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'Out of sight, out of mind?' A follow-up on HIV-infected patients with drug-resistant pulmonary tuberculosis in Uganda: A case series

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Abstract

Among new tuberculosis cases in Uganda, 10.3% are drug-resistant and 43% occur in people living with HIV. Both resistance and HIV–tuberculosis co-infection lead to unfavourable tuberculosis treatment outcomes. In this case series, we followed up eight HIV–tuberculosis co-infected patients withdrawn from a pharmacokinetics study on anti-tuberculosis drugs between April 2013 and April 2015 following a diagnosis of drug-resistant tuberculosis. We identified resistance patterns and treatment regimens and evaluated their tuberculosis treatment outcomes. Two patients were multidrug-resistant, only one out of eight was treated according to the World Health Organization guidelines applicable at that time and five had unfavourable tuberculosis treatment outcomes, that is, were lost to follow-up, could not be evaluated or died. Taken together, we found unfavourable tuberculosis treatment outcomes for patients with drug-resistant tuberculosis. This indicates the necessity of implementation of current treatment guidelines and close monitoring for patients with drug-resistant tuberculosis.

Keywords

Tuberculosis, drug-resistance, HIV–tuberculosis co-infection, treatment outcome, Sub-Saharan Africa

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Introduction

The emergence of drug-resistance (DR) represents a major problem to the treatment and global control of tuberculosis (TB).[1,2] In Uganda, resistance to any first-line anti-TB drug is found in 10.3% of new sputum smear-positive TB patients[3] and 43% of new TB cases occur in people living with human immunodeficiency virus (HIV).

Treatment of DR-TB remains difficult. At the time of this study, the World Health Organization (WHO) guidelines suggested using a prolonged regimen up to 24 months and an increased number of drugs including second-line anti-TB drugs such as injectable agents and fluoroquinolones.[4]

TB treatment success rates among newly diagnosed patients decrease with the presence of resistance, and co-infection with HIV further lowers that number with a four times higher risk of death during treatment.[2] In DR-TB patients, HIV is associated with an increased risk of unsuccessful treatment outcomes.[5] Moreover, we find higher rates of lost to follow-up cases in patients on DR-TB treatment, both across Sub-Saharan Africa and globally.[2,6,7]

The aim of this case series was to evaluate outcomes of HIV–TB co-infected patients that were withdrawn from a pharmacokinetics study following a diagnosis of DR-TB.

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Table 1. Patients' characteristics at baseline visit.

Patient	Age (years)	Gender	BMI (kg/m^2)	CD4 (cells/μL)	ART	Hb (g/dL)	Crea (mg/dL)	ALT (U/L)	Baseline smear[a]	Findings on chest x-ray[b]
1	48	F	25	419	TDF/3TC/EFV	12.4	0.72	12	No AFB seen	–
2	20	F	17	677	–	13.5	0.39	17	3+ AFBs	Pneumothorax and lung collapse
3	23	M	18.7	20	AZT/3TC/EFV	7.7	0.58	42	1+ AFB	Miliary picture; hilar adenopathy
4	36	M	18.5	484	TDF/3TC/EFV	10.6	0.73	7	No AFB seen	Cavities
5	30	F	27.2	487	TDF/3TC/EFV	11.8	0.72	7	3+ AFBs	Cavities
6	42	M	18	246	TDF/3TC/EFV	10.9	0.54	19	3+ AFBs	Hydro-pneumothorax and lung collapse
7	30	M	17.7	19	TDF/3TC/EFV	11.4	1.1	76	Scanty	Miliary picture; hilar adenopathy
8	36	M	18.6	157	–	9.1	0.53	12	3+ AFBs	Hilar adenopathy; pleural and pericardial effusion

BMI: body mass index, CD4: cluster of differentiation 4, ART: antiretroviral therapy, TDF: tenofovir, 3TC: lamivudine, EFV: efavirenz, AZT: azidothymidine = zidovudine, Hb: haemoglobin, Crea: creatinine, ALT: alanine transaminase, F: female, M: male, AFB: acid-fast bacilli.
[a]No AFB seen = 0 AFB per 30 fields, scanty = 1–29 AFB per 30 fields, 1+ = 30–299 AFB per 30 fields, 3+ = >100 AFB per field.
[b]Except for infiltrates.

