Effect of baseline CD4 cell count at linkage to HIV care and at initiation of antiretroviral therapy on mortality in HIV-positive adult patients in Rwanda: a nationwide cohort study

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Summary

Background **Continued debate exists about whether initiation of antiretroviral therapy (ART) in symptom-free patients at higher baseline CD4 cell counts results in important clinical benefits. We aimed to examine to what extent baseline CD4 cell count at linkage to HIV care and at ART initiation predicts mortality in adults with HIV in Rwanda.**

Methods **We included data for patients with HIV in Rwanda who were aged 15 years or older and linked to care or initiated ART between Jan 1, 1997, and April 30, 2014, from nationally representative databases. We analysed the effect on mortality of baseline CD4 cell count at ART initiation and at linkage to care. Follow-up time was measured from time of ART initiation and from linkage to HIV care to study exit. To account for effect modification by time, we stratified by era of linkage (before 2008 *vs* 2008 or after) and for other indications for initiation of ART. We also stratified CD4 cell count by indication to initiate ART other than CD4 cell count status. We used Cox proportional hazard regressions to examine the effect of CD4 cell count at linkage and at ART initiation on mortality.**

Findings **Our analysis was based on data from 50 147 patients who initiated ART and 72 061 patients linked to care. In the late era (2008 and after), linkage to care at a CD4 cell count of 100–199 cells per μL without any further indication was associated with higher mortality than linkage at 200–349 cells per μL (hazard ratio [HR] 1·37, 95% CI 0·95–1·97); the effect was much the same for initiation of ART in this CD4 stratum (1·37, 0·92–2·04). For higher CD4 strata, linkage to care at 500 cells per μL or more was protective (0·53, 0·39–0·72), whereas the reported effect of initiation of ART on mortality was not distinguishable from chance alone (0·82, 0·21–3·20).**

Interpretation **Efforts are needed to link and retain patients early in pre-ART HIV care. In settings where ART is not yet available for immediate treatment, retention in a strong pre-ART programme is effective at improving survival.**

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Introduction

CD4 T-cell count at the time of initiation of antiretroviral therapy (ART) is one of the strongest predictors of mortality in patients with HIV.[1–4] On the basis of the results of several studies showing the benefit of earlier initiation of ART with respect to reduced morbidity and mortality, incidence,[5] and programme simplification,[6] WHO guidelines now recommend that ART be initiated for all people living with HIV who have CD4 counts of 500 cells per μL or less, and all HIV-positive pregnant women, HIV-positive children younger than 5 years of age, individuals with concomitant hepatitis B and chronic liver disease, and active tuberculosis, irrespective of CD4 cell count. Beyond individual clinical indications, being in an HIV serodiscordant relationship is also an indication for immediate ART.[7] However, despite these changes in worldwide clinical guidance, CD4 cell counts at linkage to care and at ART initiation in sub-Saharan Africa have not appreciably increased during the past decade.[8]

Previous assessments of the prognostic value of CD4 cell counts on the survival of people living with HIV in sub-Saharan Africa have generally been done in an era with poor ART uptake, small sample sizes, and low CD4 cell counts at ART initiation;[9–12] they have also assessed the prognostic value of CD4 cell counts at ART initiation rather than at clinical linkage with care. These and other studies[12,13] concur that reduced CD4 cell counts, particularly at initiation of ART, are associated with worse survival. Earlier linkage to clinical care might also have important benefits with respect to survival because it provides clinical and social support that might include health education, anti-infectives, and nutritional support before initiation of ART. Late ART initiation typically results from late clinical linkage, and the mechanisms by which clinical linkage and ART initiation affect survival are distinguishable, therefore a need exists to understand the effect of CD4 cell counts at ART initiation and at linkage to care.

Despite the established detrimental effects of late initiation, debate about whether initiation of ART at higher CD4 cell counts results in improved clinical benefits and whether the new threshold for ART initiation recommended by WHO should be implemented in resource-limited settings where access to ART remains a structural and financial challenge still continues.[13–18] To

Research in context

Evidence before this study

We searched Medline and Embase to identify studies reporting the association between CD4 cell counts at time of ART initiation and at time of linkage to care. We used the search terms "HIV" or "AIDS" and "CD4". Our search included all studies published from Jan 1, 2002, to May 29, 2015, with no language restrictions. Our search identified studies from the When to Start Consortium, the North American AIDS Cohort Collaboration on Research & Design, and the HIV-Causal Collaboration. We also reviewed a meta-analysis that synthesised the existing evidence on CD4 cell counts at linkage to care and at ART initiation from 2002 to 2012 in sub-Saharan Africa. Finally, we identified the stopped-early Strategic Timing of AntiRetroviral Treatment randomised trial and the Temprano ANRS 12136 trial.

