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

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Summary

Tuberculosis claims more human lives than any other infectious disease. This alarming epidemic has fueled 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, bacteriologic, and host factors among which concomitant HIV infection is of critical importance. Preventing

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BK and JP 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 Interest

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person-to-person spread is central to halting the epidemic and consequently, tuberculosis transmission is now being studied with renewed interest. Herein, 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 wherein transmission occurs and is sustained in populations. We focus specifically on how HIV infection affects these aspects with a view to describing novel transmission blocking strategies for HIV-endemic settings.

Background

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, wreaking havoc on impoverished communities in the developing world. In Africa, HIV co-infection has remained a key driver of the tuberculosis epidemic for almost two decades as the two diseases synergize 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 these have been thwarted by a relatively poor understanding of how transmission occurs and how this process is affected by HIV co-infection.[3]

Successful transmission is reliant on many factors, including specific features of the index case, the susceptibility of the exposed host, behavior of bio-aerosols, pathogen inherent factors, and the environment wherein 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 this, eliminating transmission depends on the ability to detect and treat infected individuals at highest risk of becoming infectious, using new prognostic and diagnostic biomarkers to target preventive and curative therapies. Herein, we review these key features of transmission in the context of HIV co-infection with an outlook to developing novel transmission blocking strategies. This review represents a synthesis of discussions that took place at an NIH/SAMRC/Bill and Melinda Gates Foundation-funded workshop on tuberculosis transmission in HIV-endemic settings 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, as well as the influence of antiretroviral therapy (ART) in mitigating this effect, at the individual and population level. Increasing attention on vulnerable populations in tuberculosis and HIV-endemic settings 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 living with HIV.[14–19] There is also evidence suggesting substantial transmission between

these populations and the general population.[20–22] Thus, targeted interventions to limit transmission in these populations may provide substantive benefit in the fight to improve tuberculosis control in the broader population.[20,23,24]

Tuberculosis transmission

The increase in the incidence of tuberculosis concurrently with the surge of the HIV pandemic in sub-Saharan Africa implies noteworthy transmission among HIV-positive individuals.[25] Transmission of tuberculosis requires the expulsion of viable tubercle bacilli from an active source case in the form of aerosolized droplet particles.[26] These bio-aerosols are then taken up by an exposed, susceptible host through the normal process of breathing. Following uptake, two scenarios can occur. The first is elimination of bacteria with no lasting immunological signature of infection. Alternatively, a combination of adaptive and innate immunity can ultimately lead to containment of bacteria in the form of latent tuberculosis infection (LTBI, figure 1).[27] In a small subset estimated at 5–10%, and much higher for HIV-infected individuals, containment is lost, resulting in active disease.[27,28] This can be preceded by a phase of incipient tuberculosis, defined as early asymptomatic disease that is microbiologically and radiologically negative, yet may be identified by an immune biomarker for progression from infection to disease.[29,30] This state is followed by subclinical disease, defined as asymptomatic, pulmonary disease that is radiologically/microbiologically detectable (figure 1).[30] Progression to active disease results in destruction of infected lung tissue leading to the formation of cavities, which then leak bacteria into the airways to allow for transmission.[31] Considering this, the progression and intensity of lung damage in an infected individual will directly affect their transmission potential. HIV coinfection severely alters disease presentation and pathology; how this affects the ability to transmit remains unresolved.[1,32–34] HIV infection may enhance the proportion of successful transmission events, leading to infection and/or disease, and thus plays a significant role in remodeling 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 time frame, rather than during a small window.[35–37] Individuals may expectorate organisms prior to the onset of symptoms[36] and may further transmit for months before to seeking medical care. This delay in treatment initiation can prolong the transmission window.[38,39] This is particularly problematic in high prevalence areas when associated with social tendencies that promote transmission to large numbers of people such as the use of public transport.[40] Additionally, after individuals present to the healthcare system, there are often delays in diagnosis and initiation of treatment, due to weak health systems,[41] which can further extend the transmission window. It is unclear whether HIV infection shortens or prolongs the transmission window (figure 1).[42–44]

