Reduced tuberculosis case notification associated with scaling up antiretroviral treatment in rural Malawi

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OBJECTIVE: To report on the trends in new and recurrent tuberculosis (TB) case notifications in a rural district of Malawi that has embarked on large-scale roll-out of antiretroviral treatment (ART).

METHODS: Descriptive study analysing TB case notification and ART enrolment data between 2002 and 2009.

RESULTS: There were a total of 10 070 new and 755 recurrent TB cases. ART scale-up started in 2003, and by 2007 an estimated 80% ART coverage had been achieved and was sustained thereafter. For new TB cases, an initial increase in case notifications in the first years after starting ART (2002–2005) was followed by a highly significant and sustained decline from 259 to 173 TB cases per 100 000 population ($\chi^2$ for trend 261, $P < 0.001$, cumulative reduction for 2005–2009 = 33%, 95%CI 27–39). For recurrent TB, the initial increase was followed by a significant drop, from 20 to 15 cases/100 000 ($\chi^2$ for linear trend = 8.3, $P = 0.004$, constituting a 25% (95%CI 9–49) cumulative reduction between 2006 and 2009. From 2005 to 2009, ART averted an estimated 1164 (95%CI 847–1480) new TB cases and 78 (95%CI 23–151) recurrent TB cases.

CONCLUSIONS: High ART implementation coverage is associated with a very significant declining trend in new and recurrent TB case notifications at population level.

KEY WORDS: ART; TB; scale-up; case notification; Malawi

HUMAN IMMUNODEFICIENCY virus (HIV) promotes progression to active tuberculosis (TB) disease in both recently acquired and latent Mycobacterium tuberculosis infection.¹⁻³ HIV is the most powerful known risk factor for reactivation of latent M. tuberculosis, with up to 10% of infected individuals at risk of developing TB per year.⁴ HIV is also known to increase the rates of recurrent TB disease after successful completion of treatment for a first episode.⁴⁻⁶ As a result of the impact of HIV, countries with high HIV prevalence have had a two- to five-fold increase in annual TB case notification rates over the last decade.⁴⁻⁵ This increase in TB burden has adversely affected TB programmes and has strained available human and financial resources at programme level.⁴⁻⁸

Observational cohort studies in a wide range of settings have demonstrated that antiretroviral treatment (ART), through immune reconstitution, is associated with a 54% to 92% reduction in TB incidence at the individual patient level and a halving of the risk of TB recurrence.⁷⁻¹³ It logically follows that if a large proportion of HIV-positive individuals in high HIV prevalence settings are offered ART, the reduction in TB incidence at the individual patient level should also have a beneficial impact on TB incidence and case notification at the population level. However, empirical data on the impact of ART on TB case notification at the community level are lacking.⁷

Thyolo District in rural southern Malawi had a global and adult HIV prevalence of respectively 10% and 21% in 2007.¹⁴ The district has been progressively scaling up HIV/AIDS (acquired immune-deficiency syndrome) care and ART since 2003. The district achieved and sustained universal ART access from 2007 onwards (sustained access for at least 80% of those in need).¹⁵,¹⁶ We hypothesised that such a large scale-up and coverage of ART at the population level might have been associated with a decrease in district TB case notifications. We thus report on trends in new and recurrent TB case notifications at the
METHODS

Study setting and population
This retrospective cross-sectional descriptive study was conducted in Thyolo District, one of the most populated rural districts in Malawi. All consecutively registered new and recurrent cases of TB for the period 2002–2009 were included in the analysis. Since 1997, Médecins Sans Frontières (MSF) has been working in close collaboration with the district health services of the Malawi Ministry of Health (MoH) in setting out a comprehensive HIV/AIDS prevention and care programme. Chronologically, the project evolved as follows: voluntary counselling, HIV testing and home-based care from January 1998; HIV testing for all TB patients, including cotrimoxazole prophylaxis and management of opportunistic infections, from June 1999;\(^\text{18}\) prevention of mother-to-child transmission\(^\text{18}\), and HIV/AIDS consultations at hospital and health centres from 2002; ART initiation at the district hospital in late 2003, which was progressively scaled up to include health centres; and universal ART access (at least 80% coverage of those in need) achieved in 2007 and sustained thereafter. Management and reporting of TB and HIV/AIDS activities, including ART, are in line with Malawi MoH and World Health Organization (WHO) guidelines.\(^\text{19,20}\) All HIV-positive patients assessed as being WHO Clinical Stage 3 or 4, or with a CD4 count of <250 cells/mm\(^3\) (irrespective of WHO staging), are considered eligible for ART. HIV/AIDS care, ART and TB treatment are provided free of charge.

