CASE REPORT

Combined antiretroviral and anti-tuberculosis drug resistance following incarceration

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We describe a case of HIV/tuberculosis (TB) co-infection from KwaZulu-Natal, South Africa, characterised by drug resistance in both pathogens. The development of drug resistance was linked temporally to two periods of incarceration. This highlights the urgent need for improved integration of HIV/TB control strategies within prison health systems and within the broader public health framework.

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The twin epidemics of HIV and tuberculosis (TB) have had a devastating impact on individuals, families and communities in South Africa (SA) over the past two decades.[1] SA alone is responsible for almost one-third of the global burden of HIV-associated TB.[2] While much progress has been made in the last few years with robust responses to these epidemics, many challenges remain.[3] Antiretroviral and anti-TB drug resistance pose considerable threats to the control of these epidemics.[4,5] The breakdown in HIV/TB control within prisons is another emerging threat.[6,7] We describe one of the first reports of combined antiretroviral and anti-TB drug resistance, where the development of resistance was closely associated with two periods of incarceration.

Case report

A 34-year-old unemployed male presented to a primary healthcare (PHC) clinic in Hlabisa sub-district, KwaZulu-Natal, in February 2012 with a cough, night sweats and weight loss. He had been diagnosed with HIV infection in 2002, but had not accessed HIV care until April 2009 when he presented with his first episode of smear-negative pulmonary TB. At that time, his CD4$^+$ cell count was 85 cells/μl and he was initiated on a standard first-line antiretroviral therapy (ART) regimen of stavudine (d4T), lamivudine (3TC), and efavirenz (EFV). He achieved complete virological suppression (HIV viral load <50 copies/ml) and a good immunological response (CD4$^+$ count 482 cells/μl) after 5 months of ART (Fig. 1). In May 2010, he was incarcerated (in a correctional facility approximately 50 km from home) and as a result of non-disclosure of HIV status to prison officials, his ART was interrupted. Following release in September 2010, he had re-engaged with care at the PHC clinic and had been restarted on ART (tenofovir (TDF), 3TC and EFV). Within 6 months, he was once again detained in prison and his ART was interrupted once again for several months. He reported that he shared a cell with up to 50 people during this second spell in prison, several of whom were coughing and one had apparently stated that he had multidrug-resistant TB (MDR-TB).

Xpert® MTB/RIF was performed on sputum and detected *Mycobacterium tuberculosis* resistant to rifampicin. He was referred to the provincial drug-resistant TB unit (approximately 250 km from home) and was commenced on a standardised regimen of kanamycin, moxifloxacin, ethionamide, terizidone, pyrazinamide and isoniazid. Two weeks later, he was re-initiated on ART (TDF, 3TC and EFV). He completed the intensive phase of drug-resistant TB treatment with a good treatment response (acid-fast bacilli smear and culture negative after 2 months) and no evidence of nephrotoxicity, but there was no virological response to ART (viral load 390 845 copies/ml 6 months after restarting ART), despite documented good adherence.

Genotypic resistance testing was performed and revealed non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance mutations (K103N and V106M) and nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations (K65R and M184V), conferring high-level resistance to EFV and 3TC, and intermediate-level resistance to TDF. Hepatitis B surface antigen (HBsAg) was negative and haemoglobin was 12.7 g/dl. As a result, he was switched to a second-line ART regimen consisting of co-formulated zidovudine (AZT) and 3TC with lopinavir/ritonavir (LPV/r). At this stage, the total number of pills taken daily was 27 (including co-trimoxazole and pyridoxine). As of June 2013, he continues to be followed up at his local PHC clinic (2 km from home) and at the drug-resistant TB unit.

Consent

Written informed consent was given by the patient prior to publication.

Discussion

The issue of TB control in SA prisons has recently received much attention, as a result of the successful legal action against the Minister of Correctional Services by a former prison inmate who contracted TB while in a correctional facility awaiting trial.[8] Here we have described a case where acquisition of drug-resistant TB most likely occurred in prison and the clinical course was compounded by the emergence of antiretroviral drug resistance. This has significance, not only for individual health, with increased treatment complexity and adverse clinical outcomes, but also for the health of the wider community, with the risk of onward transmission of drug-resistant infections. The case here highlights the need for an improved and more integrated approach to HIV/TB prevention and care in prisons, as well as better linkage between prison health services and the public health system.

The incidence of TB disease in prisons worldwide has been shown to be more than 20 times that of the general population.[9] This is widely attributed to factors such as overcrowding, poor nutrition, insufficient ventilation and inadequate health services in prisons.[7,10-12] The problem is amplified in countries with a high HIV burden, as HIV infection is the strongest individual risk factor for developing active TB.[12-14] HIV prevalence is also often higher than that among the general population, with estimates of 40 - 45% in SA prisons.[15,16] Only 40% of SA correctional centres report segregating inmates on medical grounds, although drug-resistant TB has been cited as the most common reason for such segregation.[17] Ventilation is frequently poor;[6,11] our patient described small, slit-like windows high up on one exterior wall of his cell. There is a shortage of medical personnel in prisons and delays in accessing care are frequently an issue;[6,8,11,17] our patient stated that, during his second period of detention, he had reported his cough and night sweats to prison officials for 3 weeks before he was taken to the prison health facility.

