



# HIV treatment cascade in tuberculosis patients

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## Purpose of review

Globally, the number of deaths associated with tuberculosis (TB) and HIV coinfection remains unacceptably high. We review the evidence around the impact of strengthening the HIV treatment cascade in TB patients and explore recent findings about how best to deliver integrated TB/HIV services.

## Recent findings

There is clear evidence that the timely provision of antiretroviral therapy (ART) reduces mortality in TB/HIV coinfecting adults. Despite this, globally in 2013, only around a third of known HIV-positive TB cases were treated with ART. Although there is some recent evidence exploring the barriers to achieve high coverage of HIV testing and ART initiation in TB patients, our understanding of which factors are most important and how best to address these within different health systems remains incomplete. There are some examples of good practice in the delivery of integrated TB/HIV services to improve the HIV treatment cascade. However, evidence of the impact of such strategies is of relatively low quality for informing integrated TB/HIV programming more broadly. In most settings, there remain barriers to higher-level organizational and functional integration.

## Summary

There remains a need for commitment to patient-centred integrated TB/HIV care in countries affected by the dual epidemic. There is a need for better quality evidence around how best to deliver integrated services to strengthen the HIV treatment cascade in TB patients, both at primary healthcare level and within community settings.

## Keywords

antiretroviral therapy, HIV, HIV testing, integrated care, tuberculosis

## INTRODUCTION

In 2013, there were an estimated 1.1 million cases of tuberculosis (TB) disease in people living with HIV and 360 000 deaths attributable to HIV-associated TB [1]. Africa is home to around four in every five cases of HIV-associated TB disease [1]. Although there is evidence of decreasing mortality from HIV-associated TB (reduction by one-third in the last decade), the rate of mortality decline is slower than for TB in individuals who are HIV negative [1,2].

The main steps in the HIV treatment cascade for TB patients involve diagnosis of HIV infection, linkage to care, initiation of cotrimoxazole prophylaxis and antiretroviral therapy (ART), and achieving and maintaining viral load suppression (Fig. 1) [3,4]. Delivery of these services is guided by the World Health Organization (WHO) policy on collaborative TB/HIV activities [5]. Most countries with a high burden of TB/HIV now have specific policies promoting HIV counselling and testing for those with presumptive or confirmed TB, and most now recommend ART for all TB cases regardless of CD4<sup>+</sup>

cell count [6]. Routine TB programme reports indicate that despite scale-up of collaborative TB/HIV services, there is still significant attrition along the HIV cascade for TB patients. In 2013, only 48% of TB cases notified globally had a documented HIV test result, and of those known to be HIV positive, only 70% were started on ART (Fig. 2) [1]. This suggests that overall only around a third of HIV-positive TB cases were treated with ART. Even these figures mask the fact that 3 million TB cases are estimated to be undiagnosed each year and do not

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**KEY POINTS**

- Only around a third of HIV-positive TB patients currently receive ART, highlighting a significant gap between evidence and impact.
- Scale-up of collaborative TB/HIV services has improved coverage of HIV testing and uptake of ART, particularly in some countries with the highest burden of HIV-associated TB.
- Significant barriers to TB/HIV integration exist at all levels of the health system and there is a paucity of evidence around how to improve integration.
- Targeted measures to strengthen the HIV treatment cascade for TB patients may be necessary within the framework of broader health system strengthening but this should be combined with strategies to find people with undiagnosed TB/HIV.

enter the cascade, many of whom are likely to have HIV-associated TB [1,7].

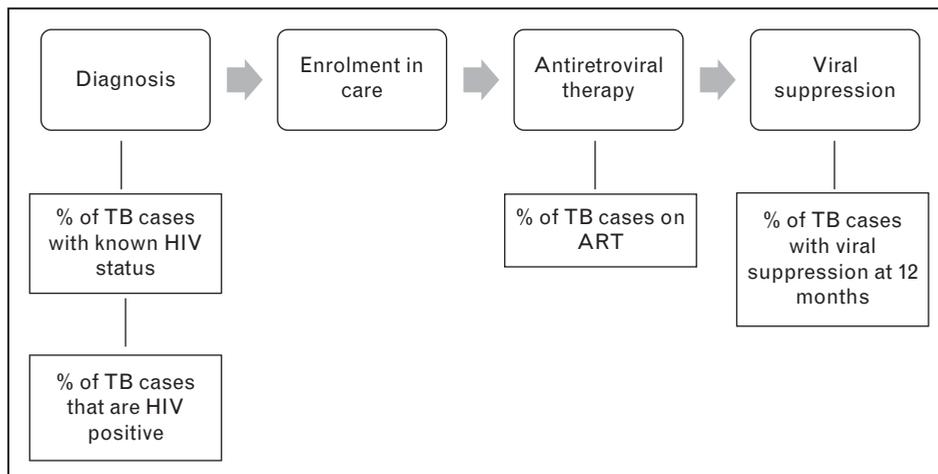
Strengthening the HIV treatment cascade is important to reduce the number of deaths from HIV-associated TB. There is quite significant heterogeneity between countries in the key measures of HIV testing and ART initiation for TB patients (Tables 1 and 2). These differences highlight that a one-size-fits-all approach to strengthen the cascade may not be appropriate. There do continue to be issues about the quality of routine programme data, which are emphasized in the context of TB/HIV wherein there may be discrepancies in reporting the same indicator by TB and HIV programmes [1]. Caution is therefore required when interpreting routine aggregated national data alongside data collected in research settings or well defined implementation projects.

