### HIV and tuberculosis co-infection programmes



#### **KEY POINTS**

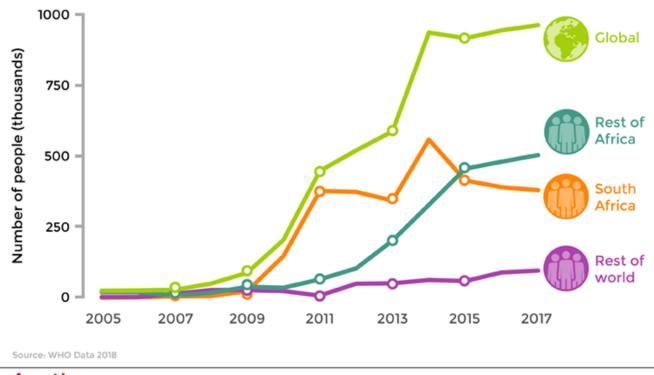
- People living with HIV who have a low CD4 count are at a much higher risk of falling ill from TB infection than HIV negative people.
- It is important to offer both HIV testing to TB patients and TB diagnosis in HIV patients. Early detection and effective treatment are essential to preventing TB-associated deaths.
- WHO and UNAIDS have strongly advised countries to ensure that HIV programmes integrate regular TB screening, preventive therapy and early treatment.

Explore this page to find out more about reducing the burden of HIV in people with TB, reducing the burden of TB in people living with HIV, progress in implementing HIV/TB programmes, funding for HIV/TB programmes, multi-drug resistant TB (MDR-TB) and looking to the future.

Tuberculosis (TB) and HIV are strongly linked. Whereas people with healthy immune systems may not fall ill from latent TB infection (when a person has TB but does not have any symptoms), people living with HIV with a low CD4 count are much more susceptible to active TB (when TB infection leads to illness). In fact, the risk of developing active TB is estimated to be 20 times greater in people living with HIV than in people who are HIV-negative.1

In 2017, 10 million people developed active TB, 9% of whom were also living with HIV.2 According to the World Health Organization (WHO), around one-third of the 36.9 million people living with HIV and AIDS worldwide are co-infected with TB. Sub-Saharan Africa is the hardest hit region, as it is home to 70% of all people living with HIV/TB co-infection in the world.3 4

## Global overview of provision of TB preventive treatment to people newly enrolled in HIV care, 2005-2017



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In 2014, TB surpassed HIV as the world's leading infectious disease killer, a worrying trend for an illness that is essentially treatable and curable. In 2017, 1.3 million people died from TB, and an additional 300,000 TB-related deaths occurred among people living with HIV. 5 It remains the leading cause of death among people living with HIV.

Globally, the proportion of people with HIV/TB co-infection who died during treatment in 2017 was 11%, about three times the level among other people with TB (4%).6 Progress on reducing TB-related deaths among people living with HIV is being made, as the number of deaths declined by 100,000 between 2015 and 2017, mainly due to the rapid expansion of antiretroviral HIV treatment.7 8

The 2016 United Nations Political Declaration on Ending AIDS includes a goal to reduce TB-related deaths among people living with HIV by 75% by 2020. In addition, all countries belonging to WHO and the United Nations have committed to ending TB as a public health problem by 2030. To reach this goal, TB deaths must reduce by 90% and incidence of active TB by 80% from 2015 levels. However, progress towards ending TB is slow, and persistent gaps in preventing, diagnosing and treating TB remain.9

If progress continues to stall, in the next 20 years, almost one billion people will become newly infected with TB, and 35 million people will die of the disease.10

Along with WHO, UNAIDS has called for urgent action on this issue, advising countries to integrate HIV and TB services by ensuring HIV prevention and treatment programmes include regular TB screening, preventive therapy and early treatment.11

### Reducing the burden of HIV in people with

## tuberculosis (TB)

### Increasing knowledge of HIV status

HIV testing and counselling (HTC) is recommended both for those people with diagnosed TB and those with signs and symptoms consistent with TB infection. Combining HIV testing and TB facilities has been shown to increase the uptake of HTC.12

While the rate of testing has increased significantly in the last decade, in 2017, only 60% of people diagnosed with TB had a documented HIV test. Coverage is highest in Africa, where 86% of all TB patients had a documented HIV test result, but this varies between countries.13

