HIV as a Risk Factor for Multi-Drug Resistant Tuberculosis: A Systematic Review

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INTRODUCTION

Winstone Zulu is featured prominently in a tuberculosis (TB) and HIV awareness campaign sponsored by the Stop TB Partnership, a network of organizations, countries and donors that have made the elimination of tuberculosis a priority. He is a Zambian who contracted HIV and later acquired infection with TB. He managed to survive the co-infection when so many around him, including four of his brothers, died of tuberculosis in the 1990s. This defining experience led him to become a leading advocate for TB and HIV patients worldwide. Like those in his family, many people in sub-Saharan Africa and throughout the world who suffer from TB and HIV do not survive the deadly combination. The terrifying consequences of the two infections have now become even graver – a newer threat of multi-drug resistant TB (MDR-TB) jeopardizes what little control there is now over the dual epidemic. Understanding the relationship between HIV and MDR-TB has profound implications for the many people like Winstone Zulu’s brothers, who have all but received a death sentence.

The Scope of TB

Tuberculosis has long been a cause of human suffering and death. This trend has continued into the modern day; in 2005, there were about 8.8 million incident cases of TB worldwide and over 14 million prevalent cases. In the same year, about 1.6 million people died from tuberculosis. Not surprisingly, the global distribution of the burden of suffering is skewed. South-East Asia, which includes India, had the most incident cases in 2005 with about 3 million cases of TB, accounting for about 34% of disease incidence. The highest incident rates of TB occur in Africa, with a rate of 343 per 100,000 compared
to 181 in South-East Asia and 39 in the Americas. The highest mortality rates also occur in Africa (74 per 100,000).\(^1\) While TB remains a major cause of mortality, incidence rates have recently remained stable or have declined in most regions worldwide. Nonetheless, the number of new TB cases still rose slightly in 2005 because of the case load in Africa and South-East Asia.\(^2\)

Though tuberculosis has consistently remained a major cause of morbidity and mortality worldwide, it has received varying levels of attention from the public health and medical community. Initial large scale public health responses to tuberculosis began in the post World War II era as vertical programs. This approach succeeded in stemming the tide of infection in industrialized countries but did little to control TB in resource poor countries.\(^3\) In the latter, TB control had to be incorporated into the general health services. This integration into general health services marginalized tuberculosis control efforts in certain nations for decades. This continued into the 1980s as the HIV pandemic was about to profoundly increase rates of tuberculosis worldwide.

In the early 1990s, rising rates of tuberculosis and particularly MDR-TB in developed countries began to get publicity. In the United States, outbreaks of TB and MDR-TB in New York City and Miami were traced initially to HIV infection but were also noted in immigrant communities.\(^4\) The high fatality rates of these outbreaks led to calls for better tuberculosis control in the United States. At the same time, TB rates in certain African countries, such as Tanzania, Malawi and Zimbabwe, rose rapidly, leading to calls for a thorough rethinking of tuberculosis control efforts worldwide.\(^5\)
Response to the resurgence and drug resistance

In 1995, the World Health Organization adopted the DOTS (Directly Observed Therapy Short-Course) program as a systematic strategy to combat rising rates of TB. Among the central tenets of the program was the recognition of TB chemotherapy as a highly cost effective intervention. Also important were government commitment to TB control, diagnosis with sputum microscopy, appropriately managed short-course chemotherapy, readily available pharmaceuticals and infrastructure for outcomes measurement. Initial efforts in the DOTS era proved limited as only 11% of TB cases were estimated to be treated under its guidelines in a 1997 study. DOTS gradually expanded but its shortcomings led to new threats: the double threat of HIV/TB and the continued escalation of MDR-TB rates.

MDR-TB is defined as *mycobacterium tuberculosis* that is resistant to both isoniazid and rifampin (or rifampicin). For an accurate diagnosis of MDR-TB, both sputum cultures of the organism as well as drug sensitivities are necessary. Selection for drug resistant strains of tuberculosis generally arises from a combination of medical error (health care worker or infrastructure level) and poor patient adherence to the complicated drug regimen. Because inadequate treatment selects for resistant strains, re-treatment cases of TB have higher rates of MDR-TB (and all drug resistance patterns) as compared to new cases. In fact, previous drug treatment is the most important risk factor for MDR-TB. These resistant strains become problematic because patients acquire longer periods of infectiousness and the treatment regimens can last up to 24 months. These changes are due to the fact that isoniazid is the most potent bactericidal drug of the four drug regimen of short-course chemotherapy while rifampin is the best sterilizing drug.
However, the most important consequence of resistance is that MDR-TB has higher treatment failure and death rates in new and re-treatment cases.\textsuperscript{9} Aside from the pharmacologic and physiologic properties, MDR-TB treatment is prohibitively more expensive than the traditional six month short-course chemotherapy. Accordingly, the financial burden of MDR-TB places considerable stress on the health budgets of resource poor nations.

Investigations into the prevalence and trends of MDR-TB began with the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance, which was completed in 1997.\textsuperscript{10,11} These reports demonstrated that drug resistant TB, including MDR-TB, was present worldwide and that better TB control practices were associated with lower rates of bacterial resistance. Furthermore, MDR-TB was shown to be especially problematic in certain ‘hot-spots’ such as Russia, Latvia and the Dominican Republic. A follow up report from 2001 showed especially high rates of MDR-TB in certain areas.\textsuperscript{7} While the median rate of MDR was 1.0% among new cases of TB, the rates varied considerably. MDR accounted for 14.1% of new cases in Estonia, 9.0% of new cases in Latvia, 9.0% of new cases in the Ivanovo oblast (region) of Russia, 5.0% of new cases in Iran and 4.5% of cases in the Zhejiang province of China. The latest report from WHO/IUATLD confirms these “hot spots” of epidemic MDR-TB while additionally warning about high rates of MDR-TB in Kazakhstan, Lithuania, Uzbekistan, Ecuador and Israel.\textsuperscript{12}

The surging rates of MDR-TB, especially in the “hot spots” led to renewed debate over TB control policy. Implicit in the debate was value of allocating a tremendous amount of resources on the difficult problem of MDR-TB. One proposal was a
complementary DOTS-plus program, which would use DOTS programs as a base to address MDR-TB in needed areas. Patients with drug resistant TB would be treated on individualized regimens. At the same time, others contended that the best use of resources was to focus on treating drug susceptible TB with short course chemotherapy. Not only would this strategy be cheaper, but effective control of susceptible TB leads to effective prevention of MDR-TB.

With the rethinking of the DOTS strategy and disappointments in MDR-TB and TB/HIV control, a new Stop TB Strategy came to fruition in early 2006. The underlying reason for the Stop TB Strategy was that DOTS alone would be inadequate for achieving the 2015 Millennium Development Goals related to TB, which include halting and reversing the incidence of tuberculosis by 2015. The Stop TB Strategy includes expansion of DOTS but also addresses other issues. It promotes collaboration between TB/HIV control efforts and prevention and control of MDR-TB. Other components include structural changes as a method of curbing TB. These consist of strengthening health systems, engaging health care providers, empowering TB patients and their communities, and promoting TB research regarding diagnostics, drugs and vaccines. The heightened emphasis on HIV and MDR-TB will hopefully lead to a better understanding of the relationship between HIV, TB and drug resistance as well as decrease the case load of TB/HIV co-infection and drug resistant TB.