Added value of this study

These data from Rwanda constitute the largest African cohort so far to investigate the effect of CD4 cell counts at linkage to care in addition to CD4 cell counts at ART initiation on mortality. Our study supports findings from developed settings that initiation of ART at 500 cells per μL has survival benefits compared with a threshold of 350 cells per μL. However, at high CD4 cell counts, linkage to care might be warranted as a priority.

Implications for all available evidence

After the 2013 change to the WHO ART guidelines, many resource-limited settings have accordingly adapted their own guidelines to the 500 cells per μL threshold. These findings suggest that efforts to improve earlier engagement and retention in HIV care, through methods such as improved integration of HIV testing, HIV treatment, and care services, might be as effective at improving survival as are efforts directed at immediate ART initiation.

our knowledge, an assessment of CD4 strata at both linkage to care and ART initiation on mortality outcomes in sub-Saharan Africa has not occurred. Rwanda is an ideal setting in which to study this because the country has an established national ART monitoring and assessment programme and has made remarkable progress in expanding access in recent years.[19,20] The Rwandan Ministry of Health raised the CD4 threshold for ART initiation to 500 cells per μL and now includes a test and treat strategy for key populations.[21] We aimed to examine the predictive value of baseline CD4 cell count at clinical linkage to care and at ART initiation on mortality in HIV-positive patients in Rwanda.

Methods

Study design and data sources

In this nationwide cohort study, we used routinely collected data from the Rwanda Biomedical Center for research and surveillance (the International Quality Clinical HIV/AIDS Registry Tool [IQ] Chart database and electronic medical records). The centre oversees surveillance of HIV and scale-up of ART. Both the IQ Chart database and electronic medical records contain demographic and clinical characteristics and longitudinal HIV-specific clinical factors and vital statistics for HIV-positive patients enrolled in care. The records contain data for both periods of care before and after ART roll-out. The IQ Chart database contains information about all HIV-positive patients from 110 health facilities, representing 25% of ART-providing health facilities in Rwanda. The sampled health facilities slightly over-represent rural settings; however, the sample of patients seems to be representative because it is similar to the overall population with HIV as reported by TRACnet, the national surveillance database, with respect to mortality, loss to follow-up, and other demographic and clinical variables.[20]

We included patients aged 15 years or older with a known follow-up time (ie, those who did not enter and exit the programme on the same day) and who were linked to care or initiated ART between Jan 1, 1997, and April 30, 2014. For the main analysis, we needed patients to have a known ART initiation date.

Outcomes

Our analyses were done with mortality and follow-up time measured from time of ART initiation to study exit and from linkage to HIV care to study exit. Study exit was defined as end of study period, death, loss to follow-up, or transfer to facilities outside of the study. Mortality data were ascertained in health facilities and through home follow-up. Demographic variables for this analysis included sex and age at ART initiation (categorised by decade of life). Clinical variables included CD4 cell count (<50, 50–99, 100–199, 200–349, 350–499, or ≥500 cells per μL, unreported) at ART initiation, year of linkage to care, WHO HIV disease stage (1, 2, 3, 4, or unknown), tuberculosis screening (positive, negative, or unknown), and reason for diagnosis. Methods of diagnosis included voluntary counselling and testing, prevention of mother to child transmission, and other means; the other category includes provider-initiated testing, which began in 2010, HIV-associated hospital admissions, and testing initiated by indication of comorbidities. Year of linkage was dichotomised into a late era (2008 or later) and an early era (before 2008). This marks a distinct turning point in testing availability, patient behaviour, and ART guidelines.[22] Outcomes were stratified by CD4 cell count at time of linkage to HIV care. Both CD4 cell count variables included an unreported category. CD4 cell

count at ART initiation was recorded as unknown if measured more than 6 months before ART initiation or more than 2 weeks after initiation. We created a composite variable specifying whether patients had an indication to initiate ART other than CD4 cell count. These reasons included having a WHO disease stage of 3 or 4 at linkage to care, a positive tuberculosis screen, hospital admission as the reason for ART initiation, or initiation of ART through a prevention of mother-to-child transmission programme.

Statistical analysis

We described data sources using summary statistics. The first analysis consisted of assessment of the association between CD4 counts at time of ART initiation and mortality, with a particular emphasis on the 500 cells per μL and 350 cells per μL cutoffs. The second analysis assessed the association between CD4 cell counts at time of linkage to care and mortality and related this to CD4 cell counts at ART initiation. Both analyses used Cox proportional hazards regression models. In the first analysis, we used the composite indication variable as an effect modifier to CD4 count at ART initiation, with initiation between 200 cells per μL and 349 cells per μL and without known additional indications for ART initiation as the reference category. The second analysis used similar models with CD4 cell count at linkage to care rather than at ART initiation. In both models, time was used as an effect modifier as well. Models were fitted to establish whether time was an effect modifier to all variables; however, the model with the triple effect modification between CD4, indication, and time, and no other modification had the best fit. All conditions for survival analysis were verified with tests based on the Schoenfeld residuals and all assumptions were met.[23] Transfers are vigilantly recorded and verified in Rwanda and thus should be viewed as a non-informative censoring mechanism. For loss to follow-up, a comparison of propensity score distributions for mortality between those lost to follow-up and those not lost to follow-up suggested non-informative censoring; those lost to follow-up tended to be young and healthy.

