoint AIDS or death, compared with starting cART in the range 351-450 cells/mm^3. As expected, the excess of AIDS or death associated with deferring cART became more pronounced as the CD4 threshold for starting cART decreased. Effects of deferring cART on mortality alone were less pronounced, but patterns were consistent with those for rates of the combined endpoint of AIDS or death. Beneficial effects of early initiation tended to be greater during the first two years of follow up than subsequently.

In contrast to previous studies that have compared rates of progression from the time of initiation of cART,[8-10] we accounted for both the treatment-free time spent by patients who defer treatment, and for the events that occur before initiation of treatment in these patients. Our analyses thus aimed to estimate the intervention effects that would be observed in studies in which patients were allocated either to starting treatment in a higher CD4 range or to deferring to a lower CD4 range. Because of the large number of patients included in this collaborative study, our analyses had reasonable power to detect differences in progression rates. In contrast, previous studies that compared mortality rates among patients who initiated cART and patients who delayed cART until reaching a lower CD4 cell range were limited by a small number of endpoints.[39,40] The analysis of the HIV Outpatient Study showed that mortality was reduced by 39% in patients who started cART in the range of 350-500 CD4 cells, compared to patients who deferred treatment to after the CD4 cell count had fallen to below 350 cells/mm^3, however, this did not reach conventional levels of statistical significance (p=0.17).[39] Previous analyses that used the method employed here to account for lead-time and unseen AIDS and death events were also based on a much smaller number of patients.[12,41]

Data on large numbers of patients were combined in this collaborative analysis. This meant that we were able to compare relatively narrow CD4 strata, of width 100 cells/mm^3, with the aim of locating CD4 ranges within which earlier initiation has beneficial effects on rates of AIDS and death. Had we compared wider CD4 ranges, hazard ratios might have increased, at the cost of reduced clinical relevance. For example, a comparison of initiation in the range 301-500

cells/mm3 with deferral to the range 101-300 cells/mm^3 would compare some patients who started at 490 cells/mm^3 with some patients who started at 110 cells/mm^3.

Patients who experienced an AIDS event before initiation of cART were excluded: they have worse prognosis and are likely to start cART regardless of their CD4 count.[42] Analyses nevertheless included patients from many countries from Europe and North America, both in the pre-cART era and on cART, who were treated in different settings. The range of patients was broad: men and women, from teenagers to elderly people were included, and patients presumed to have been infected through heterosexual as well as homosexual sex between men were well represented. We analysed data from patients infected by IDU separately, to avoid possible confounding due to co-morbidities, deferred treatment and non-adherence in these patients. HIV-infected intravenous drug users have a high prevalence of comorbidities,[13] and worse prognosis on cART.[14,15] Given that our conclusions were similar in these patients, our results should be applicable to many patients starting cART or considering cART in industrialized countries. The clear disadvantages of delaying initiation of cART to below 200 CD4 cells/mm^3 may also have implications for resource-limited settings, where eligibility criteria for initiating cART are often advanced immunodeficiency or clinical disease.[43]

An important assumption made in these analyses is that progression rates and mortality in the pre-cART era, i.e. 1989 to 1995, are an appropriate reflection of what they would have been in the absence of cART in recent years. During the 1990s, the introduction of chemoprophylaxis, immunization, and better strategies for managing acute opportunistic infections contributed to preventing clinical progression and improving survival. In particular, the introduction of prophylaxis against Pneumocystis jiroveci pneumonia (PCP)[44] and for Mycobacterium avium complex (MAC) disease in 1993[45] were important. Although substantially less effective than cART, monotherapy (mainly with zidovudine)[46] became available in the late 1980s while dual therapy with two nucleoside reverse transcriptase inhibitors[47] became available during the mid 1990s. These factors will have acted in opposite directions: early pre-cART era rates of AIDS and death may have been higher than contemporary rates in the absence of treatment because of lower rates of prophylaxis, while later pre-cART era rates may have been reduced because some patients were treated with mono or dual therapy. We suggest that biases introduced by these factors will have been limited. First, both prophylaxis and treatment were used mainly in patients with CD4 counts less than 200 cells/mm^3, in whom the adverse consequences of delayed

initiation of cART are clear. Second, monotherapy was of only limited, transient benefit,[46] while dual therapy became widely available only during late 1994 and early 1995. Third, as shown in Web Table 2 we found little evidence that rates of AIDS and death differed, comparing the earlier (1989-91) with later (1992-95) years of the pre-cART era within the different CD4 ranges. A proportion of patients included in the on-cART dataset and who started cART soon after 1998 had an initial cART regimen including an un-boosted protease inhibitor, which may have attenuated the beneficial effect of cART in the early portion of follow up.

As is the case for any observational study, our results may have been affected by confounding and selection biases, if patient characteristics associated with deferred initiation of cART are also predictive of progression rates on or off cART. We aimed to deal with such biases by excluding patient groups known to have higher progression rates. As well as excluding patients infected by IDU and those who experienced an AIDS event before initiation of cART, we excluded patients who started cART before 1998, when regimens were less effective than those now available.[48,49] Nonetheless it remains possible that our results are affected by unmeasured confounding factors. Only an RCT would overcome such concerns: moreover an RCT could take into account factors outside the scope of our analysis, including both AIDS-defining and non- AIDS defining events, severe and non-severe AIDS events, and drug related toxicities. Therefore, a definitive answer to the question of when to initiate cART will only be given when results become available from RCTs such as the Strategic Timing of AntiRetroviral Treatment (START) trial, which aims to determine whether immediate initiation of cART is superior (in terms of morbidity and mortality) to deferral of cART until the CD4 count declines below 350 cells/mm^3 in HIV-1 infected persons who are antiretroviral naïve with a CD4 count greater than 500 cells/mm^3.

In the absence of definitive evidence from RCTs, it is necessary to rely on observational evidence in formulating guidelines on the CD4 cell count at which patients should start cART. When patients and their physicians consider when to initiate cART they must balance its beneficial effects on rates of progression to AIDS and death with a number of other issues.[50,51] Eradication of HIV from an individual is not currently possible,[52] so that treatment is expected to be lifelong. Antiretroviral drugs can be inconvenient to take, and have side effects that include nausea, diarrhea, and headache. cART has serious toxicities including lipodystrophy and lipoatrophy syndromes,[53,54] hepatitis, renal failure and mitochondrial toxicity,[55] and an increased

risk of cardiovascular disease.[56] However these toxicities may be to some extent avoidable through choice of cART regimen: for example increases in cardiovascular risk appear greater for protease inhibitors than for non-nucleoside reverse transcriptase inhibitors,[57] and lipoatrophy is related to thymidine analogues.[58] Further, the hazard ratio of 1.28, comparing starting cART in the CD4 range 351-450 cells/mm^3 with deferring to 251-350 cells/mm^3 represents only a small absolute difference in the risk of AIDS or death over the follow up period considered here.

