Mortality, AIDS-Morbidity, and Loss to Follow-up by Current CD4 Cell Count Among HIV-1–Infected Adults Receiving Antiretroviral Therapy in Africa and Asia: Data From the ANRS 12222 Collaboration

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Background: In resource-limited countries, estimating CD4-specific incidence rates of mortality and morbidity among patients receiving antiretroviral therapy (ART) may help assess the effectiveness of care and treatment programmes, identify program weaknesses, and inform decisions.

Methods: We pooled data from 13 research cohorts in 5 sub-Saharan African (Benin, Burkina Faso, Cameroon, Cote d'Ivoire, and Senegal) and 2 Asian (Cambodia and Laos) countries. HIV-infected adults (18 years and older) who received ART in 1998–2008 and had at least one CD4 count available were eligible. Changes in CD4 counts over time were estimated by a linear mixed regression. CD4-specific incidence rates were estimated as the number of first events occurring in a given CD4 stratum divided by the time spent within the stratum.

Results: Overall 3917 adults (62% women) on ART were followed up during 10,154 person-years. In the ≤50, 51–100, 101–200, 201–350, 351–500, 501–650, and >650 cells/mm^3 CD4 cells strata, death rates were 20.6, 11.8, 6.7, 3.3, 1.8, 0.9, and 0.3 per 100 person-years; AIDS rates were 50.5, 32.9, 11.5, 4.8, 2.8, 2.2, and 2.2 per 100 person-years; and loss-to-follow-up rates were 4.9, 6.1, 3.5, 3.1, 2.9, 1.7, and 1.2 per 100 person-years, respectively. Mortality and morbidity were higher during the first year after ART initiation.

Conclusions: In these resource-limited settings, death and AIDS rates remained substantial after ART initiation, even in individuals with high CD4 cell counts. Ensuring earlier ART initiation and optimizing case finding and treatment for AIDS-defining diseases should be seen as priorities.

Key Words: adults, morbidity, mortality, CD4, HIV, Africa, antiretroviral

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INTRODUCTION

In the last decade, considerable efforts have been made to scale-up antiretroviral therapy (ART) in resource-limited countries, to decrease HIV/AIDS-related mortality and morbidity.[1–4] The number of patients on ART dramatically increased from 400,000 in 2003, when the World Health Organization (WHO) launched the "3 by 5" initiative, to 6.6 million in 2010. However, this latter figure only represents 47% of the patients in need of treatment, while universal access to ART was targeted for 2010.[5,6] Moreover, mortality and morbidity among treated patients was reported to be higher in resource-limited settings than in rich countries, partly because patients still frequently start ART at an advanced stage of HIV disease with pronounced immunodeficiency.[7–9]

The CD4 cell count is the most important determinant of HIV-related mortality and morbidity.[10–15] Incidence rates of death or AIDS by CD4 cell count among patients receiving ART in the context of resource-limited countries have been mainly estimated in low CD4 cell count strata and based on pre-ART CD4 values.[12,16] Estimating these incidence rates according to the current CD4 cell count (CD4-specific rates) across a wide range of CD4 values could help inform clinical outcomes in patients on ART and adapt treatment recommendations to improve the quality of care and the effectiveness of treatment programmes.

The reasons why CD4-specific rate estimates have rarely been reported in sub-Saharan Africa are inherent to the methodological limitations of cohort studies and of large program databases.

In cohort studies, CD4 counts are measured regularly, the magnitude of missing data and of loss to follow-ups are limited, and morbidity/mortality are properly documented, but the number of patients per CD4 stratum is limited. In operational programmes, sample sizes are much larger, but the rates of loss to follow-up and of missing data are high and morbidity and mortality documentation is poorer.[17]

In this study, we pooled available data from cohorts of HIV-infected adults on ART in low-resource settings, to estimate CD4-specific rates of death and AIDS.

