

# Accounting for and responding to HIV-associated mortality

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In 2000, only 2% of people living with HIV worldwide were receiving life-saving antiretroviral therapy (ART). Of these, less than 1% (11 000 of the 700 000 on ART) lived in sub-Saharan Africa. By 2014, the percentage of HIV-positive people receiving ART had risen to 40%, representing almost 15 million people, with over two-thirds (10.7 million) living in sub-Saharan Africa [1].

The successful scale up of ART over the last 15 years is therefore largely an African success story. The evaluation of Botswana's public ART programme published in this issue of *AIDS* provides a national example of the progress made by almost all high HIV-burden countries in Africa [2]. By the end of 2014, the national programme had started almost 250 000 people on ART, from 3500 in 2002. Adult mortality during the first year on ART declined from 7 to 2%, likely as a result of the progressively earlier access to treatment, with average CD4<sup>+</sup> at start of ART rising from 88 cells/ $\mu$ l in 2002 to 258 cells/ $\mu$ l in 2013.

Some uncertainty about the true impact on mortality, however, remains in Botswana and elsewhere. Deaths among patients lost to follow-up were not ascertained and rates will underestimate the mortality experienced by all patients who started ART. Also, some of the decline in mortality observed in Botswana [2] may be because of declining ascertainment of mortality as the programme

expanded and retention in care got worse. Finally, the inverse probability of censoring weights implemented in the regression analysis [2] may perform poorly in the absence of additional information on mortality in patients lost to follow-up [3].

Reported factors for adult mortality in the Botswana national programme [2] are consistent with other reports, and include severe immune deficiency at start of ART [4], male sex [5,6], older age [7], and receipt of suboptimal (i.e. less potent/tolerable) ART regimens [8,9]. Although most countries are now providing tenofovir-based regimens as standard first-line ART, too little progress has been made in identifying and implementing interventions to reduce mortality associated with these and other well established risk factors. There is a need to move beyond descriptive epidemiology and identify interventions to help enrol people into care earlier in their disease progression, engage and support men, and respond to the multiple morbidities faced by older people living with HIV [10–12].

The lessons from Botswana's HIV programme are indicative of both the successes made in increasing access to treatment and reducing mortality – ART scale up is estimated to have averted almost 8 million deaths worldwide [1] – and the challenges that need to be overcome to further reduce HIV-associated mortality.

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To further reduce mortality and severe morbidity, the first priority for HIV programmes is to identify HIV-positive individuals earlier in their disease progression and start ART as soon as possible following diagnosis. A succession of international and national guideline changes have recommended earlier initiation of ART [13], and this has been associated with an increase in the average CD4<sup>+</sup> cell count at start of ART [14]. In October 2015 the World Health Organization released guidance recommending that all HIV-positive individuals should receive ART irrespective of CD4<sup>+</sup> cell count [15]. This follows the results of the START [16] and TEMPRANO [17] trials to recommend immediate initiation of ART independent of clinical or immunological status. However, while the average CD4<sup>+</sup> cell count at the start of ART has increased over the years, still around a quarter of people continue to start ART very late, at CD4<sup>+</sup> less than 100 cells/ $\mu$ l [3,18], which in the Botswana study increased the odds of death by 1.9 times. Late diagnosis remains part of the problem – around a third of HIV-positive hospitalized individuals only learn of their status at the time of hospitalization because of a severe illness event [19] – indicating that changes to ART initiation thresholds in the clinic will not completely overcome the challenge of late presentation to care, and innovative testing approaches including community and self-testing need to be brought to scale [20].

The second priority is to establish clinical and operational mechanisms to improve outcomes for patients who present to care with advanced disease in spite of attempts to identify patients earlier and link them to care. Analyses of mortality on ART miss the very high mortality in patients eligible for ART who never get to start ART [21,22].

The third priority in reducing mortality among people on ART is to address the important number of patients who disengage from care following ART initiation [23], which is of increasing importance as the fraction of the HIV population on ART continuously increases. Studies suggest that around a third of patients who are lost to care are subsequently found to have died [24], with substantial regional variation which is partly explained by differences in programme resources invested in patient tracing and individual opportunities to reengage in care. Population-based studies of HIV-associated mortality demonstrate that an increasing proportion of HIV-associated deaths are in patients who had previously been on ART [21].

These latter two challenges – reducing mortality among late presenters and keeping those on ART in long-term care – have led to calls for services to adapt service intensity according to the specific needs of different groups of individuals across the cascade [25]. With a global policy shift towards starting ART immediately, improving coverage of HIV testing, and providing adapted care are the key ART service delivery priorities

for the coming years to address the specific challenges of different patient populations – late presenters, those disengaging from care, men and elderly populations as highlighted by this report, but also children [26], adolescents [27], and key populations [28], all of whom continue to be underserved by the broader HIV response.

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### Conflicts of interest

There are no conflicts of interest.

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