Associations between isoniazid preventive therapy, non-tuberculous mycobacterial infection, and incipient TB signatures in people with HIV

Ethan Valinetz

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2021

Committee:

Anna Wald

Thomas Hawn

David Horne

Gerard Cangelosi

Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

Associations between isoniazid preventive therapy, non-tuberculous mycobacterial infection, and incipient TB signatures in people with HIV

Ethan Valinetz

Chair of the Supervisory Committee:

Anna Wald

Department of Medicine, Division of Allergy and Infectious Diseases

Department of Epidemiology

Objective(s): To examine the association between isoniazid preventive therapy and incipient tuberculosis (TB) transcriptome-based signatures in persons with HIV (PWH) and to describe the association between non-tuberculous mycobacteria (NTM) and incipient TB signatures in PWH.

Design: Cross-sectional study using clinical information and specimens obtained at one visit from previous cohort.

Methods: Participants ages 18 to 70 years were enrolled at two clinics in western Kenya caring for PWH. Clinical information, including whether participants had previously received isoniazid preventive therapy, and laboratory studies were obtained at the initial visit. Incipient TB signatures were calculated using gene expression data from qRT-PCR with the Fluidigm 96.96 dynamic array platform. The primary signature of interest was the RISK6 signature. Mean RISK6 scores by IPT status were compared using the Mann-Whitney U test. Multivariable linear regression was used to analyze the association between prior receipt of IPT and RISK6 scores and the association between NTM and RISK6 scores.

Results: 386 participants (86.8% with prior history of IPT) were included in the analysis. Almost all (99%) participants were taking antiretroviral therapy (ART) at the time of study enrollment. Persons who had

received IPT had an average RISK6 score that was 0.099 lower (95% CI: 0.057, 0.139; $p < 0.001$) than persons without IPT history. This association remained significant when adjusting for age, sex, and HIV viral load. There was no significant association between NTM and RISK6 scores.

Conclusions: History of IPT was associated with significantly lower RISK6 scores in people with HIV compared to people who had not received IPT. We did not detect an association between NTM and RISK6 scores.

INTRODUCTION

Tuberculosis (TB) remains a significant public and global health problem, and the leading cause of death among people with HIV, with approximately 208,000 TB-associated deaths in 2019 (1). Improved diagnostics to identify persons at increased risk of developing active TB disease are needed to interrupt transmission and decrease overall burden of disease. One strategy to end the TB pandemic has been to provide TB preventive therapy to those at risk for progression to active TB disease, but current methods, which include the tuberculin skin test (TST) and interferon gamma release assays (IGRAs), have several drawbacks. These tests do not differentiate between those who are at a higher imminent risk of developing active TB and those who will not develop TB for many years if ever. (2). TST and IGRA results may not change with TB preventive therapy making it impossible to know whether the treatment was successful. Furthermore, the sensitivity of TST and IGRA testing may be reduced in immunocompromised persons, including people with HIV, who are at high risk for progression to active TB disease. For these reasons, biomarkers that can accurately identify those at highest risk for progression to active TB disease are urgently needed to efficiently target TB preventive therapy to reduce TB incidence, while sparing low-risk persons from medical treatment and adverse events.

Several investigators have studied the performance of various blood transcriptomic signatures, known as "correlates of risk" (COR) signatures, for their ability to predict progression to active TB disease in infected people, to distinguish between healthy controls and persons with active TB disease, and to monitor treatment response in those undergoing treatment for active TB (3-9). Discovering signatures that identify people with incipient TB disease, which is defined as the period of TB infection that occurs before a person progresses to sub-clinical or active TB disease has been emphasized (10). Zak et al described one of the first signatures, which contained 16 genes, that was used to predict progression to TB disease (9). Several signatures have been described and have included varying numbers of genes from as few as two up to hundreds of genes. Some, but not all, of these genes are involved in the type I interferon pathway.

The RISK6 signature, first identified by Penn-Nicholson and colleagues (7), distinguished between people who did and did not progress to active TB disease over a period of 12 months. The investigators demonstrated that the RISK6 score could also potentially be used as a triage test for active TB and that RISK6 scores declined with treatment of TB. Their cohorts included persons with and without HIV infection; overall, the signature appeared to perform similarly regardless of HIV status, although other transcriptomic signatures have not performed as well among persons with HIV (Darboe et al 2019, Sweeney et al 2016). Penn-Nicholson et al also showed that persons with a detectable plasma HIV RNA had, on average, significantly higher RISK6 scores compared to persons with an undetectable viral load. Because the RISK6 signature contains 3 interferon stimulated genes (ISGs), their conclusion was that HIV viral load is a confounder in signatures containing ISGs (7). The potential association between HIV viral load and other signatures has not been as well characterized.

In comparative studies, the performance of these gene signatures for identifying incipient tuberculosis varied. Warsinske et al compared 16 signatures, including Maertzdorf4 and Sweeney3, and in their analysis found that the Sweeney3 signature performed well in several measures while the Maertzdorf4 signature was not as reliable (11). Another comparison by Turner et al examined 27 signatures, which included RISK6, Maertzdorf4, Suliman4, and Sweeney3; however, of these 4 signatures only Sweeney3 performed well enough to be reported in the main findings of the paper (12). Lastly, Gupta et al analyzed 17 signatures in their performance to detect incipient TB, including Maertzdorf4, Suliman4, and Sweeney3, but none of the signatures reached the minimum WHO target product profile parameters over a 2-year period (minimum sensitivity and specificity of 75% for incipient TB detection).