#### Starting antiretroviral treatment (ART)

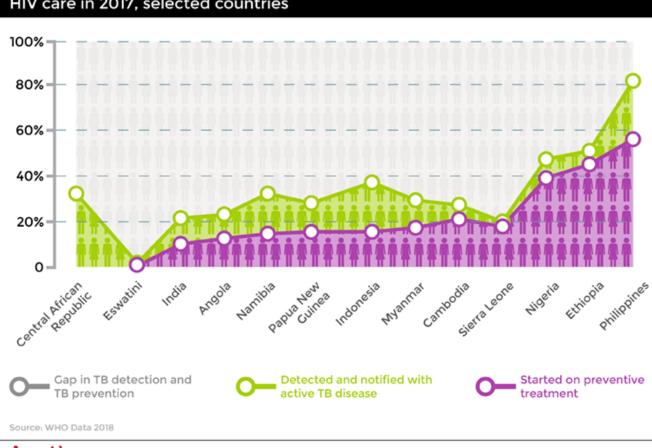
Programmes need to ensure that people with active TB who are diagnosed with HIV begin antiretroviral treatment (ART) as soon as possible, preferably within integrated services or TB facilities.

ART reduces the risk of TB infection in people living with HIV by 65%.14 Data from almost 40,000 patients with HIV/TB co-infection in South Africa showed that people who received ART had almost half the risk of death than others, with particular benefit for those with a CD4 count below 350, which indicates high levels of HIV within the body.15

A national study from Malawi found increased TB prevalence in the country, which began in 1985, to be strongly associated with the advent of HIV, while relative decrease is also linked to the expansion of ART. The study traced the start of the continuous decline in TB in the country to 2005, one year after national scale-up of ART had begun.16

ART also prevents the progression of HIV, reduces the chances of another opportunistic infection that could make management of care more complicated, and reduces the chance of TB recurring. However, treating both conditions at the same time can be challenging because of side effects, pill burden and drug interactions.

In 2017, around 84% of people diagnosed with HIV/TB co-infection were on ART, a significant increase from 36% in 2005.17 In 30 countries with the highest TB/HIV burden in the world, in 2017, 85% of people with TB known to be living with HIV were on ART, and in eight of these countries (eSwatini, Kenya, Malawi, Mozambique, Namibia, Papua New Guinea, Uganda and Tanzania) coverage was more than 90%.18



# Gaps in TB detection and TB prevention for people who were newly enrolled in HIV care in 2017, selected countries

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In contrast, in six high TB/HIV burden countries (Angola, Botswana, Brazil, Guinea-Bissau, Indonesia and Liberia) less than 50% of people with TB known to be living with HIV were started on ART in 2017.19

In Côte d'Ivoire, national care guidelines recommend that people who test positive for HIV are screened for TB and initiated on TB treatment before they begin ART, in line with WHO guidance. Yet a study of more than 3,500 adults starting ART between 2004 and 2007 at 34 health facilities in the country found 'low screening rates overall' with wide variations between facilities. Around 2% of those testing positive for HIV during the study were already on TB treatment; of the remainder, just 36% received some form of TB screening. Of these, 11% were diagnosed with TB and started TB treatment before beginning ART.20

#### Co-trimoxazole preventative therapy

Another important element for people with HIV/TB co-infection is co-trimoxazole preventive therapy (CPT), an agent that prevents a range of secondary bacterial and parasitic infections. Uptake of this daily medication has improved considerably in recent years, reaching 87% of people with TB who also have HIV in 2015.21

A study of primary healthcare clinics in Zimbabwe echoes this, reporting 88% of people diagnosed with HIV and TB co-infection initiated on CPT and 90% initiated on ART. Interestingly, the study found just 38% of people diagnosed with HIV (rather than HIV/TB) were started on ART and 40% on CPT.22

In some countries with high TB prevalence, awareness of CPT remains poor. For example, a study of people living with HIV in Nigeria found 90% had not been made aware of CPT. Of those who had

received CPT counselling, only 19% had adequate knowledge of what CPT was and its benefits.23

### Reducing TB among people living with HIV

It is unacceptable that so many people living with HIV die from tuberculosis, and that most are undiagnosed or untreated. Only by stepping up collaboration between HIV and tuberculosis programmes to accelerate joint action can the world reach its critical HIV and tuberculosis targets.

