Reference	**Abbott 1995[1]**
Study type	Cross-sectional
Study methodology	Data source: HIV-positive inpatients and outpatients Recruitment: recruited from the Department of Infectious Diseases (Monsall Unit Manchester, U.K.) from November 1992 to May 1993
Number of patients	Total n = 49 (impaired/abnormal rapid ACTH stimulation test n = 14, normal rapid ACTH test n = 35)
Patient characteristics	Age, median (range): 36 (25-56) years Gender (male to female ratio): 42:7 Ethnicity: not reported Setting: Department of Infectious Diseases, single centre Country: UK Inclusion criteria: HIV-positive inpatients and outpatients with CD4 counts ≤ 50 x 10^6/l Exclusion criteria: taking systemic steroids (except megestrol acetate)
Target condition(s)	Cortisol deficiency
Index test(s) and reference standard	Index tests Fatigue: subjects filled in a questionnaire to assess fatigue (graded 0 = no fatigue, 1 = occasional and mild, 2=frequent and affecting function, 3=debilitating, house-bound, 4 = severe, bed-bound) Systolic postural drop (≥ 10 mmHg): measured by erect and supine blood pressures. Insufficient data to calculate sensitivity/specificity (data missing). Serum sodium (<135 mmol/l)

Reference	**Abbott 1995[1]**				
	Serum potassium (>5 mmol/l) Reference standard Serum cortisol was measured immediately before and 30 mins after an injection of 250µg Synacthen (tetracosactrin). Cortisol responses were graded according to the 'post' value achieved. A 'normal' response was defined as a post-stimulation cortisol of ≥450 nmol/l (16 µg/dl), an 'abnormal' response was defined as a post stimulation cortisol <350 nmol/L (12.5µg/dl), and an 'impaired' response was any intermediate result. Time between measurement of index test and reference standard: not reported				
2×2 tables		Reference standard +	Reference standard −	Total	Fatigue ≥2
	Index test +	12	26	38	
	Index test −	2	9	11	
	Total	14	35	49	
		Reference standard +	Reference standard −	Total	Fatigue ≥3
	Index test +	4	9	13	
	Index test −	10	26	36	
	Total	14	35	49	
		Reference standard +	Reference standard −	Total	Serum sodium (<135 mmol/l)
	Index test +	1	6	7	
	Index test −	13	29	42	
	Total	14	35	49	
		Reference standard +	Reference standard −	Total	Serum potassium (>5 mmol/l)
	Index test +	0	1	1	
	Index test −	14	34	48	
	Total	14	35	49	
Statistical measures	Index text: fatigue ≥2 Sensitivity: 0.86 (95% CI 0.57-0.98) Specificity: 0.26 (95% CI 0.12-0.43)				

Reference	Abbott 1995[1]
	PPV: 0.32 NPV: 0.82 PLR: 1.15 NLR: 0.56 Index text: fatigue ≥2 Sensitivity: 0.29 (95% CI 0.08-0.58) Specificity: 0.74 (95% CI 0.57-0.88) PPV: 0.31 NPV: 0.72 PLR: 1.11 NLR: 0.96 Index text: serum sodium (<135 mmol/l) Sensitivity: 0.07 (95% CI 0.00-0.34) Specificity: 0.83 (95% CI 0.66-0.93) PPV: 0.14 NPV: 0.69 PLR: 0.42 NLR: 1.12 Index text: serum potassium (>5 mmol/l) Sensitivity: 0.00 (95% CI 0.00-0.23) Specificity: 0.97 (95% CI 0.85-1.00) PPV: 0.00 NPV: 0.71 PLR: 0.00 NLR: 1.03
Source of funding	Not reported
Limitations	Risk of bias: very serious (unclear reporting on patient selection; whether index tests and reference standard were conducted without knowledge of the other's results; or timing between index test and reference standard) Indirectness: serious population indirectness (concerns over applicability of evidence from HIV population to general population)

Reference	**Abbott 1995[1]**
Comments	Study reports systolic postural drop (≥ 10 mmHg), measured by erect and supine blood pressures, but insufficient data to calculate sensitivity/specificity (data missing). Since no separate differences in clinical and biochemical features were demonstrated between patients with an impaired and those with an abnormal test result, the two were grouped together by the study authors for the purposes of statistical evaluation. Diagnostic accuracy data calculated by NICE from raw data