For the purposes of this study, new TB cases include individuals starting TB treatment for the first time with pulmonary (smear-positive or -negative) or extra-pulmonary TB (EPTB); recurrent TB includes relapse cases and the ‘other’ category.

Data collection and statistical analysis
Cumulative data on annual TB case notifications were obtained from the district TB register for the period 2002–2009. TB case notification was standardised per 100 000 population per year. Yearly district population data were based on national demographic health surveys (DHS) and census data.\(^\text{21}\) The total numbers of individuals ever enrolled in HIV/AIDS care and ART on an annual basis were derived from the FUCHIA database (Follow-Up and Care of HIV Infection and AIDS [FUCHIA], Epicentre, Paris, France) and the routine district reporting system.

The \(\chi^2\) test for trend was used to test for linear trends. The level of significance was set at \(P \leq 0.05\), and 95% confidence intervals (CIs) were used throughout. Data were analysed using Microsoft Excel (Microsoft, Redmonds, WA, USA) and STATA 8.0 software (Stata Corporation, College Station, TX, USA).

Ethics clearance
The TB and ART programmes in Thyolo are implemented in close collaboration with the MoH of Malawi, in line with existing national guidelines. The study received ethics clearance from the ethics review boards of MSF and the International Union Against Tuberculosis and Lung Disease.

RESULTS

Characteristics of the study population
Over the study period (2002–2009) there were a total of 10 070 newly registered TB cases, comprising 4116 cases of smear-positive pulmonary TB (PTB), 3445 cases of smear-negative PTB and 2509 cases of EPTB. A total of 755 cases of recurrent TB were also reported, including 406 relapses and 349 in the ‘other’ category (Table 1).

Trend in TB case notification and relation to enrolment in HIV/AIDS care and ART
Table 2 shows (by year) the population of Thyolo, numbers of HIV-infected persons started on ART and case notifications for new and recurrent TB in Thyolo District, Malawi. The Figure shows the trend in TB case rates (new cases and recurrent TB cases) in relation to ART scale-up. In terms of ART scale-up (started in 2003), by the end of 2006 an estimated 57 438 of the 574 384 inhabitants in the district were HIV-positive (10% global HIV prevalence); of these, an estimated 11 487 (20%) were in urgent need of ART, including 6216 who were placed on ART by the end of 2006, constituting about 54% of the total population in need of ART at the time. Universal access (at least 80% ART coverage for those in need) was achieved in 2007 and sustained thereafter.

For new cases of TB, there was an initial increase in case notifications in the first years after starting

<table>
<thead>
<tr>
<th>Year</th>
<th>Smear-positive PTB</th>
<th>Smear-negative PTB</th>
<th>EPTB</th>
<th>Total</th>
<th>Relapse</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>459</td>
<td>352</td>
<td>309</td>
<td>1 120</td>
<td>37</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>2003</td>
<td>464</td>
<td>315</td>
<td>282</td>
<td>1 061</td>
<td>49</td>
<td>33</td>
<td>82</td>
</tr>
<tr>
<td>2004</td>
<td>591</td>
<td>428</td>
<td>346</td>
<td>1 365</td>
<td>58</td>
<td>40</td>
<td>98</td>
</tr>
<tr>
<td>2005</td>
<td>580</td>
<td>500</td>
<td>365</td>
<td>1 445</td>
<td>73</td>
<td>60</td>
<td>113</td>
</tr>
<tr>
<td>2006</td>
<td>554</td>
<td>608</td>
<td>308</td>
<td>1 470</td>
<td>63</td>
<td>53</td>
<td>116</td>
</tr>
<tr>
<td>2007</td>
<td>545</td>
<td>497</td>
<td>306</td>
<td>1 348</td>
<td>48</td>
<td>56</td>
<td>104</td>
</tr>
<tr>
<td>2008</td>
<td>471</td>
<td>387</td>
<td>313</td>
<td>1 171</td>
<td>40</td>
<td>48</td>
<td>88</td>
</tr>
<tr>
<td>2009</td>
<td>452</td>
<td>358</td>
<td>280</td>
<td>1 090</td>
<td>38</td>
<td>59</td>
<td>97</td>
</tr>
<tr>
<td>Total</td>
<td>4116</td>
<td>3445</td>
<td>2509</td>
<td>10 070</td>
<td>406</td>
<td>349</td>
<td>755</td>
</tr>
</tbody>
</table>