- Michel Sidibé, Executive Director of UNAIDS24

In 2017, TB caused around one out of every three deaths among people living with HIV.25

Due to the increased susceptibility to TB among people living with HIV, early detection of TB and effective treatment are essential to prevent TB-associated deaths.26 Despite this, around 40% of HIV-associated TB was undiagnosed and untreated in 2017. Although this is an improvement from 2015, when 57% of active TB among people living with HIV was undiagnosed, this substantial gap leads to many unnecessary deaths.27

In 2017, data from countries in which 94% of people diagnosed with HIV/TB co-infection live, reported that 77% of HIV positive people on TB treatment were successful in their TB treatment. However this is still worse than the treatment success rate for TB among HIV negative people, which stands at 82%.28 In the same year, 11% of people with HIV/TB co-infection on TB treatment died, about three times more than the number of HIV negative people with TB who died (4%).29

In order to reduce TB among people living with HIV, WHO recommends an approach known as 'the Six I's' (previously 'the Three I's'). These stand for:

- Intensified case-finding
- Isoniazid preventive therapy
- Infection control
- TB/HIV integration
- Initiating antiretroviral (ARV) treatment
- Involvement of the community.30

A number of these approaches are discussed below.

#### Intensified case-finding

Just as it is important to offer HIV testing to people with TB, it is vital to diagnose active TB in people living with HIV. In 2017, around 464,600 cases of active TB were diagnosed among people living with HIV worldwide. However, this is estimated to be just half of the number of people living with HIV who developed active TB that year.31

All people living with HIV should be regularly screened for TB symptoms, including cough, fever, weight loss or night sweats. If any of these symptoms are present, they may have active TB and

should be further evaluated.

However, appropriate diagnostics are not always available, as TB activist, Blessima Kumar explains:

When I started feeling ill, I was in a small town in southern India. I really couldn't get anyone to diagnose me properly. Then, the doctors put me on treatment anyway — without a confirmed diagnosis. I took the treatment for six months without knowing whether it was TB or not. So getting access to an accurate diagnosis was definitely one of my biggest challenges.32

Historically, TB has been diagnosed by looking for evidence of TB bacteria, either through the use of the chest X-ray through sputum smear microscopy, or through the culturing of bacteria. However, each of these TB tests has their disadvantages. The newer GeneXpert test can dramatically improve case finding and is recommended as the diagnostic test for people living with HIV who have a cough, fever, weight loss or night sweats.33

GeneXpert is a self-contained testing unit that does not require a sophisticated laboratory set-up and can provide results within two hours. Using a sputum sample, the molecular test diagnoses TB by detecting the presence of TB bacteria, as well as testing for resistance to the drug, rifampicin – a likely indication that the individual has multi-drug-resistant tuberculosis (MDR-TB).34

National policies in 93% of the 30 countries with the highest burden of TB in the world have made GeneXpert the primary diagnostic test for MDR-TB, and 80% recommend it as the primary test for people living with HIV.35

For example, Ethiopia and South Africa have made the test available at primary healthcare facilities where it has substantially improved TB diagnosis rates for people living with HIV.36 However, in many other countries the test is restricted to secondary and tertiary healthcare facilities, in large part due to its cost. This means it is primarily used to diagnose MDR-TB, rather than being routinely used for case-finding in patients living with HIV.37

In an attempt to increase access to GeneXpert in low-and lower-middle-income countries, in 2013 UNITAID negotiated an agreement that reduced the cost of GeneXpert cartridge prices by 41% in 145 countries. UNITAID also funded the expansion of GeneXpert in 21 countries. Countries where GeneXpert was introduced on a wide scale reported large increases in TB case detection rates. Those with more limited implementation reported increases in MRD-TB detection rates. Overall, the UNITAID programme resulted in more than 201,500 detected cases of active TB, including 18,850 cases in people living with HIV, and 45,250 detected cases of MDR-TB.38

### Isoniazid preventive therapy (IPT)

In order to prevent cases of latent TB infection (where a person's immune system is able to keep TB under control) from progressing to active TB (causing illness), people with HIV need both prompt initiation of ART and isoniazid preventive therapy (IPT).