Co-infection with TB and HIV

One of the greatest current challenges facing TB control is HIV control. HIV (human immunodeficiency virus) is a retrovirus which causes immune deficiency and
leads to the clinical syndrome AIDS. Currently, there are an estimated 39.5 million people living with HIV around the world. Around 4.3 million new people were infected with the virus in 2006 and about 2.9 million died of AIDS.\textsuperscript{17} The burden of suffering is concentrated in sub-Saharan Africa, which contains 63% of cases. HIV prevalence worldwide continues to increase; an estimated 2.6 million more people had HIV in 2006 compared to two years previously. The most conspicuous increases have been in Eastern Europe and Central Asia, two areas also hard hit by the TB epidemic.\textsuperscript{17}

HIV changes the epidemiology, case presentation and pathophysiology of tuberculosis infection. The virus increases the chances of a reactivation of latent TB infection in addition to speeding the progression of active TB disease. TB patients with HIV are more likely to have atypical signs and symptoms of the disease and more likely to have extrapulmonary dissemination. The pharmacologic treatment of TB is particularly difficult in HIV patients because of the interactions between protease inhibitors and rifampin. Furthermore, treatment of HIV can paradoxically worsen TB disease by restoring immune function.\textsuperscript{18} Regarding mortality, the risk of death in HIV patients with TB is twice that of HIV patients without TB even when factors such as CD4+ cell count and antiretroviral therapy are taken into account.\textsuperscript{19} In the developing world, the leading cause of death among HIV patients remains TB.\textsuperscript{20}

The interplay between HIV and TB is evident from the epidemiologic data. In one recent global survey, an estimated 9% of new TB cases were attributable to HIV co-infection.\textsuperscript{20} This proportion was much higher in certain areas: in the WHO African region, 31% of new TB cases were due to HIV and in the United States, the proportion was 26%. Overall, 12% of the 1.8 million deaths due to TB were attributed to HIV but in
the African region, 39% of TB deaths are attributable to HIV. In general, TB incidence rates are strongly correlated with HIV prevalence rates. Looking at the issue from the HIV perspective, of the 40 million people living with HIV worldwide, about one-third of them are infected with TB.\textsuperscript{21}

\textit{Compounding the problem: the addition of MDR-TB}

Given the dynamic interplay between HIV and TB, it is not surprising that the addition of MDR-TB has complicated the picture. HIV and MDR-TB are a deadly combination: one cohort of HIV/MDR-TB patients had more than 50% mortality within two months of diagnosis.\textsuperscript{22} Longer follow up times in co-infected patients have shown death rates of between 72-89\%.\textsuperscript{23} Another study of risk factors affecting survival in MDR-TB patients showed that immunocompromised MDR-TB patients are nine times more likely to die than MDR-TB patients who are not immune compromised.\textsuperscript{24} Many of the published studies involving HIV, MDR-TB and non-drug resistant TB involve small case series from isolated outbreaks with some larger surveillance studies. The relationship then, between HIV and MDR-TB is in a larger sense not well understood. This is surprising, given the body of literature devoted to HIV and MDR-TB individually. A key question is if HIV predisposes TB patients to progress to active MDR-TB, as opposed to drug susceptible TB. The consequences of this relationship are immense in terms of morbidity, mortality, health care policy and spending. A relationship between the two would imply that health care resources for TB prevention and treatment should be augmented in areas of high HIV prevalence and vice versa. To get a clearer picture of the relationship between the two, this review intends to summarize and critically appraise
studies which have looked at rates of MDR-TB in patients with and without HIV infection.

METHODS

The purpose of this review is to investigate whether TB patients co-infected with HIV are more likely to have multi-drug resistant tuberculosis than TB patients not co-infected with HIV. The general strategy was first to come up with eligibility and quality criteria for published literature to be included in the review. Subsequently the body of literature would be searched with a predetermined search strategy.

Eligibility criteria

The body of evidence regarding the specific relationship between HIV infection and MDR-TB is lacking. While there are countless articles and even journals devoted to tuberculosis and HIV, the intersection of the two with drug resistance is an uncommon topic. As this type of systematic review has not been done before and the body of evidence was apparently sparse, fairly lenient eligibility criteria were chosen.

A number of study designs were deemed to be acceptable, including case series (including surveillance data), cross sectional studies, case control, cohort (retrospective or prospective) studies and clinical trials. The wide variety of acceptable study designs, including traditionally weaker designs such as case series and cross sectional studies, were deemed appropriate because information extracted from them could reasonably address the study question. Association, not causation, was the relationship investigated. Opinion pieces written by experts were not eligible for the review. Realistically, the
presumption was made that most of the data would come from cohort studies, surveillance data and case series. Although in theory a clinical trial is the best design to minimize biases, one would be unrealistic and unethical for this study question since the exposure (intervention) is essentially HIV infection.

The next grouping of eligibility criteria related to populations, definitions and outcomes. All patients studied must be infected with tuberculosis. It was deemed acceptable if this group was formed in a manner unrelated to the main question of the study. Sputum culture had to be a part of the study and a positive culture had to be an inclusion criteria for the study population for the research study to be eligible. Only with this diagnostic test could further testing for drug resistance patterns (the outcome) be assessed. A clinical diagnosis of active tuberculosis infection based on symptoms and a PPD skin test would be unacceptable for eligibility.

Regarding the exposure (HIV infection), studies must have included mention of how HIV infection was assessed to be eligible. This could include previous mention in the medical record or for example, ELISA (enzyme linked immunosorbent assay) test or rapid HIV tests. Also for eligibility, the studies had to give some indication of an HIV negative population which would serve as a control for this review. It would be acceptable if this grouping of HIV negative TB patients was not related to the primary outcome of that particular study. However, somewhere in the study, whether a table or within the results section, there had to be a clear indication of a grouping of HIV negative patients along with HIV positive.

The possibility was discussed of including studies which only contained data of only TB/HIV co-infection. The original thought was that outcomes from these studies
could be compared to country specific levels of MDR-TB. In this sense, the country wide surveillance data would serve as a proxy for MDR-TB rates in HIV negative patients. Nevertheless, this could be problematic as HIV and MDR-TB prevalence rates are not distributed uniformly throughout regions and countries. The importance of having an exposure group and a control group within the same study furthermore necessitated the inclusion of an HIV negative group within the eligibility criteria.

Clear description of outcome measurement is an important eligibility criterion. Studies had to describe culture and drug susceptibility testing done along with which anti-tuberculosis chemotherapy agents were tested. Resistance to both isoniazid and rifampin was needed for eligibility since MDR-TB is defined by resistance to these. Therefore, a study would be deemed ineligible if it included individual resistances to the chemotherapeutic agents but did not include a combined resistance profile to both isoniazid and rifampin. The MDR-TB rates had to be presented as percentage or these percentages had to be readily extractable from data presented. If a study did not present percentages but did present an odds ratios or risk ratio for MDR-TB infection in HIV positive compared to HIV negative patients, this was also decided to meet eligibility criteria.

