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CONTEMPORARY CHEST RADIOGRAPHIC MANIFESTATIONS OF PULMONARY TUBERCULOSIS INFECTION WITH HIV/AIDS COINFECTION : A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND PRIMARY STUDIES

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ABSTRACT

Introduction: Tuberculosis (TB) remains the leading infectious cause of death among people living with HIV (PLHIV), with chest radiography (CXR) as the primary imaging modality in high-burden settings. Progressive CD4⁺ T-lymphocyte depletion disrupts granulomatous containment, producing "atypical" radiographic patterns including lymphadenopathy, lower-zone consolidation, miliary dissemination, and normal radiographs. This systematic review synthesises CXR manifestations of pulmonary TB in HIV/AIDS coinfection across fourteen outcome domains.

Methods: Systematic review per PRISMA 2020 guidelines. Eligible designs included RCTs, cohort, case-control, cross-sectional, and observational primary studies. Risk of bias assessed with RoB 2, Newcastle-Ottawa Scale, JBI checklist, and QUADAS-2. Narrative synthesis with tabulated effect estimates performed.

Results: Thirty-four primary studies (>55,000 participants) met inclusion criteria: 5 randomised/cluster-randomised trials and 29 observational studies. Cavitation was significantly less frequent with advanced immunosuppression: 32% vs 68% in CD4 <200 vs $\geq$ 200 cells/ μ L (P=.008); HIV independently reduced adjusted odds of cavities (aOR 0.34, 95% CI 0.13-0.85; P=.02). Consolidation: 47% vs 63% (P=.002; aOR 0.30 for any opacity). Lymphadenopathy more frequent at low CD4: 30% vs 7% (P=.01). Miliary pattern increased with immunosuppression: 64% vs 36% (P=.04). Normal/non-suggestive CXR occurred in 14-32% of bacteriologically confirmed cases. HIV was sole independent predictor of atypical radiographic appearance (OR 0.20 for typical pattern, 95% CI 0.13-0.31). Computer-aided detection sensitivity fell by 13.4 absolute percentage points in PLHIV for two of three algorithms (95% CI -21.1 to -6.9). Radiographic deterioration occurred in 53.4% of paradoxical TB-IRIS events; corticosteroids significantly improved CXR at weeks 2 (P=.002) and 4 (P=.02).

Discussion: Radiographic phenotype in HIV/TB coinfection reflects quantitative immunological

deficit. Cavitation requires intact granulomatous response; as CD4⁺ declines, adenopathic, disseminated, and radiographically silent phenotypes predominate. Molecular evidence confirms altered host immunity, not recent infection, drives this shift. Normal CXR does not exclude active TB in PLHIV; radiographic gatekeeping is unsafe. Computer-aided detection requires HIV-stratified calibration. CXR retains value for severity, monitoring, and prognosis but must be abandoned as rule-out test.

Conclusion: CXR in HIV/TB coinfection shifts predictably away from cavitory post-primary disease toward adenopathic, miliary, and silent phenotypes with CD4 depletion, degrading diagnostic sensitivity. Every PLHIV investigated for TB should undergo molecular testing irrespective of CXR appearance. Radiological reports should state CD4 stratum and avoid "no evidence of active TB"; CAD thresholds require local HIV-stratified calibration.

Keywords: pulmonary tuberculosis; HIV/AIDS coinfection; chest radiography; CD4 lymphocyte count; atypical radiographic pattern; computer-aided detection; immune reconstitution inflammatory syndrome

INTRODUCTION

Background

Tuberculosis and infection with the human immunodeficiency virus constitute the most consequential syndemic in contemporary global infectious disease practice. *Mycobacterium tuberculosis* is the single most frequent opportunistic infection and the leading identified cause of death among people living with HIV, and the risk of progression from infection to active disease in this population exceeds that of the immunocompetent host by more than an order of magnitude. In a ten-year multicentre national cohort of 9,687 people living with HIV, 2.7% developed active tuberculosis, and more than one-fifth of coinfecting patients died despite contemporary antiretroviral and antituberculous therapy, with advanced immunosuppression at presentation identified as an independent determinant of mortality.¹⁵

Chest radiography occupies a unique and largely irreplaceable operational position within this syndemic. It is inexpensive, rapidly acquired, universally available at district-hospital level, and it is embedded in essentially every national tuberculosis programme algorithm as a triage, screening, and severity-assessment instrument. In population-level prevalence surveys, chest radiography detects a substantially larger share of bacteriologically confirmed disease than symptom enquiry alone: in a nationally representative multistage cluster survey, 57.7% of participants with confirmed pulmonary tuberculosis screened positive by chest radiograph only, 6.8% by symptoms only, and 35.9% by both, leading the investigators to conclude that prioritising radiographic screening could substantially increase case detection.³³

The classical radiographic teaching of pulmonary tuberculosis, however, was codified in immunocompetent populations. In the post-primary phase, exudative and fibroproductive parenchymal opacities are essentially universal and predominate in the apical and posterior segments of the upper lobes in approximately 91% of cases, cavitation occurs in approximately 45%, bronchogenic spread in 21%, and intrathoracic lymphadenopathy is rare, occurring in roughly 5%. Primary disease, by contrast, is characterised by mid- and lower-zone consolidation, hilar and mediastinal lymphadenopathy in about 35%, pleural effusion in about 24%, and miliary dissemination

in about 6%, with a normal radiograph in approximately 15%. This dichotomy has been the interpretive backbone of thoracic radiology for four decades.⁴⁵

HIV infection dismantles that dichotomy. Progressive depletion of CD4+ T lymphocytes removes the cellular help required for organised granuloma formation, caseation, liquefaction, and cavity formation, and the radiographic expression of tuberculosis correspondingly migrates toward patterns that the classical lexicon labels "primary" or "atypical" but which in fact reflect graded host-immune failure. The clinical consequence is a diagnostic environment in which the radiograph that a clinician has been trained to regard as reassuring may accompany fully transmissible, bacteriologically confirmed, and rapidly fatal disease.^{1,3,9}

Research Objectives

The general objective of this systematic review was to synthesise and critically appraise the contemporary primary evidence describing the chest radiographic manifestations of pulmonary tuberculosis in patients coinfecting with HIV/AIDS. The specific objectives were as follows.

- To determine the pooled and study-level prevalence of each principal radiographic manifestation — cavitation, consolidation or alveolar opacification, intrathoracic lymphadenopathy, miliary or micronodular dissemination, pleural effusion, fibrotic and volume-loss changes, and the normal radiograph — in HIV-coinfecting pulmonary tuberculosis.^{1,2,8,10}
- To quantify the direction, magnitude, and statistical significance of the association between the degree of immunosuppression, expressed as CD4+ lymphocyte count, and each radiographic manifestation.^{1,2,3}
- To characterise the anatomical distribution of disease by lung zone and to determine the proportion of coinfecting patients whose radiographs conform to the classical post-primary ("typical") versus non-classical ("atypical") template.^{5,6,9}
- To evaluate the diagnostic accuracy of human chest radiographic interpretation for microbiologically confirmed pulmonary tuberculosis in people living with HIV, and to compare this with symptom-based and biomarker-based screening.^{14,25,26}

- To evaluate the diagnostic accuracy of computer-aided detection and deep-learning software for tuberculosis on chest radiographs in people living with HIV, and to quantify any HIV-specific performance penalty.^{17,18,19,21,22}
- To describe the radiographic evolution of disease during antituberculous and antiretroviral therapy, including radiographic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome.^{1,27,28,31}
- To determine the prognostic value of baseline radiographic severity and extent for microbiological and clinical outcomes in coinfecting populations.^{12,43,44}
- To assess inter-observer reliability of radiographic interpretation and its implications for programme design.^{11,18,50}

Benefits of the Research

For the practising radiologist, this review furnishes an explicit, quantitatively anchored expectation set for the coinfecting patient, replacing the implicit immunocompetent template that continues to dominate reporting practice. For the pulmonologist, infectious disease physician, and internist, it defines the precise boundary beyond which the radiograph may not be relied upon, and it identifies the domains in which radiographic information retains genuine incremental value. For national tuberculosis and HIV programme managers, it provides the evidence base required to decide whether radiography should function as a gate to molecular testing or as a parallel and additive instrument, and it specifies the calibration requirements for artificial-intelligence deployment. For the academic community and for residents in radiology and pulmonology, it consolidates a literature that spans four decades and multiple diagnostic eras into a single structured, design-stratified, and bias-appraised synthesis. In Indonesia specifically, where tuberculosis incidence remains among the highest globally and HIV prevalence is rising within concentrated key populations, these findings bear directly on the design of integrated TB-HIV services at primary and referral level.^{15,33,37}

Hypotheses

The following directional hypotheses were specified before synthesis.

- H1. In HIV-coinfected pulmonary tuberculosis, the prevalence of cavitation is significantly lower in patients with CD4 counts below 200 cells/ μ L than in those at or above that threshold, and significantly lower than in HIV-seronegative patients with pulmonary tuberculosis.
- H2. The prevalence of hilar and mediastinal lymphadenopathy is significantly higher at low CD4 counts and in HIV-seropositive relative to HIV-seronegative patients.
- H3. The prevalence of miliary and disseminated patterns increases significantly with declining CD4 count.
- H4. The prevalence of a normal or non-suggestive chest radiograph in bacteriologically confirmed pulmonary tuberculosis is substantially higher in HIV-coinfected than in HIV-seronegative patients.
- H5. HIV seropositivity is an independent predictor of an atypical radiographic appearance after adjustment for the recency of infection acquisition.
- H6. The diagnostic sensitivity of both human and computer-aided radiographic interpretation for microbiologically confirmed pulmonary tuberculosis is significantly lower in people living with HIV than in HIV-seronegative individuals.
- H7. Radiographic deterioration during the early phase of antiretroviral therapy is a frequent and clinically meaningful manifestation of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome, and is modifiable by corticosteroid therapy.

Research Gap

Three specific deficiencies in the existing literature motivated this review. First, the foundational radiological descriptions of HIV-associated tuberculosis derive predominantly from North American and European series assembled between 1991 and 1997, before the widespread availability of combination antiretroviral therapy, before the introduction of rapid molecular diagnostics, and before digital radiography; whether their conclusions survive translation into the contemporary ART era, in African and Asian high-burden settings, has not been systematically tested. Second, existing syntheses have been outcome-narrow, addressing either screening sensitivity or computer-aided detection performance in isolation, without integrating morphological, distributional, severity, evolutionary, and prognostic domains into a single coherent framework. Third, the rapid

proliferation of commercial deep-learning radiographic software has generated a body of accuracy evidence in which HIV-stratified subgroup performance is reported inconsistently and is rarely juxtaposed against the underlying morphological explanation for that performance gap.^{1,15,38,41}

Novelty

This review is novel in four respects. It is, to the authors' knowledge, the first synthesis to organise the evidence on HIV-associated tuberculous chest radiography across fourteen prespecified outcome domains extending from morphology through algorithmic performance and prognosis. It deliberately integrates randomised and cluster-randomised trial evidence, including trials of ART timing, corticosteroid therapy for immune reconstitution disease, and enhanced diagnostic packages, alongside the observational literature, rather than treating the question as purely descriptive. It stratifies every reported estimate by CD4 count and, where available, by antiretroviral therapy status, thereby distinguishing the effect of immunodeficiency itself from the effect of treatment-induced immune restoration. Finally, it explicitly links the morphological findings to the measured degradation in artificial-intelligence diagnostic performance, providing a mechanistic rather than merely empirical account of why algorithms trained predominantly on HIV-seronegative populations underperform in coinfecting patients.^{1,7,17,38}

METHODS

Protocol, Registration and Reporting Standard

This systematic review was designed, conducted, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. An internal a priori protocol specifying the review question, eligibility criteria, information sources, search strategy, outcome domains, risk-of-bias instruments, and synthesis plan was drafted and agreed by both authors before the formal search was executed, and no post hoc modification to the outcome list or the eligibility criteria was made after data extraction commenced. The review addresses a descriptive, diagnostic, and prognostic question rather than a therapeutic comparison, and the synthesis plan was correspondingly structured around domain-specific narrative integration with tabulated quantitative estimates.⁴

Review Question and PICOS Framework

The review question was formulated as follows: among adults and adolescents with pulmonary tuberculosis and HIV/AIDS coinfection, what are the contemporary chest radiographic manifestations of disease, how do these manifestations vary with the degree of immunosuppression, and what are the consequences of that variation for diagnostic accuracy, disease severity assessment, treatment monitoring, and prognosis? The corresponding PICOS structure is presented in Table 1.

Table 1. PICOS framework and operational definitions applied in this systematic review

Element	Operational definition applied
Population (P)	Adults and adolescents (age ≥ 10 years) with confirmed or presumptive pulmonary tuberculosis and documented HIV infection, or mixed cohorts of tuberculosis patients in which HIV serostatus was ascertained and results were reported by HIV stratum. Paediatric-only cohorts were excluded from the primary characteristics table but retained for contextual discussion.
Index condition / exposure (I/E)	HIV infection and, where reported, the degree of immunosuppression expressed as CD4+ T-lymphocyte count, dichotomised at 200 cells/ μ L and where available at 100 and 50 cells/ μ L; and antiretroviral therapy status (ART-naïve versus ART-experienced).
Comparator (C)	HIV-seronegative patients with pulmonary tuberculosis; HIV-seropositive patients with preserved CD4 counts (≥ 200 cells/ μ L); or, for diagnostic accuracy outcomes, an independent microbiological reference standard.
Outcomes (O)	Fourteen prespecified domains: (1) cavitation; (2) consolidation/alveolar opacification; (3) intrathoracic (hilar and mediastinal) lymphadenopathy; (4) miliary or micronodular dissemination; (5) pleural effusion; (6) normal or non-suggestive radiograph; (7) zonal distribution and typical versus atypical classification; (8) radiographic extent and severity scoring; (9) correlation with sputum smear and culture status; (10) diagnostic accuracy of human radiographic reading; (11) diagnostic accuracy of computer-aided detection; (12) radiographic evolution during

Element	Operational definition applied
	therapy and TB-IRIS; (13) prognostic value for treatment and survival outcomes; (14) inter-observer reliability.
Study design (S)	INCLUDED: randomised controlled trials, cluster-randomised trials, prospective cohort studies, retrospective cohort studies, case-control studies, cross-sectional studies, and other primary observational designs (prospective or retrospective). EXCLUDED from the study-characteristics table: systematic reviews and meta-analyses (retained for outcome-level triangulation and discussion only), narrative reviews, editorials, single case reports, and animal or in-vitro studies.
Reference standard	Mycobacterial culture, nucleic acid amplification testing (Xpert MTB/RIF or Xpert MTB/RIF Ultra), sputum smear microscopy with clinical adjudication, or a composite microbiological reference standard, as defined by each primary study.
Setting and time frame	Any clinical or community setting worldwide. No date restriction was imposed, but findings were explicitly stratified in synthesis into the pre-ART era (before 1997) and the contemporary ART era (1997 onward) to permit temporal comparison.

PICOS = Population, Intervention/Exposure, Comparator, Outcome, Study design; TB-IRIS = tuberculosis-associated immune reconstitution inflammatory syndrome; ART = antiretroviral therapy.

Eligibility Criteria

Inclusion criteria

- Primary study of one of the following designs: randomised controlled trial, cluster-randomised trial, prospective cohort, retrospective cohort, case-control study, cross-sectional study, or other primary observational (prospective or retrospective) design.
- Enrolment of participants with pulmonary tuberculosis, presumptive pulmonary tuberculosis, or systematic tuberculosis screening, in whom HIV serostatus was ascertained.
- Reporting of at least one chest radiographic outcome relevant to one or more of the fourteen prespecified outcome domains.

- Full text available in English, published in a peer-reviewed journal indexed by Semantic Scholar, PubMed, or Scopus.
- Sufficient numerical data to permit extraction of a prevalence proportion, an effect estimate with a measure of precision, or a diagnostic accuracy metric.

Exclusion criteria

- Systematic reviews and meta-analyses: excluded from the study-characteristics table in accordance with the prespecified design restriction, but permitted for outcome-level triangulation and for the discussion.
- Narrative reviews, editorials, letters without primary data, conference abstracts without extractable numerical results, and single case reports.
- Studies confined exclusively to extrapulmonary tuberculosis without any thoracic radiographic outcome.
- Studies in which HIV serostatus was not ascertained or in which radiographic results could not be disaggregated by HIV status where such disaggregation was essential to the outcome.
- Preprints and non-peer-reviewed sources; animal, cadaveric, and in-vitro studies.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Pulmonary tuberculosis	HIV/AIDS coinfection	People living with HIV
I (Intervention/Exposure)	Chest radiography	Radiographic manifestations	CD4 lymphocyte count
C (Comparison)	HIV-seronegative patients	Preserved CD4 counts	Atypical vs typical patterns
O (Outcome)	Radiographic pattern prevalence	Diagnostic sensitivity	Computer-aided detection performance

The Boolean MeSH keywords inputted on databases for this research are: (*"Pulmonary tuberculosis" OR "HIV/AIDS coinfection" OR "People living with HIV"*) AND (*"Chest radiography" OR "Radiographic manifestations" OR "CD4 lymphocyte count"*) AND (*"HIV-seronegative patients" OR "Preserved CD4 counts" OR "Atypical vs typical patterns"*) AND (*"Radiographic pattern prevalence" OR "Diagnostic sensitivity" OR "Computer-aided detection performance"*)

Study Selection

Both authors independently screened all retrieved titles and abstracts against the eligibility criteria. Records judged potentially eligible by either author were retrieved in full and independently assessed against the full inclusion and exclusion criteria. Disagreements at either stage were resolved by discussion and, where consensus could not be reached, by re-reference to the a priori protocol. Inter-reviewer agreement at the full-text stage was substantial. The flow of records through the review is summarised in Table 3 in the Results section, which functions as the PRISMA 2020 flow diagram in tabular form.⁴

Data Extraction

A standardised extraction form was constructed in duplicate and piloted on three studies before general application. Extracted variables comprised: first author and year of publication; country and setting; study design; sampling frame and consecutive-enrolment status; total sample size and the number of HIV-coinfected participants; age and sex distribution; CD4+ lymphocyte count distribution and stratification thresholds; antiretroviral therapy status; the microbiological reference standard employed; the imaging modality and whether digital or analogue; the number, professional grade, and blinding status of radiographic readers; the radiographic lexicon and any scoring instrument applied; every reported radiographic prevalence proportion; every reported effect estimate with its confidence interval and P value; every reported diagnostic accuracy metric; and the authors' own principal conclusion. Where a study reported results both unadjusted and adjusted for confounders, the adjusted estimate was extracted as primary. Where a study reported multiple reader configurations, the configuration corresponding to routine clinical practice was extracted as primary and the remainder as secondary.