The latter intervention involves taking the TB drug, isoniazid, daily for at least six months to prevent progression to active TB. Studies conducted in Brazil and South Africa show an up to 90%

reduction in TB risk among people living with HIV who have latent TB infection, who receive both ART and IPT. $39\ 40$ 

While more recent studies find IPT to be beneficial, researchers have associated it with a smaller risk reduction. For example, a study in Jimma, Ethiopia, found IPT use was associated with a 50% reduction in new cases of TB among people living with HIV who were enrolled in pre-ART care.41 While a study from Indonesia found IPT to be associated with a 79% reduction in TB among people living with HIV.42

A study of more than 18,500 South African gold miners working in areas with high levels of TB and HIV who had undergone IPT found that the therapy's protective effect was lost within 6 to 12 months of the treatment ending. This is one of only a few studies to specifically address the durability of IPT's preventative effects and suggests that persistent latent infection plays a role in the rapid return to TB incidence.43

Provision of isoniazid has grown rapidly since 2008, especially in South Africa. Across the world, around a million people living with HIV received IPT in 2017. Of those, around 640,200 were people newly enrolled on HIV treatment.44 Of the 30 countries with the highest prevalence of TB/HIV in the world, 15 reported providing IPT to people newly enrolled in HIV care in 2017, up from 11 in 2016. Coverage ranged from 1% in eSwatini to 53% in South Africa.45

However, the number of people living with HIV who received IPT remains relatively low when compared to the 21.7 million people with HIV who received ART in 2019.46

One perceived barrier to the expansion of IPT is the fear that people may develop drug-resistant TB as a result of the therapy. However, large trials have shown that drug-resistant TB rates are not higher among those who develop active TB following IPT.47

#### Infection control

Infection control relates to measures in healthcare facilities and other settings where people with TB and people with HIV are frequently crowded together. This is to ensure that people receiving HIV care and the staff providing it are not exposed to TB in the process.

In 2017, around 9,300 healthcare workers from 65 countries were reported as developing active TB. China accounted for 35% of these cases. In six countries (Brunei, Colombia, Dominican Republic, Honduras, Paraguay and Zimbabwe), the number of TB cases per 100,000 healthcare workers was more than double the rate in the general adult population.48 A study examining infection control measure in TB-designated hospitals in Zhejiang Province, China found just under half (49%) were monitoring TB infection control in high-risk areas, 42% had introduced shorter waiting times for people with TB, and 46% provided a separate waiting area for patients with suspected TB. Effective respirators were available in 97% of hospitals, although just half checked these respirators regularly.49

Similarly, a study of infection control measures implemented by facilities in Ugu and Uthungulu health districts of Kwazulu-Natal province, South Africa found levels of relatively low compliance. Overall, 18 out of 37 infection control measures were complied with by around 80% of facilities surveyed.50

### Implementing integrated HIV/TB programmes

Between 2005 and 2017, joint TB/HIV activities saved an estimated 6.6 million lives.51

However, much more needs to done to establish and strengthen the mechanisms within health

systems that enable TB and HIV services to be accessed in one place. Models of TB/HIV integration range from TB clinics referring patients to HIV clinics and vice versa, to full integration where both services are available at a single facility, on the same day, by the same healthcare worker. Although significant progress has been made on this in the past decade, health services do not always work in integrated ways and may even fail to provide screening for common co-infections.52

For example, in South Africa, the Department of Health has developed guidelines and policies supportive for the integration of TB/HIV services. These include testing and counselling for HIV in all people diagnosed with active TB, IPT for people living with HIV who screen negative for TB, CPT for people living with HIV/TB, strategies to support people to be retained in care and stay on treatment, and fully integrated data management (described as 'one patient, one appointment, one file, one data system'). However, a 2017 analysis of primary healthcare in rural South Africa found many of these approaches have not been adopted, resulting in poor integration.53

#### India

India has the highest burden of tuberculosis in the world, a high HIV prevalence, and high rates of HIV-associated TB.54 While the TB epidemic is countrywide, the HIV epidemic is concentrated in a few states.55

In its 2016 Global TB Report, WHO increased its estimates for TB in India for the period 2000 to 2015, from those published in previous reports. This follows accumulating evidence, taken from surveys and routinely collected TB data, that previous estimates of cases and deaths were too low.56 The 2016 report estimated that 2.8 million cases of active TB occurred in 2015. Previously this had been estimated at 1.7 million, suggesting that only 59% of incidence was officially reported originally.57

In 2017, the number of new cases of active TB remained high but relatively stable, at 2.7 million. Around 86,000 of these new TB cases were among people living with HIV.58 In the same year, 11% of people newly enrolled in HIV care in India had active TB, and 11,000 people with HIV died due to TB, equivalent to around 20% to 25% of all annual deaths among people living with HIV.59 60

Around 58% of people with HIV-TB co-infection are estimated not to have reached TB care in 2017.61