This review will summarize recent data that provide insight into the cascade in different settings, with a particular focus on evidence around interventions to strengthen the cascade and more broadly to support the delivery of integrated TB/HIV services.

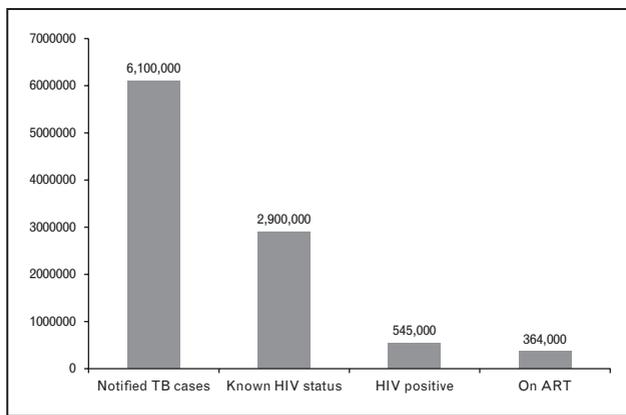
**HIV TESTING FOR TUBERCULOSIS PATIENTS**

There was quite substantial variation globally in the proportion of TB cases with known HIV status in 2013 – highest in the WHO African region at 76% and below 50% in south-east Asia, Western Pacific, and Eastern Mediterranean regions [1]. Even within these regions there is considerable heterogeneity in performance between countries (Table 1) [8].

There are several recent examples of good performance in different high-burden TB/HIV countries. In South Africa, individual reports have confirmed the high national-level uptake of HIV testing and have shown that high uptake (>90%) can be achieved in primary healthcare facilities regardless of the level of integration of TB and HIV services [9], and in drug-resistant TB services regardless of whether centralized or decentralized [10]. Although the overall proportion of TB patients tested for HIV in India is low, one study described new referral pathways for TB patients in Delhi, allowing direct referral to ART centres rather than first sending patients to separate HIV counselling and testing sites. Over the 9-month period following implementation, 92% of TB patients received HIV counselling and testing, and of those that tested positive, 93% engaged in care [11]. More broadly in India, there have been concerted efforts to scale-up an intensified package of collaborative TB/HIV activities facilitated by a joint national TB/HIV



**FIGURE 1.** HIV treatment cascade in TB patients and indicators used to evaluate the cascade.



**FIGURE 2.** Cascade graph of diagnosis and treatment of HIV in TB cases, 2013 (global data) [1].

policy [12<sup>\*</sup>]. Colocation of TB and HIV testing facilities in India has been shown to increase HIV testing coverage and is now a priority intervention within the national strategic plan [12<sup>\*</sup>].

Despite calls to move testing upstream and ensure that all people investigated for TB are offered HIV testing [5,13], there is a scarcity of data to show to what extent programmes are achieving this. There are also few data describing HIV testing for children undergoing investigation and treatment for TB disease. National-level data in South Africa showed some evidence of recent programmatic improvement, with the proportion of child TB cases (under 15 years) reported to have unknown HIV status declining from 77 to 25% between 2008 and 2012 [14].

In order to optimize the uptake of HIV testing, there is a need to better understand the factors behind TB patients not being tested for HIV. In terms of patient-level factors, it would be interesting to know whether or not there are issues particular to TB patients that could potentially be addressed with improved counselling or other specific interventions. One study from Ethiopia, with a high uptake of HIV testing among TB patients (92%), suggested that patient-level barriers were not issues specific to TB/HIV but rather general factors, such as lack of formal education and lower levels of knowledge about HIV [15<sup>\*</sup>].