The recently published CORTIS trial randomized participants with positive RISK11 scores to either receive TB preventive treatment or active surveillance only. The RISK11 signature was derived from the 16-gene signature described by Zak et al, and was shown to predict progression to active TB with equal performance (6, 9). At the end of the 15-month follow up period, the TB incidence between the two groups did not differ (13). The reason for these results is unclear, but further studies examining the association between TB preventive therapy and COR scores are needed.

Many species of non-tuberculous mycobacteria (NTM), environmental mycobacteria that are related to *Mycobacterium tuberculosis,* can cause infections in people, particularly those who are immunocompromised (including people with HIV) or have structural lung disease. Although NTM infections are less common than TB in endemic settings, disseminated NTM infections in immunocompromised populations have a high mortality (14). Cowman et al compared transcriptomes in persons with pulmonary NTM infections and persons with other respiratory diseases, finding more than 200 transcripts with differential expression between the two groups (15). To our knowledge, the potential association between NTM infection and COR signatures has not been previously studied.

Although some studies involving these transcriptomic signatures have included people living with HIV, many have excluded this population. Additionally, while some signatures have been shown to decrease in response to TB treatment, to our knowledge the relationship between isoniazid preventive therapy and transcriptomic signatures has not been examined. Our objective is to examine the association between the receipt of isoniazid preventive therapy (IPT), a commonly used option for TB preventive therapy and RISK6 scores. We will also explore the relationship between the RISK6 signature and several other COR signatures, and evaluate for a possible association between NTM and RISK6 scores.

METHODS

Study Design

This study was cross-sectional in nature, using clinical information and specimens collected at a single visit that was part of a prospective study conducted previously (16).

Study Setting

Participants were enrolled in the original study from March 2017 to September 2018. They were enrolled from two clinics that care for patients living with HIV in western Kenya.

Study Subjects

All participants had an established diagnosis of HIV infection. Participants were enrolled if they were age 18-70 and had either never received isoniazid preventive therapy (IPT), or if they had received IPT more than 6 months prior to study enrollment. Participants were excluded if they could not provide consent in English or Dholuo, if they were pregnant or incarcerated, or if they were unwilling to provide a home location. For our analysis, only participants with available IPT history were included.

Data Collection

At enrollment, participants were interviewed to collect demographic information, HIV history, TB history, and IPT history. IPT history was confirmed through chart review, and adherence to IPT was self-reported. Laboratory results, such as HIV viral load and CD4 count, were extracted from charts. Tuberculin skin tests (TSTs) were also performed at study enrollment. Finally, phlebotomy was performed to test for a variety of biomarkers which were analyzed in the original paper. If HIV viral load was unavailable from the patient chart, this was also tested with this blood draw. Additional blood was drawn and stored in PAXgene Blood RNA tubes for future use.

Laboratory assays

For this study, RNA extraction was performed on all available PAXgene tubes using the MagMAX RNA Isolation Kit. The RNA concentration from each sample after extraction was determined using the

NanoDrop spectrophotometer. Next, each sample was converted to cDNA using the High Capacity cDNA Reverse Transcriptase Kit (Applied Biosystems). qRT-PCR was performed using the Fluidigm 96.96 dynamic array platform in order to determine the expression of the genes used to calculate the RISK6, Thompson5, Suliman4, Maertzdorf4, and Sweeney3 gene signatures. Afterwards, the output from the Fluidigm instrument was extracted. Previously written scripts to calculate the signatures were used using RStudio version 1.4.1106. Quality control procedures were performed by including a positive control on all Fluidigm plates and analyzing the minimum, maximum, and average values for signature scores by plate. In the initial Fluidigm run, 24 out of 48 samples run on one plate failed. Due to concern for laboratory error, these samples were repeated along with a selection of samples that passed in order to perform additional quality control.

Data Analysis

The main aim of the study was to examine the association between isoniazid preventive therapy (predictor) and RISK6 scores (outcome). RISK6 scores range from 0 to 1. The IPT status variable was binary, defined as either “yes” or “no.” Participants who completed any length of isoniazid preventive therapy were counted as “yes.” A boxplot was created to show the distribution of RISK6 scores by IPT status. We compared the mean RISK6 score in each IPT status group using the Mann-Whitney U test. We also planned to perform multivariable linear regression using age, sex, and HIV viral load as potential confounders. Additionally, we log transformed the RISK6 score (outcome variable) in the model to correct for a non-normal distribution (demonstrated by Kolmogorov-Smirnov test). The potential for effect modification of this association by HIV viral load was assessed by adding an interaction term to the model; the HIV viral load term was coded as either detectable or undetectable, with the threshold of 1000 copies/mL. Effect modification was also explored by comparing the mean difference in RISK6 scores by IPT status in people with detectable HIV viral load to those with undetectable HIV viral load using the Mann-Whitney U test. We analyzed the possible association between length of time since IPT receipt, which was a categorical variable coded as the year IPT was started, and RISK6 scores. The mean RISK6 score by year of IPT receipt was compared using the Kruskal-Wallis test.

