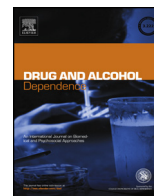




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### Review

# Tuberculosis, drug use and HIV infection in Central Asia: An urgent need for attention

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### ARTICLE INFO

#### Article history:

Received 2 May 2013

Received in revised form 11 July 2013

Accepted 12 July 2013

Available online xxx

#### Keywords:

Tuberculosis

Injection drug use

HIV

Central Asia

### ABSTRACT

**Introduction:** Rates of tuberculosis in Central Asia are extremely high, and even more alarming are the very high rates of multidrug-resistant tuberculosis (MDR-TB) in Kazakhstan, Uzbekistan, Tajikistan and Kyrgyzstan. In addition, rates of HIV infection related to injection drug use seems to be rising as well, thus creating conditions for a potentially devastating co-epidemic of TB/HIV and MDR-TB/HIV which would have terrible consequences for public health in these countries.

**Current status:** In many countries of Central Asia, diagnosis of tuberculosis still rests on clinical grounds or simple technologies such as chest radiograph and sputum smear examination. Modern molecular techniques such as GenExpert are being introduced in Kazakhstan and Uzbekistan, and perhaps soon in Kyrgyzstan. Treatment of TB is still often centered around prolonged inpatient stay at TB hospitals. Only a minority of patients with HIV infection are receiving ART, and TB and HIV services are not well integrated. Needle exchange programs are becoming increasingly available, but opioid substitution therapy is rarely used in Central Asia. TB, drug treatment and HIV services are generally not well-integrated.

**Conclusions:** To combat this developing storm, integration of TB services, HIV care, and substance abuse treatment programs is needed urgently to allow efficient and effective diagnosis and treatment of these conditions in a coordinated manner.

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## 1. Introduction

Tuberculosis is one of the world's leading public health problems. Twenty years after the World Health Organization classified tuberculosis as a global public health emergency, it remains the 10th leading cause of death in the world, and cases seem to be declining globally only at a rate of about 1% per year, according to WHO estimates. In the last twenty years, two features of global tuberculosis epidemiology have posed great challenges to worldwide control efforts: HIV infection and the emergence of multidrug-resistant tuberculosis (MDR-TB, defined as a case of tuberculosis resistant to at least isoniazid and rifampin). Both of these threaten to erase any and all gains that have been made in controlling tuberculosis globally in the past several decades, and both are of particular importance for the overall situation of tuberculosis in Central Asia.

### 1.1. Tuberculosis in Central Asia

Incidence rates for TB overall in Kazakhstan, Uzbekistan, Tajikistan and Kyrgyzstan are extremely high (see Table 1). More worrisome, all of these countries of Central Asia are among the 27 high-burden countries for MDR-TB in the world. The percentages both of new cases and previously treated cases of tuberculosis that demonstrate multidrug-resistance in Kazakhstan, Uzbekistan, Tajikistan and Kyrgyzstan are among the highest in the world (see Table 1). The burden of HIV-associated tuberculosis, an enormous problem in sub-Saharan Africa, seems to be much lower in Central Asia at present, although HIV infection rates in Central Asia seem to be rising quite rapidly, and in some estimates are the fastest rising rates in the world (Thorne et al., 2010).

According to WHO, the percentage of TB cases in which there is HIV co-infection in Kazakhstan, Uzbekistan, and Tajikistan is 2%, 3%, and 2%, respectively, and in all these countries 82–100% of TB patients have been tested for HIV. (Data from Kyrgyzstan are sparse and unreliable in regards to HIV-testing of TB patients.) Given the rapidly rising HIV infection rates in Central Asia and the already very high rates of tuberculosis and MDR-TB, it seems likely that in the very near future, the incidence of HIV infection among persons with tuberculosis will begin to rise quickly, and this will pose enormous challenges to the tuberculosis control programs in these countries. This will require substantial efforts and improvements in diagnosis and treatment to control the staggering epidemics of tuberculosis and especially drug-resistant tuberculosis in Central Asia.

In many ways, the situation in Central Asia is reminiscent of, though certainly worse than, the tuberculosis epidemic in New York in the late 1980s and early 1990s. At its peak in 1992, there was an overall incidence rate of 50.4/100,000 and 13% of new cases were MDR. At that time, there were very high rates of substance abuse among TB patients in New York, and this similarly posed great challenges for the TB control program there (Selwyn et al., 1989). Currently, the brewing storm of TB and HIV among IDUs in Central Asia is under-recognized, almost unknown, and without prompt recognition, it threatens to grow quickly.

This paper will focus on the following issues related to diagnosis and treatment of TB in HIV-infected IDUs: the need for more

intensive diagnostic approaches, the complex problems of simultaneous treatment of TB and HIV, adherence to treatment, and the need to integrate programs of care for TB, HIV and substance abuse.