India's National AIDS Control Programme (NACP) and the revised National TB Control Programme (RNTCP) have been instrumental in reducing the burden of HIV and TB. Since 2001, they have implemented collaborative TB-HIV activities.62

The national HIV-TB response includes intensified TB case finding in HIV care settings, intensified, integrated TB/HIV packages for patients, and a focus on TB prevention for people living with HIV.63

These activities were initially launched in the six high HIV burden states. The adoption of the national TB/HIV policy framework in 2007 lead to a nationwide scale-up of joint TB/HIV programmes, which was achieved in 2012.64

India HIV/AIDS Alliance (Alliance India) implements the largest national HIV/TB care and support programme, in close coordination with the central TB division, India's National AIDS Control Organization (NACO) and communities most affected by HIV and TB. As part of this, Vihaan Care and Support Centres have been offering community-led, integrated TB and HIV services since 2017, leading to an expansion of services across the country. 65

People living with HIV made almost 11 million visits to ART centres in 2017. In 83% of these visits, people received an evaluation for TB. Of those who were evaluated, 6% had TB symptoms.66

India's experience shows how collaboration can enable the scaling up of TB/HIV programmes and promote shared ownership of interventions. It also demonstrates that political and administrative commitment is critical.67

#### South Africa

South Africa also has a high HIV/TB burden. As of 2017, 60% of people with TB in the country were HIV positive, 193,000 people living with HIV were diagnosed with active TB, and 56,000 HIV-positive people died as a result of TB.68 There is also significant incidence of drug-resistant TB.69

In the past decade, the country has made robust efforts to tackle the two diseases simultaneously. In 2009, TB was integrated into the mandate of the South African National AIDS Council (SANAC) alongside HIV, and a joint national strategic plan was developed.70This policy has stipulated integration of HIV and TB services nationwide, by the co-location of services.

The country's 2017-2022 national strategic plan for HIV, TB and STIs describes South Africa as having 'turned a corner' on integration since 2012. This follows the introduction of various national initiatives including the proactive diagnosis of TB among people living with HIV through the use of GeneXpert technology. The country has also provided integrated HIV/TB services for people in correctional facilities, the mining industry, and communities surrounding gold mines and informal settlements, where transmission of both HIV and TB is high. It is also collecting detailed, localised data on HIV/TB disease patterns, related social and economic factors and the uptake on TB and HIV services. HIV/TB 'hotspots' can then be identified within key districts and integrated services targeted more effectively. As a result, TB treatment success rates among people living with HIV are steadily improving.71

However, there remains significant disparities between provision in various areas due to a lack of staff qualified to address HIV and TB, as well as drug stock-outs, and inadequate infrastructure (such as a lack of private rooms to conduct pre- and post-test counselling).72

### Funding for TB/HIV programmes

In 2017, annual global funding for TB was US\$3.5 billion short of what was required.73

This is calculated by the Stop TB Partnership's Global Plan to End TB (Global Plan), which covers the period 2016-2020. This estimated that, in low- and middle-income countries, US\$10.4 billion was required in 2018, increasing to US\$12.3 billion in 2020, while an additional US\$2 billion per year is needed for TB research and development. However, data reported to WHO suggests US\$6.9 billion was available for TB prevention, diagnosis and treatment in 2018.74

Of the total available in 2018, US\$4.8 billion was allocated to treat patients with active TB that responded to first-line treatment, US\$2.0 billion was allocated for multi-drug resistant TB treatment and the remainder was allocated for TB/HIV interventions.75Although 86% of TB spending in 2018 came from domestic sources, this is strongly skewed by the amount Brazil, Russia, India, China and South Africa spend on their TB responses. In other countries where TB is highly prevalent, international donor funding remains crucial, for example, it accounted for 57% of TB funding in low-income countries in 2018.76 Yet international donor support for the TB response is shrinking: it stood at US\$0.9 billion in 2018, far short of the US\$ 2.6 billion needed. The Global Fund to Fight AIDS, Tuberculosis and Malaria is the single largest source of international funding, providing 74% of the total.77

International donor funding for TB is dwarfed by HIV and malaria funding. The latest data from the Organisation for Economic Co-operation and Development (OECD) shows totals of US\$ 6.8 billion for HIV, US\$1.9 billion for malaria and US\$ 0.9 billion for TB in 2016. To provide some context for

these amounts, the latest estimates (for 2016) of the burden of disease in terms of disabilityadjusted life years lost due to illness and death are 58 million for HIV and AIDS, 56 million for malaria and 44 million for TB.78

