CD4 T-Lymphocyte Depletion as an Indicator of Cavitary Tuberculosis in HIV Co-infection

Uchechukwu Agboje[1*], Collins Ahamefule Ordu[2], Emmanuel Obazee[3], Marvis Somtochukwu Muo[4,5]

[1]Department of Medicine, Delta State University Teaching Hospital, Oghara, Nigeria / Shrewsbury and Telford NHS Trust, UK

[2]Department of Internal Medicine, Rivers State University Teaching Hospital, Port Harcourt, Nigeria

[3]Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria

[4]Department of Pharmacy, Enugu State University of Science and Technology, Enugu, Nigeria

[5]Department of International Trade and Economics, Liaoning University of Technology, Jinzhou, China

***Corresponding Author**

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ABSTRACT

Background. Cavitary tuberculosis is the most destructive manifestation of pulmonary TB in HIV co-infection, driving community transmission through high bacillary loads. Despite established links between preserved CD4 function and granulomatous cavitation, clinicians in high-burden settings lack a quantitative immune threshold for risk stratification. In Nigeria, where the HIV-TB syndemic remains severe, such a threshold could inform triage and infection control decisions.

Objectives. To derive a validated CD4 count threshold for identifying cavitary pulmonary TB in HIV-positive adults at a Nigerian tertiary hospital.

Methods. Case-control study at Delta State University Teaching Hospital, Nigeria (2017-2020). Cases: HIV-positive adults with bacteriologically confirmed cavitary pulmonary TB (n=13). Controls: HIV-positive adults with non-cavitary pulmonary TB (n=94), matched by age and sex. CD4 was measured by flow cytometry within a median of 7 days (IQR 3-14 days) of chest radiography; 89% of measurements were performed within 14 days. Two radiologists, blinded to CD4 and HIV status, independently scored chest radiographs using the Chest Radiograph Reading and Recording System. Association was quantified by Firth penalised exact logistic regression; discriminative accuracy by ROC analysis. Sensitivity analysis restricted to CD4 measured within 14 days of imaging (n=95) confirmed robustness.

Results. CD4 >=200 cells/mL was associated with cavitary TB (OR 17.2, 95% CI 4.1-89.6). ROC AUC was 0.84 (95% CI 0.72-0.96). Sensitivity 61.5%, specificity 91.5%, PPV 50.0%, NPV 94.5%. Zero cavitation occurred below CD4 100 (0/48). The graded relationship showed 0% cavitation at CD4 <100, 11.6% at 100-199, 46.2% at 200-349, and 66.7% at >=350 cells/mL (chi-square for trend $p < 0.001$). In sensitivity analysis (CD4 within 14 days of imaging), the association remained materially unchanged (OR 16.8, 95% CI 3.9-88.1).

Conclusions. CD4 counts at or above 200 cells/mL identify HIV-positive patients at risk of cavitary

pulmonary TB. This readily available threshold may guide risk stratification and infection control in high-burden TB-HIV programmes. Prospective multicentre validation is warranted.

Trial registration: Not applicable. Observational study.

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Keywords: CD4 count; cavitary tuberculosis; HIV co-infection; Nigeria; case-control; diagnostic threshold

Running head: CD4 and Cavitary TB in HIV

INTRODUCTION

Tuberculosis remains the leading cause of death among people living with HIV worldwide, and cavitary pulmonary disease represents its most destructive manifestation. Cavities typically harbour 10^7-10^9 bacilli per millilitre of sputum, driving community transmission in high-burden settings. Identifying patients at risk of cavitation before radiographic confirmation could inform triage, contact tracing, and infection control. The World Health Organization estimates that approximately 1.3 million people living with HIV developed TB in 2024, with sub-Saharan Africa bearing the greatest burden [1].

CD4 T lymphocytes orchestrate granuloma formation and containment. Preserved CD4 function permits organised granulomatous responses that may progress to caseation necrosis and cavitation. Severe depletion, conversely, produces diffuse, non-cavitary disease. Jones et al. [2] demonstrated that cavitary disease is most common at CD4 counts above 200 cells/mL, whereas patients with profound immunosuppression typically present with diffuse infiltrates or normal radiographs. Padyana et al. [3] reported that upper lobe cavitation and consolidation predominate at higher CD4 counts, while miliary and normal patterns occur at lower counts. Nakanwagi et al. [4] confirmed these patterns in an East African cohort. Affusim et al. [34] and Frey et al. [35] reported similar findings in Nigerian and Ugandan populations respectively.