The source case and transmission: Impact of HIV co-infection

Prevailing evidence suggests that HIV is associated with reduced infectiousness for various reasons, including decreased sputum bacillary load, a reduction in cavitary disease, and

shorter duration of exposing others due to more rapid progression to death or diagnosis[45,46] (table 1). A meta-analysis on the infectiousness of HIV-infected individuals demonstrated that overall rates of tuberculin skin test conversion of household contacts were similar regardless of HIV sero-status of index cases (odds ratio [OR], 1.04; 95% confidence interval [CI], 0.23–1.84). Furthermore, the likelihood of infected contacts to develop active disease was also similar regardless of HIV sero-status of index cases (OR, 1.17; 95% CI, 0.78–1.56), suggesting that HIV-infected tuberculosis patients are not more infectious compared to their HIV uninfected counterparts.[47] A meta-analysis incorporating 37 studies reported that smear positivity and cavitary disease resulted in a higher likelihood of infectivity (adjusted OR, 2.15 [95% CI; 1.47–3.17], I^2=38% and 1.9 [95% CI 1.26–2.84], I^2=63% respectively). Both of these attributes are known to be reduced in HIV-infected individuals, hence in this meta-analysis, the infectiousness of HIV-infected individuals was reduced (AOR, 0.45 [CI 0.26–0.80], I^2=52%).[48] A study in Uganda reported decreased infectiousness of HIV infected tuberculosis index cases with smear-negative tuberculosis or non-cavitary disease, compared to HIV-uninfected tuberculosis cases. However, there was no difference in infectiousness among HIV infected tuberculosis index cases who had positive sputum smears or cavitary disease.[49] This suggests that disease severity of the index case may modify the infectiousness of tuberculosis cases coinfected with HIV. Furthermore, a study on intravenous drug users revealed that smear positive pulmonary tuberculosis patients 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 to smear negative tuberculosis.

In two studies in Peru and Botswana, household contacts of HIV-positive tuberculosis cases with low CD4 counts had substantially less LTBI compared to household contacts of HIV-negative index cases.[33,51] This suggests that, infectiousness may be reduced in the setting of advanced HIV disease. It has been hypothesized that a depleted CD4 T-cell count in advanced HIV is associated with reduced lung inflammation leading to a reduction in cavities and sputum bacillary load, both of which impact infectiousness. In support of this, in South African mineworkers living with HIV, the proportion of patients with lung cavitation increased as CD4 counts increased; however, sputum smear bacillary load was not linearly associated with CD4 count[52]. Taken together, these studies suggest that HIV may alter infectiousness in some settings by reducing the probability that individuals develop smear-positive or cavitary disease, and that this effect may be particularly important in the context of advanced HIV disease.

ART may have implications for the infectiousness of HIV-positive tuberculosis patients through the restoration of immune function, which may increase the risk of smear-positive and cavitary disease. However, in a study in South Africa, ART 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.[53] A recent household contact study in Malawi found no difference in infectiousness between HIV-positive patients on and off ART[54] (Table 1). This study however did not measure CD4 count.[55] As ART has rendered HIV infection a chronic disease, the sheer number of these survivors with tuberculosis, and the length of time that they remain in the community, may

be sufficient to contribute substantially to the overall tuberculosis burden.[56] Further research is needed to illuminate the effect of ART of tuberculosis transmission dynamics in settings with a high burden of both HIV and tuberculosis.

An alternate explanation of why tuberculosis HIV-infected cases seem to infect fewer close contacts is that persons living with HIV on ART may be diagnosed with tuberculosis sooner due to increased contact with the healthcare system. As ART is lifelong, regular follow-up visits offer intensified tuberculosis case finding and prompt treatment, thus reducing the risk of transmission at a population level.[57] As HIV epidemics continue to mature, and due to the uncertainties concerning the influence of further uptake of ART, additional studies are needed to improve understanding of tuberculosis transmission in HIV-endemic settings.[58]

Impact of HIV on susceptibility to tuberculosis

The impact of HIV infection on the risk of developing active tuberculosis is unmistakable, often demonstrated by increased estimates of HIV prevalence among those with tuberculosis compared to those without it.[59,60] A study 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 time period.[61] The relationship between HIV and susceptibility to tuberculosis infection rather than disease progression is more difficult to demonstrate, though suggested when recent tuberculosis transmission can be proven. A study in a Catalonian prison with a high proportion of HIV-positive individuals indicated recent transmission rather than reactivation of LTBI as a driver of tuberculosis incidence.[62] A meta-analysis of tuberculosis incidence in HIV-positive individuals showed that incidence rates were higher in individuals with lower CD4 counts, which was dependent on the tuberculosis burden in the immediate community, suggesting that reduced immunity enhances LTBI acquisition.[63]