Recent results from the SMART trial of structured treatment interruptions have also brought new perspectives to our understanding of the benefits and risks of cART.[6] In that trial, patients who had started cART at relatively high CD4 counts and subsequently interrupted therapy experienced higher rates not only of AIDS and death, but also of serious non-AIDS events including myocardial infarction, stroke, liver cirrhosis and renal failure. The analyses presented in this paper do not account for non-fatal serious non-AIDS events, which may be the major causes of morbidity and mortality at higher CD4 counts. It may be that non-AIDS deaths in untreated individuals account for the early high mortality hazard ratios for deferred compared with immediate initiation during the first two years of follow up (Web Table 3). Data from the EuroSIDA study show that rates of death from non-AIDS causes declined dramatically at the start of the HAART era.[59,60]

In conclusion, these findings should help guide physicians and patients in deciding when to initiate antiretroviral treatment. The evolution of guidelines has been likened to the swings of a pendulum,[61,62] from initial enthusiasm for early treatment[63] through caution due to concern over toxicities and the risk of resistance and loss of treatment options,[64] to more recent calls again for earlier treatment.[65] The International AIDS Society USA Panel recommended in August 2008 that antiretroviral therapy is started in individuals with CD4<350 cells/mm^3, and that the decision should be individualized when the CD4 is greater than 350 cells/mm^3.[66] Recent US[67] and European guidelines make similar recommendations.[68] Because we found evidence that deferring treatment to CD4 <350 cells/mm^3 was associated with increased progression rates, and in the light of diminished concerns about toxicities and resistance[51,69], our results support the minimum threshold for initiation of antiretroviral therapy being 350 cells/mm^3.

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Conflict of interest statements

JACS has received travel grants from GlaxoSmithKline and honoraria from Gilead Sciences

MM has received travel grants from GlaxoSmithKline

DC has received travel grants, consultancy fees, and honoraria from various pharmaceutical companies including Abbott, GlaxoSmithKline, Bristol-Myers-Squibb, Gilead, Roche and Boehringer-Ingelheim.

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Amsterdam Cohort Studies

Maria Prins and Hanneke Scchuitemaker for the Amsterdam Cohort Studies on HIV infection and AIDS, a collaboration between the Health Service of Amsterdam, the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation and the University Medical Center Utrecht, are part of the Netherlands HIV Monitoring Foundation and financially supported by the Netherlands National Institute for Public Health and the Environment. Website: http://www.amsterdamcohortstudies.org/

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Table 1. Characteristics at baseline and events recorded during follow up of patients followed up in the pre-cART era and after starting cART. Baseline is date of start of follow up in the pre-cART era, and date of initiation of cART, for patients on cART.

	Pre-cART era	On cART
No. of patients	21247	24444
Baseline characteristics		
Median age in years (IQR)	34 (28-41)	37 (31-45)
Females (%)	4813 (23%)	7154 (29%)
Median CD4 cell count (IQR)	354 (264-448)	230 (130-330)
Median log10 HIV-1 RNA (IQR)	Not available	4.9 (4.4-5.3)
Transmission group (%)*		
Heterosexual sex	6961 (33%)	11382 (51%)
Men who have sex with men	11874 (56%)	8483 (38%)
Other / unknown	2412 (11%)	2485 (12%)
Calendar periods of enrolment (%)		
1989-1990	5784 (27%)	
1991-1992	6586 (31%)	
1993-1995	8877 (42%)	
1998-1999		7000 (29%)
2000-2002		9490 (39%)
2003-2006		7954 (33%)
Initial cART regimen (%)	Not applicable	
PI-based triple regimen§		11644 (48%)
NNRTI-based triple regimen§		8696 (36%)
NRTI only		2347 (10%)
Other#		1757 (6%)
AIDS and death during follow up		
Total follow up (years)	68253	81071
Median years of follow up (IQR)	3.1 (1.9-4.5)	3.2 (1.5-5.3)
Number developing AIDS (%)	5356 (25.2%)	1860 (7.6%)
Number of deaths (%)	3630 (17.1%)	808 (3.3%)
Number with AIDS or death (%)	5893 (27.7%)	2366 (9.7%)

* Excluding 2064 patients from the VACS cohort, in whom transmission group was classified only as IDU or other

§ PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor

Non-standard regimen consisting of more than one PI and/or NNRTI, or more than three drugs (excluding ritonavir-boosting of PIs)

Table 2 - Hazard ratios for AIDS or death, (naïve, and adjusted for lead times and unseen AIDS and death events), comparing deferring cART to a lower CD4 range with starting in a higher CD4 range.

CD4 ranges have widths of 100 cells/mm^3, in increments of 25 cells/mm^3.

Higher CD4 range	**Lower CD4 range**	**Pre-cART data**			**On cART data**			**Hazard ratio (95% CI) for AIDS or death**	
		No. of patients in higher CD4 range	Estimated median lead time* (years)	Estimated % (95% CI) progressing to AIDS/death before upper threshold of lower CD4 range	No. of patients	No. of AIDS/death events	Estimated no. of unseen events	Naïve	Adjusted for lead times and unseen events
451-550	351-450	5015	0.67	1.6 (1.1 to 2.1)	5047	260	53	1.04 (0.81 to 1.34)	0.99 (0.76 to 1.29)
426-525	326-425	5792	0.77	2.3 (1.7 to 2.9)	5898	314	91	1.12 (0.89 to 1.42)	1.12 (0.87 to 1.43)
401-500	301-400	6536	0.80	2.7 (2.0 to 3.4)	6874	366	126	1.04 (0.84 to 1.29)	1.09 (0.85 to 1.38)
376-475	276-375	7029	0.84	2.8 (2.2 to 3.5)	7926	400	151	1.11 (0.91 to 1.37)	1.19 (0.96 to 1.47)
351-450	251-350	7433	0.84	3.2 (2.5 to 3.9)	8989	472	189	1.17 (0.97 to 1.41)	1.28 (1.04 to 1.57)
326-425	226-325	7775	0.86	3.3 (2.7 to 3.8)	10067	530	208	1.08 (0.90 to 1.28)	1.21 (1.01 to 1.46)
301-400	201-300	8226	0.89	3.8 (3.1 to 4.5)	10980	584	258	1.15 (0.98 to 1.36)	1.34 (1.12 to 1.61)
276-375	176-275	8519	0.91	5.3 (4.3 to 6.3)	11775	640	366	1.23 (1.05 to 1.44)	1.59 (1.30 to 1.95)
251-350	151-250	8748	0.92	6.1 (5.2 to 7.0)	12104	719	412	1.30 (1.12 to 1.51)	1.71 (1.43 to 2.04)
226-325	126-225	8788	0.91	7.0 (6.2 to 7.8)	12206	763	452	1.47 (1.27 to 1.70)	2.01 (1.73 to 2.35)
201-300	101-200	8878	0.92	8.1 (7.2 to 9.1)	11976	822	485	1.59 (1.38 to 1.82)	2.21 (1.91 to 2.56)
176-275	76-175	8282	0.90	9.5 (8.6 to 10.4)	11534	908	523	1.82 (1.60 to 2.08)	2.61 (2.27 to 3.00)
151-250	51-150	7484	0.95	10.8 (9.9 to 11.7)	10926	957	549	1.76 (1.55 to 2.01)	2.59 (2.29 to 2.92)
126-225	26-125	6742	0.95	13.1 (12.1 to 14.1)	10276	1088	642	2.01 (1.78 to 2.27)	2.88 (2.56 to 3.25)
101-200	0-100	5871	0.92	17.6 (16.3 to 18.9)	10014	1332	969	2.25 (2.01 to 2.51)	3.35 (2.99 to 3.75)