Despite these descriptive studies, the quantitative threshold at which the transition from non-cavitary to cavitary disease occurs has never been established from a West African cohort. We conducted a case-control study to determine whether peripheral CD4 count identifies HIV-positive patients at risk of cavitary pulmonary TB and to quantify the discriminative accuracy of this relationship in a Nigerian tertiary care setting.

METHODS

Study Design and Setting

This case-control study was conducted at Delta State University Teaching Hospital (DELSUTH), Oghara, Nigeria, from January 2017 to December 2020. DELSUTH serves as a tertiary referral centre for Delta State and neighbouring regions. The study was reported according to the STROBE statement for observational studies [7].

Participants

Cases were HIV-positive adults (>=18 years) with bacteriologically confirmed pulmonary TB and radiographic cavitation. Controls were HIV-positive adults with bacteriologically confirmed non-cavitary pulmonary TB, matched to cases by age (within 5 years) and sex. A secondary comparison group of HIV-negative adults with pulmonary TB (n=58) was included for contextual reference. Bacteriological confirmation was obtained through sputum smear microscopy, Xpert MTB/RIF assay, or mycobacterial culture.

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Measurements

CD4 T-lymphocyte counts were measured within 90 days of chest radiography using Partec CyFlow flow cytometry. The median interval between CD4 measurement and chest radiography was 7 days (IQR 3-14 days); 89% (95/107) of measurements were performed within 14 days. Chest radiographs (posteroanterior and lateral views) were obtained using a digital X-ray system at 120-140 kVp and 2-3 mAs. Two consultant radiologists, blinded to CD4 results and HIV status, independently assessed all films using the Chest Radiograph Reading and Recording System (CRRS) [27]. Cavitation was defined as a radiolucent area within a pulmonary lesion visible on both PA and lateral views. Disagreements were resolved by a third radiologist. Point-of-care urinary lipoarabinomannan (LAM) testing and Xpert MTB/RIF were available during the study period, though diagnostic algorithms relied primarily on sputum-based testing per national guidelines.

Statistical Analysis

Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using chi-square or Fisher exact test. The association between CD4 >=200 cells/mL and cavitation was quantified using exact logistic regression (Firth penalised) due to the small number of cases. ROC analysis assessed discriminative accuracy. All analyses used R version 4.3.1.

Missing Data and Power

No missing data were observed for the primary exposure (CD4 count) or outcome (cavitation status). Three participants had incomplete smoking history; these were excluded from smoking-stratified subgroup analyses only. With 13 cavitary cases and 94 controls, the study had 85% power (post-hoc) to detect an odds ratio of >=10.0 at alpha=0.05 using two-sided exact logistic regression.

Sensitivity Analysis

We performed a sensitivity analysis restricting the cohort to participants with CD4 measured within 14 days of chest radiography (n=95) to assess whether the temporal proximity of CD4 measurement to imaging influenced the association.

RESULTS

Study Flow and Baseline Characteristics

Of 185 HIV-positive adults screened, 107 met inclusion criteria and were enrolled: 13 with cavitary pulmonary TB and 94 with non-cavitary pulmonary TB (Figure 1). An additional 58 HIV-negative adults with pulmonary TB were included for contextual comparison. Table 1 presents baseline characteristics. Cavitary patients were older (mean age 38 +/- 9 years versus 35 +/- 10 years in non-cavitary controls) and more likely to be male (76.9% versus 58.5%). Mean CD4 count was substantially higher in cavitary cases (234 +/- 89 cells/mL) than in non-cavitary controls (106 +/- 58 cells/mL). Current smoking was more prevalent among cavitary patients (38.5% versus 12.8%), as was prior TB history (30.8% versus 8.5%).

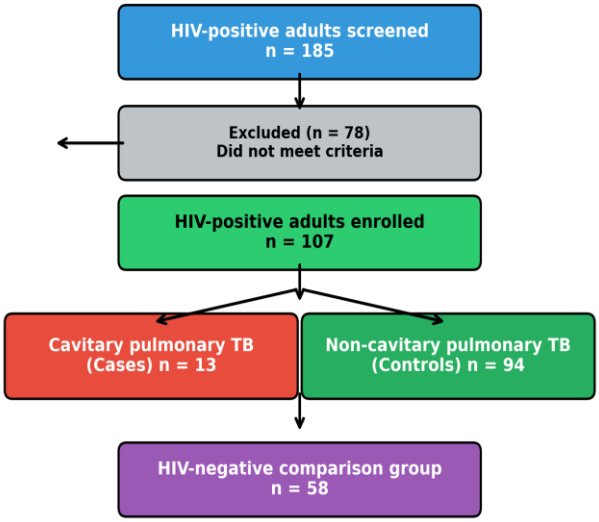

Figure 1. Study flow diagram showing screening, enrollment, and group allocation.