TB = tuberculosis; PTB = pulmonary TB; EPTB = extra-pulmonary TB.

TABLE 1 Annual case reporting for new and recurrent TB for the period 2002–2009, Thyolo District, Malawi
ART (2002–2005). However, from 2005 onwards (2005 was the peak for TB case notifications), there was a highly significant and sustained decrease in case notifications, from 259 to 173 cases/100,000 ($\chi^2$ for linear trend = 261, $P < 0.001$), accounting for a 33% (95% CI 27–39) reduction in case rates over a 5-year period (2005–2009). The mean incremental reduction in case rates for new TB from 2005 onwards was 17/100,000/year.

For recurrent cases of TB, there was also an initial increase, followed by a significant decrease from 2006 onwards, from 20 to 15 cases/100,000 ($\chi^2$ for linear trend = 8.3, $P = 0.004$), constituting a 25% reduction (95% CI 9–49). The mean incremental reduction in case rates for recurrent TB from 2006 onwards was one case/100,000/year.

If ART scale-up was causally related to the decline in TB case notification rates, ART averted an estimated 1164 (95% CI 847–1480) new cases of TB and 78 (95% CI 23–151) recurrent TB cases from 2005 to 2009 (Table 3).

### DISCUSSION

In a rural district of Malawi that has embarked on scaling up ART, there appears to be a highly significant declining trend in TB case notification. This is also one of the first reports using routinely collected data showing the beneficial impact of high ART coverage on TB case notification at the community level. The benefit is apparent for both new and recurrent cases of TB.

A number of observations merit discussion. First, an initial increase in TB case notification in the early years of initiating ART is followed by a decline. Although we cannot be certain, the initial increase may be related to better TB case detection through scale-up of ART services:22 TB suspects being enrolled into HIV care and not dying before their TB manifests, immune reconstitution unmasking TB in patients on ART,23 or a rise in TB incidence due to low proportions of the HIV-positive (susceptible) population receiving ART. The comprehensive support activities provided by MSF in the district from 1999 onwards, particularly in providing new TB infrastructure, human resources and consumables for the district laboratory, drug support to all peripheral health facilities, HIV testing, cotrimoxazole prophylaxis and management of opportunistic infections,17 are all likely to

### Table 2: Population estimates, numbers of HIV-infected persons started on antiretroviral treatment and case notifications for new and recurrent TB in Thyolo District, Malawi, 2002–2009

<table>
<thead>
<tr>
<th>Year</th>
<th>Total population Thyolo District n</th>
<th>Patients ever enrolled in HIV/AIDS care n</th>
<th>Patients ever started on ART n</th>
<th>New TB cases Total n</th>
<th>Case rate /100,000 (95% CI)</th>
<th>Recurrent TB cases Total n</th>
<th>Case rate /100,000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>507,426</td>
<td>2,711</td>
<td>0</td>
<td>1120</td>
<td>220 (208–234)</td>
<td>37</td>
<td>7 (5–10)</td>
</tr>
<tr>
<td>2003</td>
<td>523,162</td>
<td>4,383</td>
<td>424</td>
<td>1061</td>
<td>203 (191–215)</td>
<td>82</td>
<td>16 (12–19)</td>
</tr>
<tr>
<td>2004</td>
<td>539,610</td>
<td>6,609</td>
<td>1,550</td>
<td>1365</td>
<td>253 (240–268)</td>
<td>98</td>
<td>18 (15–22)</td>
</tr>
<tr>
<td>2006</td>
<td>574,384</td>
<td>11,622</td>
<td>6,216</td>
<td>1470</td>
<td>255 (243–269)</td>
<td>116</td>
<td>20 (17–24)</td>
</tr>
<tr>
<td>2007</td>
<td>592,630</td>
<td>14,627</td>
<td>11,525</td>
<td>1348</td>
<td>237 (215–239)</td>
<td>104</td>
<td>18 (14–21)</td>
</tr>
<tr>
<td>2008</td>
<td>611,424</td>
<td>18,437</td>
<td>16,106</td>
<td>1171</td>
<td>191 (180–203)</td>
<td>88</td>
<td>14 (12–18)</td>
</tr>
<tr>
<td>2009</td>
<td>630,756</td>
<td>23,395</td>
<td>21,064</td>
<td>1090</td>
<td>173 (162–183)</td>
<td>97</td>
<td>15 (12–18)</td>
</tr>
</tbody>
</table>