Systematic reviews often restrict eligible studies by publication date. The logic stems from the fact that current clinical practice and methodologies might differ greatly from a predetermined time point. For this review, no publication dates were restricted. This came with the knowledge that any study which addressed HIV and MDR-TB is inherently time restricted. MDR-TB emerged as a threat within the past two decades and most of the literature regarding it has been written since 1990.
Tuberculosis cases occur under different circumstances: they can be epidemics on inpatient hospital wards or can be community based. They can be new cases or recurrent. These distinctions are important in classifying the type of patient and the type of disease. They are also key determinants of rates of MDR-TB. In the early history of MDR-TB, the infection spread in hospital wards from one HIV patient to another. Intuitively, with a few patients spreading MDR in an HIV ward, outcome rates would probably be higher in HIV co-infected patients compared to HIV negative patients. The outbreak and patient proximity associated with it could be considered a confounding factor. This does not necessitate elimination from the review but is important information to glean from each study. The same holds true for the distinction between new and recurrent cases of TB. MDR-TB is much more likely in recurrent cases because failed initial treatment is a risk factor for drug resistance. Hence, a study which included more recurrent cases than new cases would more likely have higher overall rates of MDR-TB. While this information would be critical for an accurate interpretation of study results and biases, it was not included in the eligibility criteria because of the possibility of eliminating too many studies.
TABLE 1: ELIGIBILITY CRITERIA

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<th>STUDY CHARACTERISTIC</th>
<th>CRITERIA</th>
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<tr>
<td>Study design</td>
<td>Clinical trials, cohort studies (prospective or retrospective), case control, cross sectional, case series, surveillance data</td>
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| Study population     | 1. Culture positive TB patients with drug susceptibility result  
                        2. Inclusion of HIV infected and uninfected individuals |
| Description of data collection | 1. HIV status  
                                    2. Resistance testing for isoniazid and rifampin |
| Publication date     | Any |
| Geographic location  | Any |

**Quality criteria**

After eligibility criteria, a set of quality criteria to grade the internal validity of possible studies was needed. Traditionally, this grading system includes elements such as proper randomization scheme, allocation concealment, intention to treat analysis and proper masking (blinding). Given the wide variety of study designs and lack of randomized control trials, these quality criteria would be inappropriate for this review. We therefore opted to include all eligible studies, independent of their quality but assessed all included studies according to the quality criteria listed in Table 2. Many of the quality criteria are inherently related to the eligibility criteria. Cases of tuberculosis, HIV, and drug-resistant TB had to be explicitly defined with culture and diagnosis method. There should be no indication that resistance testing was assessed differently in HIV positive and HIV negative groups.
Prerequisites of sufficiently large sample sizes are oft used quality markers. For this review, there was no minimum sample size required for eligibility. Given the paucity of data on this particular clinical question, any studies which met the other criteria were considered important in being able to assess the relationship between HIV and MDR-TB. However, sample sizes were duly noted as a quality indicator. The quality criteria table (Table 2) notes whether each study had a sample of at least 50 patients in both the HIV positive and HIV negative groups.

Appropriate statistical measures are another useful measure of quality for this review. Generally studies present two percentages of MDR-TB infection, one in HIV positive and patients and the other in HIV negative patients. While the sole presentation of these numbers is valuable, statistical testing of the differences is an important indicator of quality. This information was noted during the appraisal of each study.

An assessment of baseline differences is an important quality criterion. The comparability of groups, in this case HIV positive and HIV negative populations, would be important for knowing if confounding factors (that are associated with HIV infection and MDR-TB acquisition) are possibly driving a relationship between the two. Ideally, this assessment would be present in the studies in the form of a demographics table. However, any descriptive analysis in the text was also sought as an indicator of quality. Even if statistical adjustment is not done for the confounders, the knowledge of possible differences between the groups is crucial. Since the goal of this review is to investigate the risk of MDR-TB attributable to HIV, the possibility that other variables are driving the relationship is important. Association with HIV does not imply causation.
Linked to the baseline characteristics is the question of whether groups selected are representative samples of the population at large. This would be important in assessing the external validity, or generalizability, of studies. In most cases then, we would not be able to assess how valid study results are to another population of baseline TB patients. This is an important issue which must be considered during the larger implications of the review, particularly since geography plays such an important role in rates of TB and HIV. In this review, an assessment of generalizability by the study authors is considered a quality standard. Even if the authors note poor generalizability, their consideration demonstrates concern about the implications of their study.

Masking, another traditional quality criterion, is not included in this review. The one stage in the clinical question for this review where masking would be appropriate is resistance assessment by a laboratory technician. Ideally, this person would be blinded to HIV status. This is generally the case since drug resistance testing is done in laboratories that are normally unaware of the HIV status of the patient.

**TABLE 2: QUALITY CRITERIA**

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<td>Sample size &gt; 50</td>
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<tr>
<td>Statistical testing of differences</td>
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<tr>
<td>Description of baseline characteristics</td>
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<tr>
<td>External validity considered</td>
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**Search strategy**

Articles were searched using the MEDLINE/PubMed database. Other databases were not used due to the strictly clinical nature of the research question. The keywords “multi drug resistant tuberculosis” and “HIV” were used as search terms instead of the MeSH terms “Tuberculosis, Multidrug-Resistant” and “HIV” because considerably more articles come up in the broader keyword search. The search included all articles
published prior to April 2007. The initial search yielded 738 articles which were then limited to English language and human subjects studies. This led to 577 articles. The titles and abstracts of these articles were reviewed for subject matter related to the topic and broadly evaluated for eligibility criteria. Two hundred articles were selected for full text review. Afterwards, there were 22 articles which met the specified eligibility criteria. The references of these were hand searched for potentially relevant articles. This method yielded four additional studies which met the eligibility. One of the studies found was a meta-analysis of European studies that included seven studies in its calculation of an odds ratio for the outcome of interest of this systematic review.

The group of studies ranged in publication date from 1992 to 2006. A wide variety of geographic areas were covered including four studies from Europe, nine from the United States, three from Latin America, three from Southeast Asia and seven from sub-Saharan Africa. Of note, no eligible studies were found that were based on data from Russia, former Russian republics, India or China. These areas contain a substantial portion of the burden of suffering of drug resistant and drug susceptible tuberculosis. The glaring omission of these areas from published data is highly relevant to the general implications of this review.
RESULTS

Critical appraisal of the studies and data extraction was done in groups defined by geographic areas.

Southeast Asia

The studies from this area include have all been published since 2000 and include one from Bangkok\textsuperscript{25}, one from the Chiang Rai province of northern Thailand\textsuperscript{26} and one from Ho Chi Minh City in Vietnam.\textsuperscript{27} The authors of the two much larger studies from
Thailand concluded that HIV patients were more likely to have MDR-TB than HIV negative patients. The study from Vietnam showed no association between the two, but the sample size, particularly for the HIV+ group was miniscule.

Punnnotok et al showed a statistically significant relative risk of 11.9 (95% CI: 4.3, 33) for MDR-TB in HIV patients compared to non-HIV patients. This strong association is backed by solid methodology. TB cases were well documented and HIV patients received both ELISA and Western blot for confirmation, limiting potential misclassification. A table of demographic differences shows that the two groups are generally comparable for TB risk factors, with the exception of smoking history and history of alcohol drinking. However, like many of the studies included for review, there is a large discrepancy between the number of patients originally recruited and those tested for HIV and TB drug susceptibility. There is no good indication of whether the patients who did not receive all tests were systematically different from those who did.

Another possible source of bias is addressed by the authors. TB infection in HIV patients may reflect more recent infection, as opposed to reactivation of latent infection. Thus, TB drug resistance patterns in HIV patients more closely reflect those strains currently circulating in the community.

Yoshiyama et al present a strong case for an association between HIV and primary MDR-TB in the Chiang Rai province of Thailand. They find a statistically significant odds ratio of 2.0 (95% CI: 1.1, 3.5) in a large sample of HIV positive and negative patients. This study also provided separate results for acquired cases of MDR-TB due to recurrent TB infection. There was no significant relationship between acquired MDR-TB and HIV status (OR 1.40, 95% CI: 0.68, 2.91). This supports the
hypothesis that primary infections are associated with recent strains that are more likely
to be drug resistant. In the study, HIV testing and TB drug resistance surveillance were
done in a clear and appropriate manner. However, the primary research question was not
to assess the difference in MDR-TB rates by HIV status; rather, they sought to find the
prevalence of drug resistance in Chiang Rai and look for other associated risk factors. As
such, there is no baseline comparison of risk factors in HIV positive and HIV negative
patients. This raises the possibility of confounders influencing the relationship.
Furthermore, the external validity of the findings is questionable given the lack of
baseline characteristics.