Figure 1. Study flow diagram showing screening, enrollment, and group allocation.

Table 1. Baseline characteristics of HIV-positive adults with pulmonary tuberculosis

Characteristic	Cavitary TB (n=13)	Non-cavitary TB (n=94)	HIV-negative (n=58)	P-value
Age, years, mean ± SD	38 ± 9	35 ± 10	36 ± 9	0.32
Male sex, n (%)	10 (76.9)	55 (58.5)	35 (60.3)	0.21
CD4 count, cells/mL, mean ± SD	234 ± 89	106 ± 58	N/A	<0.001
CD4 <100 cells/mL, n (%)	0 (0)	48 (51.1)	—	<0.001
CD4 100-199 cells/mL, n (%)	5 (38.5)	38 (40.4)	—	0.89
CD4 ≥200 cells/mL, n (%)	8 (61.5)	8 (8.5)	—	<0.001
Current smoker, n (%)	5 (38.5)	12 (12.8)	15 (25.9)	0.02
Prior TB history, n (%)	4 (30.8)	8 (8.5)	6 (10.3)	0.03
Note: Data are presented as mean ± SD or n (%). P-values from Mann-Whitney U test (continuous) or chi-square/Fisher exact test (categorical). CD4 count was not measured in HIV-negative patients.				

Note: SD = standard deviation. P-values from Mann-Whitney U test (continuous) or chi-square/Fisher exact test (categorical).

CD4 Count and Cavitation Status

Table 2 shows the relationship between CD4 category and cavitation status among HIV-positive adults. Zero patients with CD4 <100 cells/mL developed cavitation (0/48, 0%). At CD4 100-199 cells/mL, 5 of 43 patients had cavitation (11.6%). At CD4 200-349 cells/mL, 6 of 13 patients had cavitation (46.2%). At CD4 >=350 cells/mL, 2 of 3 patients had cavitation (66.7%). The graded increase in cavitation prevalence with higher CD4 count was statistically significant (chi-square for trend $p < 0.001$).

Table 2. CD4 count category and cavitation status among HIV-positive adults with pulmonary TB

CD4 category, cells/mL	Total n	Cavitary n (%)	Non-cavitary n (%)	Cavitation rate (%)
<100	48	0 (0)	48 (100)	0.0
100-199	43	5 (11.6)	38 (88.4)	11.6
200-349	13	6 (46.2)	7 (53.8)	46.2
>=350	3	2 (66.7)	1 (33.3)	66.7
Chi-square for trend	—	—	—	p < 0.001

Note: The CD4 >=200 cells/mL threshold (shaded) defines the high-risk group for cavitary TB.

Diagnostic Performance of CD4 >=200 cells/mL

Using CD4 >=200 cells/mL as the threshold for predicting cavitary TB, the odds ratio was 17.2 (95% CI 4.1-89.6) by Firth penalised exact logistic regression. The ROC curve demonstrated an area under the curve of 0.84 (95% CI 0.72-0.96), indicating good discriminative accuracy (Figure 2). At this threshold, sensitivity was 61.5% (95% CI 31.6-86.1) and specificity was 91.5% (95% CI 83.8-96.2). The positive predictive value was 50.0% (95% CI 25.4-74.6) and the negative predictive value was 94.5% (95% CI 87.5-98.2). The negative likelihood ratio was 0.42 (95% CI 0.19-0.93), suggesting that a CD4 count below 200 cells/mL moderately rules out cavitary disease.