METHODS

Study Population

The ANRS 12222 collaboration was established in 2009 with the objective to describe CD4-specific rates of mortality and morbidity among HIV-infected patients living in resource-limited countries. In this collaboration, we pooled data from research cohort studies sponsored by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) or associated partners in Africa and Asia from 1996 to 2009. Methods and results among patients without ART have been published elsewhere.[17,18] For the present analysis, cohorts were eligible if the initial study procedures included (1) repeated CD4 cell count measurements, (2) a follow-up period on ART, and (3) an active strategy to retain patients. Within eligible cohorts, patients were included if (1) they were aged 18 years or older at enrolment, (2) they had at least one CD4 measurement available, and (3) they were followed-up at least one day on ART.

Procedures

In all but one participating cohorts, visits, drugs, hospitalizations, and biological or radiological tests were free of charge for patients during the entire study period; in the Senegalese cohort, ART was provided commensurate with their income for most patients or free of charge for the others between 1998 and 2003 and became free for all patients thereafter.[19] All studies implemented the following procedures: scheduled visits once a month up to every 3 months (except one cohort with visits every 4 months during a first calendar period and every 6 months thereafter); CD4 cell count measurements at the time of ART initiation and every 6 months thereafter; active strategies to contact patients who did not show up for a scheduled visit (including phone calls, home visits, and hospital records); standardized definitions and procedures to document ART initiation and follow-up events, and standardized data collection. The absolute CD4 cell counts were determined using flow cytometers. All study protocols had been approved by the national ethics committees or institutional review boards.

Statistical Analysis

The time scale considered in this analysis was the time since ART initiation. Data were censored at the date of the first event among the following: death, AIDS-defining event (for morbidity analysis), last contact with the study team for the patients lost to follow-up, or database cutoff date for this study.

We considered the following CD4 cell count strata: $\leq$50, 51–100, 101–200, 201–350, 351–500, 501–650, and $>$650 cells/mm^3. We first determined the time spent in a given CD4 cell count stratum by estimating the CD4 cell count evolution at individual levels with a linear mixed effect model. Patients were included in this model if they had at least one CD4 measurement available in the last 6 months before ART initiation. The fixed effects were the participating cohort, gender, baseline age, baseline CD4 cell count ($\leq$50, 51–150, 151–250, and $>$250 cells/mm^3), baseline WHO clinical stage, and year of ART initiation (2004 or earlier versus after 2004). We used a model with 2 slopes (a first during the first 3 months of follow-up and a second thereafter) and a quadratic term on the second slope. The random effects were composed of the 2 slopes and of the quadratic term on the second slope. The underlying assumptions were verified by graphically studying model residuals. This model was performed using the MIXED procedure of the SAS software, version 9.1 (SAS institute Inc., Cary, NC).

We then estimated the current CD4 cell count-specific rates of death, of AIDS, of a combined criterion of death or AIDS, and of loss to follow-up per 100 person-years by dividing the number of first given events that occurred in each CD4 cell count stratum by the time spent in the corresponding stratum (for patients who did not have the event) or by the time between entry in the stratum and first event (for patients who experienced the event). Prevalent events at ART initiation were excluded. AIDS events were defined according to the Centers for Disease Control and Prevention classification (CDC stage C). Patients were considered as lost to follow-up if their last contact was more than 6 months before the database cutoff for this study and if they were not known to be dead. Confidence intervals (95% CI) were calculated assuming a Poisson distribution if the number of events was less than 50 and normal approximation otherwise.

RESULTS

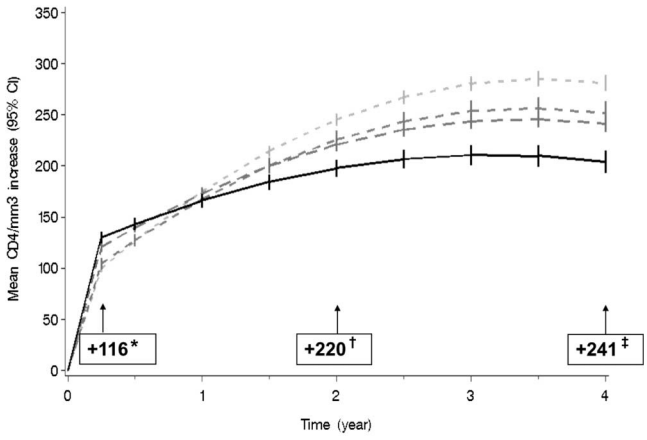
Characteristics of Patients

Among the 17 longitudinal cohort studies of HIV-infected adults in resource-limited settings included in the ANRS 12222 collaboration, 13 followed patients on ART. These studies were conducted in 5 sub-Saharan African countries (Benin, Burkina

