

# Diagnosis and presenting features of autoimmune hepatitis at a central referral hospital in South Africa

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**Background.** Autoimmune hepatitis (AIH) has scarcely been reported on in patients of black African descent. Similarly, few studies have focused on the relationship between AIH and HIV infection.

**Objective.** To describe the presenting features of AIH from a single referral centre in a sub-Saharan African setting. We also compare the clinical and biochemical features of people with HIV to people without HIV.

**Methods.** This study was a retrospective chart review. Patients were included if they fulfilled criteria for the International AIH Group simplified score for probable or definite AIH, were  $\geq 18$  years old at inclusion, and attended the adult gastroenterology clinic at a central referral hospital in South Africa for the period 1 January 2015 to 31 December 2020 on at least two occasions.

**Results.** Forty cases were included, of which 33 (82.5%) were female and 33 (82.5%) were black African. Median age at diagnosis was 26 years. A diagnosis of a coexistent autoimmune disease was made in 22.5% of patients, with systemic lupus erythematosus being the most common (12.5%). There were 16 people living with HIV, all of whom were female ( $p=0.03$ ), with a significantly older age of disease onset compared with people without HIV (median age 38 v. 17.5 years,  $p<0.001$ ).

**Conclusion.** AIH is a disease most commonly affecting young females. Female sex and older age of onset is associated with AIH in people living with HIV.

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Autoimmune hepatitis (AIH) is a chronic inflammatory condition of the liver, with a reported annual incidence rate of 0.5 - 2.2 per 100 000 population.<sup>[1]</sup> The female-to-male ratio is approximately 4:1 in type 1 AIH and 10:1 for type 2 AIH.<sup>[2]</sup> It can affect people of any age group and of all ethnic backgrounds.<sup>[3,4]</sup> Clinical presentation may range from asymptomatic to fulminant hepatic failure. Diagnosis was aided with the development of the 1999 International Autoimmune Hepatitis Group (IAIHG) scoring system, and the subsequent 2008 simplified score intended for routine clinical practice.<sup>[5]</sup>

Studies reporting on the presenting features of AIH in patients of black African descent are exceedingly rare.<sup>[6]</sup> In addition, the coexistence of AIH and HIV infection has been rarely reported in the literature. People living with HIV often have other more common reasons for developing liver injury, such as medication, opportunistic infections, steatosis/steatohepatitis, alcoholic or viral hepatitis and AIDS cholangiopathy.<sup>[7]</sup> Therefore, an autoimmune process may not be considered early in the differential for such patients, or the patient expires prior to the completion of diagnostic testing.<sup>[8]</sup> To our knowledge, direct comparisons between people living with HIV and those living without HIV within the same population have not previously been reported on.

This study aims to describe the presenting features of AIH from a single referral centre in a sub-Saharan African setting. We also compare the clinical and biochemical features of people with HIV to people without HIV in this cohort.

## Methods

The study was conducted at a central referral hospital in South Africa (SA).

Patients were included if they met the following criteria:

- (i) Diagnosis of AIH based on the IAIHG simplified scoring criteria with a score  $\geq 7$  for definite, and  $\geq 6$  for probable.
- (ii) Attended the adult gastroenterology clinic for the period 1 January 2015 to 31 December 2020 on at least two occasions.
- (iii)  $\geq 18$  years old at inclusion.

## Case capture

Electronic outpatient hospital records were searched using ICD 10 codes for AIH (K75.4) and cirrhosis (K74). In addition, the terms primary biliary cholangitis (K74.3) and primary sclerosing cholangitis (K83.0) were searched to identify any possible cases with overlap syndromes, as well as drug-induced liver injury (K71) to identify any cases fulfilling criteria for AIH, but for which a drug(s) obscured the diagnosis. Diagnostic evaluation for AIH was conducted by retrospectively employing the IAIHG simplified score to each case based on available electronic biochemical, immunological and histological data.

Incident cases (AIH diagnosis after 1 January 2015) and prevalent cases (AIH diagnosis before 1 January 2015 plus a minimum of two outpatient visits after 1 January 2015) were included. Information was collected using a bespoke data collection tool – a Word (Microsoft, USA) document designed to facilitate capture of patient demographic and clinical data. Each case was cross-checked to minimise inconsistencies and errors in data capturing.

## Statistics

Data were analysed using Excel (Microsoft, USA) and SPSS (IBM, USA). Continuous variables were expressed as means and standard deviations, or medians and interquartile ranges (IQR). Chi-square

and Fisher's exact tests were used for categorical data comparisons. The *t*-test or Mann-Whitney U test was used to compare groups. *P* was significant at <0.05.

