Outcomes of the Botswana national HIV/AIDS treatment programme from 2002 to 2010: a longitudinal analysis

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Summary

Background **Short-term mortality rates among patients with HIV receiving antiretroviral therapy (ART) in sub-Saharan Africa are higher than those recorded in high-income countries, but systematic long-term comparisons have not been made because of the scarcity of available data. We analysed the effect of the implementation of Botswana's national ART programme, known as Masa, from 2002 to 2010.**

Methods **The Masa programme started on Jan 21, 2002. Patients who were eligible for ART according to national guidelines had their data collected prospectively through a clinical information system developed by the Botswana Ministry of Health. A dataset of all available electronic records for adults (≥18 years) who had enrolled by April 30, 2010, was extracted and sent to the study team. All data were anonymised before analysis. The primary outcome was mortality. To assess the effect of loss to follow-up, we did a series of sensitivity analyses assuming varying proportions of the population lost to follow-up to be dead.**

Findings **We analysed the records of 126 263 patients, of whom 102 713 had documented initiation of ART. Median follow-up time was 35 months (IQR 14–56), with a median of eight follow-up visits (4–14). 15 270 patients were deemed lost to follow-up by the end of the study. 63% (78 866) of the study population were women; median age at baseline was 34 years for women (IQR 29–41) and 38 years for men (33–45). 10 230 (8%) deaths were documented during the 9 years of the study. Mortality was highest during the first 3 months after treatment initiation at 12·8 deaths per 100 person-years (95% CI 12·4–13·2), but decreased to 1·16 deaths per 100 person-years (1·12–1·2) in the second year of treatment, and to 0·15 deaths per 100 person-years (0·09–0·25) over the next 7 years of follow-up. In each calendar year after the start of the Masa programme in 2002, average CD4 cell counts at enrolment increased (from 101 cells/μL [IQR 44–156] in 2002, to 191 cells/μL [115–239] in 2010). In each year, the proportion of the total enrolled population who died in that year decreased, from 63% (88 of 140) in 2002, to 0·8% (13 of 1599) in 2010. A sensitivity analysis assuming that 60% of the population lost to follow-up had died gave 3000 additional deaths, increasing overall mortality from 8% to 11–13%.**

Interpretation **The Botswana national HIV/AIDS treatment programme reduced mortality among adults with HIV to levels much the same as in other low-income or middle-income countries.**

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See Comment page e6

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Introduction

Starting in 2002, Botswana was the first African country to establish a national HIV/AIDS treatment programme, calling it "Masa", the Setswana word for "a new dawn". Before the introduction of Masa, Botswana had one of the highest rates of HIV/AIDS in the world. By 2001, the national prevalence of HIV/AIDS had reached 27%.[1]

Key characteristics of Botswana's antiretroviral therapy (ART) programme are that it is free and universal—it is open to all citizens who meet the national guidelines; however, some of the population have not been tested for HIV, and thus their status is not known. In 2008, the eligibility criteria for ART changed from a CD4 cell count of 200 cells/μL to 250 cells/μL and, in 2013, to 350 cells/μL.[2] Since the start of the Masa programme in 2002, the national guidelines have changed to take into account the improved understanding of the biology of HIV, reduce adverse events associated with stavudine and zidovudine, and accommodate the availability of improved drugs (table). After the 2008 guideline change, tenofovir (plus emtricitabine in almost all cases) replaced zidovudine as the first-line nucleoside reverse transcriptase inhibitor in Botswana. In 2002, 3500 patients were receiving treatment. By November, 2012, that number had reached 201 822 patients treated via more than 200 clinics and 35 hospitals around the country.

To track patients eligible for ART and monitor the progress and effectiveness of the Masa programme, the Government of Botswana, with the support of the US President's Emergency Plan for AIDS Relief (PEPFAR), established a monitoring and evaluation unit within the national ART programme in the Department of HIV/AIDS Prevention and Care of the Ministry of Health. This electronic patient tracking and outcomes monitoring system has been crucial for the effective scale-up of the programme. Through capture of individual-level patient data, the system is able to generate facility-level reports that aid in both clinic management and care of patients.