Another phenomenon of interest is the high rates of tuberculosis recurrence among patients in tuberculosis and HIV high-burden settings, reported among 5 to 20% of patients who have completed tuberculosis treatment.[64–67] A number of molecular epidemiological studies in these settings found that the prevailing underlying mechanism for this depends on the time since the end of treatment. Relapse is more common in the first year, which is superseded by reinfection thereafter.[68–72] HIV infection was strongly associated with increased risk of reinfection in three of four studies.[64,66,69,71] Tuberculosis incidence is significantly reduced in HIV-positive individuals starting ART with CD4 counts above 500 cells/μl.[73,74] Coupled with early detection, early ART initiation is strongly protective, reducing the risk of active tuberculosis in HIV-infected children.[75]

Host genetic factors that modulate susceptibility to infection

Susceptibility to tuberculosis infection is primarily determined by assessing immunological response to the *Mycobacterium tuberculosis* complex. In this case, there is a disproportionate reliance on CD4+ T cell acquired immunity against mycobacterial antigens either by the TST or interferon-γ release assays (IGRAs). In HIV-positive patients these assays are less sensitive which reduces their negative predictive value in high transmission

settings.[76] The presence of apparently infection-resistant persons, termed “resistors”, is historically well documented in HIV-negative individuals.[77,78] In contrast, the impact of HIV-positive infection resistors on TB transmission is understudied. As HIV-positive individuals display significantly increased susceptibility to tuberculosis, it is clear that the virus abrogates critical host resistance mechanisms.

In HIV negative subjects, a significant contribution of host genetic factors to TST and IGRA reactivity have been demonstrated,[79–81] leading to studies aimed at identifying mediators of infection resistance (table 2). A genome-wide linkage analysis of TST-negativity in Uganda identified protective determinants on chromosomes 2 and 5.[82] Another candidate gene study in West Africa implicated an IL10 haplotype associated with low circulating levels of the IL10 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* on loci 11p14. TST response (induration in mm) was linked to another locus termed *TST2* on loci 5p15.[84] The *TST1* locus was confirmed in a second independent sample from the Paris region[85] and was genetically indistinguishable from an independently mapped locus termed *TNF1*[86] suggesting that infection resistance may be linked to the secretion of TNF, a well-established anti-tuberculosis 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.[87,88] ULK1 is involved in the regulation of TNF secretion while TOLLIP is part of the TLR signaling cascade leading to TNF production.

A recent study, focused on a small sample of HIV-positive subjects who remain uninfected in the presence of documented exposure, reported strong genetic association with degree of TST positivity in the vicinity of the IL9 gene. This implicated mast cells in infection resistance, which is an attractive proposal as IL9 variants have previously been associated with pulmonary hyper-responsiveness.[89] While the main locus appears specific for HIV-infected patients, the study also detected the loci on chromosomes 2 and 5 previously identified in HIV-negative patients.

Genome-wide linkage analyses in HIV-negative subjects identified two major loci, one on chromosome region 8q12-q22, which impacted on interferon-γ production following stimulation of whole blood with live BCG, and a second on 3q13-q22 was implicated in interferon-γ release following stimulation with ESAT-6 (table 2).[90] The association of chromosome 3 with interferon-γ production via the ZDXC gene has been confirmed in a separate study.[91] These preliminary findings underscore the need for more comprehensive analysis of protective genomic biomarkers. Moreover, in people who do not resist infection, but are able to contain it in the form of LTBI, biomarkers for identifying those individuals who are likely to lose bacterial containment and progress to disease would be of tremendous utility in targeting resources for preventive therapy.