Reference	**Casanova-Cardiel 2003[2]**
Study type	Prospective cohort study (index test and reference standard data collected cross-sectionally)
Study methodology	Data source: patients with HIV-infection Recruitment: From January to August 2000, adult patients with HIV-infection and CD4 counts less than 200/mm^3were recruited from a single hospital
Number of patients	Total n = 106 (n with AI dependent on criteria used)
Patient characteristics	Age, mean (range): 37.7 (20-65) years. Gender (male to female ratio): 94:12 Ethnicity: not reported Setting: Department of Infectious Diseases of Adults, single hospital Country: Mexico Inclusion criteria: one or more clinical or laboratory determination suggesting adrenal insufficiency: tiredness, weakness, wasting syndrome, weight loss, anorexia, hyperpigmentation, dizziness, nausea, vomiting, diarrhoea, hypotension, hyponatremia, and/or hyperkalaemia. Exclusion criteria: under steroidal, ketoconazole or megestrol therapies.
Target condition(s)	Adrenal insufficiency

Reference	**Casanova-Cardiel 2003[2]**				
Index test(s) and reference standard	Index tests A questionnaire was designed to ask for several symptoms and signs: Fatigue Weight loss Salt intake Diarrhoea Skin hyperpigmentation Mucoses hyperpigmentation Orthostatic hypotension Hyponatraemia (serum Na < 135 mEq/L) Hyperkalaemia (serum Potassium > 5 mEq/L) Reference standard Low dose (10µg 1.V. bolus dose of synthetic ACTH-Cortrosyn, Organon Inc., West Orange. NJ, USA) short ACTH test was performed between 08.00 and 09.00 hours; basal ACTH, cortisol, and aldosterone and 60 min cortisol and aldosterone, were determined by RIA (all kits from CIS bio international). Abnormal response considered when cortisol peak response at 60 min was < 11 µg (Δ 11) with respect to basal; also analysed the data with three different criteria to define subnormal response to ACTH-stimulation test: 1) twofold value of basal cortisol; 2) any cortisol value above 18 µg/dL; and 3) any cortisol value above 20 µg/dL. Time between measurement of index test and reference standard: not reported.				
2×2 table (AI: cortisol peak response at 60 min < 11 µg (Δ 11) with respect to basal)		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	34	40	74	
	Index test −	13	19	32	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	32	39	71	
	Index test −	15	20	35	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Salt intake
	Index test +	7	14	21	
	Index test −	40	45	85	

Reference	**Casanova-Cardiel 2003[2]**				
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	8	13	21	
	Index test −	39	46	85	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	19	22	41	
	Index test −	28	37	65	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Mucoses hyperpigmentation
	Index test +	3	4	7	
	Index test −	44	55	99	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	16	20	36	
	Index test −	31	39	70	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Hyponatraemia (serum Na < 135 mEq/L)
	Index test +	24	21	45	
	Index test −	23	38	61	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Hyperkalaemia (serum Potassium > 5 mEq/L)
	Index test +	5	7	12	
	Index test −	42	52	94	
	Total	47	59	106	
2×2 table (AI: twofold value		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	58	16	74	
	Index test −	20	12	32	

Reference	**Casanova-Cardiel 2003[2]**				
of basal cortisol)	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	56	15	71	
	Index test −	22	13	35	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Salt intake
	Index test +	15	6	21	
	Index test −	63	22	85	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	17	4	21	
	Index test −	61	24	85	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	31	10	41	
	Index test −	47	18	65	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Mucoses hyperpigmentation
	Index test +	3	4	7	
	Index test −	75	24	99	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	24	12	36	
	Index test −	54	16	70	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Hyponatraemia (serum Na < 135 mEq/L)
	Index test +	36	9	45	
	Index test −	42	19	61	

Reference	**Casanova-Cardiel 2003[2]**				
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Hyperkalaemia (serum Potassium > 5 mEq/L)
	Index test +	10	2	12	
	Index test −	68	26	94	
	Total	78	28	106	
2×2 table (AI: any cortisol value > 18 µg/dL)		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	2	72	74	
	Index test −	3	29	32	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	4	67	71	
	Index test −	1	34	35	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Salt intake
	Index test +	1	20	21	
	Index test −	4	81	85	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	0	21	21	
	Index test −	5	80	85	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	1	40	41	
	Index test −	4	61	65	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Mucoses hyperpigmentation
	Index test +	1	6	7	
	Index test −	4	95	99	

Reference	Casanova-Cardiel 2003[2]				
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	2	34	36	
	Index test −	3	67	70	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Hyponatraemia (serum Na < 135 mEq/L)
	Index test +	2	43	45	
	Index test −	3	58	61	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Hyperkalaemia (serum Potassium > 5 mEq/L)
	Index test +	3	9	12	
	Index test −	2	92	94	
	Total	5	101	106	
2×2 table (AI: any cortisol value > 20 µg/dL)		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	2	72		
	Index test −	4	28		
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	5	66	71	
	Index test −	1	34	35	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Salt intake
	Index test +	1	20	21	
	Index test −	5	80	85	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	0	21	21	
	Index test −	6	79	85	