Faso, Cameroon, Cote d'Ivoire, and Senegal) and 2 Asian countries (Cambodia and Laos). Between August 1998 and June 2008, 4313 adults were followed at least one day with ART, of whom 3917 (91%) had at least one CD4 cell count measurement and were therefore included in the present analysis (2318 in Africa and 1599 in Asia). The main baseline characteristics of patients are shown in Table 1. Two-thirds of patients were women. The median age was 34 years and median pre-ART CD4 cell count was 148 cells/mm^3. The overall follow-up cumulated was 10,154 person-years, of which one-third was in the 201–350 CD4 cells/mm^3 stratum and almost half was in the CD4 strata above 350 cells/mm^3. The median follow-up was 2.3 years and median number of CD4 cell counts per patient was 6.

Evolution of the CD4 Cell Count After ART Initiation

Figure 1 shows the modelized CD4 cell count evolution after ART initiation according to pre-ART value. The CD4 cell count increase was important in all CD4 strata during the first 3 months of treatment (more importantly in the highest strata) and slowed down and differed according to strata thereafter ($P < 0.001$). Beyond the first months of treatment, the lower the pre-ART CD4 cell count was, the higher the CD4 increase was. At two years, the mean CD4 cell count increase was 245 cells/mm^3 for pre-ART CD4 cell count less than 50 cells/mm^3 and 198 cells/mm^3 for pre-ART CD4 cell count more than 200 cells/mm^3. At 4 years, the mean CD4 cell count increase was 281 and 204 cells/mm^3, respectively. We observed a curve level off after 2–3 years of ART in all CD4 cell count strata.



3 months	+100	+104	+121	+130
2 years	+245	+226	+221	+198
4 years	+281	+252	+242	+204

FIGURE 1. Mean increase in CD4 cell count (CD4 modelized adjusted on covariates [cohort, gender, baseline age, baseline CD4 cell count, baseline WHO clinical stage, and year of ART initiation]) among HIV-infected patients receiving ART in Africa and Asia by baseline value, ANRS 12222 Morbidity/Mortality Collaboration. *Mean CD4 increase at 3 months; †Mean CD4 increase at 2 years; and ‡Mean CD4 increase at 4 years.

TABLE 1. Baseline and Follow-up Characteristics of HIV-Infected Patients With ART in Africa and Asia, ANRS 12222 Morbidity/mortality Collaboration

No. Participants	3917
Baseline characteristics	
Women, %	62
Median age, yrs (IQR)	34 (29–40)
Median CD4 count/mm^3 (IQR)	148 (54–224)
WHO stage 3 or 4, %	48
Follow-up characteristics with ART	
Follow-up (yrs), median (IQR)	2.3 (1.5–3.5)
Number of CD4 count per patient, median (IQR)	6 (4–10)
Person-years of follow-up	
Overall	10,154
Per CD4 stratum/mm^3*	
0–50	102
51–100	280
101–200	1505
201–350	3564
351–500	2807
501–650	1227
>650	669
Status at study termination, %	
Alive	84
Lost to follow-up	8
Dead	9

*Modelized.
IQR, interquartile range.

Mortality and Morbidity

During follow-up, 335 patients (9%) died, 525 (13%) experienced at least one AIDS-defining event, and 760 (19%) died or experienced at least one AIDS-defining event. The most frequent AIDS-defining events were pulmonary tuberculosis (n = 249), disseminated tuberculosis (n = 121), recurrent bacterial pneumonia (n = 69), cryptococcosis (n = 50), *Cytomegalovirus* infection (n = 42), toxoplasmosis (n = 35), oesophageal candidiasis (n = 24), Kaposi's sarcoma (n = 17), wasting syndrome (n = 13), nontuberculous mycobacteriosis (n = 11), and systemic mycosis (n = 11).