In general, however, other than colocation of services, there is a lack of high-quality evidence around interventions to maximize uptake of HIV testing in TB patients. Although there are several reports of high uptake of HIV testing in various settings, in themselves, these may have limited impact as there is often no clear evidence of what precisely has contributed to high uptake.

**Table 1.** Proportion of notified tuberculosis cases with known HIV status in high-burden TB/HIV countries, 2013 [1]

	Country	Proportion
≥90%	Rwanda	98
	Mali	97
	Togo	97
	Burkina Faso	96
	Kenya	94
	Malawi	92
	Namibia	92
	Zimbabwe	92
	Swaziland	91
	Botswana	91
	Mozambique	91
	Lesotho	91
	Uganda	91
	Sierra Leone	91
Zambia	90	
South Africa	90	
70–89%	Côte d'Ivoire	89
	Nigeria	88
	Ukraine	88
	Burundi	87
	Haiti	86
	United Republic of Tanzania	83
	Thailand	83
	Cambodia	82
	Ghana	73
	Ethiopia	71
Viet Nam	70	
50–69%	Brazil	65
	India	63
	Djibouti	51
30–49%	Central African Republic	45
	Democratic Republic of Congo	44
	Cameroon	41
	Angola	40
	Chad	40
	China	39
	Congo	30
<30%	Sudan	27
	Myanmar	12
	Indonesia	2

No data for Russian Federation.

## UPTAKE AND TIMING OF ANTIRETROVIRAL THERAPY FOR TUBERCULOSIS PATIENTS

Since 2010, WHO guidelines have recommended that all HIV-positive TB patients should be

**Table 2.** Proportion of notified HIV-positive tuberculosis cases started on antiretroviral therapy in high-burden TB/HIV countries, 2013 [1]

	Country	Proportion
≥90%	Mali	100
	Congo	100
	Burkina Faso	98
70–89%	Cambodia	89
	Malawi	88
	India	88
	Kenya	84
	Namibia	80
	Swaziland	80
	Rwanda	79
	Zimbabwe	77
	Myanmar	74
	United Republic of Tanzania	73
	Togo	72
	Botswana	72
	Mozambique	72
	Lesotho	70
50–69%	Ethiopia	68
	Zambia	67
	Nigeria	67
	China	67
	South Africa	67
	Uganda	65
	Sierra Leone	64
	Burundi	64
	Cameroon	64
	Viet Nam	61
	Thailand	59
	Haiti	57
	Côte d'Ivoire	55
	30–49%	Ukraine
Democratic Republic of Congo		48
Ghana		42
Sudan		39
Djibouti		30
<30%	Indonesia	21

No data for Russian Federation, Brazil, Central African Republic, Angola, Chad.

commenced on ART, regardless of CD4<sup>+</sup> cell count [16,17]. Despite this, coverage of ART in TB patients remains suboptimal – globally in 2013 only 70% of known HIV-positive TB patients were commenced on ART prior to or during TB treatment [1].

There is high-quality evidence from randomized controlled trials (RCTs) that the initiation of ART during TB treatment improves survival in HIV-

positive TB patients [18–21]. A recent meta-analysis of 12 observational studies supported this result, finding that the use of ART led to a reduction of between 44 and 72% in mortality during TB treatment [22<sup>■</sup>]. There is also recent evidence that confirms that ART substantially improves survival for patients with multidrug-resistant and extensively drug-resistant TB [23<sup>■</sup>,24<sup>■</sup>].

Observational data from Cape Town has confirmed earlier findings from the RCTs that the impact of ART is most pronounced amongst patients with low CD4<sup>+</sup> cell counts (<350 cells/μl) [25<sup>■</sup>]. In view of this, some continue to question the benefits of ART during TB treatment in patients with higher CD4<sup>+</sup> cell counts. A recent multicentre RCT in Africa reported that for HIV-positive TB patients with CD4<sup>+</sup> cell count of at least 220 cells/μl, there was no difference in the composite endpoint of TB treatment failure, TB recurrence, and death between those randomized to early ART (after 2 weeks of TB treatment) or delayed ART (at the end of 6 months of TB treatment) [26<sup>■</sup>]. However, the trial was not powered to detect a difference between the arms in mortality alone and overall mortality was low. Also the proportion of those allocated to the delayed ART arm that nonetheless initiated ART during TB treatment was not reported. There was no evidence of any adverse effect of early ART and therefore this evidence does not support any change in treatment guidelines.