We also investigated the association between non-tuberculous mycobacteria and RISK6 scores. A boxplot was created to visualize the distribution of RISK6 scores by sputum culture result: positive for NTM, positive for TB, or negative. The Kruskal-Wallis test was used to compare the mean RISK6 score between persons with a positive sputum culture for NTM and persons with a negative sputum culture. A multivariable linear regression was performed with the log of RISK6 scores as the outcome and NTM status as the predictor while also adjusting for age, sex, and HIV viral load. NTM status was binary and was defined as either having a sputum culture positive or negative for NTM.

We compared the performance of the RISK6 signature to four other signatures: Thompson5, Suliman4, Maertzdorf4, and Sweeney3. The association between each signature and IPT status was compared by creating separate boxplots and by determining the mean difference in each signature score by IPT status with confidence intervals and p-values generated by the Mann-Whitney U test. A correlation matrix was created to compare the correlation coefficients between each signature.

RESULTS

Study Participants

In the original cohort, 390 participants with HIV were screened for inclusion, two of whom declined study participation. Of those, 386 had an available IPT history and were included in the present study analysis. The mean age overall was 38.3 ± 10.2 years and 58% of participants were women (Table 1). Of 386 participants, 335 (86.8%) endorsed a prior history of IPT while 51 (13.2%) participants denied prior IPT use. Almost all (99%) participants were currently taking antiretroviral therapy for HIV. The mean CD4 count was 316 ± 181 cells/mm^3 among participants without IPT history and 443 ± 230 cells/mm^3 among participants with IPT history. Of note, the CD4 count was missing for 30/51 (58.8%) of participants without IPT history compared to 40/335 (11.9%) of participants with IPT history. TST results were available for 333 participants for which; 38 (11%) had a TST induration greater than 10mm. Of 378 participants with available sputum culture results, 5 (1.3%) were positive for *Mycobacterium tuberculosis*, 41 (11.0%) were positive for non-tuberculous mycobacteria, and 328 (87.0%) were negative (Table 1).

Association between IPT status and RISK6 scores

The distribution of RISK6 scores by IPT status is demonstrated in in Figure 1. The mean RISK6 score among persons with a history of IPT was 0.146, while the mean RISK6 score among persons without a history of IPT was 0.245. In an unadjusted analysis, the mean RISK6 score in participants with a history of IPT was 0.099 lower (95% CI: 0.057, 0.139; $p < 0.001$) than those without a history of IPT. When adjusting for age, sex, and HIV viral load, the geometric mean RISK6 score was 0.48 times lower (95% CI: 0.33, 0.68; $p < 0.001$) in participants with a prior history of IPT compared to those without prior IPT history. As demonstrated in Figure 2, there was no statistically significant difference in RISK6 scores by year of IPT receipt ($p = 0.38$).

We also assessed for the possibility of effect modification by HIV viral load on the association between IPT status and RISK6 scores. Boxplots showing the distribution of RISK6 scores by IPT status among participants with a detectable HIV viral load and among participants with an undetectable HIV viral load suggested that the difference in average RISK6 scores by IPT status was greater among participants with

a detectable HIV viral load (Figure 3). The difference in mean RISK6 scores by IPT status was 0.195 (95% CI: 0.064, 0.298; p = 0.006) in participants with a detectable HIV viral load, with higher mean RISK6 scores in those without prior IPT history. Among those with an undetectable HIV viral load, the difference in mean RISK6 scores by IPT status was 0.069 (95% CI: 0.029, 0.110; p = 0.0008), with higher mean RISK6 scores in those without prior IPT history as well. However, adding an interaction term to the multivariable linear regression model adjusting for age and sex revealed no statistically significant effect modification (interaction term p = 0.21).

Association between positive sputum cultures for NTM and RISK6 scores

RISK6 distributions by sputum culture result (positive for NTM, positive for MTB, or negative) are shown in Figure 4. There was no statistically significant difference between the mean RISK6 score in persons with a positive sputum culture for NTM, a positive sputum culture for MTB, and negative sputum cultures (p = 0.18). In the multivariable regression model adjusting for age, sex, and HIV viral load, the difference between RISK6 scores by sputum culture result remained insignificant, with an estimated geometric mean RISK6 score 1.09 times higher (95% CI: 0.74, 1.62; p = 0.66) in participants with a positive sputum culture for NTM compared to those with a negative sputum culture.

