

Life Expectancy of Persons Receiving Combination Antiretroviral Therapy in Low-Income Countries: A Cohort Analysis From Uganda

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Background: Little is known about the effect of combination antiretroviral therapy (cART) on life expectancy in sub-Saharan Africa.

Objective: To estimate life expectancy of patients once they initiate cART in Uganda.

Design: Prospective cohort study.

Setting: Public sector HIV and AIDS disease-management program in Uganda.

Patients: 22 315 eligible patients initiated cART during the study period, of whom 1943 were considered to have died.

Measurements: All-cause mortality rates were calculated and abridged life tables were constructed and stratified by sex and baseline CD4 cell count status to estimate life expectancies for patients receiving cART. The average number of years remaining to be lived by patients who received cART at varying age categories was estimated.

Results: After adjustment for loss to follow-up, crude mortality rates (deaths per 1000 person-years) ranged from 26.9 (95% CI, 25.4 to 28.5) in women to 43.9 (CI, 40.7 to 47.0) in men. For patients with a baseline CD4 cell count less than 0.050×10^9

cells/L, the mortality rate was 67.3 (CI, 62.1 to 72.9) deaths per 1000 person-years, whereas among persons with a baseline CD4 cell count of 0.250×10^9 cells/L or more, the mortality rate was 19.1 (CI, 16.0 to 22.7) deaths per 1000 person-years. Life expectancy at age 20 years for the overall cohort was 26.7 (CI, 25.0 to 28.4) additional years and at age 35 years was 27.9 (CI, 26.7 to 29.1) additional years. Life expectancy increased substantially with increasing baseline CD4 cell count. Similar trends are observed for older age groups.

Limitations: A small (6.4%) proportion of patients were lost to follow-up, and it was imputed that 30% of these patients had died. Few patients with a CD4 cell count greater than 0.250×10^9 cells/L initiated cART.

Conclusion: Ugandan patients receiving cART can expect an almost normal life expectancy, although there is considerable variability among subgroups of patients.

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Increased access to combination antiretroviral therapy (cART) has led to a substantial decrease in morbidity and mortality among patients who are HIV positive in resource-constrained settings (1, 2). The effect of increased survival has allowed patients who are HIV positive and receiving cART to contribute to their family and local economies and social structure (3–5).

Life expectancy and mortality are important indicators of population health. Studies have shown a negative relationship between HIV prevalence and life expectancy at a population level (6). A recent collaborative cohort analysis by the Antiretroviral Therapy (ART) Cohort Collaboration demonstrated that patients in Europe and the United States initiating cART at age 20 years could expect to live an additional 49 years, with an overall increase of 81% in life expectancy since 1996 (7). This group also showed that men had lower life expectancy than women and that life expectancy improved with increasing baseline CD4 cell count status (7).

In contrast, the long-term life expectancy of patients receiving cART in resource-constrained settings is unclear and remains speculative. Mortality estimates vary, owing to small sample sizes, overrepresentation of certain groups, high rates of loss to follow-up, and associated misclassification of mortality (1, 8, 9). Sub-optimal initial drug regimens and co-infection with chronic untreated comorbid conditions, such as tuber-

culosis, hepatitis, and malnutrition, are also problematic in resource-constrained settings and may affect life expectancy (10–12). Knowledge about life expectancy of patients infected with HIV in resource-limited settings is of critical importance at individual and population levels as prognostic and effectiveness indicators and with regard to investment in cART rollout programs.

In Uganda, life expectancy at birth is approximately 55 years and increases as persons survive key milestone ages (13). By using data from a national cohort of patients with HIV in Uganda, we estimated life expectancy among a large, nationally representative cohort of persons receiving free cART.

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Appendix
Appendix Table
Conversion of graphics into slides

Context

Combination antiretroviral therapy has dramatically increased life expectancy in persons with HIV infection in the United States and northern Europe, but its effect in resource-constrained countries is unknown.

Contribution

Treatment with combination regimens increased life expectancy to nearly normal levels in persons infected with HIV in Uganda. Women derived greater benefit than men, as did patients who began therapy at higher CD4 cell counts.

Caution

Some data were missing. Regimens were older and more toxic than those in use in developed countries.

Implication

Antiretroviral therapy for HIV infection can dramatically increase life expectancy in Africa, where the burden of disease is greatest.

—The Editors

METHODS**Participants**

Our study used data collected by The AIDS Support Organization (TASO). This organization provides clinical care, psychosocial support, and antiretroviral therapy to persons with HIV at 11 major clinical sites and 35 smaller clinics throughout Uganda, involving both urban and rural populations. This organization began providing widespread cART in 2004 with resource support from the U.S. President's Emergency Plan for AIDS Relief. More than 24 000 patients are currently receiving this treatment, and more than 80 000 patients await cART initiation. Criteria for starting antiretroviral therapy include having a World Health Organization (WHO) stage 3 or 4 diagnosis or a CD4 cell count status of less than 0.250×10^9 cells/L (14). The Uganda Ministry of Health National Antiretroviral Treatment and Care Guidelines for Adults and Children does not yet reflect the WHO's newest recommendations for immunologic classification and initiation of cART ($\leq 0.350 \times 10^9$ cells/L) (15). Patients initiating antiretroviral therapy typically receive a nonnucleoside reverse transcriptase inhibitor with first-line treatment with fixed-dose combinations comprising nevirapine or efavirenz plus lamivudine and stavudine; second-line therapy consists of boosted lopinavir, didanosine, and zidovudine (16, 17).

