CASE REPORT

Combined antiretroviral and anti-tuberculosis drug resistance following incarceration

K E Stott, MB ChB, MSc; T de Oliviera, BSc (Hons), PhD; R J Lessells, BSc (MedSci), MB ChB, MRCP, DTM&H, Dip HIV Med

1 Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Mtubatuba, South Africa
2 Research Department of Infection, University College London, London, United Kingdom
3 Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, United Kingdom

Corresponding author: R J Lessells (rlessells@africacentre.ac.za)

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.

S Afr J HIV Med 2013;14(3):135-137. DOI:10.7196/SAJHIVMED.957

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. SA alone is responsible for almost one-third of the global burden of HIV-associated TB. While much progress has been made in the last few years with robust responses to these epidemics, many challenges remain. The breakdown in HIV/TB control within prisons is another emerging threat. 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+ cell 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.[9] 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.[9,10-12] 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] The problem here is not unique to SA; other African countries,[15,16] India[17] and 40% of those who received sentences were imprisoned for less than one year.[18] Thus, in SA, as elsewhere, 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.[19] 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.[9,10,12,14] 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.[22] 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.[23] The recent announcement that correctional facilities in SA will now be prioritised for deployment of Xpert MTB/RIF offers strong encouragement.[24] 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.

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[14,25] and poor health services in prisons[26,27] 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.[21] 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.[19] 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.[9,10,12,14] 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.[22] 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.[23] The recent announcement that correctional facilities in SA will now be prioritised for deployment of Xpert MTB/RIF offers strong encouragement.[24] 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.10-12 At a time when considerable progress is being made in the public health sector in SA,13 the failure to address the emergence and spread of drug-resistant TB and HIV point to the need for improved health services, surveillance and control. Stage 1 of this project showed 11.6% prevalence of drug-resistant TB in the prison population.12

Acknowledgement. This work was supported by the Wellcome Trust (grant 090999/Z/09/Z), European Union (SANTE 2007 147–790), the United States Centres for Diseases Control via the Centre for the AIDS Programme of Research in South Africa (CAPRISA) (project title: Health Systems Strengthening and HIV Treatment Failure (HIV-TFC)) and the Swiss South African Joint Research Programme (SSJRIP) research grants entitled ‘Swiss Prot South Africa: Protein Bioinformatics Resource Development for Important Health-related Pathogens.’ The funders had no role in data collection and analysis, decision to publish or preparation of the manuscript.

Author contributions. KES and RJL looked after the patient. KES wrote the first draft of the manuscript. All authors contributed to revision of the manuscript and approved the final version.

References

1. Abdool Karim SS, Churchyard GJ, Abdool Karim Q, Lawn SD. HIV infection and tuberculosis in South Africa: An urgent need to escalate the public health response. Lancet 2009;373(9693):921–933. [http://dx.doi.org/10.1016/S0140-6736(09)60696-8]

2. Getahun H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: The epidemiology and the response. Clin Infect Dis 2010;50(suppl 3):S201–S207. [http://dx.doi.org/10.1086/651492]

3. Mayosi BM, Lawn JE, van Niekerk A, Bradshaw D, Abdool Karim SS, Coovadia HM. Health in South Africa: Changes and challenges since 2009. Lancet 2012;380(9858):2029–2043. [http://dx.doi.org/10.1016/S0140-6736(12)61814-5]

4. Gandhi NR, Nunn P, Dheda K, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: A threat to global control of tuberculosis. Lancet 2010;375(9728):1830–1843. [http://dx.doi.org/10.1016/S0140-6736(10)60410-2]

5. Hamers RL, Kityo C, Lange JM, De Wit R, Mugyenyi P. Global threat from drug-resistant HIV in sub-Saharan Africa. BMJ 2012;344:e4159. [http://dx.doi.org/10.1136/bmj.e4159]

6. Reid SE, Topp SM, Turnbull ER, et al. Tuberculosis and HIV control in sub-Saharan African prisons: “Thinking outside the prison cell.” J Infect Dis 2012;205(suppl 2):S265–S273. [http://dx.doi.org/10.1093/infdis/jit309]

7. Todrys KW, Amon JJ. Criminal justice reform as HIV and TB prevention in African prisons. PLoS Med 2012;9(5):e1001215. [http://dx.doi.org/10.1371/journal.pmed.1001215]

8. South African Legal Information Institute. Lee v Minister of Correctional Services (1041/04). Johannesburg: South African Legal Information Institute, 2011. http://www.safiia.org.za/cases/ZAWHC/2011/13.html (accessed 18 June 2013).

9. Poorman A, Jefferies R, Konje M, et al. Drug resistance to second-line therapy in South Africa: a cross-sectional study. Trop Med Int Health 2011;16(11):1192-1199. [http://dx.doi.org/10.1111/j.1365-3148.2011.02708.x]

10. O’Grady J, Juma P, Bates M, Kapata N, Zulu M. Tuberculosis in prisons in sub-Saharan Africa: A potential time bomb. S Afr Med J 2011;101(12):107–108.

11. Johnstone-Robertson S, Lawn SD, Welte A, Bekker LG, Wood R. Tuberculosis in a South African prison: A transmission modelling analysis. S Afr Med J 2011;101(11):809–813.

12. O’Grady J, Hoefflischer M, Atun R, et al. Tuberculosis in prisons in sub-Saharan Africa – the need for improved health services, surveillance and control. Tuberculosis 2011;91(2):173–178. [http://dx.doi.org/10.1016/j.tube.2010.12.002]

13. Ferrand R. Eleven million adult co-infected with AIDS, TB. CMAJ 2004;171(5):437. [http://dx.doi.org/10.1503/cmaj.1041249]