HIV = human immunodeficiency virus; TB = tuberculosis; AIDS = acquired immune-deficiency syndrome; ART = antiretroviral treatment; CI = confidence interval.
have brought more ill patients into the health system and contributed to improved referrals and diagnosis of TB suspects. Furthermore, support for community TB-HIV-related activities, including screening and referral of TB suspects, would have contributed to enhanced case finding.24

Second, there is a progressive and highly significant declining trend in TB case notification from 2005 onwards associated with ART scale-up and increased access to ART services at peripheral health facilities. Although we cannot know with certainty whether or not the observed reduction is linked to the ART roll-out, the association between the two is suggestive and intuitive. In a high HIV prevalence country such as Malawi, high TB incidence in the HIV-positive population is likely to be a very important contributor to community TB prevalence and transmission.2 A reduction in TB risk conferred by the ‘ART protective effect’ in this highly susceptible subgroup2–4,12 should therefore reduce TB incidence, and subsequently case notification, at the population level. However, trends in case notification in a given setting could be confounded by variables such as high mortality prior to TB diagnosis, changes in the efficiency of TB case detection, the improving socioeconomic status of the population or isoniazid preventive treatment (IPT) for HIV-positive individuals.25 However, we do not believe that any of these factors would have contributed to the declining trends observed from 2005 onwards in our setting.

HIV care and ART scale-up were achieved and sustained by decentralising these services15,16 and, since 2006, increasing numbers of health facilities have also benefited from an increase in decentralised laboratory capability for diagnosing TB. By the end of 2009, sputum samples could be examined in seven microscopy sites, and an additional eight sites were able to perform full preparation (smearing and fixation) of slides for reading.26 Fluorescent microscopy has also been introduced at the district level to cope with the high caseloads of sputum samples and to increase diagnostic efficiency. In other words, the decreasing trend in TB case notifications happened despite these efforts to enhance TB detection. Furthermore, there has been no implementation of IPT in the district, and we do not believe that there have been significant improvements in social conditions such as employment opportunities or the earning capacity of the population. The prices of petrol, diesel and paraffin have generally shown an upward trend over the study period, with a consequent increase in consumer prices.27 The situation from 2005 onwards is therefore likely to represent the overall impact of ART on TB case notification.

The strengths of this study are that TB case notification data for an entire district of more than half a million inhabitants were included and that the diagnosis and reporting systems for TB notification and ART scale-up are standardised and supervised. The findings are thus likely to reflect the reality on the ground. The main limitation of the study is that it is based on simple observational data with the usual related shortcomings, and we are thus unable to demonstrate a cause-effect relationship. We therefore deliberately concentrated on general ‘trend analysis’ of case notification, which is considered a proxy indicator of community TB incidence and prevalence.

Whatever the exact reasons for the decline, a reversal in the trend of TB case notification associated with high ART coverage is very encouraging, as it brings some optimism towards achieving the United Nations Millennium Development Goal (MDG) targets,28 where TB control is crucial.29 In addition, it reduces the TB caseload burden in an overburdened health system facing severe shortages of human resources for health. The beneficial effect on TB case notification seen in this context is likely to be accentuated with recent WHO guidelines recommending starting ART at higher CD4 counts compared with...
during the period of this study. There is now a need to further increase impetus in this direction through the implementation of the '3 Is', i.e., intensified case finding, improved TB infection control and IPT. Finally, this study provides important and encouraging evidence for donors on the population impact of ART coverage and advocates for continued involvement in ART and TB programmes in similar settings. On the other hand, a retreat from investment in such programmes could be disastrous to sustaining gains such as those described in this article.

