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Mortality according to CD4 count at start of combination antiretroviral therapy among HIV positive patients followed for up to 15 years after start of treatment: collaborative cohort study

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Summary:

The strong association of CD4 count at start of combination therapy with subsequent survival in HIV positive patients diminished during the first five years of treatment. After five years, lower baseline CD4 counts were not associated with higher mortality.

Abstract

Background: CD4 count at start of combination antiretroviral therapy (ART) is strongly associated with short-term survival, but its association with longer-term survival is less well characterised.

Methods: We estimated mortality rates (MR) by time since start of ART (<0.5, 0.5-0.9, 1-2.9, 3-3.9, 5-9.9 and ≥10 years) among patients from 18 European and North American cohorts who started ART during 1996-2001. Piecewise exponential models stratified by cohort were used to estimate crude and adjusted (for sex, age, transmission risk, period of starting ART [1996-7, 1998-9, 2000-1], AIDS and HIV-1 RNA at baseline) mortality rate ratios (MRR) by CD4 count at start of ART (0-49, 50-99, 100-199, 200-349, 350-499, ≥500 cells/μL) overall and separately according to time since start of ART.

Results: 6,344 of 37,496 patients died during 359,219 years of follow up. The MR per 1000 person-years was 32.8 (95% CI 30.2-35.5) during the first 6 months, declining to 16.0 (15.4, 16.8) during 5-9.9 years and 14.2 (13.3-15.1) after 10 years duration of ART. During the first year of ART there was a strong inverse association of CD4 count at start of ART with mortality. This diminished over the next 4 years. The adjusted MRR per CD4 group were 0.97 (0.94-1.00), p=0.054 and 1.02 (0.98-1.07), p=0.32 among patients followed for 5-9.9 and >10 years respectively.

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Conclusions: After surviving five years of ART, the mortality of patients who started ART with low baseline CD4 count converged with mortality of patients with intermediate and high baseline CD4 counts.

Introduction

Combination antiretroviral therapy (ART) based on three or more antiretroviral drugs including either a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI) or integrase inhibitor (II) has substantially improved the prognosis of HIV-1 positive patients since its introduction in high income settings in 1996 (1). ART suppresses HIV-1 replication, leading to declines in plasma HIV-1 RNA, increased CD4 T-cell counts and eventually decreased morbidity and mortality (2). Because patients have now been treated with ART for up to 20 years, it is of major interest to explore predictors of long-term prognosis.

The Antiretroviral Therapy Cohort Collaboration (ART-CC) was initiated in 2000 by investigators from HIV cohort studies in North America and Europe, in order to assemble datasets that were sufficiently large to study the prognosis of HIV-1 positive patients who started ART. Prognostic models that estimated 3 and 5 year survival were published in 2002 and 2007 (3, 4) and showed CD4 count at start of ART (baseline) to be the strongest predictor of short-term mortality. However, baseline CD4 count becomes less prognostic when 6 month response to treatment is taken into account (5). HIV-1 viral load at 6 months and changes in CD4 count from 6 to 36 months after start of ART are prognostic for AIDS in patients who have survived three years of ART (6).

To date short-term prognosis has been extrapolated to predict long-term disease-free survival (7, 8). Since mortality in the general population varies by age, sex and country of residence, estimates of mortality rate ratios (MRR) may be more informative when corrected for background mortality (9).

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We investigated how long patients bear the burden of increased mortality due to starting ART with low CD4 counts, by studying the prognostic value of baseline CD4 count for mortality up to 15 years after start of ART, using both standard survival analysis models and models for relative survival.

Methods

Study sample

The Antiretroviral Therapy Cohort Collaboration (ART-CC), which is described in detail elsewhere (http://www.art-cohort-collaboration.org) (10), is an international collaboration of HIV cohort studies from North America and Europe that combines data on HIV-positive individuals aged 16 years or older who were antiretroviral-naïve when they started ART with a combination of at least three drugs. Eligible regimens include at least one PI, NNRTI or II and two nucleoside-analogue reverse-transcriptase inhibitors (NRTI). The present study included data from eighteen cohorts, which are listed in the appendix. All were approved by local ethics committees. The NHS Health Research Authority South West - Cornwall and Plymouth Research Ethics Committee, UK, approved the study (REC reference 12/SW/0253). The data used here included follow up from 1996 until 31st July 2013. We included patients who started ART between 1996 and 2001 (so had at least 12 years' potential follow up) and had at least one available baseline (within 3 months prior to starting ART) measurement of CD4 count and viral load.

