

Tuberculosis transmission in HIV-endemic settings 1



Advances in the understanding of *Mycobacterium tuberculosis* transmission in HIV-endemic settings

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Tuberculosis claims more human lives than any other infectious disease. This alarming epidemic has fuelled the development of novel antimicrobials and diagnostics. However, public health interventions that interrupt transmission have been slow to emerge, particularly in HIV-endemic settings. Transmission of tuberculosis is complex, involving various environmental, bacteriological, and host factors, among which concomitant HIV infection is important. Preventing person-to-person spread is central to halting the epidemic and, consequently, tuberculosis transmission is now being studied with renewed interest. In this Series paper, we review recent advances in the understanding of tuberculosis transmission, from the view of source-case infectiousness, inherent susceptibility of exposed individuals, appending tools for predicting risk of disease progression, the biophysical nature of the contagion, and the environments in which transmission occurs and is sustained in populations. We focus specifically on how HIV infection affects these features with a view to describing novel transmission blocking strategies in HIV-endemic settings.

Introduction

Despite worldwide vaccination, potent therapeutic intervention, and the development of faster diagnostics, tuberculosis defiantly stands out as the most lethal infectious disease humanity faces today, impacting impoverished communities in developing countries. In Africa, HIV co-infection has remained a key driver of the tuberculosis epidemic for almost two decades, as the two diseases combine to present unique programmatic and treatment challenges.^{1,2} To achieve a rapid reduction in the burden of tuberculosis, new interventions to reduce transmission are needed; however, efforts to develop them have been thwarted by a relatively poor understanding of how transmission occurs and how it is affected by HIV co-infection.³

Successful transmission relies on many factors, including specific features of the index case, the susceptibility of the exposed host, behaviour of bioaerosols, pathogen-inherent factors, and the environment in which transmission occurs.^{4,6} Sustained community-wide transmission also requires certain social mixing elements and the associated movement of infectious bacilli between individuals.⁷ In light of these factors, eliminating transmission depends on the ability to detect and treat infected individuals at high risk of becoming infectious, using new prognostic and diagnostic biomarkers to target preventive and curative therapies. In this Series paper, we review these key features of transmission in the context of HIV co-infection with an outlook to developing novel transmission-blocking strategies. This Series paper represents a synthesis of discussions that took place at a workshop on tuberculosis transmission in HIV-endemic settings, funded by the US National Institutes of Health, South African Medical Research Council, and Bill & Melinda Gates Foundation, in South Africa, May 1–2, 2017.

Why is a focus on tuberculosis transmission important in HIV-endemic settings?

In HIV-endemic settings, the increased risk of active and recurrent tuberculosis due to HIV infection is well established.^{8–10} However, many questions remain about the mechanisms through which HIV affects tuberculosis transmission at the individual and population level, as well as the role of antiretroviral therapy in mitigating this transmission. Increasing attention on vulnerable populations in settings where tuberculosis and HIV are endemic has provided opportunities for identifying concentrated tuberculosis epidemics and, therefore, transmission hotspots or reservoirs.^{11–13} These vulnerable populations include miners, children, migrants, prisoners, sex workers, people who use drugs or alcohol, and people with HIV.^{14–19} Evidence suggesting substantial transmission between these vulnerable populations and the general population also exists.^{20–22} Thus, targeted interventions to reduce transmission in these populations might provide substantial benefit in the fight to improve tuberculosis control in the broader population.^{20,21,23}

Tuberculosis transmission

The increased incidence of tuberculosis concurrent with the surge in the HIV pandemic in sub-Saharan Africa implies noteworthy transmission among HIV-positive individuals.²⁴ Transmission of tuberculosis requires the expulsion of viable tubercle bacilli from an active source case in the form of aerosolised droplet particles.²⁵ These bioaerosols are then taken up by an exposed, susceptible host through the normal breathing process. Following uptake, two scenarios can occur. In the first scenario, bacteria are eliminated with no lasting immunological signature of infection. In the second scenario, a combination of adaptive and innate immunity can

Lancet Infect Dis 2019;
19: e65–76

Published Online
December 13, 2018
[http://dx.doi.org/10.1016/S1473-3099\(18\)30477-8](http://dx.doi.org/10.1016/S1473-3099(18)30477-8)

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This is the first in a *Series* of three papers about tuberculosis transmission in HIV-endemic settings

