

Predictors of recurrent TB in sputum smear and culture positive adults: a prospective cohort study

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Abstract

Objective: To explore simple inexpensive non-culture based predictors of recurrent pulmonary tuberculosis (PTB).

Setting and study population: HIV-infected and uninfected adults with the first episode of smear positive, culture-confirmed pulmonary tuberculosis in a high tuberculosis burden country.

Design: A nested prospective cohort study of participants with pulmonary tuberculosis (PTB) presenting to a hospital out-patient clinic.

Results: A total of 630 TB culture confirmed participants were followed up for eighteen months of which 57 (9%) developed recurrent recurrent TB. On univariate analysis, 4.7% low grade(1+) pre-treatment sputum smear participants developed recurrent tuberculosis Vs 8.8% with high grade(3+) smears (OR=0.31,95%CI: 0.10-0.93, p=0.037). On multivariate analysis: participants with extensive fibro-cavitation had a high risk of recurrent TB Vs minimal end of treatment fibro-cavitation (18%Vs12%,OR=2.3,95%CI:1.09-4.68, p=0.03). Weight gain with HIV infection was associated with a high risk of recurrent TB Vs weight gain with no HIV infection(18%Vs 6%,OR=6.8,95%CI:1.65-27.83,p=0.008) where as weight gain with a low pre-treatment high bacillary burden was associated with a low risk of recurrent TB Vs weight gain with a high pre-treatment-bacillary burden(6.5%Vs7.9%,OR=0.2,95%CI:0.05-0.79,p=0.02).

Conclusion: Extensive end of treatment pulmonary fibro-cavitation, high pre-treatment bacillary burden with no weight gain and HIV infection could be reliable predictors of recurrent tuberculosis.

Keywords: Grade, fibrosis, cavities, weight.

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Introduction

Long term, non-relapsing cure is the ultimate goal of anti-TB treatment; unfortunately recurrent disease (relapse/re-infection) occurs on average in about two to six percent of patients with drug-susceptible TB treated with modern rifampicin-containing short course regimens¹². Recurrent TB may result from recurrent disease with the

original or new infection strain of *M. tuberculosis*²⁸. This may be due to several scenarios that include: poor adherence, immunosuppression mainly due to HIV co-infection^{10,13,28}, Initial TB infection with a high bacillary burden¹⁷, drug resistant strains³⁰, sub-optimal exposure in fixed dose combinations¹, variation in biological response to TB treatment³¹ or exogenous re-infection with a new strain²³.

Clinicians have sought to identify factors associated with an increased risk for recurrent TB after successful initial treatment. This can guide them in identifying patients and groups where treatment might be modified or where post-treatment follow-up might be useful. Lack of weight gain⁸, HIV infection¹³, pre-treatment greater radiographic involvement⁹, pre-treatment high bacillary burden¹⁷, post treatment residual fibro-cavitation⁹, sub-optimal exposure

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in fixed dose combinations¹, cavitory disease on chest radiograph & a positive sputum culture after completing the first two months of anti-TB treatment have been associated with recurrent tuberculosis.

Sputum culture is costly and less affordable in many high TB burden settings²⁶. Genexpert is as well costly and less specific in diagnosis of recurrent TB^{26,27}. There is a programmatic intuitive need to identify simple, robust, inexpensive, convenient, non culture (non-molecular) based tools that rely on readily available assessments at the point of care to identify patients at risk for recurrent TB. Most TB suspects have a chest radiograph³¹ and sputum smear done during evaluation³³. Patients with newly diagnosed TB are offered HIV testing by most programmes³² and even peripheral TB units have a weighing balance to measure body weight for anti-TB drug dosing. Sputum smear microscopy is a commonly used TB diagnostic tool even in resource constrained settings³³. To our knowledge, no previous study has ever come up with a predictive non-culture based tool for recurrent TB from the list of previously identified risk factors. In this prospective cohort study, we examined whether one or any combination of weight gain, sputum smear grade, pre-treatment cavitation, end of treatment residual fibro-cavitation, radiographic extent of TB disease and HIV co-infection could form a non-culture based a predictive tool to identify patients at risk for recurrent TB in the initial eighteen months post-treatment in a well-followed up treatment cohort in Uganda, a nation with a high burden of TB.

