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Decline in adverse outcomes and death in tuberculosis patients in Malawi: association with HIV interventions

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Between 2000 and 2012, the annual numbers of patients treated for tuberculosis (TB) in Malawi declined by 28%, from 28 234 to 20 463. During this time, the proportion of TB patients tested for the human immunodeficiency virus (HIV) increased from 6% to 87%. Most HIV-infected patients received cotrimoxazole preventive therapy, and the proportion receiving antiretroviral therapy increased to 88%. Between 2000 and 2008 there was a significant decline in all adverse outcomes (from 31% to 14%), and particularly in deaths (from 23% to 10%) and loss to follow-up (from 5.2% to 1.9%, $P < 0.001$). After 2008, there was no decrease in any adverse outcome. Ways to further reduce TB-associated mortality are discussed.

In 2000, the United Nations established eight Millennium Development Goals (MDGs) with targets set for 2015.[1] Tuberculosis (TB) was included in MDG 6: namely, to reduce the incidence of the disease. Two global targets for halving TB prevalence and mortality by 2015, compared with the 1990 baseline, were also included within the MDG framework. According to the World Health Organization (WHO), in 2012 the global TB mortality rate had been reduced by 45% since 1990, and the global target of a 50% reduction by 2015 appears to be within reach.[2] However, the WHO African region does not appear to be on track to meet this mortality rate target, with high TB burden and high human immunodeficiency virus (HIV) prevalence countries such as Zimbabwe and South Africa experiencing particular difficulties.[2,3]

Before the advent of HIV-related interventions, HIV-infected patients with TB had a high mortality rate in sub-Saharan Africa.[4] The introduction and scale-up of two HIV-related adjunctive treatments led to a considerable reduction in case fatality: cotrimoxazole preventive therapy (CPT) was associated with a 25–46% reduction in mortality, antiretroviral therapy (ART) was associated with a 64–95% reduction in mortality, and a synergistic effect is observed when the two interventions are combined.[5] The updated WHO policy on collaborative TB-HIV activities provides countries with guidance on HIV testing, CPT and ART to reduce the burden of HIV in TB patients,[6] and many high HIV prevalence countries in southern Africa have adopted these policies in their joint TB-HIV plans, with varying degrees of implementation.[3]

Malawi has been scaling up ART for over a decade. It has an excellent national recording and reporting system for TB patients, including HIV-related parameters and ART status, disaggregated by the timing of ART initiation in relation to anti-tuberculosis treatment. Based on national aggregated programme data from 2000 to 2012, we analysed the association between uptake and coverage of HIV testing, CPT and ART in TB patients and adverse outcomes such as death, loss to follow-up and transfer out.

METHODS AND RESULTS

This was a retrospective descriptive study using national reports. Malawi is a poor country in central-southern Africa with a population of 16 million, of whom one million are estimated to be HIV-infected.[7] National ART scale-up started in 2004. In the first 6 years, first-line treatment was a fixed-dose combination of stavudine, lamivudine and nevirapine, but since 2011 there has been a gradual change to tenofovir, lamivudine and efavirenz. By June 2014, 505 123 HIV-infected patients were alive and on ART, representing 51% coverage of the HIV-infected population in the country.[7]

Since 1985, Malawi has had a well-respected DOTS-based National TB Control Programme (NTP), with case finding, diagnosis, registration, treatment and treatment outcomes following agreed international guidelines.[8] National guidelines for the care and management of TB patients infected with HIV are in line with WHO policy:[6,9] all patients should be tested for HIV through provider-initiated testing and counselling, and all those who are HIV-infected should be offered CPT and ART as soon as possible after the start of anti-tuberculosis treatment.

The study included all adults and children in Malawi notified each year as having TB (2000–2012). Sources of data were national reports from the National TB Control Programme, Ministry of Health, Malawi. Data were analysed descriptively. Across different time points, comparisons were made between the highest and lowest annual TB numbers and between proportions of TB patients with an adverse outcome (combined and separately for death, loss to follow-up and transfer out), using the χ^2 test, risk ratios (RR) and 95% confidence intervals (CI). Levels of significance were set at 5%.

The study received ethics approval from the Malawi National Health Science Research Committee and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France. As the study was based on aggregate data from national reports, informed patient consent was not required.