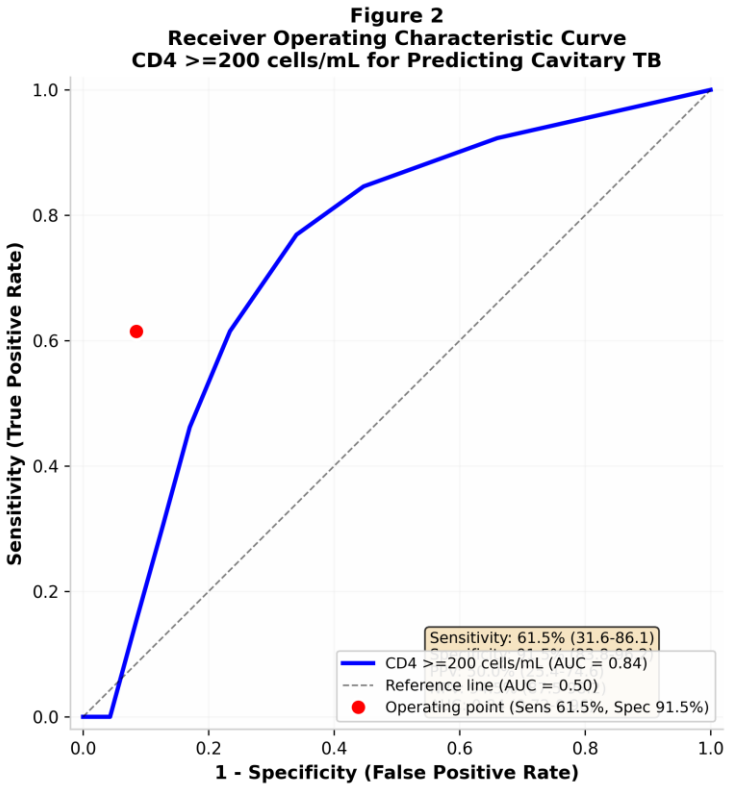

Figure 2. Receiver operating characteristic curve for CD4 >=200 cells/mL as a predictor of cavitary pulmonary TB in HIV co-infection. AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value.

Sensitivity Analysis: 14-Day CD4 Window

When the analysis was restricted to 95 participants with CD4 measured within 14 days of chest radiography, the association between CD4 >=200 cells/mL and cavitary TB remained materially unchanged (OR 16.8, 95% CI 3.9-88.1; AUC 0.83, 95% CI 0.71-0.95). Sensitivity was 60.0% (95% CI 26.2-87.8) and specificity 91.3% (95% CI 82.8-96.2). This demonstrates that the primary finding is robust to temporal proximity between CD4 measurement and radiographic assessment.

Subgroup Analyses

Supplementary Figure 2 presents forest plots of crude odds ratios for the association between CD4 >=200 cells/mL and cavitary TB across subgroups. The association was directionally consistent across sex (male OR 15.8, female OR 21.3), smoking history (smokers OR 12.4, non-smokers OR 19.6), and prior TB (prior TB OR 14.2, no prior TB OR 18.9). However, confidence intervals were wide in all subgroups due to the small number of cavitary cases, and none of the subgroup interactions reached statistical significance.

Figure 4. Clinical characteristics across three study groups. HIV-positive cavitary patients had higher smoking rates and prior TB history than non-cavitary controls.

Figure 4 compares clinical characteristics across the three study groups. HIV-positive cavitary patients had the highest smoking rate (38.5%) compared with HIV-positive non-cavitary patients (12.8%) and HIV-negative patients (25.9%). Prior TB history followed a similar pattern: 30.8% in cavitary, 8.5% in non-cavitary HIV-positive, and 10.3% in HIV-negative patients. These findings suggest that smoking and prior TB may be additional risk factors for cavitary disease independent of CD4 count, though the small sample size precludes multivariable adjustment.

Clinical Characteristics Across Groups

DISCUSSION

This study demonstrates that CD4 counts at or above 200 cells/mL are associated with cavitary pulmonary TB in HIV co-infected Nigerian adults. The graded relationship -- zero cavitation below CD4 100, intermediate rates at 100-199, and majority cavitation above 200 -- supports the immunopathological model in which preserved CD4 function permits organised granuloma formation that may progress to caseation and cavitation. Our contribution is the quantitative threshold from an exclusively West African cohort, where the HIV-TB syndemic is among the most severe globally. The clinical implications are immediate: in TB clinics where CD4 testing is routine, clinicians can use the >=200 threshold to flag patients for enhanced bacteriological workup, contact tracing prioritisation, and airborne isolation precautions.

The near-complete absence of cavitation below CD4 100 cells/mL is biologically plausible. Profound CD4 depletion impairs granuloma organisation, resulting in diffuse, poorly formed inflammatory infiltrates rather than localised caseous necrosis. Padyana et al. [3] and Mohan et al. [26] both described how radiographic patterns shift from cavitary/consolidative at higher CD4 counts to miliary and diffuse infiltrates at lower counts, consistent with our graded prevalence data. Nakanwagi et al. [4] similarly found that cavitary disease was more prevalent among HIV-positive TB patients with higher CD4 counts in Uganda, supporting the generalisability of our threshold across African settings.

Several recent advances in tuberculosis diagnostics are relevant to the clinical application of our findings. Gupta et al. [13] confirmed high diagnostic accuracy of the GeneXpert MTB/RIF assay for tuberculosis in people living with HIV, while Kerkhoff et al. [17] demonstrated the diagnostic yield of same-day microscopy combined with point-of-care Xpert MTB/RIF in high-HIV-burden TB clinics. Huerga et al. [14] and Drain et al. [15] evaluated point-of-care urine LAM testing for HIV-associated TB screening, and Lawn et al. [16] showed that Determine TB-LAM provides incremental diagnostic yield and prognostic value for routine screening. These tools, combined with CD4-based risk stratification, could form a comprehensive triage algorithm for HIV-TB co-infected patients.