### 1.2. Drug use and HIV infection in Central Asia

The total number of drug users in the four Central Asian countries is estimated to be between 340,000 and 417,000 (Renton et al., 2006). One of the well-studied countries in Central Asia in terms of drug use is Kazakhstan. Overall, it is estimated that 1% of the population of Kazakhstan are injection drug users, although as many as 10% of the population along major drug trafficking routes inject drugs. The government estimates that there are a total of 122,850 injection drug users in the country, of whom 17,000 reside in Almaty, the country's largest city (Yusopov et al., 2012).

In a recent study from Uzbekistan, nearly 30% of a sample of injection drug users was HIV positive (Sanchez et al., 2006). A study carried out in Almaty, the largest city in Kazakhstan, similarly found that 28% of injection drug users were HIV infected (El-Bassel et al., 2013). Contributing to the problem is the relatively limited availability of harm reduction programs such as substitution therapy in this region (Thorne et al., 2010). HIV infections increased by 20% in Eastern Europe and Central Asia from 2005 to 2011, and most of the increase was seen in young injection drug users. UNAIDS estimates that only about 25% of HIV-infected persons in the region are receiving antiviral therapy, and as a result AIDS-related mortality increased by 21% in Eastern Europe and Central Asia from 2005 to 2011 (UNAIDS, 2012).

Extant data therefore suggests the potential for rapid escalation of an already serious problem regarding tuberculosis in Central Asia: very high rates of tuberculosis and MDR-TB in a region with a high-prevalence of injection drug use, an increasing incidence of HIV infection among drug users, and few services related to harm reduction for drug use. Injection drug use, independent of HIV infection, has repeatedly been shown to be a risk for tuberculosis, owing to a combination of behavioral and biological factors related to TB knowledge, shared living quarters, and immune dysregulation (Casal et al., 2005; Nyamathi et al., 2004).

## 2. Tuberculosis, drug use and HIV infection in Central Asia

Few studies have examined the convergence of tuberculosis and HIV infection in Central Asia especially among people who use drugs, but experience in other regions around the world points to several areas of great challenges, mostly related to diagnosis of tuberculosis in HIV positive patients, difficulties of drug treatment in persons co-infected with HIV and TB, and problems of adherence to therapy for tuberculosis patients, particularly those with ongoing substance abuse problems. We will comment briefly on each of these challenges.

**Table 1**  
Incidence and prevalence of tuberculosis and multidrug-resistant tuberculosis in Central Asia.

|   | Kazakhstan | Uzbekistan | Tajikistan | Kyrgyzstan |
|---|------------|------------|------------|------------|
| TB incidence (per 100,000 population)               | 129        | 101        | 193        | 128        |
| Percentage of new cases of TB that are MDR          | 30%        | 23%        | 13%        | 26%        |
| Percentage of previously treated cases that are MDR | 51%        | 62%        | 54%        | 52%        |

WHO Global TB Report, 2012.

### 2.1. Diagnosis of tuberculosis in persons with co-occurring tuberculosis, injection drug use and HIV-infection

In the countries of Central Asia, national tuberculosis programs (NTP) are responsible for tuberculosis control; these programs in general are highly centralized, reflecting the systems put in place under the former Soviet Union. Diagnosis is generally made in one of two ways. Either patients present to local polyclinics (community health centers) for evaluation of typical complaints of fever, cough and weight loss, or as part of routine health screening with mini mass chest radiographs (MMR). The exact contribution of each of these two methods is difficult to assess with accuracy however. A recent study noted that in Uzbekistan, for example, the NTP reported that at least 50% of the population is screened with MMR and that 73% of cases are detected by this method (Hasker et al., 2008b). However, when researchers interviewed a randomly selected sample of patients, only 16% were detected by mass chest radiographic screening.

It seems that presentation to a polyclinic and then referral to a specialized TB hospital for diagnosis, primarily by AFB smear, is a more common scenario. This approach at times introduces long diagnostic delays. A recent report from Tajikistan noted that total delays to TB treatment were heavily affected by site of first presentation—the type of facility of first presentation was the strongest predictor of diagnostic delays, which reached as long as 52 days (Aye et al., 2010). Recent attempts in some Central Asian countries to improve diagnostic services in primary care settings have been met with modest success. The Practical Approach to Lung Health strategy (a 10-step program based on WHO-recommended best practices) instituted in Kyrgyzstan failed to achieve any improvement in tuberculosis case detection (Brimkulov et al., 2009; Erhola et al., 2009). Because of diagnostic delays and the high prevalence of multidrug resistant tuberculosis in the region, there has been great interest in rapid molecular diagnostics for tuberculosis, and four GenExpert machines, capable of diagnosing tuberculosis and detecting rifampin resistance in less than two hours, were recently delivered to Kazakhstan and Uzbekistan, and machines may soon arrive in Kyrgyzstan. No data are yet available on the impact of these machines on TB diagnosis in that country, however. Uptake and implementation of these sophisticated new diagnostic modalities will be critical for improvements in tuberculosis control (Boehme et al., 2010). WHO urges use of this system in regions with a high prevalence of MDR-TB, and all countries of Central Asia have this need. Analyses in nearby regions with similar challenges indicate that this approach is likely to be cost-effective (Winetsky et al., 2012).