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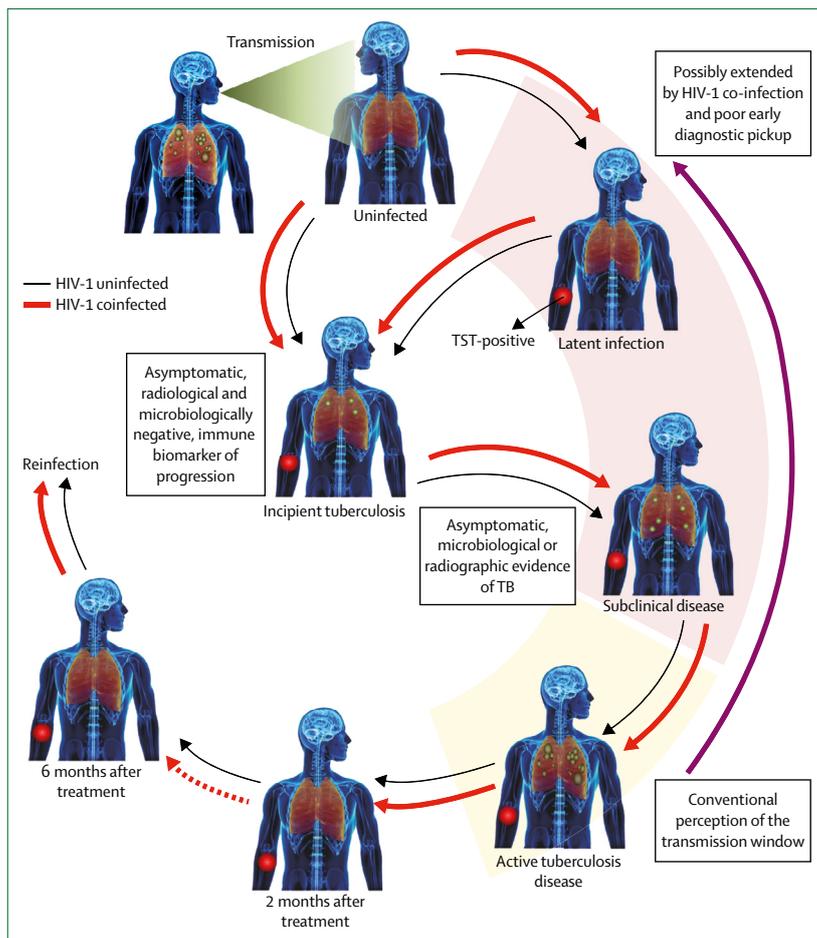


Figure: Effects of HIV-1 infection on the progression of tuberculosis and the transmission window
 Progression to active, pulmonary tuberculosis involves a complex sequence of events that is dependent on initial exposure intensity and the interplay between innate and acquired immunity. Thicker arrows represent an enhanced risk and broken arrows indicate poor progression or reversion to the next or preceding phase. Red arrows indicate the sequence in the case of tuberculosis-HIV infection, with a question mark denoting where the effect of HIV on tuberculosis progression is unclear. The purple arrow represents possible extension of the period in which transmission of tuberculosis can occur. Most cases of exposure lead to the development of asymptomatic latent tuberculosis infection, which is characterised by an immunological response to mycobacterial antigens (using the TST). Latent infection can progress to incipient tuberculosis, which is defined as asymptomatic disease with no radiological or microbiological signs of disease, but can be distinguished from latent infection by an immune biomarker progression from infection to disease. Subclinical disease subsequently develops and is classified as asymptomatic disease associated with either radiological or microbiological confirmation of tuberculosis. In some cases, individuals can spontaneously revert to being TST-negative, reflecting an uninfected state. HIV co-infection alters the dynamics of immune control and can favour progression to infection or incipient tuberculosis in exposed individuals. Whether HIV infection increases the risk of becoming infected with latent tuberculosis infection is unclear. The risk of progression to active pulmonary tuberculosis can also be substantially enhanced in the presence of HIV co-infection. Conventionally, the transmission window (shown in yellow) has been assumed to restrict the development of granulomatous tuberculosis disease, with a high bacterial load and cavities. HIV co-infection can extend this window (shown in pink) by creating a larger proportion of individuals with incipient or subclinical tuberculosis, within whom the propensity to transmit is unclear. Infection with HIV also creates a larger pool of actively diseased individuals who can transmit. Furthermore, HIV infection can result in poor treatment outcomes, owing to extra-pulmonary tuberculosis or drug-drug interactions, resulting in the lack of functional cure, which can lead to continued transmission potential. TST=tuberculin skin test.

ultimately lead to containment of bacteria in the form of latent tuberculosis infection (figure).²⁶ Upon the establishment of infection, several further scenarios can occur. In a small subset of infected people, estimated at

5–10% and much higher for individuals with HIV, containment is lost, resulting in active disease.^{26,27} This active disease can be preceded by a phase of incipient tuberculosis, defined as early asymptomatic disease that is microbiologically and radiologically negative, yet might be identified by an immune biomarker for progression from infection to disease.^{28,29} This state is followed by subclinical disease, defined as asymptomatic, pulmonary disease that is radiologically or microbiologically detectable (figure).²⁹ Progression to active disease results in destruction of infected lung tissue leading to the formation of cavities, which then leak bacteria into the airways, allowing transmission.³⁰ Therefore, the progression and intensity of lung damage in an infected individual will directly affect their transmission potential. HIV co-infection severely alters disease presentation and pathology; however, its effect on tuberculosis transmission remains unresolved.^{1,31–33} HIV infection might enhance the proportion of successful transmission events, leading to infection and disease, and, therefore, has a substantial role in altering transmission dynamics in the community.