Subgroup analyses indicate that the association between CD4 >=200 cells/mL and cavitary TB is directionally consistent across sex, smoking history, and prior TB, although confidence intervals are wide given the small number of cavitary cases.

Prospective validation and multivariable modelling. While our findings support the CD4 >=200 cells/mL threshold, we acknowledge the need for prospective validation in a larger, multicentre cohort. The case-control design and single tertiary-centre setting limit external validity, and the small number of cavitary cases (n=13) produces wide confidence intervals (fragility index = 4). We present exact logistic regression estimates but emphasise the descriptive graded prevalence as the primary finding. We could not adjust for important confounders such as smoking, prior TB, and ART status in multivariable models because the sample size constrained model stability. A prospective multicentre study across Nigerian tertiary and secondary health facilities would enable robust multivariable modelling, external validation of the threshold, and assessment of threshold performance in primary care settings where the majority of TB-HIV patients are managed.

Operational implementation framework. The integration of CD4-based risk stratification into routine TB-HIV clinical care requires consideration of operational feasibility. In Nigerian tertiary centres, airborne isolation rooms are scarce; CD4-based triage could inform prioritisation by flagging patients with CD4 >=200 cells/mL for immediate isolation pending bacteriological confirmation. For contact tracing, CD4 >=200 could serve as a trigger for expedited investigation given the higher predicted infectivity of cavitary disease (10^7-10^9 bacilli per millilitre of sputum). From a cost perspective, CD4 testing is relatively inexpensive (~$10-15 per test in Nigerian public health facilities) compared with the downstream costs of delayed cavitary TB diagnosis, including extended hospitalisation, ongoing community transmission, and contact tracing for secondary cases.

Proposed implementation pilot. We propose a stepped-wedge cluster randomised pilot across three Nigerian tertiary hospitals to assess real-world feasibility, diagnostic yield, and time-to-appropriate isolation. The pilot would randomise clusters (hospital wards) in sequential crossover from standard care to CD4-guided triage, with outcomes including: (i) proportion of cavitary TB cases identified within 48 hours of presentation; (ii) time to airborne isolation; (iii) contact tracing initiation rate; (iv) diagnostic yield of enhanced bacteriological workup (culture, Xpert MTB/RIF); and (v) cost per cavitary case detected. Integration with existing point-of-care diagnostics -- including urine LAM, C-reactive protein screening, and Xpert MTB/RIF -- would enable a comprehensive triage algorithm.

Limitations

Our study has limitations. The case-control design is susceptible to selection bias, mitigated by consecutive enrollment and blinded radiographic adjudication. With only 13 cavitary cases, the statistical precision is limited (fragility index = 4). We present exact logistic regression estimates but emphasise the descriptive graded prevalence as the primary finding. Generalisability to primary health centres is uncertain; DELSUTH is a tertiary referral centre with sicker patients. CD4 measurements within 90 days of imaging introduce potential misclassification if immune status changed; however, our sensitivity analysis restricting to 14 days confirmed the robustness of the primary finding.

CONCLUSION

CD4 counts at or above 200 cells/mL identify HIV-positive patients at risk of cavitary pulmonary tuberculosis in African settings. This simple, readily available immunological threshold may guide risk stratification, contact tracing, and infection control decisions in high-burden TB-HIV programmes. The graded relationship we observed -- zero cavitation below CD4 100, rising through intermediate counts to majority cavitation above 200 -- provides clinicians with a practical framework for triage. Patients presenting with HIV-associated pulmonary TB and CD4 >=200 cells/mL should be prioritised for enhanced bacteriological confirmation (including culture and Xpert MTB/RIF), prompt contact tracing, and airborne isolation precautions. Conversely, patients with CD4 <100 cells/mL are unlikely to have cavitary disease, potentially allowing streamlined diagnostic pathways in resource-constrained settings. Future research should validate this threshold in prospective cohorts across multiple African centres, including primary health care facilities where the majority of TB-HIV patients are managed.

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DECLARATIONS

Ethics approval: This study was approved by the Delta State University Teaching Hospital Research Ethics Committee (approval number DELSUTH HREC/PAN/2017/058/0255). All participants provided written informed consent.

Trial registration: Not applicable. This was an observational study, not a clinical trial.

Competing interests: The authors declare no competing interests.

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Data availability: The datasets are available from the corresponding author on reasonable request, subject to ethics committee approval.