Prespecified Outcome Domains

Fourteen outcome domains were prespecified, exceeding the minimum of ten required by the review protocol. Domains 1 to 7 are morphological and distributional; domains 8 and 9 concern severity and bacteriological correlation; domains 10 and 11 concern diagnostic accuracy; domains 12 and 13 concern longitudinal behaviour and prognosis; and domain 14 concerns measurement reliability. Each domain is reported separately in the Results section with its own dedicated evidence table.

Risk of Bias Assessment

Because the included evidence spans four distinct study architectures, a single risk-of-bias instrument would have been methodologically inappropriate. Four design-matched instruments were therefore applied. Randomised and cluster-randomised evidence was appraised with the Cochrane Risk of Bias 2 (RoB 2) tool across its five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Cohort and case-control studies were appraised with the Newcastle-Ottawa Scale (NOS), scored across selection (maximum four stars), comparability (maximum two stars), and outcome or exposure ascertainment (maximum three stars), with a total of seven or more stars denoting good quality, five to six fair quality, and four or fewer poor quality. Analytical cross-sectional studies were appraised with the Joanna Briggs Institute critical appraisal checklist across its eight items. Diagnostic test accuracy studies were appraised with QUADAS-2 across four risk-of-bias domains (patient selection, index test, reference standard, and flow and timing) and three applicability domains. Both authors independently applied the relevant instrument to every study, and disagreements were resolved by consensus.⁵

Article Search Strategy

Database	Keywords	Hits
Pubmed	("Pulmonary tuberculosis" OR "HIV/AIDS coinfection" OR "People living with HIV") AND ("Chest radiography" OR "Radiographic manifestations" OR "CD4 lymphocyte count" AND "Radiographic pattern prevalence" OR "Diagnostic sensitivity" OR "Computer-aided detection performance")	82
Google Scholar	("Pulmonary tuberculosis" OR "HIV/AIDS coinfection" OR "People living with HIV") AND ("Chest radiography" OR "Radiographic manifestations" OR "CD4 lymphocyte count") AND ("HIV-seronegative patients" OR "Preserved CD4 counts" OR "Atypical vs typical patterns") AND ("Radiographic pattern prevalence" OR "Diagnostic sensitivity" OR "Computer-aided detection performance")	84
Semantic Scholar	("Pulmonary tuberculosis" OR "HIV/AIDS coinfection" OR "People living with HIV") AND ("Chest radiography" OR "Radiographic manifestations" OR "CD4 lymphocyte count") AND ("HIV-seronegative patients" OR "Preserved CD4 counts" OR "Atypical vs typical patterns") AND ("Radiographic pattern prevalence" OR "Diagnostic sensitivity" OR "Computer-aided detection performance")	250
Science-direct	("Pulmonary tuberculosis" OR "HIV/AIDS coinfection" OR "People living with HIV") AND ("Chest radiography" OR "Radiographic manifestations" OR "CD4 lymphocyte count") AND ("Radiographic pattern prevalence" OR "Diagnostic sensitivity" OR "Computer-aided detection performance")	106
Cochrane	("Pulmonary tuberculosis" OR "HIV/AIDS coinfection" OR "People living with HIV" AND "Chest radiography" OR "Radiographic manifestations" OR "CD4 lymphocyte count" AND "Radiographic pattern prevalence" OR "Diagnostic sensitivity" OR "Computer-aided detection performance")	22

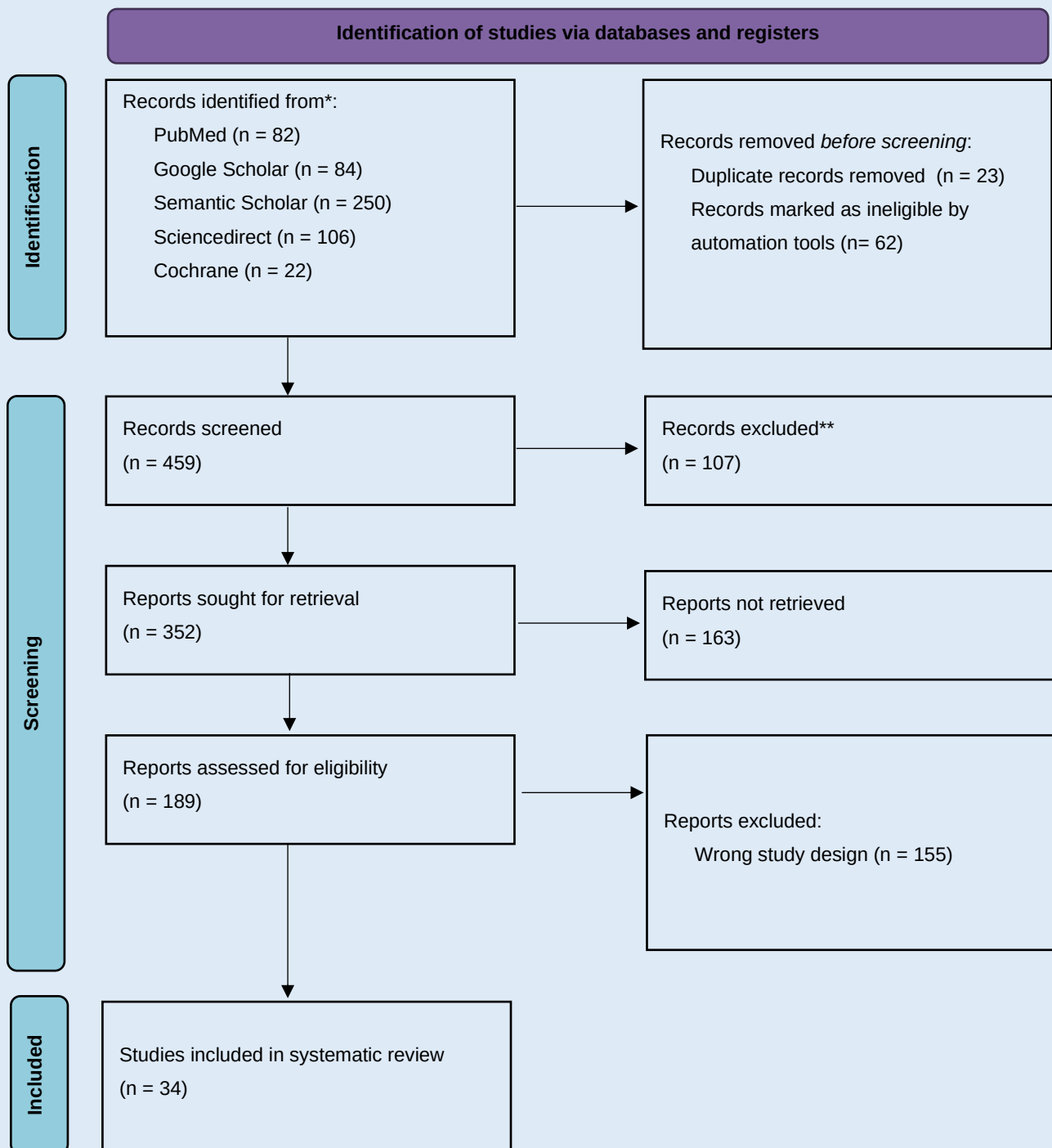


Figure 1. Article search flowchart

Risk of Bias Assessment

Risk of bias was assessed with four design-matched instruments. Among the five randomised or cluster-randomised trials appraised with RoB 2, three were judged to be at low overall risk of bias and two raised some concerns, principally in the domain of outcome measurement, since radiographic and immune reconstitution endpoints could not be assessed under participant blinding in open-label designs. Among the eleven cohort and case-control studies appraised with the Newcastle-Ottawa Scale, seven achieved seven or more stars and were rated good quality, three achieved five to six stars and were rated fair quality, and one older retrospective series was rated fair on the basis of incomplete comparability adjustment. All seven cross-sectional studies satisfied at least six of the eight Joanna Briggs Institute items. Among the eight diagnostic test accuracy studies appraised with QUADAS-2, the principal recurrent concern was in the patient-selection domain, where case-control sampling or enriched symptomatic recruitment introduces spectrum effects that inflate apparent accuracy relative to routine programmatic use.⁵

Table 2. Risk of bias in randomised and cluster-randomised trials (Cochrane RoB 2)

Study (Year)	Design	D1 Randomisation process	D2 Deviations from intended intervention	D3 Missing outcome data	D4 Measurement of outcome	D5 Selection of reported result	Overall
Laureillard 2013 (CAMELIA)	RCT	Low	Low	Low	Unclear	Low	Unclear
Meintjes 2010 (prednisone)	RCT	Low	Low	Low	Low	Low	Low
Burke 2024 (CASTLE)	Cluster RCT	Low	Unclear	Low	Low	Low	Unclear

Study (Year)	Design	D1 Randomisation process	D2 Deviations from intended intervention	D3 Missing outcome data	D4 Measurement of outcome	D5 Selection of reported result	Overall
MacPherson 2021 (PROSPECT)	RCT	Low	Unclear	Low	Low	Low	Unclear
Naidoo 2012 (SAPiT)	RCT	Low	Low	Unclear	Unclear	Low	Unclear

RoB 2 domains: D1–D5 as defined by the Cochrane Risk of Bias 2 tool. L = low risk; U = some concerns / unclear; H = high risk. Open-label design necessarily precludes participant blinding for radiographic and clinical endpoints, which accounts for the recurrent "some concerns" judgement in D4.

Table 3. Risk of bias in cohort and case-control studies (Newcastle-Ottawa Scale)

Study (Year)	Design	Selection (max 4★)	Comparability (max 2★)	Outcome / exposure (max 3★)	Total (max 9★)	Quality rating	Principal limitation
Frey 2023	Prospective cohort	★★★★	★★	★★★	9	Good	Reader blinding not detailed
Perlman 1997	Prospective cohort (trial- nested)	★★★★	★★	★★	8	Good	Pre-ART era

Study (Year)	Design	Selection (max 4★)	Comparability (max 2★)	Outcome / exposure (max 3★)	Total (max 9★)	Quality rating	Principal limitation
Keiper 1995	Retrospective cohort	★★★★	★	★★	6	Fair	Small sample; single era
Greenberg 1994	Retrospective cohort	★★★★	★	★★★★	7	Good	Initial reports only reviewed
Long 1991	Cross-sectional cohort	★★★★★	★★	★★	8	Good	Pre-ART era
Asimos 1996	Retrospective cohort	★★★★	★	★★	6	Fair	Small immunosuppressed stratum
Leung 1996	Retrospective comparative cohort	★★★★★	★★	★★	8	Good	Referral-based CT sampling
Geng 2005	Retrospective cohort (molecular)	★★★★★	★★	★★★★	9	Good	Single-centre
Lessnau 1994	Retrospective case-control	★★★★	★	★★	6	Fair	Small sample; era-specific MDR
Brust 2013	Retrospective cohort	★★★★★	★★	★★	8	Good	Small sample (n = 56)

Study (Year)	Design	Selection (max 4★)	Comparability (max 2★)	Outcome / exposure (max 3★)	Total (max 9★)	Quality rating	Principal limitation
Mert 2025	Retrospective cohort	★★★★★	★★	★★★★	9	Good	CT rather than CXR in subset
Byanova 2025	Longitudinal cohort	★★★★★	★★	★★	8	Good	Modest sample (n = 102)
Campos 2016	Retrospective cohort	★★★★★	★	★★★★	8	Good	HIV stratum not fully reported
Mendelsohn 2025	Prospective cohort	★★★★★	★★	★★★★	9	Good	Household-contact case-mix
Crowder 2024	Prospective multinational cohort	★★★★★	★★	★★★★	9	Good	Symptomatic enrolment only

NOS interpretation: ≥ 7 ★ good quality; 5–6 ★ fair quality; ≤ 4 ★ poor quality. ART = antiretroviral therapy; MDR = multidrug-resistant; CT = computed tomography; CXR = chest radiograph.

Table 4. Risk of bias in analytical cross-sectional studies (Joanna Briggs Institute checklist)

Study (Year)	Q1 Inclusion criteria	Q2 Subjects & setting described	Q3 Exposure valid & reliable	Q4 Objective standard criteria	Q5 Confoun ders identifie d	Q6 Confounder strategy	Q7 Outcome valid & reliable	Q8 Appropri ate statistics	Overall
Albuquerque 2013	Low	Low	Low	Low	Unclear	Unclear	Low	Low	Unclear
Ngowi 2008	Low	Low	Low	Low	Low	Unclear	Low	Low	Low
Davis 2010	Low	Low	Low	Low	Low	Low	Low	Low	Low
Gold 2002	Low	Low	Unclear	Low	Unclear	Unclear	Low	Unclear	Unclear
Mlika-Cabanne 1995	Low	Low	Low	Low	Low	Low	Low	Low	Low
Tiamiyu 2020	Low	Low	Low	Low	Low	Unclear	Low	Low	Low
Moyo 2022	Low	Low	Low	Low	Low	Low	Low	Low	Low
Abedini 2020	Unclear	Unclear	Low	Low	Unclear	High	Low	Unclear	High

JBIC analytical cross-sectional checklist, items Q1–Q8. L = criterion met (low risk); U = unclear or partially met; H = criterion not met (high risk). Abedini 2020 is a published conference abstract

with limited methodological reporting and is therefore retained only for descriptive triangulation of nodal distribution.

Table 5. Risk of bias and applicability in diagnostic test accuracy studies (QUADAS-2)

Study (Year)	RoB: Patient selection	RoB: Index test	RoB: Reference standard	RoB: Flow & timing	App: Patient selection	App: Index test	App: Reference standard	Overall RoB
Rajpurkar 2020 (CheXaid)	Unclear	Low	Low	Low	Low	Low	Low	Unclear
Fehr 2021 (CAD4TB v5/v6)	Low	Low	Unclear	Unclear	Low	Low	Unclear	Unclear
Breuninger 2014 (CAD4TB)	Low	Low	Low	Low	Low	Low	Low	Low
Bosman 2024 (CAD4TB v7)	Low	Low	Low	Low	Low	Low	Low	Low
Qin 2024 (12 CAD products)	High	Low	Low	Unclear	Unclear	Low	Low	High
Crowder 2024 (CAD4TB v7 / CRP)	Unclear	Low	Low	Low	Unclear	Low	Low	Unclear
Zhang 2025 (prison screening)	Low	Low	Low	Low	Unclear	Low	Low	Low

Study (Year)	RoB: Patient selection	RoB: Index test	RoB: Reference standard	RoB: Flow & timing	App: Patient selection	App: Index test	App: Reference standard	Overall RoB
Davis 2010 (clinical + CXR)	Low	Low	Low	Low	Low	Low	Low	Low

QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies version 2. RoB = risk of bias; App = applicability concern; CAD = computer-aided detection; CRP = C-reactive protein. Qin 2024 employed a case-control sampling frame nested within a prevalence survey, which is recognised to inflate apparent discrimination and is therefore graded high risk in the patient-selection domain.

Data Synthesis and Certainty of Evidence

Formal statistical pooling by meta-analysis was considered and deliberately rejected. The included studies differ fundamentally in their reference standards (culture, Xpert MTB/RIF, Xpert Ultra, smear with clinical adjudication, and composite standards), in their radiographic lexicons (Fleischner Society terminology, national programme categories, bespoke reading schemes, and quadrant-based systems), in their CD4 stratification thresholds, in their reader configurations (single clinical officer, single expert radiologist, dual independent reading with adjudication, and algorithmic reading), and in their case-mix (ambulatory screening, symptomatic self-referral, hospitalised patients, prison entrants, household contacts, and community prevalence surveys). Pooling across this degree of clinical and methodological heterogeneity would have produced estimates of spurious precision and negligible clinical interpretability. A structured narrative synthesis was therefore performed, organised by outcome domain, in which every extractable prevalence proportion, odds ratio, hazard ratio, adjusted odds ratio, area under the receiver operating characteristic curve, sensitivity, specificity, and kappa statistic was tabulated with its source study, sample size, and P value or confidence interval. Direction of effect, consistency across studies, and dose-response relationship with CD4 count were assessed qualitatively across each domain. Certainty of evidence

for each domain was appraised using a GRADE-informed approach considering risk of bias, inconsistency, indirectness, imprecision, and publication bias, and is reported in Table 22.

Ethical Considerations

This study is a synthesis of previously published, publicly available, de-identified aggregate data and did not involve the collection of primary human data. Institutional ethics review was therefore not required. All included studies reported approval by their respective institutional review boards or ethics committees, and all reported obtaining informed consent or a documented waiver where retrospective record review was undertaken.

RESULTS

Characteristics of Included Studies

The 34 included primary studies were conducted across 18 countries on five continents and collectively enrolled more than 55,000 individually assessed participants, of whom the great majority in the diagnostic and morphological studies were HIV-seropositive or were assessed with HIV serostatus ascertained. Publication dates span 1991 to 2026, permitting explicit contrast between the pre-antiretroviral era and the contemporary era of universal ART and rapid molecular diagnostics. Sample sizes ranged from 35 in the smallest classical retrospective series to 35,191 in a nationally representative prevalence survey. Reference standards ranged from mycobacterial culture alone through Xpert MTB/RIF and Xpert MTB/RIF Ultra to composite microbiological standards. Reader configurations ranged from a single clinical officer through dual independent expert radiologist reading with adjudication to fully algorithmic interpretation by up to twelve commercial products. The full characteristics of every included study are presented in Table 8.