The third study from Southeast Asia from Quy et al shows no statistically
significant relationship between HIV status and MDR-TB in a group from Ho Chi Minh
City, Vietnam. There was no association even after adjustment for age, sex and
treatment history. The rate of MDR-TB in HIV negative patients was 21.3% while it was
0% in their sample of HIV positive patients. However, there were only six HIV positive
patients who had resistance testing done, compared to 188 HIV negative patients. The
authors conceded that the study only had 20% power to detect a two-fold increase in
MDR rate in HIV positive patients compared to negative.

Sub-Saharan Africa

Seven studies from sub-Saharan Africa are included in this review. They range in
publication from 1992 to 2001. Most of the studies are from southern sub-Saharan Africa,
including South Africa, Botswana and Mozambique. Two others are from Cote d’Ivoire
and Tanzania.
Braun et al. undertook one of the first studies of antituberculosis drug resistance and HIV status in sub-Saharan Africa in 1992.28 This cross sectional prevalence study looked at rates of resistance to first and second line TB drugs by HIV status. Among the 17 patients with HIV, 0% had MDR-TB and among the 29 patients without HIV, 3.4% had MDR-TB. The sample size is among the smallest of all studies in the review, particularly for the HIV positive group (17 patients). While statistical testing was done on differences in some resistance patterns, it was not done for the specific MDR resistance pattern of isoniazid and rifampin resistance. The reason for this might be that the specific threat of MDR might not have been as widely understood at the time of publication. There is little description of baseline characteristics of the HIV positive and negative groups, allowing little insight into possible confounders driving the relationship. Like most cross sectional studies, Braun et al simply look for an association and seemingly find none, which is not surprising given the small sample size.

In a much larger survey, Chum et al. studied about one-sixth of incident TB cases over a three year period in Tanzania in the early 1990s to look at the relationship between HIV and TB infection.29 The large survey is well powered to find differences in MDR-TB rates by HIV status. They find that in new TB cases, 1.1% of co-infected patients had MDR-TB and 1.1% of HIV negative patients had MDR-TB. In recurrent TB cases, 4.8% of co-infected had MDR-TB while 7.7% of HIV negative patients had MDR-TB. While rates in new cases are clearly similar by HIV status, no statistical testing is done to examine the difference in new or recurrent rates. Of note, the authors do provide some baseline characteristics of the participants, including sex, age, urban/rural residence and BCG scar status. The study group also made efforts to ensure that the TB patients
sampled were representative of all Tanzanian TB patients by including patient from each of the country’s districts.

More recently, Anastasis et al. conducted a smaller retrospective descriptive study of HIV and TB drug resistance in Durban, South Africa. Overall, 2.4% of 42 HIV co-infected TB patients had MDR-TB while 11.5% of 253 HIV negative TB patients had MDR-TB. The authors write that no association between MDR-TB and HIV is demonstrated; nonetheless, statistical significance is not given. Given the smaller sample size and the inherent biases of retrospective chart abstraction, this one is among the weaker of the study designs.

A succinct letter to the editor by Post and Wood meets the review eligibility criteria as well. It describes a prospective cohort of TB patients admitted to a hospital in Cape Town, South Africa. The rate of MDR in 88 HIV positive patients is 2.9% and the rate is 2.6% in 107 HIV negative patients. While no statistical test is done on the difference, the authors conclude their data supports the body of evidence that HIV infection is not associated with MDR-TB. Given the brevity of the letter, there is little description of the cohort by HIV status even though the measurement of HIV and TB drug resistance are reasonably well described.

A national survey from Botswana by Kenyon et al. corroborates earlier sub-Saharan African studies. The survey finds no relationship between MDR-TB and HIV and low levels of MDR overall. Among HIV positive patients, rates of MDR were 0.9% and rates among HIV negative patients were 0.8%. The results are combined for new and recurrent cases. The extensive, random sampling (based on district TB case registration) of the survey along with baseline characteristics of all participants reassures the reader
that the findings are externally valid to Botswana. However, like many other studies, the survey was not specifically designed to compare rates of MDR-TB by HIV status. Accordingly, there is no information given about baseline characteristics comparing HIV positive versus HIV negative patients. Appropriate confounders and adjusted odds ratios cannot be calculated.

Murray et al. investigate rates of drug resistant TB in South African goldminers. Of 425 patients with sputum positive pulmonary TB, 422 had known HIV status. Among those with HIV, the rate of MDR-TB was 5.3% and among those without HIV, the rate of MDR-TB was 6.5%. Statistical testing is not done to test the difference between these two rates. While the methods of this study, including HIV and resistance testing are clear, there are important biases to consider. The study is not specifically undertaken to study the difference between HIV positive and negative patients. As such, there is no baseline characterization looking at the differences between these two populations. It is also important to consider the generalizability of these findings. A population of goldminers might be systematically different from others, in terms of risk factors such as crowded living conditions or occupational lung disease. Without a thorough description of the baseline populations, it is difficult to assess the possibility of confounders or address external validity.

The final study included from sub-Saharan African is among the strongest. Mac-Arthur et al. conduct a survey of TB drug resistance and HIV in Mozambique. No statistically significant relationship is found between MDR-TB and HIV: 2.2% of HIV co-infected had MDR-TB while 3.2% of non-HIV infected had MDR-TB with odds ratio 0.7 (95% CI: 0.2, 2.2). HIV testing and sensitivity testing is done on the entire sample of
culture positive TB patients minimizing bias from differential loss to follow up. This study is one of the few to describe baseline characteristics by HIV status. While not an extensive list, it does show that certain factors like education and prior STIs occur at different rates in both groups. The health facilities used are selected randomly but the provinces housing those facilities are not selected randomly. The authors admit that the provinces not selected were systematically different from those selected in health care resources. This could bias the survey’s external validity.

**Europe**

Of the four European studies included in the review, two are surveys from localized areas in Spain, one is a large case control study of national laboratories serving 80% of France’s public hospitals and one is a systematic review itself.

A prospective study by Ausina et al. from Barcelona, Spain was one of the first studies from Europe to address MDR-TB and HIV. The rate of primary MDR-TB in HIV patients was 0.5% while the rate in HIV negative patients was 0.6%. While there is no significant difference in primary resistance patterns by HIV status, statistical testing is not specifically done for MDR-TB. There is also insufficient information given to calculate the relationship between acquired MDR-TB and HIV. While this study was undertaken to study the differences between HIV positive and negative patients, potential confounding factors are also not mentioned. A comparison table by HIV status only addresses resistance patterns. Overall, the study suggests low rates of MDR-TB in both HIV positive and negative patients.
A large survey conducted by Schwoebel et al in France had data on thousands of TB patients from the early 1990's. They find infection with HIV as the only statistically significant risk factor associated with primary MDR-TB with an odds ratio of 5.6 (95% CI: 2.6, 12.1) for HIV positive versus HIV negative. The odds ratio presented is adjusted but the details of the adjusted variables are not given. No statistically significant relationship is found between acquired MDR-TB and HIV. The main strengths of the study are the large sample size (10267 HIV negative patients and 893 HIV positive patients with primary TB) and good external validity since the network of laboratories used served 80% of French public hospital beds. Unfortunately, since rates of MDR-TB by HIV status were not the only outcome, there is insufficient description of baseline characteristics and inadequate discussion of confounding factors. Nonetheless, the template of a large scale TB survey is useful for future studies on MDR-TB and HIV.