The transmission window

The spectrum of disease presentation and pathology suggests that tuberculosis symptoms are likely to develop over a protracted timeframe.^{34–36} Individuals can expectorate organisms before the onset of symptoms³⁵ and might further transmit for months before seeking medical care. This delay in treatment initiation can prolong the transmission window,^{37,38} which is particularly problematic in high-prevalence areas when associated with behaviours that promote transmission to large numbers of people, such as the use of public transport.³⁹ Additionally, after individuals present to the health-care system, delays in diagnosis and initiation of treatment often occur, due to weaknesses in these systems,⁴⁰ which can further extend the transmission window. Whether HIV infection shortens or prolongs the transmission window is unclear (figure).^{41–43}

The effect of HIV co-infection on tuberculosis transmission

Prevailing evidence suggests that HIV is associated with reduced infectiousness for various reasons, including decreased sputum bacillary load, a reduction in cavitory disease, and shorter duration of exposure to others because of a more rapid progression to death or diagnosis (table 1).^{47,48} A meta-analysis on the infectiousness of individuals with HIV showed that overall rates of tuberculin skin test (TST) conversion of household contacts were similar regardless of the HIV serostatus of index cases (odds ratio [OR] 1.04, 95% CI 0.23–1.84). Furthermore, the likelihood of infected contacts developing active disease was also similar regardless of the HIV serostatus of index cases (OR 1.17, 0.78–1.56), suggesting that patients co-infected with HIV and

tuberculosis are not more infectious than their HIV-uninfected counterparts.⁴⁴ A meta-analysis⁴⁹ incorporating 37 studies reported that smear positivity resulted in a higher likelihood of infectivity (adjusted OR 2.15, 1.47–3.17; $I^2=38\%$) and cavitory disease also increased the likelihood (1.9, 1.26–2.84; $I^2=63\%$). Both these attributes are known to be reduced in individuals with HIV, hence in this meta-analysis, the infectiousness of individuals with HIV was reduced (adjusted OR 0.45, 0.26–0.80; $I^2=52\%$).⁴⁹ A study⁴⁵ in Uganda reported decreased infectiousness of HIV-infected tuberculosis index cases with smear-negative tuberculosis or non-cavitory disease, compared with HIV-uninfected tuberculosis cases. However, no difference was observed in infectiousness among HIV-infected tuberculosis index cases who had positive sputum smears or cavitory disease. This finding suggests that disease severity of the index case might modify the infectiousness of those co-infected with HIV and tuberculosis. Furthermore, a study on intravenous drug users revealed that patients with smear-positive pulmonary tuberculosis who were HIV-seropositive were more likely to transmit tuberculosis, suggesting that bacterial load in the sputum is an important indicator of transmissibility, even in the context of HIV.⁵⁰ However, this study assessed smear-positive cases, with no comparison with smear-negative tuberculosis.

In two studies in Peru³² and Botswana,⁵¹ household contacts of patients co-infected with HIV and tuberculosis with low CD4 cell counts had substantially less latent tuberculosis infection compared with household contacts of HIV-negative index cases, suggesting that infectiousness might be reduced in the setting of advanced HIV disease. A depleted CD4 cell count in advanced HIV has been hypothesised to be associated with reduced lung inflammation, leading to a reduction in cavities and sputum bacillary load, both of which affect infectiousness. In support of this hypothesis, in South African mine-workers with HIV, the proportion of patients with lung cavitation increased as CD4 cell counts increased; however, sputum smear bacillary load was not linearly associated with CD4 cell count.⁵² Taken together, these studies suggest that HIV might alter infectiousness in some settings by reducing the probability that individuals develop smear-positive or cavitory disease, and that this effect might be particularly important in the context of advanced HIV disease.

Antiretroviral therapy could have implications for the infectiousness of HIV-positive patients with tuberculosis through the restoration of immune function, which might increase the risk of smear-positive and cavitory disease. However, in a study in South Africa,⁵³ antiretroviral therapy was not associated with increased sputum smear positivity or lung cavitation, indicating that the ability to generate large amounts of bacteria in sputum is driven by a complex array of factors. A recent household contact study⁴⁶ in Malawi of patients with HIV

	Relative risk* (95% CI)	Adjusted relative risk* (95% CI)
Cruciani et al⁴⁴		
HIV negative	1 (Ref)	..
HIV positive	0.66 (0.60–0.72)	..
Huang et al³²†		
HIV negative	1 (Ref)	1 (Ref)
HIV positive with a CD4 count ≥ 250 cells per μL	0.9 (0.6–1.3)	0.9 (0.5–1.5)‡
HIV positive with a CD4 count < 250 cells per μL	0.6 (0.4–1.1)	0.5 (0.3–0.9)‡
Martinez et al⁴⁵†		
HIV negative with smear positivity	1 (Ref)	1 (Ref)
HIV positive with smear positivity	0.94 (0.86–1.04)	0.93 (0.85–1.01)‡
HIV negative with smear negative results	1 (Ref)	1 (Ref)
HIV positive with smear negative results	0.75 (0.63–0.90)	0.76 (0.64–0.90)‡
HIV negative with cavitory disease	1 (Ref)	1 (Ref)
HIV positive with cavitory disease	1.07 (0.97–1.17)	1.03 (0.96–1.12)‡
HIV negative with non-cavitory disease	1 (Ref)	1 (Ref)
HIV positive with non-cavitory disease	0.75 (0.65–0.87)	0.74 (0.65–0.85)‡
Khan et al⁴⁶†		
HIV negative	1 (Ref)	1 (Ref)
HIV positive with ART for ≥ 1 years	0.3 (0.1–0.9)	0.4 (0.1–1.3)§
HIV positive with no ART or ART < 1 year	0.2 (0.1–0.7)	0.5 (0.2–1.3)§
TST=tuberculin skin test. Ref=reference. ART=antiretroviral therapy. *Measures of association here represent the relationship between positive TST results in household contacts exposed to HIV-negative index cases and household contacts exposed to varying types of HIV-positive index cases (high CD4 cell count vs low CD4 cell count; cavitory vs noncavitory tuberculosis disease; antiretroviral therapy vs no or recent antiretroviral therapy). All crude models here are adjusted for household clustering while Huang et al ³² is also adjusted for age of the household contact. Martinez et al ⁴⁵ and Huang et al ³² use modified Poisson regression models to derive relative risks whereas Khan et al ⁴⁶ calculated crude and adjusted odds ratios. Khan et al ⁴⁶ reported odds ratios with HIV, no ART, and ART less than 1 year as the reference category, not HIV-negative index cases as is shown here. Odds ratios shown here were kindly supplied by the authors. †A positive TST was defined as an induration reaction of 10 mm or more for all three recent studies. For Huang et al ³² a positive TST for household contacts that were HIV-positive was differentially defined as an induration reaction of 5 mm or more. Khan et al ⁴⁶ included only child household contacts 2–10 years of age whereas Huang et al ³² and Martinez et al ⁴⁵ included contacts of all ages. ‡Adjusted for age, education level, and alcohol status of the household contact; sputum smear and cavitory status of the tuberculosis case; and the number of individuals in the household. §Adjusted for age, sex of the household contact; degree of exposure of the household contact to the index case; sputum smear, age, and sex of the tuberculosis index case; whether index case was the mother of the contact, number of adults in household, household clustering; household socioeconomic status; and duration of symptoms.		
Table 1: Select studies investigating the differential infectiousness of tuberculosis patients based on their HIV status and determined by a positive TST in household contacts of tuberculosis cases		

