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MAJOR ARTICLE

# Prevalence, Clinical Features, and Predictors of Adrenal Insufficiency in Adults With Tuberculosis or HIV: A Systematic Review and Meta-analysis

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***Background.*** Despite the high frequency of adrenal insufficiency (AI) in patients with tuberculosis or HIV, its diagnosis is often missed or delayed resulting in increased mortality. This systematic review and meta-analysis aimed to document the prevalence, significant clinical features, and predictors of AI in adult patients with tuberculosis or HIV.

***Methods.*** We systematically searched databases (Medline, Embase, CINAHL, Cochrane Library, and Africa Journal Online) for published studies on AI in adult patients with tuberculosis or HIV. The pooled prevalence of AI was determined by a random-effect model meta-analysis. A narrative review was used to describe the significant clinical features and predictors of AI in adult patients with tuberculosis or HIV.

***Results.*** A total of 46 studies involving 4044 adults were included: 1599 with tuberculosis and 2445 with HIV. The pooled prevalence of AI was 33% (95% CI, 22%–45%; $I^2 = 97.7\%$, $P < .001$) in participants with tuberculosis and 28% (95% CI, 18%–38%; $I^2 = 98.9\%$, $P < .001$) in those with HIV. Presentation with multidrug-resistant tuberculosis, abdominal pain, salt craving, myalgia, increased severity and duration of tuberculosis disease, and the absence of nausea predicted AI in participants with tuberculosis in 4 studies. Cytomegalovirus antigenemia positivity, rifampicin therapy, and eosinophilia >3% predicted AI in participants with HIV in 2 studies.

***Conclusions.*** AI is relatively common in adults with tuberculosis or HIV. Its timely screening, diagnosis, and management in patients with these 2 conditions should be encouraged to avert mortality.

**Keywords.** adrenal insufficiency; clinical features and predictors; HIV; prevalence; tuberculosis.

Adrenal insufficiency (AI) is a potentially life-threatening endocrine disorder characterized by the inability of the adrenal cortex to secrete adequate concentrations of glucocorticoids and/or mineralocorticoids, which play a fundamental role in glucose, salt, and fluid homeostasis, as well as stress adaptation and immune response [1, 2]. Biochemically, a diagnosis of AI is based on the presence of a low early-morning or stimulated serum cortisol concentration in the presence of elevated adrenocorticotrophic hormone (ACTH) concentrations [1].

Diagnosing AI in patients who are critically ill with tuberculosis (TB) or HIV poses a significant clinical challenge because it presents with nonspecific and subtle signs and symptoms, such as fatigue, weight loss, abdominal pain, nausea, vomiting, and myalgias, which often overlap with those of TB or HIV [1, 2]. Because of this overlap in the clinical presentation, the diagnosis is frequently missed or delayed resulting in increased mortality, especially in cases of clinical presentation with an acute adrenal crisis. Mucosal and skin hyperpigmentation, orthostatic hypotension, salt craving, hyponatremia, hyperkalemia, and metabolic alkalosis are additional clinical features associated with AI [2].

Persons with TB or HIV are prone to developing AI because of the direct and indirect effects of both conditions on the adrenal glands. The risk increases greatly in cases of advanced disease (low CD4 count, high HIV viral load, and disseminated TB disease) [3–6]. Both conditions directly damage the adrenal gland resulting in hormonal deficiencies. Additionally, the effect of drugs (notably rifampicin and ketoconazole), coinfections such as cytomegalovirus (CMV) infection, disseminated cryptococcosis, toxoplasmosis, and neoplasms such as Kaposi

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sarcoma further contribute to reduced adrenocortical function in patients with TB or HIV [3, 5].

Because TB and HIV continue to pose significant public health challenges globally, especially in low- and middle-income countries in Asia and sub-Saharan Africa, understanding the prevalence, associated clinical features, and predictors of TB- or HIV-related AI is important for clinicians who regularly treat patients with TB or HIV. This will influence timely screening, diagnosis, and initiation of optimal management of AI, hence reducing mortality associated with the condition.

This systematic review and meta-analysis aimed to document the prevalence, significant clinical features, and predictors of AI in adult patients with TB or HIV to provide contemporary information on the frequency and characterization of this endocrine disorder in adults with these 2 medical conditions.

## METHODS

The systematic review and meta-analysis were conducted according to the criteria outlined in the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [7]. The PRISMA checklist is available as Supplementary Table 1. The study protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42023445672). No amendments were made on the protocol from its time of registration.

### Search Strategy

With the help of an experienced librarian (B. M.), we searched Embase, Medline, CINAHL, African Journals Online, and Google Scholar for studies on AI in adult patients with TB or HIV published from 1946 to July 2023.

The following search terms were used:

"adrenal insufficiency" OR "hypoadrenalism" OR "hypocortisolism" OR "Addison's disease" AND "tuberculosis" OR "TB" OR "active TB disease" OR "TB disease" OR "pulmonary TB" OR "extra-pulmonary tuberculosis" OR "extra-pulmonary TB" OR AND "HIV infection" OR "HIV" OR "human immunodeficiency virus" OR "AIDS" AND "Africa" OR "sub-Saharan Africa" OR "SSA" OR "Europe" OR "Western Europe" OR "Eastern Europe" OR "Central Europe" OR "Northern Europe" OR "Southern Europe" OR "Asia" OR "Southeast Asia" OR "South Asia" OR "East Asia" OR "Central Asia" OR "Western Asia" OR "Northeast Asia" OR "North America" OR "South America" OR "Oceania" OR "Australia."

In addition to the database searches, reference and citation checking of key articles and reviews was performed.

### Study Selection Criteria

The preliminary screening of titles and abstracts to identify potentially eligible articles was done independently by 4 reviewers (D. K., N. O., A. P. K., and F. B.). Duplicates were removed, and full texts of the potentially eligible studies were retrieved and extensively reviewed for the information of interest.

The inclusion criteria of studies were as follows: cross-sectional, retrospective, case-control, and cohort studies in addition to conference proceedings, poster presentations, and research theses published in the English language and reporting of any information on the prevalence, associated factors, and predictors of AI in adult patients with TB or HIV. The population of interest was adults with TB or HIV.

In cases of any disagreements, an independent reviewer (I. A.-B.) was consulted. We excluded review articles, case reports, and series; studies published in languages other than English; and studies whose full texts could not be retrieved.

### Data Extraction

After selection of the eligible studies, 1 author (D. K.) extracted the relevant study information of interest using a Microsoft Excel 2016 form: last name of the first author and year of publication, country and continent where the study was performed (Africa, Asia, Europe, North America, and South America), study design, number of participants, population (participants with HIV or TB), number and proportion of female participants, mean (SD) age, body mass index (BMI), mean or median duration of HIV, CD4 count, related comorbidities, method used to diagnose AI (early-morning or stimulated serum cortisol levels), dose of synthetic ACTH or Synacthen if the stimulated method was used, and prevalence of AI, as well as the significant signs, symptoms, and predictors of AI.

### Assessment of the Quality and Publication Bias of Studies

The quality of all eligible studies in the systematic review was assessed with the modified Newcastle-Ottawa Scale (NOS) [8]. This was done independently by 1 author (A. P. K.).