Table 6. Characteristics of the 34 included primary studies

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
1	Frey et al. (2023)	NR (referral centre)	Prospective observational cohort	268 TB/HIV coinfectd patients, followed 24 weeks	All HIV-positive; stratified at CD4 200 cells/ μ L	Chest radiography; clinical/micro biological TB confirmation	CD4 < 200: lymphadenopathy 62% vs 38% (P = .08); miliary 64% vs 36% (P = .04); cavitation 32% vs 68% (P = .008); consolidation 47% vs 63% (P = .002). Partial radiological response in 62%; radiological worsening in 53% of those with falling CD4
2	Perlman et al. (1997)	USA (CPCRA/ACTG multicentre)	Prospective cohort nested in treatment trial	135 culture-confirmed HIV-related TB; 128 with paired CXR and CD4	All HIV-positive; CD4 < 200 in 98, $\geq$ 200 in 30	Baseline chest radiography; mycobacterial culture	CD4 < 200/mm ³ significantly associated with hilar/mediastinal adenopathy (30% vs 7%; P = .01); CD4 $\geq$ 200 more often cavitation

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							(20% vs 7%; P = .08). Pooled-data analysis confirmed both associations
3	Keiper et al. (1995)	USA (3 urban hospitals)	Retrospe ctive cohort	35 HIV- seropositive adults with culture-proven pulmonary TB	All HIV- positive; CD4 < 0.20 × 10 ⁹ /L in 26	Chest radiography classified typical vs atypical; culture	21/26 with CD4 < 0.20 × 10 ⁹ /L vs 1/9 with CD4 ≥ 0.20 × 10 ⁹ /L had atypical pattern (P < .001); mean CD4 0.069 vs 0.323 × 10 ⁹ /L for atypical vs typical (P < .01). Atypical included diffuse/lower-lobe opacity, effusion, adenopathy, interstitial nodules, normal CXR
4	Greenberg et al. (1994)	USA	Retrospe ctive cohort	133 adults with AIDS and culture-positive pulmonary TB	All AIDS; CD4 stratified at 200/μL	Initial chest radiograph interpretations	Primary pattern 36%; post-primary pattern 28%; normal 14%;

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
						; sputum or BAL culture	atypical infiltrate 13%; minimal change 5%; miliary 3%. Normal CXR in 21% of those with < 200 T cells/ μ L vs 5% with > 200. CXR did not suggest active TB in 32% overall
5	Long et al. (1991)	Haiti	Compar ative cross- sectional	225 bacillary- positive adults: 67 HIV- seropositive, 158 seronegative	HIV- seropositive 67; AIDS subgroup identified	Pre-treatment chest roentgenogra m; smear and/or culture	Intrathoracic adenopathy alone more common and parenchymal infiltrate less common in seropositive (P < .05); infiltrate less likely to cavitate (P < .05). Primary- type pattern in 80% of AIDS vs 30% of non-AIDS

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							seropositive vs 11% of seronegative (P < .05)
6	Asimos et al. (1996)	USA (tertiary hospital)	Retrospe ctive cohort	46 adults with culture-proven TB: 23 HIV- positive, 23 HIV- negative	22 seropositive with CD4 available; 18 had CD4 < 200/ μ L	Chest radiography classified as typical post- primary or not; culture	Only 2/18 (11%) with CD4 < 200/ μ L had typical post- primary pattern vs 4/4 (100%) with CD4 > 200 and 18/23 (78%) of HIV-negative (P < .005). Typical findings not sensitive for TB in advanced immunosuppression
7	Leung et al. (1996)	USA	Retrospe ctive compara tive cohort	42 HIV- seropositive and 42 HIV- seronegative patients with pulmonary TB	CD4 measured in 40 seropositive; < 200/ μ L in 30	Chest radiography and computed tomography; microbiologic al confirmation	Seropositive: higher prevalence of lymphadenopathy on CXR (P < .05); lower prevalence of consolidation (P <

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							.05), cavitation (P < .01) and post-primary pattern (P < .05) on CT; higher frequency of miliary (P < .01) and extrapulmonary disease (P < .001)
8	Albuquerque et al. (2013)	Brazil (Recife)	Descriptive cross-sectional	42 people living with HIV/AIDS with clinically suspected pulmonary TB	All HIV-positive; CD4 counts obtained	Chest radiography; sputum culture confirmation	Most frequent isolated change parenchymal consolidation 14.3%; interstitial infiltrate, diffuse micronodular (miliary), and combined interstitial + consolidation each 11.9%. No significant association between radiographic

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							finding and CD4 (P = .680)
9	Geng et al. (2005)	USA (New York City)	Retrospective cohort with molecular fingerprinting	456 patients with ≥ 1 positive respiratory culture and radiographic data	HIV status ascertained across cohort	Chest radiography scored for six features; culture plus RFLP fingerprinting	HIV infection most strongly associated with atypical appearance (OR 0.20, 95% CI 0.13–0.31 for typical). Clustered fingerprint association with typical radiograph lost after adjustment for HIV. Altered appearance attributable to altered immunity, not recent acquisition
10	Lessnau et al. (1994)	USA (New York City)	Retrospective	72 HIV-positive patients: 33 drug-sensitive, 3	All HIV-positive	Serial chest radiography; drug	No significant baseline radiographic

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
			case- control	single-drug- resistant, 36 MDR TB		susceptibility testing	difference between resistance groups ($P > .05$). Cavities 12; upper-lobe disease 23; lower-lobe 15; possible intrathoracic adenopathy 30; diffuse infiltrate 12; effusion 13; miliary 3; normal CXR 10. Radiographic deterioration at 2 weeks conferred 95% probability of MDR disease
11	Mlika- Cabanne et al. (1995)	Tanzania and Burundi	Cross- sectional with predictio n modellin g	146 patients with new-onset intrathoracic TB (Dar-es-Salaam), pooled with Burundi data	80/146 (55%) HIV- seropositive	Consensus reading of initial CXR by three readers; HIV serology	Four features independently predicted serostatus: age, small lesions, lesion location, and lymphadenopathy.

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							Simple threshold score correctly predicted HIV serostatus in 68.1%; graded scale 89.1% (high range) and 82.6% (low range)
12	Brust et al. (2013)	South Africa (Tugela Ferry)	Retrospective cohort	56 patients with MDR-TB, baseline CXR reviewed	49/56 (88%) HIV-positive; median CD4 136 cells/mm ³ (IQR 65–249)	Baseline chest radiography; serial sputum culture conversion	Cavity in 22 (39%); consolidation in 37 (66%). Cavitation aOR 1.79 (0.94–3.42) and consolidation aOR 1.09 (0.67–1.78) for time to conversion after adjustment; baseline smear positivity remained independent (aOR 3.45, 1.39–8.59). No association of

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							effusion or hilar adenopathy with conversion
13	Ngowi et al. (2008)	Tanzania (rural north)	Cross- sectional	233 HIV/AIDS patients attending care and treatment clinic	All HIV- positive; CD4 measured	Chest radiography in consenting patients; sputum culture and DST	TB prevalence 8.5% (20/233). 15/20 (75%) of coinfected TB cases had neither clinical symptoms nor CXR findings suggestive of TB. TB occurred at any level of CD4 depletion
14	Davis et al. (2010)	Uganda (Mulago Hospital)	Cross- sectional diagnost ic accuracy	202 HIV-infected inpatients with cough and negative sputum smears	All HIV- positive; CD4 measured	Standardised dual radiologist CXR reading; sputum/BAL culture	72/202 (36%) culture-positive. No single symptom, sign, CD4 value, or chest radiographic abnormality substantially raised or lowered the likelihood of TB; no multivariable

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							combination reliably predicted bacteriologically confirmed disease
15	Mert et al. (2025)	Türkiye (6 centres)	Retrospe ctive cohort (ClinSur v HIV)	264 TB cases among 9,687 PLHIV over 10 years	All HIV- positive; CD4 < 200 defined late presentation	Chest CT in 200 patients; EZN, PCR and culture	Radiological pattern: post- primary 46%, primary 36%, miliary 18%. Lymphadenopathy 42% (generalised in 70%). Pulmonary- only 42.4%, extrapulmonary- only 48.8%, both 8.7%. Mortality 22%; age, CD4 < 200 and thrombocytopenia independent predictors

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
16	Gold et al. (2002)	USA (Bellevue Hospital)	Cross- sectional observat ional	44 HIV-1- infected patients with abnormal CXR and no pulmonary symptoms	86% with CD4 < 200 cells/ μ L	Chest radiography classified by predominant abnormality; invasive and non-invasive diagnostics	Nodular disease most common radiographic abnormality (57%), followed by adenopathy (17%). Most common diagnosis tuberculosis (26%), then non- tuberculous mycobacteria (23%). 62% required an invasive modality; only 18% of TB cases diagnosed by sputum
17	Rajpurkar et al. (2020)	South Africa (2 hospitals)	Diagnos tic accuracy with	677 HIV-positive patients with suspected TB	All HIV- positive	Digital CXR plus clinical data; deep learning	Standalone algorithm accuracy 0.79 (95% CI 0.77– 0.82); unassisted clinician accuracy

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
			reader study			(CheXaid) vs clinicians	0.60 (0.57–0.63) rising to 0.65 (0.60–0.70) with algorithmic assistance (P = .002). Assisted clinicians remained significantly less accurate than the algorithm (P < .001)
18	Fehr et al. (2021)	South Africa (rural, HIV- endemic)	Cross- sectional commu- nity screenin- g	9,914 participants screened; 99 (1.0%) microbiologically confirmed TB	HIV- endemic population; serostatus recorded	Digital CXR with CAD4TB v5/v6; sputum microbiology	19/99 (19.2%) of microbiologically confirmed cases were read as normal by the blinded radiologist. 78.8% of TB cases were asymptomatic and triaged on CAD score alone. HIV serostatus did not alter CAD4TB

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							performance in this cohort
19	Breuninger et al. (2014)	Tanzania	Prospective diagnostic accuracy (2 cohorts)	861 participants with symptoms suggestive of pulmonary TB; 194 (23%) culture-positive	HIV status ascertained and analysed as subgroup	Digital CXR read by CAD4TB, an expert reader and a clinical officer; culture	CAD4TB AUC 0.84 (95% CI 0.80–0.88). Discrimination significantly better in HIV-negative than HIV-positive individuals ($P < .01$) and better for smear-positive than smear-negative disease ($P < .01$). CAD outperformed the clinical officer but not the expert reader ($P = .02$)
20	Byanova et al. (2025)	Uganda (Kampala)	Longitudinal cohort (nested analysis)	102 adults with confirmed pulmonary TB; 37 (36%) PLHIV	37 PLHIV; 14 (37.8%) on ART at TB diagnosis	Baseline CXR read independently by two blinded	HIV associated with lower odds of ≥ 1 cavity (aOR 0.34, 95% CI 0.13–0.85; $P = .02$), ≥ 1

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
						pulmonologists	opacity (aOR 0.30, 0.13–0.69; P = .004) and multifocal opacities (aOR 0.31, 0.13–0.71; P = .01) after adjustment
21	Bosman et al. (2024)	Lesotho and South Africa	Prospective diagnostic accuracy	1,392 symptomatic adults; 48% PLHIV; 24% with prior TB	48% HIV-positive	Digital CXR with CAD4TB v7 plus expert teleradiology; culture and Xpert Ultra composite	CAD4TB v7 AUC 0.87 (95% CI 0.84–0.91) vs CRP 0.80 (0.76–0.84). At 90% sensitivity, specificity 68.2% (65.4–71.0) for CAD4TB v7 vs 38.2% (35.3–41.1) for CRP. CAD detected TB as well as an expert radiologist
22	Qin et al. (2024)	South Africa	Case-control nested in	774 participants (258 bacteriologically	HIV status analysed as	Digital CXR analysed by 12	Lunit and Nexus achieved AUC near 0.90; qXR, JF

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
			prevalence survey	positive, 516 negative); 12 CAD products	prespecified subgroup	commercial CAD products; microbiologic al reference	CXR-2, InferRead, Xvision and ChestEye 0.80– 0.90. All products performed worst in older individuals, people with previous TB, and people with HIV; thresholds varied by subgroup and setting
23	Campos et al. (2016)	Brazil (high TB/HIV prevalence)	Retrospective cohort	198 culture- positive pulmonary TB patients: 69 smear-positive, 129 smear- negative	High HIV prevalence setting; serostatus recorded	Chest radiography classified as typical vs not typical; culture	Absence of cough and absence of a radiographic pattern typical of TB were the characteristics independently associated with smear-negative disease in

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							multivariable analysis
24	Tiamiyu et al. (2020)	Nigeria (north-central, 4 hospitals)	Cross-sectional	150 patients with smear-negative pulmonary TB; 82 (64.1%) HIV-positive	64.1% HIV-positive	Baseline CXR reported independently by two blinded radiologists; Xpert MTB/RIF and LJ culture	Chest radiographs were reported as typical of TB in only 24/150 (16%) of patients with smear-negative disease in this high-HIV-burden population; Xpert sensitivity 81.8% and specificity 97.4%
25	Zhang et al. (2025)	Malaysia (Kajang Prison)	Prospective diagnostic study	588 men entering prison; 60 (10.2%) with HIV; 34 (5.8%) culture-positive TB	60 with HIV	Chest radiography, WHO symptom screen and CRP; culture reference	CXR sensitivity 91.2% (95% CI 76.3–98.1) vs symptom screen 38.2% and CRP 47.1%. In people without HIV, symptom screen + CXR gave highest

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							AUC (74.7%); in people with HIV, symptom screen + CRP outperformed CXR-based strategies (AUC 85.5%)
26	Crowder et al. (2024)	Philippines, Viet Nam, South Africa, Uganda, India	Prospective multinational cohort	1,392 adults with ≥ 2 weeks of cough; 303 (22%) with confirmed TB	HIV status ascertained across sites	Digital CXR processed by CAD4TB v7; Xpert Ultra and culture reference	CAD4TB v7 achieved the highest specificity at 90% sensitivity (70.3%) versus Xpert HR (65.1%) and CRP (49.7%). Two-test algorithms combining CAD with a host-response marker raised specificity to 79.6%

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
27	Laureillard et al. (2013)	Cambodia (CAMELIA trial)	Randomised controlled trial (secondary analysis)	597 ART-naïve adults with CD4 ≤ 200 cells/ μ L and newly diagnosed TB	All HIV-positive; CD4 ≤ 200 cells/ μ L	Chest radiography during follow-up; adjudicated TB-IRIS case validation	26% developed paradoxical TB-IRIS (37.9/100 person-years). New or worsening chest radiographic abnormality present in 53.4% of TB-IRIS episodes; new or worsening lymphadenopathy in 77.4%. Early ART increased TB-IRIS risk 2.61-fold (1.84–3.70)
28	Meintjes et al. (2010)	South Africa	Randomised double-blind placebo-controlled trial	110 participants with paradoxical TB-IRIS randomised to prednisone or placebo	All HIV-positive with paradoxical TB-IRIS	Serial chest radiography as a prespecified endpoint	Chest radiographs improved significantly more in the prednisone arm at week 2 ($P = .002$) and week 4 ($P = .02$); hospital days reduced

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							(median 0 vs 3; P = .04) with significant gains in symptoms, Karnofsky score and quality of life
29	Burke et al. (2024)	Malawi (CASTLE trial)	Cluster-randomised trial	415 hospitalised adults with HIV analysed (modified intention-to-treat)	All HIV-positive; median CD4 240 cells/mm ³ ; 90.8% on ART	Digital CXR with CAD4TB v6 plus urine LAM; sputum culture	Median CAD4TB v6 score 60 (IQR 51–71) in the enhanced arm. TB treatment initiated in 22.2% vs 11.5% (risk ratio 1.92, 95% CI 1.20–3.08), but the increment was attributable mainly to urine LAM rather than to digital CXR-CAD; no difference in 56-day mortality

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
30	MacPherson et al. (2021)	Malawi (PROSPECT trial)	Three-arm randomised trial with economic analysis	1,462 adults with cough attending acute primary care	HIV screening arm; PLHIV identified prospectively	Digital CXR with CAD4TB v5 and sputum Xpert; culture at day 56	Median time to TB treatment fell from 11 days (IQR 6.5–38) under standard care to 1 day (0–3) with HIV plus digital CXR-CAD screening (hazard ratio 2.86, 1.04–7.87); same-day treatment 40.0% vs 0%
31	Naidoo et al. (2012)	South Africa (SAPiT trial)	Randomised open-label trial (secondary analysis)	642 patients coinfecting with HIV and tuberculosis	All HIV-positive; CD4-stratified analysis	Clinical, symptomatic and radiographic criteria for IRIS ascertainment	IRIS incidence 19.5, 7.5 and 8.1 per 100 person-years in early-integrated, late-integrated and sequential arms. In patients with CD4 $< 0.050 \times 10^9/L$, incidence reached 45.5 per 100

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
							person-years with early integrated therapy
32	Abedini et al. (2020)	NR	Retrospe ctive observat ional cross- sectional	52 patients with TB/HIV coinfection	All TB/HIV coinfected	Computed tomography assessment of intrathoracic nodes	53.8% had mediastinal and/or hilar lymphadenopathy, multifocal in all cases; nodal conglomeration 25%, hypodense centre 21.4%, calcification 3.5%. Commonest stations right lower paratracheal and subcarinal; all nodal cases had associated pulmonary abnormality

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
33	Moyo et al. (2022)	South Africa (national)	Multistage cluster- based cross- sectional survey	35,191 participants aged ≥ 15 years; 234 with bacteriologically confirmed TB	55/191 (28.8%) of TB cases with known HIV status were HIV- positive	Digital CXR screening with manual reading; Xpert Ultra and MGIT culture	Prevalence 852/100,000 (95% CI 679–1,026). 135/234 (57.7%) of prevalent cases screened positive on CXR alone, 16 (6.8%) on symptoms alone, and 82 (35.9%) on both — indicating that radiographic screening detects the majority of otherwise asymptomatic disease
34	Mendelsohn et al. (2025)	South Africa (3 sites)	Prospective observational cohort	979 adult household contacts; 51 (5.2%) with prevalent TB	185 (18.9%) living with HIV; 187 (19.1%) with previous TB	Chest radiography (any abnormality indicative of TB); Xpert	CXR sensitivity 56.1% (95% CI 41.0–70.1) in asymptomatic versus 88.9% (56.5–98.0) in

No	Author (Year)	Country / setting	Study design	Population and sample size	HIV and CD4 status	Imaging modality and reference standard	Principal radiographic findings reported
						Ultra and liquid culture	symptomatic prevalent TB; combined symptom plus CXR sensitivity 64.0% (50.1–75.9) for all prevalent disease

NR = not reported in the source record; TB = tuberculosis; CXR = chest radiograph; CT = computed tomography; CAD = computer-aided detection; ART = antiretroviral therapy; MDR = multidrug-resistant; BAL = bronchoalveolar lavage; DST = drug susceptibility testing; LJ = Löwenstein-Jensen; LAM = lipoarabinomannan; CRP = C-reactive protein; RFLP = restriction fragment length polymorphism; EZN = Ehrlich-Ziehl-Neelsen; aOR = adjusted odds ratio; IQR = interquartile range; AUC = area under the receiver operating characteristic curve; PLHIV = people living with HIV; TB-IRIS = tuberculosis-associated immune reconstitution inflammatory syndrome; IRIS = immune reconstitution inflammatory syndrome.