Data Collection

Detailed demographic information, clinical characteristics, and treatment information were collected on standardized forms at each patient visit. These data are entered into a centralized clinical database at TASO and are frequently used for research purposes (18–23). When enrolled at TASO, each patient is provided with a unique,

coded identification number. Adherence-monitoring teams are used to undertake patient retention and follow-up; they visit all patients who do not show up for any appointment or who have requested home-based care. Mortality status is actively pursued to determine vital statistics. The teams consist of medical attendants capable of HIV testing, adherence counseling, clinical observation, and providing antiretroviral therapy.

For this study, we included all patients aged 14 years or older who initiated antiretroviral therapy at TASO clinics in Uganda from 1 January 2000 to 31 December 2009. Age 14 years is when adolescents are classified as receiving adult care. Patients were followed until either time of confirmed death or end of the study (1 January 2010). The following patient information was recorded: age of the patient and year that antiretroviral therapy was started, sex of the patient, baseline CD4 cell count status, and WHO clinical disease stage. If the patient was lost to follow-up (a 3-month absence from a clinic), the date when he or she was last seen and the date of death (if applicable) were recorded.

The ethics review board at the headquarters of TASO Uganda, Mbale Regional Referral Hospital (Mbale, Uganda), and the research ethics boards of the University of British Columbia and the University of Ottawa approved the conduct of this study.

Statistical Analysis

We assessed demographic information on patients before and after 2006, the year that the projects funded by the U.S. President's Emergency Plan for AIDS Relief expanded most rapidly. We examined whether mortality differed before compared with after the expansion period.

We did a series of demographic and statistical analyses. To correct for potential misclassification of death among persons recorded as lost to follow-up, we conservatively estimated that 30% who were lost to follow-up had died; this estimation is based on results of a defaulter tracing study done in semiurban Uganda (24, 25). Among persons lost to follow-up, patients were weighted equally by age and CD4 cell count status, such that higher weight would go to persons who were older and had lower CD4 cell counts (18, 23). In doing so, patients with a higher weight would be very likely to be assigned as a death. Of this 30%, the date of last contact remained as the censor date. We applied Markov chain Monte Carlo methods of multiple imputation for missing CD4 cell count status and WHO stage information. The variables used to impute the missing values included age, follow-up time, and year of first cART through SAS PROC MI (SAS software, version 9.1, SAS Institute, Cary, North Carolina).

Mortality rates were calculated by dividing the total number of deaths by the total number of person-years of follow-up. The mortality rates are expressed as deaths per 1000 person-years, stratified by sex (men or women) and

CD4 cell count status (<0.050, 0.050 to 0.099, 0.100 to 0.149, 0.150 to 0.249, and $\geq 0.250 \times 10^9$ cells/L).

Potential years of life lost (PYLL) up to the age of 55 years was used to examine the effect of HIV on premature mortality. The PYLL estimates the average years a person or group would have lived if they had not died prematurely. This number was calculated by taking the total number of deaths in each 5-year age group and multiplying the average number of years remaining in that age group up to age 55 years—the approximate life expectancy at birth in Uganda (13). The PYLL was expressed per 1000 person-years from age 14 to 54 years (26). Values were stratified by sex and baseline CD4 cell count status.

Death during follow-up was analyzed by using Kaplan–Meier methods and the Cox proportional hazards model. Covariates of interest included age, sex, year of first cART, WHO stage, and CD4 cell count status (27). Hazard proportionality was assessed by using analysis of scaled Schoenfeld residuals.

Abridged life tables were constructed from age-specific mortality rates by using methods established by Chiang (28). Life expectancy estimated from this type of life table is viewed as depicting the lifetime mortality experience of a single cohort of persons who are subject to the mortality schedules on which the table is constructed. Therefore, life expectancy at an exact age is an indicator measuring the average number of additional years that will be lived by a person after that age, according to the age-specific mortality rates for all deaths during the study period. Because a very large population and number of deaths are required to overcome variations in mortality when constructing a complete life table by single years, we used abridged life tables by aggregated age groups, which describe the effect of mortality on a sample of persons if they were subjected to the mortality rates in the observed calendar periods (29, 30). Life expectancy was reported from age 20 to 55 years in 5-year intervals with 95% CIs. Life expectancy values were stratified by sex and baseline CD4 cell count status. Detailed methods on life expectancy approaches are widely available (28, 29, 31). The **Appendix Table** (available at www.annals.org) displays the life table approach, and the **Appendix** (available at www.annals.org) provides a worked example.

All significance tests were 2-sided, and *P* values of less than 0.05 were considered statistically significant. All analyses were done by using SAS software, version 9.1 (SAS Institute); R software, version 2.7.1 (R Foundation for Statistical Computing, Vienna, Austria); and Microsoft Excel 2008 (Microsoft, Seattle, Washington).