Reference	**Casanova-Cardiel 2003[2]**				
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	2	39	41	
	Index test −	4	61	65	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Mucoses hyperpigmentation
	Index test +	1	6	7	
	Index test −	5	94	99	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	2	34	36	
	Index test −	4	66	70	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Hyponatraemia (serum Na < 135 mEq/L)
	Index test +	2	43	45	
	Index test −	4	57	61	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Hyperkalaemia (serum Potassium > 5 mEq/L)
	Index test +	3	9	12	
	Index test −	3	91	94	
	Total	6	100	106	
Statistical measures	**Criteria for reference standard positivity: cortisol peak response at 60 min < 11 µg (Δ 11) with respect to basal** Index text: lethargy (fatigue) Sensitivity: 0.72 (95% CI 0.57-0.84) Specificity: 0.32 (95% CI 0.21-0.46) PPV: 0.46 NPV: 0.59 PLR: 1.07				

Reference	Casanova-Cardiel 2003[2]
	NLR: 0.86 Index text: weight loss Sensitivity: 0.68 (95% CI 0.53-0.81) Specificity: 0.34 (95% CI 0.22-0.47) PPV: 0.45 NPV: 0.57 PLR: 1.03 NLR: 0.94 Index text: salt intake Sensitivity: 0.15 (95% CI 0.06-0.28) Specificity: 0.76 (95% CI 0.63-0.86) PPV: 0.33 NPV: 0.53 PLR: 0.63 NLR: 1.12 Index text: diarrhoea Sensitivity: 0.17 (95% CI 0.08-0.31) Specificity: 0.78 (95% CI 0.65-0.88) PPV: 0.38 NPV: 0.54 PLR: 0.77 NLR: 1.06 Index text: skin hyperpigmentation Sensitivity: 0.40 (95% CI 0.26-0.56) Specificity: 0.63 (95% CI 0.49-0.75) PPV: 0.46 NPV: 0.57 PLR: 1.08 NLR: 0.95 Index text: mucoses hyperpigmentation Sensitivity: 0.06 (95% CI 0.01-0.18)

Reference	Casanova-Cardiel 2003[2]
	Specificity: 0.93 (95% CI 0.84-0.98) PPV: 0.43 NPV: 0.56 PLR: 0.94 NLR: 1.00 Index text: orthostatic hypotension Sensitivity: 0.34 (95% CI 0.21-0.49) Specificity: 0.66 (95% CI 0.53-0.78) PPV: 0.44 NPV: 0.56 PLR: 1.00 NLR: 1.00 Index text: hyponatraemia (serum Na < 135 mEq/L) Sensitivity: 0.51 (95% CI 0.36-0.66) Specificity: 0.64 (95% CI 0.51-0.76) PPV: 0.53 NPV: 0.62 PLR: 1.43 NLR: 0.76 Index text: hyperkalaemia (serum Potassium > 5 mEq/L) Sensitivity: 0.11 (95% CI 0.04-0.23) Specificity: 0.88 (95% CI (0.77-0.95) PPV: 0.42 NPV: 0.55 PLR: 0.90 NLR: 1.01 **Criteria for reference standard positivity: twofold value of basal cortisol** Index text: lethargy (fatigue) Sensitivity: 0.74 (95% CI 0.63-0.84) Specificity: 0.43 (95% CI 0.24-0.63) PPV: 0.78

Reference	Casanova-Cardiel 2003[2]
	NPV: 0.38 PLR: 1.30 NLR: 0.60 Index text: weight loss Sensitivity: 0.72 (95% CI 0.60-0.81) Specificity: 0.46 (95% CI 0.28-0.66) PPV: 0.79 NPV: 0.37 PLR: 1.34 NLR: 0.61 Index text: salt intake Sensitivity: 0.19 (95% CI 0.11-0.30) Specificity: 0.79 (95% CI 0.59-0.92) PPV: 0.71 NPV: 0.26 PLR: 0.90 NLR: 1.03 Index text: diarrhoea Sensitivity: 0.22 (95% CI 0.13-0.33) Specificity: 0.86 (95% CI 0.67-0.96) PPV: 0.81 NPV: 0.28 PLR: 1.53 NLR: 0.91 Index text: skin hyperpigmentation Sensitivity: 0.40 (95% CI 0.29-0.51) Specificity: 0.64 (95% CI 0.44-0.81) PPV: 0.76 NPV: 0.28 PLR: 1.11 NLR: 0.94