Comparison of 5 CoR signatures

As an exploratory analysis, we evaluated the associations between 4 additional CoR signatures (Thompson5, Suliman4, Maertzdorf4, and Sweeney3) and IPT status. Of note, Thompson5 and Suliman4 scores are between 0 and 1 while Maertzdorf4 and Sweeney3 scores may be negative or positive numbers. When adjusting for age, sex, and HIV viral load, there was a statistically significant difference in CoR scores by IPT status using the Maertzdorf4 and Sweeney3 signatures. The mean Maertzdorf4 score was 0.69 lower (95% CI: 0.32, 1.08; p = 0.0004) in those who had received IPT compared to participants who had not received IPT. Regarding the Sweeney3 signature, persons with a prior history of IPT were estimated to have a mean score 0.56 lower (95% CI: 0.24, 0.86; p = 0.001) than those without a history of IPT. We created a correlation matrix displaying the correlation coefficient between each signature (Figure 5). The correlation coefficients between signatures ranged between

-0.26 and +0.72. The RISK6, Maertzdorf4, and Sweeney3 signatures were most highly correlated with correlation coefficients between 0.59 and 0.72. Three correlation coefficients were negative or almost zero, and the correlation between RISK6 and Maertzdorf4 scores was highest at 0.72.

DISCUSSION

We investigated the association between prior receipt of IPT and RISK6 scores among people with HIV, and found that having received IPT was associated with a lower mean RISK6 score. We hypothesized that RISK6 scores would be lower among people who had received IPT, because IPT has been shown to prevent TB disease, and lower RISK6 scores have been associated with lower risk of incident TB disease. The association remained significant even when adjusting for age, sex, and HIV viral load. To our knowledge, this association has not been previously demonstrated in people with or without HIV.

We did not identify a statistically significant association between year of IPT receipt and RISK6 scores, which was a measure of whether length of time since IPT receipt would be associated with different RISK6 scores. We hypothesized that a longer period of time since IPT receipt would be associated with higher RISK6 scores because participants could have been exposed and re-infected with new TB strains in a longer period of time, and because some IPT trials demonstrated an increase in TB incidence 6 months after completion of TB preventive therapy (17) (18). On the other hand, our results demonstrating no significant difference in RISK6 scores by year of IPT receipt may be consistent with a more recent study that showed a more durable response to IPT (19).

We also evaluated the possibility of effect modification by HIV viral load on the association between previous IPT receipt and RISK6 scores. HIV viral load has previously been shown to be associated with RISK6 scores (7). We demonstrated that the association between IPT status and RISK6 scores was larger among participants with a detectable HIV viral load, although this did not reach statistical significance.

We also explored the association between prior receipt of IPT and 4 additional COR signatures, and found that IPT status was also statistically significantly associated with the Maertzdorf4 signature and the Sweeney3 signature. Interestingly, these were also the COR signatures that correlated most with the RISK6 signature. None of the genes in these 5 signatures overlap and many of them are involved in distinct biological functions.

In our study, participants who had positive sputum cultures for NTM did not have significantly different RISK6 scores compared to those with negative sputum cultures. We hypothesized that culture positivity for NTM would be associated with higher RISK6 scores since the utility of RISK6 scores as a triage test has been demonstrated and because of the relatedness between NTM and *Mycobacterium tuberculosis*. One study previously demonstrated differential expression of several genes in people with pulmonary NTM infection vs other respiratory diseases (15); the genes in the 5 signatures we analyzed in our study did not include any of the 25 genes with the top differential expression they reported, which is a possible explanation for why we did not demonstrate a significant association. Another possibility that would explain our results is that some of the participants with a positive sputum culture for NTM did not have a true NTM infection, and the positive sputum culture represented colonization. The diagnosis of pulmonary NTM infection requires chest imaging compatible with NTM infection, and none of the participants in our study had chest imaging available. Additionally, one positive sputum culture alone is not sufficient to make the diagnosis (20). Further speciation of the NTM isolated from positive sputum cultures was not available, so it is also possible that some of the participants had sputum cultures positive for a species NTM that rarely causes infection. Additional studies, ideally including persons with confirmed NTM infection, are needed to further describe the association between NTM and COR signatures.

The CORTIS trial showed that there was no significant difference in TB incidence among RISK11 positive participants who received TB preventive therapy relative to those who underwent active surveillance alone after 15 months of follow up. The reason for these results remains unclear, but there are several possibilities. One theory posed by the authors is that the regimen they chose, which was weekly isoniazid and rifapentine, was not sufficient to fully treat incipient TB. Another possibility is that some COR scores depend on genetic variations leading to differential immune activation. Our demonstration of an association between prior receipt of IPT and RISK6 scores would argue against the theory that genetic variations significantly affect COR scores, because in that case one would assume receiving IPT would not be associated with different COR scores. On the other hand, our results could be consistent with the possibility that the preventive therapy provided in the CORTIS trial was insufficient to fully treat incipient

TB. Of note, the CORTIS trial only included participants without HIV, whereas our cohort only included persons with HIV. Although we adjusted for HIV viral load in our models, it is possible that the association we observed between IPT and RISK6 scores would have been different among persons without HIV.

Our study had several limitations. The adherence to isoniazid preventive therapy was based on self-report, so it may have been subject to recall or social desirability bias. This could have had a significant impact on our results because receipt of IPT was our main predictor of interest. Another potential source of bias is that persons who are more likely to accept and be adherent to IPT may be more likely to also be adherent to HIV treatment. We attempted to mitigate this by adjusting for HIV viral load in our model, but this may not have been sufficient to fully address this source of bias. An additional limitation is that, given our study design, we cannot conclude that there is a causal relationship between IPT receipt and lower RISK6 scores. We also do not know whether the difference in mean RISK6 scores by IPT status would have been associated with different clinical outcomes, such as TB incidence, because participants were not followed prospectively.