Role of the Funding Source

The Canadian Institutes of Health Research sponsored the study. The funding source had no role in the design, conduct, or collection of data; in the analysis or interpretation of the study; or in the decision to submit the manuscript for publication.

RESULTS

Our analyses were based on a cohort of 22 315 persons aged 14 years or older who initiated cART at TASO clinics in Uganda from 2000 to 2009, contributing a total of 59 436 person-years. A total of 9899 patients who initiated cART from 2000 to 2006 were followed for median of 48 months (interquartile range [IQR], 38 to 55 months) and 12 416 patients who initiated cART from 2007 to 2009 were followed for a median of 24 months (IQR, 17 to 31 months). **Table 1** shows baseline characteristics of patients. The median age was similar in both periods of therapy initiation: 37 years (IQR, 32 to 44 years) for 2000 to 2006 and 37 years (IQR, 31 to 43 years) for 2007 to 2009. Larger proportions of women initiated therapy in the earlier period (71.8% for 2000 to 2006 vs. 67.5% for 2007 to 2009; *P* < 0.001). The median CD4 cell count increased slightly over time: 0.126×10^9 cells/L (IQR, 0.060 to

Table 1. Baseline Characteristics of Patients

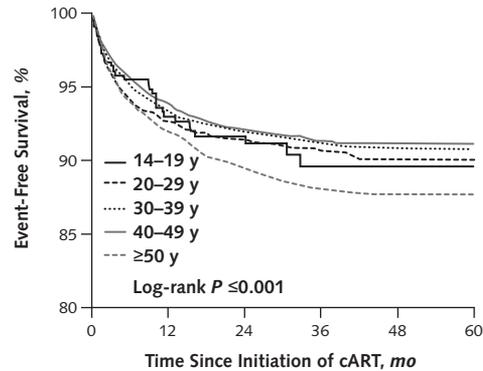
| Characteristic | Overall Patients, n | Patients, n (%) | |
|-----------------------------------|---------------------|-----------------|---------------|
| | | 2000–2006 | 2007–2009 |
| Age | | | |
| 14–19 y | 333 | 121 (1.2) | 212 (1.7) |
| 20–24 y | 866y | 270 (2.7) | 596 (4.8) |
| 25–29 y | 2620 | 1017 (10.3) | 1603 (12.9) |
| 30–34 y | 4801 | 2146 (21.7) | 2655 (21.4) |
| 35–39 y | 4973 | 2286 (23.1) | 2687 (21.6) |
| 40–44 y | 3944 | 1871 (18.9) | 2073 (16.7) |
| 45–49 y | 2348 | 1084 (11.0) | 1264 (10.2) |
| 50–54 y | 1271 | 589 (6.0) | 682 (5.5) |
| ≥ 55 y | 1159 | 515 (5.2) | 644 (5.2) |
| Sex | | | |
| Men | 6823 | 2787 (28.2) | 4036 (32.5) |
| Women | 15 492 | 7112 (71.8) | 8380 (67.5) |
| CD4 count | | | |
| <0.050 $\times 10^9$ cells/L | 3452 | 1698 (21.1) | 1754 (16.8) |
| 0.050–0.099 $\times 10^9$ cells/L | 2942 | 1458 (18.1) | 1484 (14.2) |
| 0.100–0.149 $\times 10^9$ cells/L | 3410 | 1662 (20.7) | 1748 (16.7) |
| 0.150–0.249 $\times 10^9$ cells/L | 5740 | 2506 (31.2) | 3234 (30.9) |
| $\geq 0.250 \times 10^9$ cells/L | 2954 | 720 (9.0) | 2234 (21.4) |
| Missing | 3817 | | |
| WHO stage | | | |
| 1 | 465 | 227 (4.2) | 238 (2.6) |
| 2 | 7985 | 2511 (47.0) | 5474 (58.8) |
| 3 | 4982 | 2232 (41.8) | 2750 (29.6) |
| 4 | 1220 | 376 (7.0) | 844 (9.1) |
| Missing | 7663 | | |
| Death | | | |
| No | 20 817 | 8916 (90.1) | 11 901 (95.9) |
| Yes | 1498 | 983 (9.9) | 515 (4.1) |
| Lost to follow-up | | | |
| No | 20 882 | 9160 (92.5) | 11 722 (94.4) |
| Yes | 1433 | 739 (7.5) | 694 (5.6) |

WHO = World Health Organization.

0.184 × 10⁹ cells/L) for 2000 to 2006 versus 0.156 × 10⁹ cells/L (IQR, 0.080 to 0.230 × 10⁹ cells/L) for 2007 to 2009. Most patients initiated therapy at WHO stage 2 or 3 in both periods (88.8% for 2000 to 2006 and 88.4% for 2007 to 2009). A total of 1498 (6.7%) deaths were recorded in the cohort from 2000 to 2009. An additional 1433 (6.4%) were reported as lost to follow-up. A total of 30% of persons who were lost to follow-up were assumed to have died, making the total number of estimated deaths in the cohort to be 1943. This value was used for all subsequent analyses.