Methods

Study population and setting

The participants included in this prospective cohort study were systematically selected from two parent studies. The parent studies recruited participants from several health units within a radius of 30 kilometers from the research Site in Kampala. This analysis included data from HIV-infected and -uninfected adults over 18 years-old with the first episode of smear positive, culture-confirmed, drug-susceptible pulmonary TB, treated in the Kawempe study (DMID protocol number:01-005) conducted from April 2002 to July 2012 and the EDCTP TB diagnostics study (EDCTP - IP_09_32040_011) conducted from March 2010 through March 2013. Both studies were conducted at a large out-patient TB clinic within

Mulago Hospital, a national tertiary referral hospital in Kampala, Uganda. All patients were treated with self-administered, standard short course therapy (2 months of daily INH, rifampicin, ethambutol and pyrazinamide followed by daily treatment with Isoniazid and rifampicin for 4 months). The TB drugs were dispensed as single drugs.¹ The Kawempe study enrolled TB index cases and followed up their household contacts. The Kawempe study embedded a mixture of cohort and cross sectional designs. A Kawempe community resident was defined as one who should have resided in the Kawempe area for at least three months. The Kawempe study excluded participants with recurrent TB and those who had taken more than 5 doses of anti-TB drugs for that episode of TB at the time of enrolment. Participants were followed up for eighteen months post TB treatment. A team of home health visitors ensured routine weekly field visits, phone calls and continued counseling of the participants to mitigate loss to follow up. The EDCTP TB diagnostics study was a prospective cohort study that evaluated TB cytokine signatures in blood, sputum and urine as markers of active TB infection in relation to sputum culture. It enrolled both controls and active TB cases, first episode of TB and excluded those who had taken more than 5 doses of anti-TB drugs. All culture confirmed TB cases from both parent studies were systematically selected and screened for this analysis. Data was extracted using a tested and validated questionnaire by two staffs who were blinded to the study objective.

Procedures

HIV infection was defined as having a positive result on three approved, licensed rapid HIV testing kits in a validated HIV testing algorithm. Each participant had a posterior-anterior chest radiograph taken pre-treatment, end of treatment and at the time of suspected TB recurrence. The radiographic severity of TB disease was assessed as minimal, moderate or far advanced disease using the scheme of the US National TB and Respiratory Disease Association¹⁶. Body weight was measured at baseline and at each follow up visit using a calibrated beam balance (Detecto model). Sputum smear and culture were done monthly during the treatment phase, every 6 months during follow up and at the time of suspected recurrent TB. Sputum smears were done using fluorescent auramine staining. Smear grading was by the World Health Organi-

zation scale²⁰. Sputum culture was on Lowenstein-Jensen slants. *Mycobacterium tuberculosis* speciation was by polymerase chain reaction (PCR)²⁴. Initial isolates had drug susceptibility testing done for INH, rifampicin, ethambutol, pyrazinamide and streptomycin.

All participants with suspected recurrent TB were evaluated by clinical examination, chest radiography, multiple sputum smears and cultures. Recurrent TB was defined as culture confirmed TB during 18 months of follow up in participants who were microbiologically confirmed cured at the end of the initial six months of TB treatment. Weight gain was defined as gaining at least 5% of the pre-treatment body weight by the end of the first two months of anti-TB treatment⁸.

Treatment adherence was monitored by urine INH metabolite testing in addition to participant interview at each scheduled visit and review of attendance records. Defaulters were traced by home health visitors. All participants were followed up for 18 months after TB treatment. Both parent studies were approved by institutional review boards of the Joint Clinical Research Centre, the National AIDS Research Committee and the Ugandan National Council for Science and Technology. All participants gave written informed consent for participation in the parent studies.

Statistical analysis

Categorical data was analyzed using the chi-square. For weight gain, changes from baseline by month 2 were as-

essed using paired z-tests. Logistic regression was used in determining the association between weight gain, HIV status, radiographic extent of disease, sputum smear grade, end of treatment fibro-cavitation and the likelihood of TB recurrence. Stepwise selection method of predictor variables (weight gain, HIV status, chest x-ray extent of disease, fibro-cavitation and bacillary burden) was used for inclusion in the logistic model. All tests were two-sided. The odds ratio plus the corresponding 95% confidence interval and p-value were the effect measure. A confidence interval excluding the null value of 1 and a p-value < 0.05 were considered statistically significant. All statistical analyses were done using Stata (Version 12, STATA, USA).

Results

A total of 1150 (figure 1) were screened and 690 bacteriologically confirmed PTB study participants were enrolled in the two parent studies between April 2001 and July 2012 of which 60 were excluded from this analysis since they were not followed up after completing treatment. Of the 630 followed up, 57 (9%) developed recurrent TB, 136 (22%) were HIV infected, 311 (49%) had far advanced disease on chest radiograph & 363 (58%) had pulmonary cavitation. Majority 331 (52%) were female & recurrent TB cases were older (mean age = 30 yrs, SD = 10.8) Vs the non-recurrent (NR) group (mean age 28.6 yrs: SD = 10.2). 106 (17%) had a low grade pretreatment smear & 160 (25%) had a high grade smear. Majority 510 (81%) had urine INH testing to confirm TB treatment adherence.