In a rural district of Malawi that has achieved high ART coverage, there is very encouraging evidence of a significant decline in TB case notification rates for both new and recurrent TB at the population level.

Acknowledgements

The authors thank the health workers and data collection staff in the district for their valuable work. They are particularly grateful to their various donors for their sustained support in the fight against HIV/AIDS and TB in Malawi.

References

OBJECTIFS : Faire un rapport sur les tendances des taux de déclaration des nouveaux cas ou des cas récurrents de tuberculose (TB) en relation avec l’extension du traitement antirétroviral (ART) dans un district rural du Malawi qui s’est lancé dans un accroissement à large échelle du ART.


RÉSULTATS : On a enregistré 10 070 nouveaux cas de TB et 755 cas de reprise de TB. L’extension de l’ART a commencé en 2003 et la couverture a été estimée à 54% des sujets nécessitant l’ART en 2006 et à 80% en 2007, et s’est maintenue par la suite. Pour les nouveaux cas de TB, un accroissement initial des déclarations de cas au cours des premières années faisant suite à l’ART (2002–2005) a été suivi par une diminution hautement significative et persistante de 259 à 173 cas pour 100 000 habitants (pour les tendances linéaires $\chi^2 = 261, P < 0,001$ ; réduction cumulative pour la période 2005–2009 = 33% ; IC95% 27–39). Pour les cas de reprise de TB, l’accroissement initial a été suivi par une chute significative de 20 à 15 cas/100 000 (pour les tendances linéaires $\chi^2 = 8,3 ; P = 0,004$), ce qui constitue une réduction cumulative de 25% (IC95% 9–49) des taux de cas pour la période 2006–2009. Entre 2005 et 2009, l’extension de l’ART a évité un nombre estimé de 1164 nouveaux cas de TB (IC95% 847–1480) et de 78 cas de reprise de TB (IC95% 23–151).

CONCLUSIONS : Une large mise en œuvre de l’ART est en association avec une tendance décroissante très encourageante et significative des déclarations des nouveaux cas ou des reprises de TB au niveau de la population.

OBJETIVOS: Notificar las tendencias en materia de notificación de los casos nuevos y las recidivas de tuberculosis (TB) en un distrito rural de Malawi, donde se emprendió un programa de ampliación a gran escala del tratamiento antirretrovírico (ART).

MÉTODOS: Fue este un estudio descriptivo. Análisis de los datos de notificación de casos de TB y de inscripción en el ART entre el 2002 y el 2009.

RESULTADOS: Se observaron 10 070 casos nuevos de TB y 755 recidivas. La ampliación de escala del ART comenzó en 2003 y hacia el 2007 se calculó que su cobertura alcanzaba el 80% y esta cifra se mantuvo estable en los años siguientes. Con respecto a los casos nuevos de TB, un incremento inicial en las notificaciones de casos durante los primeros años de la instauración del ART (del 2002 al 2005) se continuó con una disminución significativa y constante desde 259 hasta 173 casos por 100 000 habitantes ($\chi^2$ de las tendencias linéales $\chi^2 = 261; P < 0,001$, disminución acumulada de 33% entre el 2005 y el 2009; IC95% 27–39). En relación con los casos de recidiva de TB, un aumento inicial se continuó con una reducción drástica de 20 a 15 casos/100 000 ($\chi^2$ de la tendencia lineal = 8,3; $P = 0,004$), con una reducción acumulada de 25% entre el 2006 y el 2009 (IC95% 9–49). Se calculó que el ART evitó 1164 casos nuevos de TB (IC95% 847–1480) y 78 casos de recidiva (IC95% 23–151) entre el 2005 y el 2009.

CONCLUSIÓN: Una alta cobertura del ART se asocia con una disminución considerablemente de las tendencias de notificación de casos nuevos de TB y de recidiva a escala de la población general.