All significance tests were two-sided, and p values of less than 0·05 were deemed statistically significant. All analyses were done with SAS software version 9.3 and R version 3.1.1.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The first author (SN) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the estimated 205 000 people living with HIV in Rwanda,[20] we included data for 50 147 patients who had initiated ART and 72 061 who were linked to care (irrespective of whether they had necessarily initiated ART). The median age of patients at linkage to HIV care and at ART initiation were similar, but median CD4 cell count at ART initiation was lower than median CD4 cell count at linkage to care (table 1). ART was initiated with no known risk in two-fifths of patients; almost half of

	ART initiation (IQ Chart only) n=72 061	Linkage to care (IQ Chart and EMR) n=50 147
Age at linkage to HIV care (years)	35 (28–42)	36 (30–43)
Age at ART initiation (years)	..	37 (31–45)
Sex		
Male	26 055 (36·2%)	18 200 (36·3%)
Female	46 006 (63·8%)	31 947 (63·7%)
Marital status		
Single, widowed, or divorced	24 086 (33·4%)	12 731 (25·4%)
Married or with partner	34 508 (47·9%)	25 988 (51·8%)
Other or unreported	13 467 (18·7%)	11 428 (22·8%)
Mode of diagnosis		
VCT	45 897 (63·7%)	31 997 (63·8%)
PMTCT	12 880 (17·9%)	6691 (13·3%)
Hospital admission	2773 (3·8%)	2750 (5·5%)
Tuberculosis consultation	241 (0·3%)	143 (0·3%)
PIT	4254 (5·9%)	3310 (6·6%)
Other	6016 (8·3%)	5256 (10·5%)
Path to treatment		
Immediate at linkage to care	17 141 (23·8%)	..
PMTCT: immediate at diagnosis	2689 (3·7%)	..
After a pre-ART period	52 231 (72·5%)	..
Exit reason		
Transfer	14 884 (20·7%)	11 285 (22·5%)
Died	3917 (5·4%)	2949 (5·9%)
Lost	7034 (9·8%)	2167 (4·3%)
Other	1309 (1·8%)	498 (1·0%)
Censored at end of study	42 953 (59·6%)	33 248 (66·3%)
BMI at linkage to care (kg/m²)	21·3 (19·5–23·3)	21·1 (19·2–23·1)
CD4 cell count at linkage to care (cells per μL)	394 (210–636)	256 (145–383)
CD4 cell count at ART initiation (cells per μL)	225 (136–305)	233 (139–316)
WHO disease stage		
1	34 281 (47·6%)	19 651 (39·2%)
2	18 113 (25·1%)	13 846 (27·6%)
3	15 525 (21·5%)	14 104 (28·1%)
4	1721 (2·4%)	1734 (3·5%)
Unknown	2421 (3·4%)	812 (1·6%)
Tuberculosis screen result		
Negative	53 675 (74·5%)	39 612 (79%)
Positive	12 265 (17%)	8614 (17·2%)
Unknown	6121 (8·5%)	1921 (3·8%)

Data are n (%) or median (IQR). IQ=International Quality Clinical HIV/AIDS Registry Tool. EMR=electronic medical records. ART=antiretroviral therapy. VCT=voluntary counselling and testing. PMTCT=prevention of mother-to-child transmission. PIT=provider-initiated testing. BMI=body-mass index.

Table 1: **Demographic and clinical characteristics of patients who initiated ART and were linked to care in Rwanda**