In terms of the timing of ART initiation, a meta-analysis of six RCTs demonstrated that early ART initiation (within 4 weeks of starting TB treatment) was associated with a reduction in mortality of 25% compared with later initiation of ART (8–12 weeks after starting TB treatment) [27]. A post-hoc analysis of the Cambodian Early versus Late Introduction of Antiretrovirals (CAMELIA) RCT in Cambodia showed that, compared with early ART (after 2 weeks of TB treatment), late ART (after 8 weeks of TB treatment) was associated with more than double the risk of late mortality (after week 50), suggesting a long-lasting benefit of early ART among patients with advanced immunodeficiency [28<sup>■</sup>]. A recent RCT from Ethiopia explored the impact of even earlier initiation of ART (1 week after starting TB treatment, compared with 4 or 8 weeks) [29]. There was no evidence that starting ART after 1 week of TB treatment reduced mortality for all patients, or specifically for those with most advanced immunosuppression (CD4<sup>+</sup> cell count <50 cells/μl).

Interventions to improve uptake of ART might include integration and decentralization of TB and HIV services, and task shifting with nurse-initiated ART. A systematic review explored whether providing ART at the TB health facility improves uptake of

ART, compared with systems in which patients were referred to a separate facility [30]. This review of 12 studies, all but one from Africa, suggested that integration improved ART coverage [relative risk (RR) 1.83, 95% confidence interval (CI) 1.48–2.25]. There was also weak evidence that integrated services led to a reduction in mortality amongst HIV/TB patients (RR 0.55, 95% CI 0.29–1.05) [30].

The Integrating Tuberculosis and Anti-Retroviral Treatment (ITART) study was a prospective cohort study in five primary healthcare clinics in the Democratic Republic of Congo. This study explored outcomes with nurse-delivered decentralized and integrated TB/HIV care and compared this to a historical cohort wherein TB patients were referred to a centralized facility for ART initiation [31<sup>■</sup>]. ART uptake was 69% in the integrated TB/HIV model, compared with 17% in the historical cohort. Mortality during TB treatment was also lower with the integrated TB/HIV model (10 vs. 20% in the historical cohort) [31<sup>■</sup>]. Further analyses of the ITART study uncovered delays in initiating ART with the integrated TB/HIV care model [32<sup>■</sup>]. For this analysis, delayed ART for TB patients was defined quite tightly as more than 5 days beyond the 1, 2, or 6-month threshold for ART (depending on CD4<sup>+</sup> cell count). Overall, almost half of all patients experienced delayed ART initiation or did not initiate ART at all – delay was particularly high (59%) for those who should have started ART within 1 month (CD4<sup>+</sup> cell count <100 cells/ $\mu$ l or WHO clinical stage 4). In this analysis, delayed ART was associated with having a contraindication to at least one antiretroviral drug, intolerance to TB drugs, nondisclosure of HIV status, and lower CD4<sup>+</sup> cell count [32<sup>■</sup>]. Modelling of the same data suggested that around a third of the observed mortality during the study could have been prevented with perfect fidelity to the recommended timing of ART initiation [33<sup>■</sup>].

Elsewhere, there are other examples wherein ART coverage has improved with models of integrated service delivery. In a before–after study in a regional TB hospital in rural Guatemala, ART uptake increased from 22 and 72% and mortality within 50 weeks decreased from an extremely high level of 78 to 21% with decentralized integrated TB/HIV care [34]. In a before–after study in 17 health facilities in western Kenya, integration of TB and HIV services led to an improvement in ART uptake during TB treatment from 39 to 61% and a reduction in the median time to ART initiation from 42 to 34 days [35]. In Malawi, a before–after study compared ART uptake in an integrated TB/HIV clinic before and after the implementation of new guidelines recommending ART within 2 weeks for all TB patients.

Overall, ART uptake improved from 70 to 78% and the proportion starting ART within 2 weeks increased from 30 to 46% [36<sup>■</sup>].

Although studies consistently demonstrate that a significant number of TB patients do not start ART, there is relatively limited understanding about the factors that contribute to this. One qualitative study in the Kingdom of Swaziland involved in-depth interviews with HIV-positive TB patients that had not initiated ART [37<sup>■</sup>]. This highlighted factors operating at an individual level, such as concern about medication side-effects and pill burden as well as deeper issues such as lack of readiness for lifelong treatment. However, the interviews also uncovered important health system barriers, such as poor relationships with clinic staff, failure to receive adequate counselling, and limited availability of diagnostic tests [37<sup>■</sup>]. In Namibia, healthcare workers also identified significant structural barriers to ART initiation for TB patients, most notably human resource shortages, lack of training, and lack of physical space in which to provide care [38]. Even in an inpatient setting in Tanzania, significant health system barriers to TB/HIV integration were identified by healthcare workers [39].