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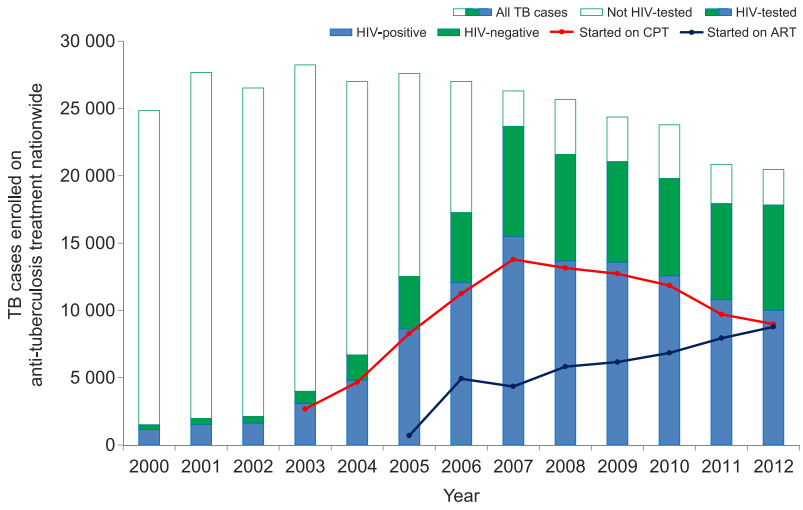

FIGURE 1 Scale-up of HIV testing, CPT and ART among patients with TB enrolled for anti-tuberculosis treatment in Malawi, 2000–2012. No data available for CPT use 2000–2002. No data available for ART use 2000–2004. HIV = human immunodeficiency virus; TB = tuberculosis; CPT = cotrimoxazole preventive therapy; ART = antiretroviral treatment.

The numbers of TB patients enrolled for treatment, along with the numbers HIV tested, HIV-positive, on CPT and on ART are shown in Figure 1. There was a decrease of 28% from the highest number of patients enrolled for treatment (28 234 in 2003) to the lowest number (20 463 in 2012). Over the 12 years, the proportion of enrolled patients tested for HIV increased from 6% to 87%. The majority of those HIV-infected received CPT (usually >90%). From 2005 to 2012, the proportion of HIV-positive patients receiving ART increased from 8% to 88%.

Annual trends in adverse outcomes in evaluated TB patients are shown in Figure 2. From 2000 to 2008, the differences between the highest and lowest proportions for all adverse outcomes were 31% vs. 14% (RR 2.3, 95%CI 2.2–2.4), 23% vs. 10% (RR 2.3, 95%CI 2.2–2.5) for death, 5.2% vs. 1.9% (RR 2.7, 95%CI 2.4–3.0) for loss to follow-up, and 3% vs. 2% (RR 1.5, 95%CI 1.3–1.7) for those transferred out without a reported outcome. From 2008 to 2012, there were no significant changes in the numbers and proportions of patients lost to follow-up or transferred out, although the numbers and proportions with all adverse outcomes and death significantly increased in the last 2 years compared with 2008 ($P < 0.01$).

DISCUSSION

This study shows that as HIV interventions were scaled up between 2000 and 2008, there was a significant decline in adverse treatment outcomes, including death. However, between 2008 and 2012, the proportion of patients with all adverse outcomes (15%) and the proportion reported to have died (10%) remained unchanged or showed statistically significant but clinically unimportant increases.

The strengths of this study are the comprehensive national reports over a 12-year period. The limitations are mainly related to the accurate ascertainment of death. The categories 'lost to follow-up' and 'transferred out' may include unreported deaths, and we included them in the analysis for this reason.

The post-2015 global TB strategy, endorsed at the 67th World Health Assembly, has an ambitious target of a 75% reduction in TB deaths by 2025 compared with 2015.[10] The current data from Malawi suggest that business as usual will not be enough to achieve this mortality reduction. So what is to be done?