* Time from first CD4 measurement in upper range to upper threshold of lower CD4 range, AIDS or death

Table 3 - Hazard ratios for death (naïve, and adjusted for lead times and unseen deaths), comparing deferring cART to a lower CD4 range with starting in a higher CD4 range. CD4 ranges have widths of 100 cells/mm^3, in increments of 25 cells/mm^3.

Higher CD4 range	**Lower CD4 range**	**Pre-cART data**			**On cART data**			**Mortality hazard ratio (95% CI)**	
		No. of patients in higher CD4 range	Estimated median lead time* (years)	Estimated % (95% CI) progressing to death before upper threshold of lower CD4 range	No. of patients	No. of deaths	Estimated no. of unseen deaths	Naïve	Adjusted for lead times and unseen deaths
451-550	351-450	5015	0.66	0.5 (0.3 to 0.7)	5053	92	15	1.06 (0.69 to 1.62)	0.93 (0.60 to 1.44)
426-525	326-425	5792	0.77	0.6 (0.3 to 1.0)	5910	108	26	1.03 (0.69 to 1.52)	0.96 (0.63 to 1.46)
401-500	301-400	6536	0.81	0.7 (0.4 to 0.9)	6887	129	29	1.15 (0.80 to 1.65)	1.01 (0.68 to 1.50)
376-475	276-375	7029	0.84	0.6 (0.4 to 0.9)	7943	149	30	1.20 (0.86 to 1.69)	0.99 (0.68 to 1.43)
351-450	251-350	7433	0.84	0.7 (0.4 to 1.1)	9013	183	41	1.38 (1.01 to 1.88)	1.13 (0.80 to 1.60)
326-425	226-325	7775	0.88	0.8 (0.5 to 1.1)	10099	208	48	1.43 (1.07 to 1.91)	1.24 (0.92 to 1.67)
301-400	201-300	8226	0.87	1.0 (0.2 to 1.8)	11021	239	67	1.43 (1.10 to 1.86)	1.25 (0.86 to 1.82)
276-375	176-275	8519	0.89	1.1 (0.8 to 1.5)	11825	264	72	1.43 (1.12 to 1.84)	1.32 (0.98 to 1.78)
251-350	151-250	8748	0.92	1.4 (0.8 to 2.0)	12159	294	90	1.32 (1.04 to 1.66)	1.23 (0.90 to 1.69)
226-325	126-225	8788	0.90	1.5 (0.9 to 2.1)	12269	324	93	1.41 (1.13 to 1.76)	1.34 (1.01 to 1.77)
201-300	101-200	8878	0.92	1.6 (1.1 to 2.0)	12051	348	84	1.44 (1.16 to 1.78)	1.34 (1.05 to 1.71)
176-275	76-175	8282	0.91	1.8 (1.6 to 2.1)	11626	362	91	1.48 (1.21 to 1.82)	1.51 (1.21 to 1.87)
151-250	51-150	7484	0.93	2.2 (1.8 to 2.6)	11044	369	104	1.48 (1.21 to 1.82)	1.61 (1.29 to 2.01)
126-225	26-125	6742	0.92	2.7 (2.2 to 3.1)	10432	417	125	1.58 (1.30 to 1.91)	1.75 (1.43 to 2.15)
101-200	0-100	5871	0.89	3.7 (3.0 to 4.4)	10248	500	184	1.73 (1.45 to 2.08)	2.04 (1.7 to 2.46)

* Time from first CD4 measurement in upper range to upper threshold of lower CD4 range, AIDS or death

Figure 1 - Comparison of analyses from initiation of treatment (upper panel a) and from the time at which the upper CD4 threshold is reached (lower panel b).