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	TST or IGRA	Resistance or susceptibility	Possible mechanism
Chromosomes 2 and 5			
	TST	Resistance	Unresolved ⁸²
<i>IL10</i> haplotype		Resistance	Low circulating interleukin-10 concentrations ⁸³
11p14			
TST1	TST	Resistance	Controls lack of TST response ^{84,85}
5p15			
TST2	TST	Resistance	Controls extent of TST response ⁸⁴
6p25			
<i>DRB1/DQA1</i>	TST	Susceptibility	TST-positivity ⁸⁶
11p14			
TNF1	TST	Resistance?	Controls TNF production upon exposure to BCG ⁸⁷
<i>ULK1</i>	TST	Susceptibility	Role in TNF production ⁸⁸
<i>TOLLIP</i>	TST	Susceptibility	Role in TNF production ⁸⁹
<i>IL9</i>	TST	Resistance	Mast cells ⁹⁰
8q12-q22			
	IGRA	Resistance	Interferon- γ production on BCG exposure ⁹¹
3q13-q22			
	IGRA	Resistance?	Interferon- γ production on BCG and ESAT-6 exposure ⁹¹
ZXDC	IGRA	Resistance?	Interferon- γ release in response to ESAT-6 ⁹²
Question marks denote instances in which an intermediary genotype was mapped that was likely linked to resistance. TST=tuberculin skin test. IGRA=interferon- γ release assay. TNF=tumour necrosis factor. ESAT-6=early secreted antigenic target of 6 kDa.			
Table 2: Summary of host genetic factors that affect outcome of tuberculosis transmission by chromosome region			

and tuberculosis found no difference in infectiousness between those on and off antiretroviral therapy (table 1). This study, however, did not measure CD4 cell counts.⁵⁴ Because antiretroviral therapy has rendered HIV infection a chronic disease, the sheer number of individuals with HIV and tuberculosis, and the length of time that they remain in the community, might be sufficient to contribute substantially to the overall tuberculosis burden.⁵⁵ Further research is needed to elucidate the effect of antiretroviral therapy on tuberculosis transmission dynamics in settings with a high burden of both HIV and tuberculosis.

An alternate explanation for why individuals with HIV and tuberculosis seem to infect fewer close contacts is that people with HIV receiving antiretroviral therapy might be diagnosed with tuberculosis sooner, owing to increased contact with the health-care system. Because antiretroviral therapy is a lifelong treatment, regular follow-up visits offer intensified tuberculosis case finding and prompt treatment, reducing the risk of transmission at a population level.⁵⁶ As HIV epidemics continue to

mature, and because of uncertainties concerning the effects of further uptake of antiretroviral therapy, additional studies are needed to improve understanding of tuberculosis transmission in HIV-endemic settings.⁵⁷

The effect of HIV on susceptibility to tuberculosis

The effect of HIV infection on the risk of developing active tuberculosis is unmistakable, often shown by increased estimates of HIV prevalence among individuals with tuberculosis compared with those without it.^{58,59} A study⁶⁰ among South African gold miners showed a marked increase in HIV prevalence accompanied by a quadrupling of annual tuberculosis case-notification rates during the same period. The association between HIV and susceptibility to tuberculosis infection, rather than disease progression, is more difficult to show, although suggested when recent tuberculosis transmission can be proven. A study⁶¹ in a Catalanian prison with a high proportion of individuals with HIV indicated recent transmission rather than reactivation of latent infection as a driver of tuberculosis incidence. A meta-analysis⁶² of active tuberculosis incidence in individuals with HIV showed that rates were higher in individuals with lower CD4 cell counts, which was dependent on the tuberculosis burden in the immediate community, suggesting that reduced immunity enhances acquisition of latent tuberculosis infection.