	Eligible adults	First-line regimen	Second-line regimen	Summary of changes
2002	WHO stages I–II: CD4 cell count <200 cells/μL WHO stages III–IV: all patients	Zidovudine and lamivudine plus efavirenz. Zidovudine and lamivudine plus nevirapine for women of reproductive potential	Didanosine plus stavudine plus nelfinavir	..
2005	WHO stages I–II: CD4 cell count <200 cells/μL WHO stages III–IV: all patients	Zidovudine or stavudine plus lamivudine and efavirenz. Zidovudine, lamivudine, and nevirapine for women of reproductive potential	Didanosine plus stavudine or zidovudine plus lopinavir or ritonavir	Eligible adults and CD4 cell count threshold stayed the same. First-line and second-line regimen changed
2008	WHO stages I–II: CD4 cell count <250 cells/μL WHO stages III–IV: all patients	Tenofovir and emtricitabine or lamivudine with efavirenz. Tenofovir and emtricitabine or lamivudine with nevirapine for women of reproductive potential	Zidovudine plus lamivudine plus lopinavir or ritonavir	CD4 cell count threshold changed and first-line and second-line regimen changed

*Adults visit clinics every 3 months for the first 2 years, and if stable, every 6 months thereafter.

Table*: Summary of Botswana national HIV/AIDS treatment guidelines

The system allows for collection and analysis of aggregate outcome data, encourages compliance with treatment protocols, tracks pharmaceutical usage, and generates lists of patients needing home follow-up.

Assessment of national ART programmes is essential to establish whether programmes are having the desired effects and to monitor any unanticipated effects or consequences. Several studies[3–15] have shown the successful implementation of ART programmes in low-income and middle-income countries with overall outcomes that are much the same as in high-income countries. Most reports of ART outcomes, however, have come from select cohorts that might not be indicative of national programme conditions.[6,8,16–20] Additionally, most reports have captured national longitudinal outcome data for patients receiving ART for only a few years.

We analysed 9 years of follow-up data for more than 100 000 adult patients who were treated in the Botswana national HIV/AIDS treatment programme and tracked at individual level in the electronic system described above. We aimed to assess mortality, loss to follow-up, changes in CD4 cell count after treatment initiation, and other predictors of mortality including clinical and demographic factors.

Methods

Data

The Masa programme started on Jan 21, 2002. Patients who were eligible for ART had their data collected prospectively through the Botswana Ministry of Health's clinical information system. Many patients did not have an HIV medical file created until they were eligible for treatment. All hospitals and most clinics had an electronic information system by the end of 2012; at the time of our data cutoff in 2010, about 15% clinics were not integrated into the national information system.

A dataset of all available electronic records for adults (≥18 years; about 18 000 records for patients <18 years were excluded from this analysis) who had enrolled by April 30, 2010, was extracted from the Ministry of Health data warehouse and sent to the study team for this analysis. All data were anonymised before the analysis. The few patients who had started ART before the launch of the national programme in 2002 were excluded because their treatment regimen was not necessarily the same as recommended by the national guidelines. At the time the dataset was transferred from the Ministry of Health for this study, not all the available data collected from clinics from September, 2009, to April, 2010, had been integrated into the central database. However, because all available data from the clinics were collected but not yet entered into the database, we do not expect non-integrated patient data to come from patients (or clinics) whose outcomes are systematically different than those included.

This study was reviewed and approved by Harvard School of Public Health's Institutional Review Board and the Human Resource Development Committe in Botswana.

Analysis

The primary outcome measure for this analysis was mortality. For this assessment, documented death referred to a death that was recorded in the database. Deaths in hospitals or in other institutions might not be reported to HIV clinic staff and non-institutional deaths might not be reported to the health-care system as is legally required. Therefore, loss to follow-up might include patients who died without a death report captured in the database. To assess the effect of loss to follow-up on the study outcome, we did a series of sensitivity analyses assuming varying proportions of the population lost to follow-up to be dead. We used number of patients whose death was documented in the numerator and patient-years of follow-up time in the denominator to directly calculate the mortality rate.

We also recorded change in median CD4 cell count and viral load over time, for the patients for whom these data were available, and type of antiretroviral drugs used.