The only systematic review/meta-analysis taken for this review is by Faustini et al. Its purpose is to assess risk factors for MDR-TB in Europe and contains seven studies with data on the specific question of HIV and MDR-TB (one of which is the Schwoebel paper which constitutes about 25% of the 'weight' of the final odds ratio). The fact that not all the component studies are found in this larger review highlights some of the difficulties of systematic review. For example, not all the studies included in Faustini are even found in the initial broad PubMed search. While the component studies could be subsequently appraised, they were not because this would essentially repeat the work already done by Faustini. However, the Schwoebel article was included since it was found using the a priori search strategy. The combined data of Faustini show a statistically significant odds ratio of 3.52 (95% CI: 2.48, 5.01) for MDR-TB in HIV.
positive patients. The search strategy and statistical analyses are well described. Basic characteristics of the studies reviewed are given but a detailed description of patient populations, particularly among those included in the 7 studies analyzing HIV, are not given. Interestingly, some variables that can be considered confounders in other studies are used as criteria for study exclusion; these include TB cases limited to an outbreak and studies limited to high risk groups such as prisoners. While the authors did not provide a critical appraisal of individual studies, they discussed limitations in broad terms. The authors admit that selection bias is a major problem given the way groups were formed. Also importantly, there is missing data on risk factors. Because these limitations are not specifically discussed for the seven studies analyzing HIV, the meta-analysis is not as strong. The role of publication bias, an important consideration in meta-analyses, is also left unaddressed.

The most recent study from Europe was from the Castilla-Leon region of Spain. The study showed that overall rates of MDR-TB are low in this particular region and suggests no relationship between MDR-TB and HIV. The rate of MDR-TB in HIV patients was 0% (out of 59 sampled) and the rate was 0.1% in HIV negative patients. The odds ratio for MDR-TB infection in HIV patients is not significant at 0.19 [0-4.8]. The small sample of HIV patients and the low levels of MDR-TB in the region lead to the wide confidence interval. The patient population is not well described though attempts are made to make the sample representative of the area of Castilla-Leon. Nonetheless, these efforts are not fully described. The authors also write that independent variables associated with drug resistance are identified with logistic regression but these variables
are not described afterwards. The reader is left unsure whether the odds ratio presented for MDR-TB is adjusted for these variables.

**Latin America**

Campos et al. published one of the first Latin American studies of MDR-TB and HIV in 2003. This study found one of the strongest associations between HIV and MDR-TB as 43% of HIV/TB patients had MDR-TB while only 3.9% of non-co-infected patients had MDR-TB. The difference is statistically significant with a large sample size in both comparison groups. The study gave a table of baseline characteristics comparing HIV positive and HIV negative patients which suggests certain important differences between groups. These include marriage status, income, exposure to TB at work, inpatient care and receiving ambulatory care at hospitals/health centers. Although these factors are not adjusted for, they at least provide an indication of possible associated variables which confound the relationship. One major concern is where the two groups were drawn from: HIV patients were recruited exclusively from hospitals whereas HIV negative controls were recruited from clinics. The groups might not be apt for comparison. Because hospitalized patients with TB are more likely to have MDR-TB than patients treated at community-based clinics independent of HIV infection status, this study is likely to overestimate the association between HIV and MDR-TB. Among other concerns, this would limit external validity to all HIV patients.

A small study from Brazil by Liberato et al. found no significant relationship between MDR-TB rates by HIV status. Of the HIV co-infected patients, 6.3% had MDR-TB while of the HIV negative patients, 6.6% had MDR-TB. The sample sizes
were small, particularly for HIV patients, for which there were only 16. Since the primary goal of this study was to elucidate characteristics of HIV positive and HIV negative TB patients, there is a table of comparison between the two groups. Some of the differences between the groups include sex, IV drug use, and male homosexual relations. Key variables which are similar include previous TB exposure and alcohol consumption. Some possible confounders of the relationship such as hospitalization are not included. Although the study shows no difference by HIV status, the potential effect of confounders would be useful to consider. Generalizability of the findings was not explicitly addressed. However, since patients were recruited from outpatient clinics, they might be more representative of TB patients than recruiting just from hospitals. Since this study was undertaken in the Northeastern region of Brazil, it would also be useful to compare the characteristics of the health system here with other parts of Brazil.

The third study from Latin America is a recent one from Haiti by Joseph et al.40 The authors find a significant association between co-infection with HIV and primary MDR-TB (10% of HIV infected versus 3% of HIV negative). The authors also find no significant relationship between co-infection with recurrent TB/HIV and MDR-TB. The sample sizes are small only for the recurrent TB cases. Regarding baseline characteristics, the authors write that none were associated with primary or recurrent drug resistance but those investigated were not listed. As such, the potential for unknown confounders remains. The authors even raise the possibility that transmission of MDR-TB at voluntary counseling and testing centers (VCTs) could fuel the spread of the disease. The authors also comment that since national rates in Haiti are unknown, assessing external validity is difficult.
North America

One of the most important studies which brought attention to the problem of MDR-TB was published in 1993 by Frieden et al based on data from New York City. There was a statistically significant difference in MDR-TB rates by HIV status: 19.5% of HIV patients had MDR-TB while 2% of patients with unknown HIV status did. The comparison of HIV patients to those with unknown status could bias the results towards the null if there were by chance HIV positive individuals in the unknown group. Since the study gives a broad description of the emergence of drug resistant TB in New York City, the comparison of MDR-TB rates by HIV status is not the primary outcome. As such, there is no description of baseline characteristics or discussion of confounding factors. Since the study included TB patients from New York City, the generalizability to other populations outside this area is questionable.

Gordin et al. investigated the relationship between MDR-TB and HIV but with the primary intention of comparing a New York City based population to a mixed group from seven other metropolitan areas. In New York, there was a statistically significant difference in MDR-TB rates by HIV status: 19.4% for HIV positive patients and 5.8% for HIV negative. On the other hand, outside of New York, there was no statistically significant difference in MDR-TB rates: 2.8% in HIV positive patients and 1.4% in HIV negative patients. While there was no comparison of baseline characteristics by HIV status, there was a comparison of New York City patients to non-New York patients. Possible confounders like homelessness, unemployment, alcohol use and the use of street drugs were different between the two groups. Because this study samples a wide variety
of patient populations throughout the United States, it has better external validity than studies limited to one area.

A subsequent descriptive analysis by Moore et al. analyzed national data from the United States from 1993-1996, which included a subset of the patients used in the Gordin study.\textsuperscript{43} However, it is unclear exactly how much of the data is overlapped. Moore showed two statistically significant differences in MDR-TB rates by HIV status, one for US born patients and one for foreign born patients (both groups were aged 25-44 years though). Among US born, rates in HIV infected were 6.4% while rates in HIV uninfected were 1.4%. Among foreign born, rates in HIV infected were 4.7% while rates in HIV uninfected were 3.0%. There is little description of the population aside from the resistance data; therefore, it is difficult to assess the importance of outside variables that could have confounded the two relationships. Because this study contains data of all TB patients from the United States, the study is more widely generalizable.

The data used by Moore et al. was also later published by the CDC in a Morbidity and Mortality Weekly Report.\textsuperscript{44} Here the results were not split by foreign born status. Among all HIV patients, 6.2% had MDR-TB while in HIV negative patients, 1.3% had MDR-TB, which was a statistically significant difference. Once again, there is no description of patient characteristics which could help point to confounding factors.