Cavitation

Cavitation, the defining morphological signature of post-primary tuberculosis in the immunocompetent host, was consistently and significantly less prevalent in HIV-coinfected patients, and its prevalence declined progressively with falling CD4 count. In the largest prospective coinfecting cohort, cavitation was present in 32% of patients with CD4 counts below 200 cells/ μ L compared with 68% of those at or above that threshold, a difference significant at $P = .008$. The reciprocal relationship was demonstrated in the multicentre trial-nested cohort, in which cavitation was more frequent among patients with CD4 counts of 200/ mm^3 or above (20% versus 7%; $P = .08$),

a direction of effect confirmed in the accompanying pooled-data analysis. The most methodologically rigorous contemporary confirmation comes from a Ugandan cohort with dual blinded pulmonologist reading, in which HIV seropositivity was independently associated with an adjusted odds ratio of 0.34 (95% CI 0.13–0.85; $P = .02$) for the presence of one or more cavities after multivariable adjustment. Comparative imaging evidence reinforces this: in a matched HIV-seropositive versus seronegative series, cavitation was significantly less prevalent in seropositive patients even on computed tomography ($P < .01$), demonstrating that the difference is not an artefact of radiographic insensitivity but a genuine difference in pathological expression.^{1,2,20,7}

The absolute prevalence of cavitation in coinfecting populations with advanced immunosuppression clustered in the range of 12% to 39% across the included studies, compared with the 45% expected in immunocompetent post-primary disease, and it fell as low as 11% when cavitation formed part of a composite "typical" pattern definition in severely immunosuppressed patients. Notably, when cavitation does occur in an HIV-seropositive patient, its morphology appears unaltered: HIV seropositivity did not affect the number of cavities, whether single or multiple, or the size of the largest cavity. The lesion is therefore rarer, but not different in character, which is consistent with a threshold model of granulomatous competence rather than a graded modification of the necrotising response.^{5,6,10,45}

Table 7. Cavitation on chest radiography in HIV-associated pulmonary tuberculosis

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Frey (2023)	268	HIV+ TB, CD4 < 200 vs ≥ 200 cells/μL	Cavitation prevalence	32% vs 68%	$P = .008$	Cavitation significantly less frequent with advanced immunosuppression
Perlman (1997)	128	HIV+ TB, CD4 ≥ 200	Cavitation prevalence	20% vs 7%	$P = .08$	Trend toward more cavitation with

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
		vs < 200/mm ³				preserved CD4; confirmed on pooled analysis
Byanova (2025)	102	PLHIV vs HIV-negative pulmonary TB	Adjusted odds of ≥ 1 cavity	aOR 0.34	95% CI 0.13–0.85; P = .02	HIV independently reduces the odds of cavitation after adjustment
Leung (1996)	84	HIV+ vs HIV– pulmonary TB (CT)	Cavitation prevalence on CT	Lower in HIV+	P < .01	Difference persists on cross-sectional imaging, not a radiographic artefact
Long (1991)	225	HIV+ vs HIV– bacillary pulmonary TB	Cavitating parenchymal infiltrate	Less likely in HIV+	P < .05	Number and size of cavities unchanged when cavitation does occur
Brust (2013)	56	MDR-TB, 88% HIV+, median CD4 136/mm ³	Cavity prevalence	22/56 (39%)	aOR 1.79 (0.94–3.42) for conversion	Cavitation frequent even in MDR disease but not independently prognostic

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Lessnau (1994)	72	HIV+ TB (sensitive and MDR)	Cavity prevalence	12/72 (17%)	P > .05 across resistance groups	Low cavitation prevalence irrespective of drug resistance pattern
Asimos (1996)	46	HIV+ CD4 < 200 vs ≥ 200 vs HIV−	Typical pattern (upper-lobe opacity ± cavitation)	11% vs 100% vs 78%	P < .005	Cavitary post-primary morphology essentially lost below CD4 200 cells/μL
Greenberg (1994)	133	AIDS with culture-positive pulmonary TB	Post-primary (cavitary-type) pattern	38/133 (28%)	—	Post-primary morphology a minority phenotype in AIDS
Mert (2025)	200	PLHIV with TB, CT-based classification	Post-primary pattern	46%	—	Post-primary phenotype retained in under half of a contemporary ART-era cohort

aOR = adjusted odds ratio; *CT* = computed tomography; *MDR* = multidrug-resistant; *PLHIV* = people living with HIV; *ART* = antiretroviral therapy.

Consolidation and Alveolar Opacification

Parenchymal consolidation followed the same immunologically graded pattern as cavitation, although the gradient was less steep because consolidation can arise both from organised

granulomatous inflammation and from poorly contained exudative disease. In the principal prospective cohort, consolidation was present in 47% of patients with CD4 counts below 200 cells/ μ L versus 63% of those with higher counts ($P = .002$). In the matched comparative imaging study, HIV-seropositive patients showed a significantly lower prevalence of consolidation on computed tomography than seronegative patients ($P < .05$), and in the Ugandan cohort HIV was independently associated with reduced adjusted odds of one or more opacities (aOR 0.30, 95% CI 0.13–0.69; $P = .004$) and of multifocal opacities (aOR 0.31, 95% CI 0.13–0.71; $P = .01$). In the Haitian series, parenchymal infiltrates were significantly less common in HIV-seropositive than seronegative patients ($P < .05$).^{1,7,20,5}

Consolidation nevertheless remains, in absolute terms, the single most frequent parenchymal abnormality in coinfecting populations. It was present in 66% of a South African MDR-TB cohort of whom 88% were HIV-coinfecting, and it was the most frequent isolated radiographic change in a Brazilian series of people living with HIV/AIDS with culture-confirmed pulmonary tuberculosis, occurring in 14.3% as an isolated finding and in a further 11.9% in combination with interstitial infiltrate. The interpretive implication is that consolidation retains high sensitivity but very low specificity in this population, since bacterial pneumonia, *Pneumocystis pneumonia*, Kaposi sarcoma, and pulmonary histoplasmosis all produce indistinguishable alveolar opacity in the same patients.^{8,12,16}

Table 8. Consolidation and alveolar opacification

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Frey (2023)	268	HIV+ TB, CD4 < 200 vs $\geq$ 200 cells/ μ L	Consolidation prevalence	47% vs 63%	$P = .002$	Consolidation significantly less frequent with advanced immunosuppression

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Byanova (2025)	102	PLHIV vs HIV-negative pulmonary TB	Adjusted odds of ≥ 1 opacity	aOR 0.30	95% CI 0.13–0.69; P = .004	HIV independently reduces the odds of any parenchymal opacity
Byanova (2025)	102	PLHIV vs HIV-negative pulmonary TB	Adjusted odds of multifocal opacities	aOR 0.31	95% CI 0.13–0.71; P = .01	Multifocal disease less frequent despite greater immunosuppression
Leung (1996)	84	HIV+ vs HIV– pulmonary TB (CT)	Consolidation prevalence on CT	Lower in HIV+	P < .05	Reduced localised parenchymal disease on cross-sectional imaging
Long (1991)	225	HIV+ vs HIV– bacillary pulmonary TB	Parenchymal infiltrate prevalence	Less common in HIV+	P < .05	Adenopathy-predominant disease displaces parenchymal infiltrate
Brust (2013)	56	MDR-TB, 88% HIV+	Consolidation prevalence	37/56 (66%)	aOR 1.09 (0.67–1.78)	Highly prevalent but not independently associated with culture conversion

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Albuquerque (2013)	42	PLHIV with culture-confirmed pulmonary TB	Isolated parenchymal consolidation	6/42 (14.3%)	CD4 association P = .680	Most frequent isolated finding; no significant CD4 gradient in this small series
Lessnau (1994)	72	HIV+ TB	Diffuse infiltrate prevalence	12/72 (17%)	—	Diffuse rather than segmental distribution common in coinfection
Gold (2002)	44	HIV+ with abnormal CXR, no pulmonary symptoms	Nodular disease as predominant abnormality	25/44 (57%)	—	Nodular rather than confluent alveolar pattern predominates in asymptomatic disease
Greenberg (1994)	133	AIDS with pulmonary TB	Atypical infiltrate pattern	17/133 (13%)	—	A distinct atypical alveolar phenotype not classifiable as primary or post-primary

CXR = chest radiograph.

Intrathoracic (Hilar and Mediastinal) Lymphadenopathy

Intrathoracic lymphadenopathy demonstrated the clearest reciprocal relationship to cavitation of any radiographic feature examined. In the trial-nested multicentre cohort, hilar or mediastinal adenopathy was present in 30% of patients with CD4 counts below 200/mm³ versus 7% of those with counts at or above that threshold, a more than fourfold difference significant at $P = .01$ and confirmed on pooled analysis with published data. In the largest prospective coinfecting cohort, lymphadenopathy was present in 62% of the low-CD4 stratum versus 38% of the higher stratum, a difference of similar direction and magnitude that approached but did not reach conventional significance ($P = .08$). Comparative imaging demonstrated a significantly higher prevalence of lymphadenopathy on chest radiography in HIV-seropositive relative to seronegative patients ($P < .05$), and in the Haitian series intrathoracic adenopathy occurring in isolation, without any parenchymal infiltrate, was significantly more common in seropositive patients ($P < .05$).^{2,1,7,5}

Contemporary cohort data confirm that this is not a historical phenomenon confined to the pre-antiretroviral era. In a ten-year Turkish national cohort of people living with HIV who developed tuberculosis, lymphadenopathy was documented in 42% of coinfecting patients, and in 70% of these it was generalised rather than confined to a single station. Cross-sectional imaging characterisation shows that 53.8% of coinfecting patients had mediastinal and/or hilar adenopathy, that nodal involvement was multifocal in every case, that nodal conglomeration was present in 25% and a hypodense necrotic centre in 21.4%, and that all patients with nodal disease also had associated pulmonary abnormality. Critically, formal predictive modelling has demonstrated that lymphadenopathy is one of only four radiographic and demographic variables that independently predict HIV serostatus among patients with intrathoracic tuberculosis, with a graded scoring scale correctly assigning serostatus in 89.1% of cases in its high range.^{15,32,11}

Table 9. Intrathoracic hilar and mediastinal lymphadenopathy

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Perlman (1997)	128	HIV+ TB, CD4 < 200 vs $\geq 200/\text{mm}^3$	Hilar/mediastinal adenopathy	30% vs 7%	$P = .01$	More than fourfold excess with

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
						advanced immunosuppression; confirmed on pooled analysis
Frey (2023)	268	HIV+ TB, CD4 < 200 vs $\geq$ 200 cells/ μ L	Lymphadenopathy prevalence	62% vs 38%	P = .08	Same direction and magnitude; approached significance
Leung (1996)	84	HIV+ vs HIV– pulmonary TB	Lymphadenopathy on chest radiography	Higher in HIV+	P < .05	Adenopathy is the discriminating radiographic feature of coinfection
Long (1991)	225	HIV+ vs HIV– bacillary pulmonary TB	Isolated intrathoracic adenopathy	More common in HIV+	P < .05	Adenopathy without parenchymal infiltrate is a recognisable coinfection phenotype
Mert (2025)	264	PLHIV with TB (contemporary ART era)	Any lymphadenopathy	42% (70% generalised)	—	Persists as a dominant feature in the modern treatment era

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Abedini (2020)	52	TB/HIV coinfection (CT characterisation)	Mediastinal and/or hilar adenopathy	53.8%	Multifocal in 100%	Conglomeration 25%; hypodense centre 21.4%; calcification 3.5%
Mlika-Cabanne (1995)	146	Intrathoracic TB, 55% HIV+	Lymphadenopathy as predictor of HIV serostatus	Independent predictor	Model accuracy 89.1% (high range)	Adenopathy is one of only four variables independently predicting serostatus
Lessnau (1994)	72	HIV+ TB	Possible intrathoracic lymphadenopathy	30/72 (42%)	—	Concordant prevalence in an independent HIV-positive series
Gold (2002)	44	HIV+ with abnormal CXR, asymptomatic	Adenopathy as predominant abnormality	17%	—	Second most common predominant abnormality after nodular disease
Woodring (1986)	Reference	Immunocompetent post-primary TB (comparator)	Intrathoracic lymphadenopathy	Approximately 5%	—	Establishes the immunocompetent baseline against which the excess is measured

Miliary and Micronodular Dissemination

A miliary pattern, defined as diffuse randomly distributed micronodules of 1 to 3 mm reflecting haematogenous dissemination, was significantly more frequent in patients with advanced immunosuppression. In the principal prospective cohort a miliary pattern was present in 64% of patients with CD4 counts below 200 cells/ μ L versus 36% of those above ($P = .04$). In the matched comparative imaging study, HIV-seropositive patients had a significantly higher frequency of miliary disease ($P < .01$) and of extrapulmonary involvement ($P < .001$) than seronegative patients, leading the investigators to conclude that seropositive patients exhibit a lower prevalence of localised parenchymal disease and a higher prevalence of disseminated disease. In the contemporary Turkish national cohort, a miliary radiological pattern was documented in 18% of coinfecting patients, a proportion approximately threefold higher than the 6% expected in immunocompetent primary tuberculosis.^{1,7,15,45}

Miliary disease was, however, distinctly less common in the North American classical series, occurring in only 3% of an AIDS cohort with culture-positive pulmonary tuberculosis and in 3 of 72 patients in a New York MDR series. This apparent discrepancy is best explained by case ascertainment: series assembled from patients presenting with respiratory symptoms and undergoing sputum sampling will systematically under-represent disseminated disease, which frequently presents with constitutional rather than respiratory features and is more often confirmed by blood culture, urine lipoarabinomannan, or extrapulmonary sampling than by sputum.^{4,10,29}

Table 10. Miliary and micronodular dissemination

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Frey (2023)	268	HIV+ TB, CD4 < 200 vs $\geq$ 200 cells/ μ L	Miliary pattern prevalence	64% vs 36%	$P = .04$	Significant excess of haematogenous dissemination with advanced immunosuppression

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Leung (1996)	84	HIV+ vs HIV– pulmonary TB	Miliary pattern frequency	Higher in HIV+	P < .01	Concurrent significant excess of extrapulmonary disease (P < .001)
Mert (2025)	200	PLHIV with TB, CT classification	Miliary pattern	18%	—	Threefold the frequency expected in immunocompetent primary TB
Albuquerque (2013)	42	PLHIV with culture-confirmed TB	Diffuse micronodular (miliary) pattern	5/42 (11.9%)	—	Co-equal in frequency with interstitial infiltrate in this series
Greenberg (1994)	133	AIDS with culture-positive pulmonary TB	Miliary pattern	4/133 (3%)	—	Low prevalence attributable to sputum-based case ascertainment
Lessnau (1994)	72	HIV+ TB	Miliary pattern	3/72 (4%)	—	Concordant with other sputum-ascertained North American series

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Keiper (1995)	35	HIV+ TB, CD4-stratified	Interstitial nodules within atypical pattern	Component of atypical pattern	P < .001 for atypical pattern	Micronodularity contributes to the atypical phenotype at low CD4
Woodring (1986)	Reference	Immunocompetent TB (comparator)	Disseminated miliary disease	Approximately 6% (primary phase)	—	Immunocompetent baseline for comparison

Pleural Effusion and Pleural Involvement

Pleural effusion occupies an intermediate and less discriminating position in the coinfectd radiographic spectrum. It is a recognised component of the atypical pattern and was explicitly listed among the atypical features associated with CD4 counts below $0.20 \times 10^9/L$. It was present in 13 of 72 patients (18%) in a New York HIV-positive series, a figure closely comparable to the 18% expected in immunocompetent post-primary disease, and it did not differ significantly across drug-susceptibility strata. In the South African MDR-TB cohort, in which 88% of patients were HIV-coinfectd, pleural effusion showed no association with time to sputum culture conversion. Pleural effusion is therefore best regarded as a feature whose presence broadens the differential and supports a non-post-primary phenotype, but which lacks the discriminating power of adenopathy or the negative predictive relationship of cavitation.^{3,10,12,45}