The crude mortality rate was 31.8 (95% CI, 30.3 to 33.2) deaths per 1000 person-years for the overall cohort. The PYLL was 795.0 years per 1000 person-years for the overall cohort. Women had a lower mortality rate than men: 26.9 (CI, 25.4 to 28.5) versus 43.9 (CI, 40.7 to 47.0) deaths per 1000 person-years, respectively. Similarly, PYLL was less for women than men (689.7 vs. 995.9 years per 1000 person-years). The mortality rate and PYLL decreased substantially with increasing baseline CD4 cell count status. For patients with a baseline CD4 cell count less than 0.050 × 10⁹ cells/L, the mortality rate was 67.3 (CI, 62.1 to 72.9) deaths per 1000 person-years. For patients with CD4 cell counts of 0.050 to 0.099 × 10⁹ cells/L, it was 36.8 (32.9 to 41.2). For patients with CD4 cell counts of 0.100 to 0.149 × 10⁹ cells/L, it was 27.5 (24.4 to 31.0). For patients with CD4 cell counts of 0.150 to 0.249 × 10⁹ cells/L, it was 20.2 (18.1 to 22.6). Among patients with baseline CD4 cell counts of 0.250 × 10⁹ cells/L or more, the mortality rate was 19.1 (CI, 16.0 to

Figure 2. Kaplan–Meier product limit estimates for probability of survival, by age group.



| Age, y | Persons at Risk, n | | Events, n | |
|--------|--------------------|------|-----------|------|
| 14–19 | 333 | 299 | 184 | 88 |
| 20–29 | 3486 | 3078 | 2077 | 1047 |
| 30–39 | 9774 | 8810 | 6454 | 3709 |
| 40–49 | 6292 | 5767 | 4322 | 2520 |
| ≥50 | 2430 | 2185 | 1590 | 897 |

cART = combination antiretroviral therapy.

22.7) deaths per 1000 person-years. Similarly, the PYLL among patients with a baseline CD4 cell count status less than 0.050 × 10⁹ cells/L was much higher (1813.3 per 1000 person-years) than in those with a baseline CD4 cell count of 0.250 × 10⁹ cells/L or more (435.5 per 1000

Table 2. Cox Proportional Hazards of Time to Death Among Persons Receiving Combination Antiretroviral Therapy in Uganda*

| Variable | Unadjusted HR (95% CI) | P Value | Adjusted HR (95% CI) | P Value |
|---------------------------------------|------------------------|---------|----------------------|---------|
| Age | | | | |
| 14–19 y | 0.83 (0.57–1.21) | 0.33 | 0.81 (0.55–1.18) | 0.263 |
| 20–29 y | 0.81 (0.69–0.95) | 0.012 | 0.83 (0.70–0.98) | 0.026 |
| 30–39 y | 0.75 (0.65–0.86) | <0.001 | 0.73 (0.63–0.84) | <0.001 |
| 40–49 y | 0.72 (0.62–0.84) | <0.001 | 0.70 (0.60–0.81) | <0.001 |
| ≥50 y | 1.00 (NA) | NA | 1.00 (NA) | NA |
| Sex | | | | |
| Men vs. women | 1.53 (1.40–1.68) | <0.001 | 1.47 (1.34–1.62) | <0.001 |
| WHO stage at baseline | | | | |
| 1 | 1.00 (NA) | NA | 1.00 (NA) | NA |
| 2 | 1.21 (0.77–1.91) | 0.38 | 1.31 (0.87–1.98) | 0.180 |
| 3 | 2.30 (1.43–3.70) | 0.002 | 2.18 (1.43–3.32) | 0.001 |
| 4 | 4.14 (2.72–6.31) | <0.001 | 4.00 (2.75–5.82) | <0.001 |
| CD4 count at baseline† | | | | |
| <0.050 × 10 ⁹ cells/L | 1.00 (NA) | NA | 1.00 (NA) | NA |
| 0.050–0.099 × 10 ⁹ cells/L | 0.61 (0.53–0.70) | <0.001 | 0.65 (0.56–0.75) | <0.001 |
| 0.100–0.149 × 10 ⁹ cells/L | 0.48 (0.41–0.55) | <0.001 | 0.53 (0.45–0.63) | <0.001 |
| 0.150–0.249 × 10 ⁹ cells/L | 0.35 (0.31–0.40) | <0.001 | 0.42 (0.37–0.47) | <0.001 |
| ≥0.250 × 10 ⁹ cells/L | 0.32 (0.27–0.37) | <0.001 | 0.39 (0.34–0.46) | <0.001 |
| Year of first cART | | | | |
| | 0.74 (0.72–0.77) | <0.001 | 0.75 (0.72–0.78) | <0.001 |

cART = combination antiretroviral therapy; HR = hazard ratio; NA = not applicable; WHO = World Health Organization.

* Results from multiple-imputation method.

† Categorical.