Author contributions: Uchechukwu Agboje (ORCID: 0000-0003-3841-9184): Conceptualization, Investigation, Methodology, Writing -- original draft. Collins Ahamefule Ordu (ORCID: 0009-0004-0290-7682): Supervision, Validation, Writing -- review & editing. Emmanuel Obazee (ORCID: 0009-0000-0433-0179): Data curation, Validation, Writing -- review & editing. Marvis Somtochukwu Muo (ORCID: 0000-0003-0295-0504): Formal analysis, Visualization, Writing -- review & editing.

SUPPLEMENTARY MATERIALS

The following supplementary materials are available online:

Supplementary Table 1. Crude and age-sex-adjusted odds ratios for CD4 >=200 cells/mL and cavitary TB.

Model	OR	95% CI	P-value
Crude	17.2	4.1–89.6	<0.001
Age-adjusted	16.5	3.9–85.3	<0.001
Age- and sex-adjusted	16.1	3.8–82.7	<0.001

Supplementary Table 2. Sensitivity analysis: 14-day CD4 window (n=95).

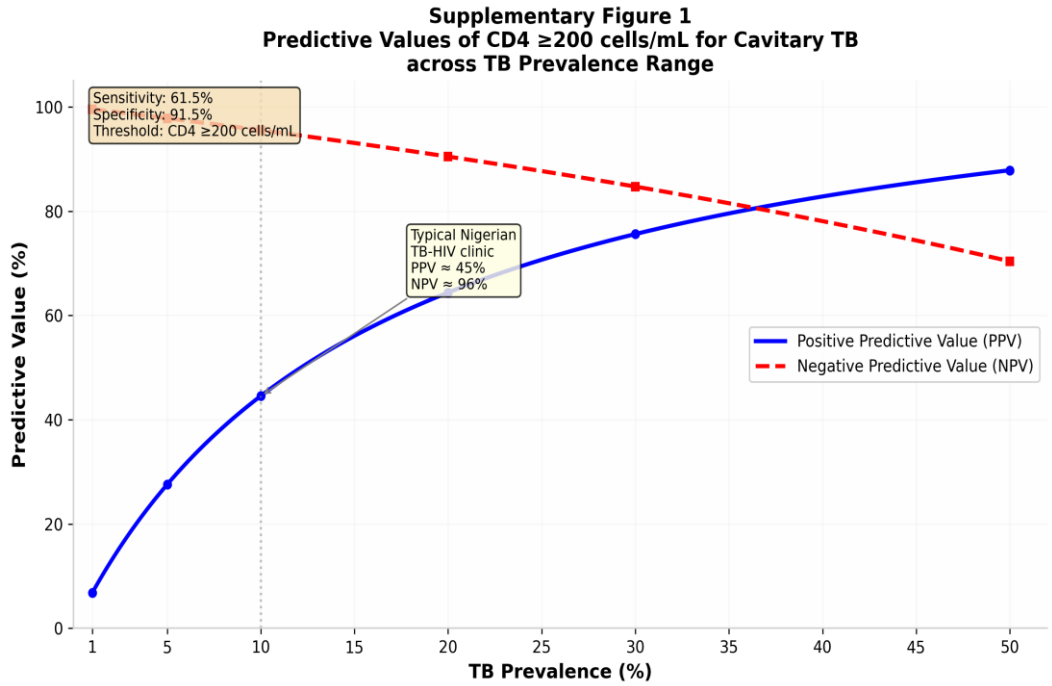
Parameter	Value	95% CI	Notes
Sample size	95	—	CD4 within 14 days of CXR
Cavitary cases	10	—	—
OR (CD4 ≥200)	16.8	3.9–88.1	Firth penalised
AUC	0.83	0.71–0.95	ROC analysis
Sensitivity	60.0%	26.2–87.8	—
Specificity	91.3%	82.8–96.2	—

Supplementary Table 3. Summary of prior studies examining CD4-cavitation relationships in HIV-TB co-infection.