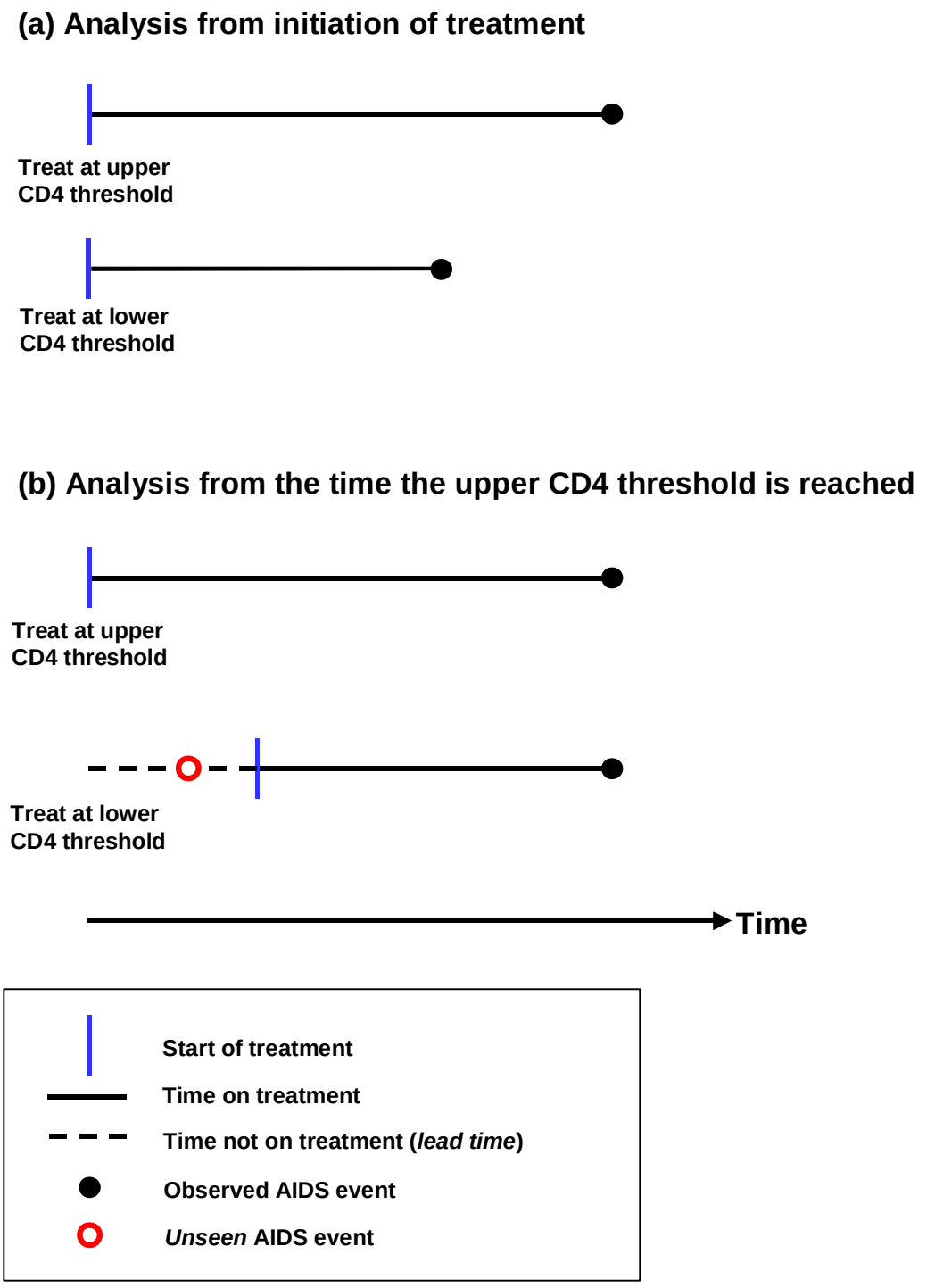
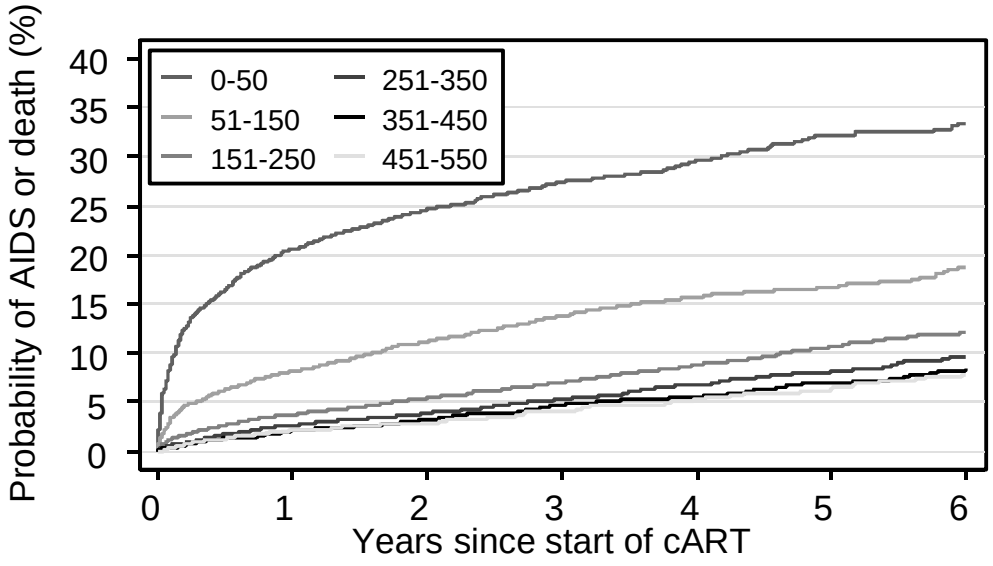
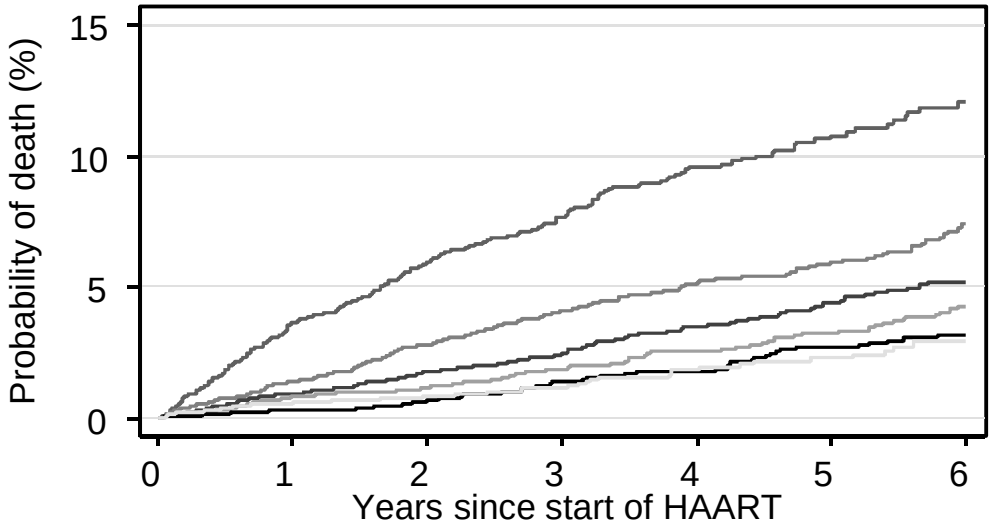


Figure 2 - Cumulative probabilities of AIDS or death (upper panel) or death (lower panel) after starting cART, according to range of CD4 count at the time of starting cART.