Reference	Casanova-Cardiel 2003[2]
	Index text: mucoses hyperpigmentation Sensitivity: 0.04 (95% CI 0.01-0.11) Specificity: 0.86 (95% CI 0.67-0.96) PPV: 0.43 NPV: 0.24 PLR: 0.27 NLR: 1.12 Index text: orthostatic hypotension Sensitivity: 0.31 (95% CI 0.21-0.42) Specificity: 0.57 (95% CI 0.37-0.76) PPV: 0.67 NPV: 0.23 PLR: 0.72 NLR: 1.21 Index text: hyponatraemia (serum Na < 135 mEq/L) Sensitivity: 0.46 (95% CI 0.35-0.58) Specificity: 0.68 (95% CI 0.48-0.84) PPV: 0.80 NPV: 0.31 PLR: 1.44 NLR: 0.79 Index text: hyperkalaemia (serum Potassium > 5 mEq/L) Sensitivity: 0.13 (95% CI 0.06-0.22) Specificity: 0.93 (95% CI 0.76-0.99) PPV: 0.83 NPV: 0.28 PLR: 1.79 NLR: 0.94 **Criteria for reference standard positivity: any cortisol value > 18 µg/dL** Index text: lethargy (fatigue) Sensitivity: 0.40 (95% CI 0.05-0.85)

Reference	Casanova-Cardiel 2003[2]
	Specificity: 0.29 (95% CI 0.20-0.39) PPV: 0.03 NPV: 0.91 PLR: 0.56 NLR: 2.09 Index text: weight loss Sensitivity: 0.80 (95% CI 0.28-0.99) Specificity: 0.34 (95% CI 0.25-0.44) PPV: 0.06 NPV: 0.97 PLR: 1.21 NLR: 0.59 Index text: salt intake Sensitivity: 0.20 (95% CI 0.01-0.72) Specificity: 0.80 (95% CI 0.71-0.87) PPV: 0.05 NPV: 0.95 PLR: 1.01 NLR: 1.00 Index text: diarrhoea Sensitivity: 0.00 (95% CI 0.00-0.52) Specificity: 0.79 (95% CI 0.70-0.87 PPV: 0.00 NPV: 0.94 PLR: 0.00 NLR: 1.26 Index text: skin hyperpigmentation Sensitivity: 0.20 (95% CI 0.01-0.72) Specificity: 0.60 (95% CI 0.50-0.70) PPV: 0.02 NPV: 0.94 PLR: 0.51

Reference	Casanova-Cardiel 2003[2]
	NLR: 1.32 Index text: mucoses hyperpigmentation Sensitivity: 0.20 (95% CI 0.01-0.72) Specificity: 0.94 (95% CI 0.88-0.98) PPV: 0.14 NPV: 0.96 PLR: 3.37 NLR: 0.85 Index text: orthostatic hypotension Sensitivity: 0.40 (95% CI (0.05-0.85) Specificity: 0.66 (95% CI 0.56-0.75) PPV: 0.06 NPV: 0.96 PLR: 1.19 NLR: 0.90 Index text: hyponatraemia (serum Na < 135 mEq/L) Sensitivity: 0.40 (95% CI 0.05-0.85) Specificity: 0.57 (95% CI 0.47-0.67) PPV: 0.04 NPV: 0.95 PLR: 0.94 NLR: 1.04 Index text: hyperkalaemia (serum Potassium > 5 mEq/L) Sensitivity: 0.60 (95% CI 0.15-0.95) Specificity: 0.91 (95% CI 0.84-0.96) PPV: 0.25 NPV: 0.98 PLR: 6.73 NLR: 0.44 **Criteria for reference standard positivity: any cortisol value > 20 µg/dL**

Reference	Casanova-Cardiel 2003[2]
	Index text: lethargy (fatigue) Sensitivity: 0.33 (95% CI 0.04-0.78) Specificity: 0.28 (95% CI 0.19-0.38) PPV: 0.03 NPV: 0.88 PLR: 0.46 NLR: 2.38 Index text: weight loss Sensitivity: 0.83 (95% CI 0.36-1.00) Specificity: 0.34 (95% CI 0.25-0.44) PPV: 0.07 NPV: 0.97 PLR: 1.26 NLR: 0.49 Index text: salt intake Sensitivity: 0.17 (95% CI 0.00-0.64) Specificity: 0.80 (95% CI 0.71-0.87) PPV: 0.05 NPV: 0.94 PLR: 0.83 NLR: 1.04 Index text: diarrhoea Sensitivity: 0.00 (95% CI 0.00-0.46) Specificity: 0.79 (95% CI 0.70-0.87) PPV: 0.00 NPV: 0.93 PLR: 0.00 NLR: 1.27 Index text: skin hyperpigmentation Sensitivity: 0.33 (95% CI 0.04-0.78) Specificity: 0.61 (95% CI 0.51-0.71) PPV: 0.05

