Prospective validation of a blood RNA TB biomarker in ambulant HIV-infected adults

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1. BACKGROUND

- New non-sputum tuberculosis (TB) biomarkers for diagnosing and predicting progression to active TB disease are needed to facilitate the WHO End TB Strategy goals.
- We previously developed and validated a host whole-blood transcriptomic correlate of risk, RISK11, that identified individuals with active TB or at high risk of progression to active TB in case-control studies.[1-2]
- This study aimed to test **diagnostic and predictive RISK11 performance** for prospective community-based TB screening in HIV+ adults, and to compare predictive performance with **QuantiFERON-TB Gold Plus** (QFT).

2. METHODS

- People living with HIV enrolled across 5 sites in South Africa underwent active surveillance for microbiologically-confirmed TB for up to 15 months (**Figure 1**).

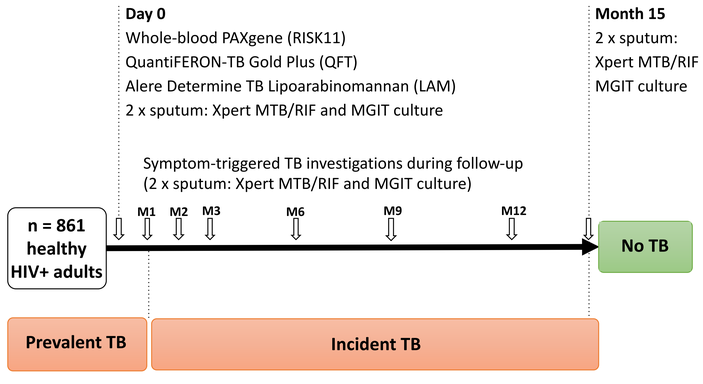


Figure 1: Study design and follow-up schedule

- ART-naïve participants were referred for ART and isoniazid preventive therapy per country guidelines.
- RISK11 was measured at baseline and double-blinded; RISK11 positivity was pre-defined at 60% score threshold.
- Primary endpoint: Two separate sputum samples positive on MGIT culture and/or Xpert MTB/RIF.

Blood RNA qRT-PCR biomarker identifies prevalent TB and predicts progression to active TB disease **within 15 months** in people living with HIV

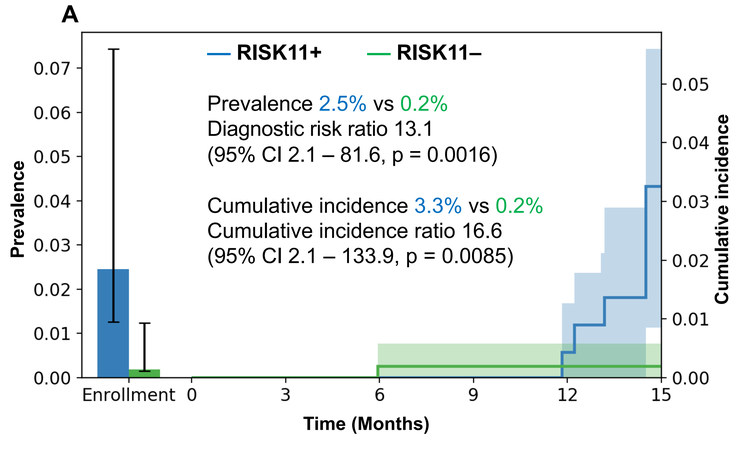


Figure 2A-C: (A) TB prevalence and cumulative incidence through 15-month follow-up by RISK11 status. RISK11 receiver operating characteristics with area under the curve (AUC) for **(B) diagnosis of prevalent TB disease at baseline**, and **(C) prediction of progression to active TB within 15 months versus QuantiFERON-TB Gold Plus** (QFT). WHO minimal (dashed box) and optimal (solid box) target product profile criteria are shown. Error bars and shading represents 95% confidence interval (CI).

3. PRELIMINARY RESULTS

- Among 861 participants (median age 35; 72% female; 78% ART-experienced with 3 years median ART duration; median CD4 count 529), ten primary endpoint active TB cases were identified at baseline (1.2% prevalence; 70% asymptomatic).
- Diagnostic test performance at baseline is summarized in **Table 1** and **Figure 2A,B**.

Table 1: Diagnostic test accuracy

	Sensitivity, % (95%CI)	Specificity, % (95%CI)
WHO minimum triage test target product profile (TPP)	**90**	**70**
TB symptom screening	30 (6.3-62.5)	94.4 (92.8-95.9)
Urine Alere LAM assay	10 (3.3-33.3)	98.5 (97.6-99.2)
RISK11 ≥ 60 (a-priori analysis)	87.5 (57.1-95.8)	65.8 (62.4-69)
RISK11 ≥ 80 (post-hoc)	87.5 (57.1-95.8)	78 (75-80.8)

- Nine primary endpoint incident TB cases were identified through 950 person-years follow-up (0.95 cases/100 person-years).
- Test performance for prediction of progression to active TB disease within 15 months is shown in **Table 2** and **Figure 2A,C**.

Table 2: Predictive test accuracy

	Sensitivity, % (95%CI)	Specificity, % (95%CI)
WHO minimum predictive test target product profile (TPP)	**75**	**75**
RISK11 ≥ 60 (a-priori analysis)	88.9 (44.5-98.8)	69.1 (65.3-72.5)
QFT-TB Gold Plus ≥ 0.35	65.8 (30.5-89.5)	56.1 (52.3-59.9)

4. CONCLUSIONS

- RISK11 performance approaches the minimum WHO triage and predictive test TPP among HIV+ adults.
- QFT performance falls short of the predictive TPP.
- RISK11 translation to a point-of-care assay may allow early identification of ambulant HIV+ adults that would benefit from further TB testing, therapy, or intensified follow-up.

5. REFERENCES

1. Zak DE, et al. Lancet, 2016 2. Darboe F, et al. Tuberculosis, 2018