Role of the funding source

The funder of the study contributed to the study design, writing of the report, and the decision to submit this paper for publication. The funder was not involved in the data analysis or interpretation; all the authors had full access to the data in this study.

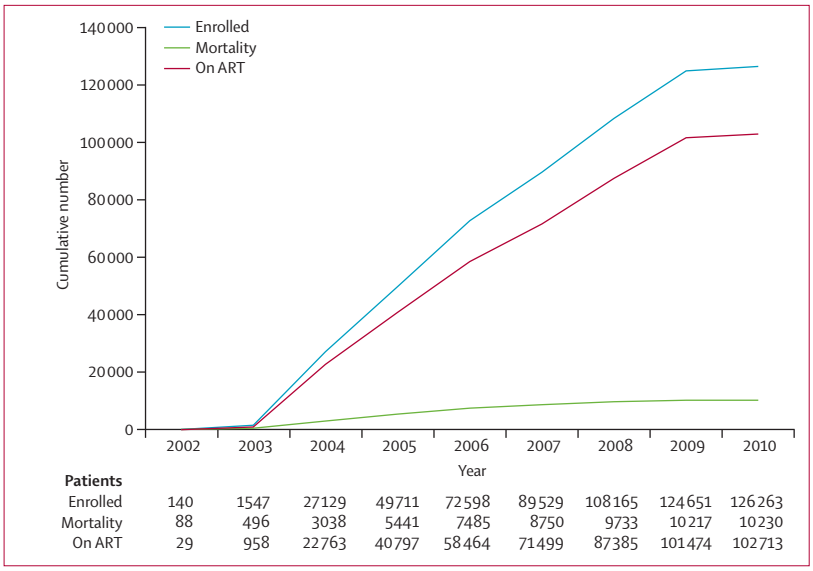
Results

The dataset provided by the Ministry of Health contained the records for 142 898 adults. The first recorded enrolment was on Jan 21, 2002, and the last enrolment in the dataset was April 30, 2010; the last recorded visit was Dec 31, 2010. We excluded records of 16 635 patients for the following reasons: 1144 patients with at least one observation after the recorded death; 924 patients with no information on drugs, death, or CD4 cell count; 295 patients with a visit dated outside the timeframe of this study; and 14 272 patients with only one observation (no follow-up records). The medical records for the remaining 126 263 patients were used for the analysis. Median follow-up time was 35 months (IQR 14–56), with a median of eight follow-up visits (4–14).

In the dataset used for this analysis, the number of patients enrolled in the Masa programme increased from 140 in 2002, to 126 263 by April 30, 2010 (figure 1). The biggest increase in enrolment, both in absolute number and proportion, occurred in 2004, when the national rollout programme started, after which the number of people in the programme continued to increase albeit at diminishing rates, because the population of people with HIV who were not already in the programme was decreasing. In 2008, the eligibility criteria for ART changed from a CD4 cell count of 200 cells/μL to 250 cells/μL; despite this change, the proportion of patients who joined the programme before they were eligible for treatment remained relatively stable over time (data not shown).

63% of the study population (78 866) were women; median age at baseline was 34 years for women (IQR 29–41) and 38 years for men (33–45). Of 126 263 patients included in the analysis, 23 550 did not have any ART drugs documented (of whom 8553 were eligible and 14 651 were not eligible for ART on the basis of their CD4 cell count). 102 713 individuals in the national programme had consistent records and documented ART provided by either the public or private sector over the study period. Of these patients, baseline CD4 cell count was available for 68% (69 852). For this analysis, we defined the last pretreatment CD4 cell count as baseline.

Among patients whose baseline CD4 cell count was recorded, the overall median baseline CD4 cell count was 151 cells/μL (IQR 86–200). The median baseline CD4 cell count for men was 134 cells/μL (70–192) and for women was 161 cells/μL (97–208). Baseline CD4 cell count was between 50 and 150 cells/μL for 36% (25 190) of patients, and below 50 cells/μL for 13% (9290). Between Jan 21, 2002, and May 1, 2008, when the national guidelines set the CD4 cell count threshold for treatment initiation at 200 cells/μL, 25% (17 467 of 69 852) of patients started their treatment with CD4 cell counts above this threshold because they were diagnosed with stage 3 or 4 disease according to the WHO criteria.[21] After the eligibility criteria increased to 250 cells/μL in 2008, 24 970 patients initiated treatment, of whom 12% (2864) had a CD4 cell count above 200 cells/μL (the previous threshold) and below 250 cells/μL (new threshold). After the guideline change in 2008, 16% (3991) of patients started treatment because they had stage 3 or 4 disease according to the WHO criteria, despite having a CD4 cell count above the guideline threshold.