Transcriptomic biomarkers for early diagnosis and screening for prevention of transmission

There is now a growing realization that individuals with asymptomatic and undiagnosed subclinical disease may also contribute to transmission.[36,37,92] This raises the question as to

whether all individuals with LTBI should be treated preventatively in order to interrupt the cycle of transmission. However, in high incidence HIV-tuberculosis-endemic settings where force of infection may exceed 10% per annum, with between 60–80% of adults infected, such an approach would not be feasible.[93] Rather, attention has shifted to identification of individuals who are at high risk of imminent progression from LTBI to disease, which may provide an opportunity for targeted intervention.[29,30]

Recent studies have described prognostic transcriptomic signatures of risk for tuberculosis progression that may identify a state of incipient or subclinical tuberculosis, clinically indistinguishable from LTBI, but differentiated on the basis of an evolving host RNA signature.[30,94] A 16-gene tuberculosis risk classification model, or Correlate of Risk (COR), was discovered within a study of more than 5000 South African adolescents and validated using a qRT-PCR platform to allow high volume testing in a research setting.[94] The COR was able to discriminate between HIV-uninfected adults who would or would not progress to active tuberculosis with 66% sensitivity and 80% specificity for disease occurring within 12 months of testing.[94] A number of diagnostic transcriptomic signatures have also been described in both HIV-infected and HIV-uninfected people.[95–98] When applied to published microarray data from tuberculosis diagnostic studies, the COR demonstrates an area under the receiver operating characteristic curve ranging from 0·86–0·99 for discrimination between active tuberculosis and LTBI or uninfected individuals.[94] These performance characteristics suggest that a biomarker-targeted screen & treat strategy might be feasible, using the COR to triage persons for definitive sputum investigation, followed by curative therapy for those sputum positive or preventive therapy for those sputum negative; and a negative COR result to identify those who need no intervention.[99] Inclusion of HIV-infected individuals in such a strategy is crucial for impact in endemic countries.

Studying the process of transmission: Aerobiology and the effect of HIV-infection

The current state of the art on airborne transmission of tuberculosis has been built on the pioneering studies of Richard Riley and colleagues nearly seventy years ago.[100,101] Vented air from patients with pulmonary tuberculosis was shown to produce tuberculosis infection in guinea pigs and the concept of infectious ‘quanta’ was developed by defining the infectious dose required to produce a guinea pig infection. The numerical value of quanta of infection was defined within a specific animal study incorporating many parameters such as particle size, environmental conditions, sampling volume, ventilation rate, lung deposition fraction, and time dependent bacterial survival.[102] More recent experimental measurements of bio-aerosol infectivity have shown a wide variation in infectivity between tuberculosis diagnosed individuals. Riley and colleagues reported that bio-aerosols from 8 of 61 tuberculosis patients (13%) were able to infect guinea pigs with an estimated mean infectious dose production of 1·25 per hour.[101] Recently, similar studies have been extended to encompass HIV-infected individuals. In Peru, a study of tuberculosis ward admissions, all of whom were HIV-infected, revealed a substantive variation in infectiousness.[103] In a subsequent study of ward admissions (82% HIV-positive), only a small proportion of HIV-infected MDR cases were responsible for 90% of infection transmitted to guinea pigs.[104]

These observations point to drug resistance and poor treatment as substantive drivers of the transmission potential of HIV-infected tuberculosis patients. However, pathogen related factors may be important in transmission as various animal models of tuberculosis disease have demonstrated that some strains are more transmissible than others.[105,106]

Studies of surfactant concentrations in exhaled bio-aerosols have shown that different respiratory activities generate bio-aerosols from different airway regions. Cough and deep sighs (exhalation after deep inspiration) generate particles from large airways and peripheral airways respectively.[107] 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 maneuvers remains an unresolved question. HIV co-infection and reducing CD4 T-cell counts may also affect the architecture of the tuberculosis infected lung and impact on bio-aerosol particle production. Monitoring cough strength and frequency, together with bio-aerosol quantity and particle composition, in both HIV-infected and non-infected individuals could help identify infectious persons and implement measures for prevention of transmission.[108–110]

Bio-aerosol characterization of 34 newly diagnosed untreated tuberculosis cases (50% of whom were HIV-co-infected) in a Respiratory Aerosol Sampling Chamber (RASC) revealed that total bio-aerosol production was found to vary between 50 μm^3 and 500 μm^3 per liter of exhaled air.[109] Electron microscopy of impacted bio-aerosols demonstrated multiple structures <5 microns consisting of organic material and the infrequent observation of bacilli-like structures.[110] Fennelly and colleagues isolated *M. tuberculosis* colony forming units (CFUs) during 5 minutes of forced coughing from 27·7% of patients with a mean of 16 CFUs and a wide distribution that varied from 1–701 CFUs.[111] A follow-up study of patients demonstrated that isolation of *M. tuberculosis* positive cough aerosols was associated with ongoing household transmission of tuberculosis, suggesting that the presence of CFUs was necessary for transmission.[112] Similarly, Pattersen and colleagues isolated *M. tuberculosis* CFUs from 42·8%, and a combination of DNA and CFUs from 77%, of newly diagnosed tuberculosis patients using a RASC.[110] As tuberculosis-HIV co-infected patients carry lower lung bacterial loads, these observations suggest that bio-aerosols from these patients are likely to harbour fewer culturable bacilli.