**Ethical approval**

Ethics approval was obtained from the relevant Biomedical Research Ethics committee (ref. no. BREC/00003867/2022) and conforms to the provisions of the Declaration of Helsinki.

**Results**

**Overall cohort**

A total of 660 records were retrieved, and 58 patients were identified as having a possible diagnosis of AIH. Of these, 18 cases were subsequently excluded as they did not meet the IAIHG simplified score due to incomplete/missing data. A final cohort of 40 patients was established. Demographic and clinical information of patients are represented in Table 1.

**Clinical features**

There were 33 (82.5%) female and 33 (82.5%) black African patients. The median age at diagnosis was 26 years. Symptoms (Fig. 1) were present in 34 (87.18%) patients, with a median duration of symptoms prior to diagnosis being 7 months. The correct diagnosis was identified in approximately half (48.28%) of patients at 6 months following the onset of symptoms. Jaundice (65.79%) and hepatomegaly (50%) were the most common clinical features on presentation (Fig. 2). Cirrhosis was present in half (50%) of patients as detected on imaging studies or on histology. Portal hypertension was diagnosed either clinically or based on imaging features and was present in 13 (32.5%) of patients. A diagnosis of a coexistent autoimmune disease was made in 22.5% of patients, with systemic lupus erythematosus (SLE) being the most common (12.5%). Almost half (47.5%) of all patients were on potentially hepatotoxic drugs at the time of presentation.

**Laboratory features**

All patients included in the study had an abnormal liver function test on presentation (Table 2). Transaminase enzymes were markedly elevated in most patients, with a median alanine transaminase (ALT) of 225.5 U/L (IQR 100 - 456.5 U/L) and aspartate transaminase (AST) of 277.5 U/L (IQR 140 - 753.5 U/L). Similarly, cholestatic enzymes were elevated to varying levels with a median alkaline phosphatase (ALP) of 264 U/L (IQR 190 - 486.5 U/L) and gamma-glutamyl transferase (GGT) of 234 U/L (IQR 112 - 594.5 U/L). The median total bilirubin was 36.5 µmol/L (IQR 18.25 - 82.5 µmol/L). Albumin was marginally reduced in most patients with a mean value of 34.02 g/L. The international normalised ratio (INR) was elevated to a level ≥1.5 in 11 (27.5%) patients at the time of presentation. All patients tested for IgG levels had values >1.1, above the upper limit of normal with a mean (standard deviation) of 36.66 (11.46) g/L. Thirty-nine (97.5%) patients had all three antibody tests, standard for suspected AIH, done. One patient had an anti-liver-kidney microsomal (anti-LKM) antibody test omitted but was classified as type 1 AIH due to a positive ANF with a titre ≥1:80 and a positive smooth muscle antibody. From these results it was determined that 36 (90%) patients could be classified as type 1 AIH, 2 (5%) patients as type 2 AIH and 2 (5%) as seronegative AIH. Tests for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) were negative in all patients.

**Histology**

Thirty-eight (95%) patients had a liver biopsy. Two patients did not have a liver biopsy, one due to an initial prolonged INR who

**Table 1. Demographics and clinical features (N=40)**

Cohort characteristics	Value, n (%)*
Female	33 (82.5)
Race	
Black	33 (82.5)
White	2 (5)
Asian	4 (10)
Coloured	1 (2.5)
Age of onset (years), median (IQR)	26 (14 - 37)
Duration of symptoms prior to diagnosis, median (months)	7
IAIHG Simplified Score	
Definite AIH	15 (37.5)
Probable AIH	25 (62.5)
Body mass index, mean (SD) kg/m <sup>2</sup>	24.41 (6.75)
Other autoimmune disease	9 (22.5)
Systemic lupus erythematosus	5 (12.5)
Limited cutaneous systemic sclerosis	1 (2.5)
Diffuse cutaneous systemic sclerosis	0 (0)
Mixed connective tissue disease	1 (2.5)
Inflammatory bowel disease	1 (2.5)
Rheumatoid arthritis	1 (2.5)
People living with HIV	16 (40)
CD4 count (cells/mm <sup>3</sup> ), median (IQR)	503 (333 - 773)
Lower than detectable viral load stated	10 (71.43)
Drug use	19 (47.5)
TB drugs	3 (7.5)
ARVs	15 (37.5)
TB drugs and ARVs	1 (2.5)