Table 3. Life Expectancy Overall and by Sex Among Persons Receiving Combination Antiretroviral Therapy in Uganda

| Age | General Ugandan Life Expectancy (WHO) by Age, y | Life Expectancy (95% CI), y | | |
|---------|---|-----------------------------|------------------|------------------|
| | | Overall | Men | Women |
| 14–19 y | 45.9* | 26.2 (23.7–28.7) | 22.2 (18.5–25.8) | 27.9 (24.5–31.4) |
| 20–24 y | 41.6 | 26.7 (25.0–28.4) | 19.1 (16.6–21.6) | 30.6 (28.7–32.5) |
| 25–29 y | 37.4 | 28.1 (26.8–29.4) | 21.3 (19.5–23.1) | 32.3 (30.8–33.8) |
| 30–34 y | 33.5 | 28.2 (27.0–29.4) | 21.8 (20.3–23.3) | 32.8 (31.4–34.2) |
| 35–39 y | 30.1 | 27.9 (26.7–29.1) | 22.0 (20.6–23.4) | 32.5 (31.1–33.9) |
| 40–44 y | 27.1 | 26.9 (25.7–28.1) | 21.9 (20.5–23.3) | 31.3 (30.0–32.6) |
| 45–49 y | 24.3 | 25.4 (24.3–26.5) | 20.9 (19.5–22.3) | 29.6 (28.3–30.9) |
| 50–54 y | 21.3 | 24.0 (22.9–25.1) | 20.2 (18.9–21.5) | 27.8 (26.6–29.0) |
| ≥55 y | NA | 22.6 (NA) | 19.2 (NA) | 26.2 (NA) |

| Age | Life Expectancy by CD4 count (95% CI) | | | | |
|---------|---------------------------------------|--|--|--|-------------------------------------|
| | <0.050 × 10 ⁹ cells/L | 0.050–0.099 × 10 ⁹ cells/L | 0.100–0.149 × 10 ⁹ cells/L | 0.150–0.249 × 10 ⁹ cells/L | ≥0.250 × 10 ⁹ cells/L |
| 14–19 y | 11.8 (8.8–14.7) | 21.0 (14.6–27.4) | 38.1 (NA) | 40.2 (32.7–47.6) | 43.4 (NA) |
| 20–24 y | 13.5 (11.6–15.4) | 23.1 (20.4–25.8) | 32.1 (28.9–35.3) | 40.5 (37.7–43.3) | 37.4 (34.2–40.6) |
| 25–29 y | 14.6 (13.1–16.1) | 24.1 (22.1–26.1) | 35.4 (33.0–37.8) | 41.0 (38.9–43.1) | 38.2 (35.8–40.6) |
| 30–34 y | 14.2 (12.8–15.6) | 24.7 (22.9–26.5) | 36.0 (33.8–38.2) | 40.3 (38.4–42.2) | 37.2 (35.1–39.3) |
| 35–39 y | 14.2 (12.8–15.6) | 24.0 (22.2–25.8) | 36.9 (34.8–39.0) | 39.0 (37.2–40.8) | 35.1 (33.0–37.2) |
| 40–44 y | 13.7 (12.2–15.2) | 22.8 (21.0–24.6) | 36.5 (34.4–38.6) | 38.0 (36.2–39.8) | 33.7 (31.7–35.7) |
| 45–49 y | 12.3 (10.8–13.8) | 21.5 (19.8–23.2) | 36.2 (34.1–38.3) | 35.8 (34.0–37.6) | 31.0 (29.1–32.9) |
| 50–54 y | 10.8 (9.3–12.3) | 20.3 (18.8–21.8) | 35.6 (33.6–37.6) | 34.3 (32.7–35.9) | 28.2 (26.4–30.0) |
| ≥55 y | 9.9 (NA) | 18.1 (NA) | 35.1 (NA) | 33.2 (NA) | 25.9 (NA) |

NA = not available; WHO = World Health Organization.

* National estimate provided for persons aged 15 to 19 y. General life expectancy of each group in column 2 is obtained from the WHO Global Health Observatory Database (13). CIs are not provided for the oldest age category because the upper interval of age was open.

person-years). There was no difference in nondisease mortality by sex (odds ratio, 0.95 [CI, 0.59 to 1.54]; $P = 0.86$).

The **Figure** shows the Kaplan–Meier product limit estimates of survival by age. The estimated probability of survival after 36 months of follow-up was 90.7% (CI, 87.0% to 94.4%); 93.4% (CI, 91.3% to 95.4%); 93.0% (CI, 91.1% to 95.0%); 93.2% (CI, 91.3% to 95.3%), and 90.9% (CI, 89.03% to 92.9%) for age groups 14 to 19 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, and older than 50 years, respectively.

Table 2 summarizes the unadjusted and adjusted Cox regression of factors associated with survival time based on multiple-imputation results. The adjusted model indicates a strong association between baseline CD4 cell count status and mortality when age, WHO stage, year of first cART, and sex are controlled for. Relative to a baseline CD4 cell status of less than 0.050×10^9 cells/L, the adjusted hazard ratio associated with mortality decreased to 0.65 (CI, 0.56 to 0.75), 0.53 (CI, 0.45 to 0.63), 0.42 (CI, 0.37 to 0.46), and 0.39 (CI, 0.34 to 0.46) for baseline CD4 cell count of 0.050 to 0.099, 0.100 to 0.149, 0.150 to 0.249, and 0.250×10^9 cells/L or more, respectively. Mortality was significantly increased according to the year of cART initiation, with patients starting therapy earlier having worse outcomes ($P \leq 0.001$).