Until recently, TB and HIV clinical services were quite separate in this region, but there have been attempts to integrate testing, and early reports have indicated some success. A recent report from Kazakhstan, where testing of all TB patients for HIV is national policy, found that from March 2009 to March 2010, the percentage of TB patients with missing HIV test results fell from 11.5% to 3.6% (UNAIDS, 2012). Data from other Central Asian countries is not readily available.

Patients who are drug users often have delays in diagnosis (Diez et al., 2004; Golub et al., 2006). Reasons for these delays may include lack of awareness of TB symptoms, lack of availability and access to healthcare facilities, and even perhaps reduced awareness of symptoms because of ongoing drug use (Deiss et al., 2009). Among patients with HIV infection, diagnostic sensitivity of tests such as the tuberculin skin test, interferon gamma release assays and the sputum smear examination are all reduced compared with patients with intact immunity, and this can lead to further delays in diagnosis (Brodie and Schluger, 2005; Schluger, 2013). In addition, active tuberculosis case finding may provide benefit in regions with a high prevalence of HIV and TB co-infection (Dowdy

et al., 2013; Kranzer et al., 2013; Nishikiori and Van Weezenbeek, 2013).

### 2.2. Treatment of latent and active tuberculosis in persons who inject drugs and are living with HIV

**2.2.1. Prolonged hospitalization.** Treatment of tuberculosis in Central Asia is often marked by prolonged hospitalization in specialized tuberculosis hospitals; this practice is a holdover from the days of the Soviet Union when this practice was the standard. It is routine for patients with drug susceptible tuberculosis in many Central Asian countries to be hospitalized for two to three months, and patients with drug resistant tuberculosis are often hospitalized for much longer durations. This is an expensive approach to treatment and it also raises concerns about infection control and nosocomial transmission of tuberculosis.

Recent WHO reports note challenges and progress to tuberculosis treatment in Central Asia, particularly in the most populous countries, Kazakhstan and Uzbekistan. In its 2011 Tuberculosis Country Work Summary Report, WHO noted that “an underlying cause of this [excessive hospitalization] is the reverse incentive system, which promotes hospitalization of TB patients and discourages ambulatory care. . . . There is a need to reduce hospitalization of TB patients and improve service delivery at the primary level of health care, while at the same time improving infection control standards and restructuring the financing system.” (WHO, 2011b).

In Uzbekistan, where the challenge is more acute: “the measures to prevent nosocomial transmission of TB need to be intensified and the recording and reporting system should be optimized in order to prevent double reporting and better serve surveillance.” (WHO, 2011c).

In the past few years, efforts are beginning to break away from the practice of prolonged hospitalization. In Tajikistan, a recent survey indicated that 58% of patients were hospitalized, and those who were male and sputum smear positive were more likely to be hospitalized than smear negative patients or women (Thierfelder et al., 2008). Directly observed therapy (DOT) for outpatients is part of the national TB guidelines in Uzbekistan, Kazakhstan and Tajikistan, although data on the performance and outcomes of DOT programs in this region is limited. Kazakhstan has reported widespread use of DOTS since 1998, and a recent report indicates that this strategy has resulted in a decrease in TB-related mortality there (Favorov et al., 2010). Uzbekistan has reported 100% DOTS coverage since 2005, for example, but acquired drug resistance appears to be common. Reports from Uzbekistan indicated that there were high levels of amplification of drug resistance under well-established DOTS program conditions, especially in patients with initial poly-drug resistance (i.e., resistance to more than one drug but not isoniazid and rifampin together; Cox et al., 2006, 2007a,b). A study of defaulters from treatment in Uzbekistan indicated that poor communication between health care staff and TB patients was a major contributor to this problem, as was the generally poor conditions found in TB hospitals, and a belief that TB was not curable under any circumstances (Hasker et al., 2008a). A second study in the same country reported that unemployment, alcoholism and homelessness were also important factors, as was obligatory hospitalization for TB treatment (Hasker et al., 2010).