In conclusion, we demonstrated that prior receipt of isoniazid preventive therapy was associated with a lower mean RISK6 score in a cohort of Kenyan people with HIV. We also found that the Maertzdorf4 and Sweeney3 signatures were associated with IPT status. Prospective studies measuring RISK6 and other COR scores before and after TB preventive therapy are needed to describe the nature of their relationship more definitively. Inclusion of a follow up period monitoring for incident TB might also allow for an assessment of whether possible changes in COR scores related to TB preventive therapy lead to decreased TB incidence. In our cohort, there was no significant association between positive sputum cultures for NTM and RISK6 scores. Studied including participants with a clinical diagnosis of NTM infection are needed to more fully explore the possible association between COR signatures and NTM infection.

REFERENCES

1. World Health Organization. Tuberculosis.2020. Available from: https://www.who.int/news-room/fact-sheets/detail/tuberculosis.

2. Getahun H, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis Infection. N Engl J Med. 2015;373(12):1179-80.

3. Sweeney TE, Braviak L, Tato CM, Khatri P. Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis. Lancet Respir Med. 2016;4(3):213-24.

4. Thompson EG, Du Y, Malherbe ST, Shankar S, Braun J, Valvo J, et al. Host blood RNA signatures predict the outcome of tuberculosis treatment. Tuberculosis (Edinb). 2017;107:48-58.

5. Darboe F, Mbandi SK, Naidoo K, Yende-Zuma N, Lewis L, Thompson EG, et al. Detection of Tuberculosis Recurrence, Diagnosis and Treatment Response by a Blood Transcriptomic Risk Signature in HIV-Infected Persons on Antiretroviral Therapy. Front Microbiol. 2019;10:1441.

6. Mendelsohn SC, Fiore-Gartland A, Penn-Nicholson A, Mulenga H, Mbandi SK, Borate B, et al. Validation of a host blood transcriptomic biomarker for pulmonary tuberculosis in people living with HIV: a prospective diagnostic and prognostic accuracy study. Lancet Glob Health. 2021.

7. Penn-Nicholson A, Mbandi SK, Thompson E, Mendelsohn SC, Suliman S, Chegou NN, et al. RISK6, a 6-gene transcriptomic signature of TB disease risk, diagnosis and treatment response. Sci Rep. 2020;10(1):8629.

8. Suliman S, Thompson EG, Sutherland J, Weiner J, Ota MOC, Shankar S, et al. Four-Gene Pan-African Blood Signature Predicts Progression to Tuberculosis. Am J Respir Crit Care Med. 2018;197(9):1198-208.

9. Zak DE, Penn-Nicholson A, Scriba TJ, Thompson E, Suliman S, Amon LM, et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. Lancet. 2016;387(10035):2312-22.

10. Drain PK, Bajema KL, Dowdy D, Dheda K, Naidoo K, Schumacher SG, et al. Incipient and Subclinical Tuberculosis: a Clinical Review of Early Stages and Progression of Infection. Clin Microbiol Rev. 2018;31(4).

11. Warsinske H, Vashisht R, Khatri P. Host-response-based gene signatures for tuberculosis diagnosis: A systematic comparison of 16 signatures. PLoS Med. 2019;16(4):e1002786.

12. Turner CT, Gupta RK, Tsaliki E, Roe JK, Mondal P, Nyawo GR, et al. Blood transcriptional biomarkers for active pulmonary tuberculosis in a high-burden setting: a prospective, observational, diagnostic accuracy study. Lancet Respir Med. 2020;8(4):407-19.

13. Scriba TJ, Fiore-Gartland A, Penn-Nicholson A, Mulenga H, Kimbung Mbandi S, Borate B, et al. Biomarker-guided tuberculosis preventive therapy (CORTIS): a randomised controlled trial. Lancet Infect Dis. 2021;21(3):354-65.

14. Kobayashi T, Nishijima T, Teruya K, Aoki T, Kikuchi Y, Oka S, et al. High Mortality of Disseminated Non-Tuberculous Mycobacterial Infection in HIV-Infected Patients in the Antiretroviral Therapy Era. PLoS One. 2016;11(3):e0151682.

15. Cowman SA, Jacob J, Hansell DM, Kelleher P, Wilson R, Cookson WOC, et al. Whole-Blood Gene Expression in Pulmonary Nontuberculous Mycobacterial Infection. Am J Respir Cell Mol Biol. 2018;58(4):510-8.

16. Gersh JK, Barnabas RV, Matemo D, Kinuthia J, Feldman Z, Lacourse SM, et al. Pulmonary tuberculosis screening in anti-retroviral treated adults living with HIV in Kenya. BMC Infect Dis. 2021;21(1):218.

17. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365(1):11-20.

18. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Mosimaneotsile B, et al. Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana: a posttrial observational analysis. AIDS. 2015;29(3):351-9.

19. Badje A, Moh R, Gabillard D, Guéhi C, Kabran M, Ntakpé JB, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. Lancet Glob Health. 2017;5(11):e1080-e9.

20. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416.

Tables and Figures

Table 1. Characteristics of participants by IPT status

Characteristic	Overall, N = 386[1]	Received IPT		p-value[2]
		No History of IPT, N = 51[1]	Prior History of IPT, N = 335[1]	
Age (years)	38.3 (10.2)	34.7 (10.4)	38.8 (10.1)	0.012
Sex				0.5
Female	223 / 386 (58%)	32 / 51 (63%)	191 / 335 (57%)	
Male	163 / 386 (42%)	19 / 51 (37%)	144 / 335 (43%)	
BMI	23.9 (20.8)	23.0 (5.4)	24.0 (22.2)	0.5
Tobacco status				0.5
Never	349 / 386 (90%)	47 / 51 (92%)	302 / 335 (90%)	
Yes, currently	11 / 386 (2.8%)	0 / 51 (0%)	11 / 335 (3.3%)	
Yes, in past but not now	26 / 386 (6.7%)	4 / 51 (7.8%)	22 / 335 (6.6%)	
Drinks alcohol				0.5
No	336 / 385 (87%)	43 / 51 (84%)	293 / 334 (88%)	
Yes	49 / 385 (13%)	8 / 51 (16%)	41 / 334 (12%)	
Missing	1	0	1	
Diabetes				0.13
No	372 / 373 (100%)	49 / 50 (98%)	323 / 323 (100%)	
Yes	1 / 373 (0.3%)	1 / 50 (2.0%)	0 / 323 (0%)	
Missing	13	1	12	
Taking ART				0.002
No	3 / 386 (0.8%)	3 / 51 (5.9%)	0 / 335 (0%)	
Yes	383 / 386 (99%)	48 / 51 (94%)	335 / 335 (100%)	
Most recent CD4 count	434.9 (229.2)	315.9 (181.2)	443.4 (230.2)	0.005
Missing	70	30	40	
Detectable HIV viral load?				<0.001
No	349 / 375 (93%)	36 / 46 (78%)	313 / 329 (95%)	
Yes	26 / 375 (6.9%)	10 / 46 (22%)	16 / 329 (4.9%)	
Missing	11	5	6	
HIV viral load	14,549.3 (180,343.1)	98,012.2 (507,422.3)	2,879.8 (25,430.1)	0.2
Missing	11	5	6	
Current ART regimen				<0.001
AZT + 3TC + EFV	4 / 380 (1.1%)	1 / 49 (2.0%)	3 / 331 (0.9%)	
AZT + 3TC + LPV/r	7 / 380 (1.8%)	2 / 49 (4.1%)	5 / 331 (1.5%)	
AZT + 3TC + NVP	36 / 380 (9.5%)	1 / 49 (2.0%)	35 / 331 (11%)	
other	19 / 380 (5.0%)	2 / 49 (4.1%)	17 / 331 (5.1%)	
TDF + 3TC + EFV	183 / 380 (48%)	41 / 49 (84%)	142 / 331 (43%)	
TDF + 3TC + LPV/r	7 / 380 (1.8%)	0 / 49 (0%)	7 / 331 (2.1%)	
TDF + 3TC + NVP	124 / 380 (33%)	2 / 49 (4.1%)	122 / 331 (37%)	
Missing	6	2	4	

[1] Mean (SD); n / N (%)

[2] Welch Two Sample t-test; Fisher's exact test

Characteristic	Overall, N = 386[1]	Received IPT		p-value[2]
		No History of IPT, N = 51[1]	Prior History of IPT, N = 335[1]	
WHO stage of HIV infection				0.003
Stage 1	112 / 386 (29%)	24 / 51 (47%)	88 / 335 (26%)	
Stage 2	166 / 386 (43%)	15 / 51 (29%)	151 / 335 (45%)	
Stage 3	99 / 386 (26%)	9 / 51 (18%)	90 / 335 (27%)	
Stage 4	9 / 386 (2.3%)	3 / 51 (5.9%)	6 / 335 (1.8%)	
History of TB				0.7
No	325 / 383 (85%)	44 / 50 (88%)	281 / 333 (84%)	
Yes	58 / 383 (15%)	6 / 50 (12%)	52 / 333 (16%)	
Missing	3	1	2	
Presence of TB symptoms				0.11
no	338 / 385 (88%)	41 / 51 (80%)	297 / 334 (89%)	
yes	47 / 385 (12%)	10 / 51 (20%)	37 / 334 (11%)	
Missing	1	0	1	
TST induration				0.4
<10 mm	295 / 333 (89%)	42 / 45 (93%)	253 / 288 (88%)	
>10 mm	38 / 333 (11%)	3 / 45 (6.7%)	35 / 288 (12%)	
Missing	53	6	47	
Sputum culture result				0.2
Contaminated (bacterial overgrowth)	3 / 378 (0.8%)	0 / 51 (0%)	3 / 327 (0.9%)	
Mycobacterium tuberculosis	5 / 378 (1.3%)	2 / 51 (3.9%)	3 / 327 (0.9%)	
Negative	328 / 378 (87%)	41 / 51 (80%)	287 / 327 (88%)	
Non-tuberculous mycobacteria (NTM)	41 / 378 (11%)	8 / 51 (16%)	33 / 327 (10%)	
Not done	1 / 378 (0.3%)	0 / 51 (0%)	1 / 327 (0.3%)	
Missing	8	0	8	