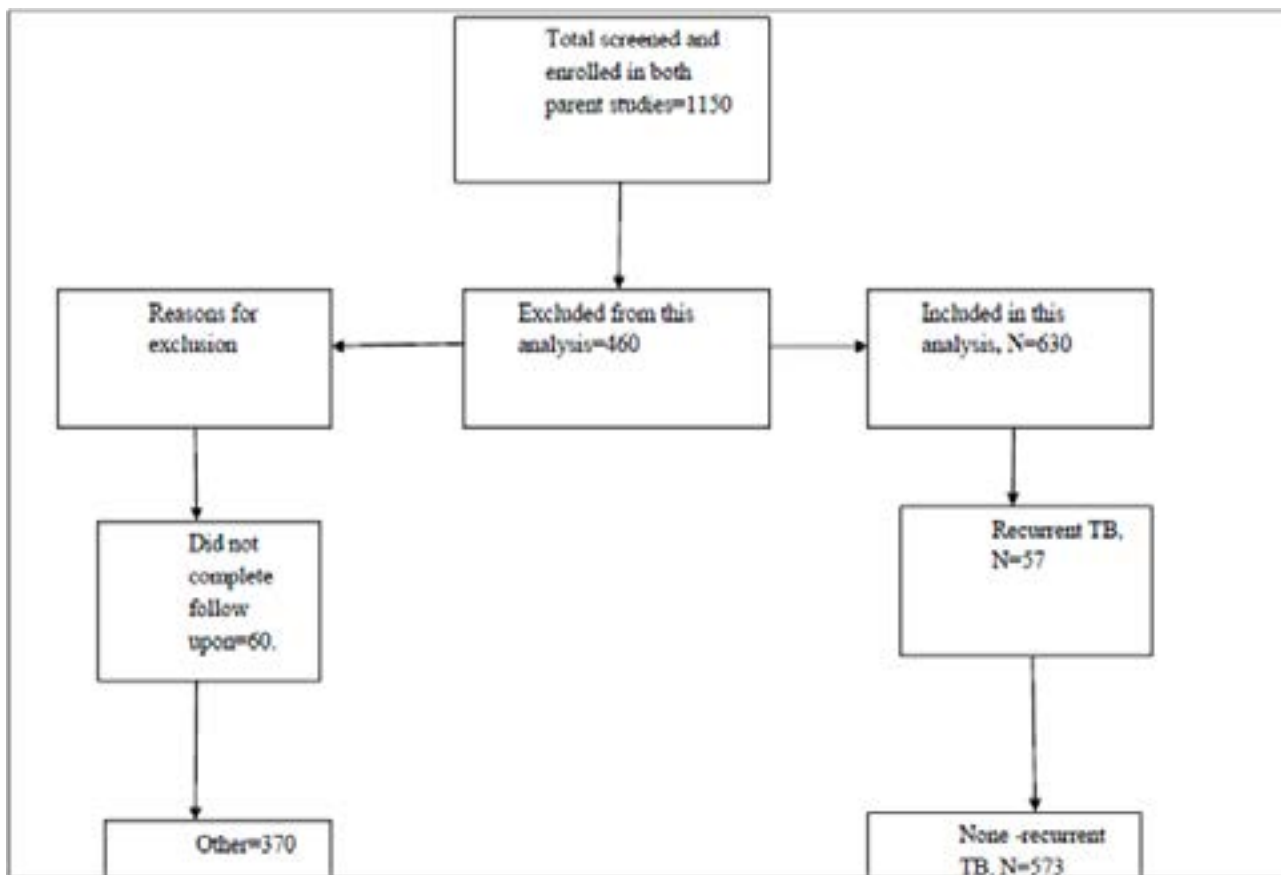


Figure 1: Study profile

Table 1: Univariate analysis

Variable	Recurrent	Non-Recurrent	Total	P-value
Weight gain <5%	38	335	362	0.45
Females	28	303	331	0.64
Alcohol	04	79	083	0.17
Smoking	09	81	090	0.71
Age:mean(SD)	30(11)	29(10)	---	0.22
HIV positive	12	124	136	0.92
Baseline cavities	38	325	363	0.15
Chest x-ray extent of disease				
Minimal				
Moderate	5	58	63	0.48
Advanced	16	193	209	0.45
	34	277	311	0.15
Smear				
1+	05	101	106	0.032
2+	16	109	125	0.844
3+	14	146	160	-----

On univariate analysis(table 1),4.7% of the low grade smear participants developed recurrent TB Vs 8.8% with a high grade smear (OR=0.31, 95%CI: 0.10-0.93, p=0.037). Weight gain and HIV infection did not independently influence the rate of recurrent TB on univariate analysis.On multivariate analysis:table 2;