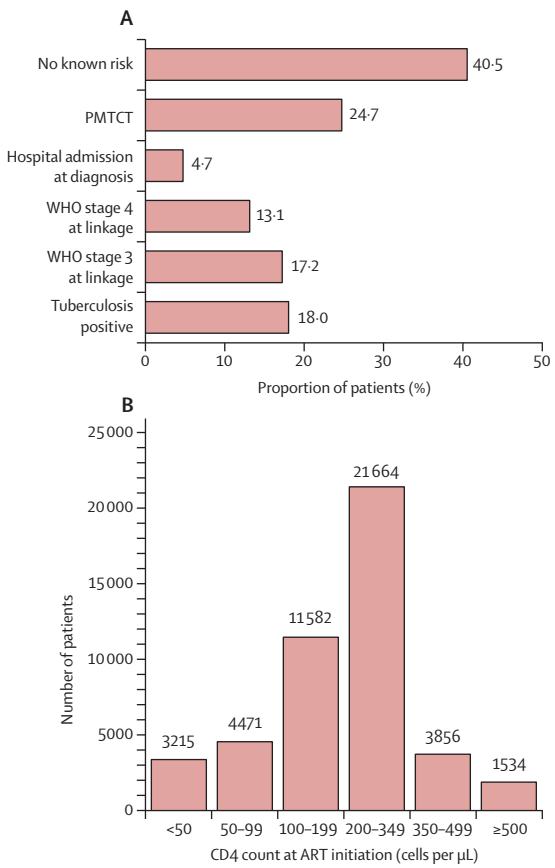

Figure 1: **Characteristics of patients and CD4 counts at ART initiation**
(A) Non-CD4 determinants of ART initiation. (B) CD4 count at ART initiation for 46 332 patients with data. PMTCT=prevention of mother-to-child transmission. ART=antiretroviral therapy.

	Hazard ratio (95% CI)
Sex	
Female	1
Male	1·37 (1·28–1·49)
Age (years)	
15–19	0·69 (0·49–0·96)
20–29	0·84 (0·74–0·96)
30–39	1
40–49	1·20 (1·10–1·32)
≥50	2·00 (1·81–2·21)
Marriage	
Married or with partner	1
Single, divorced, or widowed	1·17 (1·06–1·28)
Other	1·08 (0·98–1·18)
Era of enrolment into HIV care	
Before 2008	1·54 (1·19–2·00)
2008 or after	1

Table 2: **Cox proportional hazards ratios for mortality by demographic variables at ART initiation**

	Hazard ratio (95% CI) before 2008	Hazard ratio (95% CI) 2008–14
No indication		
0–49 cells per µL	3·34 (2·45–4·55)	7·84 (5·51–11·17)
50–99 cells per µL	2·00 (1·49–2·69)	2·58 (1·69–3·95)
100–199 cells per µL	1·25 (0·99–1·57)	1·51 (1·08–2·13)
200–349 cells per µL	1	1
350–499 cells per µL	0·95 (0·62–1·45)	1·13 (0·67–1·9)
≥500 cells per µL	0·91 (0·54–1·52)	0·73 (0·34–1·58)
With indication		
0–49 cells per µL	5·91 (4·84–7·21)	15·89 (12·39–20·36)
50–99 cells per µL	3·56 (2·89–4·38)	8·3 (6·35–10·86)
100–199 cells per µL	2·71 (2·25–3·27)	4·6 (3·55–5·97)
200–349 cells per µL	1·86 (1·54–2·25)	2·92 (2·27–3·75)
350–499 cells per µL	2·02 (1·46–2·78)	2·68 (1·79–4·01)
≥500 cells per µL	2·46 (1·68–3·6)	2·44 (1·43–4·15)
Unreported	4·98 (4·05–6·13)	1·41 (1·03–1·95)

Table 3: **Cox proportional hazard ratios for mortality by CD4 cell count at initiation with and without indication to initiate ART**

those who started ART did so with CD4 counts of 200–349 cells per µL (figure 1).

Initiation of ART in the early era of linkage into care (before 2008) compared with the late era (2008 or later) was associated with high mortality (hazard ratio [HR] 1·54, 95% CI 1·19–2·00; table 2). Compared with ART initiation at a CD4 count of 200–349 cells per µL with no indication other than CD4 status to start ART, patients who initiated treatment in the late era at a CD4 count of 500 cells per µL or more had did not have significantly reduced mortality (table 3). In patients who initiated ART without other indications, initiation of ART in the late era at CD4 cell counts of less than 200 cells per µL had significantly worse mortality outcomes compared with starting at 200–349 cells per µL without other indications. For all CD4 strata, patients with an indication for ART initiation other than CD4 counts were at higher risk of death during the study period, with HR estimates ranging from 2·92 (2·37–3·75) in those initiating ART at 200–349 cells per µL in the late era to 15·89 (12·39–20·36) in those initiating ART in the late era at 0–49 cells per µL (table 3). Risk of mortality was higher in men than in women, increased with age with HR relative to age 30–39 years (eg, from 0·69 for young adults to 2·00 in those aged 50 years or older [p<0·0001]), and was increased in people without a partner (table 2). In view of the fact that thousands of people die each year from HIV-attributable causes,[20] these results are also clinically significant.