Differences in the proportion of patients identified with culturable bacilli in their bio-aerosols may in part be due to low sensitivity and the volume of bio-aerosol sampled. Considering this, a combination of high sensitivity detection and large air sampling volumes will be required in order to detect patients with lower levels of infectivity, such as sputum smear negative individuals, with HIV co-infection and low CD4 T-cell counts. An alternate explanation for the varying levels of CFUs detected could be that the tubercle bacilli in bio-aerosols 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.[113,114] 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.[113,114] Whether such organisms are present in bio-aerosols and whether they are important

for the transmission process remains an open and exciting area for future study. Further resolution on this is important as individuals with low CFUs may contribute to endemic tuberculosis transmission in crowded, poorly ventilated environments.[115]

Transmission of tuberculosis in the community and institutional amplifiers

Achieving a clear understanding of where tuberculosis is transmitted and between whom, remains a vexing problem due to key attributes of tuberculosis described above. In this regard, molecular epidemiological tools such as genotyping with IS6110 elements or more recently, whole genome sequencing has allowed for greater understanding of transmission dynamics in the community.[116,117] A particular problem with tuberculosis is the prolonged and highly variable duration of infectiousness, providing numerous opportunities for transmission, combined with airborne infection, which may 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 and/or molecular epidemiologic methods.[118–120] Recently, 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 integrating data on ventilation in these settings.[118,121,122] These studies have implicated bars, schools, workplaces and public transit as sites for transmission potential. In this context, targeting interventions to populations within institutions that may drive tuberculosis has emerged as a potentially promising avenue for tuberculosis control.[11,20,24,122]

“Institutional amplifiers” or “reservoirs” of tuberculosis transmission represent settings where disease and transmission are concentrated within communities[123]. These institutions or locations are typically characterized by environments that are highly conducive to tuberculosis transmission, including high rates of indoor contact, poor ventilation, comorbidities influencing risk of infection and/or disease, and limited access to timely diagnosis and treatment. Several types of institutional drivers have been described in the literature including mines, hospitals, prisons, slums and homeless shelters. Many of these institutions are also highly HIV endemic.[124–126]

Prisons have been consistently identified as high tuberculosis burden institutions throughout the world, from low- to high-income countries.[23,127–129] A recent systematic review found that tuberculosis incidence rates in prisons were a median of 23 times greater than that of their reference populations.[127] 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. While prisons may account for less than 10% of tuberculosis cases in the general population from low- and middle-income countries,[23,130] their impact on community tuberculosis rates may be underestimated due to disease that occurs after release from prison, driving spillover of tuberculosis from prisons into communities.[131] This was demonstrated in the context of a large tuberculosis outbreak in the United States in the mid-1990s, in which community tuberculosis cases genotypically matched those seen in the prisons.[132,133] A recent study from Brazil demonstrated that one quarter of community tuberculosis cases occurred among ex-prisoners, and that over half of the remaining cases

were genetically linked to strains observed among prisoners.[134] A study from Moldova found that multidrug-resistant tuberculosis in the community was geographically congregated in areas with high numbers of former prisoners.[135] This suggests that prisons in Eastern Europe, known to be seedbeds for transmission of drug resistant tuberculosis,[129,136] may be contributing to the spread of multidrug resistant tuberculosis upon prisoner release. Despite these recent suggestive results, the amount of tuberculosis that is attributable to prisons may be, at least partially, 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 extraordinarily high tuberculosis transmission rates due to crowding in poorly ventilated environments, exposure to silica dust, high HIV prevalence and low socioeconomic status.[137,138] Seasonal migratory patterns by miners put the general population at substantial risk for tuberculosis transmission spillover from mines. In one study, the number of mines in a population was directly correlated to population tuberculosis incidence, prevalence, and mortality.[139] Similarly, healthcare facilities have been recognized as institutional drivers of tuberculosis for over a century. Nosocomial transmission was identified as a key driver in MDR-tuberculosis outbreaks in New York in the 1990s; more recently, XDR-tuberculosis was associated with large hospital outbreaks in South Africa. In both settings, HIV co-infection played a major role.[140–142] Recent reports have found that “programmatically incurable” XDR-tuberculosis patients, the vast majority of whom are HIV-positive, from hospital settings are released back into the community, possibly contributing to further transmission.[141]