**2.2.2. Incarceration.** Similarly, there have been numerous well-documented instances of transmission of tuberculosis and especially multidrug-resistant tuberculosis in prisons in Russia and countries of Central Asia. One carefully done study found that each percentage point increase in incarceration rates was related to an increased TB incidence of 0.34% in Central Asian nations, even when controlling for TB infrastructure, HIV prevalence, and several surveillance, economic, demographic and political indicators

(Stuckler et al., 2008). This rise was exacerbated by HIV infection in the prison population.

**2.2.3. TB drug supply.** Inadequate and non-specialized control of national supplies of TB drugs further exacerbates TB treatment efforts. In Uzbekistan the WHO reports “the increasing MDR-TB rates underline the need for improved diagnosis of TB, better patient and drug management, and infection control measures in line with international standards. . . . anti-TB drugs can be obtained without a doctor’s prescription. In addition, second line anti-TB drugs are not available throughout the whole country.” (WHO, 2011c).

### 2.3. Adherence to tuberculosis treatment in injection drug users with HIV infection

In Central Asia, there is limited attention for adherence to TB treatment for people who use drugs. There are models that have been used successfully in other locations that could inform practice in Central Asia. For example, the model used in New York City can be implemented in this region. In New York City in the mid-to-late 1980s, tuberculosis commonly occurred among patients with HIV infection and drug use, and self-administration of treatment of tuberculosis was associated with very low rates of treatment completion, with disastrous results (Brudney and Dobkin, 1991). In response to this, comprehensive programs of directly observed therapy (DOT) were instituted, and these programs were associated with high rates of treatment completion, even in patients with ongoing drug and alcohol abuse problems (Schluger et al., 1995).

A major limitation in adherence to tuberculosis treatment is ongoing drug use. In this regard, the lack of opioid substitution therapy in Central Asia may substantially limit compliance and adherence to TB treatment. A recent UNAIDS report indicates that only 0.1% of drug users in Kazakhstan and Tajikistan receive opioid substitution treatment (WHO, 2011a). The best and most effective DOT programs combine excellent nursing services, patient education, referral to or integration with HIV and substance abuse programs, and linkages to social service programs that can provide housing and food assistance. DOT programs also allow provision of complex tuberculosis treatment regimens in the community, and DOT which integrates HIV and drug abuse services obviates the need for costly and prolonged hospitalization. Central Asian nations could benefit greatly from using this approach.

## 3. Discussion

Ongoing and increasing problems of substance abuse and HIV infection in Central Asia are combining with very high rates of drug susceptible and drug resistant tuberculosis in Kazakhstan, Uzbekistan, Tajikistan and Kyrgyzstan to create a public crisis of potentially enormous proportions. Currently, HIV treatment is available only to a minority of patients in the region, with WHO estimating that 30% of eligible patients in Kazakhstan, 28% of patients in Uzbekistan, and 16% of patients in Tajikistan are being covered by ART (UNAIDS, 2012; WHO, 2013a,b,c). A recent report prepared for UNAIDS and the World Bank indicated that although needle exchange programs in Kazakhstan has expanded rapidly in the years from 2000 to 2010, availability was still limited. Furthermore, the authors of the report noted that they had significant concerns relating to data quality: “despite the appearance of a wealth of data, it was not possible to validate the behavioral and biological data collected by the AIDS Centre because of lack of availability of other comparable studies conducted at the national level. Even those conducted at regional levels were not comparable in terms of inclusion criteria and data collection tools.” (Wilson et al., 2011).

In addition, tuberculosis control programs operate largely in isolation from other healthcare services. In order to meet this challenge, substantial changes and improvements to programs of tuberculosis control, substance abuse treatment and HIV treatment are needed (Getahun et al., 2012; Grenfell et al., 2013). These programs must become highly integrated, so that diagnostic and treatment services can be provided in an efficient and effective manner. Providers must be educated in the complexities of management of all three realms. Social needs of people who use drugs, and are co-infected with HIV and tuberculosis must be attended to.

Failure to integrate and improve health services for these important problems will lead to the creation of a spiral of increasing rates of tuberculosis and HIV infection, among people who use drugs as inadequate treatment of any one of them will cause more transmission of TB and HIV. Effective programs have been created in a number of regions around the world, and these models should be adopted in Central Asia.

### Role of funding source

There was no outside funding for this review.

### Contributors

Neil Schluger performed the literature review and drafted the manuscript. Nabila El-Bassel reviewed and revised the manuscript. Sabrina Hermosilla reviewed and revised the manuscript. Assel Terlikbayeva reviewed and revised the manuscript. Meruyert Darisheva reviewed and revised the manuscript. Angela Aifah aided in performing the literature review and reviewed and revised the manuscript. Sandro Galea reviewed and revised the manuscript. All authors have contributed to and approved the final manuscript.

### Conflict of interest

All authors declare that they have no conflict of interest pertaining to this manuscript.

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