Mortality and morbidity rates decreased with increasing current CD4 cell count (Figs. 2A, B). Death rates were 20.6 per 100 person-years in the ≤50 CD4 cells/mm^3 stratum, 3.3 per 100 person-years in the 201–350 CD4 cells/mm^3 stratum, and 0.3 per 100 person-years in the >650 CD4 cells/mm^3 stratum. AIDS rates were 50.5 per 100 person-years in the ≤50 CD4 cells/mm^3 stratum, 4.8 per 100 person-years in the 201–350 CD4 cells/mm^3 stratum, and 2.2 per 100 person-years in the >650 CD4 cells/mm^3 stratum. Finally, the rates of death or AIDS were 67.0 per 100 person-years in the ≤50 CD4/mm^3 stratum, 7.5 in the 201–350 CD4 cells/mm^3 stratum, and 2.5 per 100 person-years in the >650 CD4 cells/mm^3 stratum. Unsurprisingly, mortality and morbidity incidence rates were

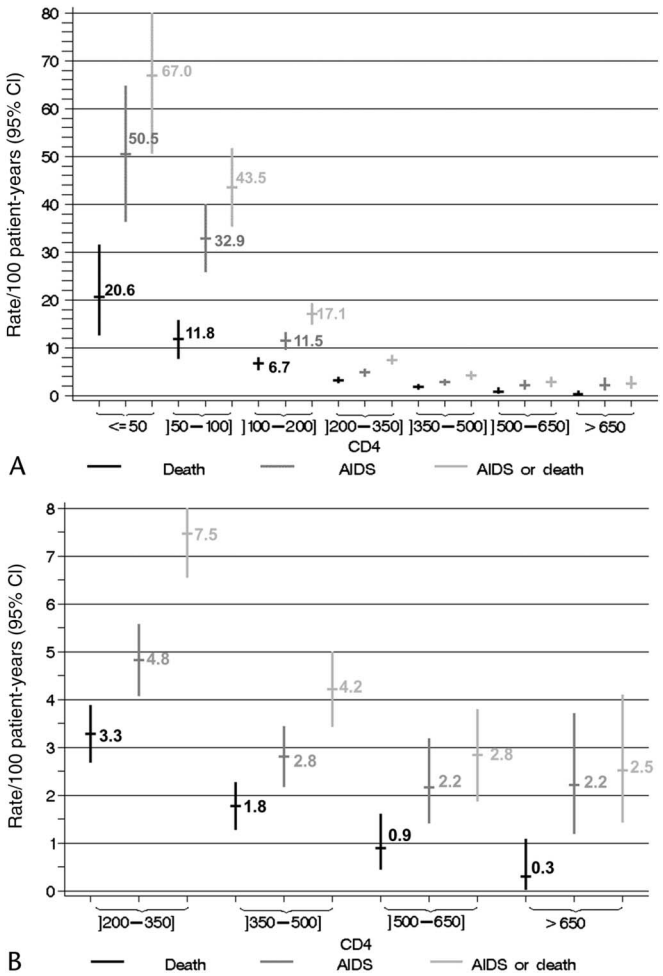


FIGURE 2. A, Mortality and morbidity incidence rates among HIV-infected patients receiving ART in Africa and Asia by current CD4 cell count, ANRS 12222 Morbidity/Mortality Collaboration. B, Mortality and morbidity incidence rates among HIV-infected patients receiving ART in Africa and Asia by current CD4 cell count (focus on CD4 >200 cells/mm^3), ANRS 12222 Morbidity/Mortality Collaboration.

higher during the first year after ART initiation compared with subsequent years (Figs. 3A, B).

Loss to Follow-up

Two hundred ninety-four patients (8%) were lost to follow-up. The incidence rate of loss to follow-up tended to decrease when the current CD4 cell count increased (Fig. 4). In the ≤50, 201–350, and >650 CD4 cells/mm^3 strata, loss-to-follow-up incidence rates were 4.9, 3.1, and 1.2 per 100 person-years, respectively. There was no significant difference between the first year and subsequent years.