Statistical analysis

We categorised CD4 counts into six groups (0-49, 50-99, 100-199, 200-349, 350-499 and ≥500 cells/μL); viral loads into three groups (0-9,999, 10,000-99,999 and ≥100,000 copies/μL); age at baseline into five groups (16-29, 30-39, 40-49, 50-59 and 60 years or over); year of starting ART into three groups (1996-7, 1998-9, 2000-1); and ART regimen into 5 groups (NNRTI-based, PI-based, NRTI including abacavir, other NRTI not including abacavir, and other regimens). Patients were followed

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up from the date of starting ART ("baseline") to the earliest of the date of death, lost to follow-up (LTFU) or administrative censoring. Patients were considered lost to follow up (LTFU) at their last clinical observation if it was over a year before the cohort specific close date of the database. Data were analysed as intent-to-continue-treatment, ignoring treatment changes and interruptions.

We used unadjusted (Kaplan-Meier) and adjusted estimates of cumulative mortality to examine whether CD4 count at start of ART was prognostic for mortality. The adjusted estimates were for a typical patient: MSM aged 30-39 years, who started ART between 1998 and 1999 in the FHDH cohort in France without a diagnosis of AIDS, and with high viral load (HIV-1 RNA > 100,000). We used Poisson models to estimate crude mortality rates (MR) with 95% confidence intervals (CI), for all patients and by baseline CD4 count. We then estimated MRs separately according to duration of time on ART (<0.5, 0.5-0.99, 1-2.99, 3-4.99, 5-9.99 and ≥10 years after ART start), overall and by baseline CD4 count. We used Cox models stratified by cohort to estimate crude and adjusted (for sex, age, transmission risk group, AIDS at baseline, baseline viral load, and year of starting ART) mortality rate ratios (MRR) by baseline CD4 group with 200-349 cells/µL as the reference category, overall and separately according to time on ART. Relative survival models based on generalized linear models (modified Poisson models) were used to account for variation in background population mortality (11). Expected death rates for each country split by sex and 5-year age group were obtained from the Human Mortality Database (www.mortality.org). We estimated adjusted (for the same set of covariates) relative MRR, overall and according to duration of time on ART. The prognostic value of baseline CD4 count according to time since start of ART was compared by estimating the adjusted MRR per CD4 count category (assuming a log-linear relationship with mortality rate across the CD4 categories). All analyses were performed using Stata version 13 (StataCorp, Texas, USA).

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Results

A total of 37,496 patients started ART between 1996 and 2001 and were eligible for analyses. The majority were male, with median age at start of ART 37 (IQR 31 to 44) years (table 1). Median follow-up time was 11.3 years (IQR 5.6 to 13.4 years) with 28,947 (77%) of patients having at least 5 years and 21,936 (58%) more than 10 years' follow-up. Numbers of patients at risk by duration of ART and baseline CD4 count are shown in web table 1. The risk transmission group distribution reflected the early HIV epidemic, with similar proportions of men who have sex with men (MSM) and heterosexually infected patients, and 20% infected via injection drug use (IDU). The median baseline CD4 count was 221 (IQR 86 to 376) cells/μL: 17,077 (46%) patients started ART with CD4 count <200 cells/μL and 10,278 (27%) with CD4 count <100 cells/μL. Compared with patients who started ART with CD4 count <350 cells/μL, those who started with higher CD4 count were more likely to be MSM and to have started ART in 1997-99, and were slightly younger on average. The majority of patients (24,313 (65%)) started on a PI-based regimen, whilst 10,146 (27%) started on a NNRTI-based regimen. The rate of LTFU was 0.04 per year.

There were 6,344 deaths during 359,219 years of follow up. Baseline CD4 count was highly prognostic for unadjusted cumulative mortality in all patients (figure 1). Baseline CD4 count was also highly prognostic for adjusted cumulative mortality which is illustrated (figure 2) for a typical patient group (MSM in the FHDH cohort, aged 30-39 years, who started ART between 1998 and 1999 without a diagnosis of AIDS, and with high viral load (HIV-1 RNA > 100,000)). There is a clearly graded increase in mortality with decreasing baseline CD4 count: cumulative 15-year mortality varied from 7.1% (95% CI 2.9% to 11.3%) for baseline CD4 count >500 cells/μL to 10.7% (95% CI 4.7% to 16.7%) for baseline CD4 count <50 cells/μL. A table showing the corresponding numbers at risk for figure 1 at different time points split by CD4 count is available from the authors on request.