Another observation of interest is the high amounts of tuberculosis recurrence among patients in settings with high burdens of tuberculosis and HIV, reported among 5–20% of patients who have completed tuberculosis treatment.^{63–66} Several molecular epidemiological studies^{67–71} in these settings found that the prevailing underlying mechanism for this recurrence depends on the time since the end of treatment. Relapse is more common in the first year, and is superseded by re-infection thereafter.^{67–71} HIV infection was strongly associated with increased risk of reinfection in three of four studies.^{63,65,68,70} Tuberculosis incidence is substantially reduced in HIV-positive individuals starting antiretroviral therapy with CD4 counts greater than 500 cells per μL .^{72,73} Coupled with early detection, prompt initiation of antiretroviral therapy is strongly protective, reducing the risk of active tuberculosis in HIV-infected children.⁷⁴

Host genetic factors that modulate susceptibility to infection

Susceptibility to tuberculosis infection is primarily determined by assessing immunological response to the *Mycobacterium tuberculosis* complex. CD4+ T cell acquired immunity against mycobacterial antigens has been relied on disproportionately, either by the TST or interferon- γ release assays (IGRAs). In patients with HIV, these assays are less sensitive, which reduces their negative predictive value in high-transmission settings.⁷⁵ The presence of apparently infection-resistant individuals, termed resistors, is historically well documented in HIV-negative

individuals.^{76,77} By contrast, the effect of HIV-positive infection resistors on tuberculosis transmission is understudied. Because HIV-positive individuals display significantly increased susceptibility to tuberculosis infection,⁷⁸ the virus clearly abrogates crucial host resistance mechanisms.

In HIV-negative individuals, a contribution of host genetic factors to TST and IGRA reactivity has been shown,^{79–81} leading to studies aimed at identifying mediators of resistance to infection (table 2). A genome-wide linkage analysis⁸² of TST-negativity in Uganda identified protective determinants on chromosomes 2 and 5. Another candidate gene study in west Africa implicated an *IL10* haplotype associated with low circulating concentrations of the interleukin-10 cytokine with *M tuberculosis* infection resistance.⁸³ A genome-wide linkage study in Cape Town, South Africa, linked TST negativity to a major locus termed *TST1* in the 11p14 band. TST response was linked to another locus termed *TST2* in the band 5p15.⁸⁴ The *TST1* locus was confirmed in a second independent sample from Paris, France,⁸⁵ and was indistinguishable by genetic mapping from an independently mapped locus named *TNF1*,⁸⁷ which controls production of tumour necrosis factor (TNF) in response to BCG vaccination. These findings suggest that resistance to infection might be linked to the secretion of TNF, a well established antituberculosis effector molecule. Implication of TNF in infection resistance is supported by the observation of genetic variants in the *ULK1* and *TOLLIP* genes as risk factors for TST-positivity.^{88,89} Unc-51-like autophagy activating kinase 1 is involved in the regulation of TNF secretion whereas Toll-interacting protein is part of the Toll-like receptor signalling cascade leading to TNF production.

A 2017 study,⁹⁰ focusing on a small sample of HIV-positive individuals who remain uninfected in the presence of documented tuberculosis exposure, reported strong genetic association with the degree of TST positivity near the *IL9* gene. This finding implicated mast cells in infection resistance, which is an attractive proposal because *IL9* variants have previously been associated with pulmonary hyper-responsiveness.⁹⁰ Although the main locus appears specific for patients with HIV, the study also detected the loci on chromosomes 2 and 5 previously identified in patients without HIV.

Genome-wide linkage analyses in HIV-negative individuals identified two major loci: one on chromosome region 8q12–q22, which affected interferon- γ production following stimulation of whole blood with live BCG, and a second on 3q13–q22, which was implicated in interferon- γ release following stimulation with arly secreted antigenic target of 6 kDa (ESAT-6; table 2).⁹¹ The association of chromosome 3 with interferon- γ production through the *ZDXC* gene has been confirmed in a separate study.⁹² These preliminary findings underscore the need for more comprehensive analysis of protective genomic biomarkers.

Moreover, in people who do not resist infection, but contain it in the form of a latent infection, biomarkers for identifying individuals who are likely to lose bacterial containment and progress to disease would be of tremendous use in targeting preventive therapy.

Transcriptomic biomarkers for early diagnosis and screening for prevention of transmission

There is now a growing realisation that individuals with asymptomatic and undiagnosed subclinical disease might also contribute to transmission.^{35,36,93} This possibility raises the question as to whether all individuals with latent tuberculosis infection should be treated preventively to interrupt the cycle of transmission. However, in high-incidence HIV–tuberculosis-endemic settings where force of infection can exceed 10% per year, with between 60–80% of adults infected, such an approach would not be feasible.⁹⁴ Rather, attention has shifted to identification of individuals who are at high risk of imminent progression from latent tuberculosis infection to disease, which could provide an opportunity for targeted intervention.^{28,29}