Understanding institutional amplifiers and how HIV infection interplays with this phenomenon could lead to more efficient deployment of interventions. Using a mathematical model and drawing upon tuberculosis incidence data across Rio de Janeiro, Dowdy and colleagues demonstrated that interventions targeted at few high-burden slums, containing just six percent of the city’s population, could have the same overall impact as achieving tuberculosis control in the remaining population.[143] To understand the potential for institutions or settings to serve as important amplifiers of tuberculosis incidence at the population level, several key attributes must be understood. These include (1) the relative size of the high-risk population compared with the overall population; (2) relative incidence of LTBI and disease (for which HIV is an important factor); (3) the level of in- and outflow migration from the institution or setting and the general population; and (4) degree of social mixing between members of the institution and the general population after re-joining the general population. Among these, perhaps the most challenging to estimate are the contact rates between the high-risk population and the general population. Molecular epidemiologic studies may provide one avenue for understanding transmission between these groups.

Conclusions and forecast

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

while at the same time creating a large pool of high susceptible individuals to drive further disease in the community setting. Understanding the effect of antiretroviral therapy on the infectiousness of HIV-positive tuberculosis cases, together with determining how HIV infection modulates the risk of reinfection or relapse in individuals with a history of tuberculosis, should feature as an important and immediate priority. Intensifying integration of HIV-tuberculosis control programs is also likely to have a great impact on limiting diagnostic delays, early case detection, prompt treatment onset and ultimately reduction of transmission. 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 intra-institution high force of infection and subsequently prevent future community-based cases. Collectively, a greater focus on limiting transmission promises to deliver significant gains in controlling tuberculosis.

Methods for literature searches

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

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Box:

Critical Knowledge Gaps

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

Box 2:

Urgent unmet needs

1. Development of technologies to distinguish a) patients at high- and low-risk for transmitting tuberculosis, and b) 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.
2. Determine optimal methods to evaluate interventions intended to halt tuberculosis transmission in HIV-endemic settings, which requires improvements in tuberculosis program monitoring capabilities and application of appropriate modeling strategies.
3. Further integration of HIV and tuberculosis programming in sub-Saharan Africa and other areas with substantial burden 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 high levels of tuberculosis, initiation of ART therapy, providing isoniazid preventive therapy to all HIV-positive patients exposed to tuberculosis, and intensified tuberculosis case finding