Numbers of deaths and crude mortality rates per 1000 person years, according to baseline CD4 count and time since start of ART are shown in table 2. Overall mortality per 1000 person years

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declined from 33 (95% CI 30 to 36) during the first 6 months of ART to 14 (95% CI 13 to 15) among those who survived 10 years from start of ART, despite the aging of the study population over this period. Patients who started ART with a CD4 count below 50 cells/μL experienced the greatest declines in mortality rates over time on ART, from 88 (95% CI 78 to 99) per 1000 person years during the first 6 months to 15 (95% CI 13 to 17) after 10 years from start of ART. Although mortality rates were strongly inversely associated with baseline CD4 counts at shorter times since start of ART, the magnitude of these associations diminished with increasing duration of ART. Beyond 10 years of ART, there was little evidence of differences in crude mortality rates according to CD4 count at start of ART.

Table 3 shows associations of CD4 count at start of ART with mortality at different durations since start of ART and averaged over all follow up time, estimated from crude, adjusted and relative survival models. Estimates are presented as MRR with 95% CIs, with CD4 200-349 cells/μL as the comparator group. As expected crude, adjusted and relative mortality rate ratios averaged over all follow-up time decreased with increasing CD4 count at start of ART. After adjusting for other prognostic factors, the MRR comparing baseline CD4 count <50 with 200-349 cells/μL during the first 6 months of ART was 2.81 (95% CI 2.12 to 3.71): this declined to 1.59 (95% CI 1.31 to 1.92) 3-4.9 years after start of ART. During the first 5 years of ART, rate ratios comparing patients whose baseline CD4 count was greater than 350 cells/ μL with 200-349 cells/μL were less than 1. However there was little evidence that baseline CD4 count was prognostic for mortality after 5 years of ART since the adjusted MRRs per CD4 category were 0.97 (95% CI 0.94 to 1.00, p=0.054) and 1.02 (95% CI 0.98 to 1.07, p=0.32) among patients followed for 5-9.9 and ≥10 years, respectively. Adjusted relative MRRs were generally further from 1 than the corresponding adjusted MRRs indicating that failing to account for expected mortality partially obscured the association of CD4 count with mortality risk. Differences between the two analyses diminished with increasing time on ART because the strength of the association of mortality with baseline CD4 count also decreased with time.

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Discussion

In our collaborative analysis of 37,496 HIV-positive patients from 18 cohorts starting triple combination ART between 1996 and 2001 there was a strong inverse association of CD4 count with mortality during the first year of ART which diminished over the next 4 years. From 5 years after start of ART, baseline CD4 count was of little prognostic value. Even patients who started ART with very low (< 50 cells/μL) CD4 counts may experience convergence of their mortality risk to that of patients with intermediate (200-349 cells/μL) or high (≥ 500 cells/μL) baseline CD4 count, from 5 years after the start of treatment. As expected, associations of baseline CD4 count with mortality were attenuated after adjusting for other prognostic factors at the time of starting ART. Associations moved away from the null after further adjusting for background mortality in relative survival models, but this did not impact our results substantially.

The importance of CD4 count nadir as a prognostic factor for survival in HIV-positive individuals starting ART is well-established (3). However, the extent to which patients with low baseline CD4 count surviving the first years of treatment remain at an increased risk of death, compared to patients starting with higher baseline CD4 counts has remained unclear. To our knowledge, our study is the first to demonstrate that patients who started treatment in later stages of HIV disease may expect their mortality risk to become similar to that of patients starting treatment with higher CD4 counts, if they survive the first five years of therapy. The majority of patients 85.7% (95% CI 85.2 to 86.3%) that started ART with CD4 count below 200 cells/mm^3 in this cohort collaboration do indeed survive 5 years. This is an important message for patients and physicians alike, as the moving from a higher to a lower risk group through long-term treatment adherence may be a powerful motivator. Our findings are consistent with previous studies which showed that current is more important than baseline CD4 count (5, 6).

For the first five years of ART there was a graded inverse relationship between baseline CD4 count and mortality, which was consistent with our previous findings (12). After five years of ART, more

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than 15% of the patients with a baseline CD4 count of less than 50 cells/µL had died. These results are consistent with the rate of immunological non-responders to ART previously observed (13, 14). Patients with poor immunological response or multiple AIDS or non-AIDS morbidity continue to have a substantially increased mortality ratio after three years of treatment (14, 15). A low CD4 nadir is not only an established risk factor for death, but also for poor CD4 recovery (16-18). This may reach a plateau after about two years of ART (18), although a very recent analysis indicates slow but steady long-term recovery of CD4 counts under continued treatment (15).