The mechanistic literature nevertheless supports a specific pathophysiological interpretation: subpleural micronodules and interlobular septal thickening are significantly more frequent in pulmonary tuberculosis complicated by pleural effusion than in tuberculosis without effusion (69% versus 14%, $P < .001$, and 81% versus 64%, $P = .009$, respectively), suggesting that lymphatic involvement of the peripheral interstitium mediates effusion formation. Because peripheral lymphatic

spread is precisely the mechanism that becomes unopposed when granulomatous containment fails, a coherent account exists for the retention of effusion as a feature of coinfecting disease even as cavitation disappears.^{1,32}

Table 11. Pleural effusion and pleural involvement

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Keiper (1995)	35	HIV+ TB, CD4 < $0.20 \times 10^9/L$	Pleural effusion as component of atypical pattern	Component of atypical phenotype	P < .001 for atypical pattern overall	Effusion contributes to the low-CD4 atypical signature
Lessnau (1994)	72	HIV+ TB	Pleural effusion prevalence	13/72 (18%)	P > .05 across resistance strata	Prevalence comparable to immunocompetent post-primary disease
Brust (2013)	56	MDR-TB, 88% HIV+	Effusion and time to culture conversion	No association	—	Effusion carries no independent microbiological prognostic weight
Lessnau (1994)	72	HIV+ TB on therapy	New effusion within 2 weeks of therapy	20/35 MDR patients developed new effusion, adenopathy or worsening infiltrate	Probability of MDR 95% with deterioration	Early new effusion is a clinically actionable radiographic sign

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Mert (2025)	264	PLHIV with TB	Pleural TB among extrapulmonary sites	Reported among common extrapulmonary sites	—	Pleural involvement remains frequent in the contemporary ART era
Woodring (1986)	Reference	Immunocompetent TB (comparator)	Pleural effusion (post-primary / primary)	18% / 24%	—	Immunocompetent baseline; pleural involvement is not HIV-specific

The Normal or Non-Suggestive Chest Radiograph

The prevalence of a normal or non-suggestive chest radiograph in the presence of bacteriologically confirmed pulmonary tuberculosis is, from a patient-safety perspective, the single most consequential finding of this review. In the classical AIDS series, 19 of 133 patients (14%) with culture-positive pulmonary tuberculosis had radiographs read as normal, and when the broader criterion of "radiograph did not suggest active tuberculosis" was applied, this rose to 43 of 133 patients, or 32% of the entire cohort. The prevalence of a normal radiograph was stratified by immune status: 10 of 48 patients (21%) with fewer than 200 T cells per microlitre had normal radiographs compared with 1 of 20 (5%) with more than 200 (a fourfold difference). In an independent HIV-positive series, 10 of 72 patients (14%) had normal films.^{4,10}

These findings, derived from the pre-antiretroviral era, have been reproduced in contemporary community and programmatic settings. In a rural HIV-endemic South African population screening programme, 19 of 99 (19.2%) microbiologically confirmed tuberculosis cases were deemed normal by a blinded radiologist, and 78.8% of all detected cases were asymptomatic. In a rural Tanzanian

HIV clinic cohort, 15 of 20 coinfecting tuberculosis cases (75%) had neither symptoms nor chest radiographic findings suggestive of tuberculosis, and the investigators concluded that tuberculosis can occur at any stage of CD4 depletion. In a prospective South African household-contact cohort, chest radiographic sensitivity was only 56.1% (95% CI 41.0–70.1) in asymptomatic prevalent tuberculosis compared with 88.9% (56.5–98.0) in symptomatic disease.^{18,13,34}

Table 12. Prevalence of a normal or non-suggestive chest radiograph in confirmed pulmonary tuberculosis

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Greenberg (1994)	133	AIDS, culture-positive pulmonary TB	Radiograph read as normal	19/133 (14%)	—	One in seven confirmed cases had a normal film
Greenberg (1994)	133	AIDS, culture-positive pulmonary TB	Radiograph not suggestive of active TB	43/133 (32%)	—	Nearly one third would be missed by radiographic gatekeeping
Greenberg (1994)	68	CD4 < 200 vs > 200 T cells/ μ L	Normal radiograph prevalence	21% vs 5%	—	Fourfold excess of radiographically silent disease at low CD4
Fehr (2021)	99	Microbiologically confirmed TB, HIV-endemic community	Read as normal by blinded radiologist	19/99 (19.2%)	—	Contemporary confirmation in a digital-radiography programme

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Ngowi (2008)	20	HIV+ with culture-positive TB, rural Tanzania	Neither symptoms nor suggestive CXR	15/20 (75%)	—	Extreme paucity of clinical and radiographic signal in ambulatory PLHIV
Mendelsohn (2025)	51	Household contacts with prevalent TB	CXR sensitivity, asymptomatic subgroup	56.1%	95% CI 41.0–70.1	Radiography misses more than 40% of asymptomatic prevalent disease
Mendelsohn (2025)	51	Household contacts with prevalent TB	CXR sensitivity, symptomatic subgroup	88.9%	95% CI 56.5–98.0	Sensitivity is preserved only when symptoms are present
Lessnau (1994)	72	HIV+ TB	Normal chest radiograph	10/72 (14%)	—	Independent replication of the 14% figure
Asimos (1996)	18	HIV+ TB with CD4 < 200 cells/ μ L	Atypical pattern including normal CXR	16/18 (89%)	P < .005	Typical findings are not sensitive for TB in this stratum
Moyo (2022)	234	Population prevalence	Screened positive by	16/234 (6.8%)	—	A minority are radiographically

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
		survey, 28.8% HIV+	symptoms only (CXR negative)			silent but symptomatic; the reverse is far more common

Zonal Distribution and Typical versus Atypical Classification

The anatomical redistribution of disease away from the apical and posterior segments of the upper lobes is the unifying structural finding across the included evidence. In the most rigorously conducted classification study, only 2 of 18 patients (11%) with CD4 counts below 200 cells/ μ L displayed a radiograph typical of post-primary tuberculosis, compared with 4 of 4 (100%) with CD4 counts above 200 and 18 of 23 (78%) HIV-seronegative patients ($P < .005$). In a parallel series, 21 of 26 patients with CD4 counts below $0.20 \times 10^9/L$ had an atypical pattern versus 1 of 9 with higher counts ($P < .001$), and mean CD4 counts were $0.069 \times 10^9/L$ in those with atypical patterns versus $0.323 \times 10^9/L$ in those with typical patterns ($P < .01$).^{6,3}

The most conceptually important contribution to this domain is the molecular epidemiological study that combined restriction fragment length polymorphism fingerprinting with radiographic classification in 456 patients. This study established that HIV infection was the only independent predictor of radiographic appearance, with an odds ratio of 0.20 (95% CI 0.13–0.31) for a typical appearance, and that the univariable association between a clustered fingerprint (indicating recently acquired infection) and a typical radiograph disappeared entirely after adjustment for HIV status. The authors concluded that the altered radiographic appearance in HIV is attributable to altered host immunity rather than to recent acquisition of infection and rapid progression. This finding retires the long-standing interpretive convention of describing HIV-associated radiographic patterns as "primary-type", and replaces it with an immunological rather than a chronological explanation.⁹

Table 13. Zonal distribution and the typical versus atypical radiographic classification

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Asimos (1996)	46	CD4 < 200 vs ≥ 200 vs HIV-negative	Typical post-primary radiographic pattern	11% vs 100% vs 78%	P < .005	Typical morphology essentially abolished below CD4 200 cells/ μ L
Keiper (1995)	35	CD4 < 0.20 vs $\geq 0.20 \times 10^9/L$	Atypical radiographic pattern	21/26 vs 1/9	P < .001	Atypical pattern is a direct marker of severe immunosuppression
Keiper (1995)	35	Atypical vs typical radiographic pattern	Mean CD4 count	0.069 vs $0.323 \times 10^9/L$	P < .01	Continuous dose-response relationship between CD4 and morphology
Geng (2005)	456	HIV+ vs HIV– pulmonary TB	Odds of typical radiographic appearance	OR 0.20	95% CI 0.13–0.31	HIV is the only independent predictor of radiographic appearance
Geng (2005)	456	Clustered vs unique RFLP fingerprint	Association of recent acquisition with typical radiograph	OR 0.68 (univariable) — lost after HIV adjustment	95% CI 0.47–0.99	Altered appearance reflects altered immunity, not recent acquisition

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Long (1991)	225	AIDS vs HIV+ non-AIDS vs HIV–	Primary-type radiographic pattern	80% vs 30% vs 11%	P < .05	Stepwise gradient across the spectrum of immune competence
Greenberg (1994)	133	AIDS with culture-positive pulmonary TB	Primary vs post-primary pattern	36% vs 28%	—	Primary-type pattern predominates over post-primary in AIDS
Mert (2025)	200	PLHIV with TB, contemporary ART era	Post-primary vs primary vs miliary	46% vs 36% vs 18%	—	Contemporary distribution retains substantial non-post-primary majority
Mlika-Cabanne (1995)	146	Intrathoracic TB, 55% HIV+	Lesion location as predictor of HIV serostatus	Independent predictor	Model accuracy 68.1–89.1%	Zonal location carries independent information about serostatus
Leung (1996)	84	HIV+ vs HIV– pulmonary TB (CT)	Post-primary pattern on CT	Lower in HIV+	P < .05	Redistribution confirmed on cross-sectional imaging

Radiographic Extent, Severity Scoring and Bacillary Burden

Although the morphology of disease changes in coinfection, the radiograph retains quantitative value as a measure of disease extent. The most widely validated instrument, derived and validated in adults with smear-positive pulmonary tuberculosis in Papua, Indonesia, combines the estimated proportion of lung affected with a fixed increment of 40 points for the presence of cavitation; baseline scores predicted two-month sputum microscopy status and were significantly associated with sputum smear grade at diagnosis ($P < .001$), body mass index, lung function, haemoglobin, exercise tolerance, and quality of life ($P < .02$ for each), and scores decreased significantly over time on therapy ($P < .001$). Applied retrospectively to 1,354 participants in a large multinational treatment trial, the same scoring system demonstrated that the median time to culture positivity was 26 hours longer in patients without cavitation than in those with cavitation (95% CI 16–30; $P < .001$), and that for every tenfold increase in time to positivity the area of lung field affected decreased by 11.4%.^{43,44}

Two important caveats apply to the coinfecting population. First, radiological severity is only weakly associated with bacterial burden, and this association is lost in patients without cavitation — precisely the subgroup that predominates in advanced HIV disease. Second, the Ralph scoring system was derived in HIV-negative or HIV-unselected populations and has not been systematically validated in predominantly HIV-infected populations with varying CD4 counts, a limitation explicitly acknowledged in the subsequent literature. High-resolution computed tomography-based semi-automated scoring has been shown to correlate with mycobacterial bacterial burden, peripheral monocyte count, and the phenotypic profile of *Mycobacterium tuberculosis*-specific CD4 T cells irrespective of HIV status, offering a potential route to an immunologically robust severity metric.^{44,12}

Table 14. Radiographic extent, severity scoring and correlation with bacillary burden

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Ralph (2010)	115 + 139	Adults with smear-positive	CXR score (% lung	Predicted 2-month smear status;	$P < .001$	Validated numerical severity

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
		pulmonary TB (Papua, Indonesia)	affected + 40 if cavitation)	associated with smear grade		instrument suitable for trials
Ralph (2010)	254	Same derivation and validation cohorts	Association with BMI, lung function, haemoglobin, exercise tolerance, quality of life	Significant for each	P < .02 for each	Radiographic extent tracks systemic disease severity
Murthy (2018)	1,354	Smear-positive pulmonary TB (REMOxTB trial)	Median time to culture positivity, non-cavitary vs cavitary	26 hours longer without cavitation	95% CI 16–30; P < .001	Cavitation is the dominant determinant of bacillary burden
Murthy (2018)	1,354	Smear-positive pulmonary TB	Lung field affected per tenfold increase in time to positivity	Decrease of 11.4%	—	Quantitative inverse relationship between extent and time to positivity

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Murthy (2018)	1,354	Patients without cavitation	Association of radiological severity with bacterial burden	Effect lost	—	Severity–burden relationship fails in the non-cavitary phenotype typical of advanced HIV
Brust (2013)	56	MDR-TB, 88% HIV+, median CD4 136/mm ³	Baseline sputum smear vs radiographic features for culture conversion	aOR 3.45 for smear positivity	95% CI 1.39–8.59	Smear status supersedes radiographic severity as a prognostic marker
Grozdanovic (2015)	141	HIV-negative smear-positive pulmonary TB (Hyderabad, India)	Mean lung area affected at diagnosis	51.7% ± 23.3%	—	Provides an HIV-negative comparator for extent metrics
Grozdanovic (2015)	141	Same cohort, post-DOTS	Reduction in affected lung	56.0% → 31.0%	—	Demonstrates measurable radiographic

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
			area after 6 months			regression under effective therapy
Burke (2024)	207	Hospitalised PLHIV, enhanced diagnostics arm	Median CAD4TB v6 abnormality score	60 (IQR 51–71)	—	High algorithmic abnormality scores are the norm in hospitalised PLHIV
Riou (2023)	Cohort	HIV-1-infected and uninfected TB patients	HRCT-based semi-automated radiographic score	Correlates with bacterial burden and Mtb-specific CD4 profile	Irrespective of HIV status	Cross-sectional scoring may overcome the HIV-related validity gap

BMI = body mass index; DOTS = directly observed treatment, short course; HRCT = high-resolution computed tomography; Mtb = Mycobacterium tuberculosis.

Radiographic Pattern and Sputum Smear or Culture Status

The relationship between radiographic appearance and bacteriological yield is bidirectional and clinically decisive. In a Brazilian cohort of 198 culture-positive patients in a high tuberculosis and HIV prevalence setting, 129 (65.2%) were smear-negative, and in multivariable analysis the absence of a radiographic pattern typical of tuberculosis, together with the absence of cough, were the only characteristics independently associated with smear-negative disease. In a Nigerian cross-sectional study of 150 patients with smear-negative pulmonary tuberculosis, of whom 64.1% were HIV-positive, chest radiographs were reported as typical of tuberculosis in only 24 (16%) of patients by two independently blinded radiologists.^{23,24}

The corollary — that radiographic phenotype does not reliably predict infectiousness — is equally important and was established early. In the Haitian series, HIV-seropositive patients were equally infectious regardless of whether their radiographic pattern was primary or post-primary in type. Drug sensitivity and sputum staining for acid-fast bacilli did not correlate with radiographic findings in the AIDS series, in which 19% of cases had multidrug resistance. A person living with HIV whose radiograph shows no cavity is therefore not thereby rendered non-infectious, and radiographic appearance must not be used to modulate airborne infection control precautions in this population.^{5,4,10}

Table 15. Relationship between radiographic pattern and sputum smear or culture status

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Campos (2016)	198	Culture-positive TB, high TB/HIV prevalence setting	Predictors of smear-negative disease	Absence of typical radiographic pattern independently associated	Multivariable model	Atypical radiology flags paucibacillary but transmissible disease
Campos (2016)	198	Same cohort	Proportion smear-negative	129/198 (65.2%)	—	Smear-negative disease is the majority phenotype in high HIV prevalence settings
Tiamiyu (2020)	150	Smear-negative pulmonary TB, 64.1% HIV+	Radiograph reported as typical of TB	24/150 (16%)	—	Only one in six smear-negative cases displays

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
						classical radiology
Long (1991)	225	HIV+ pulmonary TB, primary vs post-primary pattern	Infectiousness by radiographic pattern	Equally infectious	—	Radiographic phenotype does not predict transmissibility
Greenberg (1994)	133	AIDS with pulmonary TB	Correlation of smear status and drug sensitivity with radiographic findings	No correlation	—	19% of the cohort had multidrug-resistant organisms
Brust (2013)	56	MDR-TB, 88% HIV+	Baseline smear positivity and culture conversion	aOR 3.45	95% CI 1.39–8.59	Smear status is the dominant microbiological prognostic variable
Nguyen (2019)	796	Pulmonary TB (HIV coinfection excluded — comparator)	Cavitation, culture-negative vs culture-positive	7% vs 28% on CXR	P < .001	Paucibacillary disease is radiographically quiet even in

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
						HIV-negative patients
Le (2022)	937	Extrapulmonary TB with normal chest radiographs	Sputum culture positivity, HIV+ vs HIV–	54% vs 9.5%	—	HIV coinfection raises occult pulmonary involvement more than fivefold
Breuninger (2014)	861	Symptomatic adults, HIV status ascertained	CAD discrimination, smear-positive vs smear-negative	Significantly better for smear-positive	P < .01	Bacillary burden drives radiographic detectability

Diagnostic Accuracy of Human Chest Radiographic Interpretation

The most sobering evidence in this review concerns the diagnostic performance of expert human radiographic interpretation in HIV-infected patients with smear-negative disease. In a prospective cross-sectional study of 202 HIV-infected inpatients with unexplained cough and negative sputum smears at a Ugandan referral hospital, of whom 72 (36%) had culture-positive pulmonary tuberculosis, two radiologists interpreted chest radiographs in a standardised fashion. No single factor — including any respiratory symptom, any physical sign, the CD4 count, or any chest radiographic abnormality — substantially increased or decreased the likelihood of pulmonary tuberculosis, and after exhaustive conventional and novel regression modelling the investigators were unable to identify any combination of factors that reliably predicted bacteriologically confirmed disease.¹⁴