Table 2: Multivariate analysis

Variable	Recurrent	Non-Recurrent	Total	95%CI	P-value
Weight gain<5%,HIV+	5	80	85	0.18-1.3	0.14
Weight gain≥5%,HIV-	11	165	176	1.7-27.8	0.008
Weightgain≥5%,moderate disease	05	44	49	0.14-20.66	0.68
Weightgain≥5%,advanced disease	12	122	134	0.15-16.84	0.69
HIV-,moderate disease	15	159	174	0.6-6.8	0.23
HIV-,advanced disease	39	268	307	0.46-26.9	0.20
Smear 1+, Weight gain≥5%	3	70	73	0.05-0.79	0.02

weight gain with a low grade smear was associated with an even lower risk of recurrent TB Vs weight gain with a high pre-treatment bacillary burden (OR=0.2, 95%CI: 0.05-0.79, P=0.02). Weight gain with HIV infection was associated with a high risk of recurrent TB Vs weight gain

with no HIV infection (18% Vs 6%, OR=6.8, 95%CI: 1.65-27.83, p=0.008). About 18% of those with extensive fibro-cavitary sequelae at the end of TB treatment developed recurrent TB Vs 12% with minimal fibro-cavitary sequelae (OR=2.3, 95%CI: 1.09-4.68, P=0.03): table 3.

Table 3: Radiographic extent of disease at month 6 (fibro-cavitation)

Variable	Recurrent	Non-Recurrent	Total	95%CI	P-value
Minimal	16	123	139	-----	----
Moderate	15	108	123	0.7-2.8	0.33
Advanced	13	58	71	1.1-4.7	0.03

Discussion

In this analysis, we report a 2 fold reduction in the risk of recurrent TB among participants with low grade compared to high grade pre-treatment smears (4.7% Vs 8.8%) and inversely an increase in the risk of recurrent TB among participants with extensive end of treatment fibro-cavitary sequelae compared to those with minimal fibro-cavitary sequelae (18% Vs 12%). Rupka Singla et al 2007 and Panjab et al 2007 showed that high pre-treatment bacillary burden and residual cavitation by the end of TB treatment increases the risk for recurrent TB. Luzzo et al 2013 showed that extensive end of treatment fibrosis and cavitation was associated with recurrent TB. Therefore our findings are similar to what has been reported in previous studies^{9,17,28}. Participants with a low grade pretreatment smear and weight gain had an even lower risk of recurrent TB but weight gain alone did not independently influence the risk of recurrence⁸. We however observed a high proportion of failed weight gain in the recurrent TB group compared to their non-recurrent counterparts (67% Vs 59%) but this was not statistically significant although Khan et al 2006⁸ showed that failure to gain $\geq 5\%$ of baseline body weight by the end of the intensive phase of TB treatment was associated with an increased risk for TB recurrence. Our study found no statistically significant difference on univariate analysis although there was a higher proportion of failed weight gain in the recurrent Vs the non-recurrent group. We also observed an increased risk of recurrent TB among the HIV infected with weight gain Vs HIV uninfected with weight gain. Previous studies have shown increased rates of TB recurrence among HIV-TB patients¹⁰, this was the case with our study results too. We noted a higher pro-

portion of recurrent TB (9%) in this population contrary to previously existing scientific data¹² however, our results are in line with the findings of one previous study in the same population²⁸. The high proportion of recurrent TB could be attributed to patients presenting late with advanced PTB⁹ as evidenced in this analysis where the majority (49%) of the participants had radiographically far advanced disease. This is in agreement with Panjab et al 2007 findings of greater radiographic involvement being a risk factor for recurrent TB. Urine INH metabolite testing was not done in 19% of the cases in which case non-adherence could have confounded recurrent PTB²⁹. We also noted that about 54% of the cases presented with a high pre-treatment bacillary burden which could partially explain the high proportions of recurrent TB in this population¹⁷.

The strength of our study is that it involved an eighteen month follow-up of a large cohort of confirmed TB patients and monthly assessment of adherence by urinary INH metabolite testing during treatment. Our study had several limitations (i) the urine INH metabolite testing was only possible in 81% of the cases included in this analysis. (ii) DNA finger printing was not done to distinguish recurrent TB due to relapse from exogenous reinfection with a different strain²⁸.

Recommendation

Previous studies have listed several factors associated with TB disease recurrence but no predictive tool has been assembled out of this literature to influence management of recurrent TB. We recommend that clinicians should put into perspective the possibility of prolonging treatment and close patient monitoring for TB pa-

tients who: (i) present with a high pre-treatment bacillary burden (3+) and failure to gain at least 5% of baseline body weight by the end of the intensive phase of TB treatment. (ii) Are HIV positive. (iii) have extensive end of treatment fibrosis and residual cavitation on chest x-ray (grade 3).

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Conflict of interest

We have no conflict of interest to declare.

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