These findings raise the question of how to identify patients at high risk of mortality during the first five years of ART and what strategies could reduce this risk. These could include screening programs and intensive adherence counselling. A previous study demonstrated that patients with less than 200 CD4 cells/µL at baseline are at a higher risk especially for AIDS- but also for non-AIDS-related mortality (12). In that study, malignancies and infections were the primary causes of death, and both occurred more frequently in patients with less than 200 CD4 cells/µL. The observed convergence of survival rates after five years may be partly explained by the early death of patients with low to very low baseline CD4 count, especially immunological non-responders, while others gradually achieve immunological recovery. The suggestion of a lower risk amongst those who started ART with very low compared with intermediate CD4 count after 10 years may reflect a survivor cohort who are adherent and respond well to therapy, but is also consistent with a chance finding.

We analysed large numbers of patients from high quality clinical cohorts. We obtained more accurate comparisons by using relative survival models which adjust for both patient characteristics and the background age, sex and country general population mortality. Adjusting associations of CD4 count with mortality for age and sex as covariates in a conventional analysis which only considers mortality of those with HIV infection may be inducing bias towards the null. Whilst additionally adjusting for background mortality increased associations of baseline CD4 count with both cumulative mortality and early mortality, it did not affect our conclusions about the convergence of

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mortality in those who survived five years from starting ART. Our study has some limitations. We chose patients starting ART between 1996 and 2001 to allow ten years or more of follow-up for each person included. While only such patients have been treated with long term ART, newer drugs that have been introduced since 2002 are associated with better immune recovery (19) and/or CD4 recovery in immunological non-responders (19-21), compared with drugs on which the patients in our study started combination ART. More second line treatment options and new formulations with improved convenience have become available, allowing better treatment adherence and successful treatment of drug resistant infections. Therefore, patients across all baseline CD4 count strata are likely to experience lower mortality than for the patients included in our study.

While we included a broad range of patients with different risk factors from Europe and North America, generalizability to patients treated in other settings may be limited. Our results may be biased by LTFU. Although LTFU rates were high, cohorts have good ascertainment of death procedures and it is therefore more likely that patients transferred care to another centre not in ART-CC or dropped out of care, rather than died (22). However, our results should be generalizable to individuals remaining in HIV care. The high death rate observed in patients with unknown risk transmission is linked to the high death rate in older patients because risk group was poorly recorded in cohorts that included more patients aged over 60 years. Data on non-HIV related factors, for example socio-economic disadvantage or lifestyle risk factors, were not available, but may have contributed to excess mortality during the first five years of treatment in patients with low baseline CD4 counts.

In conclusion, CD4 count at start of ART strongly predicts mortality rates during the first five years' of ART. This finding reinforces the need for earlier diagnosis and treatment of people living with HIV. However, there is little evidence that CD4 count at start of ART predicts mortality after five years of ART. This is a positive message for patients: the burden of increased mortality associated with starting treatment late is alleviated for those who survive five years on ART.

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Conflict of interest statement

Drs. May and Sterne report grants from UK MRC and grants from UK NIHR, during the conduct of the study; Dr. Reiss reports grants from Gilead Sciences, grants from ViiV healthcare, grants from Janssen Pharmaceutica, grants from Bristol Myers Squibb, grants from Merck, other from Gilead Sciences, other from Janssen Pharmaceutica, other from ViiV healthcare, outside the submitted work; Dr. Bonnet reports grants, personal fees and non-financial support from Gilead, personal fees and non-financial support from ViiV Healthcare, personal fees and non-financial support from Janssen, personal fees and non-financial support from BMS, personal fees from Pierre Fabre Dematology, outside the submitted work; Dr. Gill reports personal fees from Occasional member of ad hoc HIV advisory boards to Merck,Gilead ViiV healthcare, outside the submitted work; Dr. Vehreschild reports grants, personal fees and non-financial support from Astellas, grants and personal fees from Basilea, grants, personal fees and non-financial support from Merck/MSD, grants, personal fees and non-financial support from Gilead, grants and personal fees from Pfizer, outside the submitted work; Dr. Cavassini reports grants from Gilead and Viiv, outside the submitted work; Dr. Burkholder reports grants from Bristol-Myers Squibb, other from Amgen, Inc., other from Definitcare, LLC, outside the submitted work; Dr. Crane reports grants from NIH, during the conduct of the study; grants from NIH, grants from PCORI, outside the submitted work; Dr. Sterling reports grants from Wellcome Trust, during the conduct of the study; Dr. Miro reports research and academic grants, personal fees and other from Abbvie, BMS, Gilead, Merck, Novartis, Pfizer and ViiV Healthcare, outside the submitted work. Other authors have no conflicts of interest to declare.