Studies have described prognostic, transcriptomic signatures of risk for tuberculosis progression that might identify a state of incipient or subclinical tuberculosis, which is clinically indistinguishable from latent tuberculosis infection but differentiated on the basis of an evolving host RNA signature.^{29,95} A 16-gene tuberculosis risk classification model, or correlate of risk (COR), was identified within a study of more than 5000 South African adolescents and validated using a quantitative real-time PCR platform to allow high volume testing in a research setting.⁹⁵ The COR was able to discriminate between adults without HIV who would or would not progress to active tuberculosis with 66% sensitivity and 80% specificity for disease occurring within 12 months of testing.⁹⁵ A number of diagnostic transcriptomic signatures have also been described in people with or without HIV.^{96–99} When applied to published microarray data from diagnostic studies of tuberculosis, the COR shows an area under the receiver operating characteristic curve ranging from 0.86 to 0.99 for discrimination between active tuberculosis and latent infection or uninfected individuals.⁹⁵ These performance characteristics suggest that a biomarker-targeted screen-and-treat strategy might be feasible, using the COR to triage individuals for definitive sputum investigation, followed by curative therapy for those who are sputum-positive or preventive therapy for those who are sputum-negative; and a negative COR result to identify those who need no intervention.¹⁰⁰ Inclusion of individuals with HIV in such a strategy is crucial for effectiveness in endemic countries.

Studying the process of transmission: aerobiology and the effect of HIV infection

Current knowledge regarding airborne transmission of tuberculosis has been built on the pioneering studies of

Richard Riley and colleagues done nearly 70 years ago.^{101,102} Vented air from patients with pulmonary tuberculosis was shown to produce tuberculosis infection in guineapigs and the concept of infectious quanta was developed by defining the infectious dose required to produce an infection in a guineapig. The numerical value of quanta of infection was defined within a specific animal study incorporating many parameters, including particle size, environmental conditions, sampling volume, ventilation rate, lung deposition fraction, and time-dependent bacterial survival.¹⁰³ More recent experimental measurements of bioaerosol infectivity have shown a wide variation in infectivity between individuals diagnosed with tuberculosis. Riley and colleagues¹⁰² reported that bioaerosols from eight (13%) of 61 patients with tuberculosis could infect guineapigs with an estimated mean infectious dose production of 1.25 per h. Similar studies have been extended to encompass individuals with HIV. In Peru, a study of tuberculosis ward admissions,¹⁰⁴ all of whom had HIV infections, revealed a substantial variation in infectiousness. In a subsequent study of ward admissions (82% HIV-positive), only a small proportion of HIV-infected multidrug-resistant cases were responsible for 90% of infection transmitted to guineapigs.¹⁰⁵ These observations point to drug resistance and poor treatment as substantial drivers of the transmission potential of patients co-infected with HIV and tuberculosis. However, pathogen-related factors might be important in transmission, because various animal models of tuberculosis disease have shown that some strains are more transmissible than others.^{106,107}

Studies of surfactant concentrations in exhaled bioaerosols have shown that different respiratory activities generate bioaerosols from different airway regions.¹⁰⁸ Cough generates particles from the large airways and deep sighs (exhalation after deep inspiration) generate particles from the peripheral airways. A strong cough will lead to a wider trajectory, particularly of large particles derived from the trachea and large airways. Exhalation after deep inspiration will produce larger numbers of small particles derived from the peripheral lung spaces, which will remain airborne for longer. How HIV infection affects the strength and frequency of respiratory manoeuvres remains an unresolved question. HIV co-infection and reduced CD4 cell counts might also affect the architecture of the tuberculosis-infected lung and affect bioaerosol particle production. Monitoring cough strength and frequency, together with bioaerosol quantity and particle composition, in individuals with or without HIV infection could help in the identification of infectious individuals and in the implementation of measures for preventing tuberculosis transmission.^{109–111}

Bioaerosol characterisation of 34 newly diagnosed untreated tuberculosis cases (50% of whom were HIV-co-infected) in a respiratory aerosol sampling chamber revealed that total bioaerosol production was found to vary between 50 nL and 500 nL per L of

exhaled air.¹¹¹ Electron microscopy of impacted bioaerosol samples showed multiple structures of less than 5 µm consisting of organic material and the infrequent observation of bacilli-like structures.¹¹¹ Fennelly and colleagues¹¹² isolated *M tuberculosis* colony forming units (CFUs) during 5 min of forced coughing from 27.7% of patients with a mean of 16 CFUs and a wide distribution that varied from one CFU to 701 CFUs. A follow-up study of patients showed that isolation of coughed aerosols positive for *M tuberculosis* was associated with ongoing household transmission of tuberculosis, suggesting that the presence of CFUs was necessary for transmission.¹¹³ Similarly, Pattersen and colleagues¹¹¹ isolated *M tuberculosis* CFUs from 42.8%, and a combination of DNA and CFUs from 77%, of newly diagnosed tuberculosis patients using a respiratory aerosol sampling chamber. Because patients co-infected with HIV and tuberculosis have lower lung bacterial loads,⁴⁹ these observations suggest that bioaerosols from these patients are likely to harbour fewer culturable bacilli.