Cases

Methods

We conducted a case series on eight HIV–TB co-infected patients with confirmed DR-TB from the SOUTH study which took place between April 2013 and April 2015 at the integrated HIV and TB clinic at the Infectious Diseases Institute (IDI) in Kampala, Uganda.[8] Ethical approval for the SOUTH study and written informed consent from all patients were obtained. Patients with resistance to any first-line anti-TB drug were withdrawn from the study as per stated exclusion criteria and referred to a routine clinic. Diagnosis of TB was confirmed by sputum direct microscopy and/or culture.[9] Phenotypical drug susceptibility testing (DST) of all first-line anti-TB drugs, that is, isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z), was performed on all isolates of *Mycobacterium tuberculosis*.

Generally, patterns of DR differ from single-drug (mono-) to multiple-drug (poly-) resistance and are classified accordingly. Multidrug-resistant TB (MDR-TB) is defined as resistance to at least H and R, the two major first-line anti-TB drugs.[2]

At the time of this study, the WHO suggested to treat H mono-resistant TB with a regimen consisting of the remaining three first-line anti-TB drugs (R, Z, E) for 6–9 months and a fluoroquinolone if necessary. Rifampicin mono-resistant TB (RR-TB), as a proxy to MDR-TB, was treated using a full MDR-TB treatment consisting of an increased number of drugs ($\geqslant 4$, including second-line anti-TB drugs such as injectable agents and additional oral bacteriostatic drugs) and a minimum duration of 20 months. Poly-resistant TB other than MDR-TB needed a prolonged treatment up to 18 months consisting of the remaining first-line anti-TB drugs plus a fluoroquinolone and/or an injectable agent.[4] The National TB programme in Uganda was suggesting similar treatment regimens at the time.[10]

Patients with MDR-TB take their treatment in a clinic near their residence under the supervision of a health care worker. However, the implementation of directly observed therapy (DOT) in Uganda has been limited so far as resources are limited.[11] Multiple other measures to support patients' retention in care are in place, for example, adherence counselling sessions, pill counts and provision of food.

Results

Eight patients out of 268 enrolled (3%) were identified with DR to at least one first-line anti-TB drug. Clinical characteristics of the patients at baseline are summarized in Table 1. All patients were HIV-infected and six of them were on antiretroviral therapy. They all presented with typical TB symptoms (cough, fever and excessive night sweats).

Two patients had MDR-TB; one patient had RR-TB; three patients were H mono-resistant; one patient was resistant to H, Z and E; and one patient was resistant to H and S.

One patient with MDR-TB (patient 1) was treated with second-line anti-TB drugs. The other patients were treated with adapted combinations of first-line anti-TB drugs, but none of them according to the WHO treatment guidelines[4,12] applicable at that time (see Figure 1).

Patient 1 showed resistance to R and H (MDR-TB) and was referred to the National Referral Tuberculosis Treatment Centre and started on a 24-month second-line MDR-TB regimen with levofloxacin, cycloserine, ethionamide and pyrazinamide, plus kanamycin for the first 6 months. She had persistent negative sputum smears and cultures and stopped taking anti-TB drugs 17 months into treatment without returning for further visits at the TB clinic (lost to follow-up). However, the patient returned to the separately operating HIV clinic and up to 2 years after, no signs of TB relapse were recorded.