Life expectancy for the overall cohort was 26.7 years (CI, 25.0 to 28.4 years) at age 20 years and 27.9 years (CI,

26.7 to 29.1 years) at age 35 years (**Table 3**) of additional life. Men had consistently shorter life expectancy than women. Life expectancy at age 20 years was 19.1 years (CI, 16.6 to 21.6 years) for men and 30.6 years (CI, 28.7 to 32.5 years) for women; at age 35 years, life expectancy was 22.0 years (CI, 20.6 to 23.4 years) for men and 32.5 years (CI, 31.1 to 33.9 years) for women. Life expectancy increased substantially with increasing baseline CD4 cell count status; for, patients with a baseline CD4 cell count status of less than 0.050×10^9 cells/L had a life expectancy of 13.5 years (CI, 11.6 to 15.4 years) and 14.2 years (CI, 12.8 to 15.6 years) at exact age 20 and 35 years, respectively, and patients with a CD4 cell count status of 0.250×10^9 cells/L or more had a life expectancy of 37.4 years (CI, 34.2 to 40.6 years) and 35.1 years (CI, 33.0 to 37.2 years) at exact age 20 and 35 years, respectively.

DISCUSSION

To our knowledge, this study is the first formal evaluation of life expectancy of patients with HIV in an African setting. We found that antiretroviral therapy in Uganda offers favorable life expectancy compared with the national average. We found that life expectancies varied considerably according to sex, with women having a greater life expectancy than men, and that higher baseline CD4 cell count status at treatment initiation strongly indicates potential life expectancy.

Studies from developed countries have shown similar decreases in mortality and increases in life expectancy with access to cART (7, 32, 33). The ART Cohort Collaboration evaluation of 18 587 patients from 14 high-income cohorts initiating cART from 1996 to 1999, when poorer drug formulations were available, demonstrated that a patient aged 20 years could expect to survive an additional 36.1 years (7). By 2003 to 2005, when drug formulations and understanding of treatments had increased, additional life-years at age 20 years had increased to 49.4 years. These studies have been conducted in Europe and in the United States, where life expectancy at birth is substantially higher than in African settings and where better access to health services, particularly secondary and tertiary care for severely ill patients, and lower rates of comorbid conditions have probably contributed to more favorable outcomes. The WHO Global Health Observatory estimates life expectancy in Uganda at age 20 years as an additional 41 years (13). Thus, despite poor baseline health and health care facilities, the additional life years come close to what would be expected in the general Uganda population, consistent with higher income settings (7). As health care in Uganda continues to improve, life expectancy will likely also improve. Similarly, as patients have access to improved cART drug regimens and routinely access care at higher CD4 T-cell counts, we expect life expectancy to improve.

Consistent with previous studies from Europe and the United States, we found that life expectancy varied according to sex and baseline CD4 cell count. This finding builds on an emerging body of literature displaying consistent shortcomings in treatment programs involving men (8, 34, 35). Men typically access care at a later stage with more advanced disease and have higher rates of mortality and loss to follow-up than women (8, 18). We also found that low CD4 cell count status at baseline was strongly predictive of lower life expectancy, a finding supportive of the latest WHO recommendation to start treatment at higher CD4 cell counts (15). Unfortunately, accessing and treating patients at early stages can be a challenge for both health infrastructure and identifying patients. In Uganda, the ministry of health guidelines do not yet recommend treatment of patients with cART until CD4 cell count status is less than 0.250×10^9 cells/L, and the median CD4 cell count of patients initiating treatment in our cohort was far less, at 0.156×10^9 cells/L. Patients with higher CD4 cell count status ($>0.250 \times 10^9$ cells/L) will typically have been allowed to begin therapy because of active tuberculosis, WHO stage 3 or 4 disease, or pregnancy, in keeping with national guidelines (14). This explains why life expectancy in patients with the highest classification of CD4 cell count ($>0.250 \times 10^9$ cells/L) was slightly less than that of patients with a CD4 cell count status in the more moderate classification (0.150 to 0.249×10^9 cells/L).

In our analysis, adolescents (14 to 19 years) had worse life expectancy than older patients (20 to 49 years). This is

because mortality among adolescents is usually higher than in older age groups (36, 37). Adolescent patients are typically long-term survivors, infected at birth, who have survived to adolescence with only recently access to therapy. In addition, adolescents may have important challenges in adherence, response to therapy, and long-term suppression (36). Efforts to expand HIV testing and improve pathways to cART may help identify patients earlier, and efforts to make treatment more accessible for patients may help initiate treatment earlier and, therefore, improve the effectiveness of resources dedicated to cART.