Reference	Casanova-Cardiel 2003[2]
	NPV: 0.94 PLR: 0.85 NLR: 1.09 Index text: mucoses hyperpigmentation Sensitivity: 0.17 (95% CI 0.00-0.64) Specificity: 0.94 (95% CI 0.87-0.98) PPV: 0.14 NPV: 0.95 PLR: 2.78 NLR: 0.89 Index text: orthostatic hypotension Sensitivity: 0.33 (95% CI 0.04-0.78) Specificity: 0.66 (95% CI 0.56-0.75) PPV: 0.06 NPV: 0.94 PLR: 0.98 NLR: 1.01 Index text: hyponatraemia (serum Na < 135 mEq/L) Sensitivity: 0.33 (95% CI 0.04-0.78) Specificity: 0.57 (95% CI 0.47-0.67) PPV: 0.04 NPV: 0.93 PLR: 0.78 NLR: 1.17 Index text: hyperkalaemia (serum Potassium > 5 mEq/L) Sensitivity: 0.50 (95% CI 0.12-0.88) Specificity: 0.91 (95% CI 0.84-0.96) PPV: 0.25 NPV: 0.97 PLR: 5.56 NLR: 0.55

Reference	**Casanova-Cardiel 2003[2]**
Source of funding	Not reported
Limitations	Risk of bias: very serious (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); or timing between index test and reference standard) Indirectness: very serious (serious population indirectness due to concerns over applicability of evidence from a population diagnosed with AIDS to the general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test)
Comments	95% CIs calculated by NICE from raw data

Reference	**Hintong 2021 ID[3]**
Study type	Cross-sectional diagnostic accuracy
Study methodology	Data source: Cross-sectional study conducted with 42 patients who were seen at the dermatology outpatient departments at the Faculty of Medicine, Chiang Mai University Hospital over a 5-month period (June – October 2020). Recruitment: Recruited participants were adult dermatological patients (≥18 years) who had used topical corticosteroids for at least 12 months.
Number of patients	Total n= 42. Adrenal insufficiency n =17. Without adrenal insufficiency n= 25
Patient characteristics	Age, mean (SD): 56.5 ±15.4 years Gender (male to female ratio): 30:12 Ethnicity: NR Setting: Dermatology outpatient department Country: Thailand Inclusion criteria: Adult patients with dermatological conditions who had been prescribed topical steroids for at least 12 months by the dermatology outpatient departments of the Faculty of Medicine, Chiang Mai University from June through October 2020 were included.

Reference	**Hintong 2021 ID[3]**				
	Exclusion criteria: Patients with pituitary or adrenal diseases, pregnant women and patients who had been treated with either systemic corticosteroids or other local corticosteroids were excluded. Treatment: The mean duration of treatment was 10.1 ± 6 years Skin condition: The majority of patients had psoriasis (n = 14, 82.4%)				
Target condition(s)	Adrenal insufficiency				
Index test(s) and reference standard	Index test Symptoms of AI included lethargy, nausea and vomiting, orthostatic hypotension and significant weight loss. Significant weight loss was defined as a loss of 5% of body weight in one month or a loss of 10% over a period of six months. Reference standard An 8AM cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL at 20 or 40 minutes after a 5 µg ACTH stimulation test was defined as having AI. Patients were instructed to suspend use of topical corticosteroids for at least 24 hours before serum morning cortisol measurement and ACTH stimulation tests. In those with serum morning cortisol between 3 and 17.9 µg/dL, ACTH stimulation tests were performed on the same day between 9–11AM to either exclude or diagnose AI. Serum cortisol levels were measured by electrochemiluminescence assay (ECLIA) (Elecsys ® Cortisol II assay, Roche Diagnostics GmbH, Mannheim, Germany). Time between measurement of index test and reference standard: Not reported				
2×2 table		Reference standard +	Reference standard −	Total	Lethargy
	Index test +	0	1	1	
	Index test −	17	24	41	
	Total	17	25	42	
		Reference standard +	Reference standard −	Total	Nausea and vomiting
	Index test +	0	0	0	
	Index test −	17	25	42	
	Total	17	25	42	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	0	0	0	
	Index test −	17	25	42	
	Total	17	25	42	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	1	0	1	

Reference	**Hintong 2021 ID[3]**				
	Index test −	16	25	41	
	Total	17	25	42	
Statistical measures	Index text: lethargy Sensitivity: 0.00 (95% CI 0.00-0.20) Specificity: 0.96 (95% CI 0.80-1.00) PPV: 0.00 NPV: 0.59 PLR: 0.00 NLR: 1.04 Index text: nausea and vomiting Sensitivity: 0.00 (95% CI 0.00-0.20) Specificity: 1.00 (95% CI 0.86-1.00) PPV: - NPV: 0.60 PLR: - NLR: 1.00 Index test: orthostatic hypotension Sensitivity: 0.00 (95% CI 0.00-0.20) Specificity: 1.00 (95% CI 0.86-1.00) PPV: - NPV: 0.60 PLR: - NLR: 1.00 Index test: weight loss Sensitivity: 0.06 (95% CI 0.00-0.29) Specificity: 1.00 (95% CI 0.86-1.00) PPV: 1.00 NPV: 0.61 PLR: - NLR: 0.94				
Source of funding	Not reported				