Number at risk

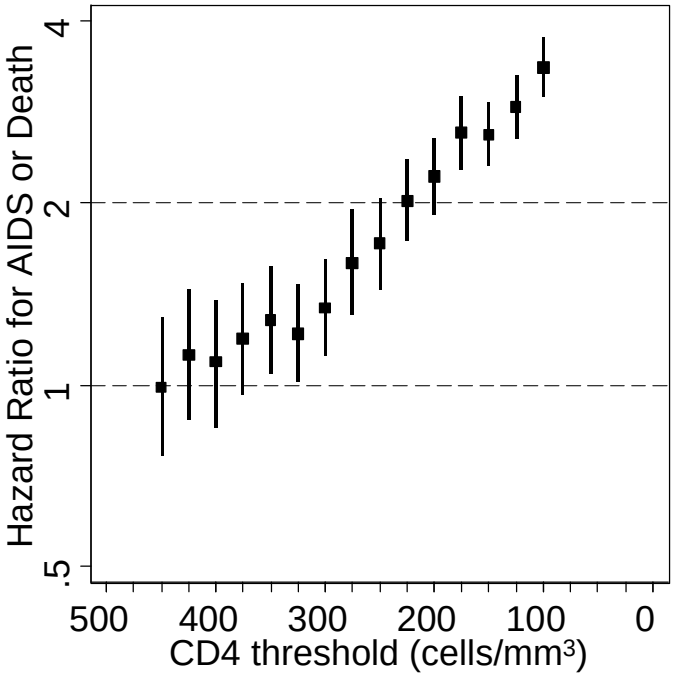
CD4 = 0-50	2594	1800	1417	1091	784	512	300
CD4 = 51-150	4638	3607	2875	2184	1570	1038	597
CD4 = 151-250	6406	4963	3763	2766	1957	1279	763
CD4 = 251-350	5753	4565	3570	2760	2058	1444	861
CD4 = 351-450	3260	2719	2315	1855	1492	1095	681
CD4 = 451-550	1793	1529	1326	1108	899	684	437



Number at risk

CD4 = 0-50	2594	2230	1842	1465	1077	728	419
CD4 = 51-150	4638	3919	3215	2516	1856	1227	718
CD4 = 151-250	6406	5177	4029	3005	2163	1439	860
CD4 = 251-350	5753	4707	3756	2947	2238	1576	943
CD4 = 351-450	3260	2793	2413	1965	1604	1188	740
CD4 = 451-550	1793	1576	1384	1182	976	744	479

Figure 3 – Adjusted hazard ratios and 95% confidence intervals for AIDS or death (upper panel) and death alone (lower panel), comparing the effects of deferring cART to a 100 cells/mm^3 lower CD4 threshold with initiation at the higher threshold. The horizontal axis shows the upper limits of the CD4 cell count ranges in the lower threshold groups (from 351 to 450 cells/mm^3, in steps of 25 cells/mm^3, to 0 to 100 cells/mm^3). The adjusted hazard ratios and confidence intervals are detailed in Table 2.



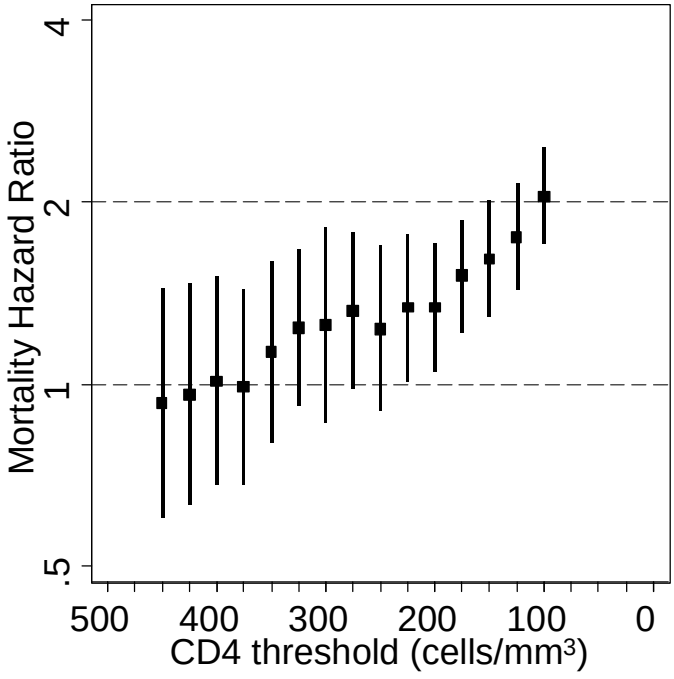
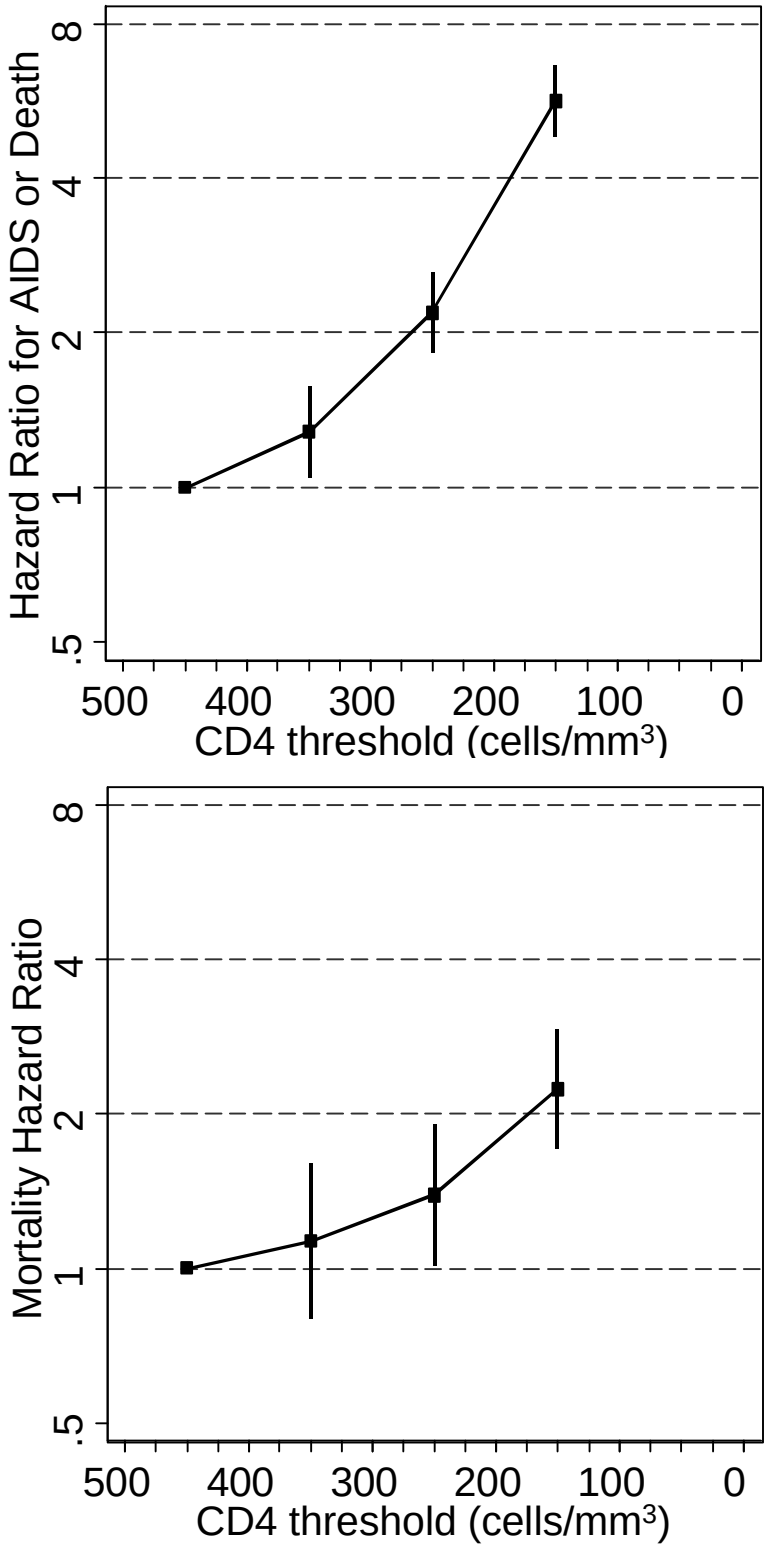