### Study Outcomes

The study outcomes were the prevalence, significant signs and symptoms, and predictors of AI.

### Data Analysis

All analyses were performed by Stata version 16.0 (Stata Corp). Results were reported in line with the PRISMA 2000 guidelines. Descriptive data of all eligible studies were summarized by mean (SD) or median (IQR) for continuous variables and by random-effect pooled raw proportions via the restricted maximum likelihood method for categorical variables. The pooled prevalence of AI as determined by each diagnostic approach was calculated via a random-effect model meta-analysis and presented in the form of forest plots.

The heterogeneity of the studies was assessed by $I^2$ values. Based on the Cochrane Collaboration guide, $I^2$ values were categorized as follows: 0% to 40%, not important; 30% to 60%, moderate levels of heterogeneity; 50% to 90%, substantial; and 75% to 100%, considerable [9]. To evaluate for potential sources of heterogeneity across studies, we conducted a meta-regression with mean age, sex, body mass index, CD4 count, duration since HIV diagnosis, year of publication, and location (by continent).

We assessed the presence of publication bias using the Egger test, with $P < .05$ indicating significant publication bias [10]. Publication bias was further visualized by contour-enhanced funnel plots for assessment of asymmetry. We conducted non-parametric trim-and-fill analysis for studies that had shown evidence of publication bias. Simple descriptive statistics were used to describe the significant signs, symptoms, and predictors of AI. Information about the studies is summarized in tables.

#### Ethical Approval

Because this was a systematic review of published studies, no prior ethical approval was required.

## RESULTS

Figure 1 summarizes the article selection in a PRISMA flow diagram.

The literature search returned 1017 articles. From these, 263 duplicates were removed. We reviewed the titles and abstracts of the remaining 754 articles, and 378 were identified for full-text retrieval. Of these, 333 were excluded, and the remaining 45 articles were included in the systematic review and meta-analysis. On hand-searching the references of the retrieved full texts, 3 published research theses were identified and added. However, during the data extraction process, we identified that 1 article had been published twice with similar content but a different title. This was excluded for a total of 47 articles in the systematic review and meta-analysis.

The 333 articles were excluded because of being case reports and series (n = 221), lacking information of interest (n = 36), being review articles (n = 39), not being published in the English language (n = 15), being systematic reviews (n = 2), and having unretrievable full text (n = 20).

#### Characteristics of Studies

Tables 1 and 2 summarize the characteristics of the studies.

Of the 47 studies in this systematic review and meta-analysis, 21 (44.7%) were conducted in patients with TB [11–31] and 26 (55.3%) in patients with HIV [32–57]. The majority of the studies on AI in patients with TB were conducted in Africa (n = 10, 47.6%) [11, 13–20, 48] and Asia (n = 8, 38.1%) [21–28]. The remaining 3 studies (14.3%) were conducted in Europe [29], South America [30], and North America [31].

Of the studies on AI in patients with HIV, 10 were conducted in Asia [32–41], 6 in North America [42–47], 5 in Africa [48–52], 3 in Europe [53–55], and 2 in South America [56, 57].

Twelve studies (25.5%) reported information on TB and HIV coinfection among the study participants [11, 13, 14, 17, 18, 38, 39, 41, 49–51, 57].

Most studies were cross-sectional in design (n = 38, 80.9%). Three articles were published research theses [12, 18, 50]. Considerable heterogeneity was noted in the analysis of studies of individuals with TB ($I^2 = 97.7\%$) and HIV ($I^2 = 98.9\%$).

#### Characteristics of Study Participants

Supplementary Table 1 and Tables 1 and 2 summarize the characteristics of all participants and findings of studies in the systematic review and meta-analysis.

The studies had 4044 adult participants: 1599 with TB and 2445 with HIV. Considering participants with TB, the cumulative mean ± SD age, BMI, and basal serum cortisol level were 36.4 ± 3.2 years, 19.6 ± 2.5 kg/m$^2$, and 451.3 ± 110.6 nmol/L, with 43.7% (95% CI, 37.3%–50.2%) being female. The pooled prevalence of HIV coinfection in participants with TB was 63.8% (95% CI, 48.5%–79.1%).

Considering participants with HIV, the cumulative mean ± SD age, BMI, CD4 count, and basal serum cortisol level were 36.4 ± 3.2 years, 20.1 ± 4.0 kg/m$^2$, 222.6 ± 175.0 cells/mm$^3$, and 566.7 ± 255.3 nmol/L, with 34.6% (95% CI, 23.7%–45.5%) being female (Supplementary Table 2).

#### Diagnostic Method and Definition of AI in Participants With TB or HIV

The majority of studies used an intravenous or intramuscular synthetic ACTH or Synacthen stimulation test with measurement of poststimulation serum or salivary cortisol levels as the method to diagnose AI (38/46, 82.6%) [11–16, 18–28, 30, 32–35, 38, 39, 42–46, 48, 50, 52–57]. The remaining studies used early-morning serum cortisol measurement as a basis for diagnosing AI (n = 8, 17.4%) [17, 31, 36, 37, 40, 47, 49, 51]. The approach to diagnose AI was not specified in 1 study [29].

Of the studies that used the Synacthen stimulation test, 14 (36.8%) utilized a low dose of Synacthen (1 μg) [14, 15, 18, 19, 26, 30, 35, 39, 46, 48, 50, 52, 56, 57]. In a study conducted in Argentina among 21 participants with HIV, AI was diagnosed by the presence of low poststimulation salivary cortisol and aldosterone levels following intramuscular administration of a low dose of Synacthen (25 μg) [56].

#### Prevalence of AI in Participants With TB

The pooled prevalence of AI in adult participants with TB was 33% (95% CI, 22%–45%; $I^2 = 97.7\%$, $P < .001$; Figure 2). The highest pooled prevalence was reported by studies conducted in Asia (40%; 95% CI, 21%–58%; $I^2 = 95.9\%$) and Africa (26%; 95% CI, 12%–40%; $I^2 = 97.6\%$; Supplementary Figure 1).