Patients	2002	2003	2004	2005	2006	2007	2008	2009	2010
Enrolled	140	1547	27 129	49 711	72 598	89 529	108 165	124 651	126 263
Mortality	88	496	3038	5441	7485	8750	9733	10 217	10 230
On ART	29	958	22 763	40 797	58 464	71 499	87 385	101 474	102 713

Figure 1: **Cumulative number of enrolments, mortality, and patients receiving treatment in Botswana's national ART programme, 2002–10**
For patients with consistent electronic records in the dataset. ART=antiretroviral therapy.

Median baseline CD4 cell count increased in each year of analysis, from 101 cells/μL (IQR 44–156) in 2002 to 191 cells/μL (115–239) in 2010 (figure 2). In general, patients' CD4 cell counts increased significantly in the first 24 weeks of treatment, followed by a gradual increase to 350 cells/μL, on average, after 2 years of treatment. A regression model of the quadratic time trend showed that patients' CD4 cell counts increased significantly ($p<0·0001$; figure 3). Additional fitted linear and log-linear models showed the quadratic time trend to be the best fit to the data.

Baseline viral load was available for 12 606 patients in the dataset. The overall median plasma viral load at baseline was 4·9 $\log_{10}$ copies/mL (IQR 4·2–5·6). Men had slightly higher viral loads than women (median 5·2 [4·3– 5·7] *vs* 4·9 [4·1–5·6]).

For the 102 713 patients with data for first-line ART drugs available in the database, zidovudine and lamivudine were the main nucleoside reverse transcriptase inhibitors used, with 78 528 of 101 481 (77%) of patients starting on zidovudine (plus lamivudine in almost all cases) compared with 7680 of 101 481 (8%) on stavudine during the first 5 years of the programme. Non-nucleoside reverse-transcriptase inhibitors were split between efavirenz (56 829 of 101 311, 56%) and nevirapine (44 482 of 101 311, 44%).

10 230 (8%) deaths (50% men, compared with 43% men in the dataset) were documented during the 9 years

of the study (figure 1). The mean age of those who died in 2003 was 35 years (SD 8·3), which increased to 40 years (10·0) in 2009. The 9-year mortality rate was 2·71 per 100 person-years (95% CI 2·66–2·76) with a total follow-up time of 377716 person-years. Mortality was greatest during the first 3 months of treatment (12·8 deaths per 100 person-years [12·4–13·2]) but decreased rapidly to 3·46 deaths per 100 person-years (3·25–3·69) after 6 months. The mortality rate in the second year of treatment was 1·16 deaths per 100 person-years (1·12–1·2), and the proportion of patients surviving increased over time. Mortality decreased steadily to 0·15 deaths per 100 person-years (0·09–0·25) over the next 7 years of follow-up. In the first year of the programme, 29% (51 of 171) of patients died in the first year of treatment compared with only 3% (349 of 11679) in 2009. In each year, the proportion of the total enrolled population who died in that year decreased, from 63% (88 of 140) in 2002, to 0·8% (13 of 1599) in 2010. For patients enrolled in 2009, the mortality rate in months 4–6 of treatment was 2·49 deaths per 100 person-years (2·0–3·1), compared with 7·16 deaths per 100 person-years (6·5–7·9) in months 4–6 of treatment for those enrolled in 2004; the mortality rate in months 10–12 of treatment for patients enrolled in 2009 was lower than the rate in the same months of treatment for those enrolled in 2004 (0·67 deaths per 100 person-years [0·4–1·1] *vs* 2·3 deaths per 100 person-years [1·9–2·7] (figure 4).