Figure 4 - Hazard ratios and 95% confidence intervals for the cumulative effect of delayed initiation of cART for the combined endpoint AIDS or death (upper panel) and death alone (lower panel). The horizontal axis shows the upper limits of the CD4 cell count ranges compared: 351-450 cells/mm^3 (reference), 251-350 cells/mm^3, 151-250 cells/mm^3 and 51-150 cells/mm^3.



Web appendix - Methods used to adjust for lead times and unseen AIDS and death events

Analyses were based on the 21247 adult HIV-infected patients followed during the pre-cART era. Appendix Table 1 shows characteristics of these patients according to contributing cohort. The majority of the patients (14286, 67%) were included in the French Hospital Database on HIV. Participants in the Multicenter AIDS Cohort Study and Amsterdam Cohort were restricted to men who have sex with men. The median of the first CD4 count below 550 cells/mm^3 was lower in the Swiss HIV Cohort than in other cohorts, indicating that patients in that study tended to be diagnosed later in the course of their disease.

For each CD4 range corresponding to a deferred initiation group, we fitted a mixture of two generalized gamma survival distributions[70] to simultaneously model the distribution of times from the first CD4 measurement in the upper CD4 range to the upper threshold of the lower CD4 range (i.e., lead-time) and the probability of progression to AIDS or death before reaching the upper threshold of the lower CD4 range. Patients who were censored were redistributed to the two groups (i.e., those who progressed to AIDS or death or who reached the upper threshold of the lower CD4 range) according to the proportion of uncensored patients in each group. We repeated all comparisons using death alone as the endpoint. Patients in the pre-cART dataset were considered to have become eligible for immediate treatmentif they progressed to AIDS. AIDS events occurring within two weeks of the upper threshold of the lower CD4 range, and deaths occurring within two weeks of AIDS, were included as endpoints on the basis that they would not have been averted by initiation of cART. The fit of the generalized gamma distributions was checked visually by comparisons with non-parametric distributions.

For each comparison of a lower (deferred initiation) with an upper (immediate initiation) CD4 range imputation, we created 25 completed datasets based on the fitted generalized gamma distributions, in which lead-time and unseen AIDS and death events were added to the data for individuals in the deferred initiation group in the on-cART data. We analyzed each completed dataset using Cox regression to estimate hazard ratios comparing deferred with immediate initiation of cART. Finally, estimated hazard ratios from the 25 completed datasets were combined using a standard formula for the combination of multiple imputed datasets.[37]

Appendix Figure 1 shows examples of non-parametric and parametric estimates of the distributions of time to progression to AIDS before crossing the upper threshold of the lower CD4 range and to crossing the upper threshold of the lower CD4 range in the absence of cART,

for the ranges 151-250 and 351-450 cells/mm^3. The rate of progression to AIDS before reaching the upper threshold of the lower CD4 range was greater for the lower CD4 range (AIDS before declining below 150 cells/mm^3) than for the higher range (AIDS before declining below 350 cells/mm^3). In the lower CD4 range, the generalized gamma mixture model appeared to somewhat underestimate the rate of progression to AIDS and death before crossing the upper threshold of the lower CD4 range, mainly due to underestimation of the number of events very soon after the first CD4 measurement in the upper range ("fast progressors"). Any bias due to underestimation of the number of fast progressors would likely be conservative because the absence of these rapid events in the deferred arm would raise the resultant survival curve to be closer to the immediate treatment arm. The fit was notably better in higher CD4 ranges. Lack of fit at lower CD4 ranges is also unlikely to be important because benefits of early initiation are clear both in the current paper and based on existing randomized evidence.[3]

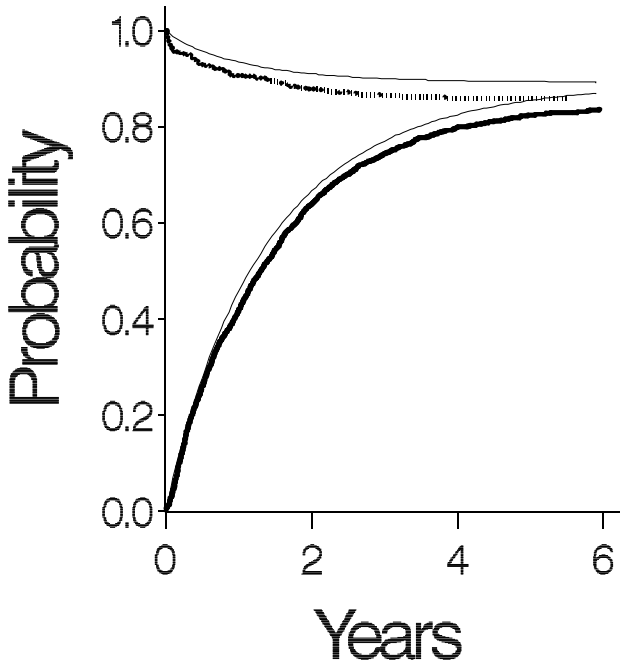
Appendix Table 1: Characteristics of 21,247 patients included in analyses in pre-cART cohorts.