The epidemiology of communicable diseases within and outside prisons is closely related; large numbers of prisoners and staff enter and leave prisons on a daily basis, acting as potential sources of transmission to the community at large. In SA in 2011/ 2012, over 80% of remand detainees[17] and 40% of those who received sentences were imprisoned for less than one year.[18] Thus, in SA, as elsewhere, prisons act as reservoirs of TB, and inevitably drug-resistant TB, that poses a threat to public health control.[12,14] Despite this, control measures for TB, HIV and other communicable diseases are often neglected, relative to measures directed at non-prison populations.[19]

Many of the same factors that enhance the spread of TB in prisons encourage the emergence of drug resistance and subsequent transmission of drug-resistant TB.[10,19] Moreover, the failure to ensure prompt recognition and appropriate treatment of drug-resistant cases results in a prolonged infective period, such that transmission risks may be even higher than those associated with drug-susceptible TB.[11] There are additional factors that may particularly promote the development of drug-resistant TB in prisons, such as: erratic drug supply and inadequate treatment; access to uncontrolled anti-TB drugs from staff and visitors; and chaotic lifestyles, including transfers between and within prisons. These enhance the likelihood of treatment interruption or default.[19]

While there is a paucity of data on antiretroviral drug resistance in prison populations, HIV-positive prisoners receiving ART in Brazil

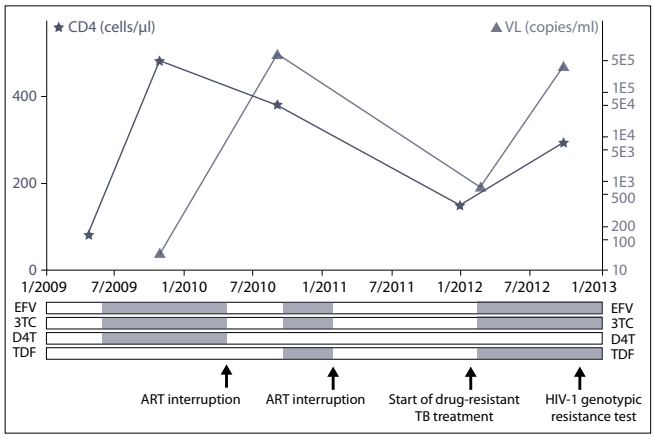

Fig. 1. Clinical course of ART with results of viral load (VL) and CD4⁺ cell count monitoring and timing of treatment interruptions.

have been found to have high rates of acquired HIV drug resistance;[20] and release from prison followed by re-incarceration has been shown to be associated with impaired virological and immunological outcomes while receiving ART.[21] Unplanned treatment interruptions are known to promote resistance;[22-24] and chaotic lifestyles,[18,19] fear of stigmatisation[18,25] and poor health services in prisons[6,25] are likely to increase the frequency of treatment interruptions. In SA, most prisons do not have dedicated HIV care programmes and those that exist are delivered by external service providers.[17] Our patient did not disclose his HIV-positive status or use of ART during either spell in prison, primarily due to fear of stigmatisation. While the timing of the development of ART drug resistance cannot be ascertained definitively in this case, it is plausible that the unscheduled interruption of treatment during the first period of incarceration could have led to the initial emergence of resistance. Certainly the interruption of ART, the emergence of ART drug resistance and the resultant drop in CD4⁺ cell count would have substantially increased the risk of developing TB disease.[26] We cannot definitively reject the possibility that ART resistance emerged prior to incarceration or that super-infection with a drug-resistant HIV strain occurred during incarceration.

The interdependence of numerous transmission risk factors necessitates a multifaceted approach to TB control in prisons, involving improvement in case finding, reductions in overcrowding and improvements in environmental conditions such as ventilation and airflow.[6,10-12,14] Robust evidence for action already exists: a modelling analysis based on conditions for inmates awaiting trial in Pollsmoor prison, Cape Town, suggested a potential reduction in TB transmission rates of 50% if active case finding and national minimum standards of cell occupancy were implemented; and a reduction of 94% if international environmental standards were adopted.[11] Screening and case detection in prisons worldwide has, until recently, been limited by suboptimal diagnostic tools and a lack of adequate laboratory facilities.[27] There is some evidence to suggest that screening prisoners using Xpert MTB/RIF could be a cost-effective means to reduce transmission of drug-resistant TB in settings with a high burden of drug resistance.[28] The recent announcement that correctional facilities in SA will now be prioritised for deployment of Xpert MTB/RIF offers strong encouragement.[29] However, research is needed to inform policies on the optimal use of Xpert MTB/RIF within prison health services, and any strategy must be linked to appropriate treatment programmes and proper segregation processes.

Furthermore, this case highlights that reducing the individual risk of TB disease should be as important, and optimising individual management of HIV disease, with the aim of virological suppression and prevention of antiretroviral resistance, should be a critical component of broader prison HIV/TB control strategies. No single intervention will adequately address the complex issues relating to TB and HIV in prisons. Ultimately, there needs to be the political will and funding to deliver sustained improvements to prison conditions and health services. Collaboration between the Department of Correctional Services and the Department of Health is necessary to facilitate better integration of prison health services within the public health system. The high costs of managing drug-resistant TB and HIV disease should be a powerful incentive to implement measures to reduce the emergence and spread of drug-resistant TB and HIV.[30-32] At a time when considerable progress is being made in the public health sector in SA,[3] the failure to address TB and HIV in prisons has the potential to seriously undermine the control of these infectious diseases in the community.

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