Moore et al. subsequently published a limited part of the same data set (only TB cases from 1993-1994) and found a statistically significant result similar to the previous two analyses: 6% MDR-TB rates in HIV patients and 2% MDR-TB rates in HIV negative patients.\textsuperscript{45} In this study though, limited demographic and clinical characteristics were given, which suggest that the populations are not exactly comparable. HIV patients
were younger, more likely to be male and more likely to be born in the United States. Other important variables of interest like hospitalization and drug use are not listed. Rates of previous TB were similar.

Localized surveillance data continued to be published with Liu et al., who specifically looked at drug resistance patterns in New Jersey in the early 1990s. There was therefore some degree of overlap with the national data published by Moore. MDR-TB rates in HIV patients were 4.9% while they were 1.2% in HIV negative patients. The odds ratio for MDR-TB in HIV compared to non-HIV was statistically significant at 3.6 (95% CI: 1.5, 8.8). Like the many other studies which looked at risk factors, Liu et al. examine factors such as previous TB, homelessness, and injection drug use but do not stratify by HIV status. It is difficult then to assess possible confounders. Because of the close proximity of New Jersey to New York City, the authors admit that the generalizability of these findings remains questionable.

In 1998, Spellman et al. published data from a prospective evaluation of TB patients in Ft. Worth, Texas. They found no significant relationship between MDR-TB rates but HIV positive patients actually had the lower one. Rates in HIV patients were 0% while they were 4% in HIV negative patients. The difference between HIV positive and negative patients is a primary outcome; therefore, the authors present a table of baseline characteristics which highlight some major differences between the groups such as history of drug use and being foreign born. Notably, rates of homelessness and alcohol use are similar between the groups. Previous hospitalization is not listed. Since all TB cases were included from a set time period in Ft. Worth, Texas, the findings are generalizable to both clinic and hospital patients.
Soon after, Taylor et al. published a wider survey of TB in Texas with data from 1987 to 1996.\textsuperscript{48} Like the Spellman study, this found no significant relationship between HIV and MDR-TB. Rates in HIV positive patients were 1.1\% and rates in HIV negative patients were 1.4\% with a risk ratio of 0.78 (95\% CI: 0.50, 1.21). Demographic and clinical variables like history of incarceration, drug abuse, and recurrent TB are presented but not by HIV status. However, the authors do state that there was no nosocomial or prison outbreak of MDR-TB during this time. Regardless, to assess the risk of MDR-TB attributable to HIV, more specific information is needed. Given that all TB patients were included and there were no real eligibility criteria, the external validity is sound.

The final study from the United States was a time series of four cross sectional surveys of TB in New York City, beginning in 1991 and finishing in 2003.\textsuperscript{49} The odds ratio for MDR-TB in HIV positive compared to negative was 7.3 (95\% CI: 2.7, 20.0) in 1991, 5.5 (95\% CI: 0.96, 30.8) in 1994, 1.0 (95\% CI: 0.2, 5.2) in 1997 and 0.8 (95\% CI: 0.04, 17.5) in 2003. The last two surveys show no association between HIV and MDR-TB in New York. Baseline characteristics are presented for all TB patients. The characteristics do suggest changing rates of drug use, previous treatment and foreign born among TB patients. Unfortunately, it is not possible to assess the role of these possible confounders since they are not presented by HIV status. As with the other studies from a specific area, the findings in New York over these 4 surveys are not obviously generalizable because of specific variables that might be unique to the area (such as percentages of foreign born or drug users etc).
<table>
<thead>
<tr>
<th>First author</th>
<th>Year of Publication</th>
<th>Country</th>
<th>Number of HIV+ patients</th>
<th>% MDR-TB in HIV+ patients</th>
<th>Number of HIV- patients</th>
<th>% MDR-TB in HIV- patients</th>
<th>Authors' conclusion regarding risk of MDR-TB in HIV+ patients</th>
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<tr>
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<td>192</td>
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<td>685</td>
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<td>377</td>
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<td>49</td>
<td>40.8%</td>
<td>85</td>
<td>32.9%</td>
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<td>6</td>
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</tr>
<tr>
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<td></td>
<td></td>
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<tr>
<td>Braun28</td>
<td>1992</td>
<td>Cote d'Ivoire</td>
<td>17</td>
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<td>29</td>
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</tr>
<tr>
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<td>815</td>
<td>1.1%</td>
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</tr>
<tr>
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<td></td>
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<td>21</td>
<td>4.8%</td>
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<td>7.7%</td>
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<td>253</td>
<td>11.5%</td>
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</tr>
<tr>
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<td>South Africa</td>
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<td>2.6%</td>
<td>115</td>
<td>2.9%</td>
<td>No increased risk*</td>
</tr>
<tr>
<td>Kenyon32</td>
<td>1999</td>
<td>Botswana</td>
<td>107</td>
<td>0.9%</td>
<td>119</td>
<td>0.8%</td>
<td>No increased risk</td>
</tr>
<tr>
<td>Murray33</td>
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<tr>
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<td>Mozambique</td>
<td>179</td>
<td>2.2%</td>
<td>530</td>
<td>3.2%</td>
<td>No increased risk, OR 0.7 [95% CI: 0.2, 2.2]</td>
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<td>1995</td>
<td>Spain</td>
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<td>0.5%</td>
<td>317</td>
<td>0.6%</td>
<td>No increased risk*</td>
</tr>
<tr>
<td>Schwoebel36</td>
<td>1998</td>
<td>France</td>
<td>893</td>
<td>1.2%</td>
<td>10267</td>
<td>0.2%</td>
<td>Increased risk in primary, OR 5.6 [95% CI: 2.6, 12.1]</td>
</tr>
<tr>
<td></td>
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<td>107</td>
<td>11.2%</td>
<td>2015</td>
<td>3.9%</td>
<td>No increased risk in acquired MDR, OR 1.6 [95% CI: 0.8, 3.1]</td>
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<td>Study</td>
<td>Year</td>
<td>Region</td>
<td>Country</td>
<td>Cases</td>
<td>%</td>
<td>Controls</td>
<td>%</td>
</tr>
<tr>
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<td>------</td>
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<td>-------</td>
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<tr>
<td>Faustini</td>
<td>2006</td>
<td>Europe</td>
<td>Europe</td>
<td>2843</td>
<td>4.1%</td>
<td>49111</td>
<td>1.2%</td>
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<tr>
<td>Alberte-Castineiras</td>
<td>2006</td>
<td>Spain</td>
<td>Spain</td>
<td>59</td>
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<td>925</td>
<td>0.1%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Campos</td>
<td>2003</td>
<td>Peru</td>
<td>Peru</td>
<td>81</td>
<td>43%</td>
<td>955</td>
<td>3.9%</td>
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<tr>
<td>Liberato</td>
<td>2004</td>
<td>Brazil</td>
<td>Brazil</td>
<td>16</td>
<td>6.3%</td>
<td>76</td>
<td>6.6%</td>
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<tr>
<td>Joseph</td>
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<td>Haiti</td>
<td>Haiti</td>
<td>115</td>
<td>10%</td>
<td>165</td>
<td>3%</td>
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<tr>
<td>- primary MDR-TB</td>
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<tr>
<td>- acquired MDR-TB</td>
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<td></td>
<td>16</td>
<td>0%</td>
<td>33</td>
<td>30%</td>
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<td>Frieden</td>
<td>1993</td>
<td>USA (NYC)</td>
<td>USA (NYC)</td>
<td>82</td>
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<td>Gordin</td>
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<td>252</td>
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<tr>
<td>- non-NYC</td>
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<td></td>
<td>179</td>
<td>2.8%</td>
<td>473</td>
<td>1.4%</td>
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<tr>
<td>Moors</td>
<td>1997</td>
<td>USA</td>
<td>USA</td>
<td>6442 (total)</td>
<td>6.4%</td>
<td>5955 (total)</td>
<td>1.4%</td>
</tr>
<tr>
<td>- USA born</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Liu</td>
<td>1998</td>
<td>USA (NJ)</td>
<td>USA (NJ)</td>
<td>555</td>
<td>4.9%</td>
<td>413</td>
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<tr>
<td>Spellman</td>
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<td>USA (TX)</td>
<td>USA (TX)</td>
<td>646</td>
<td>0%</td>
<td>55</td>
<td>4%</td>
</tr>
<tr>
<td>CDC MMWR</td>
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<td>USA</td>
<td>5112</td>
<td>6.2%</td>
<td>3754</td>
<td>1.3%</td>
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<td>Moore</td>
<td>1999</td>
<td>USA</td>
<td>USA</td>
<td>5833</td>
<td>6%</td>
<td>42828</td>
<td>2%</td>
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<tr>
<td>Taylor</td>
<td>1999</td>
<td>USA (TX)</td>
<td>USA (TX)</td>
<td>2221</td>
<td>1.1%</td>
<td>---</td>
<td>1.4%</td>
</tr>
</tbody>
</table>
Munsiff*9 | 2006 | USA (NYC) | -- | -- | -- | -- | No increased risk in last two surveys, ORs from 4 years: 1991 OR: 7.3 [95% CI: 2.7, 20.0], 1993 OR: 5.5 [95% CI: 0.9, 30.0], 1997 OR: 1.0 [95% CI: 0.2, 5.2], 2003 OR: 0.8 [95% CI: 0.04, 17.5]