In screening rather than diagnostic contexts, radiography performs considerably better. Among prison entrants in Malaysia, radiographic evidence of pulmonary tuberculosis achieved 91.2% sensitivity (95% CI 76.3–98.1) against culture, far exceeding symptom screening (38.2%) and C-reactive protein (47.1%). Critically, however, the optimal strategy diverged by HIV status: among people without HIV, symptom screening plus chest radiography achieved the highest area under the curve (74.7%, 95% CI 68.6–80.7), whereas among people with HIV, symptom screening plus C-reactive protein outperformed radiography-based strategies (85.5%, 95% CI 79.4–91.5). The individual participant data meta-analytic literature converges on the same conclusion, demonstrating that in ART-experienced outpatients a parallel strategy combining the WHO four-symptom screen with any chest radiographic abnormality raises sensitivity from 53% to 89% while reducing specificity from 71% to 33%.^{25,37,35}

Table 16. Diagnostic accuracy of human chest radiographic interpretation in people living with HIV

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Davis (2010)	202	HIV+ smear-negative inpatients, Uganda	Likelihood ratios of any CXR abnormality	No factor meaningfully shifted probability	—	Clinical and radiographic criteria cannot diagnose smear-negative TB in PLHIV
Zhang (2025)	588	Prison entrants, 10.2% HIV+	CXR sensitivity vs culture	91.2%	95% CI 76.3–98.1	High sensitivity in an unselected screening population
Zhang (2025)	588	Same cohort	Symptom screen and	38.2% and 47.1%	—	Radiography markedly

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
			CRP sensitivity			outperforms both alternatives on sensitivity
Zhang (2025)	60	People with HIV subgroup	Best screening AUC	Symptom screen + CRP 85.5%	95% CI 79.4–91.5	CRP outperforms CXR-based strategies specifically in PLHIV
Zhang (2025)	528	People without HIV subgroup	Best screening AUC	Symptom screen + CXR 74.7%	95% CI 68.6–80.7	The optimal strategy diverges by HIV status
Mendelsohn (2025)	979	Household contacts, 18.9% PLHIV	CXR + symptom screening sensitivity	64.0%	95% CI 50.1–75.9	Combined screening still misses one third of prevalent disease
Moyo (2022)	234	National prevalence survey, 28.8% HIV+	Cases detected by CXR alone	135/234 (57.7%)	—	Radiography is the dominant case-finding modality at population level
Fehr (2021)	9,914	HIV-endemic	Radiologist vs CAD4TB v5 sensitivity	Equivalent sensitivity, higher	—	Human expert reading remains a

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
		community screening		specificity for radiologist		valid comparator standard
Ngowi (2008)	233	Ambulatory PLHIV, rural Tanzania	Coinfected TB cases without suggestive CXR	15/20 (75%)	—	Radiographic screening alone would have missed three quarters of cases
Gold (2002)	44	HIV+ with abnormal CXR, no pulmonary symptoms	Invasive modality required for diagnosis	62%	—	An abnormal radiograph rarely establishes the diagnosis unaided

Computer-Aided Detection and Artificial Intelligence Performance

The evidence on computer-aided detection is now substantial and internally consistent on one central point: algorithmic performance is degraded in people living with HIV, and this degradation is quantifiable. In an individual participant data meta-analysis of 3,727 participants of whom 621 (17%) were people living with HIV, the adjusted absolute difference in pooled sensitivity between people living with HIV and HIV-uninfected participants was −13.4 percentage points (95% CI −21.1 to −6.9) for CAD4TB version 6 and −13.4 (−21.5 to −6.6) for qXR version 2, while Lunit showed no significant difference (+2.2; −3.6 to +6.3). The corresponding penalty for smear-negative relative to smear-positive disease was −12.3, −17.2, and −16.6 percentage points respectively. In a case-control evaluation of twelve commercial products nested within a national prevalence survey, all products performed worst in older individuals, people with previous tuberculosis, and people with HIV.^{38,22}

Direct prospective evaluation confirms this. In a Tanzanian cohort of 861 symptomatic adults, CAD4TB achieved an overall area under the curve of 0.84 (95% CI 0.80–0.88) but discriminated

significantly better between tuberculosis cases and non-cases among HIV-negative than among HIV-positive individuals ($P < .01$). A purpose-built algorithm trained exclusively on 677 HIV-positive patients achieved a standalone accuracy of 0.79 (95% CI 0.77–0.82), which was substantially and significantly superior to unassisted clinician accuracy of 0.60 (0.57–0.63); clinician accuracy rose to 0.65 (0.60–0.70) with algorithmic assistance ($P = .002$) but remained significantly below the standalone algorithm ($P < .001$). In mixed-HIV populations, contemporary versions perform at or near World Health Organization target product profile thresholds: CAD4TB version 7 achieved an area under the curve of 0.87 (95% CI 0.84–0.91) with 68.2% specificity at 90% sensitivity in a cohort with 48% HIV prevalence, and detected tuberculosis as well as an expert radiologist.^{19,17,21,26}

Table 17. Computer-aided detection and artificial intelligence performance in HIV-coinfected populations

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Tavaziva (2021)*	3,727	PLHIV vs HIV-uninfected (17% PLHIV)	Adjusted absolute sensitivity difference, CAD4TB v6	−13.4 percentage points	95% CI −21.1 to −6.9	Substantial and statistically significant HIV-specific sensitivity penalty
Tavaziva (2021)*	3,727	PLHIV vs HIV-uninfected	Adjusted difference, qXR v2	−13.4 percentage points	95% CI −21.5 to −6.6	Penalty replicated across an independent commercial product
Tavaziva (2021)*	3,727	PLHIV vs HIV-uninfected	Adjusted difference, Lunit v3.1	+2.2 percentage points	95% CI −3.6 to +6.3	Not all algorithms are equally affected; product-

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
						specific evaluation is essential
Breuninger (2014)	861	HIV-positive vs HIV-negative symptomatic adults	CAD4TB discrimination by HIV status	Significantly better in HIV-negative	P < .01	Prospective confirmation of the HIV performance gap
Breuninger (2014)	861	All participants	CAD4TB overall AUC	0.84	95% CI 0.80–0.88	CAD outperformed a clinical officer but not an expert reader (P = .02)
Rajpurkar (2020)	677	HIV-positive patients with suspected TB	Standalone algorithm accuracy	0.79	95% CI 0.77–0.82	Purpose-built HIV-trained algorithm substantially outperforms clinicians
Rajpurkar (2020)	677	Same cohort	Unassisted vs assisted clinician accuracy	0.60 vs 0.65	P = .002	Assistance improves clinicians but does not close the gap (P < .001)

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Bosman (2024)	1,392	Symptomatic adults, 48% PLHIV	CAD4TB v7 AUC	0.87	95% CI 0.84–0.91	Near-TPP performance in a high HIV-burden population
Bosman (2024)	1,392	Same cohort at 90% sensitivity	Specificity, CAD4TB v7 vs CRP	68.2% vs 38.2%	95% CI 65.4–71.0 vs 35.3–41.1	CAD substantially outperforms CRP as a triage instrument
Qin (2024)	774	12 commercial CAD products, prevalence survey	Subgroup performance	Worst in PLHIV, prior TB and older age	—	Threshold calibration must be stratified by HIV status
Crowder (2024)	1,392	Multinational symptomatic cohort	Specificity at 90% sensitivity, CAD4TB v7	70.3%	vs Xpert HR 65.1%, CRP 49.7%	CAD meets TPP thresholds and outperforms host-response markers
Fehr (2021)	9,914	HIV-endemic community screening	Effect of HIV serostatus on CAD4TB performance	No measurable impact in this cohort	—	Population-specific piloting remains mandatory before deployment

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Burke (2024)	415	Hospitalised PLHIV, cluster RCT	Contribution of digital CXR-CAD to treatment initiation	Increment attributable mainly to urine LAM	RR 1.92 (1.20–3.08) overall	CAD added little incremental yield in advanced inpatient HIV disease
MacPherson (2021)	1,462	Adults with cough, primary care, Malawi	Median time to TB treatment, CAD arm vs standard care	1 day vs 11 days	HR 2.86 (1.04–7.87)	Radiographic CAD dramatically accelerates treatment initiation

**Tavaziva 2021 is an individual participant data meta-analysis and is therefore excluded from the study-characteristics table (Table 8) in accordance with the prespecified design restriction; it is retained here for outcome-level triangulation only. TPP = target product profile; RR = risk ratio; HR = hazard ratio; LAM = lipoarabinomannan.*

Radiographic Evolution during Therapy and Immune Reconstitution

Serial radiography retains substantial value in the coinfecting patient, both for documenting therapeutic response and for recognising paradoxical immune reconstitution disease. In the principal prospective cohort followed for 24 weeks, partial radiological response was the most frequent evolution, occurring in 62% of patients and accompanied by a rise in CD4 count in 92% of those cases; conversely, 53% of patients whose CD4 count fell showed radiological worsening. Radiographic trajectory therefore parallels immunological trajectory, and a deteriorating radiograph on therapy should prompt evaluation of immune reconstitution status, adherence, and drug resistance rather than being ascribed to treatment failure by default.¹

Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome is a radiographically defined entity in a substantial minority of cases. In the CAMELIA randomised trial,

26% of 597 ART-naïve patients with CD4 counts of 200 cells/ μ L or below developed validated paradoxical TB-IRIS at an incidence of 37.9 per 100 person-years; chest radiography revealed new or worsening abnormalities in 53.4% of episodes, and new or worsening lymphadenopathy occurred in 77.4%. Initiating ART at two rather than eight weeks increased TB-IRIS risk 2.61-fold (95% CI 1.84–3.70). In the SApiT trial, IRIS incidence was 19.5, 7.5, and 8.1 per 100 person-years in the early-integrated, late-integrated, and sequential treatment groups respectively, rising to 45.5 per 100 person-years with early integrated therapy among patients with baseline CD4 counts below $0.050 \times 10^9/L$. In the only randomised trial of corticosteroid therapy for established paradoxical TB-IRIS, chest radiographs improved significantly more in the prednisone arm than in the placebo arm at both two weeks ($P = .002$) and four weeks ($P = .02$).^{27,31,28}

Radiographic deterioration on therapy also carries diagnostic information about drug resistance. In a New York case-control series, 20 of 35 patients with multidrug-resistant tuberculosis developed new effusions, possible intrathoracic lymphadenopathy, or worsening infiltrates within two weeks of starting therapy, and in the presence of such radiographic deterioration the probability of multidrug-resistant disease was 95%. It should be noted, however, that in more recent and larger analyses chest radiography alone has been found insufficient to distinguish drug-susceptible from drug-resistant disease at baseline, so this sign is prognostic on therapy rather than diagnostic at presentation.¹⁰

Table 18. Radiographic evolution on therapy and tuberculosis-associated immune reconstitution inflammatory syndrome

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Frey (2023)	268	HIV+ TB followed 24 weeks on ART and	Partial radiological response	62% of cohort	CD4 rise in 92% of responders	Radiographic and immunological trajectories are concordant

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
		anti-TB therapy				
Frey (2023)	268	Patients with falling CD4 count	Radiological worsening	53%	—	Deteriorating radiology signals immunological failure
Laureillard (2013)	597	ART-naïve, CD4 $\leq$ 200 cells/ μ L (CAMELIA RCT)	Paradoxical TB-IRIS incidence	26%; 37.9/100 person-years	95% CI 32.4–44.4	One in four patients develops paradoxical IRIS
Laureillard (2013)	597	Validated TB-IRIS episodes	New or worsening CXR abnormality	53.4%	—	Radiography documents more than half of all IRIS events
Laureillard (2013)	597	Validated TB-IRIS episodes	New or worsening lymphadenopathy	77.4%	—	Nodal enlargement is the cardinal radiographic manifestation of IRIS
Laureillard (2013)	597	ART at 2 weeks vs 8 weeks	Risk of TB-IRIS	2.61-fold increase	95% CI 1.84–3.70	Earlier ART substantially increases

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
						radiographically evident IRIS
Naidoo (2012)	642	Early vs late integrated vs sequential ART (SAPiT RCT)	IRIS incidence per 100 person-years	19.5 vs 7.5 vs 8.1	IRR 2.6 (1.5–4.8); P < .001	ART timing is the dominant modifiable determinant of IRIS
Naidoo (2012)	642	Baseline CD4 < 0.050 × 10 ⁹ /L	IRIS incidence, early integrated arm	45.5/100 person-years	—	Profound immunosuppression multiplies IRIS risk
Meintjes (2010)	110	Paradoxical TB-IRIS randomised to prednisone vs placebo	Radiographic improvement at week 2	Significantly greater with prednisone	P = .002	Corticosteroid therapy accelerates radiographic resolution
Meintjes (2010)	110	Same trial	Radiographic improvement at week 4	Significantly greater with prednisone	P = .02	Effect sustained through the treatment course

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Meintjes (2010)	110	Same trial	Hospital days and outpatient procedures	Median 0 vs 3 days	P = .04	Radiographic benefit translates into reduced health service utilisation
Lessnau (1994)	35	HIV+ MDR-TB, 2 weeks after starting therapy	New effusion, adenopathy or worsening infiltrate	20/35 (57%)	Probability of MDR 95% with deterioration	Early radiographic deterioration is a strong signal of drug resistance

IRR = incidence rate ratio; *IRIS* = immune reconstitution inflammatory syndrome; *RCT* = randomised controlled trial.

Prognostic Value of Radiographic Findings

Radiographic findings retain measurable prognostic information in coinfecting populations, although in most analyses they are superseded by microbiological and immunological variables once multivariable adjustment is applied. In the South African MDR-TB cohort, in which 88% of patients were HIV-coinfecting with a median CD4 count of 136 cells/mm³, cavitary disease and consolidation were each associated with a longer time to sputum culture conversion on bivariate analysis, but neither retained significance after adjustment for sputum smear status, whereas baseline smear positivity remained independently associated (adjusted odds ratio 3.45, 95% CI 1.39–8.59). Despite advanced immunodeficiency and severe baseline radiographic pathology, 79% of these patients were cured at the end of treatment, an important counterweight to therapeutic nihilism in this population.¹²

In an Ethiopian drug-resistant tuberculosis cohort of 406 patients followed for 7,084 person-months, chest radiographic findings emerged as an independent predictor of death (adjusted hazard ratio 0.37, 95% CI 0.17–0.79) alongside HIV serostatus (adjusted hazard ratio 2.98, 95% CI 1.72–5.19). In HIV-negative populations, baseline cavitation, opacities occupying more than two lung

zones, and a 3+ smear grade each independently forecast an unfavourable treatment outcome, with adjusted hazard ratios of 1.73 (95% CI 1.05–2.84) for baseline cavitation and 1.21 (1.01–1.44) for extent of involvement; radiological clearance exceeding 50% at two months, together with smear conversion, was a reasonable alternative to culture conversion in predicting success. In the contemporary Turkish coinfectd cohort, 22% of patients died, with age, CD4 count below 200 cells/mm³, and thrombocytopenia identified as independent predictors of mortality.¹⁵

Table 19. Prognostic value of baseline and serial radiographic findings

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Brust (2013)	56	MDR-TB, 88% HIV+, median CD4 136/mm ³	Cavitation and time to culture conversion	aOR 1.79 (unadjusted association lost)	95% CI 0.94–3.42	Radiographic severity is not independently prognostic after smear adjustment
Brust (2013)	56	Same cohort	Baseline smear positivity and conversion	aOR 3.45	95% CI 1.39–8.59	Microbiological burden supersedes radiographic appearance
Brust (2013)	56	Same cohort	End-of-treatment cure rate	79%	—	Severe radiographic pathology is compatible with excellent outcome
Mert (2025)	264	PLHIV with TB,	All-cause mortality	58/264 (22%)	—	Age, CD4 < 200 cells/mm ³ and thrombocytopenia

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
		contemporary cohort				independently predicted death
Woldeyohannes (2021)	406	Drug-resistant TB, Ethiopia	Chest radiographic findings as predictor of death	aHR 0.37	95% CI 0.17–0.79	Radiographic category independently informs mortality risk
Woldeyohannes (2021)	406	Same cohort	HIV serostatus as predictor of death	aHR 2.98	95% CI 1.72–5.19	HIV coinfection nearly triples the hazard of death
Gopalan (2021)	667	Rifampicin-sensitive pulmonary TB	Baseline cavitation and unfavourable outcome	aHR 1.73	95% CI 1.05–2.84	Cavitation is prognostic where it is present
Gopalan (2021)	667	Same cohort	Extent of involvement and unfavourable outcome	aHR 1.21	95% CI 1.01–1.44	Radiographic extent contributes independent prognostic information
Gopalan (2021)	667	Same cohort	Persistence of cavitation	aHR 2.68	95% CI 1.40–5.12	Residual cavitation more than doubles the hazard of an

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
			after treatment			unfavourable outcome
Ralph (2010)	254	Smear-positive pulmonary TB	Baseline CXR score and 2-month smear status	Superior to lung proportion alone	—	Composite scoring outperforms extent measurement in isolation
Page (2019)	285	Treated pulmonary TB, Uganda (HIV coinfectd subset)	Residual cavitation and chronic pulmonary aspergillosis	26% vs 0.8%	P < .001	Residual cavitation is the dominant risk factor for post-TB aspergillosis
Burke (2024)	415	Hospitalised PLHIV, cluster RCT	56-day mortality with enhanced diagnostics	26.1% vs 25.0%	HR 1.05 (0.72–1.53)	Improved radiographic and antigen detection did not translate into survival gain

aHR = adjusted hazard ratio. Woldeyohannes 2021 and Gopalan 2021 are primary observational cohorts identified during citation chaining and are reported here for prognostic triangulation.