After stratification by indication status and adjustment for demographic differences, the lower CD4 cell count strata at either time of linkage to care or ART initiation in the late era were similarly associated with an increased risk of mortality (table 4). For example, linkage to care in the late era at 100–199 cells per µL without any further indication was harmful compared with linkage at 200–349 cells per µL, which was the same for initiation of ART in this

	Hazard ratio (95% CI) from time of linkage to care	Hazard ratio (95% CI) from time of ART initiation
ART before 2008		
No indication		
0–49 cells per μL	4·01 (3·11–5·18)	3·11 (2·24–4·32)
50–99 cells per μL	1·97 (1·5–2·6)	1·95 (1·43–2·67)
100–199 cells per μL	1·31 (1·05–1·63)	1·21 (0·95–1·55)
200–349 cells per μL	1	1
350–499 cells per μL	0·8 (0·63–1·03)	0·8 (0·43–1·47)
≥500 cells per μL	0·59 (0·48–0·73)	0·86 (0·32–2·33)
With indication		
0–49 cells per μL	5·88 (4·88–7·07)	5·88 (4·78–7·22)
50–99 cells per μL	3·29 (2·7–4)	3·5 (2·82–4·34)
100–199 cells per μL	2·26 (1·89–2·71)	2·6 (2·14–3·15)
200–349 cells per μL	1·91 (1·59–2·29)	1·85 (1·52–2·25)
350–499 cells per μL	1·55 (1·26–1·9)	2·07 (1·45–2·96)
≥500 cells per μL	1·16 (0·96–1·41)	3·95 (2·62–5·97)
Unknown	2·41 (1·74–3·33)	9·78 (7·55–12·67)
ART after 2008		
No indication		
0–49 cells per μL	6·3 (4·27–9·31)	7·22 (4·75–10·98)
50–99 cells per μL	2·15 (1·37–3·38)	1·95 (1·15–3·3)
100–199 cells per μL	1·37 (0·95–1·97)	1·37 (0·92–2·04)
200–349 cells per μL	1	1
350–499 cells per μL	0·77 (0·55–1·09)	0·94 (0·41–2·16)
≥500 cells per μL	0·53 (0·39–0·72)	0·82 (0·21–3·20)
With indication		
0–49 cells per μL	15·2 (11·7–19·6)	15·7 (11·9–20·5)
50–99 cells per μL	7·27 (5·49–9·63)	8·33 (6·23–11·14)
100–199 cells per μL	4·43 (3·38–5·8)	4·54 (3·42–6·02)
200–349 cells per μL	2·90 (2·21–3·8)	2·93 (2·24–3·85)
350–499 cells per μL	1·89 (1·4–2·57)	2·43 (1·47–4·02)
≥500 cells per μL	1·18 (0·88–1·58)	4·78 (2·65–8·62)
Unknown	2·84 (1·51–5·34)	2·66 (0·84–8·43)

Data for patients in the International Quality Clinical HIV/AIDS Registry Tool Chart database in Rwanda from 2004 to 2011. For models using time from linkage to care, the CD4 cell counts used are those at linkage to care, and for models using time from ART initiation, the CD4 cell counts are those at ART initiation. ART=antiretroviral therapy.

Table 4: **Survival analysis by CD4 cell count at linkage or initiation with or without other ART indication**

	Hazard ratio (95% CI) from time of linkage to care	Hazard ratio (95% CI) from time of ART initiation
Simple unadjusted models		
CD4 cell count at linkage or initiation* (cells per μL)		
<50	4·82 (4·36–5·32)	4·90 (4·38–5·49)
50–99	2·32 (2·07–2·59)	2·55 (2·25–2·88)
100–199	1·43 (1·29–1·58)	1·55 (1·39–1·72)
200–349	1	1
350–499	0·70 (0·63–0·79)	0·96 (0·75–1·22)
≥500	0·47 (0·42–0·52)	1·55 (1·15–2·11)
Unknown	1·62 (1·24–2·11)	7·59 (6·18–9·33)
Full models		
Sex		
Female	1	1
Male	1·56 (1·27–1·67)	1·43 (1·32–1·56)
Age (years)		
15–19	0·69 (0·52–0·90)	0·78 (0·56–1·11)
20–29	0·93 (0·84–1·02)	0·87 (0·77–0·99)
30–39	1	1
40–49	1·23 (1·14–1·34)	1·28 (1·16–1·42)
≥50	2·02 (1·84–2·21)	2·05 (1·83–2·29)
Marital status		
Married or with partner	1	1
Single, divorced, or widowed	1·43 (1·33–1·55)	1·31 (1·19–1·44)
Other	1·89 (1·74–2·05)	1·72 (1·55–1·91)
Era of enrolment into HIV care		
Before 2008	1·40 (1·07–1·84)	1·45 (1·09–1·92)
2008 or after	1	1

ART=antiretroviral therapy. *For models using time from linkage to care, the CD4 cell counts used are those at linkage to care, and for models using time from ART initiation, the CD4 cell counts are those at ART initiation.

Table 5: **Survival analysis for time from linkage to HIV care and time from ART initiation in patients in the International Quality Clinical HIV/AIDS Registry Tool Chart database in Rwanda from 2004 to 2011**

CD4 stratum (table 4). However, these similarities were not true for increased CD4 strata. Compared with CD4 cell counts of 200–349 cells per μL, linkage to care in the late era at 500 cells per μL or more was protective, whereas the effect of initiation of ART in the late era at 500 cells per μL or more was not distinguishable from chance alone (table 4). Effects of sex, age, and having a partner were similar in both analyses (table 5). The benefit of high CD4 stratum at linkage but not at ART initiation is distinguishable in survival analysis (figure 2).