DISCUSSION

This pooled analysis of data from 13 cohorts in Africa and Asia allowed us to estimate the incidence rates of death, AIDS, a combined criterion of death or AIDS, and loss to follow-up by current CD4 cell count among HIV-infected adults receiving ART in resource-limited countries. As expected, mortality and morbidity incidence rates decreased with increasing CD4 count and were higher in the first year of treatment. However, mortality and morbidity rates remained substantial, even in high CD4 cell count strata. Finally, the rate of loss to follow-up tended to decrease with increasing CD4 cell count, without significant difference between the first year and thereafter.

In a previous report of mortality and morbidity CD4-specific rates among untreated patients in the same settings, we found higher mortality rates in the CD4 cell count strata below 200 cells/mm^3, similar mortality rates above 200 cells/mm^3, and similar AIDS rates across the spectrum of CD4 counts.[17,18]

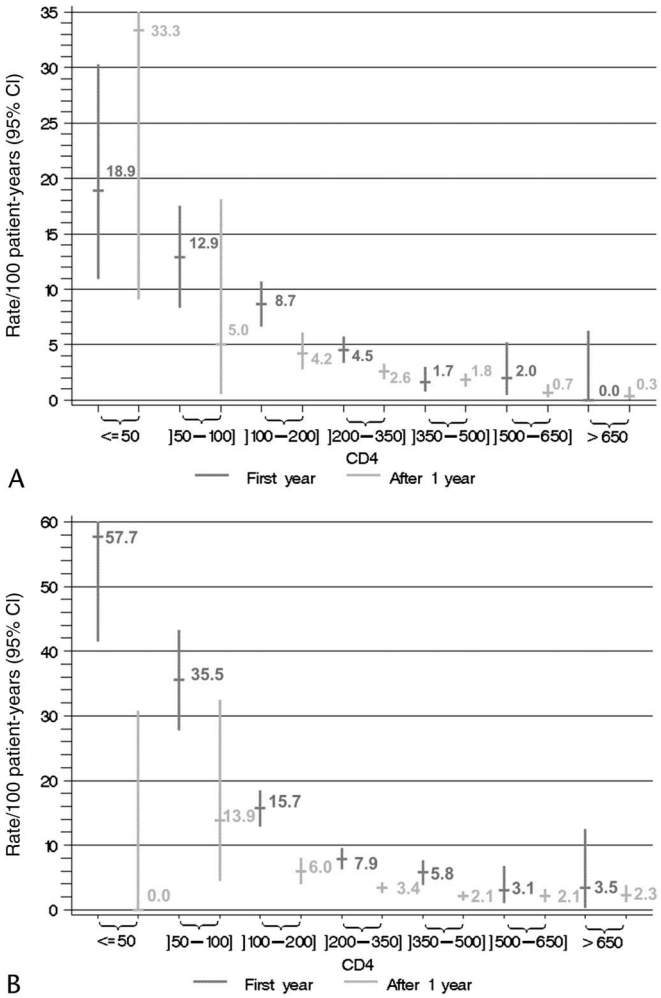


FIGURE 3. A, Mortality incidence rates during the first year and thereafter among HIV-infected patients receiving ART in Africa and Asia by current CD4 cell count, ANRS 12222 Morbidity/Mortality Collaboration. B, AIDS incidence rates during the first year and thereafter among HIV-infected patients receiving ART in Africa and Asia by current CD4 cell count, ANRS 12222 Morbidity/Mortality Collaboration.

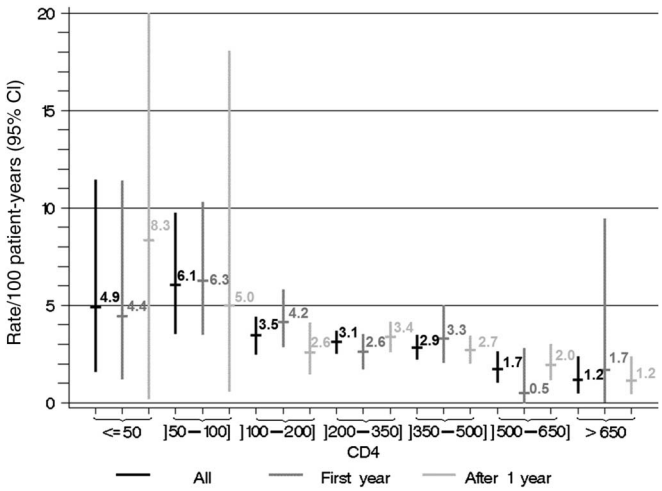


FIGURE 4. Loss to follow-up incidence rates during the first year, thereafter, and overall among HIV-infected patients receiving ART in Africa and Asia by current CD4 cell count, ANRS 12222 Morbidity/Mortality Collaboration.