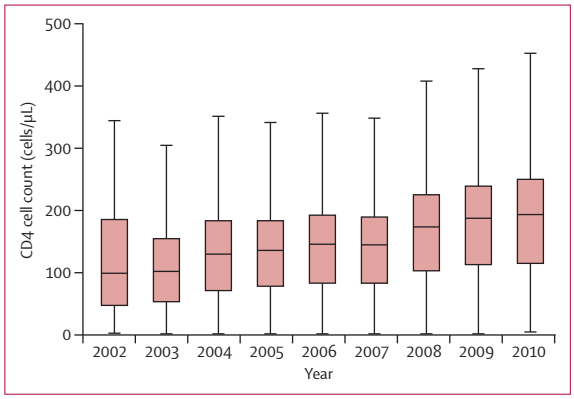


Figure 2: **Baseline CD4 cell counts**
Excludes outliers.

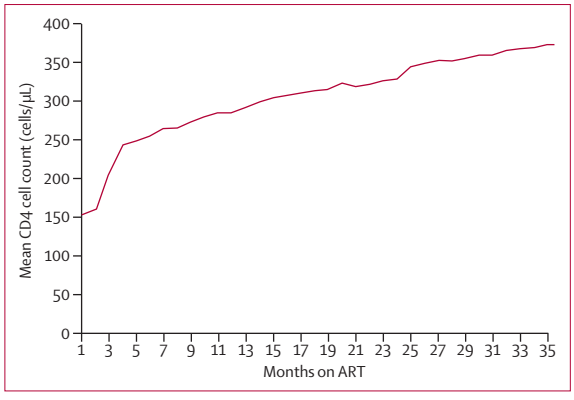


Figure 3: **Changes in mean CD4 cell count over time for surviving patients receiving ART**
ART=antiretroviral therapy.

15 270 patients were deemed lost to follow-up over the whole study period. 5911 patients in the dataset were identified by the treatment clinics as lost to follow-up because they did not return to a treatment centre for more than 90 days. In addition to those identified as lost to follow-up by treatment clinics, other issues led us to mark patients as lost. Some records were lost because of patient transfers between clinics. Of 20 583 transfer cases from 2002 to 2010, there were 8384 patients who transferred between clinics whose records were not linked because of erroneous personal identifiers. We categorised them as lost to follow-up for the purpose of this analysis. The medical records for 975 patients visiting clinics from September, 2009, to April, 2010, were not integrated into the central database because of a logistical issue at the Ministry of Health data warehouse and were deemed lost to follow-up.

The loss to follow-up during the first year of treatment initiation was 21·9% (95% CI 21·6–22·1), with the lowest proportion of loss to follow-up being 12·4% (11·98–12·79) in 2004, and the highest proportion being 53% (53·1–84·66) in 2009. The rate of loss to follow-up in the first year after treatment initiation was less than ten patients per 100 patient-years up to 2009, when it increased to 37 patients per 100 patient-years. However, the high proportion and rate of loss to follow-up in 2009 might be explained by the data that were not integrated into the Ministry of Health database after September, 2009. Overall, loss to follow-up was 7·3 patients per 100 patient-years (7·2–7·4) in the first year after treatment initiation, 34·6 patients per 100 patient-years (33·9–35·3) in the first 90 days, and 23·7 patients per 100 patient-years (23·2–24·3) after 90 days.

In the sensitivity analyses, mortality over time remained the same with varying proportions of the population lost to follow-up assumed to be dead (data not shown). Assuming that 60% of the population lost to follow-up had died in accordance with available scientific literature[22,23] resulted in 3000 additional deaths, which would increase mortality from 8% to 11–13%.

Discussion

Of 126 263 adult patients enrolled in the Botswana national ART programme from 2002 to 2010, 102 713 had documented initiation of ART. 8% of patients died during the 9 years of the study. Mortality was highest during the first 3 months after treatment initiation, but decreased substantially in the second year of treatment, and remained low in subsequent years of follow-up. In each calendar year after the start of the programme, average CD4 cell counts at enrolment increased. A sensitivity

analysis assuming that 60% of the population lost to follow-up had died gave 3000 additional deaths, increasing overall mortality from 8% to 11–13%.