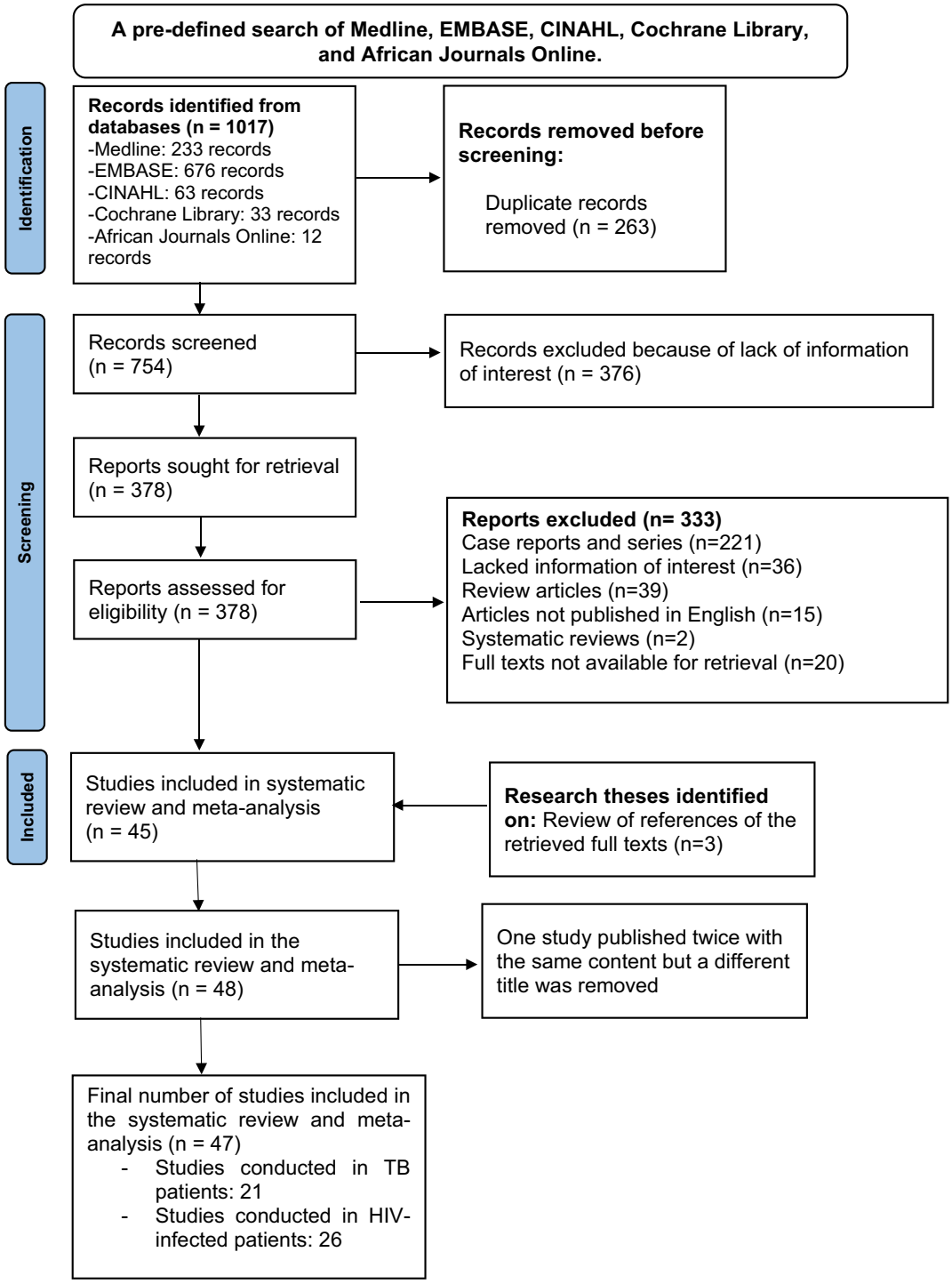


**Figure 1.** PRISMA flow diagram of selection of eligible studies. TB, tuberculosis.

#### Prevalence of AI in Participants With HIV

The pooled prevalence of AI in adult participants with HIV was 28% (95% CI, 18%–38%; $I^2 = 98.9\%$, $P < .001$; Figure 3). Studies conducted in Africa reported the highest pooled prevalence of AI in participants with HIV (38%; 95% CI, 10%–67%; $I^2 = 98.9\%$, $P < .001$), followed by those conducted in Asia (29%; 95% CI, 13%–45%; $I^2 = 97.9\%$, $P < .001$), South America (26%; 95% CI, 8%–44%; $I^2 = 62.3\%$, $P < .001$), North America (21%; 95% CI, 4%–47%; $I^2 = 93.1\%$, $P < .001$), and Europe (12%; 95% CI, 3%–20%; $I^2 = 79.2\%$, $P < .001$; Supplementary Figure 2).

A pooled prevalence of 29% (95% CI, 13%–46%; $I^2 = 98.8\%$, $P < .001$) was noted in the 12 studies that reported information

**Table 1. Studies on Adrenal Insufficiency in Adult Patients With Tuberculosis**

| First Author (Year), Country | Study Design | No. and Characteristics of the Participants [a] | Method and Diagnostic Criteria of AI | Prevalence of AI, % | Significant Associated Factors and Predictors of AI |
|---|---|---|---|---|---|
| **Africa (n = 10)** | | | | | |
| Beadsworth (2008) [11], Malawi | Cross-sectional | • 51 with recently confirmed TB<br>• 29 women, 56.9%<br>• Mean age, 32 y (18–62)<br>• HIV coinfection, 88.3% (38% in World Health Organization stage IV) | • Intravenous 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <550 nmol/L | 3.9 | |
| Broodryk (2010) [12], South Africa | Cross-sectional | • 73 with smear-positive or culture confirmed TB<br>• 49 women, 67.1%<br>• Mean age, 38 y (20–91) | • Intramuscular 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <500 nmol/L | 6.9 | |
| Hawken (1996) [13], Kenya | Cross-sectional | • 174 with confirmed PTB and EPTB<br>• 84 women, 48.3%<br>• Mean age, 28 y (16–89)<br>• HIV comorbidity, 51.7%<br>• Mean basal cortisol, 601 nmol/L (56–1700) and 649 nmol/L (56–1711) in those with and without HIV, respectively | • Intravenous 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation increment in the serum cortisol level <195 nmol/L | 52.3 | |
| Kaplan (2000) [14], South Africa | Cross-sectional | • 40 with newly diagnosed smear-positive PTB<br>• 24 women (60%)<br>• Mean age, 39.7 y (18–79)<br>• Mean BMI, 19.4 kg/m$^2$ (13.3–28.8)<br>• HIV coinfection, 45%<br>• Mean CD4 count of the participants with HIV, 192 cells/mm$^3$<br>• Mean basal cortisol level, 559 nmol/L | • Intravenous 1-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <414 nmol/L | 2.5 | |
| Mabuza (2020) [15], South Africa | Cross-sectional | • 75 with features of TB<br>• 32 women, 43.1%<br>• Mean age, 40.3 ± 15.7 y<br>• Median basal serum cortisol: 398.0 nmol/L (255–509) | • Intravenous 1-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <500 nmol/L | 37.3 | Significant associated factors: loss of libido |
| Mugusi (1990) [16], Tanzania | Cross-sectional | • 50 with smear-positive and radiologically confirmed TB<br>• 16 women, 32%<br>• Mean age, 26 y (19–70)<br>• Median BMI: 16.6 kg/m$^2$ (11.7–22.1)<br>• Mean basal serum cortisol levels, 453 nmol/L (107–1884) | • Intravenous 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <600 nmol/L or if increment in plasma cortisol <300 nmol/L | 32.0 | Significant associated factors: lower mean supine and erect diastolic blood pressure |
| Naggirinya (2020) [17], Uganda | Cross-sectional | • 272 hospitalized with drug-susceptible TB (57%) and drug-resistant TB (43%)<br>• Median age: 32 years (18–66)<br>• 92 women, 33.8%<br>• HIV coinfection: 57% | • AI diagnosed if early-morning serum cortisol <414 nmol/L | 59.8 | Predictors: drug-resistant TB, abdominal pain, and, paradoxically, mucosal and skin hyperpigmentation associated with reduced odds of AI |
| Namuleme (2009) [18], Uganda | Cross-sectional | • 200 with newly diagnosed sputum-positive PTB<br>• 102 women, 51%<br>• Mean age, 32 y<br>• HIV coinfection, 75% | • Intravenous 1-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 μg/dL | 12.0 | Predictors: abdominal pain, salt craving, myalgia, and, paradoxically, absence of nausea |
| Odeniyi (2017) [19], Nigeria | Cross-sectional | • 44 with smear-positive PTB | • Intravenous 1-μg ACTH (Synacthen) stimulation test | 31.8 | |