Cohort	Number (%) of patients	Number (%) male	Presumed mode of transmission			Median (IQR) first CD4 <550 cells/mm^3	Total years follow up	Number of AIDS events	Number of deaths	Number of patients with AIDS or death
			MSM*	Het*	Other					
Swiss HIV Cohort Study	2059 (10)	1572 (76)	1134 (55)	828 (40)	97 (5)	342 (230-448)	7447	747	544	807
Multicenter AIDS Cohort Study	1324 (6)	1324 (100)	1324 (100)	0	0	387 (284-474)	5863	639	496	669
French Hospital Database on HIV	14286 (67)	10522 (74)	7044 (49)	5385 (38)	1857 (13)	347 (261-439)	41620	2873	1825	3231
Aquitaine Cohort	1238 (6)	907 (73)	579 (47)	431 (35)	228 (18)	350 (268-438)	4495	344	247	377
South Alberta Cohort	410 (2)	383 (93)	355 (87)	41 (10)	14 (3)	378 (280-465)	1598	133	85	135
Amsterdam Cohort	342 (2)	342 (100)	342 (100)	0	0	400 (310-490)	1575	140	109	150
CASCADE	1588 (7)	1386 (87)	1096 (69)	276 (17)	216 (14)	400 (298-475)	5653	480	324	524
Total	21247	16436 (77)	11874 (56)	6961 (33)	2412 (11)	354 (264-448)	68253	5356	3630	5893

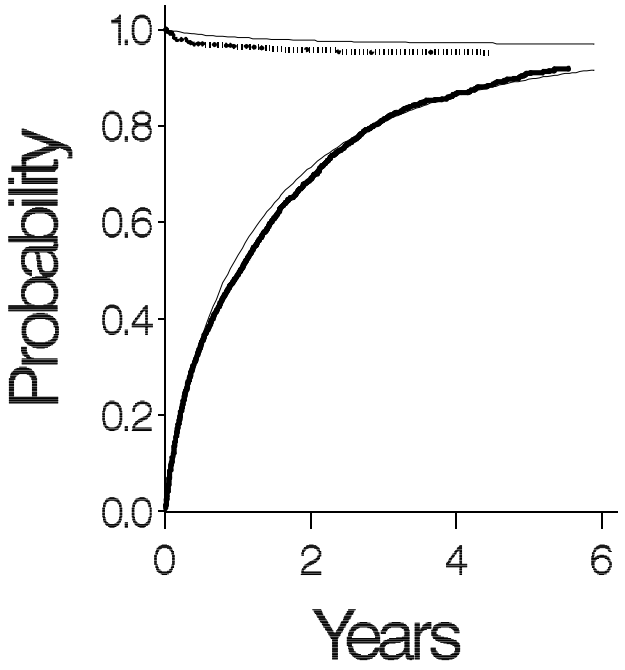
* MSM: Men who have sex with men; Het: Heterosexual sex

Appendix Figure 1: Fitted parametric estimates (thin solid lines) and non-parametric estimates (dotted line and heavy line) of cumulative proportions free of AIDS before reaching the lower CD4 threshold (upper curves) and the cumulative proportion crossing the lower CD4 threshold without AIDS diagnosis (lower curve) for (i) the range 151-250 cells/mm^3 and (ii) the range 351-450 cells/mm^3.

(i)



(ii)



Web table 1: Estimated incidence rate ratios comparing the later (1992-95) with earlier (1989-91) years the pre-cART data, after adjusting for age at start of follow up, sex and risk group (MSM/other).

CD4 range	Incidence rate ratio (95% CI)	
	AIDS or death	Death
351 - 450	1.30 (0.73,2.30)	0.99 (0.39,2.50)
251 - 350	1.01 (0.72,1.41)	0.81 (0.40,1.63)
151 - 250	1.28(1.01,1.64)	0.93 (0.57,1.53)
51 - 150	1.05 (0.88,1.26)	1.45 (0.93,2.25)
0 - 50	1.02 (0.86,1.20)	1.06 (0.70,1.62)

Web table 2: Estimated hazard ratios comparing progression rates from the time of starting cART (naïve hazard ratios), after adjusting for age at initiation, sex and risk group (MSM/other).

Lower CD4 range	Higher CD4 range	Adjusted hazard ratio (95% CI) for AIDS or death	Adjusted mortality hazard ratio (95% CI)
351-450	451-550	1.04 (0.81 to 1.34)	1.04 (0.68 to 1.59)
326-425	426-525	1.07 (0.85 to 1.35)	0.96 (0.65 to 1.43)
301-400	401-500	1.04 (0.84 to 1.29)	0.98 (0.66 to 1.45)
276-375	376-475	1.12 (0.92 to 1.37)	0.99 (0.68 to 1.44)
251-350	351-450	1.16 (0.96 to 1.39)	1.08 (0.76 to 1.53)
226-325	326-425	1.06 (0.89 to 1.25)	1.13 (0.83 to 1.53)
201-300	301-400	1.16 (0.98 to 1.36)	1.09 (0.82 to 1.45)
176-275	276-375	1.24 (1.07 to 1.45)	1.15 (0.80 to 1.67)
151-250	251-350	1.30 (1.13 to 1.50)	1.07 (0.82 to 1.40)
126-225	226-325	1.47 (1.28 to 1.69)	1.17 (0.89 to 1.53)
101-200	201-300	1.54 (1.35 to 1.76)	1.25 (0.97 to 1.59)
76-175	176-275	1.76 (1.55 to 2.00)	1.32 (1.07 to 1.64)
51-150	151-250	1.77 (1.57 to 2.00)	1.47 (1.19 to 1.82)
26-125	126-225	2.07 (1.85 to 2.32)	1.50 (1.23 to 1.83)
0-100	101-200	2.41 (2.17 to 2.68)	1.81 (1.47 to 2.23)

Web table 3. Hazard ratios (adjusted for lead times and unseen AIDS and death events), split by follow up period (0-1.99 years and 2-6 years) and comparing deferring cART to a lower CD4 range with starting in a higher CD4 range. CD4 ranges have widths of 100 cells/mm^3, in increments of 25 cells/mm^3.