Overall, our estimates of mortality seemed to be in the range of those reported among patients receiving ART in Western countries, while our estimates of AIDS rates tended to be higher. Reported death rates among patients with a CD4 cell count between 351 and 500 cells/mm^3 were 1.6 per 100 person-years in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD),[20] and 0.8 per 100 person-years in the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE).[21] In patients with >500 CD4 cells/mm^3, death rates were 1.3 per 100 person-years in the NA-ACCORD,[20] 0.4 per 100 person-years in the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE)[22] and 0.7 per 100 person-years in CASCADE.[21] Finally, the death rate was 0.7 per 100 person-years among patients with a CD4 cell count >350 cells/mm^3 in the EuroSIDA study.[23] This latter study also reported death rates similar to our estimates in lower CD4 cell count strata and lower rates of AIDS across the entire CD4 spectrum.[23]

Of note, three-quarters of patients included in studies from high-income countries were male, whereas two-thirds of our patients were women, and mortality has been repeatedly reported to be higher in men.[11,21]

In sub-Saharan Africa, a recent study in Kenya, Malawi, and Uganda reported estimates of mortality after the first 9 months of ART, but a comparison with our study is difficult because of methodological differences.[24] In South Africa, reported death rates in patients on ART were 2.0 per 100 person-years among patients with 300–499 CD4 cells/mm^3, and 1.2 per 100 person-years among those with CD4 >500 cells/mm^3.[25]

Three main recommendations can be drawn, directly or indirectly, from our findings to improve the quality of HIV care and maximize the effectiveness of ART programmes in resource-limited countries.

First, despite the present global economic crisis and its negative consequences on HIV/AIDS funding, it is critical to ensure that national AIDS programmes, who have devoted considerable efforts to adopt the WHO 2010 recommendation of increasing the ART initiation CD4 threshold from 200 cells/mm^3 to 350 cells/mm^3 in asymptomatic patients, do not reverse their guidelines, as some are tempted to do.[5,26,27] Rather, additional resources both at international and national levels should be mobilized. Moreover, the national programmes that have not yet adopted the CD4 threshold of 350 cells/mm^3 should move toward it. Finally, initiation of ART above the CD4 threshold of 350 cells/mm^3 in asymptomatic or mildly symptomatic patients in low-resource settings should be envisaged in the near future. As a matter of fact, rich countries with lower rates of AIDS in patients with >350/mm^3 already recommend starting ART >500 cells/mm^3 or at any CD4 count.[28,29]

Second, additional efforts in terms of laboratory equipment, training, mentoring, and supervision of health-care workers, accessibility to preventive and curative drugs, and education of patients are necessary to improve the diagnosis and treatment of opportunistic infections in patients receiving ART.

Third, the schedule of clinical visits should take into account not only the time on ART but also the current CD4 cell count. This finding underlines once more the need for immunological monitoring in treated patients.[30–32]