The Government of Botswana has made substantial progress in development of health infrastructure (including health-care facilities, specialised laboratories, information systems, and training of health-care workers) to treat large numbers of people with HIV/AIDS across the country. The most notable outcome of the rapid scaling up of the Botswana national ART programme from 2002 to 2010, which provided treatment to more than 100 000 previously ART-naive adult patients with HIV, is its success in decreasing mortality from 12·8 deaths per 100 person-years within 3 months of treatment initiation to 1·16 deaths per 100 person-years after a year of ART. This outcome is especially impressive in view of the fact that Botswana's population is 2 million with 300 000 (95% CI 280 000–310 000) individuals estimated to have HIV infection.[24] This reduction in mortality, to levels much the same as in other resource-limited countries,[12,14,25,26] was sustained across the subsequent 7 years of follow-up. The mortality rate after 3 months of treatment in Zambia is 26 deaths per 100 person-years[12] and in China is 22·6 deaths per 100 person-years.[14] Some researchers have suggested that the relatively high mortality within the first few months of treatment is attributable to a reconstituting immune system.[27] Other factors corresponding to increased mortality within the first 3 months of ART include low baseline CD4 cell count, anaemia, tuberculosis, and hepatitis.[28,29] The overall mortality in this study was 2·71 deaths per 100 person-years. This result is similar to the 3·7 deaths per 100 person-years calculated in 2 years of follow-up in the Rwandan national programme[20] and substantially lower than the 16·1 deaths per 100 person-years in Zambia (over 18 months of follow-up).[12]

Our findings also suggest that mortality after the first 3 months of treatment is decreasing, since mortality after 4–6, 7–9, and 10–12 months of treatment was lower for patients enrolled in 2009 than for those enrolled in 2004. This finding can be explained, to some extent, by the fact that the system adjusted itself through better trained personnel and an improved health information system.

Loss to follow-up, or lack of electronic documentation, seems to be an important issue to be addressed, because some researchers suggest that retention of patients might be a good overall indicator of programme effectiveness.[10] Two systematic reviews[7,30] showed that, at 2 years, African ART programmes retain only about 60% of their patients, largely because of high loss to follow-up. The underlying determinants of this loss are not well understood. In their systematic review, Brinkhof and colleagues[22] showed that, in ART programmes in resource-limited settings, a substantial minority of adults lost to follow up could not be traced, and among those traced 20–60% had died. Using a method to trace patients, a study[23] of 524 patients in Botswana in early 2003 showed that more than half of the 68 patients originally deemed to be lost to follow-up were confirmed to be dead after tracing. The scientific literature regarding tracing of patients in ART programmes suggests a similarity between those who die among the population lost to follow-up and those with documented death in terms of summary statistics for risk factors, including baseline CD4 cell count, sex, and age.[23] In our study, patients declared as lost to follow-up by clinics were more similar to those with documented death than to those who survived, whereas patients deemed lost to follow-up because of absence of electronic documentation had much the same baseline CD4 cell counts and demographic characteristics as the overall study population (data not shown). Therefore, we assumed 60% of patients reported as lost to follow-up by the clinics to be dead in our sensitivity analysis, but we did not identify any meaningful changes to our results.

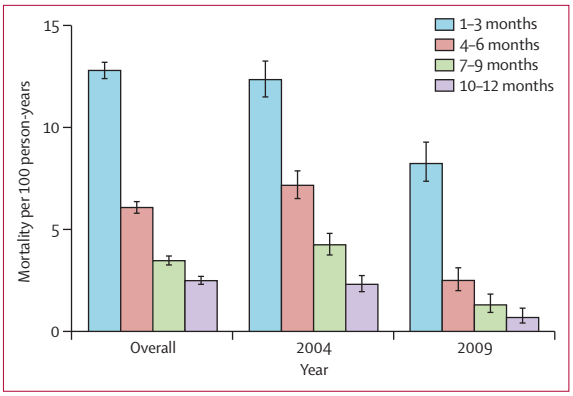


Figure 4: **Mortality in the first year after treatment initiation**
Error bars are 95% CI.