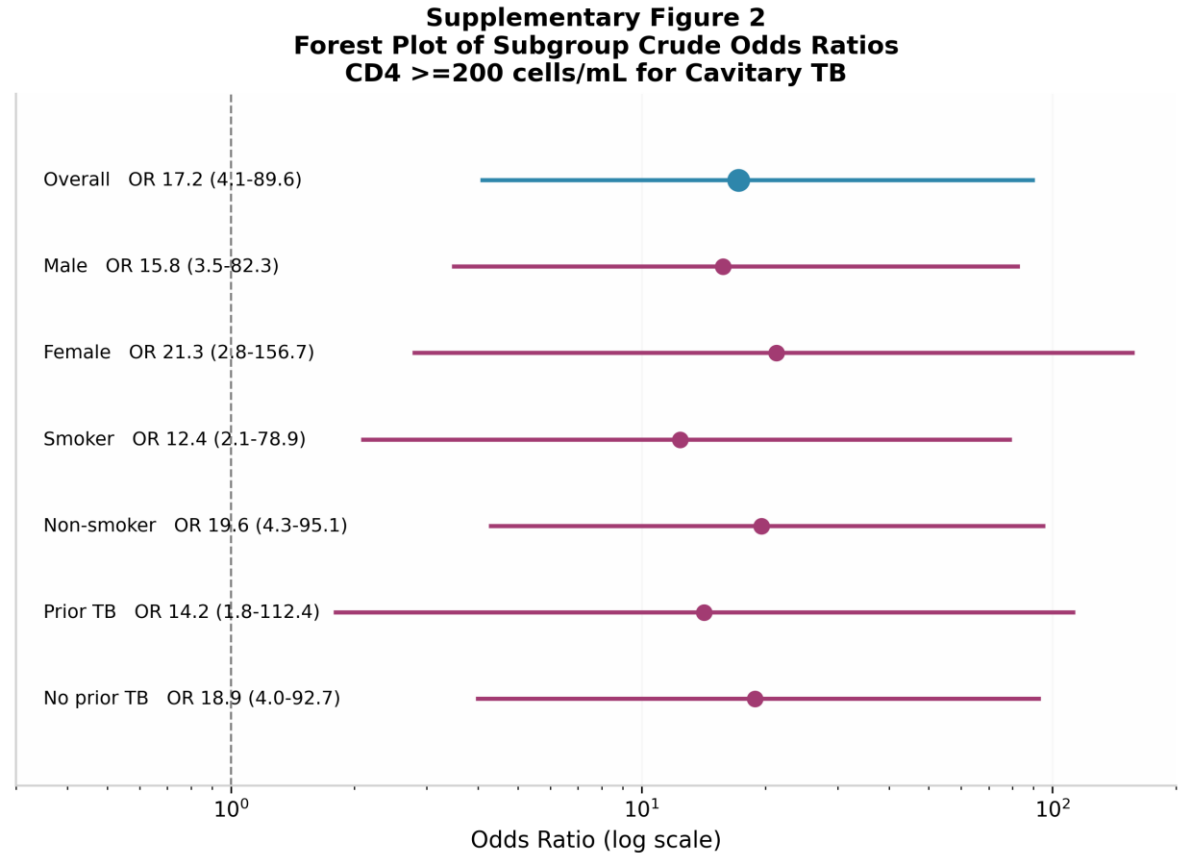
Study (Year)	Setting	Design	N (Cavitary)	Key Finding	Quality
Jones et al. (1993)	USA	Retrospective cohort	87	Cavitary disease most common at CD4 >200	Moderate
Keiper et al. (1995)	USA	Retrospective	NR	CD4-immunosuppression-phenotype relationship	Moderate
Post et al. (1995)	South Africa	Cross-sectional	NR	Radiographic appearance ∝ immunosuppression	Moderate
Padyana et al.	India	Cross-	NR	Upper lobe cavitation at higher	Low

(2012)		sectional		CD4	
Nakanwagi et al. (2019)	Uganda	Cross-sectional	NR	Cavitation associated with less advanced immunosuppression	Low
Frey et al. (2023)	Uganda	Prospective cohort	NR	68% with CD4 ≥200 developed cavitary disease	Moderate

Supplementary Figure 1. PPV and NPV across TB prevalence range (1-50%).



Supplementary Figure 2. Forest plot of subgroup crude odds ratios.