**Table 1. Continued**

| First Author (Year), Country | Study Design | No. and Characteristics of the Participants [a] | Method and Diagnostic Criteria of AI | Prevalence of AI, % | Significant Associated Factors and Predictors of AI |
|---|---|---|---|---|---|
| | | • Mean age, 34.39 ± 11.27 y<br>• Mean BMI, 18.89 ± 2.91 kg/m$^2$<br>• Mean basal cortisol, 263.04 ± 122.96 nmol/L | • AI diagnosed if poststimulation peak serum cortisol levels <380.2 nmol/L and increment from basal to stimulated cortisol level <158.5 nmol/L | | |
| Post (1994) [20], South Africa | Cross-sectional | • 50 with newly diagnosed sputum-positive TB<br>• 9 women, 18%<br>• Mean age, 38 y (18–68)<br>• Mean BMI, 18 kg/m$^2$ (11–32)<br>• Mean basal serum cortisol, 625 nmol/L (394–1185) | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <550 nmol/L | 0 | |
| **Asia and Oceania (n = 8)** | | | | | |
| Barnes (1989) [21], Papua New Guinea | Cross-sectional | • 90 with PTB, miliary TB, and EPTB | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation serum cortisol level increment <200 nmol/L above the basal serum cortisol level | 17.8 | |
| Chan (1993) [22], Hong Kong | Cross-sectional | • 39 with active PTB (87.2%) and EPTB (12.8%)<br>• 10 women, 25.6%<br>• Mean age, 68 y (51–86) | • Intramuscular 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation serum cortisol rise is <200 nmol/L above the basal level | 41.0 | |
| Keleştimur (1994) [23], Turkey | Case-control | • 20 with active TB disease (group 1) and 41 with chronic TB disease (group 2)<br>• Mean age, 39 ± 19 y (group 1) and 44 ± 13 y (group 2)<br>• 16 women, 26.2% | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <550 nmol/L | 4.9 | |
| Laway (2013) [24], India | Case-control | • 45 with sputum-positive active PTB<br>• 17 women, 37.8%<br>• Mean age, 42.4 ± 20.4 y<br>• Mean BMI, 21.0 ± 1.1 kg/m$^2$<br>• Mean basal serum cortisol, 413.57 ± 108.42 nmol/L | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation serum cortisol level <496 nmol/L | 0 | |
| Neogi (2021) [25], India | Cross-sectional | • 84 with smear-positive and negative TB<br>• 28 women, 33.3%<br>• Mean age, 39.7 ± 16.7 y<br>• Mean BMI, 19.3 ± 1.91 kg/m$^2$ | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 µg/dL, an increment in cortisol ≤9 mg/dL, or basal serum cortisol <5 µg/dL with elevated ACTH >46 pg/mL | 58.3 | Predictors: radiologic severity of TB and increased duration of TB had a negative correlation with serum cortisol |
| Sarin (2017) [26], India | Cross-sectional | • 100 with active TB<br>• 54 women, 54%<br>• Age ranges, 14–80 y | • Intravenous 1-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation serum cortisol level increment <200 nmol/L above the basal serum cortisol level or poststimulation serum cortisol levels <500 nmol/L | 76.0 | Significant associated factors: more females with EPTB presented with AI |
| Tyagi (2007) [27], India | Case-control | • 17 with spinal TB | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation | 47.1 | |

**Table 1. Continued**

| First Author (Year), Country | Study Design | No. and Characteristics of the Participants [a] | Method and Diagnostic Criteria of AI | Prevalence of AI, % | Significant Associated Factors and Predictors of AI |
|---|---|---|---|---|---|
| | | | peak serum cortisol levels <20 μg/mL | | |
| Zargar (2001) [28], Pakistan | Case-control | • 40 with PTB (70%) and EPTB (30%)<br>• 18 women, 45%<br>• Mean age, 35.68 ± 5.71 y<br>• Mean basal serum cortisol, 421.19 ± 149.75 nmol/L | • Intramuscular 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation serum cortisol rise is <200 nmol/L above the basal level | 35.0 | Predictors: radiologic severity of TB and increased duration of TB had a negative correlation with serum cortisol |
| **Europe (n = 1)** | | | | | |
| Lindh (2023) [29], Sweden | Case-control | • 8 with adrenal TB<br>• 3 women, 37%<br>• Median age: 72.5 y (20–89) | | 88.0 | |
| **South America (n = 1)** | | | | | |
| Rodríguez-Gutiérrez (2016) [30], Mexico | Cross-sectional | • 48 with MDR-TB and HIV negative<br>• 19 women, 39.6%<br>• Mean age, 38.5 ± 12.5 y<br>• Mean BMI, 23.6 ± 5.9 kg/m$^2$<br>• Mean basal serum cortisol, 464.1 ± 211.2 nmol/L | • Intravenous 1-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <550 nmol/L | 8.3 | Significant associated factors: weight loss, arthralgia, and myalgia |
| **North America (n = 1)** | | | | | |
| York (1992) [31], Canada | Cross-sectional | • 38 participants<br>• 14 women, 36.8%<br>• Mean age ranges, 52–60 y | • Early-morning and afternoon serum cortisol levels<br>• AI confirmed if the early-morning and afternoon serum cortisol levels <100 and <30 nmol/L, respectively | 0 | |

Abbreviations: ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; BMI, body mass index; EPTB, extrapulmonary tuberculosis; MDR, multi-drug resistant; PTB, pulmonary tuberculosis; TB, tuberculosis.

[a]Mean data are presented as mean ± SD (range). Median data are presented as median (IQR).

on TB and HIV coinfection in the study participants (Supplementary Figure 3). Six studies reported no evidence of AI in participants with TB or HIV [20, 24, 31, 42, 43, 45].

#### Significant Clinical Features and Predictors of AI in Participants With TB

Information on the significant clinical features and predictors associated with AI in the participants with TB was reported by 8 studies [15–18, 25, 26, 28, 30]. AI in these participants was significantly associated with loss of libido [15], lower mean supine and erect diastolic blood pressure [16], and nonspecific symptoms (eg, weight loss, arthralgia, and myalgia) [30]. In a study by Sarin et al, AI was more common in females presenting with extrapulmonary TB [26].

Regarding the predictors of AI, presentation with multidrug-resistant TB, abdominal pain, salt craving, myalgia, and the absence of nausea independently predicted AI in 2 adult Ugandan populations with TB [17, 18]. Paradoxically, 1 of these studies reported reduced odds of AI in the presence of mucosal and skin hyperpigmentation [17]. Two studies reported a negative correlation between serum cortisol concentrations and (1) increased radiologic severity of TB and (2) duration of TB [25, 28].