The Masa programme is perhaps the largest single cohort of patients receiving ART yet to be described. As of Nov 30, 2012, more than 201 822 patients had been enrolled into HIV care and treatment, and more than 180 000 had started ART. We believe one of the major factors behind the success of the rapid expansion of the programme and its favourable clinical outcomes is the decision of the Government of Botswana to offer universal free routine testing and counselling and HIV care and treatment, despite the negative demographic and economic consequences associated with the HIV/AIDS epidemic. By taking an HIV test publicly in June, 2003, the President of Botswana started a large public awareness campaign against HIV that probably contributed to the success of Masa programme.

Another important factor was international donations that supported capacity building. The financial resources made available by PEPFAR, the African Comprehensive HIV/AIDS Partnerships (ACHAP), and other international donors have allowed rapid implementation and maintenance of the training and information systems much needed for this resource-intensive care system that has saved many lives.

Panel: **Research in context**

Systematic review

We searched Google Scholar, PubMed, and JStor for reports in English using the term "antiretroviral therapy scale-up". The last search was done on March 21, 2013. We focused our search on scaled-up programmes in resource-limited settings. All the studies that we identified were done to assess the effectiveness of the antiretroviral therapy (ART) programmes at different levels. All of them showed that survival of patients has improved to various degrees as a result of these ART programmes.

Interpretation

Using a national longitudinal database, the present study shows that thousands of patients have benefited from ART in Botswana. Many of these patients were still alive after several years of treatment. When added to existing studies, the present study reinforces the evidence that global efforts have managed to change HIV infection, especially in resource-limited settings, from death sentence to a chronic disease. In view of the fact that individuals with HIV are now living longer, clinicians should know how to treat ART-related toxicities and non-AIDS defining disorders.

At the outset of the Masa programme, Botswana, like other sub-Saharan countries, faced a human resource crisis. The country had low physician to patient ratios. The challenge was not only the scarcity of all cadres of trained health-care workers, because of government economic and fiscal constraints, but also the scarcity of training mechanisms to meet the demands of the HIV/AIDS epidemic. At the start of the scale-up process, the Ministry of Health of Botswana anticipated that the situation would be exacerbated by an increase in the volume of patients attending outpatient clinics for HIV-related care and treatment and consistent over-capacity at medical wards. Botswana has circumvented a subset of these issues by creating successful partnerships that offer national training programmes for HIV and AIDS care. For example, as of 2012, more than 9000 health-care workers had received training from the Botswana Ministry of Health's Knowledge Innovation and Training Shall Overcome AIDS Training Program, supported by ACHAP. Additionally, the PEPFAR Clinical Master Training Program offers routine, on-site education to ensure that health-care professionals stay motivated and receive up-to-date training and sufficient technical support on HIV and AIDS care. The country has additionally initiated creative partnerships between the private and public sectors. The purpose of the partnerships was to help alleviate the shortages in the public sector by enabling private physicians to share the burden of patients. Physicians now receive incentives to act as agents of Masa by providing publicly funded services. The partnership presents an opportunity for expansion of service provision and enables physicians in the private sector to have many poor patients who could not afford their services otherwise.

Our analysis of the Botswana national ART programme shows areas of success and areas needing improvement. The programme successfully reduced mortality among patients with AIDS to levels much the same as those reported by other low-income or middle-income countries, and continued to improve this low mortality rate over the study period. The programme also reduced mortality in the first year of treatment initiation; the high initial mortality after treatment initiation shows the importance of the recent change in the national guidelines, which requires earlier treatment, from CD4 cell counts below 200 cells/μL in 2002, to below 250 cells/μL in 2008, and to below 350 cells/μL in 2013. The programme encouraged earlier HIV treatment through increased screening and worked to reduce stigma and discrimination, which deter people from being screened and accessing care. As treatment improves and patients live longer, the national ART programme will need to deal with ART-related toxicities and non-AIDS defining disorders.[31,32]

Contributors

MF, KS, GM, and RM designed the study. KCSM, RL, MA, AA, TC, and TG collected the data. HT, DR, and LB contributed to data cleaning and management. MF and AV analysed the data. MF, RL, MA, AA, TC, and RM interpreted the results. MF, AV, DR, TM, TC, and RM wrote the report.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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