A large portion of patients with CD4 counts of less than 350 cells per μL enrolled in care and initiated ART at very similar CD4 counts (figure 3). Immediate initiation does occur but is less common for patients enrolling in care with CD4 counts of more than 350 cells per μL. For patients who enrol with CD4 counts between 350 cells per μL and 500 cells per μL, many initiate ART at CD4 cell counts lower than 250 cells per μL, partly because CD4 tests are done every 6 months (figure 3).

For patients linking to care with CD4 cell counts lower than 350 cells per μL, the median time between linkage to care and ART initiation was 24 days (IQR 14–48). One of the features leading to longer delays in ART initiation was screening positive for tuberculosis. This is because these patients probably initiated treatment for tuberculosis before initiation of ART. In patients linking to care early, the median time between linkage and ART initiation was 311 days (IQR 168–496). Finally, loss to follow-up within the pre-ART period was low at 5·5 cases lost per 100 person-years, which is similar to what has been reported for the entire country.[20]

Discussion

Our study identified a strong association between increasing survival outcomes with increasing CD4 cell

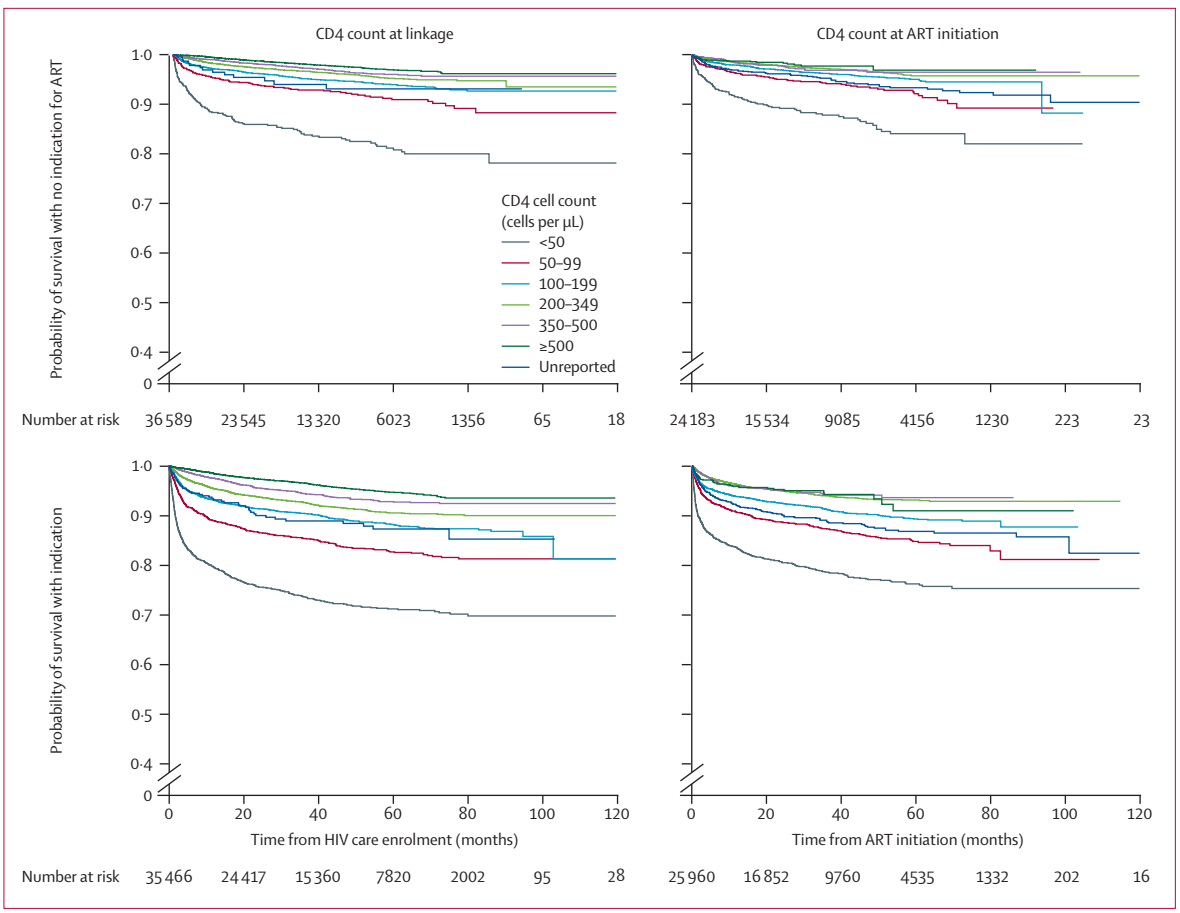

Figure 2: **Survival by CD4 cell count strata at linkage to care and at ART initiation and separated by presence or absence of other indications for ART**
Kaplan-Meier curves with data for 72 061 HIV-positive Rwandans. ART=antiretroviral therapy.