Higher CD4 range	Lower CD4 range	AIDS or death		Death	
		Hazard ratio 0-1.99 years	Hazard ratio 2-6 years	Hazard ratio 0-1.99 years	Hazard ratio 2-6 years
451-550	351-450	0.97 (0.64,1.48)	0.99 (0.68,1.45)	0.87 (0.39,1.98)	0.97 (0.55,1.69)
426-525	326-425	1.06 (0.68,1.64)	1.17 (0.78,1.77)	1.12 (0.50,2.52)	0.83 (0.49,1.41)
401-500	301-400	1.15 (0.78,1.69)	1.00 (0.72,1.40)	1.60 (0.79,3.25)	0.77 (0.48,1.25)
376-475	276-375	1.30 (0.93,1.84)	1.05 (0.76,1.43)	1.97 (0.99,3.96)	0.69 (0.44,1.11)
351-450	251-350	1.42 (1.04,1.94)	1.11 (0.83,1.50)	1.94 (1.02,3.69)	0.87 (0.58,1.29)
326-425	226-325	1.41 (1.06,1.86)	1.02 (0.77,1.35)	1.73 (1.03,2.88)	0.98 (0.65,1.49)
301-400	201-300	1.55 (1.20,2.00)	1.14 (0.88,1.47)	1.41 (0.70,2.86)	1.03 (0.69,1.53)
276-375	176-275	1.90 (1.44,2.51)	1.29 (0.99,1.67)	1.61 (1.01,2.57)	1.13 (0.79,1.61)
251-350	151-250	1.86 (1.47,2.35)	1.52 (1.19,1.95)	1.44 (0.97,2.13)	1.06 (0.75,1.51)
226-325	126-225	2.38 (1.92,2.94)	1.63 (1.27,2.09)	1.64 (1.11,2.43)	1.08 (0.78,1.49)
201-300	101-200	2.56 (2.07,3.17)	1.77 (1.36,2.30)	1.62 (1.12,2.35)	1.13 (0.84,1.52)
176-275	76-175	2.92 (2.43,3.50)	2.01 (1.59,2.53)	1.78 (1.28,2.46)	1.28 (0.94,1.76)
151-250	51-150	2.90 (2.42,3.47)	2.00 (1.60,2.50)	1.79 (1.26,2.55)	1.42 (1.02,2.00)
126-225	26-125	3.33 (2.83,3.91)	2.26 (1.81,2.82)	1.82 (1.17,2.84)	1.54 (1.04,2.29)
101-200	0-100	3.55 (3.04,4.14)	2.89 (2.33,3.57)	2.19 (1.59,3.03)	1.88 (1.42,2.48)

Web table 4. Hazard ratios comparing deferring cART to a lower CD4 range with starting in a higher CD4 range, among patients with presumed transmission via IDU.

CD4 ranges have widths of 100 cells/mm^3, in increments of 25 cells/mm^3.

Lower CD4 range	Higher CD4 range	Hazard ratio (95% CI) for AIDS or death		Hazard ratio (95% CI) for death	
		Naïve	Adjusted for lead times and unseen AIDS and death events	Naïve	Adjusted for lead times and unseen deaths
351-450	451-550	1.13 (0.72 to 1.75)	0.90 (0.56 to 1.46)	1.20 (0.64 to 2.26)	0.99 (0.48 to 2.00)
326-425	426-525	1.31 (0.88 to 1.95)	0.94 (0.57 to 1.53)	1.23 (0.70 to 2.16)	1.11 (0.60 to 2.05)
301-400	401-500	1.49 (1.03 to 2.17)	1.28 (0.86 to 1.90)	1.49 (0.88 to 2.54)	1.28 (0.69 to 2.39)
276-375	376-475	1.23 (0.88 to 1.74)	1.18 (0.82 to 1.71)	1.26 (0.77 to 2.04)	1.24 (0.68 to 2.26)
251-350	351-450	1.33 (0.97 to 1.83)	1.35 (0.97 to 1.89)	1.41 (0.90 to 2.20)	1.42 (0.87 to 2.31)
226-325	326-425	1.28 (0.96 to 1.71)	1.22 (0.86 to 1.73)	1.54 (1.03 to 2.31)	1.35 (0.87 to 2.08)
201-300	301-400	1.31 (1.00 to 1.72)	1.20 (0.88 to 1.64)	1.50 (1.04 to 2.19)	1.22 (0.81 to 1.85)
176-275	276-375	1.56 (1.20 to 2.02)	1.36 (1.01 to 1.84)	1.63 (1.13 to 2.34)	1.29 (0.87 to 1.91)
151-250	251-350	1.39 (1.08 to 1.78)	1.21 (0.93 to 1.59)	1.38 (0.98 to 1.94)	1.17 (0.80 to 1.72)
126-225	226-325	1.36 (1.07 to 1.73)	1.34 (1.05 to 1.71)	1.20 (0.86 to 1.67)	0.91 (0.54 to 1.53)
101-200	201-300	1.25 (0.99 to 1.57)	1.31 (1.00 to 1.72)	1.10 (0.80 to 1.52)	1.05 (0.73 to 1.52)
76-175	176-275	1.14 (0.91 to 1.43)	1.25 (0.99 to 1.58)	1.11 (0.81 to 1.52)	1.07 (0.78 to 1.49)
51-150	151-250	1.21 (0.97 to 1.52)	1.28 (0.93 to 1.74)	1.13 (0.83 to 1.55)	1.16 (0.84 to 1.60)
26-125	126-225	1.29 (1.04 to 1.61)	1.62 (1.30 to 2.02)	1.21 (0.89 to 1.66)	1.29 (0.91 to 1.83)
0-100	101-200	1.49 (1.20 to 1.84)	2.00 (1.61 to 2.49)	1.32 (0.98 to 1.79)	1.54 (1.13 to 2.11)

Web Table 5. Hazard ratios for AIDS or death, (naïve, and adjusted for lead times and unseen AIDS and death events), comparing deferring cART to a lower CD4 range with starting in a higher CD4 range, restricted to four cohorts that provided both pre-cART and on-cART data.

		Hazard ratio (95% CI) for AIDS or death	
Lower CD4 range	Higher CD4 range	Naïve	Adjusted for lead times and unseen AIDS and death events
351-450	451-550	1.00 (0.66,1.52)	0.93 (0.59,1.47)
326-425	426-525	1.09 (0.74,1.59)	1.10 (0.72,1.66)
301-400	401-500	1.11 (0.79,1.56)	1.18 (0.81,1.72)
276-375	376-475	1.22 (0.88,1.69)	1.33 (0.94,1.88)
251-350	351-450	1.33 (0.98,1.79)	1.46 (1.02,2.08)
226-325	326-425	1.26 (0.95,1.66)	1.42 (1.07,1.89)
201-300	301-400	1.11 (0.85,1.43)	1.37 (1.06,1.78)
176-275	276-375	1.15 (0.90,1.46)	1.64 (1.27,2.13)
151-250	251-350	1.20 (0.96,1.51)	1.76 (1.37,2.27)
126-225	226-325	1.39 (1.12,1.73)	2.07 (1.64,2.63)
101-200	201-300	1.69 (1.36,2.10)	2.63 (2.12,3.25)
76-175	176-275	2.02 (1.64,2.48)	3.09 (2.49,3.85)
51-150	151-250	1.85 (1.51,2.27)	3.02 (2.48,3.68)
26-125	126-225	2.04 (1.68,2.46)	3.28 (2.73,3.94)
0-100	101-200	2.17 (1.81,2.60)	3.76 (3.15,4.49)

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