#### Significant Clinical Features and Predictors of AI in Participants With HIV

Seven studies reported information on significant clinical features and related independent predictors in participants with HIV [32–34, 38, 44, 51, 54]. In these participants, AI was significantly associated with CMV antigenemia positivity [33, 34], metabolic derangements (hypoglycemia and hyperkalemia) [38], rifampicin use, World Health Organization HIV stage IV, and eosinophilia >3% on a full blood count [51]. Two studies reported a significant association with nonspecific symptoms of fatigue, weakness, and weight loss [32, 54].

Rifampicin therapy, CMV antigenemia positivity, and eosinophilia >3% on a full blood count independently predicted AI in 2 studies [44, 51].

#### Assessment of Study Quality and Publication Bias

Assessment of the quality of studies and funnel plots evaluating publication bias are summarized in Supplementary Tables 3 to 8 and Supplementary Figures 4 and 5, respectively.

**Table 2. Studies on Adrenal Insufficiency in Adult Patients With HIV Infection**

| First Author (Year), Country | Study Design | No. and Characteristics of the Participants [a] | Method and Diagnostic Criteria of AI | Prevalence of AI, % | Significant Associated Factors and Predictors of AI |
|---|---|---|---|---|---|
| **Asia (n = 10)** | | | | | |
| Afreen (2017) [32], Pakistan | Cross-sectional | • 64 with HIV<br>• 10 women, 15.6%<br>• Mean duration of HIV, 4.23 ± 2.46 y<br>• Mean CD4 count, 507.16 ± 282.78 cells/$mm^3$<br>• Mean basal serum cortisol, 21.99 ± 4.89 µg/dL | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 µg/dL | 14.1 | Significant associated factors: fatigue and weight loss |
| Hoshino (1997) [33], Japan | Cross-sectional | • 30 with HIV<br>• 3 women, 10%<br>• Mean age, 30 y (12–56)<br>• Mean CD4 count, $8 \times 10^6$ cells/L<br>• Comorbidities: CMV retinitis (46.7%) | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 µg/dL (500 nmol/L) and <7 µg/mL (200 nmol/L) increment in serum cortisol | 36.7 | Significant associated factor: CMV antigenemia positivity |
| Hoshino Y et al 2002) [34], Japan | Cross-sectional | • 60 with HIV with advanced disease<br>• 3 women, 5%<br>• Mean age, 30 y (12–56 y)<br>• Mean CD4 count, 10.5 cells/$mm^3$ (0.1–48)<br>• Comorbidities: CMV infection (63.3%) | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 µg/dL (500 nmol/L) | 26.7 | Significant associated factor: CMV antigenemia positivity |
| Madi (2012) [35], India | Cross-sectional | • 50 with HIV<br>• Mean CD4 count, 138.7 ± 56.17 and 171.87 ± 25.41 cells/$mm^3$ in those with and without AI, respectively | • Intravenous 1-µg ACTH (Synacthen) stimulation test | 74.0 | |
| Meena (2011) [36], India | Cross-sectional | • 150 males with HIV<br>• Mean age, 35.81 ± 8.85 y<br>• Mean BMI, 17.38 ± 2.85 kg/$m^2$<br>• Mean basal serum cortisol, 25.04 ± 14.8, 22.55 ± 10.78, and 16.59 ± 9.00 µg/dL in with CD4 < 200, 200–350, and >350 cells/$mm^3$, respectively | Early-morning basal serum cortisol level <5 µg/mL | 2.7 | |
| Sanjay (2013) [37], India | Cross-sectional | • 48 male with HIV<br>• Mean age, 35 ± 6.9 y (26–50)<br>• CD4 count: 43–189 cells/$mm^3$ (CD4 count <100 cells: 50%) | Early-morning serum cortisol level <10 µg/mL | 8.3 | |
| Sharma (2018) [38], India | Cross-sectional | • 359 with HIV<br>• Mean age, 35 and 38 y in those with and without AI, respectively<br>• Mean duration of HIV, 61.44 ± 39.42 m<br>• CD4 count <200 cells/$mm^3$: 9.8%<br>• Comorbidities: TB (40.4%) | • Intravenous 250-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 µg/dL (500 nmol/L) | 24.2 | Significant associated factors: hypoglycemia and hyperkalemia |
| Shashidhar (2012) [39], India | Cross-sectional | • 50 with HIV<br>• 12 women, 24%<br>• Mean age, 37.86 ± 7.91 y (20–60)<br>• Mean BMI, 19.32 ± 3.13 kg/$m^2$<br>• Mean CD4 count, 144 ± 49.78 cells/$mm^3$<br>• Comorbidities: TB (30%), PCP (28%), cryptococcosis (8%), and CMV (6%) | • Intravenous 1-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 µg/dL (500 nmol/L) | 74.0 | |
| Tripathy (2015) [40], India | Cross-sectional | • 43 with HIV<br>• 29 women, 67.4%<br>• Mean age, 37.88 ± 7.8 y<br>• Mean BMI, 17.8 ± 2.12 kg/$m^2$<br>• Mean CD4 count, 201.5 ± | Lower limit of the early-morning serum cortisol <9.4 µg/mL | 11.6 | |