count at time of linkage to HIV care and, despite having a large sample and accounting for other mechanisms by which ART is initiated, identified little evidence of survival benefits through ART initiation at CD4 counts of 500 cells per µL or greater in comparison with initiation at 350 cells per µL. The limited evidence of survival benefits is in agreement with similar studies in developed settings. This result is timely in view of the fact that changes in ART eligibility according to CD4 strata are still new, particularly in sub-Saharan Africa. In view of the fact that many patients are still initiating ART at low CD4 cell counts,[8] the improved outcomes reported in individuals entering HIV care at high CD4 cell counts suggests that reductions in morbidity and mortality are possible with retention in pre-ART care while the scale-up of universal treatment is being implemented.

Three major observational studies from developed settings have examined the predictive value of CD4 cell count on mortality outcomes at time of ART initiation.[13,17,24] The When to Start Consortium, a cohort collaboration in several countries, identified a 13% increased risk of death in patients delaying ART initiation to less than 350 cells per µL. This effect was larger with a composite outcome of AIDS defining events plus mortality (28%).[17] The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) reported a finding that mortality was greatly increased in those initiating ART with a CD4 cell count lower than 500 cells per µL.[24] However, this finding has since been disputed because the analysis did not adequately account for confounding by indication.[25–27] The HIV-CAUSAL Collaboration combined data from Europe and the USA and identified that initiation of ART at CD4 cell counts of 500 cells per µL or more reduced AIDS-defining illnesses, but not survival.[13] Other cohorts have more substantial limitations including small sample sizes, aggregate data, and confounding issues, including important lead-time bias and loss to follow-up.[1,3,28–30] Nonetheless, smaller studies in sub-Saharan Africa have also shown improved survival associated with ART initiation in the lower CD4 cell count strata.[12] Several randomised trials[16] examining when to start by CD4 cell count are underway. In May, 2015, the National Institute of Allergy and Infectious Diseases reported that the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial was stopped early because the results showed that immediate treatment

reduced the risk of morbidity and mortality by 53%.[31] The START trial randomly assigned treatment-naive patients to immediate treatment or treatment at a CD4 cell count of less than 350 cells per μL and assessed the composite outcomes of serious AIDS events, serious non-AIDS events, and death. The Temprano ANRS 12136 trial in Cote d'Ivoire has also reported a benefit of immediate initiation of ART and early isoniazid prophylaxis, independently.[32] Evidence from these trials has helped to inform the development of new WHO treatment guidelines to be released later in 2015.

The reported improvement in survival outcomes in patients linking to care early suggest that a safe deferral strategy for ART initiation might be possible in regions where ART uptake remains poor so long as efforts are made to engage and retain patients in pre-ART care services. Little doubt exists that earlier linkage to care is needed for timely initiation of ART, but it is not sufficient. There are complex reasons for this, including fear of social isolation and stigma, that might lead to treatment refusal or disengagement in care.[33] However, our study has shown that in a health system with good patient engagement and retention outcomes, such as in Rwanda, patients can be linked and retained in care before the initiation of ART with good survival outcomes. The pre-ART programme in Rwanda includes various clinical and social support. All pre-ART patients have monthly clinic visits to pick up co-trimoxazole and, if necessary, other therapeutics and nutritional supplements. These visits provide an opportunity to communicate with health-care workers and to learn about HIV. Various community associations (clubs) also exist; these are sought and joined at the patient's discretion, but provide further education and social support. Although use of co-trimoxazole has been consistent over time, the popularity of associations and use of nutritional supplements have increased. All of these help explain the reported improved survival in patients in care before ART initiation. Interventions to improve the retention of patients in pre-ART care in low-income and middle-income settings have been synthesised elsewhere.[34] In Rwanda, these might include a responsive national surveillance system,[35] universal health coverage,[36] task shifting of health-care providers,[37] performance-based financing,[38] and strong donor support.[39] However, linkage to clinical care from the point of testing remains low in Rwanda,[20,40] as in many sub-Saharan African countries,[20,41] and a greater effort must be made to improve the integration of HIV testing, treatment, and care services.[20,41]