The main limitation to our study was the relatively small sample size, especially in the CD4 cell count strata <100 cells/mm^3. However, estimates of incidence rates in higher CD4 cell count strata, where the sample size was larger, are of higher interest as they concern the current debate on the timing of ART initiation.[20,33–35] The sample size also prevented any data stratification on major determinants of mortality and morbidity such as gender and age and on duration of ART beyond the first year. Data in larger and longer-term cohort studies would be useful. On the other hand, our mortality and morbidity estimates should be seen as minimum rates, due to unknown events (deaths or AIDS) among patients lost to follow-up.[36] Indeed, although censoring due to losses to follow-up may be informative, they were treated as censoring due to end of the study period. The number and distribution of events across CD4 cell count strata among the patients lost to follow-up are unknown but our mortality and morbidity estimates were probably more accurate in the high CD4 cell count strata focused in the present study than in the low strata because the rate of losses to follow-up on the one hand and the expected rate of events (deaths or AIDS) in those patients lost to follow-up on the other hand were lower in the former. It is worth noting that the rates of loss to follow-up in high CD4 cell count strata were comparable with the rates of death and AIDS. Yet, the underestimation of the death rates in the high CD4 cell count strata, for example, is likely to be lower in treated patients than in their untreated counterparts included in the ANRS 12222 study, where loss to follow-up rates were 1.5–5 times higher.[17] An underestimation of the morbidity estimates could also have arisen because of the common difficulties in the diagnosis of opportunistic infections in resource-limited settings. Unfortunately, data on non-AIDS morbidity was not available. Finally, our pooled data concealed the heterogeneity between the studies, especially between the African and Asian studies, but our sample size did not allow stratifying the analysis by region. Moreover, we hypothesized that the trend of incidence rates

of mortality and morbidity across CD4 cell count strata does not differ in large proportions according to the context. Nevertheless, this pooled analysis of data from numerous standardized research studies with good monitoring and rather low rates of patients lost to follow-up provided fairly accurate mortality and morbidity estimates in the context of resource-limited countries.

In conclusion, this collaborative study of 13 cohorts of adult patients receiving ART in Africa and Asia showed that mortality and morbidity decreased with increasing current CD4 cell count but remained substantial even with high CD4 cell counts. Death rates seemed comparable with those observed in Western countries, whereas AIDS rates seemed higher. Additional efforts are necessary to allow early initiation of ART and better diagnosis and treatment of opportunistic infections in resource-limited settings.