\* Unless otherwise indicated. IQR = interquartile range; IAIHG = International Autoimmune Hepatitis Group AIH = autoimmune hepatitis; TB = tuberculosis; ARV = antiretroviral drugs.

was treated for presumed AIH and demonstrated a good response to corticosteroid therapy, and the other due to patient refusal. Histology results were classified as typical of AIH if stated as such by the pathologist or if the description of the pattern met criteria stipulated by the IAIHG in the simplified criteria for the diagnosis of autoimmune hepatitis. Of these, 14 (36.84%) patients had typical features and 22 (57.89%) patients had features compatible with AIH, with only 2 (5.26%) patients having a suboptimal biopsy owing to there being inadequate representative tissue on either sample for any meaningful conclusions to be drawn. Interface hepatitis (80.56%) and a lymphoplasmacytic infiltrate (80%) were the most common histological findings. Hallmark features such as emperipolesis and rosette formation were exceedingly rare. Both patients with seronegative AIH had typical features on liver biopsy. All patients living with HIV had a liver biopsy, with 9 having typical findings for AIH, 6 having compatible features, and 1 with a suboptimal biopsy.

**Diagnosis**

The IAIHG simplified scoring system was applied retrospectively to all patients. Fifteen (37.5%) patients were classified as definite AIH, and 25 (62.5%) patients as probable AIH.

**Subgroup comparison**

**People with HIV and people without HIV**

Sixteen (40%) patients were living with HIV at the time of their AIH diagnosis (Tables 3 and 4). All patients living with HIV were female, with a significantly older age of disease onset as

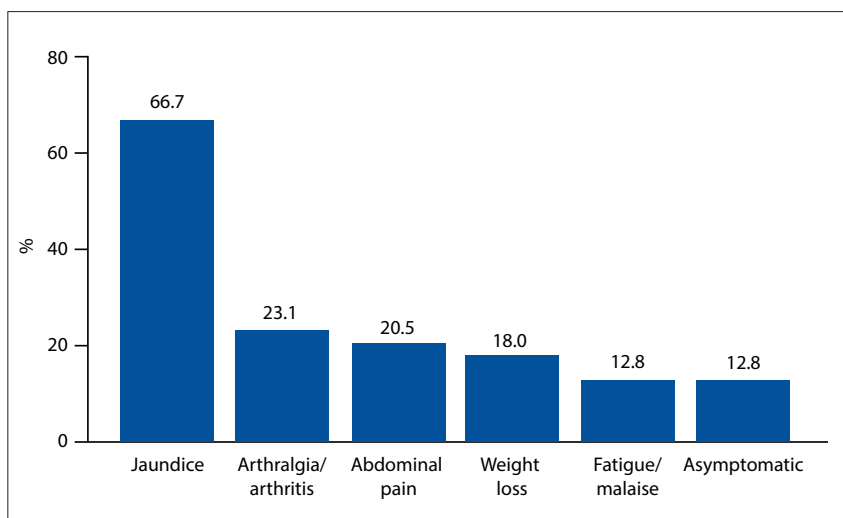


Fig. 1. Presenting symptoms.

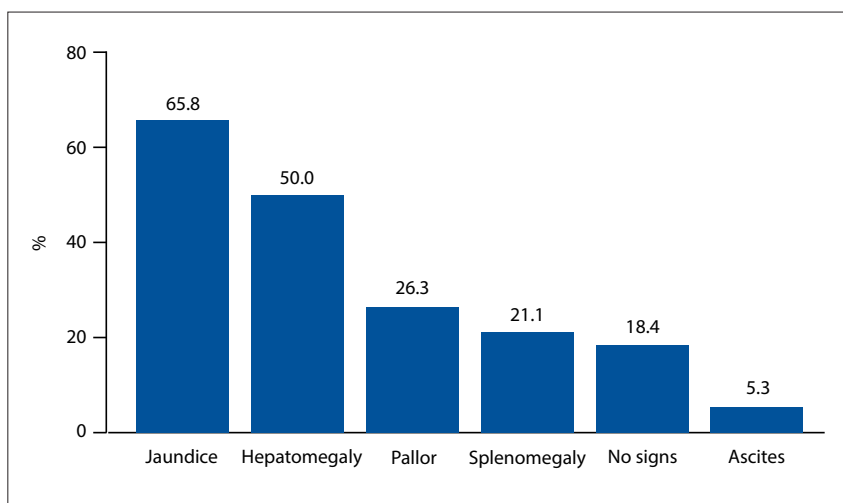


Fig. 2. Signs at presentation.

compared with patients without HIV (median age 38 v. 17.5 years,  $p < 0.001$ ). In addition, all patients living with HIV were already on antiretroviral drugs at the time of AIH diagnosis. The median duration of antiretroviral (ARV) therapy prior to onset of symptoms of AIH was 4 years (IQR 2 - 5 years), with only two patients (12.5%) presenting within 6 months. The median CD4 count was 503 cells/mm<sup>3</sup> (IQR 333 - 773 cells/mm<sup>3</sup>). Among the 14 patients who had a viral load result, only 4 had a detectable viral load.