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Cohorts contributing to this analysis

French Hospital Database on HIV (FHDH); the Italian Cohort of Antiretroviral-naïve patients (ICONA); the Swiss HIV Cohort Study (SHCS); the AIDS Therapy Evaluation project, Netherlands (ATHENA); the Aquitaine Cohort; the Royal Free Hospital Cohort, UK; the South Alberta Clinic Cohort; 1917 Clinic Cohort, University of Alabama at Birmingham, USA; The Danish HIV Cohort Study, Denmark; HAART Observational Medical Evaluation and Research (HOMER), Canada; HIV Atlanta Veterans Affairs Cohort Study (HAVACS), USA; Osterreichische HIV-Kohortenstudie (OEHIVKOS), Austria; Proyecto para la Informatizacion del Seguimiento Clinico-epidemiologico de la Infeccion por HIV y SIDA (PISCIS), Spain; University of Washington HIV Cohort, USA; VACH, Spain; Veterans Aging Cohort Study (VACS), USA; Vanderbilt, USA and the Koln/Bonn Cohort.

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Figure 1: Unadjusted estimates of overall cumulative mortality by CD4 count at start of ART.

Figure 2: Adjusted estimates of cumulative mortality by CD4 count at start of ART for a typical patient group (MSM aged 30-39 years, who started ART between 1998 and 1999 without a diagnosis of AIDS, with high viral load (HIV-1 RNA > 100,000) from the FHDH cohort based in France).

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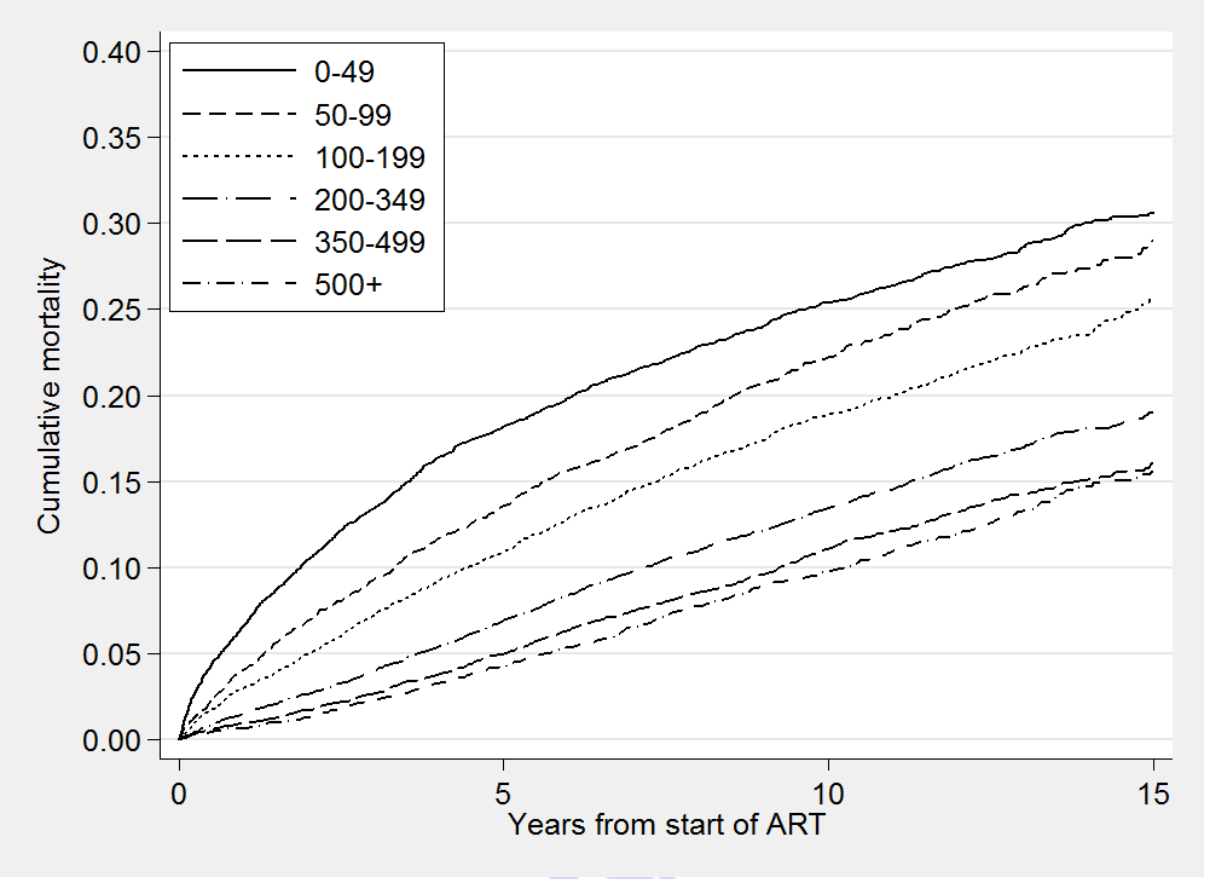