Reference	Hintong 2021 ID[3]
Limitations	Risk of bias: very serious (unclear reporting on patient selection; whether index tests and reference standard were conducted without knowledge of the other's results; or timing between index test and reference standard) Indirectness: very serious (serious population indirectness (concerns over applicability of evidence from long term topical steroid use population to the general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 5 µg ACTH test)
Comments	Diagnostic accuracy data calculated by NICE from raw data

Reference	Mabuza 2020 ID[4]
Study type	Cross-sectional
Study methodology	Data source: A researcher administered questionnaire was used to collect data related to signs, symptoms, and laboratory findings of TB-suspect patients admitted to the three hospitals over a six months' period. Data comprised baseline characteristics (age, sex, marital status, and educational level); symptoms of AI (dry itchy skin, muscle and joint pains, tiredness, craving for salt, loss of libido in males, amenorrhoea in females, dizziness, loss of weight and nausea and vomiting) and signs of AI (systolic hypotension, low pulse volume, tachycardia, hypothermia, mucosal and skin hyperpigmentation, and general body wasting). Serum cortisol, sodium, potassium, and fasting serum glucose to establish patients' electrolyte status vis-à-vis cortisol levels were also conducted. Recruitment: study population consisted of all TB-suspect patients admitted to the three hospitals over a six months' period (1st September 2014 - 28th February 2015), which worked out to the following numbers: DGMAH (ward 35), 31 patients, ODH, 23 and JDH 38, giving a total of 92 patients.
Number of patients	Total n = 92 (n=75 analysed). Adrenal insufficiency n = 28, no adrenal insufficiency n = 47.
Patient characteristics	Age, mean (SD): 40.3 (15.7) Gender (male to female ratio): 43:32 Ethnicity: NR Setting: Tertiary hospital located in Pretoria, and two referring district hospitals

Reference	**Mabuza 2020 ID[4]**				
	Country: South Africa Inclusion criteria: The study population consisted of all TB-suspect patients admitted to the three hospitals over a six months' period (1st September 2014 - 28th February 2015). Exclusion criteria: NR				
Target condition(s)	Adrenal insufficiency				
Index test(s) and reference standard	Index tests Three medical officers (one for each setting) were hired to collect data. They used the researcher-administered data collection sheets. Data comprised baseline characteristics and symptoms of AI (dry itchy skin, muscle and joint pains, tiredness, craving for salt, loss of libido in males, amenorrhoea in females, dizziness, loss of weight and nausea and vomiting) and signs of AI (systolic hypotension, low pulse volume, tachycardia, hypothermia, mucosal and skin hyperpigmentation and general body wasting). systolic hypotension skin hyperpigmentation salt craving weight loss nausea vomiting tiredness Reference standard The low-dose (1µg/ml intravenously) short corticotropin (Synacthen®) stimulation test was used. The test drug was administered to patients between 07h00 and 09h00. The low dose Synacthen solution was constituted as follows: one ampoule of 250µg of Synacthen diluted into 249ml of sterile 0.9% saline solution to obtain a concentration of 1µg/ml. This procedure was carried out by the three data collectors in the wards under sterile conditions, each using a graduated measuring jar to prepare the solution. Two blood samples from each patient were taken to measure the pre-corticotropin and post-corticotropin serum cortisol levels. The time interval between the first and second specimens was 30 - 60 minutes. All the assays were performed in one reference laboratory, the National Health Laboratory Service (NHLS), at Dr George Mukhari Academic Hospital. (AI definition = serum cortisol level < 500nmol/L) Time between measurement of index test and reference standard: No details provided for all tests.				
2×2 table		Reference standard +	Reference standard −	Total	Systolic hypotension
	Index test +	24	42	66	

Reference	Mabuza 2020 ID[4]				
	Index test −	4	5	9	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	22	35	57	
	Index test −	6	12	18	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Salt craving
	Index test +	23	38	61	
	Index test −	5	9	14	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	6	3	9	
	Index test −	22	44	66	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Nausea
	Index test +	16	21	37	
	Index test −	12	26	38	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Vomiting
	Index test +	19	35	54	
	Index test −	9	12	21	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Tiredness
	Index test +	7	7	14	
	Index test −	21	40	61	
	Total	28	47	75	

Reference	Mabuza 2020 ID[4]
Statistical measures	Index text: Hypotension Sensitivity: 0.86 (95% CI 0.67-0.96) Specificity: 0.11 (95% CI 0.04-0.23) PPV: 0.36 NPV: 0.56 PLR: 0.96 NLR: 1.34 Index text: Skin hyperpigmentation Sensitivity: 0.79 (95% CI 0.59-0.92) Specificity: 0.26 (95% CI 0.14-0.40) PPV: 0.39 NPV: 0.67 PLR: 1.06 NLR: 0.84 Index text: Salt craving Sensitivity: 0.82 (95% CI 0.63-0.94) Specificity: 0.19 (95% CI 0.09-0.33) PPV: 0.38 NPV: 0.64 PLR: 1.02 NLR: 0.93 Index text: Weight loss Sensitivity: 0.21 (95% CI 0.08-0.41) Specificity: 0.94 (95% CI 0.82-0.99) PPV: 0.67 NPV: 0.67 PLR: 3.36 NLR: 0.84 Index text: Nausea Sensitivity: 0.57 (95% CI 0.37-0.76) Specificity: 0.55 (95% CI 0.40-0.70) PPV: 0.43