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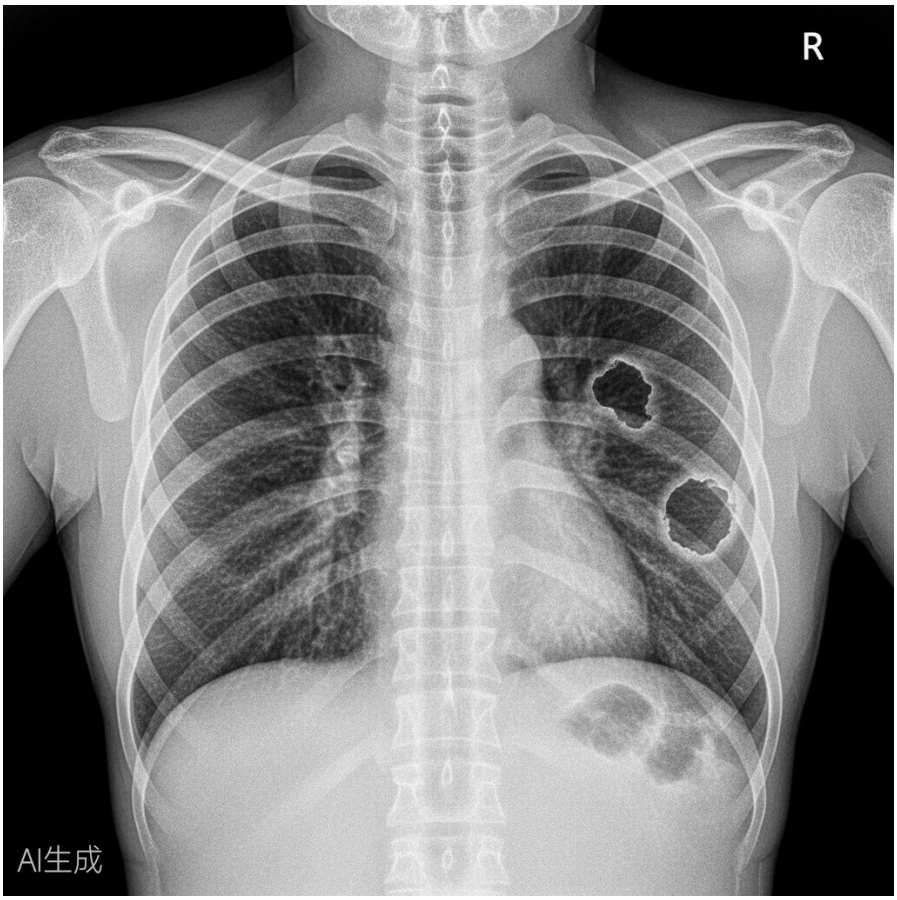
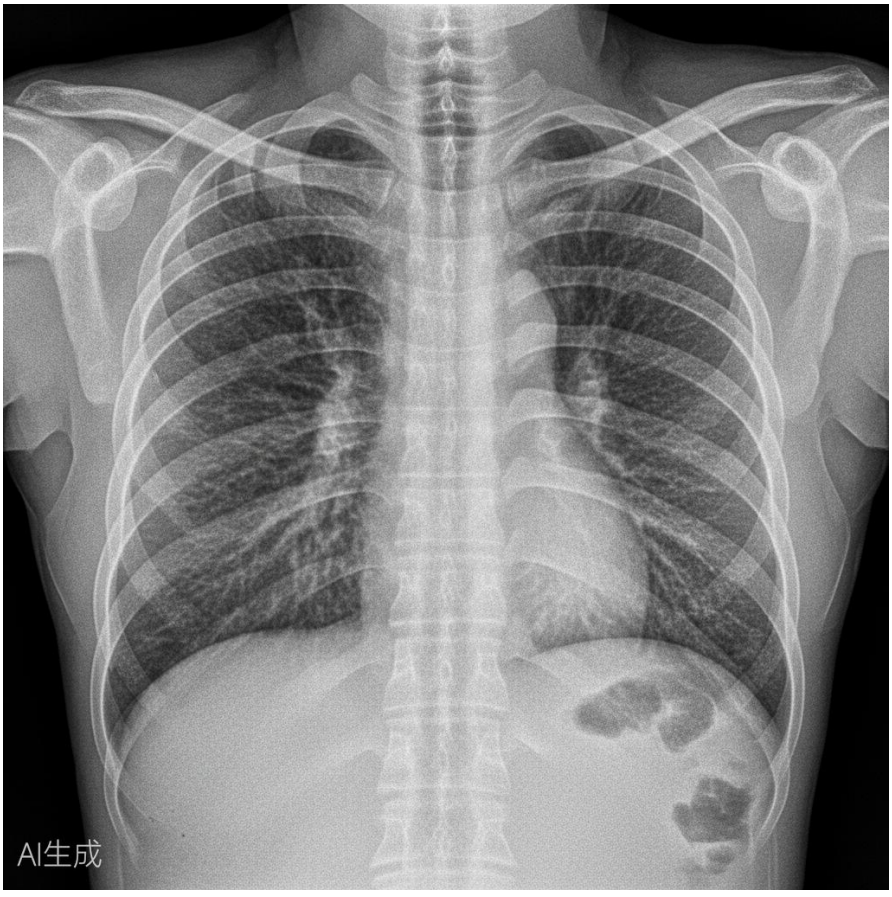
Supplementary Figure 3. Representative de-identified chest radiographs: (A) cavitary disease, CD4 312 cells/mL; (B) non-cavitary disease, CD4 67 cells/mL.





(B) Non-cavitary disease, CD4 <100 cells/μL.

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Supplementary Figure 4. Clinical triage flowchart for CD4-based risk stratification.