One strength of our analysis is our nationally representative sample, which includes a diverse population of patients who would likely be found in other parts of Africa (20, 38). Another strength is that our loss to follow-up is low compared with most AIDS service organizations in Africa, in which loss to follow-up can exceed 50% (9, 39), because of our use of default tracers. However, we recognize that there will be misclassification of deaths among patients lost to follow-up and attempted to correct for this bias by applying an assumption that 30% of these patients were dead (24). The fact that our analysis includes a relatively small number of patients initiating therapy at high CD4 cell count ($>0.250 \times 10^9$ cells/L) will probably have reduced our estimate of life expectancy at the very highest CD4 baseline status. Also, most patients began initiating therapy after 2004, and thus, the number of years receiving cART is variable. This possibly affects the stability of our projections, although our overall number of life-years is large (30).

A total of 3817 patients did not have baseline CD4 cell count evaluations, so we imputed them. Missing initial CD4 cell count is common in programs across Africa, owing to clinical circumstances or poor laboratory infrastructure. We explored the effect of these patients on our overall analysis and did not find a different effect (data not shown). TASO does not conduct routine viral-load assessments, and therefore, we cannot make inferences about risks for treatment failure on life expectancy, although other studies have shown that clinically driven care outcomes are similar to laboratory-informed care in the short term (40). Finally, as with any observational study, our mortality rate may be subject to residual confounding beyond those confounders adjusted for in multivariate analysis.

The substantial life expectancy afforded by widespread access to cART underscores the fact that HIV diagnosis in resource-limited settings is no longer a death sentence. Viewing HIV and AIDS as a chronic disease implies that models of care need to be developed to ensure that fragile health systems do not become overwhelmed with a growing caseload of asymptomatic persons; such models of home-based cART are already being tested in Uganda, with demonstrated efficacy (41). In our analysis, older patients (55 years or older) had the highest mortality rates. Important future challenges include development of

chronic disease management among patients—particularly elderly persons—because most resource-limited settings are unable to provide care for comorbid conditions, such as cardiovascular and neurologic disease (23).

We believe that our study is generalizable to Uganda and to many other settings in Africa in which patients access simplified HIV/AIDS care in rural, semirural, and urban settings. The TASO clinics serve all major regions of Uganda and cover broad populations involving children; men and women; and vulnerable populations, including adolescents, internally displaced persons, and persons experiencing economic and food insecurity (20, 38). The organization provides care in both clinic-based services as well as decentralized care to serve persons who are geographically distant from clinics. This approach has been shown to result in outcomes similar to those of clinic-based care (41).

In summary, our study adds to the growing body of evidence that the benefits of cART are many and extend well beyond reduced early mortality. Widespread access to cART includes a reduction in the incidence of tuberculosis (42), reduced transmission of HIV (43), and increased productivity and economic benefits (44). These benefits will only be realized if there is continued support for antiretroviral scale-up by the international donor community and national governments (45).

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APPENDIX

Mortality and PYLL

By using methods that we previously reported (7), we calculated mortality rates by age categories from the number of deaths (D_x) in a given calendar year between exact age x and $x + n$ and the persons at risk who lived in that age interval and time period (P_x). Rates were expressed as deaths per 1000 person-years.

PYLL before age 55 years was used to examine the effect of HIV on premature mortality. PYLL represents of the sum of years that patients lost because of premature mortality. PYLL is a convenient summary measure that accounts for not only the number of deaths but also the ages at which death occurs. To obtain PYLL, the total number of deaths for a particular cause in each 5-year age group is multiplied by the average number of years remaining in that age group to age 55 years, as follows:

$$PYLL = \sum d_i(55 - Y_i)$$

where Y_i is the age at the midpoint of age group i .

Life Tables

The abridged life tables were constructed by using techniques described by Chiang (28). Life-expectancy values were reported from

age 14 years to older than 55 years. The rows in the life tables refer to exact age groups. The columns in the life tables include the following functions (note that the suffix x refers to an exact age and the prefix n refers to the length of an age group):

x, n : The period of life between 2 exact ages (x and $x + n$)—e.g., when $x = 20$ and $n = 5$, this means the 5-year interval between the 20th and 25th birthdays.

${}_n m_x$: The death rate in the population between exact age x and exact age $x + n$.

${}_n q_x$: The proportion of people in the population who reach exact age x who are not still living at exact age $x + n$.

l_x : The number of survivors from a hypothetical cohort at exact age x .

${}_n d_x$: The number of members of a hypothetical cohort who die between exact age x and exact age $x + n$.

${}_n L_x$: The number of person-years lived by members of a hypothetical cohort between exact ages x and $x + n$.

T_x : The number of person-years lived by a hypothetical cohort above exact age x ;

e^0_x : The expected number of years that a person in this hypothetical cohort who reaches exact age x will live.

SE $_i$: The SE of e^0_x .

The first column in an abridged life table, ${}_n q_x$, is calculated from crude age-specific population and death data. The ${}_n q_x$ formula in the construction of the abridged table is as follows:

$$q_x = \frac{n_i m_x}{1 + (1 - a_i) n_i m_x}$$

The age-specific death rate is expressed as m_x , which is the quotient of the number of deaths (D_x) in a given interval between exact age x and $x + n$ and the total number of person-years at-risk in that age interval and period (P_x).

$$m_x = \frac{D_x}{P_x}$$

The trend in mortality does not vary much from one population to another; therefore, a_i can be regarded as a constant at most ages. In these analyses, a_i was assumed to be 0.5, as we presume that deaths are evenly distributed. Finally, n_i refers to the number of years in each interval, which in this case would be 5. In the open interval, q_x is assumed to be 1.