Reference	Mabuza 2020 ID[4]
	NPV: 0.68 PLR: 1.28 NLR: 0.77 Index text: Vomiting Sensitivity: 0.68 (95% CI 0.48-0.84) Specificity: 0.26 (95% CI 0.14-0.40) PPV: 0.35 NPV: 0.57 PLR: 0.91 NLR: 1.26 Index text: Tiredness Sensitivity: 0.25 (95% CI 0.11-0.45) Specificity: 0.85 (95% CI 0.72-0.94) PPV: 0.50 NPV: 0.66 PLR: 1.68 NLR: 0.88
Source of funding	This study was funded through the VLIR (Belgium) Grant Number: ZA2020IUC021A102.
Limitations	Risk of bias: very serious (unclear patient selection (no information provided), unclear application of the index test, unclear application of the reference standard (unclear if blinded) and high risk of bias arising from the patient flow (17 of 92 missing data sheets) Indirectness: Not serious
Comments	Diagnostic accuracy data calculated by NICE from raw data

Reference	Naguib 2022[5]
Study type	Cross-sectional study
Study methodology	Data source: clinical and laboratory tests of 132 individuals with liver cirrhosis Recruitment: The study included 132 individuals with liver cirrhosis who were recruited from Alexandria Main University Hospital, Internal Medicine Department, Hepatology Outpatient Clinic between February and June 2021.

Reference	Naguib 2022[5]
Number of patients	Total n = 132. Adrenal insufficiency n = 85. Normal adrenal function n = 46
Patient characteristics	Age, mean (SD): 55.2 (8.9) years Gender (male to female ratio): 84:48 Ethnicity: NR Setting: Tertiary care hospital Country: Egypt Inclusion criteria: Patients were considered for the study if they met the following criteria: age 18 years and above, hemodynamically stable with a mean arterial pressure (MAP) > 70 mm Hg and not on vasopressors. Exclusion criteria: The following were the criteria for exclusion: history of pituitary or adrenal disease, taking steroids or other medicines that affect cortisol production (eg, etomidate, ketoconazole), severe cardiopulmonary and kidney disease, hepatocellular carcinoma, critical illness, sepsis, active infection, receiving oral or parenteral antibiotic therapy within the last 30 days before enrolment and pregnancy.
Target condition(s)	Adrenal insufficiency
Index test(s) and reference standard	Index test Hyponatraemia < 135mEq/l. The clinical information of the patients, including basic demographics, clinical features, additional comorbidities, and the results of routine laboratory tests, was recorded. No further details provided. Reference standard The adrenal function of all subjects was evaluated by measuring basal and peak cortisol after 60 minutes following the short Synacthen test (SST). Basal cortisol was defined as the morning cortisol concentration (between 8:00 and 9:00 am) before Synacthen administration. The highest cortisol concentration at 60 minutes after 250 µg Synacthen injection was considered as peak cortisol. A normal response to the Synacthen stimulation test (SST) was defined as a peak total serum cortisol concentration of at least 18 µg/dl. For the purposes of this study, AI was defined as having a basal cortisol of less than 9 µg/dl and/or a peak cortisol of less than 18 µg/dl. Time between measurement of index test and reference standard: Not reported.

Reference	**Naguib 2022[5]**				
2×2 table		Reference standard +	Reference standard −	Total	Hyponatraemia (< 135mEq/l)
	Index test +	32	4	36	
	Index test −	54	42	96	
	Total	86	46	132	
Statistical measures	Index text: Hyponatraemia (< 135mEq/l) Sensitivity: 0.37 (95% CI 0.27- 0.48) Specificity: 0.91 (95% CI 0.79 - 0.98) PPV: 0.89 NPV: 0.44 PLR: 4.28 NLR: 0.69				
Source of funding	This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fast-track Research Funding Program				
Limitations	Risk of bias: serious (unclear patient selection (no information provided), unclear application of the reference standard (unclear if blinded) and unclear timing between index test and reference standard) Indirectness: serious population indirectness (concerns over applicability of evidence from people with stable liver cirrhosis to general population)				
Comments	Diagnostic accuracy data calculated by NICE from raw data				