Strengths of this study include the nationally representative sample and large sample size—larger than any previous assessments in sub-Saharan Africa. Rwanda is one of the few countries in Africa that has implemented a nationwide monitoring and assessment programme of their HIV care delivery and thus offers an ideal, heterogeneous population in which to assess system-level prognostic variables. Our analysis also includes many patients (1534; 15·7%) with CD4 cell counts of more than 500 cells per μL at ART initiation. However, only 350 patients initiated ART with such high CD4 cell counts in the absence of an indication, and the non-significance might result from the small sample size in this stratum. Moreover, our analysis did not examine the incidence of serious non-fatal AIDS events or AIDS-defining events and we might have identified different rates of these events according to CD4 cell count status. An important limitation is the potential presence of measurement bias with respect to indications for initiation of ART. Some health-care providers do not record the presence of opportunistic infections in health records at linkage to care. Some opportunistic infections, for example, might need laboratory resources that are unavailable in Rwanda. Our sample includes most patients who began ART with very low CD4 cell counts, although these proportions have changed over time. Therefore, although we have substantial data for risk of death at lower CD4 cell count status, particularly in the early years of treatment scale-up, we have heterogeneous power at different CD4 cell count strata. Comparison of CD4 cell count strata at ART initiation when treatment guidelines have changed over time also introduces important selection bias into the raw data. We addressed this issue by incorporation of all observed indicators of ART initiation and examination of the effect of CD4 cell

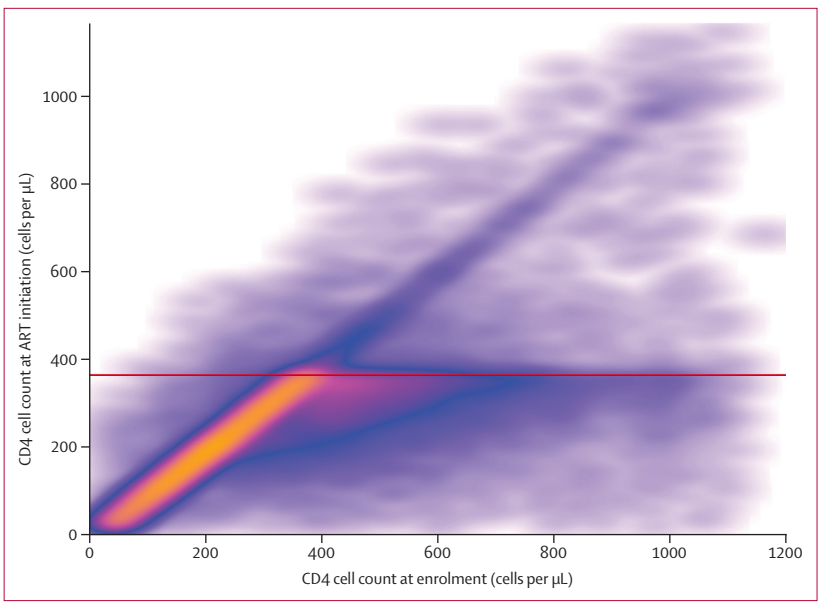

Figure 3: **Association between CD4 cell counts at linkage to care and CD4 cell counts at ART initiation**
Smoothed scatter plot with data for 41 144 Rwandans who initiated ART between 2004 and 2011. The horizontal red line is at 350 cells per μL, an older threshold established in 2008 for immediate initiation of ART. Intensity of colour indicates the density of observations, with orange indicating thousands of observations in the immediate vicinity, dark blue indicating hundreds of observations, and purple indicating few observations in the immediate vicinity. Patients who enrol with low CD4 cell counts seem to initiate treatment immediately. Among those who linked to care with CD4 counts above about 400 cells per μL two distinct lines exist: immediate starts and delayed starts. The area of interest is the non-negligible cluster of individuals who have linkage to care above 350 cells per μL, yet delay initiation well below this level. ART=antiretroviral therapy.

count on mortality, after including the effect modifier of other known indications to start ART. Finally, the possibility of confounding can be ruled out only by a well designed and well done randomised clinical trial.

In summary, our study identified that initiation of ART at a CD4 count of at least 500 cells per μL was not associated with improved survival, whereas linkage to care at CD4 counts of at least 500 cells per μL was associated with increased survival. These results should contribute to the discussion that earlier linkage to care even with a delay in ART initiation might result in substantial reductions in mortality in sub-Saharan Africa.

Contributors

SN had full access to all of the data in the study. SN takes responsibility for the integrity of the data, the accuracy of the data analysis, and the final decision to submit for publication. SN, SK, ER, JIF, AB, and EJM designed and conceived the study. SN, ER, JIF, SK, AB, JC, and EJM acquired, analysed, and interpreted the data. SN, SK, JIF, NF, MV, and EJM drafted the manuscript. SN, SK, ER, JIF, AB, JC, NF, MV, KT, HB, and EJM critically revised the manuscript. SK, EM, and SN did the statistical analysis. SN, JC, AB, and EJM obtained funding. SN, ER, JIF, JC, and EJM provided administrative, technical, or material support. SN, HB, KT, AB, and EJM supervised the study.

Declaration of interests

We declare no competing interests.

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