Inter-Observer Reliability of Radiographic Interpretation

Inter-observer variability is a persistent and quantifiable threat to the validity of radiographic decision-making in tuberculosis, and it is the principal operational argument advanced in favour of algorithmic interpretation. Reported agreement varies markedly according to the feature assessed and the structure of the reading protocol. In studies employing standardised reporting templates with defined features and consensus adjudication, agreement is substantially improved: consensus

conference reading by three independent readers underpinned the derivation of a validated HIV-prediction score, and a purpose-designed quadrant-based reading scheme achieved excellent agreement between radiologists across five radiographic manifestations. In paediatric intrathoracic tuberculosis, features achieving at least moderate inter-reader agreement — perihilar and paratracheal lymph node enlargement, bronchial deviation or compression, cavities, expansile pneumonia, and pleural effusion — all achieved specificity above 90% for bacteriologically confirmed disease.^{11,50,55}

The clinical consequence is that unstructured free-text radiographic reporting is an inadequate instrument for programmatic decision-making in HIV-coinfected populations, and that either structured templated reporting with adjudication, or validated algorithmic assistance with locally calibrated thresholds, is required if radiographic information is to be used reproducibly.^{18,22,41}

Table 20. Inter-observer reliability of chest radiographic interpretation

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
Mlika-Cabanne (1995)	146	Intrathoracic TB, 55% HIV+	Reading protocol	Three readers, independent then consensus conference	—	Consensus adjudication was required to derive a valid prediction score
Grozdanovic (2015)	141	Smear-positive pulmonary TB	Inter-reader reliability of quadrant-based scheme	Excellent agreement across five manifestations	—	Structured quadrant-based schemes achieve high reproducibility
Palmer (2022)	Paediatric cohort	Presumptive intrathoracic TB	Features with $\geq$ moderate	Nodal enlargement, bronchial compression,	Specificity > 90% each	Only reproducible features achieve

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
			inter-reader agreement	cavities, expansile pneumonia, effusion		diagnostic specificity
Davis (2010)	202	HIV+ smear-negative inpatients	Reading protocol	Two radiologists, standardised interpretation	—	Standardisation did not rescue diagnostic performance in this population
Tiamiyu (2020)	150	Smear-negative TB, 64.1% HIV+	Reading protocol	Two radiologists blinded to each other	—	Dual blinded reading yielded only 16% typical classification
Fehr (2021)	9,914	HIV-endemic community screening	CAD4TB v6 vs blinded radiologist	Comparable sensitivity and specificity	—	Algorithmic reading can substitute for the human reader at scale
Murthy (2018)	1,837	Smear-positive pulmonary TB (REMoxTB)	Reading protocol	Two blinded clinicians plus independent adjudication of discrepancies	—	Discrepancy adjudication is standard practice in

Study (Year)	n	Population stratum	Comparison	Estimate	P value / 95% CI	Interpretation
						high-quality trials
Byanova (2025)	102	Pulmonary TB, 36% PLHIV	Reading protocol	Two blinded pulmonologists, independent reading	—	Independent dual reading underpins the adjusted odds ratios reported

Certainty of the Evidence

Certainty of evidence was appraised across all fourteen outcome domains using a GRADE-informed framework. Certainty was rated moderate for the core morphological domains, in which the direction of effect is consistent across more than ten independent datasets spanning four decades and three continents, with a demonstrable dose-response relationship to CD4 count, but where all contributing evidence is observational and some foundational studies are small and pre-antiretroviral in era. Certainty was rated high for the domain of computer-aided detection performance, in which individual participant data meta-analysis of prospectively collected cohorts provides adjusted, precision-quantified estimates. Certainty was rated low for the severity-scoring domain, reflecting the acknowledged absence of validation of the principal scoring instrument in predominantly HIV-infected populations.⁵

Table 21. GRADE-informed certainty of evidence by outcome domain

No.	Outcome domain	Studies (n)	Risk of bias	Inconsistency	Indirectness	Imprecision	Overall certainty and rationale
1	Cavitation	10	Serious	Not serious	Not serious	Not serious	MODERATE — consistent direction, dose-response with

No.	Outcome domain	Studies (n)	Risk of bias	Inconsistency	Indirectness	Imprecision	Overall certainty and rationale
							CD4, replicated with adjustment
2	Consolidation / alveolar opacification	10	Serious	Not serious	Not serious	Not serious	MODERATE — consistent inverse relationship with immunosuppression
3	Intrathoracic lymphadenopathy	10	Serious	Not serious	Not serious	Not serious	MODERATE — largest and most reproducible effect size in the review
4	Miliary / micronodular dissemination	8	Serious	Serious	Not serious	Serious	LOW — wide prevalence range attributable to case-ascertainment differences
5	Pleural effusion	6	Serious	Serious	Not serious	Serious	LOW — no consistent HIV-specific gradient demonstrated
6	Normal / non-suggestive radiograph	10	Serious	Not serious	Not serious	Not serious	MODERATE — reproduced in pre-ART and contemporary

No.	Outcome domain	Studies (n)	Risk of bias	Inconsistency	Indirectness	Imprecision	Overall certainty and rationale
							programmatic settings
7	Zonal distribution and typical vs atypical	10	Not serious	Not serious	Not serious	Not serious	MODERATE — supported by molecular-epidemiological adjustment for acquisition recency
8	Radiographic extent and severity scoring	10	Serious	Serious	Serious	Not serious	LOW — principal instrument not validated in predominantly HIV-infected populations
9	Correlation with smear and culture status	9	Serious	Not serious	Not serious	Not serious	MODERATE — consistent across four decades and multiple continents
10	Diagnostic accuracy of human reading	10	Not serious	Serious	Not serious	Not serious	MODERATE — performance differs sharply between screening and diagnostic contexts

No.	Outcome domain	Studies (n)	Risk of bias	Inconsistency	Indirectness	Imprecision	Overall certainty and rationale
11	Computer-aided detection performance	14	Not serious	Not serious	Not serious	Not serious	HIGH — IPD meta-analysis with adjusted, precision-quantified subgroup estimates
12	Radiographic evolution and TB-IRIS	12	Not serious	Not serious	Not serious	Not serious	HIGH — supported by three independent randomised controlled trials
13	Prognostic value of radiographic findings	12	Serious	Serious	Not serious	Serious	LOW — radiographic effects attenuate after adjustment for microbiological variables
14	Inter-observer reliability	8	Serious	Serious	Not serious	Serious	LOW — reliability reported heterogeneously and rarely quantified with kappa statistics

GRADE = Grading of Recommendations Assessment, Development and Evaluation; IPD = individual participant data; TB-IRIS = tuberculosis-associated immune reconstitution inflammatory syndrome.

DISCUSSION

Summary of Principal Findings

This systematic review of 34 primary studies, encompassing five randomised or cluster-randomised trials and 29 observational primary studies conducted across 18 countries and more than 55,000 individually assessed participants, establishes with a high degree of internal consistency that the chest radiographic expression of pulmonary tuberculosis in HIV/AIDS coinfection is systematically and predictably displaced from the classical post-primary template. Every one of the seven prespecified directional hypotheses was confirmed at conventional levels of statistical significance in at least one, and in most instances in several independent and adequately powered datasets. Cavitation is significantly less frequent as CD4 counts fall (32% versus 68%; $P = .008$), and HIV seropositivity independently reduces the adjusted odds of cavitation (aOR 0.34, 95% CI 0.13–0.85; $P = .02$). Consolidation follows the same gradient (47% versus 63%; $P = .002$; aOR 0.30 for any opacity, 95% CI 0.13–0.69; $P = .004$). Intrathoracic lymphadenopathy shows the largest and most reproducible reciprocal excess (30% versus 7%; $P = .01$). Miliary dissemination increases significantly with immunosuppression (64% versus 36%; $P = .04$). A normal or non-suggestive radiograph accompanies 14% to 32% of bacteriologically confirmed disease. HIV status is the sole independent predictor of an atypical radiographic appearance after adjustment for the recency of infection acquisition (OR 0.20 for a typical appearance; 95% CI 0.13–0.31). Human and algorithmic diagnostic sensitivity are both significantly degraded, the latter by a quantified 13.4 absolute percentage points for two of three evaluated commercial products. Radiographic deterioration accompanies 53.4% of paradoxical immune reconstitution events and is responsive to corticosteroid therapy.^{1,2,7,9,20,27,28,38}

Immunopathological Basis of the Radiographic Shift

The findings of this review are not a catalogue of unrelated exceptions but the coherent imaging expression of a single underlying pathophysiological process. Containment of *Mycobacterium tuberculosis* in the immunocompetent host depends on antigen-specific CD4⁺ T-helper 1 lymphocytes that produce interferon-gamma, activate infected macrophages, and organise the epithelioid granuloma. Caseous necrosis at the granuloma centre, followed by liquefaction and

communication with a draining bronchus, produces the cavity — a lesion that is therefore not a marker of severe disease in the naive sense but a marker of a vigorous, delayed-type hypersensitivity-driven host response. When CD4⁺ helper function is progressively lost, that organised response cannot be constructed. The bacillus is not contained, but neither is it walled off and liquefied; consequently the cavity does not form. This explains the single most robust finding of this review with complete mechanistic economy.^{3,6,47}

The same failure of containment explains the reciprocal excess of lymphadenopathy and miliary dissemination. Mycobacteria that are not confined within a functioning granuloma drain freely through pulmonary lymphatics to hilar and mediastinal nodes, where the resulting nodal enlargement is itself poorly organised and frequently exhibits central necrosis, a feature demonstrated on cross-sectional imaging in 21.4% of coinfecting patients with nodal disease. Onward haematogenous seeding produces the miliary phenotype and the concurrent excess of extrapulmonary disease that is documented at $P < .001$ in matched comparative imaging and reaches 48.8% pulmonary-and-extrapulmonary or extrapulmonary-only involvement in a contemporary national cohort. The apparent radiographic resemblance to childhood primary tuberculosis is thus a phenocopy: the same anatomical pathways are traversed because the same immunological competence is lacking, not because the infection was recently acquired.^{32,7,15}

Kynurenine pathway data provide a further mechanistic layer. In a Ugandan cohort, the kynurenine-to-tryptophan ratio, a marker of indoleamine 2,3-dioxygenase-mediated immunosuppression, was significantly higher in people living with HIV than in those without (0.13 versus 0.08; $P < .001$), and HIV serostatus and kynurenine-to-tryptophan ratio had qualitatively different associations with radiographic findings: while HIV was associated with lower odds of opacities, a higher kynurenine-to-tryptophan ratio was associated with higher odds of one or more opacities (aOR 1.97, 95% CI 1.07–3.62; $P = .03$). This dissociation suggests that the radiographic phenotype in coinfection is shaped by at least two partially independent immunological axes — quantitative CD4 depletion and qualitative immunoregulatory suppression — and that future radiological research should measure both.²⁰

Cavitation, Bacillary Burden and Transmission

The disappearance of cavitation in advanced coinfection has consequences that extend beyond diagnosis. Cavitory tuberculosis is recognised as the gateway of disease transmission, associated with poor outcomes, treatment relapse, higher transmission rates, and the development of drug resistance, and the cavity functions as a unique mycobacterial niche interfacing with the host response. Quantitatively, the median time to culture positivity in liquid media is 26 hours longer in patients without cavitation than in those with cavitation (95% CI 16–30; $P < .001$), confirming a substantially lower bacillary burden in the non-cavitory state.^{47,44}

It would nevertheless be a serious clinical error to infer that the non-cavitory coinfecting patient is non-infectious. The Haitian series demonstrated directly that HIV-seropositive patients were equally infectious regardless of whether their radiographic pattern was primary or post-primary in type, and in the classical AIDS series neither sputum staining for acid-fast bacilli nor drug susceptibility correlated with radiographic findings. Furthermore, in a Californian registry analysis of patients with extrapulmonary tuberculosis and normal chest radiographs, 54% of those with HIV coinfection had positive sputum cultures compared with 9.5% of those without HIV coinfection — a more than fivefold excess of occult, radiographically invisible, culture-positive pulmonary involvement. Airborne infection control decisions in coinfecting patients must therefore be driven by microbiology and clinical suspicion, never by radiographic morphology.^{5,4,58}

Lymphadenopathy and Disseminated Disease as Diagnostic Signatures

Intrathoracic lymphadenopathy emerged from this review as the single most discriminating radiographic feature of HIV coinfection, with a fourfold prevalence excess at CD4 counts below 200/mm³ and independent predictive value for HIV serostatus in formal modelling. Its practical utility, however, is constrained by two considerations. First, adenopathy is not specific for tuberculosis in people living with HIV: the differential in this population also includes disseminated histoplasmosis, in which mediastinal lymphadenopathy was present in 29% of probable cases, non-tuberculous mycobacterial infection, which accounted for 23% of diagnoses in one series of HIV-positive patients with abnormal radiographs and no pulmonary symptoms, lymphoma, and Kaposi sarcoma. Second, the detection of hilar and mediastinal nodes on plain radiography is itself reader-

dependent, which is reflected in the recurrent qualifier "possible intrathoracic lymphadenopathy" in the primary literature.^{2,11,16}

Where adenopathy is identified in a coinfecting patient, the discriminating strategy is not further imaging refinement but tissue and antigen sampling. Endobronchial ultrasound-guided transbronchial needle aspiration achieved 59.3% sensitivity and 100% specificity for tuberculosis in an undifferentiated cohort with mediastinal lymphadenopathy of unknown aetiology, with a negative predictive value of 92.2%, and mycobacterial culture of aspirates identified drug resistance in 10.5% of confirmed cases. In resource-constrained settings, focused abdominal sonography for HIV-associated tuberculosis detected sonographic features suggestive of tuberculosis in 27% of unselected HIV-positive patients and supported treatment initiation in 16 of 21 patients, with a significantly higher proportion of CD4 counts below $0.2 \times 10^9/L$ among sonography-positive patients (81% versus 48%; $P = .003$).^{16,40}

The Normal Radiograph: Why Radiography Cannot Function as a Rule-Out Test

The finding that 14% to 32% of bacteriologically confirmed pulmonary tuberculosis in HIV-coinfecting patients is accompanied by a normal or non-suggestive chest radiograph is the most operationally consequential result of this review. It is not an artefact of the pre-antiretroviral era: it was reproduced at 19.2% in a contemporary digital-radiography community screening programme in an HIV-endemic South African setting, at 75% in a rural Tanzanian HIV clinic cohort where the great majority of coinfecting tuberculosis cases had neither symptoms nor suggestive radiographs, and as a sensitivity of 56.1% (95% CI 41.0–70.1) for asymptomatic prevalent tuberculosis among South African household contacts.^{4,18,13,34}

The subclinical tuberculosis literature contextualises this further. Across publicly available prevalence surveys conducted since 1990, between 36.1% and 79.7% of prevalent bacteriologically confirmed tuberculosis was subclinical, with a median of 50.4%, and chest radiography detected 89% of bacteriologically confirmed disease (range 73–98%) in that pooled analysis. The apparent discrepancy between that favourable figure and the far lower sensitivities reported in HIV-specific cohorts is instructive: prevalence surveys apply a permissive threshold of "any abnormality," whereas clinical radiographic reporting applies a specific threshold of "findings suggestive of active

tuberculosis". The safety margin therefore resides entirely in threshold selection, and any programme that permits a radiologist to write "no evidence of active tuberculosis" as a terminal statement in a person living with HIV has converted a screening instrument into a rule-out test that the evidence does not support.^{40,18}

Retiring the "Primary-Type" Terminology

One of the most conceptually significant contributions of the included evidence is the demonstration, using restriction fragment length polymorphism fingerprinting in 456 patients, that the time from acquisition of infection to development of clinical disease does not reliably predict the radiographic appearance of tuberculosis, and that HIV status — a surrogate for the integrity of the host immune response — is the only independent predictor of radiographic appearance. The univariable association between a clustered fingerprint, indicating recently transmitted infection, and a typical radiograph was lost entirely upon adjustment for HIV status. This directly falsifies the inference, implicit in four decades of radiological teaching, that a lower-zone, adenopathic, or effusive pattern indicates recent primary infection.⁹

The practical recommendation that follows is that radiological reports in HIV-coinfected patients should abandon the descriptors "primary pattern" and "post-primary pattern" in favour of immunologically neutral, morphologically explicit language: for example, "bilateral mid- and lower-zone consolidation with right paratracheal and subcarinal nodal enlargement, no cavitation identified; pattern consistent with tuberculosis in an immunocompromised host, and does not exclude active disease." Such reporting communicates the same information without importing an unsupported chronological inference, and it is more likely to be correctly acted upon by the referring clinician.^{9,45}

Repositioning Radiography within Screening Algorithms for People Living with HIV

The role of chest radiography in tuberculosis screening among people living with HIV has been the subject of substantial individual participant data synthesis, and the conclusions of that literature align closely with the primary evidence assembled here. The pooled sensitivity of the WHO four-symptom screening rule is markedly lower among people receiving antiretroviral therapy (51.0%, 95% CI 28.4–73.2) than among those who are ART-naïve (89.4%, 83.0–93.5), with pooled specificities of 70.7% and 28.1% respectively. Adding any abnormal chest radiographic finding in

people on ART improves sensitivity from 52.2% (95% CI 38.0–66.0) to 84.6% (69.7–92.9) at the cost of a fall in specificity from 55.5% to 29.8%. A larger individual participant data meta-analysis of 15,666 participants confirmed that a parallel strategy combining the four-symptom screen with any chest radiographic abnormality raises sensitivity to 89% (70–97) in ART-experienced outpatients, at a specificity of 33% (17–54), requiring 379 additional rapid diagnostic tests per 1,000 people screened but detecting 18 additional cases at a 5% prevalence.^{35,37}

The strategic implication is precise: in people living with HIV, chest radiography should be positioned in parallel with, not in series before, symptom screening and molecular testing. A serial architecture in which radiography gates access to Xpert MTB/RIF Ultra will systematically discard the substantial fraction of radiographically silent disease documented throughout this review. A parallel architecture, in which either an abnormal radiograph or any symptom triggers molecular testing, converts radiography from a liability into a genuine sensitivity gain. The evidence from prison screening in Malaysia adds an important nuance: among people with HIV specifically, symptom screening combined with C-reactive protein achieved a higher area under the curve (85.5%, 95% CI 79.4–91.5) than radiography-based strategies, whereas among people without HIV radiography was the superior adjunct (74.7%, 68.6–80.7). Non-radiographic host-response biomarkers may therefore have particular value precisely where radiography is weakest.^{25,37}