Reference	**Wolff 2001[7]**
Study type	Prospective cohort study (index test and reference standard data collected cross-sectionally)
Study methodology	Data source: Patients with a confirmed diagnosis of AIDS. Recruitment: Between July 1996 and March 1998, 272 patients with a presumptive diagnosis of AIDS admitted to the Hospital de Clínicas de Porto Alegre for treatment, were evaluated for entry to the study. Those meeting inclusion/exclusion criteria were enrolled.
Number of patients	Total n = 72, total analysed n = 63 (abnormal response to ACTH n = 12, normal rapid ACTH test n = 51)
Patient characteristics	Age, mean (range): 34.6 (16-62) years. Gender (male to female ratio): 50:13

Reference	**Wolff 2001[7]**				
	Ethnicity: 73% Caucasian Setting: single hospital Country: Brazil Inclusion criteria: confirmed diagnosis of AIDS, admitted to hospital for treatment. Exclusion criteria: diagnosis of AIDS not confirmed, using glucocorticoids or had used them during the month prior to the study, unable to sign the informed consent form or to answer the questionnaire, no venous line access, died or discharged before the ACTH test.				
Target condition(s)	Adrenal hypofunction				
Index test(s) and reference standard	Index tests A standard questionnaire and clinical examination were used to assess signs or symptoms that could be related to adrenal insufficiency (presence of weakness, fatigue, weight loss, anorexia, nausea, vomiting, diarrhoea, muscle or joint pain, arterial hypotension, hyperpigmentation, electrolyte abnormalities or a history of glucocorticoid use). Reference standard Low-dose ACTH test: 250 µg vial of 1-24 ACTH (Cortrosyn®, Organon International Oss) diluted in sterile saline solution to a concentration of 1 µg/mL. An indwelling intravenous catheter was inserted into the forearm between 7:00 a.m. and 8:00 a.m. Blood samples was taken right before, and 30 and 40 minutes following the injection of 1 mg of 1-24 ACTH. HPA axis considered as normal when the patient had a serum cortisol level ≥ 18 µg/dL in at least 1 measurement (based on measurements in healthy controls). Time between measurement of index test and reference standard: not reported.				
2×2 table		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	9	27	36	
	Index test −	3	24	27	
	Total	12	51	63	
		Reference standard +	Reference standard −	Total	Lethargy (weakness)
	Index test +	5	26	31	
	Index test −	7	25	32	
	Total	12	51	63	

Reference	**Wolff 2001[7]**				
		Reference standard +	Reference standard −	Total	Nausea
	Index test +	6	20	26	
	Index test −	6	31	37	
	Total	12	51	63	
		Reference standard +	Reference standard −	Total	Vomiting
	Index test +	5	16	21	
	Index test −	7	35	42	
	Total	12	51	63	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	3	16	19	
	Index test −	9	35	44	
	Total	12	51	63	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	10	36	46	
	Index test −	2	15	17	
	Total	12	51	63	
Statistical measures	<u>Index text: lethargy (fatigue)</u> Sensitivity: 0.75 (95% CI 0.43-0.95) Specificity: 0.47 (95% CI 0.33-0.62) PPV: 0.25 NPV: 0.89 PLR: 1.42 NLR: 0.53 <u>Index text: lethargy (weakness)</u> Sensitivity: 0.42 (95% CI 0.15-0.72) Specificity: 0.49 (95% CI 0.35-0.63) PPV: 0.16 NPV: 0.78 PLR: 0.82 NLR: 1.19				

Reference	Wolff 2001[7]
	Index text: nausea Sensitivity: 0.50 (95% CI 0.21-0.79) Specificity: 0.61 (95% CI 0.46-0.74) PPV: 0.23 NPV: 0.84 PLR: 1.28 NLR: 0.82 Index text: vomiting Sensitivity: 0.42 (95% CI 0.15-0.72) Specificity: 0.69 (95% CI 0.54-0.81) PPV: 0.24 NPV: 0.83 PLR: 1.33 NLR: 0.85 Index text: diarrhoea Sensitivity: 0.25 (95% CI 0.05-0.57) Specificity: 0.69 (95% CI 0.54-0.81) PPV: 0.16 NPV: 0.80 PLR: 0.80 NLR: 1.09 Index text: weight loss Sensitivity: 0.83 (95% CI 0.52-0.98) Specificity: 0.29 (95% CI 0.17-0.44) PPV: 0.22 NPV: 0.88 PLR: 1.18 NLR: 0.57
Source of funding	Rio Grande Research Support Foundation do Sul (FAPERGS).
Limitations	Risk of bias: very serious (unclear reporting on patient selection; whether reference standard was conducted without knowledge of index test results; or timing between index test and reference standard)

Reference	**Wolff 2001[7]**
	Indirectness: very serious (serious population indirectness due to concerns over applicability of evidence from AIDS population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/mL ACTH test)
Comments	Diagnostic accuracy data calculated by NICE from raw data