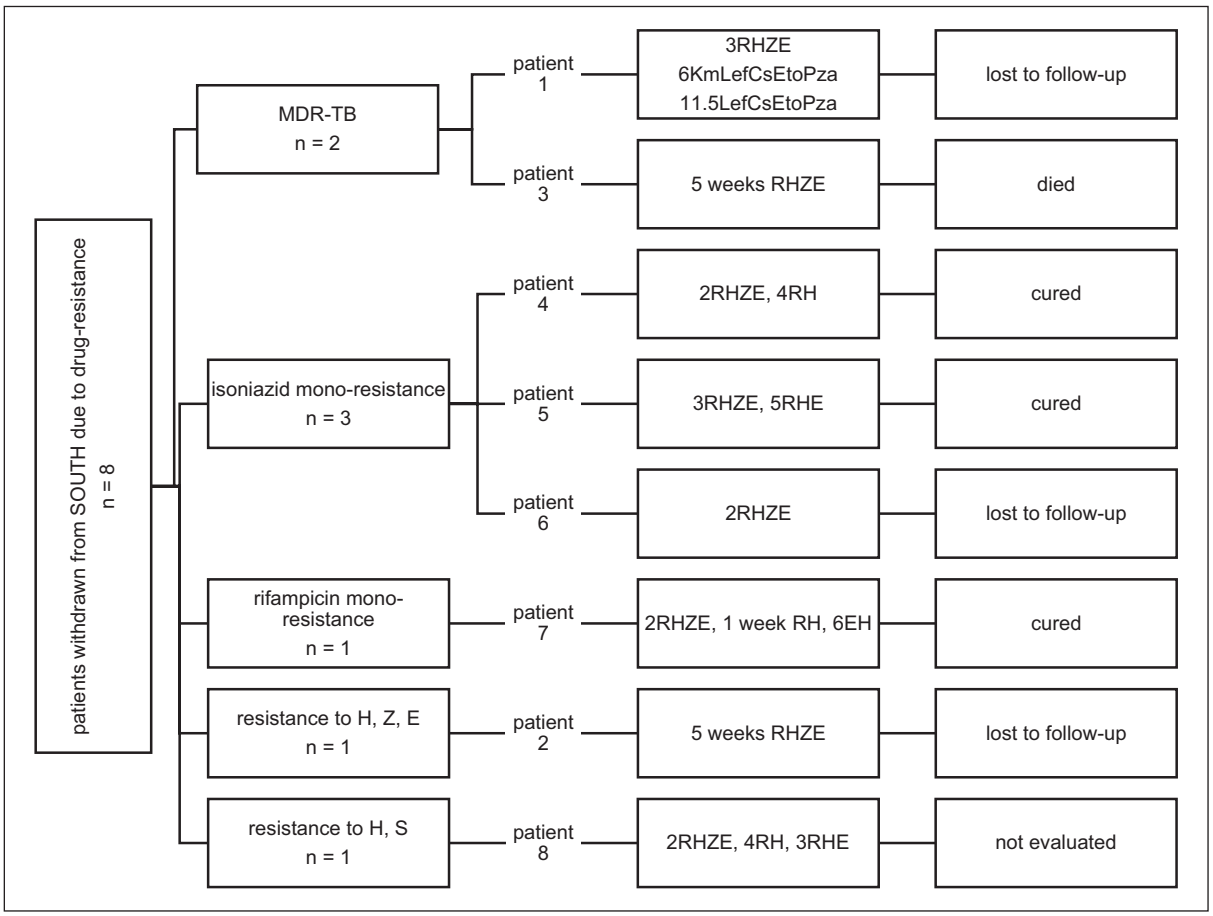

Figure 1. SOUTH: study on outcomes related to tuberculosis and HIV drug concentrations in Uganda, MDR-TB: multidrug-resistant tuberculosis, R: rifampicin, H: isoniazid, Z: pyrazinamide, E: ethambutol, Km: kanamycin, Lef: levofloxacin, Cs: cycloserine, Eto: ethionamide, Pza: pyrazinamide. If not otherwise stated, the numbers preceding the anti-TB drugs refer to the number of months (e.g. 3RHZE means 3 months of RHZE).