On the HIV front, Malawi has just completed its national strategic plan for HIV and the acquired immune-deficiency syndrome (AIDS), 2015–2020.[11] The main goal of this plan is to meet the ambitious 90–90–90 treatment targets released by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2014. By 2020, Malawi aims to have 1) diagnosed 90% of all people living with HIV, 2) started and retained 90% of those diagnosed on ART, and 3) achieved viral suppression for 90% of patients on ART. Meeting the first target is crucial, as this will identify as many HIV-infected people as possible who can then be linked to care and treatment. Provider-initiated HIV testing and counselling (PITC) is the primary testing model to be implemented in all health facilities and targeted to high-risk groups. From the NTP perspective, this means focused PITC for patients diagnosed with TB and those with presumptive TB, and ensuring that those found to have smear-negative TB are also offered testing. Vulnerable

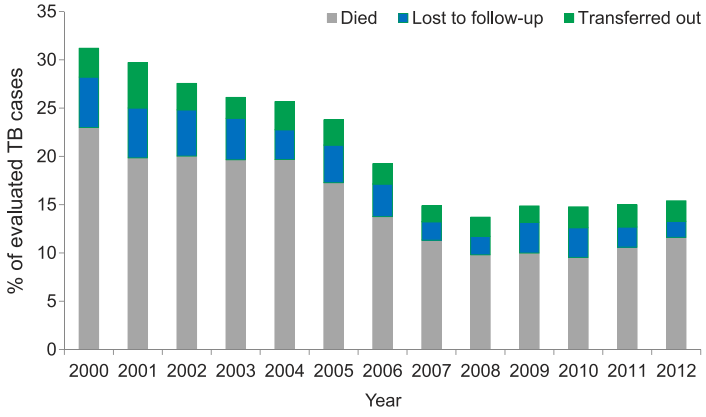

FIGURE 2 Adverse treatment outcomes for all TB patients evaluated each year in Malawi, 2000–2012. Adverse treatment outcomes include death, loss to follow-up and transfer out. TB = tuberculosis.

groups, such as prisoners, persons working on estates, children and female sex workers, are to be included. This expansion of HIV testing will require additional staff. To achieve this, a new position of 'HIV diagnostic assistant' will be established and posted to health facilities.

To meet the second target, all HIV-infected TB patients will be started on ART within 2 weeks of initiating anti-tuberculosis treatment. This will be facilitated by strengthening links between services, and in particular increasing the number of facilities with co-location or integration of TB and ART services. On the TB front, it will be important to ensure that patients with TB are diagnosed and treated for their TB as soon as possible, through intensified case finding in high-risk places, such as ART clinics, prisons and households of index TB patients, and through more sensitive diagnostic technology such as Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) where it is available.

NTPs will thus need 100% implementation of HIV-related interventions, and they will also need to ensure optimal core public health practice within the WHO End TB Strategy. This will need to be accompanied by expanded scale-up and coverage of ART to HIV-infected people, as this can reduce the TB burden and its associated mortality in high HIV prevalence areas in sub-Saharan Africa. There is no time to lose.

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Entre 2000 et 2012, le nombre annuel de patients traités pour tuberculose (TB) au Malawi a décliné de 28%, passant de 28 234 à 20 463. Pendant cette période, la proportion de patients TB testés pour le virus de l'immunodéficience humaine (VIH) a augmenté de 6% à 87%, la majorité des patients infectés par le VIH a bénéficié d'un traitement préventif par cotrimoxazole et la proportion de patients recevant un traitement antirétroviral est passée à 88%. Entre 2000 et 2008, il y a eu un déclin significatif de toutes les évolutions défavorables (de 31% à 14%), en particulier des décès (de 23% à 10%) et des perdus de vue (de 5,2% à 1,9% ; $P < 0,001$). Après 2008, il n'y a plus eu de diminution des évolutions défavorables. L'article discute des manières de poursuivre la réduction de la mortalité associée à la TB.

Del año 2000 al 2012, el número anual de pacientes tratados por tuberculosis (TB) en Malawi disminuyó un 28%, de 28 234 a 20 463. Durante este período, la proporción de pacientes TB en quienes se practicó la prueba diagnóstica de infección por el virus de la inmunodeficiencia humana (VIH) aumentó del 6% al 87%. La mayoría de los pacientes VIH positivo recibió tratamiento preventivo con cotrimoxazol, y la proporción de pacientes que recibía tratamiento antirretrovírico aumentó al 88%. Del 2000 al 2008 se observó una disminución considerable de todos los desenlaces desfavorables (del 31% al 14%) y sobre todo de las muertes (del 23% al 10%) y las pérdidas durante el seguimiento (del 5,2% al 1,9%; $P < 0,001$). Después del 2008, no se presentó disminución en ninguno de los desenlaces desfavorables. En el artículo se analizan modalidades que permitan disminuir aun más la mortalidad asociada con la TB.

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