**Table 2. Continued**

| First Author (Year), Country | Study Design | No. and Characteristics of the Participants [a] | Method and Diagnostic Criteria of AI | Prevalence of AI, % | Significant Associated Factors and Predictors of AI |
|---|---|---|---|---|---|
| | | 159.9 cells/mm$^3$ (CD4 <200 cells/mm$^3$, 55.8%) | | | |
| Prasanthai (2007) [41], Thailand | Cross-sectional | • 26 with HIV<br>• 7 women, 26.9%<br>• Mean age, 33.6 ± 6.8 y (22–46)<br>• Mean CD4 count, 75.6 ± 10.0 cells/mm$^2$ (1–321)<br>• Basal serum cortisol: 34.6 ± 61.8 μg/mL<br>• Comorbidities: PTB (42.3%), cryptococcosis (11.5%), and toxoplasmosis (11.5%) | • Intravenous 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 μg/dL | 19.2 | |
| **North America (n = 6)** | | | | | |
| Findling (1994) [42], USA | Case-control | • 53 with HIV<br>• 5 women, 9.4%<br>• Mean age, 38 ± 2 y | • Intravenous 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <500 nmol/L | 0 | |
| Freda (1997) [43], USA | Cross-sectional | • 37 hospitalized with HIV<br>• 12 women, 32.4%<br>• CD4 count <200 cells/mm$^3$ in all participants<br>• Mean basal serum cortisol, 18.4 ± 1.0 μg/mL | • Intravenous 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <20 μg/mL | 0 | |
| Marik (2002) [44], USA | Cross-sectional | • 28 critically ill with HIV<br>• 8 women, 28.6%<br>• Mean age, 43 ± 9 y<br>• Comorbidities: esophageal candidiasis (25%) and CMV infection (14.3%) | • Intravenous 1- and 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 μg/mL and <25 μg per the 1- and 250-μg doses, respectively | 21.0 | Predictors: CMV antigenemia positivity |
| Peter (1995) [45], USA | Cross-sectional | • 30 with HIV<br>• 5 women, 16.7%<br>• Mean age, 37.4 y (24–52)<br>• CD4 count: 1–390 cells/mm$^3$ | • Intravenous 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 μg/mL | 0 | |
| Smolyar (2003) [46], USA | Cross-sectional | • 31 with HIV | • Intravenous 1-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 μg/mL or an increment in serum cortisol levels from the basal level <7 μg/mL | 45.0 | |
| Sokalski (2016) [47], Canada | Retrospective study | • 192 with HIV<br>• 192 women, 100%<br>• Median age: 40 y (35–47; range, 25–67)<br>• Median BMI: 26 kg/m$^2$ (22–30)<br>• Median duration of HIV infection: 11 y (7–15)<br>• Median CD4 count: 470 cells/mm$^2$ (330–670) | • Low early-morning serum cortisol below lower limit and diagnosis confirmed by an endocrinologist | 0.5 | |
| **Africa (n = 5)** | | | | | |
| Akase (2019) [48], Nigeria | Cross-sectional | • 350 with HIV<br>• 178 women, 50.9%<br>• Mean age, 39.75 ± 9.22 y | • Intravenous 1-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 μg/mL (500 nmol/L) | 16.3 | |
| Ekpebegh (2011) [49], South Africa | Cross-sectional | • 66 hospitalized with HIV<br>• 39 women, 59.1%<br>• Mean age, 35.9 ± 11.9 y (17–71)<br>• Median CD4 count: 180.2 ± 186.6 cells/mm$^3$ | • AI was diagnosed by a basal serum cortisol level <400 nmol/L with or without overt signs and symptoms | 27.0 | |

**Table 2. Continued**

| First Author (Year), Country | Study Design | No. and Characteristics of the Participants [a] | Method and Diagnostic Criteria of AI | Prevalence of AI, % | Significant Associated Factors and Predictors of AI |
|---|---|---|---|---|---|
| | | • CD4 count <200 cells/mm$^3$: 66.7%<br>• Basal serum cortisol: 586.4 ± 318.0 nmol/L<br>• Comorbidities: history of CMV (100%) and current or previous TB (68.2%) | | | |
| Kaabwe-Yavwa (2013) [50], Zambia | Cross-sectional | • 51 with HIV<br>• 27 women, 52.9%<br>• Median age: 37 y (30–45)<br>• Comorbidities: previous TB (36.5%) and current TB (63.5%) | • Intravenous 1-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if random serum cortisol <10 μg/mL or change between basal and poststimulation serum cortisol levels <9 μg/mL | 94.1 | |
| Meya (2007) [51], Uganda | Cross-sectional | • 113 critically ill with HIV<br>• 63 women, 56%<br>• Mean age, 35 ± 9 y<br>• Comorbidities: TB (38%), Kaposi sarcoma (14%), cryptococcal meningitis (14%) | • Early-morning serum cortisol level <25 μg/mL | 19.0 | Significant associated factors: rifampicin use, World Health Organization stage IV HIV disease, and eosinophilia >3% on a full blood count. Predictors: rifampicin therapy and eosinophilia |
| Odeniyi (2013) [52], Nigeria | Case-control | • 43 with HIV<br>• 20 women, 46.5%<br>• Mean age, 39.3 ± 11.7 y<br>• Mean CD4 count, 197.8 ± 50.6 cells/mm$^3$<br>• Mean basal serum cortisol, 154.9 ± 27.2 nmol/L | • Intravenous 1-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <380.2 nmol/L or an increment from the basal cortisol level <158.5 nmol/L | 34.8 | |
| **Europe (n = 3)** | | | | | |
| Brockmeyer (2000) [53], Germany | Cross-sectional | • 31 ART-naive males with HIV<br>• Mean age, 37.0 ± 7.2 y (24–52) | • An elevated ACTH level and no increase in the serum cortisol levels poststimulation | 6.5 | |
| Piédrola (1996) [54], Spain | Retrospective | • 74 with HIV<br>• Mean age, 33.3 y | • Intravenous 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <496 nmol/L | 21.6 | Significant associated factors: weakness and fatigue |
| Pommier (2019) [55], France | Case-control | • 100 transwomen (group 1) and 192 men with HIV (group 2)<br>• Median age: 39 y (34–44) and 41 y (36–47) for groups 1 and 2, respectively<br>• Median duration of HIV infection: 11.3 y (5.3–10.1) and 7.9 y (3.1–12.4)<br>• Current CD4 count: 655 (510–840) and 570 (460–790) cells/mm$^3$<br>• Undetectable viral load (<50 copies): 81% and 90% | • Intravenous 250-μg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <500 nmol/L and a low basal serum cortisol level <140 nmol/L | 8.9 | |
| **South America (n = 2)** | | | | | |
| Cardoso (2007) [56], Argentina | Cross-sectional | • 21 with HIV<br>• 5 women, 23.8%<br>• Basal serum cortisol levels: 152–500 nmol/L<br>• Salivary cortisol levels: 2.5–18.0 nmol/L<br>• Salivary aldosterone levels: 13.5–55.0 pmol/L | • Intramuscular low-dose 25-μg ACTH (Synacthen) and saliva samples collected 30 min later for measurement of salivary cortisol and aldosterone<br>• AI diagnosed if salivary cortisol and aldosterone levels <20 nmol/L and <100 pmol/L, respectively | 38.1 | |

**Table 2. Continued**

| First Author (Year), Country | Study Design | No. and Characteristics of the Participants [a] | Method and Diagnostic Criteria of AI | Prevalence of AI, % | Significant Associated Factors and Predictors of AI |
|---|---|---|---|---|---|
| Wolff (2001) [57], Brazil | Case-control | • 63 with HIV<br>• 13 women, 20.8%<br>• Mean age, 34.6 y (16–22)<br>• Comorbidities: TB (31.3%), PCP (20.3%), CMV (7.8%), toxoplasmosis (6.3%) | • Intravenous 1-µg ACTH (Synacthen) stimulation test<br>• AI diagnosed if poststimulation peak serum cortisol levels <18 µg/mL (500 nmol/L) | 19.1 | |

Abbreviations: ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; ART, antiretroviral therapy; BMI, body mass index; CMV, cytomegalovirus; PCP, pneumocystis carini pneumonia; PTB, pulmonary tuberculosis; TB, tuberculosis.

[a]Mean data are presented as mean ± SD (range). Median data are presented as median (IQR).