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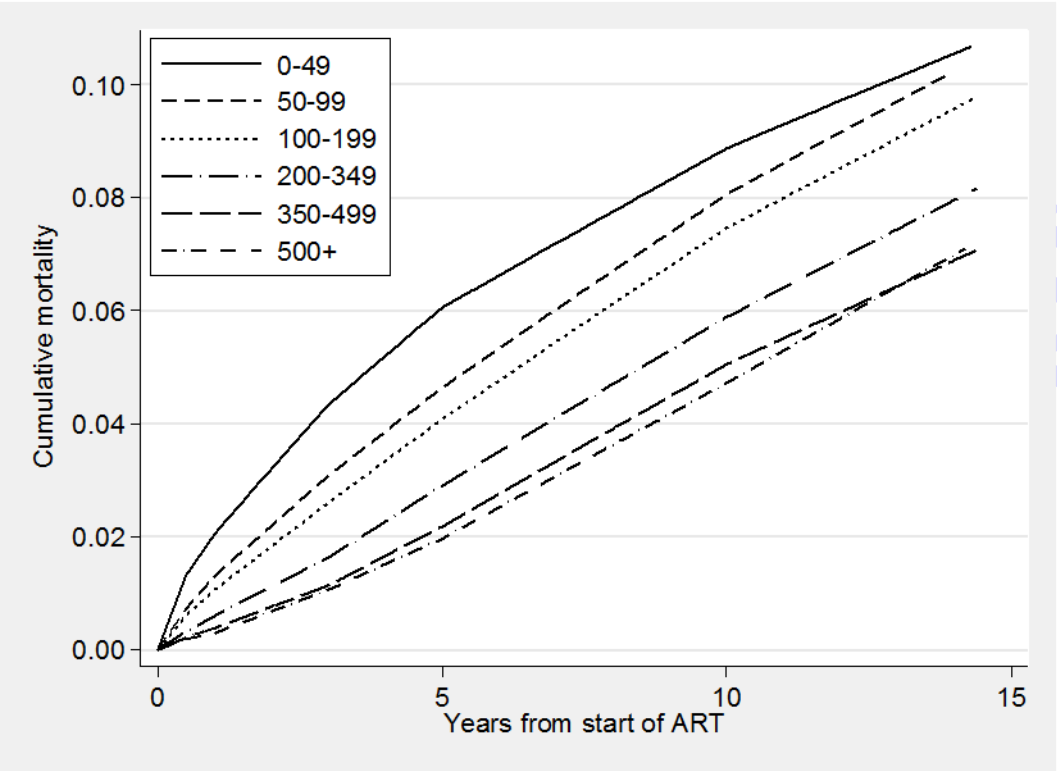

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Table 1: Demographic and clinical characteristics at start of ART (N = 37,496)