Differences in the proportion of patients identified with culturable bacilli in their bioaerosols could in part be due to low sensitivity and the volume of bioaerosol sampled. Considering this factor, a combination of highly sensitive detection and large air sampling volumes will be required to detect patients with low infectivity, such as individuals that are sputum-smear negative, with HIV co-infection and low CD4 cell counts. An alternate explanation for the varying amounts of CFUs detected could be that the tubercle bacilli in bioaerosols adopt a differentially culturable state. Several studies have highlighted the presence of a population of differentially culturable tubercle bacilli in the sputum of treatment-naïve individuals.^{114,115} These organisms are unable to grow on plates but can be recovered in liquid media supplemented with culture filtrate as a source of growth-stimulatory molecules.^{114,115} Whether such organisms are present in bioaerosols and whether they are important for the transmission process remains an open area for future study. Further study of this area is important because individuals with low CFUs might contribute to endemic tuberculosis transmission in crowded, poorly ventilated environments.¹¹⁶

Transmission of tuberculosis in the community and institutional amplifiers

Achieving a clear understanding of where tuberculosis is transmitted and between whom, remains an issue owing to the aforementioned key attributes of tuberculosis. In this regard, molecular epidemiological tools, such as genotyping with IS6110 elements or whole-genome sequencing, have allowed for greater understanding of transmission dynamics in the community.^{117,118} A particular problem with tuberculosis is the prolonged and highly variable duration of infectiousness, providing numerous opportunities for transmission, combined with airborne infection, which can occur without close

contact. As a result, in endemic settings, only a small minority of transmission events can be linked between individuals using social network or molecular epidemiological methods.^{7,117,119} Several studies have identified high-risk environments for transmission potential in high-HIV-burden settings by mapping social interactions, including age-specific mixing patterns, in various private and public environments, as well as integrating data for ventilation in these settings.^{7,120,121} These studies have implicated bars, schools, workplaces, and public transport as sites for transmission potential. In this context, targeting interventions to populations within institutions that might drive tuberculosis transmission has emerged as a promising avenue for tuberculosis control.^{11,20,23,121}

Institutional amplifiers or reservoirs of tuberculosis transmission are settings where disease and transmission are concentrated within communities.¹²² These institutions or locations are typically characterised by environments that are highly conducive to tuberculosis transmission, including large amounts of indoor contact, poor ventilation, comorbidities affecting risk of infection or disease, and poor access to timely diagnosis and treatment. Several types of institutional drivers have been described in the published literature including mines, hospitals, prisons, slums, and homeless shelters.^{123–125} Many of these institutions are also highly endemic for HIV infection.^{123–125}

Prisons have been consistently identified as having high burdens of tuberculosis throughout the world, from low-income to high-income countries.^{13,21,126,127} A systematic review¹³ found that tuberculosis incidence rates in prisons were a median of 23 times greater than that of their reference populations. Crowding, poor ventilation, malnutrition, poor access to tuberculosis care, HIV co-infection, smoking, and drug use have all been cited as common factors driving the extraordinarily high incidence of tuberculosis infection and disease reported in prisons globally. Although prisons can account for less than 10% of tuberculosis cases in the general population from low-income and middle-income countries,^{21,22} their effect on community tuberculosis rates might be underestimated owing to disease that occurs after release from prison, driving spillover of tuberculosis from prisons into communities.¹²⁸ This effect was shown in the context of a large tuberculosis outbreak in the USA in the mid-1990s, where tuberculosis cases in the community genotypically matched those seen in prisons.^{129,130} A study from Brazil showed that a quarter of community tuberculosis cases occurred in ex-prisoners, and that over half of the remaining cases were genetically linked to strains observed among prisoners.²⁰ A study from Moldova¹³¹ found that multidrug-resistant tuberculosis in the community was geographically concentrated in areas with high numbers of former prisoners. This finding suggests that prisons in eastern Europe, which are known to be sources of transmission of drug-resistant

Panel 1: Key knowledge gaps

- Does antiretroviral therapy increase the infectiousness of HIV-positive tuberculosis cases?
- How does HIV infection modulate the risk of reinfection or relapse in individuals with a history of tuberculosis treatment?
- What are the optimal ways to measure tuberculosis transmission and re-infection at the individual and population level?
- Are genetic determinants of infection resistance altered in HIV-infected tuberculosis cases?
- Will early detection of subclinical disease in HIV-infected and uninfected cases improve linkage to care and reduce transmission?
- How does HIV infection alter the manifestation of pulmonary disease and the capacity of diseased individuals to transmit?
- What proportion of tuberculosis cases in the general population are attributed to different institutional amplifiers (eg, mines, hospitals, prisons)?
- What interventions can be directed towards institutional amplifiers to lower the intra-institution high force of infection and subsequently prevent future community cases?

Panel 2: Urgent unmet needs

- Development of technologies to distinguish patients at high and low risk for transmitting tuberculosis, and patients at high risk for tuberculosis infection and subsequently at high risk for progressing to active tuberculosis disease, based on both host and bacillary characteristics.
- Determine optimal methods to evaluate interventions intended to halt tuberculosis transmission in HIV-endemic settings, which requires improvements in tuberculosis programme monitoring capabilities and application of appropriate modelling strategies.
- Further integration of HIV and tuberculosis programmes in sub-Saharan Africa and other areas with substantial burdens of both HIV and tuberculosis. Programmatic practices that are useful for integration include HIV testing for individuals at high risk of tuberculosis, infection control in areas with large amounts of tuberculosis, initiation of antiretroviral therapy, providing isoniazid preventive therapy to all HIV-positive patients exposed to tuberculosis, and intensified tuberculosis case finding.

tuberculosis,^{127,132} might be contributing to the spread of multidrug-resistant tuberculosis upon prisoner release. Despite these results, the amount of tuberculosis that is attributable to prisons might be, at least partly, dependent on setting-specific features, such as the overall prisoner population, contact between prisoner or ex-prisoner populations and the general community, and average duration of incarceration. Further study is needed to determine whether, and to what extent, tuberculosis in prisons leads to meaningful spillover into the general population.