The function l_x refers to the survivors of a cohort of living children to the exact age x . The initial value of this column, l_0 , is known as the radix, which was taken as 1000.

$$l_{x+n} = l_x - d_x$$

The function d_x refers to the deaths experienced by the life table cohort within the interval x to $x + n$. It can be obtained as follows:

$$d_x = l_x q_x \text{ or } d_x = l_x - l_{x+n}$$

The function L_x is the number of person-years lived by the cohort during the interval between x and $x + n$ years. It can be obtained as follows:

$$L_x = n_i(l_x - d_x) + a_i n_i d_x$$

The function T_x is derived directly from L_x . This function is the summation of the L_x column, as follows:

$$T_x = L_x + T_{x+n}$$

The final age interval in a life table is a half-open interval, which is referred to as w . The following equations are used to estimate L_w and T_w :

$$L_w = \frac{l_w}{m_w}$$

$$T_w = L_w$$

The function e^0_x is the expectation of life remaining at exact age x . The function is derived from the l_x and T_x columns, as follows:

$$e^0_x = \frac{T_x}{l_x}$$

The final column refers to the standard error around the function of e^0_x .

The following is an example using age category 14 to 19 years from the table below.

Proportion of people in the population who are not still living:

$$q_x = \frac{n_i m_x}{1 + (1 - a_i) n_i m_x}$$

$$= \frac{(6 \times 0.1020)}{(1 + (1 - 0.5) \times (6 \times 0.1020))}$$

$$= 0.4685$$

Death rate in the population:

$$m_x = \frac{D_x}{P_x}$$

$$= \frac{16}{156.90}$$

$$= 0.1020$$

Survivors from a hypothetical cohort:

$$l_{x+n} = l_x - d_x$$

$$= 1000 - 469$$

$$= 531$$

Deaths from a hypothetical cohort:

$$d_x = l_x - l_{x+n}$$

$$= 1000 - 531$$

$$= 469$$

Number of person-years lived from a hypothetical cohort:

$$L_x = n_i(l_x - d_x) + a_i n_i d_x$$

$$= [6 \times (1000 - 469)] + (6 \times 0.5 \times 469)$$

$$= 4594$$

The number of person-years lived in a hypothetical cohort of persons older than 20 to 24 years:

$$T_x = L_x + T_{x+n}$$

$$= 4594 + 7164$$

$$= 11758$$

The expected number of life-years remaining:

$$e^0_x = \frac{T_x}{l_x}$$

$$= \frac{11758}{1000}$$

$$= 11.8$$

Appendix Table. Example of Life-Expectancy Analysis by Using Data From the TASO Data of Patients, at a CD4 Cell Count of 0–0.049 cells × 10⁹ cells/L

| Age (x) | Number of Years in Category (n) | Population-Years at Risk (P _x) | Number of Deaths (D _x) | Mortality Rate (m _x) | Proportion Surviving Period (q _x) | Alive at Start of Interval (l _x) | Probable Deaths in Hypothetical Cohort (d _x) | Person-Years Lived in Hypothetical Cohort (L _x) | Person-Years Lived Beyond Start of Interval (T _x) | Observed Expectation of Life (e ⁰ _x) | SE of e ⁰ _x (Sei) |
|---------|---------------------------------|--|------------------------------------|----------------------------------|---|--|--|---|---|---|---|
| 14–19 y | 6 | 157 | 16 | 0.1020 | 0.4685 | 1000 | 469 | 4594 | 11758 | 11.8 | 1.50 |
| 20–24 y | 5 | 365 | 32 | 0.0876 | 0.3594 | 531 | 191 | 2180 | 7164 | 13.5 | 0.96 |
| 25–29 y | 5 | 1004 | 64 | 0.0638 | 0.2750 | 340 | 94 | 1468 | 4984 | 14.6 | 0.62 |
| 30–34 y | 5 | 1794 | 125 | 0.0697 | 0.2967 | 247 | 73 | 1051 | 3516 | 14.2 | 0.53 |
| 35–39 y | 5 | 1941 | 126 | 0.0649 | 0.2792 | 174 | 48 | 747 | 2464 | 14.2 | 0.53 |
| 40–44 y | 5 | 1585 | 86 | 0.0543 | 0.2389 | 125 | 30 | 551 | 1718 | 13.7 | 0.56 |
| 45–49 y | 5 | 873 | 54 | 0.0618 | 0.2677 | 95 | 25 | 412 | 1167 | 12.3 | 0.60 |
| 50–54 y | 5 | 416 | 33 | 0.0794 | 0.3313 | 70 | 23 | 291 | 754 | 10.8 | 0.59 |
| ≥55 y | + | 338 | 34 | 0.1006 | 1.0000 | 47 | 47 | 463 | 463 | 9.9 | NA |

NA = not applicable; TASO = The AIDS Support Organization.