[1] Mean (SD); n / N (%)

[2] Welch Two Sample t-test; Fisher's exact test

Figure 1. Distribution of RISK6 Scores by IPT Status

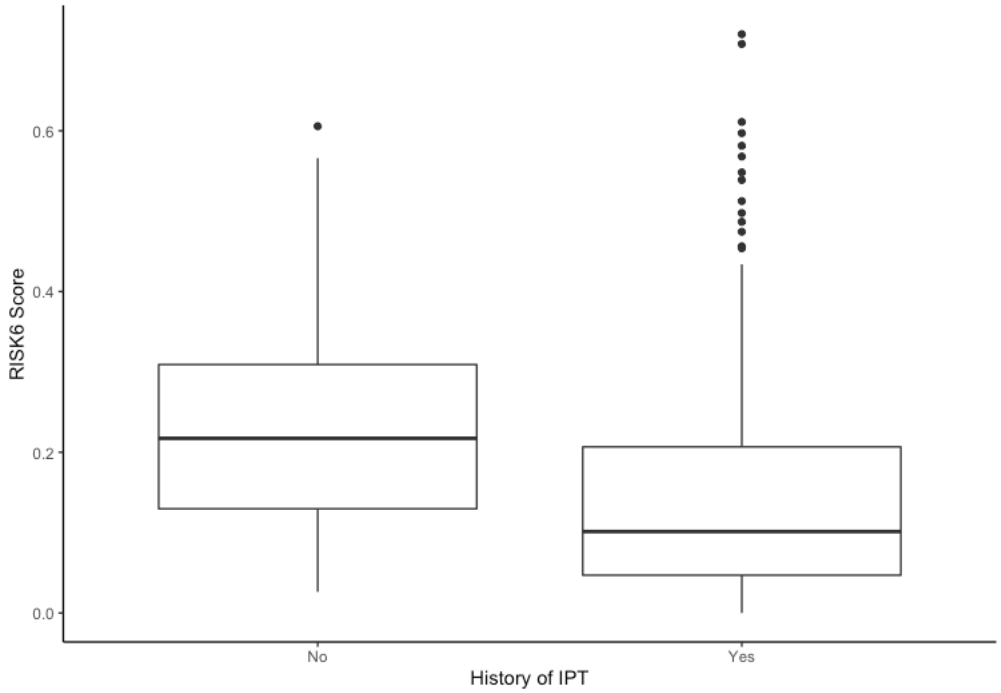

Figure 2. Distribution of RISK6 Scores by Year of IPT Receipt

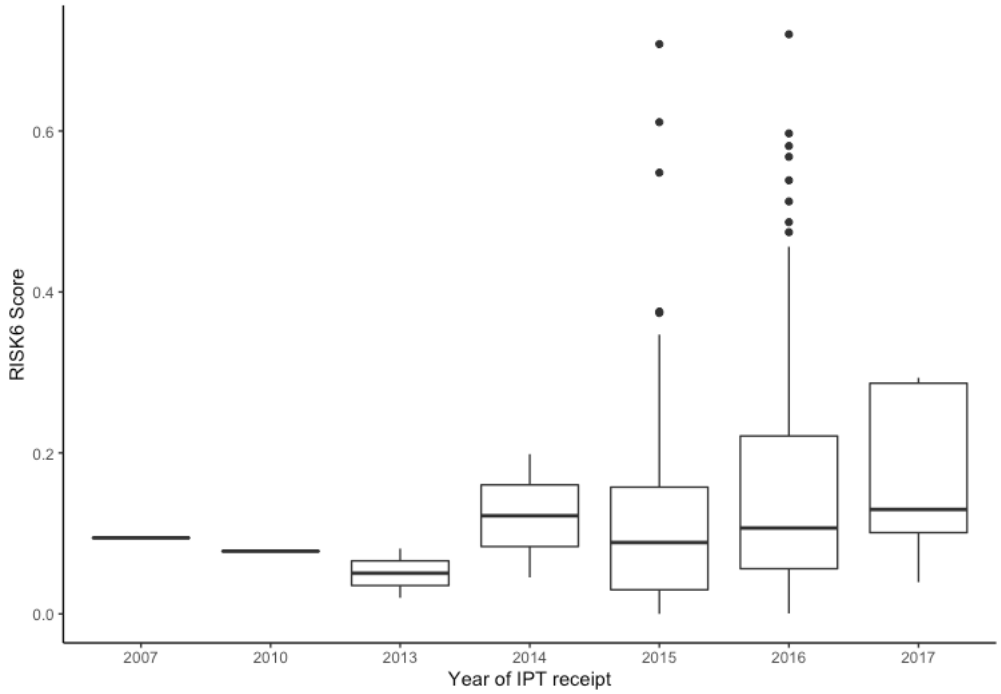

Figure 3a. RISK6 Scores by IPT Status, HIV viral load detectable (>1000)