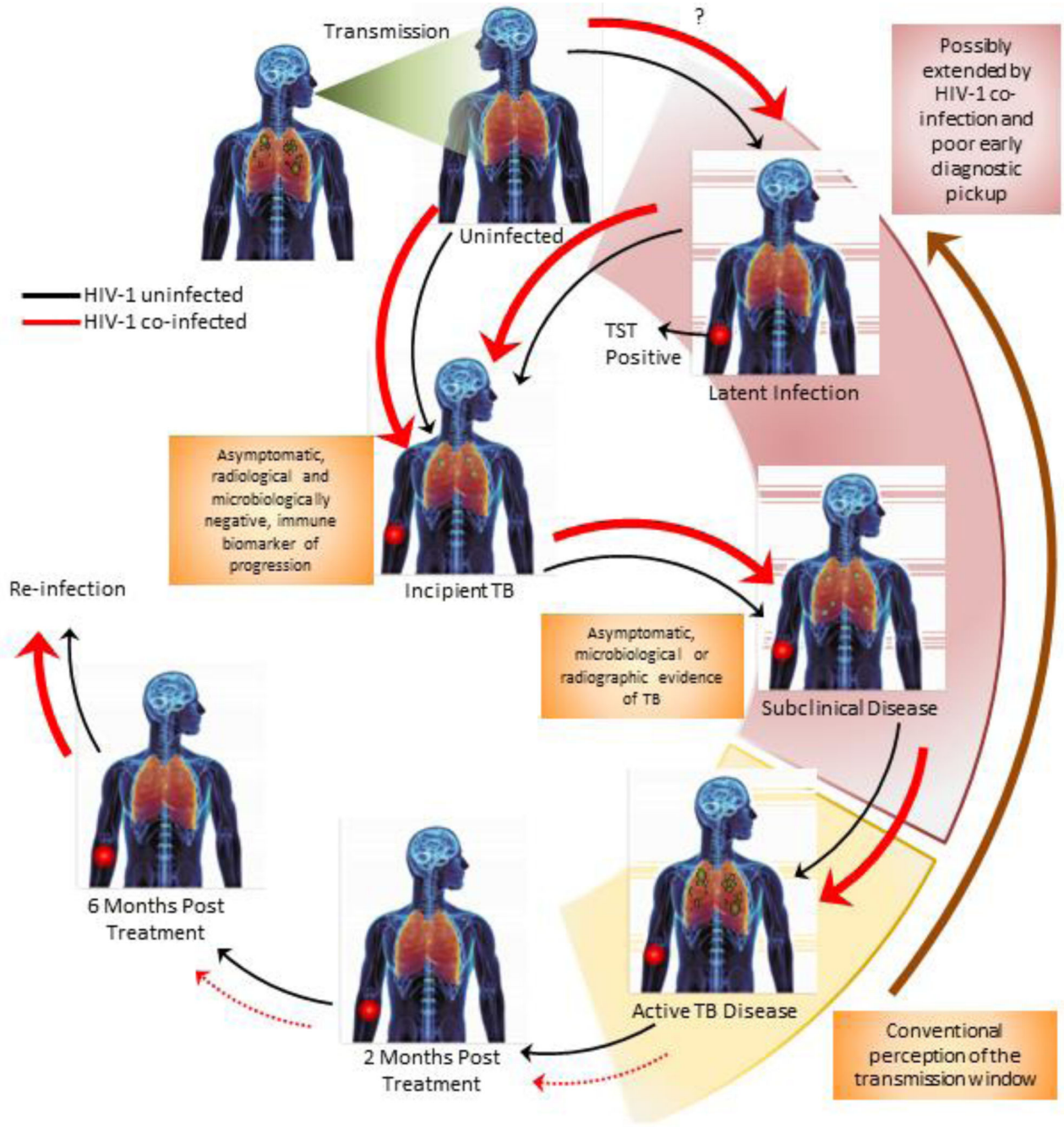

Figure 1. Effects of HIV-1 infection on the progression of tuberculosis disease and the transmission window.

Progression to active, pulmonary tuberculosis disease 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/reversion to the next/preceding phase. Red arrows indicate the sequence in the case of tuberculosis-HIV infection. Most cases of exposure lead to the development of asymptomatic latent tuberculosis infection (LTBI), which is characterized by an immunological response to mycobacterial antigens (using the tuberculin skin test [TST]).

This can progress to incipient tuberculosis, which is defined as asymptomatic disease with no radiological or microbiological signs of disease but can be distinguished from LTBI by an immune biomarker progression from infection to disease. Subclinical disease develops thereafter and is classified as asymptomatic disease associated with either radiological or microbiological confirmation of tuberculosis. In some cases, individuals can spontaneously convert their TST to become uninfected again. HIV co-infection alters the dynamics of immune control and can favour progression to infection, in exposed individuals, and/or progression to incipient tuberculosis. It remains unclear if HIV infection increases the risk of becoming infected with LTBI. The risk of progression to active pulmonary tuberculosis can also be substantively enhanced in the presence of HIV co-infection. Conventionally, the transmission window (shown in yellow) has been assumed to circumscribe the development of granulomatous tuberculosis disease, with a high bacterial load and cavities. HIV co-infection can potentially extend this window (shown in pink) by (I) creating a larger proportion of individuals with incipient/subclinical tuberculosis, within whom the propensity to transmit is as yet unclear (II) creating a larger pool of actively diseased individuals who can transmit and (III) presenting poor treatment outcomes due to extra-pulmonary tuberculosis and drug-drug interactions.

Table 1.