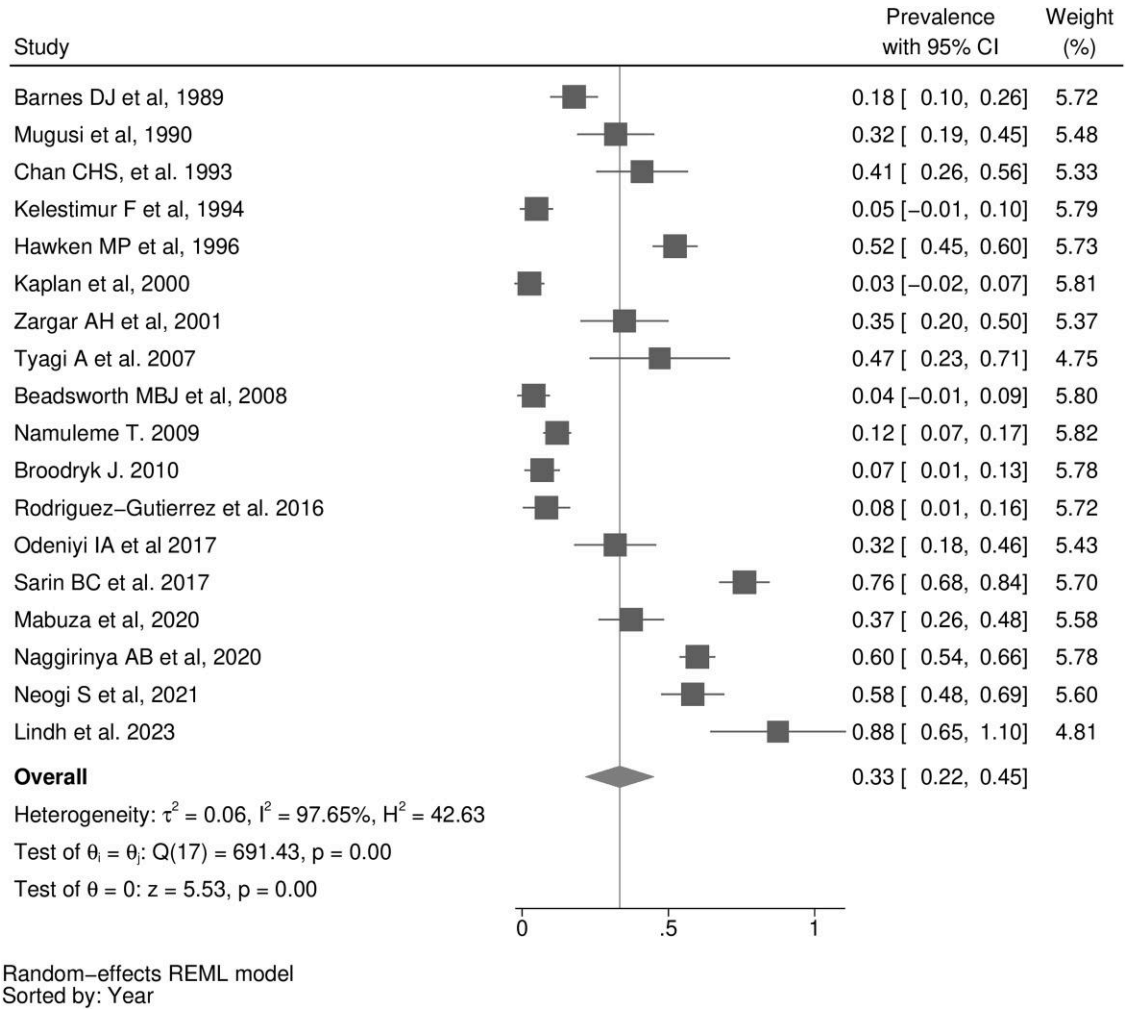


**Figure 2.** Studies on adrenal insufficiency in participants with tuberculosis. CI, confidence interval; REML. restricted maximum likelihood.

Based on the modified NOS, only 10 studies (21.3%) were classified as very good or good on assessment of study quality.

Regarding the meta-analysis for AI in participants with HIV, the Egger test yielded a *P* value of .065, suggesting marginal evidence for the presence of small-study effects or potential publication bias, although these results do not conclusively indicate bias. Asymmetry observed in funnel plots (Supplementary Figures 4 and 5) may imply such bias, but the contour-enhanced funnel plot revealed that this asymmetry is not predominantly associated with studies yielding nonsignificant results.

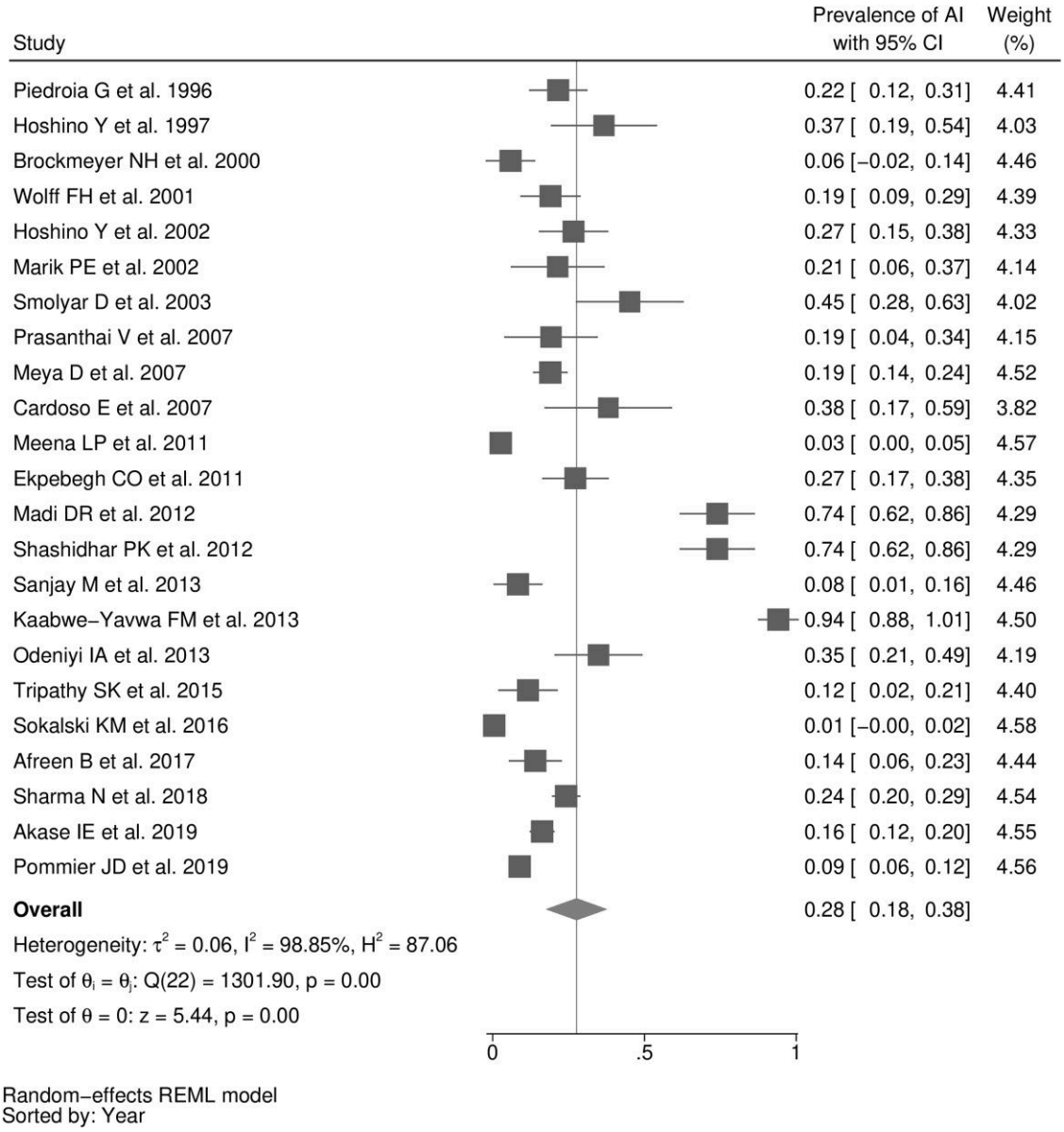


**Figure 3.** Studies on adrenal insufficiency in participants with HIV. CI, confidence interval; REML, restricted maximum likelihood.