Year of starting ART	**Number of patients (%)**	**Deaths (%)**
1996 - 97	8,304 (22%)	1,550 (19%)
1998 - 99	15,599 (42%)	2,760 (18%)
2000 - 01	13,593 (36%)	2,034 (15%)
Female	8,293 (22%)	817 (10%)
AIDS at start of ART	8,516 (23%)	2,103 (25%)
CD4 count/µL	*Median: 221, IQR (86, 376)*	
0 - 49	6,512 (17%)	1,654 (25%)
50 - 99	3,766 (10%)	844 (22%)
100 - 199	6,799 (18%)	1,292 (19%)
200 - 349	9,633 (26%)	1,338 (14%)
350 - 499	5,990 (16%)	697 (12%)
≥500	4,796 (13%)	519 (11%)
HIV-1 RNA (copies/µL)	*Median: 75,000, IQR (18,000, 239,000)*	
0 - 9,999	6,834 (18%)	843 (12%)
10,000 - 99,999	14,149 (38%)	2,186 (15%)
≥100,000	16,513 (44%)	3,315 (20%)
Age (years)	*Median: 37, IQR (31,44)*	
16-29	6,734 (18%)	514 (8%)
30-39	16,572 (44%)	2,094 (13%)
40-49	9,104 (24%)	1,989 (22%)
50-59	3,766 (10%)	1,184 (31%)
≥60	1,320 (4%)	563 (43%)
Risk transmission group		
MSM	11,067 (30%)	1,056 (10%)
Injection drug use	7,626 (20%)	1,625 (21%)
Heterosexual	11,709 (31%)	1,122 (10%)
Blood	440 (1%)	77 (18%)
Other or unknown	6,654 (18%)	2,464 (37%)
Length of follow-up (years)	*Median: 11.3, IQR (5.6, 13.4)*	
Regimen		
NNRTI-based	10,146 (27%)	1,559 (15%)
PI-based	24,313 (65%)	4,371 (18%)
Triple NRTI (including abacavir)	2,006 (5%)	240 (12%)
Other-NRTI	760 (2%)	112 (15%)
Other	271 (1%)	62 (23%)

IQR inter-quartile range

MSM men who have sex with men

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Table 2: Numbers of deaths and crude mortality rates (95% CI) per 1000 person years by CD4 count at start of ART and duration of follow-up. (6314 deaths overall)

	Duration of follow up from start of ART (years)											
	< 0.5		**0.5-0.99**		**1-2.99**		**3-4.99**		**5-9.99**		**≥ 10**	
N patients	37,496		35,928		34,841		31,185		28,944		21,931	
CD4 at ART start (cells/µL)	**N**	**MR (95% CI)**	**N**	**MR (95% CI)**	**N**	**MR (95% CI)**	**N**	**MR (95% CI)**	**N**	**MR (95% CI)**	**N**	**MR (95% CI)**
0 - 49	275	88 (78.2, 99.0)	145	48.9 (41.6, 57.5)	414	38.1 (34.6, 42.0)	275	28.4 (25.3, 32.0)	381	18.6 (16.8, 20.6)	164	14.8 (12.7, 17.2)
50 - 99	84	45.8 (37.0, 56.7)	64	36.5 (28.5, 46.6)	181	27.9 (24.1, 32.2)	143	24.4 (20.7, 28.8)	258	21.1 (18.7, 23.9)	114	17.8 (14.8, 21.4)
100 - 199	115	34.7 (28.9, 41.7)	82	25.7 (20.7, 31.9)	261	21.9 (19.4, 24.7)	224	20.7 (18.2, 23.6)	426	18.9 (17.2, 20.8)	184	15.8 (13.7, 18.3)
200 - 349	75	15.9 (12.6, 19.9)	62	13.5 (10.5, 17.4)	221	12.7 (11.2, 14.5)	248	15.5 (13.7, 17.6)	490	14.6 (13.4, 16.0)	242	13.6 (12.0, 15.4)
350 - 499	30	10.2 (7.1, 14.6)	22	7.7 (5.0, 11.6)	96	8.8 (7.2, 10.7)	122	12 (10.1, 14.4)	288	13.3 (11.9, 14.9)	139	11.5 (9.7, 13.6)
≥ 500	20	8.5 (5.4, 13.2)	10	4.3 (2.3, 8.1)	73	8.4 (6.6, 10.5)	79	9.8 (7.9, 12.2)	206	11.9 (10.4, 13.6)	131	13.5 (11.4, 16.1)
ALL	599	32.8 (30.2, 35.5)	385	21.8 (19.7, 24.1)	1246	18.8 (17.8, 19.9)	1091	18.0 (17.0, 19.1)	2049	15.0 (15.4, 16.8)	974	14.2 (13.3, 15.1)

MR Mortality Rate; CI Confidence Interval

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Table 3: Crude and adjusted associations of CD4 count at start of ART with mortality at increasing durations since start of ART. The relative survival model accounts for age, sex and country matched population mortality.