Recent 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

Study	HIV index strata*	Relative Risk**(95% CI)	Adjusted Relative Risk**(95% CI)
Previous Meta- analysis			
Cruciani, 2001[47]	HIV-negative	1 (Referent)	–
	HIV-positive	0.66 (0.60 – 0.72)	–
Recent studies¶			
Huang, 2014[33]	HIV-negative	1 (Referent)	1 (Referent)
	HIV-positive with a CD4 count ≥250	0.9 (0.6 – 1.3)	0.9 (0.5 – 1.5)†
	HIV-positive with a CD4 count <250	0.6 (0.4 – 1.1)	0.5 (0.3 – 0.9)†
Martinez, 2016[49]	HIV-negative with smear positivity	1 (Referent)	1 (Referent)
	HIV-positive with smear positivity	0.94 (0.86 – 1.04)	0.93 (0.85 – 1.01)†
	HIV-negative with smear negative results	1 (Referent)	1 (Referent)
	HIV-positive with smear negative results	0.75 (0.63 – 0.90)	0.76 (0.64 – 0.90)†
	HIV-negative with cavitary disease	1 (Referent)	1 (Referent)
	HIV-positive with cavitary disease	1.07 (0.97 – 1.17)	1.03 (0.96 – 1.12)†
	HIV-negative with cavitary disease	1 (Referent)	1 (Referent)
	HIV-positive with noncavitary disease	0.75 (0.65 – 0.87)	0.74 (0.65 – 0.85)†
Khan, 2017[54]	HIV-negative	1 (Referent)	1 (Referent)
	HIV-positive with ART for ≥1 year	0.3 (0.1–0.9)	0.4 (0.1–1.3)††
	HIV-positive with no ART or ART<1 years	0.2 (0.1–0.7)	0.5 (0.2–1.3)††

*All index cases have tuberculosis disease. This column stratifies tuberculosis index cases by their HIV status and other secondary modifying variables related to the severity of HIV or tuberculosis disease.

≠Adjusted for age, sex, smoking status, alcohol intake, nutritional status, number of BCG scars, household smoke exposure, relation to the tuberculosis case from household contacts; age, sex, cavitary lung disease, smear status, and treatment delay from tuberculosis cases.

†Adjusted for age, education level, and alcohol status of the household contact; sputum smear and cavitary 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.

¶A positive tuberculin skin test was defined as an induration reaction ≥10-millimeters for all three recent studies. For Huang, 2014, a positive tuberculin skin test for household contacts that were HIV-positive was differentially defined as an induration reaction ≥5-millimeters. Khan, 2017 included only child household contacts 2–10 years of age while Huang, 2014 and Martinez, 2016 included contacts of all ages.

**Measures of association here represent the relationship between positive tuberculin skin test results in household contacts exposed to HIV-negative index cases and household contacts exposed to varying types of HIV-positive index cases (high versus low CD4 count; cavitary versus noncavitary tuberculosis disease; antiretroviral therapy versus no or recent antiretroviral therapy). All crude models here are adjusted for household clustering while Huang, 2014 is also adjusted for age of the household contact. Martinez, 2016 and Huang, 2014 use modified Poisson regression models to derive relative risks while Khan, 2017 calculated crude and adjusted odds ratios. The Khan, 2017 manuscript reports odds ratios with "HIV, no ART and ART<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.

Table 2.

Summary of host genetic factors that affect outcome of TB transmission

Chromosome	Gene	TST/IGRA	Resistance/Susceptibility	Possible Mechanism
2 and 5		TST	Resistance	Unresolved[82]
	IL10 haplotype		Resistance	Low circulating IL10[83]
11p14	*TST1*	TST	Resistance	Controls lack of TST response[84,85]
5p15	*TST2*	TST	Resistance	Controls extent of TST response[84]
6p25	*DRB1/DQA1*	TST	Susceptibility	TST-positivity[144]
11p14	*TNF1*	TST	Resistance?	Controls TNF production upon exposure to BCG[86]
	ULK1	TST	Susceptibility	Role in TNF production[88]
	TOLLIP	TST	Susceptibility	Role in TNF production[87]
	IL9	TST	Resistance	Mast cells[89]
8q12-q22		IGRA	Resistance	IFN_{γ} production on BCG exposure[90]
3q 13-q22		IGRA	Resistance?	IFN_{γ} production on BCG and ESAT-6 exposure[90]
	ZXDC	IGRA	Resistance?	IFN_{γ} release in response to ESAT-6[91]