Patient 2 was resistant to H, E and Z. After starting with RHZE, some clinical improvement was seen, but sputum remained positive up to the time she was declared lost to follow-up 5 weeks into TB treatment. Three attempts were made to track her through phone calls which were not successful.

Patient 3 was resistant to R and H (MDR-TB). She had no clinical or mycobacterial improvement after 2 weeks of treatment with RHZE and developed a tuberculous cervical lymphadenitis. The patient didn't return for follow-up visits and died in the hospital shortly after.

Patient 4 had mono-resistance to H. At standard TB treatment completion, smear and culture results were negative (cured). Ten months later, however, a diagnosis of a TB relapse was made based on a positive Genexpert without showing resistance to rifampicin, and a retreatment regimen (2RHZE + S, 1RHZE, 5RHE) was successfully completed.

Patient 5 was resistant to H and continued treatment with RHZE up to week 8, where smear was still positive. Therefore, the patient was continued on RHZE for another month (extended intensive phase), followed by 5 months of RHE. Smear results at month 5 and the end of treatment (month 8) were both negative and the patient was declared cured.

Patient 6 was resistant to H and disengaged from care after 2 months. The patient died 4 months after TB diagnosis from an unknown cause.

Patient 7 had RR-TB. Drug sensitivity testing (DST) results were available 10 days into continuation phase. Being clinically stable with negative smear and culture results, he was not referred to the MDR-TB clinic and switched to EH for continuation phase. After completion of standard TB treatment, the patient was declared as cured.

Patient 8 was resistant to H and S. After completion of standard TB treatment, he was continued on RHE for 3 months and then transferred to another health centre, where his treatment outcome could not be evaluated as tracking was unsuccessful.

Discussion

We find a lower prevalence of DR-TB among the SOUTH study population compared to Lukoye et al.[3] in a national survey in Uganda and global estimates by WHO at that time[1]

(3% vs 10.3% and 17%, respectively). The prevalence of MDR-TB however was comparable to the prevalence found in the national survey (0.75% vs 1.4%).

Except for patient 1, none of the patient was treated according to WHO treatment guidelines. One main reason is the limited availability of single-drug formulations of anti-TB drugs as a result of fixed dose combinations. In addition, second-line anti-TB drugs such as fluoroquinolones were only available in specialized DR-TB treatment centres.

In our case series, three of the eight (37.5%) patients were cured, which is lower than reported elsewhere in the literature,[13–15] but representative of worse outcomes of patients with DR-TB compared to drug-susceptible TB.[2] Furthermore, with half of the patients being lost to follow-up or not evaluated we find a much higher number than regionally and globally estimated.[2] Several studies identified high pill burden, long duration of treatment, unemployment, homelessness, history of imprisonment and alcohol abuse as independent predictors of lost to follow-up.[7,16] Additional reasons may be limited resources and existing difficulties in tracking patients in a setting like Uganda.

Conclusion

In order to improve compliance with current treatment guidelines for DR-TB, single-drug formulations of anti-TB drugs and alternative regimens including second-line anti-TB drugs should be made readily available through National TB Programmes.

Furthermore, as half of our cases were lost to follow-up, it highlights the need for a more intensified follow-up, especially as successful treatment is key to prevent further spread of DR-TB. There is hope that the new WHO short regimen without injectables which is now being used in Uganda may lead to a smaller number of lost to follow-up cases by reducing the length of treatment and the number of adverse events.[17]

In conclusion, this case series highlights the need of strong health programmes to manage and treat DR-TB according to guidelines.

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Ethical approval

Ethical approval for the SOUTH study and following reports was obtained from the Joint Clinical Research Centre Research Ethics Committee and the Uganda National Council for Science and Technology. Approval for the use of data routinely collected at IDI was obtained by the School of Medicine Research and Ethics Committee, Makerere University Medical School (#2009-120), and the Uganda National Council for Science and Technology.

Informed consent

Written informed consent prior to enrolment into the SOUTH study was obtained from the patients for their anonymized information to be published in this article.

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