Jaundice was a less common presenting feature in patients living with HIV (56.3% v. 72.7%), but this was not statistically significant ( $p = 0.3$ ). Cirrhosis and portal hypertension were noted in 58.3% and 37.5%, respectively, of patients without HIV, as compared with 37.5% and 25% in patients with HIV. There were no significant differences identified in the clinical and histological findings between the two groups.

Transaminase and IgG levels were consistently lower in patients living with HIV. Gamma-glutamyl transferase levels were elevated to a greater degree in patients living with HIV, with the difference between the two groups reaching statistical significance. Antinuclear factor (ANF) and anti-smooth muscle antibody (ASMA) were positive in 11 (68.75%) and 10 (62.5%) patients living with HIV, respectively.

## Discussion

Autoimmune hepatitis is a disease that affects people of all ages, genders and ethnic groups.<sup>[3,4]</sup> However, like with many autoimmune conditions, a female preponderance is well established.<sup>[2]</sup> In this study, a female predominance was noted, with similar ratios demonstrated in population studies in various nations across the globe.<sup>[9]</sup> The median age at diagnosis was 26 years (IQR 14 - 37 years). This is in stark contrast to population studies from Europe,

Asia and the Americas, where age of onset is often reported to be in middle-aged or post-menopausal women.<sup>[9]</sup> However, a London-based study comparing the median age of onset between black and white patients with AIH demonstrated a statistically significant difference between the two groups, with black patients presenting at a younger age (median 38 years v. 45 years).<sup>[10]</sup> Nonspecific symptoms were uncommon, ranging from 12.82% to 23.08%. An epidemiological study of AIH in the USA revealed marginally higher rates of similar nonspecific symptoms of 23 - 44%.<sup>[11]</sup>

Cirrhosis was detectable at or shortly after diagnosis in 50% of patients in the current study, reflecting the chronicity of the disease. This is similar to a SA study examining the characteristics of AIH in a paediatric population in which cirrhosis was detected in 56% of cases.<sup>[12]</sup> Lower rates of cirrhosis have been reported in other studies with 6.4 - 35.4% of patients having cirrhosis observed at diagnosis in East Asian countries and in many European countries such as the Netherlands, Denmark and Sweden (12, 28.3 and 30%, respectively).<sup>[13-18]</sup> Marginally lower rates have been reported in other developed nations such as Italy (23%), the UK (25%), Canada (33.9%) and the USA (43.6%).<sup>[11,19-21]</sup> In contrast, cirrhosis was a frequent finding in Southeast Asia, with cohorts from Pakistan and India reporting frequencies of 84.1% and 71.2%, respectively.<sup>[22,23]</sup> Approximately half (48.48%) of black patients in the present study had evidence of cirrhosis. A study published in 2001 reported cirrhosis as being a far more common finding on initial liver biopsy among African American patients with AIH compared with white Americans (85 v. 38%).<sup>[24]</sup> With very few patients from other race groups in this cohort, no meaningful comparison could be made.

In keeping with other reports, this study demonstrated type 1 AIH as being the most common (90%), with type 2 AIH being rare (5%).<sup>[25,26]</sup> In contrast to the local paediatric study that demonstrated a high proportion (40%) of seronegative AIH patients, we found this group to be relatively rare (5%).<sup>[12]</sup>

The presence of concomitant autoimmune conditions was a common occurrence in this cohort (22.5%). However, most of these patients were diagnosed with systemic autoimmune conditions such as SLE, as compared with a predominance of organ-specific autoimmune conditions such as autoimmune thyroid disease reported elsewhere.<sup>[27-31]</sup>