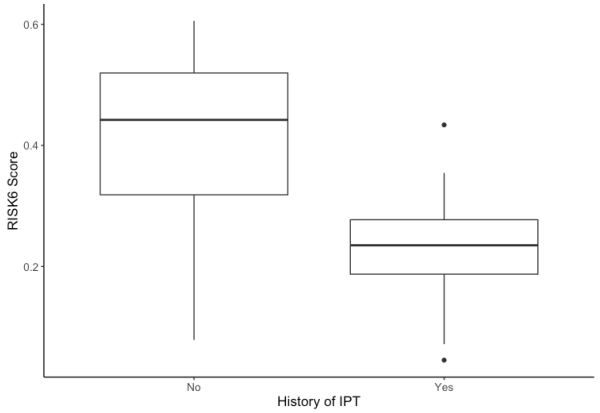

Figure 3b. RISK6 Scores by IPT Status, HIV viral load undetectable (<1000)

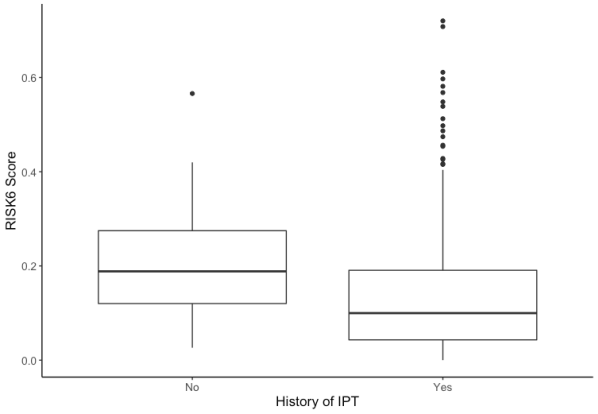

Figure 4. RISK6 Scores by Sputum Culture Result

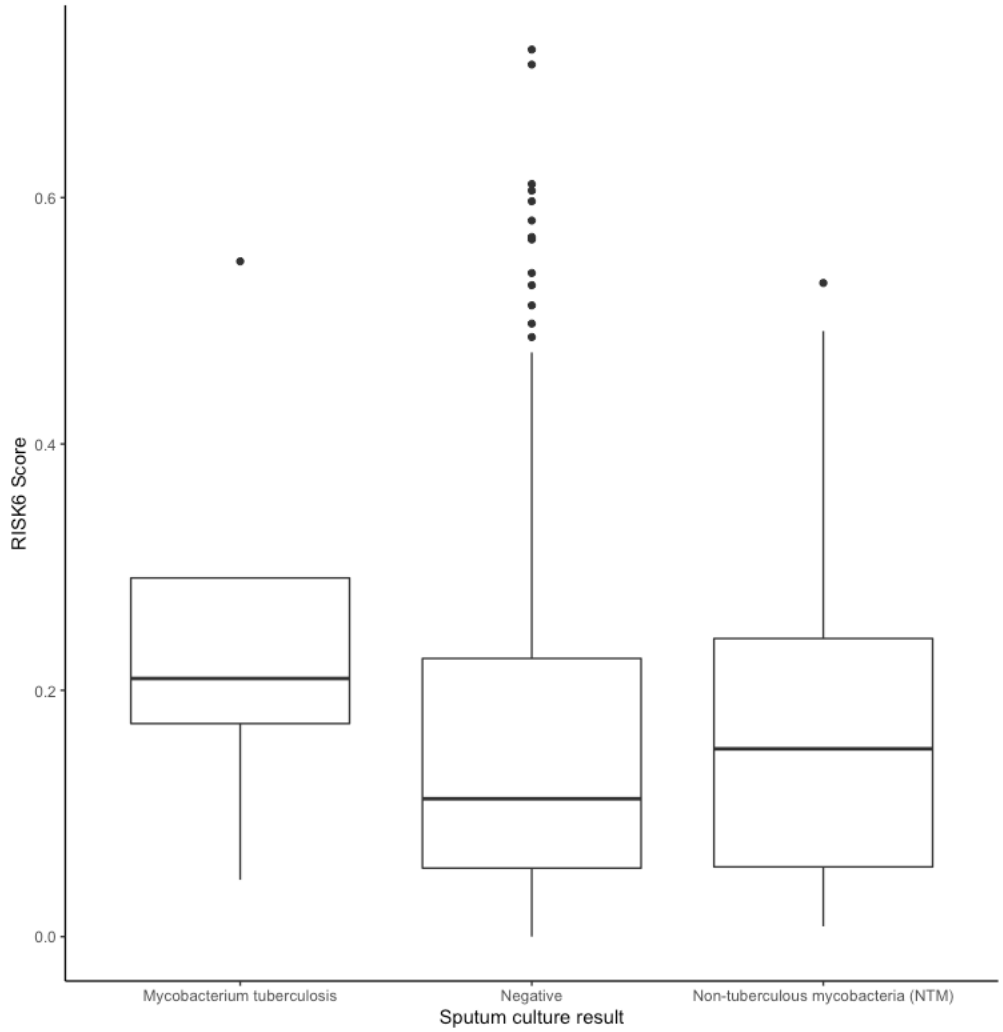

Figure 5. Correlation matrix comparing 5 CoR Signatures