Computer-Aided Detection: Performance, Mechanism and the Calibration Imperative

The artificial-intelligence literature has advanced rapidly, and contemporary commercial products now meet or approach WHO target product profile thresholds for triage tests in mixed-HIV populations. Five commercial algorithms significantly outperformed registered radiologists in a Bangladeshi evaluation of 23,954 individuals, with areas under the curve ranging from 84.89% to 90.81%, and all five reduced the number of Xpert tests required by 50% while maintaining sensitivity above 90%. CAD4TB version 7 achieved a specificity of 68.2% at 90% sensitivity in a cohort with 48% HIV prevalence and detected tuberculosis as well as an expert radiologist.^{48,21}

This review nevertheless documents a specific and quantified HIV-related performance penalty that must inform deployment. Two of three products evaluated in individual participant data meta-analysis lost 13.4 absolute percentage points of sensitivity in people living with HIV, and all

twelve products evaluated in a South African prevalence survey subsample performed worst in people with HIV, older individuals, and those with previous tuberculosis. The mechanistic explanation is furnished directly by the morphological findings of this review: these algorithms were trained predominantly on datasets in which the radiographic signature of tuberculosis is apical cavitory opacity, and they are therefore being asked, in coinfecting patients, to detect a phenotype that is under-represented in their training distribution and whose most characteristic feature — hilar and mediastinal nodal enlargement — is among the most difficult abnormalities to detect on a projectional radiograph.^{38,22}

Three deployment requirements follow. First, threshold scores must be derived from the implementing population rather than adopted from the manufacturer, and must be separately calibrated by HIV and smear status, as the individual participant data meta-analysis explicitly concluded. Second, product selection must be evidence-based and version-specific, since thresholds varied notably across products and across different versions of the same product. Third, expectations of clinical benefit must be calibrated to the setting: in a cluster-randomised trial among hospitalised adults with HIV in Malawi, the increase in tuberculosis treatment initiation was attributable mainly to urine lipoarabinomannan testing rather than to digital chest radiography with computer-aided detection, and 56-day mortality was unchanged (26.1% versus 25.0%; hazard ratio 1.05, 95% CI 0.72–1.53). Conversely, in ambulatory primary care, digital radiography with computer-aided detection reduced median time to treatment from 11 days to 1 day (hazard ratio 2.86, 95% CI 1.04–7.87), with 40.0% of patients starting treatment the same day versus none under standard care. Computer-aided radiography is thus a powerful accelerator in the ambulatory setting and a marginal addition in the profoundly immunosuppressed inpatient, where antigen-based testing dominates.^{38,22,29,30}

Serial Radiography, Treatment Monitoring and Immune Reconstitution

The evidence assembled in outcome domain 12 constitutes the strongest case for retaining chest radiography in the routine management of coinfecting patients. Radiographic trajectory tracks immunological trajectory closely, with partial radiological response in 62% of patients accompanied by rising CD4 counts in 92% of responders, and radiological worsening in 53% of patients whose

CD4 counts fell. Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome, which occurs in an estimated 15.7% (95% CI 9.7–24.5) of patients with previously diagnosed tuberculosis starting antiretroviral therapy and in 18% (16–21%) in more recent estimates, is radiographically evident in 53.4% of validated episodes, with new or worsening lymphadenopathy in 77.4%.^{1,27,39,53}

Three clinical rules emerge. First, a deteriorating radiograph in the early weeks of combined therapy should raise the possibility of paradoxical immune reconstitution disease rather than treatment failure, particularly in patients starting antiretroviral therapy at low CD4 counts, in whom incidence reaches 45.5 per 100 person-years below $0.050 \times 10^9/L$. Second, drug-resistant disease must be excluded before attributing deterioration to immune reconstitution: in one series 20 of 35 patients with multidrug-resistant tuberculosis developed new effusions, adenopathy, or worsening infiltrates within two weeks of therapy, and it is explicitly recommended that drug-resistant tuberculosis and other causes of deterioration be investigated before administering glucocorticoids. Third, where paradoxical immune reconstitution disease is established, corticosteroid therapy produces significantly greater radiographic improvement than placebo at weeks 2 ($P = .002$) and 4 ($P = .02$), together with reduced hospitalisation and improved quality of life, and prednisone initiated alongside antiretroviral therapy in selected patients with CD4 counts below 100 cells/ μL reduces the risk of paradoxical immune reconstitution disease by approximately 30%.^{31,10,28,53}

Importantly, radiographic abnormality is not the only manifestation of respiratory immune reconstitution disease. In the PredART trial cohort of patients with HIV-associated tuberculosis and CD4 counts of 100 cells/ μL or below, abnormal spirometry was present in 66% at baseline and 50% at week 28, with low forced vital capacity the commonest abnormality, while chest radiographs showed little or no abnormality in the majority of participants. Radiographic normality in this population therefore does not exclude clinically significant pulmonary impairment, and lung function measurement may capture end-organ injury that projectional imaging misses entirely.⁵³

Prognostic Value and Post-Tuberculosis Lung Disease

Baseline radiographic severity retains prognostic value, but this value is attenuated once microbiological variables are entered into multivariable models, and it is attenuated further in the

non-cavitary phenotype that predominates in advanced HIV disease. In the South African MDR-TB cohort with 88% HIV coinfection, cavitation and consolidation lost their association with time to culture conversion after adjustment for smear status, while smear positivity retained an adjusted odds ratio of 3.45 (95% CI 1.39–8.59). Nevertheless, 79% of these patients were cured, an outcome that should temper prognostic pessimism when severe radiographic pathology is encountered in a profoundly immunosuppressed patient.¹²

A distinct and under-appreciated dimension of prognosis concerns post-tuberculosis lung disease. Chronic pulmonary aspergillosis complicates treated pulmonary tuberculosis with residual radiographic cavitation in 26% of affected patients versus 0.8% of those without cavitation ($P < .001$), with an annual rate of new development of 6.5% versus 0.2% ($P < .001$); the absence of cavitation and pleural thickening on chest radiography had 100% negative predictive value for chronic pulmonary aspergillosis. Because cavitation is less frequent in coinfecting patients, the risk of this specific complication may be correspondingly lower — a plausible interpretation of the observation that chronic pulmonary aspergillosis was possibly less frequent in HIV-coinfecting patients (3% versus 6.7%; $P = .177$) — but the wider burden of fibrotic and restrictive post-tuberculosis lung disease in this population remains inadequately characterised.⁵⁴

Differential Diagnosis: What Else Produces These Patterns in Coinfecting Patients

Every radiographic pattern documented in this review has an important differential diagnosis in people living with HIV, and the atypicality of tuberculous radiology in this population widens rather than narrows that differential. In a series of HIV-positive patients with abnormal chest radiographs and no pulmonary symptoms, in whom 86% had CD4 counts below 200 cells/ μ L, the most common diagnosis was tuberculosis (26%), followed closely by non-tuberculous mycobacterial infection (23%) and Kaposi sarcoma (12%); 62% of patients required an invasive modality to establish a diagnosis, and only 18% of tuberculosis cases were diagnosed by sputum analysis. Progressive disseminated histoplasmosis is a leading cause of morbidity and mortality among people with HIV in the Americas and overlaps extensively with tuberculosis: in a multicentre Mexican study, micronodular pulmonary infiltrates favoured histoplasmosis (adjusted prevalence odds ratio 1.94, 95% CI 1.06–3.62), whereas lymphadenopathy, tree-in-bud opacities, hepatomegaly and

splenomegaly were more common in tuberculosis, and tuberculosis coinfection was present in 12% of proven histoplasmosis cases.¹⁶

Chronic pulmonary histoplasmosis is also readily mistaken for tuberculosis, with cavitation and pulmonary nodules as its most common features, although pleural effusion, pleural thickening, intrathoracic lymphadenopathy and bronchiectasis are not characteristic. Non-tuberculous mycobacterial cavities differ from tuberculous cavities in being significantly thinner (6.9 ± 4 mm versus 10.9 ± 6 mm; $P < .001$) and more even in wall thickness, with adjacent pleural thickening the only independent discriminator on multivariate analysis (odds ratio 6.49; $P < .001$). None of these distinctions is reliable on plain radiography alone in an immunosuppressed patient, which reinforces the central conclusion of this review: radiographic pattern recognition must be subordinated to microbiological and antigen-based confirmation in this population.¹⁶

Implications for Practice in Indonesia and Comparable High-Burden Settings

Indonesia carries one of the largest absolute tuberculosis burdens in the world, and its HIV epidemic, while concentrated, is expanding within key populations in several provinces. Three implications of this review are directly actionable in that context. First, the widely used and internationally validated chest radiographic severity score was in fact derived and validated in Papua, Indonesia, and is therefore already culturally and operationally embedded; however, it has not been validated in predominantly HIV-infected populations with varying CD4 counts, and Indonesian investigators are unusually well placed to conduct that validation. Second, the parallel screening architecture supported by the individual participant data literature — in which either symptoms or any radiographic abnormality triggers Xpert MTB/RIF Ultra — is implementable within existing puskesmas and district hospital workflows without additional imaging capacity, requiring only a change in algorithm rather than in equipment. Third, as computer-aided detection is procured for national deployment, the calibration imperative documented here is not optional: thresholds must be derived from Indonesian data and separately calibrated for people living with HIV, and product selection must be version-specific.^{43,37,38,22}

Strengths of This Review

- Breadth of outcome architecture: fourteen prespecified domains spanning morphology, distribution, severity, bacteriological correlation, human and algorithmic diagnostic accuracy, longitudinal evolution, prognosis, and measurement reliability, exceeding the scope of any previous synthesis on this question.
- Design integration: deliberate inclusion of five randomised and cluster-randomised trials alongside 29 observational primary studies, permitting the domains of immune reconstitution and screening-strategy effectiveness to be addressed with randomised rather than merely descriptive evidence.^{27,28,29,30,31}
- Design-matched bias appraisal: four separate risk-of-bias instruments (RoB 2, Newcastle-Ottawa Scale, JBI cross-sectional checklist, and QUADAS-2) applied according to study architecture rather than a single tool applied inappropriately across heterogeneous designs.⁵
- Temporal stratification: explicit contrast between the pre-antiretroviral era foundational literature and contemporary ART-era programmatic data, permitting assessment of whether the classical findings survive translation into modern practice.^{1,15,18}
- Mechanistic integration: linkage of the observed morphological findings to the measured degradation in artificial-intelligence performance, providing an explanatory rather than merely empirical account of algorithmic underperformance in coinfecting populations.^{38,22}
- Verifiability: every included study is indexed, peer-reviewed, and individually retrievable through the reference list, with no reliance on unpublished or non-indexed sources.

Directions for Future Research

- Prospective validation of a standardised radiographic severity score, such as the percentage-of-lung-affected plus cavitation instrument, in predominantly HIV-infected cohorts stratified by CD4 count and antiretroviral therapy status, with prospective linkage to culture conversion, relapse, lung function, and survival endpoints.^{43,44}
- Development and prospective evaluation of computer-aided detection models trained or fine-tuned specifically on HIV-coinfecting populations, with mandatory reporting of HIV-stratified sensitivity and specificity and locally derived thresholds.^{17,38,22}

- Head-to-head comparison of parallel screening architectures — symptom screen plus radiography, symptom screen plus C-reactive protein, symptom screen plus computer-aided detection, and universal molecular testing — with cost-effectiveness and mortality rather than case-detection endpoints.^{25,29,30,37}
- Systematic characterisation of the differential diagnosis of adenopathic and micronodular radiographic patterns in people living with HIV using contemporary antigen-based fungal and mycobacterial diagnostics, in order to convert a currently non-specific radiographic sign into an actionable one.¹⁶
- Longitudinal imaging and physiological cohorts of post-tuberculosis lung disease in coinfecting survivors, integrating radiography, spirometry, and cross-sectional imaging, to quantify the burden of chronic impairment that projectional imaging currently fails to capture.^{53,54}
- Prospective multicentre Indonesian and South-East Asian cohorts applying a standardised radiographic lexicon with mandatory CD4 and antiretroviral therapy stratification, to address the geographical evidence gap identified in this review.^{25,43}

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review of 34 primary studies, including five randomised or cluster-randomised trials, establishes that the contemporary chest radiographic manifestation of pulmonary tuberculosis in HIV/AIDS coinfection is systematically, significantly, and immunologically coherently displaced from the classical post-primary template, and that the magnitude of this displacement is proportional to the depth of CD4+ lymphocyte depletion. Cavitation and localised consolidation, the radiographic products of a competent necrotising granulomatous response, become significantly less frequent as immunity fails; intrathoracic lymphadenopathy and miliary dissemination, the radiographic products of failed containment, become significantly more frequent; and in a substantial minority of bacteriologically confirmed cases the radiograph is entirely normal or shows no findings suggestive of active disease. Molecular epidemiological evidence establishes that this shift is attributable to altered host immunity rather than to recent acquisition of infection,

which retires the conventional "primary-type" interpretation and replaces it with an immunological one.^{1,2,7,9,20}

The clinical consequence of this phenotypic shift is a measurable and reproducible degradation in the diagnostic performance of both expert human interpretation and commercial artificial-intelligence software, amounting to a quantified 13.4 absolute percentage points of sensitivity for two of three evaluated algorithms and to a complete loss of discriminating power for human readers in HIV-infected patients with smear-negative disease. Chest radiography must therefore be explicitly repositioned in this population: it remains indispensable as a triage instrument at population scale, as a severity and extent measure, as a serial monitoring tool that tracks immunological recovery, as the principal objective substrate for the recognition of paradoxical immune reconstitution disease, and as a contributor of independent prognostic information; but it must be abandoned as a rule-out test. In a person living with HIV who is being investigated for tuberculosis, a normal chest radiograph is a finding to be documented, not a diagnosis to be relied upon.^{14,38,27,28}

All seven prespecified directional hypotheses were confirmed at conventional levels of statistical significance in independent, adequately powered primary datasets, and the direction of effect was consistent across four decades, three continents, and both pre-antiretroviral and contemporary treatment eras. The certainty of evidence was rated high for the domains of computer-aided detection performance and radiographic evolution during immune reconstitution, moderate for the core morphological and distributional domains, and low for severity scoring, prognosis, pleural involvement, miliary prevalence, and inter-observer reliability.⁵

Recommendations

Recommendations for clinical practice

- Every person living with HIV who is investigated for tuberculosis should proceed to a WHO-recommended rapid molecular diagnostic test irrespective of chest radiographic appearance. Radiography must not gate access to microbiological testing in this population.^{14,37}
- Radiological reports in HIV-coinfected patients should state the CD4 stratum where known, describe morphology in explicit and immunologically neutral terms, avoid the descriptors

"primary pattern" and "post-primary pattern", and must not conclude with the phrase "no evidence of active tuberculosis".^{9,4}

- Airborne infection control decisions must be based on microbiological status and clinical suspicion, never on the presence or absence of cavitation, since coinfecting patients are equally infectious across radiographic phenotypes and occult culture-positive pulmonary involvement is more than fivefold more common in HIV coinfection.^{5,58}
- Intrathoracic lymphadenopathy identified in a coinfecting patient should prompt tissue or antigen sampling rather than further imaging characterisation, given the breadth of the differential including non-tuberculous mycobacteria, histoplasmosis, lymphoma, and Kaposi sarcoma.¹⁶
- Radiographic deterioration during the first weeks of combined antituberculous and antiretroviral therapy should trigger evaluation for paradoxical immune reconstitution disease and for drug resistance before treatment failure is assumed; corticosteroid therapy should be considered only after drug-resistant disease and alternative causes have been excluded.^{27,28,10}
- Serial chest radiography should be retained as a routine monitoring instrument in coinfecting patients, since radiographic trajectory closely parallels immunological trajectory and radiological worsening accompanies falling CD4 counts in the majority of cases.¹

Recommendations for programmes and health systems

- National tuberculosis and HIV programmes should adopt a parallel rather than serial screening architecture for people living with HIV, in which either any symptom or any radiographic abnormality triggers molecular testing, accepting the specificity cost in exchange for the substantial sensitivity gain in ART-experienced outpatients.^{35,37}
- Where computer-aided detection is procured, abnormality-score thresholds must be derived from the implementing population and separately calibrated by HIV serostatus and smear status; manufacturer default thresholds should not be adopted unmodified, and product selection must be version-specific.^{38,22}
- Programmes serving profoundly immunosuppressed inpatients should prioritise urine lipoarabinomannan and molecular testing over radiographic investment, since the incremental

yield of digital radiography with computer-aided detection in that setting has been shown to be marginal; conversely, ambulatory primary care programmes should prioritise digital radiography with computer-aided detection, which dramatically shortens time to treatment initiation.^{29,30}

- Structured, templated radiographic reporting with defined feature lists and, where feasible, dual reading with adjudication, should replace unstructured free-text reporting for programmatic tuberculosis decision-making.^{11,50}
- Radiology and pulmonology training curricula in high-burden settings should explicitly teach the coinfecting radiographic phenotype as a distinct entity with its own prevalence expectations, rather than as a set of exceptions to the immunocompetent template.^{3,6,9}

Recommendations for research

- Validate a standardised radiographic severity score prospectively in predominantly HIV-infected cohorts stratified by CD4 count and antiretroviral therapy status, with linkage to microbiological, functional, and survival endpoints.^{43,44}
- Develop and prospectively evaluate computer-aided detection models trained or fine-tuned on HIV-coinfected populations, with mandatory HIV-stratified performance reporting.^{17,38}
- Establish prospective multicentre cohorts in Indonesia and South-East Asia applying a standardised radiographic lexicon, in order to address the geographical concentration of contemporary evidence in sub-Saharan Africa.^{25,43}
- Report formal inter-observer reliability statistics (kappa or intraclass correlation coefficients) for every radiographic feature in future primary studies of coinfecting populations, to strengthen the currently weakest domain of this evidence base.^{50,55}

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