Mines in sub-Saharan Africa have very high tuberculosis transmission rates due to crowding in poorly ventilated environments, exposure to silica dust, high HIV prevalence, and low socioeconomic status.^{133,134} The seasonal migratory patterns of miners put the general population at substantial risk for spillover of tuberculosis transmission from mines. In one study,¹³⁵ the number of

Search strategy and selection criteria

We searched PubMed for articles in English only with the search terms “Tuberculosis”[Mesh] AND “HIV”[Mesh] AND “transmission”, which returned 99 results. After reviewing the results for relevance, we generalised the PubMed search with the terms “Tuberculosis”[Mesh] AND “HIV”[Mesh] only, which returned 2163 results. We reviewed results from the previous 5 years, with additional review of references from relevant manuscripts.

mines in a population was directly correlated with population tuberculosis incidence, prevalence, and mortality. Similarly, health-care facilities have been recognised as institutional drivers of tuberculosis for more than a century. Nosocomial transmission was identified as a key driver of multidrug-resistant tuberculosis outbreaks in New York, NY, USA, in the 1990s;^{136,137} more recently, extensively drug-resistant-tuberculosis was associated with large hospital outbreaks in South Africa.^{118,138,139} In both settings, HIV co-infection had a major role. Recent reports have found that programmatically incurable patients with extensively drug-resistant-tuberculosis, the vast majority of whom are HIV-positive, from hospital settings are released back into the community, possibly contributing to further transmission.¹¹⁸

Understanding institutional amplifiers and how HIV infection interplays with this notion could lead to more efficient deployment of interventions. Using a mathematical model and tuberculosis incidence data across Rio de Janeiro, Brazil, Dowdy and colleagues¹⁴⁰ showed that interventions targeted at a few high-burden slums, containing just 6% of the city’s population, could have the same overall effect as achieving tuberculosis control in the remaining population. To understand the potential for institutions or settings in serving as important amplifiers of tuberculosis incidence at the population level, several key attributes must be understood. These attributes include the relative size of the high-risk population compared with the overall population, the relative incidence of latent tuberculosis infection and disease (for which HIV is an important factor), the level of inflow and outflow migration from the institution or setting and the general population, and the degree of social mixing between members of the institution and the general population after rejoining society. Among these attributes, perhaps the most challenging to estimate are the amounts of contact between the high-risk population and the general population. Molecular epidemiological studies might provide one avenue for understanding transmission between these groups.

Conclusions and future directions

Transmission of tuberculosis remains a multifaceted, poorly understood process that is further complicated by HIV infection, which affects the ability of individuals to

transmit, while creating a large pool of highly susceptible individuals that can further transmit tuberculosis in the community setting. Understanding the effect of antiretroviral therapy on the infectiousness of individuals with HIV and tuberculosis, together with determining how HIV infection modulates the risk of re-infection or relapse in individuals with a history of tuberculosis, should feature as an important and immediate priority (panel 1). Intensifying integration of HIV and tuberculosis control programmes is also likely to have an impact on reducing diagnostic delays, increasing early case detection, providing prompt treatment onset, and ultimately reducing transmission (panel 2). Effort should also be focused on investigating the proportion of tuberculosis cases in the general population that are attributable to institutional amplifiers, and what interventions can be directed towards these amplifiers to lower the high intra-institution force of infection and subsequently prevent future community-based cases. Collectively, a greater focus on reducing transmission promises to provide substantial gains in controlling tuberculosis.

Contributors

JSP and BDK compiled the first draft with input from all authors. All authors were involved in conceiving the overall structure of the review, undertaking literature searches, and critically revising drafts.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Thomas Scriba for his critical evaluation of the manuscript. This publication and workshop have been funded in whole or in part with Federal Funds from the Division of AIDS, National Institute of Allergy and Infectious Diseases, US National Institutes of Health (NIH), Department of Health and Human Services under contract number HHSN272201600001G Research Support Services for the Division of AIDS. Funding support was also provided in part by NIH grants to JRA (K01 AI104411, R01 AI30058 and DP2 AI131082), LM (T32 AI 052073), ES (R01 AI124349), and YvdH (K08 AI106420). BDK was supported by funding from an International Early Career Scientist Award from the Howard Hughes Medical Institute and the South African National Research Foundation. JSP, MH, RW, and BDK were supported by the South African Medical Research Council with funds received from the National Department of Health. The authors acknowledge support from the Bill & Melinda Gates Foundation to MH (OPP1137034 and OPP1151915), SH (STBP/TBreach/GSA/W5–29), BDK (OPP1100182), JSP, and RW (OPP116641). SH receives salary support from the Stop TB Partnership’s TB REACH initiative co-funded by the Government of Canada. LM was supported by the Ruth L Kirschstein National Research Service Award. ES was supported by the Canadian Institutes of Health Research (FDN-143332). YvdH was supported by the US Civilian Research and Development Foundation (OISE-16–62061–1). The South African Medical Research Council co-hosted the workshop. The Gates Foundation and NIH provided funding support for some participants travel to the workshop. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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