Given the number of people living with HIV identified in the study, a comparison

**Table 2. Serum parameters at presentation**

Parameter	Value	Patients with result, <i>n</i>
Haemoglobin (g/dL), mean (SD)	11.45 (2.24)	40
White cell count (× 10 <sup>9</sup> /L), mean (SD)	6.29 (3.08)	40
Platelet count (× 10 <sup>9</sup> /L), mean (SD)	202.47 (111.38)	40
Total protein (g/L), mean (SD)	90.25 (12)	40
Albumin (g/L), mean (SD)	34.02 (7.09)	40
Total bilirubin (µmol/L), median (IQR)	36.5 (18.25 - 82.5)	40
ALT (U/L), median (IQR)	225.5 (100 - 456.5)	40
AST (U/L), median (IQR)	277.5 (140 - 753.5)	36
ALP (U/L), median (IQR)	264 (190 - 486.5)	40
GGT (U/L), median (IQR)	234 (112 - 594.5)	40
INR, median (IQR)	1.19 (1 - 1.55)	40
Immunoglobulin G (g/L), mean (SD)	36.66 (11.46)	36
Autoantibody tests		
ANF, <i>n</i> (%)	24 (60)	40
≥ 1:40	2 (5)	
≥ 1:80	22 (55)	
Anti-smooth muscle antibody, <i>n</i> (%)	27 (67.5)	40
Anti-liver-kidney microsomal antibody, <i>n</i> (%)	2 (5.13)	39

SD = standard deviation; IQR = interquartile range; ALT = alanine transaminase; AST = aspartate transaminase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; INR = international normalized ratio; ANF = antinuclear factor.

**Table 3. Comparison by HIV status – Clinical characteristics and histology**

Characteristic	People with HIV	People without HIV	<i>p</i> -value
Female gender, <i>n</i> (%)	16 (100)	17 (70.8)	0.03
Age of onset, years, median (IQR)	38 (32 - 52.5)	17.5 (9.5 - 30)	< 0.001
Duration of symptoms, months, median (IQR)	6 (3.5 - 12)	8.5 (5 - 12.5)	0.5
HAART duration prior to onset of symptoms, <i>n</i> (%)			
0 - 3 months	1 (6.3)	-	-
4 - 6 months	1 (6.3)	-	-
>6 months	14 (87.5)	-	-
Clinical finding, <i>n</i> (%)			
Jaundice	9 (56.3)	16 (72.7)	0.3
Pallor	5 (31.3)	5 (22.7)	0.6
Ascites	0 (0)	2 (9.1)	0.5
Encephalopathy	1 (6.3)	0 (0)	0.4
Splenomegaly	1 (6.3)	7 (31.8)	0.1
Hepatomegaly	8 (50)	11 (50)	0.9
Histology, <i>n</i> (%)			
Interface hepatitis	12 (75)	17 (85)	0.7
Lymphoplasmacytic infiltrate	14 (87.5)	14 (73.7)	0.4
Emperipolesis	2 (12.5)	0 (0)	0.2
Rosette formation	1 (6.3)	0 (0)	0.5
Biliary changes	0 (0)	1 (5.3)	0.9
Other changes	1 (6.3)	1 (5.3)	0.9
Cirrhosis	6 (37.5)	14 (58.3)	0.2
Portal hypertension, <i>n</i> (%)	4 (25)	9 (37.5)	0.5

IQR = interquartile range; HAART = highly active antiretroviral therapy

was made between this group of patients and people without HIV. To our knowledge, this is the first head-to-head comparison of this nature reported in the literature. In keeping with published literature, a female predominance was noted. The median CD4 count of 503 cells/mm<sup>3</sup> was very similar to the median of 557 cells × 10<sup>6</sup>/L published in a 2019 case series, which reported 13 people with HIV diagnosed with AIH.<sup>[32]</sup> Only 4 patients had a detectable viral load, and 2 cases had unreported viral loads. This is consistent with a

2019 systematic review of the published literature on AIH in patients with HIV infection that demonstrated most patients as having suppressed viral loads (7 out of 35 had detectable viral loads, and 2 cases had unreported viral loads). Similarly, all patients were already on highly active antiretroviral therapy (HAART) at the time of their AIH diagnosis. Other autoimmune conditions coexisted in 17.1% of patients in the systematic review, with this cohort demonstrating a comparable percentage (18.75%), all of whom had SLE.<sup>[33]</sup> Cirrhosis