Data on uptake and timing of ART initiation for children with TB disease are particularly scarce. In the ITART study, 30 ART-naïve children aged 3–18 years were included. Overall, 73% initiated ART either during TB treatment or on completion of TB treatment, yet in some cases, similarly to the adults in the same study, there were significant delays in starting ART [40].

## **VIRAL SUPPRESSION FOR TUBERCULOSIS PATIENTS ON ANTIRETROVIRAL THERAPY**

With the potential for drug–drug interactions, drug toxicity, and challenges to adherence with combined TB treatment and ART, it is important to understand whether virologic outcomes are compromised by concurrent TB treatment. A systematic review of 17 studies found no evidence of a difference in virologic suppression between those on TB treatment and those not on TB treatment at the time of ART initiation [41<sup>■</sup>]. Overall, the random-effects RR for virologic suppression at 11–12 months was 0.99 (95% CI 0.94–1.05). In a recent single study in five Ethiopian health centres, the overall proportion with virologic suppression (<50 copies/ml) at 6 months was similar for participants with and without concurrent TB at the time of ART initiation (71 vs. 72%,  $P=0.74$ ) [42]. In patients unable to tolerate efavirenz in first-line ART, nevirapine remains an option in the absence of alternative drugs, although efavirenz-based ART is associated with superior rates

of virological suppression when coadministered with TB treatment [43].

There are specific issues with combined TB treatment and ART in children, particularly young children using protease inhibitors. In a large hospital programme in South Africa, 92 of 199 children aged 0–8 years were on TB treatment at the time of ART initiation. Overall, TB treatment did not affect the likelihood of achieving virological suppression (proportion with viral load <50 copies/ml at 12 months 63% for TB patients vs. 62% for those without TB) or of experiencing viral rebound over 24 months of follow-up [44].

### MODELS OF TUBERCULOSIS AND HIV SERVICE INTEGRATION

Integration of TB/HIV services is aimed at improving the efficiency and effectiveness of the health system and reducing opportunities for attrition in the cascade of care [45]. It is not clear how integration should be measured, although attempts have been made to develop instruments capable of determining the extent of clinical and organizational integration [45]. This tool was used to evaluate the impact of integration on clinical outcomes in 33 clinics within Cape Town. There was some evidence that, after adjusting for individual-level and clinic-level factors, two of the derived domains of TB/HIV integration (integrated service delivery and care provided by the same clinician) were associated with lower mortality in TB/HIV coinfecting patients [46].

There is a paucity of evidence around how different models of TB/HIV integration might influence retention in care and viral suppression. Encouragingly, two ongoing clinical trials are exploring models of integrated TB/HIV care and the impact on retention in care [47,48]. In the MERGE cluster randomized trial in South Africa, the intervention being studied is a set of clinic-specific activities to optimize integration of TB and HIV services [47]. The Start TB Patients on ART and Retain on Treatment study in Lesotho is testing a multifaceted intervention package incorporated into integrated HIV/TB care – nurse training and clinical mentoring as well as support for patients (health education, adherence support, and financial support) [48].

Integration of TB and HIV services can encompass different models and the organization and delivery of services needs to be context specific and focused on the needs of patients, families, and communities. Colocation of services within health facilities in itself does not necessarily meet the needs of patients if service delivery remains fragmented [45]. As the delivery of HIV treatment and care is increasingly decentralized and moved out of health facilities

into the community, there is a need for research into community-based integrated models of TB/HIV care [49,50,51]. Most of the published evidence about integration focuses on clinical integration, yet there remain significant barriers to higher-level organizational or functional integration of programmes within the broader health system [45,52]. In most settings, HIV and TB programmes remain vertical programmes with separate organizational structures, separate policies and guidelines, separate budgeting, and separate monitoring and evaluation systems. There are often historical and cultural differences between TB and HIV programmes that provide challenges to integration [53,54]. In many countries, HIV and TB programmes are also dependent on funding from international donors and may be somewhat restricted in how services can be developed. Encouragingly, the Global Fund now stipulates that the 41 countries with a high burden of TB–HIV coinfection should submit applications that encompass integrated and joint programming for the two diseases [55].

### CONCLUSION

For TB patients globally, considerable progress will be needed to achieve the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90–90–90 targets by 2020. Strengthening of the HIV treatment cascade for TB patients needs to be coordinated with initiatives to find undiagnosed TB/HIV cases within the health system and more broadly in the community. There is a need for higher quality evidence, combined with economic analysis, to inform the scale-up of efficient TB/HIV services in different settings.

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### Conflicts of interest

There are no conflicts of interest.

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