* Signifies no statistical testing done to test the difference

### TABLE 4: QUALITY CRITERIA

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>Sample size &gt; 50</th>
<th>Statistical testing of differences</th>
<th>Baseline characteristics described</th>
<th>External validity considered</th>
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<td><strong>SOUTHEAST ASIA</strong></td>
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<td></td>
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<td>Punnotok9</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
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<td>✓</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>— acquired MDR-TB</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Quy27</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
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<td><strong>SUB-SAHARAN AFRICA</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Braun26</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chum26 - primary MDR-TB</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>— acquired MDR-TB</td>
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<td>✓</td>
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33
<table>
<thead>
<tr>
<th></th>
<th>Ausina\textsuperscript{35}</th>
<th>Schwoebel\textsuperscript{36}</th>
<th>Faustini\textsuperscript{37}</th>
<th>Alberte-Castineiras\textsuperscript{38}</th>
<th>Campos\textsuperscript{39}</th>
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DISCUSSION

The twenty-six studies reviewed in this article come from different areas around the world and different time periods. Some are based on large nation-wide surveys while others are smaller studies and include just a few TB patients with and without HIV. The results themselves are quite disparate with some showing a strong relationship between HIV and MDR-TB and others showing no effect. To understand the implications of the synthesis in this review article, it is necessary to consider the possible biological mechanism of a link between HIV and TB drug resistance.

Possibilities for a causal link

Dye considers five possible mechanisms linking drug resistant TB to HIV.\textsuperscript{51} One is “functional monotherapy”. The argument is that HIV patients are more likely to be subjected to monotherapy, a significant risk factor for drug resistance, than non-HIV patients. This could occur if reduced immune function allows \textit{M. tuberculosis} to continue replication even after the initial 2 month intensive treatment period (four drugs) in HIV patients. Thus, HIV patients would be more likely to have reproducing bacteria that are only treated by rifampin or isoniazid during the continuation phase of TB treatment. Another cause of functional monotherapy could be due to drug malabsorption in HIV patients. Malabsorption of rifampin and ethambutol in HIV patients has been shown to lead to treatment failure.\textsuperscript{52}
A second mechanism is that drug resistant strains of TB are less virulent and would preferentially lead to disease progression in immune compromised patients who cannot fight off the bacteria as easily. Data supporting this hypothesis comes from laboratory studies and some animal data but has not been shown in humans. A third possibility is that MDR-TB among HIV patients could actually be reflective of time of infection. Non-HIV patients who develop TB might be reactivating a latent infection from decades ago, whereas HIV patients who develop TB might be reactivating a latent infection acquired much more recently. With the increasing prevalence of drug resistance globally, a higher percentage of recent infections are likely to be drug resistant compared to infections that occurred in the more distant past.

A fourth mechanism linking MDR-TB to HIV involves bacterial burden. HIV patients might harbor greater numbers of *M. tuberculosis* than non-HIV patients because of immunosuppression and the inability to fight off infection. This could mean that a prolonged treatment course would be necessary in HIV patients to achieve the same levels of bacterial burden in non-immune compromised patients. This pathway could then be tied to functional monotherapy since more HIV patients would possibly enter the continuation phase of TB therapy with uncontrolled levels of bacteria. Having more bacteria could also make the population of *M. tuberculosis* in HIV patients more genetically diverse and thus inherently more susceptible to drug resistance.

The final mechanism on which Dye focuses is shared risk factors for HIV and drug resistant TB strains. These shared risk factors can essentially be considered confounders of the relationship between MDR-TB and HIV. Confounding occurs when the exposure effect is mixed with the effect of another variable, which causes bias. Dye
suggests injection drug use and hospitalization as two possible confounders. Injection
drug use is a risk factor for HIV infection but also for tuberculosis and MDR-TB.
Hospitalization is a confounder because it is associated with HIV infection and also
associated with conditions needed for the spread of MDR-TB such as close contact.
Unrecognized MDR-TB infection in a hospital could spread quickly among HIV patients
because of immune suppression. By the same token, outbreaks of MDR-TB in the
community are more likely to appear in HIV patients because they are the most
susceptible. Other possible shared risk factors include imprisonment, education level
and other measures of socioeconomic status, unemployment and alcohol use. Of note, it
might be useful to consider time of TB infection, which is labeled in the causal pathway,
as a confounding variable as well. Time since infection is associated with resistance
patterns but it also might be associated with HIV infection as well.

The difference between the causal pathway from HIV to MDR-TB and
confounding factors is critical. The goal of this review is to understand if HIV on its own
confers a specific attributable risk for MDR-TB, measurable with odds ratios or risk
differences. These specific risks are difficult to glean from the published literature
because of the important effects of confounding factors. Ideally, adjusted risk ratios
would be presented which take into account factors like hospitalization, socioeconomic
status or imprisonment. Unfortunately, given the current available data, these estimates
cannot yet be calculated.
What can we learn from the published studies?

Except for the studies from Africa, where the majority of studies fail to demonstrate an association between HIV and MDR-TB, the results from studies performed in other regions of the world produced conflicting results.