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REFERENCES

1. Jahn A, Floyd S, Crampin AC, et al. Population-level effect of HIV on adult mortality and early evidence of reversal after introduction of antiretroviral therapy in Malawi. *Lancet*. 2008;371:1603–1611.
2. Mermin J, Were W, Ekwaru JP, et al. Mortality in HIV-infected Ugandan adults receiving antiretroviral treatment and survival of their HIV-uninfected children: a prospective cohort study. *Lancet*. 2008;371:752–759.
3. Lawn SD, Myer L, Orrell C, et al. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS*. 2005;19:2141–2148.
4. Toure S, Kouadio B, Seyler C, et al. Rapid scalingup of antiretroviral therapy in 10,000 adults in Cote d'Ivoire: 2-year outcomes and determinants. *AIDS*. 2008;22:873–882.
5. World Health Organization. *Global HIV/AIDS Response. Epidemic Update and Health Sector Progress Towards Universal Access. Progress Report 2011*. Geneva, Switzerland: World Health Organization/UNICEF/UNAIDS; 2011.
6. World Health Organization. Towards universal access by 2010. How WHO is working with countries to scale-up HIV prevention, treatment, care and support. 2006. Available at: http://www.who.int/hiv/toronto2006/towardsuniversalaccess.pdf. Accessed February 14, 2013.
7. The Antiretroviral Therapy in Lower Income Countries (ART-LINC) Collaboration and ART Cohort Collaboration (ART-CC) groups. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet*. 2006;367:817–824.
8. Keiser O, Orrell C, Egger M, et al. Public-health and individual approaches to antiretroviral therapy: township South Africa and Switzerland compared. *PLoS Med.* 2008,5:e148.
9. De Beaudrap P, Etard JF, Diouf A, et al. Incidence and determinants of new AIDS-defining illnesses after HAART initiation in a Senegalese cohort. *BMC Infect Dis.* 2010;10:179.
10. May M, Boulle A, Phiri S, et al. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. *Lancet*. 2010;376:449–457.
11. Brinkhof MW, Boulle A, Weigel R, et al. Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality. *PLoS Med.* 2009;6:e1000066.
12. Moh R, Danel C, Messou E, et al. Incidence and determinants of mortality and morbidity following early antiretroviral therapy initiation in HIV-infected adults in West Africa. *AIDS*. 2007;21:2483–2491.
13. Seyler C, Messou E, Gabillard D, et al. Morbidity before and after HAART initiation in Sub-Saharan African HIV-infected adults: a recurrent event analysis. *AIDS Res Hum Retroviruses*. 2007;23:1338–1347.
14. Zhou J, Kumarasamy N. Predicting short-term disease progression among HIV-infected patients in Asia and the Pacific region: preliminary results from the TREAT Asia HIV Observational Database (TAHOD). *HIV Med.* 2005;6:216–223.
15. Fregonese F, Collins IJ, Jourdain G, et al. Predictors of 5-years mortality in HIV-infected adults starting highly active antiretroviral therapy (HAART) in Thailand. *J Acquir Immune Defic Syndr*. 2012;60:91–98.
16. Mills EJ, Bakanda C, Birungi J, et al. Mortality by baseline CD4 cell count among HIV patients initiating antiretroviral therapy: evidence from a large cohort in Uganda. *AIDS*. 2011;25:851–855.
17. Lewden C, Gabillard D, Minga A, et al. CD4-specific mortality rates among HIV-infected adults with high CD4 counts and no antiretroviral treatment in West Africa. *J Acquir Immune Defic Syndr*. 2012;59:213–219.
18. Anglaret X, Minga A, Gabillard D, et al. AIDS and non-AIDS morbidity and mortality across the spectrum of CD4 cell counts in HIV-infected adults before starting antiretroviral therapy in Cote d'Ivoire. *Clin Infect Dis.* 2012;54:714–723.
19. Etard JF, Ndiaye I, Thierry-Mieg M, et al. Mortality and causes of death in adults receiving highly active antiretroviral therapy in Senegal: a 7-year cohort study. *AIDS*. 2006;20:1181–1189.
20. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med.* 2009;360:1815–1826.
21. Writing Committee for the CASCADE Collaboration. Timing of HAART initiation and clinical outcomes in human immunodeficiency virus type 1 seroconverters. *Arch Intern Med.* 2011;171:1560–1569.
22. Lewden C, Bouteloup V, De Wit S, et al. All-cause mortality in treated HIV-infected adults with CD4 $\geq$ 500/mm^3 compared with the general population: evidence from a large European observational cohort collaboration. *Int J Epidemiol.* 2012;41:433–445.
23. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362:22–29.
24. Maman D, Pujades-Rodriguez M, Nicholas S, et al. Response to antiretroviral therapy in sub-Saharan Africa: improved survival associated with CD4 above 500 cells/μL. *AIDS*. 2012;26:1393–1398.
25. Lawn SD, Little F, Bekker LG, et al. Changing mortality risk associated with CD4 cell response to antiretroviral therapy in South Africa. *AIDS*. 2009;23:335–342.
26. World Health Organization. *Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for a Public Health Approach. 2010 Revision*. Geneva, Switzerland: World Health Organization/UNICEF/UNAIDS; 2010.
27. Laurent C. Commentary: early antiretroviral therapy for HIV infection in sub-Saharan Africa, a challenging new step. *J Public Health Policy*. 2010;31:401–406.
28. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA*. 2010;304:321–333.

29. European AIDS Clinical Society. Guidelines for Treatment of HIV Infected Adults in Europe, version 6.0. 2011. Available at: http://www.europeanaidsclinicalsociety.org/. Accessed February 14, 2013.
30. Mugyenyi P, Walker AS, Hakim J, et al. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. *Lancet*. 2010;375:123–131.
31. Mermin J, Ekwaru JP, Were W, et al. Utility of routine viral load, CD4 cell count, and clinical monitoring among adults with HIV receiving antiretroviral therapy in Uganda: randomised trial. *BMJ*. 2011;343:d6792.
32. Laurent C, Kouanfack C, Laborde-Balen G, et al. Monitoring of HIV viral loads, CD4 cell counts, and clinical assessments versus clinical monitoring alone for antiretroviral therapy in rural district hospitals in Cameroon (Stratall ANRS 12110/ESTHER): a randomised non-inferiority trial. *Lancet Infect Dis.*. 2011;11:825–833.
33. Walensky RP, Wolf LL, Wood R, et al. When to start antiretroviral therapy in resource-limited settings. *Ann Intern Med*. 2009;151:157–166.
34. Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*. 2009;373:1352–1363.
35. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365:493–505.
36. Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. *PLoS One*. 2009;4:e5790.