Despite having far fewer resources, in 2016, UNAIDS reported that national TB programmes were including more TB/HIV activities than national HIV and AIDS programmes.79 HIV grants have been found to be 59% less likely to fund TB/HIV activities when compared with TB grants.80

Considering the huge overlap between these two infections, funding needs to be scaled-up in order to successfully tackle both TB and  $\rm HIV.81$ 

### Multi drug-resistant TB (MDR-TB)

One of the greatest challenges faced by both TB programmes and joint HIV/TB programmes, is multi drug-resistant TB (MDR-TB) – strains of TB that are resistant to the drugs, isoniazid and rifampicin (the most effective first-line treatment drug for TB).

In 2017, 558 000 people developed TB that was resistant to rifampicin, and of these, 82% had MDR-TB. Three countries accounted for almost half of the world's cases: India (24%), China (13%) and Russia (10%).82

In the same year around 160,680 people initiated treatment for MDR-TB globally, a small increase from 153,120 in 2015.83

Treatment success rates for people with MDR-TB remains low, at 55% globally. However, some countries such as Bangladesh, Ethiopia, Kazakhstan, Myanmar and Viet Nam are providing more effective MDR-TB treatment services, resulting in all having treatment success rates above 70%.84

Among people notified as having MDR-TB in 2017, half also tested positive for resistance to other types of treatment (fluoroquinolones and second-line injectable agents), a significant increase from 39% in 2016. These people are classified as having extensively drug-resistant TB (XDR-TB). A total of 10,800 cases of XDR-TB were reported in 2017, around 200 more than the previous year. Belarus, India, Russia, South Africa and Ukraine accounted for the majority of cases. Those with XDR-TB face an even lower likelihood of treatment success, with only a third (34%) receiving effective treatment.85

The low treatment success for people with drug-resistant TB is largely because patients find it very hard to keep taking second- or third-line drugs, which can be quite toxic, for prolonged periods of time.86

As Ethiopian activist, Endalkachew Fekadu explains, the most widely used treatments for MDR-TB have considerable side-effects:

There were eight pills and an injection each day. They were so toxic, with many adverse effects. I remember my mama waking me up every morning to take me to hospital because sometimes I just vomited all night and became faint.87

After decades without new drugs in the pipeline, an opportunity has arisen to address MDR-TB

more effectively with the introduction of new drugs, which shorten the treatment period from two years to between 9-12 months. WHO now recommends this new drug regimen, along with a rapid diagnostic test that can detect how resistant a patient's form of TB is. It is hoped that these developments will lead to fewer interruptions in treatment and reduce the number of people who are not retained in care. It is important to note that this regimen is not suitable for those with XDR-TB where its use could lead to worsening resistance.88

As of 2017, 68 countries and territories reported that they had started using new regimens bedaquiline and 42 reported that they had started using delamanid to treat MDR-TB.89 However, the cost of treatment for MDR-TB continues to stop many countries from making it widely available. In 2017, the median cost per person with drug-susceptible TB was US\$1,224, compared to US\$7,141 for MDR-TB.90

### TB/HIV co-infection: looking to the future

In 2018, WHO, the Stop TB Partnership, and the Global Fund to Fight AIDS, Tuberculosis and Malaria launched Find.Treat.All, a joint initiative to scale up the End TB response towards universal access to TB prevention and care. The initiative is for the five-year period 2018–2022. It includes a target to diagnose, treat and report 40 million people with TB, including 1.5 million people with drug-resistant-TB, between 2018 and 2022. The initiative encompasses all countries, with priority given to the 30 high TB burden countries and has become a flagship initiative at WHO. The initiative stresses the need for a multisectoral approach to addressing the specific needs of people living with HIV/TB co-infection. 91

The rapid expansion of ART for people living with HIV has helped to improve the health of millions of people, but for those who are still unable to access effective HIV treatment, the risk of developing active TB remains a great risk. These people are often the poorest, most marginalised in society and many face criminalisation that prevents them from accessing healthcare. Until access to HIV treatment improves for these groups, and until HIV and TB services are integrated more effectively, the number of HIV-positive people developing active TB will remain unacceptably high.

Greater political commitment is needed to acknowledge and address HIV/TB co-infection, starting with an increase in funding. Until this happens, countless people living with HIV will continue to die from TB – a disease that is entirely preventable and curable.

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