The meta-regression showed no significant association of mean age, CD4 count, year of publication, and location (by continent) with the pooled prevalence of AI in patients with HIV (Supplementary Table 9). Increasing duration since diagnosis with HIV (in months) was associated with an increase in the pooled prevalence of AI in patients with HIV, but this was marginally significant (β = 0.003; 95% CI, .000–.006; $P$ = .07).

For AI in participants with TB, the Egger test for small-study effects showed a statistically significant publication bias ($P$ = .009). The funnel plot also exhibited asymmetry, and the contour-enhanced funnel plot substantiated the presence of small-study effects, as studies with high prevalence estimates are disproportionately located outside the area of nonsignificance. However, the subsequent nonparametric trim-and-fill analysis did not impute any missing studies, indicating no evidence of publication bias affecting the symmetry of the funnel plot.

We performed subgroup analysis by location and cumulative meta-analysis by year of publication, as well as meta-regression by age, BMI, continent, and year of publication. Meta-regression analyses showed that continent, mean age of participants, and BMI were not significant predictors of the reported prevalence of AI in participants with TB (Supplementary Table 10). However, the prevalence estimates for AI in participants with TB increased slightly with increasing year of publication, although this was marginally significant (β = 0.01; 95% CI, −.00 to .02; $P$ = .061). This trend was also not clearly reflected in the visual

distribution of prevalence over time in the forest plot (Supplementary Figure 5). High levels of residual heterogeneity across models ($I^2 > 95\%$) suggest that the variance in prevalence estimates is largely due to unmeasured factors not captured by these covariates.

## DISCUSSION

In this systematic review and meta-analysis, we demonstrated that AI is relatively common in adult patients with TB or HIV. A higher prevalence was noted in Africa and Asia, 2 continents with the highest burden of TB and HIV globally [58, 59]. This finding could be explained by the majority of patients in Africa and Asia usually being diagnosed late with severe disease, characterized by low CD4 counts, extensive radiologic involvement, and multiple coinfections [4, 5]. The health care systems in both regions are also not well developed to optimally diagnose and treat most medical conditions [60–62].

AI has an insidious onset and presents with nonspecific and subtle clinical features that overlap with those of TB or HIV, delaying early diagnosis and prompt initiation of optimal therapy. Because of this, the condition is often referred to as one of the great mimickers of medicine [2, 63–66]. Such nonspecific signs and symptoms include weight loss, arthralgia, myalgia, abdominal pain, and hypotension, as reported by most clinical studies [16–18, 30, 67]. Loss of libido and hypotension, as reported by Mabuza and Sarpong [15] and Mugusi et al [16], are clinical features associated with AI; they develop due to adrenal androgen deficiency and the loss of the synergistic action of cortisol and catecholamines on vascular reactivity resulting in vasodilatation, respectively [2, 65].

Hypoglycemia and hyperkalemia, as reported by Sharma et al [38], in addition to euvolemic hyponatremia, are relatively common metabolic disorders in patients with AI. Reduced hepatic glucose release and gluconeogenesis explain the observed hypoglycemia, while mineralocorticoid deficiency is associated with increased water and sodium loss with potassium retention resulting in hyponatremia and hyperkalemia [63–66]. In addition to the metabolic disorders commonly encountered in patients with AI, glucocorticoid deficiency is often associated with immunologic and cellular dysfunction. This is due to the loss of the cortisol-mediated suppressive action on endogenous glucocorticoids, which results in elevated levels of proinflammatory cytokines (eg, tumor necrosis factor α and interleukins 1 and 6), neutropenia, eosinophilia, and lymphocytosis [2, 65]. Eosinophilia was reported as one of the independent predictors of AI in a study conducted in critically ill cases of HIV in Uganda [51].

Extensive or progressive hyperpigmentation is one of the clinical signs that are highly suggestive of AI. It often occurs in the sun-exposed areas of the face, neck, and arms or in areas that are subjected to repeated mechanical shear stress, such as the elbows, knees, palmar creases, and buccal mucosa [2, 63, 65, 66]. The loss of the negative feedback by cortisol in patients with AI results in an increased release of pro-opiomelanocortin and proopiomelanocortin-derived peptides, such as ACTH and α melanocyte-stimulating hormone, which bind to the melanocortin 1 receptor and cause increased melanogenesis, hence the observed hyperpigmentation [64, 65].

Rifampicin therapy, as reported by Meya et al [51], has been shown to be associated with glucocorticoid deficiency. The drug is a potent CYP3A4 (cytochrome $p^{450}$ 3A4) enzyme inducer that results in enhanced glucocorticoid metabolism [2]. Drugs that possess a similar CYP3A4-inducing effect and are often used in the management of patients with TB or HIV include anticonvulsants (eg, phenytoin) and antifungal drugs (eg, ketoconazole) [2, 65].

### Strengths and Limitations of the Systematic Review and Meta-analysis

This is the first systematic review and meta-analysis to investigate the prevalence, significant clinical features, and predictors of AI in adult patients with TB or HIV. Most studies had a low risk of publication bias.

Despite these strengths, it had some limitations. Only 10 studies (21.3%) were classified as very good or good on assessment of the study quality based on the modified NOS.

## CONCLUSION

This systematic review and meta-analysis reported that AI is relatively common in patients with TB or HIV. The presence of these nonspecific clinical features, such as weight loss, myalgia, arthralgia, abdominal pain, hypotension, and hypoglycemia, in patients with TB or HIV should raise the clinical suspicion of AI and influence prompt screening, diagnosis, and initiation of glucocorticoid therapy. This will ultimately translate into reduced mortality, which often occurs in cases of clinical presentation with an acute adrenal crisis.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

***Author contributions.*** D. K. developed the research idea to perform this systematic review and meta-analysis. B. M. conducted the database search. D. K., N. O., A. P. K., and F. B. performed the preliminary search of the titles and abstracts following the database search. R. O. performed the statistical analysis. D. K. extracted the key information from the eligible articles and wrote the initial draft of the manuscript. A. P. K. assessed the quality of the included studies. All authors provided input to the first draft of the manuscript and read and approved the final draft of the manuscript.

***Data availability statement.*** The data file used in this systematic review and meta-analysis is attached as a supplementary file. All included studies are published and freely accessible.

***Patient consent statement.*** Because this is a systematic review and meta-analysis, patient consent and ethical review committee approval were not required.

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