		CD4 count (cells/μL)				
		0-49	50-99	100-199	200-349	350-499	≥500
	N (Deaths)	6,512 (1,654)	3,766 (844)	6,799 (1,292)	9,633 (1,338)	5,990 (697)	4,796 (519)
		Crude mortality rate ratios (95% CI)					
Duration of ART (years)	**<0.5**	5.51 (4.26, 7.12)	2.92 (2.14, 3.99)	2.22 (1.66, 2.97)	1	0.63 (0.41, 0.96)	0.53 (0.32, 0.87)
	0.5-0.9	3.47 (2.57, 4.68)	2.71 (1.91, 3.84)	1.92 (1.38, 2.67)	1	0.56 (0.34, 0.91)	0.32 (0.17, 0.63)
	1-2.9	2.85 (2.42, 3.36)	2.16 (1.78, 2.63)	1.72 (1.44, 2.06)	1	0.69 (0.54, 0.86)	0.67 (0.51, 0.87)
	3-4.9	1.72 (1.45, 2.05)	1.55 (1.26, 1.90)	1.34 (1.12, 1.61)	1	0.78 (0.63, 0.97)	0.65 (0.51, 0.84)
	5-9.9	1.17 (1.02, 1.34)	1.42 (1.22, 1.65)	1.30 (1.15, 1.49)	1	0.92 (0.80, 1.07)	0.83 (0.71, 0.98)
	≥10	1.03 (0.84, 1.25)	1.31 (1.05, 1.64)	1.17 (0.97, 1.42)	1	0.84 (0.68, 1.03)	0.98 (0.79, 1.21)
	All time	**1.87 (1.74, 2.02)**	**1.69 (1.55, 1.84)**	**1.44 (1.33, 1.55)**	**1**	**0.81 (0.74, 0.89)**	**0.77 (0.69,0.85)**
		Adjusted mortality rate ratios (95% CI)					
	<0.5	2.81 (2.12, 3.71)	1.71 (1.24, 2.37)	1.67 (1.25, 2.25)	1	0.70 (0.46, 1.07)	0.62 (0.38, 1.02)
	0.5-0.9	2.50 (1.80, 3.47)	2.04 (1.41, 2.93)	1.65 (1.18, 2.31)	1	0.59 (0.36, 0.96)	0.35 (0.18, 0.69)
	1-2.9	2.33 (1.95, 2.79)	1.76 (1.44, 2.16)	1.53 (1.28, 1.83)	1	0.72 (0.57, 0.91)	0.72 (0.55, 0.94)
	3-4.9	1.59 (1.31, 1.92)	1.36 (1.10, 1.69)	1.22 (1.02, 1.47)	1	0.80 (0.64, 1.00)	0.70 (0.55, 0.91)
	5-9.9	1.01 (0.87, 1.17)	1.20 (1.02, 1.40)	1.16 (1.02, 1.32)	1	0.96 (0.83, 1.11)	0.92 (0.78, 1.08)
	≥10	0.85 (0.68, 1.05)	1.07 (0.85, 1.35)	1.01 (0.83, 1.22)	1	0.88 (0.71, 1.09)	1.09 (0.88, 1.35)
	All time	**1.51 (1.40,1.64)**	**1.37 (1.25,1.50)**	**1.26 (1.16,1.36)**	**1**	**0.85 (0.78,0.93)**	**0.84 (0.76,0.93)**
		Adjusted relative mortality rate ratios (95% CI)					
	<0.5	3.15 (2.28, 4.36)	1.87 (1.29, 2.72)	1.84 (1.31, 2.59)	1	0.66 (0.39,1.11)	0.52 (0.27, 1.02)
	0.5-0.9	2.91 (1.97, 4.31)	2.38 (1.55, 3.65)	1.80 (1.20, 2.70)	1	0.46 (0.22, 0.94)	0.30 (0.12, 0.75)
	1-2.9	2.78 (2.23, 3.48)	2.01 (1.57, 2.58)	1.66 (1.32, 2.09)	1	0.65 (0.47, 0.91)	0.65 (0.45, 0.93)
	3-4.9	1.74 (1.39, 2.20)	1.42 (1.09, 1.85)	1.31 (1.04, 1.63)	1	0.78 (0.59, 1.03)	0.63 (0.45, 0.90)
	5-9.9	0.99 (0.81, 1.21)	1.27 (1.03, 1.56)	1.20 (1.00, 1.43)	1	0.94 (0.77, 1.14)	0.79 (0.63, 1.00)
	≥10	0.79 (0.55, 1.15)	0.98 (0.65, 1.47)	1.01 (0.73, 1.40)	1	0.79 (0.55, 1.14)	1.12 (0.79, 1.58)
	All time	**1.72 (1.56, 1.91)**	**1.51 (1.35, 1.70)**	**1.35 (1.22, 1.50)**	**1**	**0.80 (0.70,0.91)**	**0.75 (0.64, 0.86)**

Models were stratified by cohort. Adjusted and relative survival models were adjusted for sex, age, transmission risk group, AIDS at baseline, viral load, and year of starting ART.

CI Confidence Interval

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