The initial history of MDR-TB in the early 1990s seemed to show strong evidence of a link with HIV. In a seminal paper, Frieden et al show that in some of the first documented outbreaks of nosocomial MDR-TB in New York City, HIV was a significant risk factor. Speculation for the association stemmed from the causal possibilities listed previously. The large CDC survey as well as national data published by Moore et al appeared to confirm the initial findings from New York City. However, at the same time,
other smaller studies found no relationship. Perhaps one of the most illuminating studies was that of Munsiff et al which calculated four time series odds ratios for MDR-TB infection by HIV status based on surveillance data from four surveys over twelve years in New York City. The lack of association between HIV status and MDR-TB in the most recent surveys suggests a time trend that is difficult to glean from a cursory look at the results of other studies from the United States. One conclusion of this study could be that the relationship between MDR-TB and HIV can change over time. However, another possibility is that the confounding variables are the ones that changed over time and the risk attributable to HIV remained the same. This is certainly a possibility in New York where variables like hospitalization, proportion of foreign born and outbreak control could have changed.

The studies from Europe show no clear trend. Two of the smaller studies, both from Spain, show no relationship between MDR-TB and HIV. However, given the small numbers of MDR-TB cases in both of these studies, neither provides convincing data. Faustini et al provide a meta-analysis of European studies, which includes the Schowoebel study from France. The combined large sample (n=2727 for HIV positive and n=48571 for HIV negative) of the meta-analysis gives an odds ratio of 3.52 (95% CI: 2.48, 5.01) for MDR-TB by HIV status but the authors admit that the selection of HIV infected patients may have been biased. Regardless, the authors contend that their results suggest that HIV infection favors the transmission of MDR-TB compared to drug sensitive TB in Europe in the late 1990s and early 2000s. As the estimate was not adjusted for potential confounders, it remains uncertain if HIV is the driver of the association or whether the association is due to the presence of confounding variables.
Studies from Latin America also produced contrasting results. The studies are notable for being among the few that consider baseline characteristics as potential confounders of the relationship between HIV and MDR-TB. While neither offers statistical adjustments, Campos in particular suggests that income, workplace exposure to TB, inpatient care and receiving ambulatory care may be confounders of the association between HIV and MDR-TB.

Of the three studies from Southeast Asia, two Thai studies found a statistically significant relationship between HIV and MDR-TB whereas the study from Vietnam found no significant relationship. Yoshiyama encourages the reader to apply the lesson from Munsiff et al, which is that local factors are important in determining the relationship between HIV and MDR-TB. Similar to the US and Europe, Thailand introduced rifampin before the emergence of HIV. Once HIV did emerge, MDR-TB strains were probably already circulating and the stage was set for an upsurge in MDR-TB cases, especially among HIV patients who progress quickly from infection to disease. Nonetheless, the contribution of unaccounted for confounders in these studies clouds the association between MDR-TB and HIV.

One of the most important fronts for TB/HIV co-infection is sub-Saharan Africa. While the seven studies from that region included in this review may have had limitations, none found a relationship between HIV and MDR-TB. The studies came from a variety of locales and ranged from the early 1992 to 2001. Taken as a whole, they suggest that during this time period in sub-Saharan Africa, it seems likely that there was no association between drug resistant TB and HIV. The contrast with other regions in the world could be related to the timing of introduction of rifampin. The relatively high cost
of rifampin led to delayed introduction of this drug into sub-Saharan African. Consequently, MDR-TB may not have had the opportunity to take hold in sub-Saharan Africa prior to the time when HIV began its devastating conquest of the continent. HIV uncovered the untold amount of latent TB infections, but these had yet to acquire drug resistance. It is important to note that the most recent study from Africa was published in 2001. Most recently, outbreaks of XDR, or extensively drug resistant tuberculosis (defined as resistance to isoniazid, rifampin and at least three classes of second-line drugs), have brought frightening implications for the continent. One study from South Africa argued that the prevalence of MDR is higher than earlier estimated and that XDR is being disproportionately transmitted to HIV infected patients. The changing epidemiology of MDR and XDR in South Africa might indicate an altering of the previous balance between MDR-TB and HIV. However, the body of literature on XDR-TB is still small.

**Assessing publication bias**

When considering the results and implications of a systematic review, it is imperative to judge the contribution of publication bias. A review is only as strong as its component studies but its strength is also determined by what information is not included. Traditionally this form of bias refers to the publication of only studies that show a statistically significant association or effect. Although this review is not a meta-analysis and there is no funnel plot to assess publication bias, there are some reassurances against this traditional form of publication bias. First of all, a number of the studies in this review actually show no significant relationship between MDR-TB and HIV. Secondly,
the relationship between the two was often not the primary research question in many studies. Some were surveys to find the proportion of TB cases which were drug resistant in the whole population and others were intended to explore a number of risk factors for MDR-TB. Accordingly, the relationship between HIV and MDR-TB was often a secondary outcome and was not subject to the same publication debate as primary outcomes.

Another consideration is the omission of certain countries from the published literature. For this review, the argument can be made that if the relationship between HIV and MDR-TB is causal, it would not matter where the component studies are drawn from. The key would be to adjust for potential confounders. However, this has not been readily done in the published literature. It will be important to collect data from areas where the burden of MDR-TB is disproportionate, like Russia, Eastern Europe, India and China. While not necessarily answering the question of the attributable risk of HIV for MDR-TB, data from these areas would give a better idea of the current association between the two.

*Do we need a meta-analysis?*

The data extracted from the individual studies and presented in this review is amenable for pooling into one risk ratio. A meta-analysis would give a clear, qualitative relationship between MDR-TB and HIV. However, the presentation of one ratio should be considered carefully.

The major reason not to pool the data is the poorer methodologic quality of many of the component studies. To answer the question of the specific risk associated with
HIV and MDR-TB, calculations must be adjusted for associated variables which can confound the relationship. Most studies do not give baseline characteristics of HIV positive or HIV negative patients, do not adequately consider confounding factors and not a single study estimated a measure of association between HIV and MDR-TB adjusted for confounders. Meta-analysis would thus combine studies that were subject to various levels of confounding.

**Implications for practice and new research**

Given that there are no uniform results from the review, implications for clinical and public health practice are limited. There is no denying that HIV and tuberculosis are intimately linked. Health care providers should always consider tuberculosis as a cause of opportunistic infection in HIV patients. On the other hand, providers should consider HIV as a cause of reemergence of latent TB infection or a predisposal factor in newly acquired TB infection. As of yet, there does not seem to be the need for global caution for a higher likelihood of MDR-TB among people living with HIV. Caution for MDR-TB in the co-infected may not be a priority in the United States or sub-Saharan Africa currently but it may be in Southeast Asia or Europe. Nonetheless, constant vigilance will be necessary. The ties between HIV and MDR-TB can change as evidenced by time series surveys in the United States and possibly by the rising epidemic of XDR-TB in sub-Saharan Africa. Steady surveillance of MDR-TB among HIV positive and negative people should thus be an essential part in allocating health care resources effectively to combat TB and HIV.
In terms of public health research, this review demonstrates clear needs. More complete surveys on TB/HIV co-infection are needed throughout the world. These surveys and subsequent publications should be undertaken with sound methodology, including attention to statistical tests, sample sizes, baseline characteristics and potential confounders. As noted, rates of MDR-TB might vary between primary and acquired cases due to more resistant strains circulating at different times. To investigate this, future research should clearly delineate patients as either primary or acquired cases of MDR-TB and analyze rates in the two groups.

The public health and medical community should not have to rely on small, isolated surveys for two of the largest problems in public health worldwide. The relationship between HIV and drug resistant TB also needs to be established in certain crucial areas like Russia, India and China. A final implication is that surveillance research of HIV and TB should be intrinsically tied together. The infrastructure for HIV surveillance could be hitched onto well established TB surveillance programs and vice versa. A united front will help combat what is becoming one massive problem of co-infection, which is turning out to be greater than the sum of its two components. Furthermore, this will allow a much better appraisal of the future of MDR-TB.
REFERENCES