**Table 4. Comparison by HIV status – serum parameters**

Characteristic	People with HIV		People without HIV		p-value
	n	Median (IQR)	n	Median (IQR)	
Biochemical data					
ALT (U/L)	16	138.5 (92.5 - 410)	24	279.5 (119 - 462)	0.4
AST (U/L)	16	211 (144.5 - 554)	20	445.5 (92 - 846)	0.6
ALP (U/L)	16	289.5 (226 - 514.5)	24	234.5 (184 - 468)	0.3
GGT (U/L)	16	528.5 (270.5 - 888.5)	24	159 (91.5 - 274)	0.002
INR	16	1.1 (1 - 1.43)	24	1.2 (1 - 1.6)	0.6
Immunoglobulin G (g/L)	15	31.5 (28.1 - 38.2)	21	38.1 (29.4 - 40.8)	0.4
Haemoglobin (g/dL)	16	11.4 (10 - 12.4)	24	11 (10.3 - 13.2)	0.6
White cell count (× 10 <sup>9</sup> /L)	16	6.3 (4.9 - 7.9)	24	6 (3.7 - 7)	0.4
Platelet count (x 10 <sup>9</sup> /L)	16	191 (153 - 276)	24	193.5 (73.5 - 264.5)	0.5
Total protein (g/L)	16	88 (81.5 - 90.5)	24	91 (84 - 95.5)	0.3
Albumin (g/L)	16	35 (30 - 38.5)	24	32 (30 - 40.5)	0.8
Total bilirubin (µmol/L)	16	33.5 (11 - 104)	24	40 (19.8 - 60)	0.7

ALT = alanine transaminase; AST = aspartate transaminase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; INR = international normalised ratio.

and portal hypertension were more frequently encountered in patients without HIV, but the differences were not statistically significant given the small number of patients for comparison in each group. There was a trend toward lower transaminase levels observed in patients with HIV, and although not statistically significant, a proposed explanation for this finding is a less robust immune response in this patient group. The degree of elevation of transaminases was comparable between this study and the 2019 case series (median ALT 138.5 U/L v. 177 U/L, AST 211 U/L v. 178 U/L). Regarding the consistently higher GGT levels among patients with HIV, it is unclear whether this represents a unique feature of AIH in this subgroup or whether this was a result of some external influence such as being drug related. All patients had elevated IgG levels in comparison with the 85% reported in the 2019 case series.<sup>[32]</sup> Interestingly, there were no other significant differences between people with HIV and people without HIV, which may be explained by the lack of severe immunodeficiency noted in the former group.

People living with HIV often have other more common reasons for developing liver injury, such as medication, opportunistic infections, steatohepatitis, alcoholic or viral hepatitis and AIDS cholangiopathy, hence a liver biopsy remains a useful diagnostic procedure in this setting.<sup>[7]</sup> The occurrence of AIH following the initiation of HAART, with recovery of CD4 cell count, may suggest a manifestation of immune reconstitution, or may be recognition of a previously subclinical disease process. However, the argument for this association is not supported by this study, as most patients had been on HAART for >6 months prior to the onset of AIH symptoms. This finding is similar to that of the 2019 case series, in which 11 of the 13 people living with HIV had been initiated on ARVs at the time of diagnosis of HIV infection, with a median duration of ARV therapy to AIH diagnosis of 6 years.<sup>[32]</sup> Additionally, despite the differing pathogenetic mechanisms between the two disease processes, with HIV infection resulting in progressive depletion and AIH the hyper-reactivity of T-lymphocytes, it has been shown that HIV has the potential to initiate an autoimmune process through polyclonal stimulation of B cells.<sup>[34]</sup> The mechanisms by which AIH emerges in HIV infection remain poorly understood. Nonetheless, further research is needed to unravel the relationship between these

two conditions, and thus improve the approach to managing both conditions simultaneously.

The limitations of this study include its small sample size, missing data and it being limited to a single facility, as well as to patients who had sought medical treatment only within the public sector.

## Conclusion

The results of this study indicate that, in a predominantly black African population, AIH mainly affects younger adult females. The presence of other autoimmune diseases, particularly SLE, was not uncommon. A comparison between people with HIV and people without HIV with concomitant AIH demonstrated a significantly older age of onset and a female predominance for AIH occurrence in the former group. GGT levels were higher among people living with HIV, although the reason for this remains unclear. Further research into AIH and HIV is required to elucidate the clinical, immunological and pathological features in this group of patients.

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**Author contributions.** The study concept and design were carried out by YM and VGN. Acquisition, analysis and interpretation of the data, as well as drafting of the work was carried out by YM. Critical revision of the manuscript for important intellectual content was performed by VGN. Final approval of the manuscript was carried out by YM and VGN. Statistical analysis was performed by Ms Cathy Connolly.

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**Conflicts of interest.** None.

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