Case Report

Acute Intermittent Porphyria with a Secondary Porphyria Cutanea Tarda–like Biochemical Pattern in a patient with co-morbid Human Immunodeficiency Virus infection

Kagiso M. Masemola[1,2*], Kgaogelo R. Masemola[2,3], Mogomotsi Dintshi[1,2], Taryn Pillay[2,3]

[1]*Department of Chemical Pathology, School of Pathology, University of the Witwatersrand, Johannesburg (South Africa)*
[2]*National Health Laboratory Services (South Africa)*
[3]*School of Laboratory Medicine, Medical Science, College of Health Sciences, University of KwaZulu-Natal (South Africa)*

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[*]***Corresponding Author:***
Kagiso Masemola
University of the Witwatersrand
Johannesburg, South Africa, 2193
Email: kagiso.masemola@nhls.ac.za

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Abstract

Introduction: Porphyrias are rare inherited disorders of heme synthesis caused by reduced activity of one of the eight enzymes in the pathway. When early precursors accumulate, acute hepatic porphyrias occur, which present as severe neurovisceral attacks. When later, light-sensitive porphyrins accumulate, they cause cutaneous forms with chronic photosensitivity, blistering and skin fragility. Although these patterns are usually distinct, acute, and cutaneous features may appear together. This may reflect two separate genetic defects, but more often occurs when oxidative stress, such as from iron overload, chronic infection, or drugs, secondarily inhibits the fifth enzyme, uroporphyrinogen decarboxylase. This creates a mixed porphyrin pattern in which the usual distinctions between acute and cutaneous porphyrias are blurred, making diagnosis challenging.

Case Presentation: A 22-year-old woman living with human immunodeficiency virus (HIV) infection presented with recurrent abdominal pain during the luteal phase of menstruation, autonomic instability, and limb weakness that improved following heme arginate therapy. Urine porphobilinogen was markedly elevated, and hydroxymethylbilane synthase (*HMBS)* gene sequencing confirmed acute intermittent porphyria (AIP). However, her porphyrin studies also demonstrated pronounced urinary uroporphyrin elevation together with faecal isocoproporphyrins, a pattern characteristic of porphyria cutanea tarda (PCT).

Discussion: The findings are consistent with AIP complicated by secondary hepatic inhibition of uroporphyrinogen decarboxylase. In this patient, secondary uroporphyrinogen decarboxylase (UROD) inhibition was likely driven by persistent HIV viraemia, antiretroviral-associated hepatic oxidative stress, and chronic inflammatory activation which are well-recognised risk factors for acquired PCT-like biochemical patterns.

Conclusion
This case demonstrates how co-morbidities can modify classical porphyria biochemical patterns and reinforces the need for integrated urine, plasma, and faecal interpretation, especially when biochemical profiles appear mixed. Clinically, patients living with HIV who have porphyria may benefit from closer monitoring for factors that increase liver stress, especially ongoing viraemia, hepatotoxic or porphyrinogenic drugs, alcohol use and iron overload. When virological control is poor, the risk of secondary UROD inhibition and mixed biochemical findings may increase. Regular review of HIV virological control, liver function, medication safety and porphyrin profiles may therefore help prevent recurrent attacks and reduce diagnostic confusion.

Introduction
Porphyrias are disorders caused by reduced activity of one of the eight enzymes in the heme biosynthesis pathway [1]. When an enzyme is impaired, intermediates before the metabolic block accumulate [1,2]. These accumulating precursors, rather than reduced heme production, cause the clinical features [2,3]. The pattern of precursor accumulation determines the clinical phenotype [1,3].
Acute porphyrias such as AIP, from reduced porphobilinogen deaminase activity, present with severe neurovisceral attacks [2,3]. In contrast, cutaneous porphyrias such as PCT, due to reduced UROD activity, cause blistering photosensitivity [2,4]. Some forms such as variegate porphyria show both acute and cutaneous manifestations [1].
Acute attacks are medical emergencies because rapid rises in delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) disrupt neuronal function [3]. Acute porphyria presents with severe abdominal and autonomic symptoms, which may progress to seizures, behavioural changes or respiratory failure [2,3].
Cutaneous porphyrias occur when photoactive porphyrins accumulate in the skin, causing blistering and fragility on light exposure [2,4,5].
Although porphyrias are usually considered separate entities, mixed biochemical patterns do occur [1,3]. Simultaneous accumulation of early and late intermediates may indicate true dual porphyria or a single inherited defect complicated by secondary reduction of uroporphyrinogen decarboxylase activity. In people with HIV, drug-induced cytochrome P450 induction, hepatotoxicity and disordered iron metabolism can create this secondary block [5,6].
This report describes a young woman with genetically confirmed AIP and a PCT biochemical pattern, illustrating the diagnostic complexity in HIV-related hepatic stress.

Case Description
A 22-year-old Black South African woman with HIV infection, diagnosed three years prior, was receiving fixed-dose, once daily, antiretroviral therapy (ART) in the form of tenofovir (TDF) 300 mg, lamivudine (3TC) 300 mg and dolutegravir 50 mg (TLD). She presented with recurrent, cyclical episodes of acute abdominal pain, tachycardia, vomiting, and progressive limb weakness that reliably coincided with the luteal phase of hermenstrual cycle. She denied alcohol use, prolonged fasting, or recreational drugs.

Initial laboratory investigations revealed hypo-osmolar hyponatraemia with serum sodium of 127 mmol/L (135–145 mmol/L) and serum osmolality of 264 mmol/kg (275–295 mmol/kg), with an inappropriately concentrated urine osmolality of 649 mmol/kg (50–1200 mmol/kg) consistent with syndrome of inappropriate anti-diuresis. A microcytic anaemia with biochemical iron deficiency was identified. Renal and hepatic function were otherwise unremarkable. Vitamin B12, serum folate, and viral hepatitis serology were unremarkable. There was no family history of porphyria identified.
HIV infection was diagnosed three years earlier with an initial cluster of differentiation 4 (CD4) cell count of 229 cells/μL. Ongoing adherence challenges were noted. Since commencing ART, her CD4 count has increased to 383 cells/μL, while the HIV viral load has risen from 18 200 copies/mL to 77 905 copies/mL. Given the neurovisceral symptoms, tachycardia and hyponatraemia, acute porphyria was suspected. Biochemical porphyrin analyses are summarized in Table 1. A light protected spot urine sample screened strongly positive for porphobilinogen using the Hoesch test, a recommended rapid screening method for acute hepatic porphyrias, confirming an acute porphyric attack [7]. The urine PBG:creatinine ratio was markedly increased at 69 mmol/mmol (reference <1.5 mmol/mmol), in keeping with guideline-recommended quantitative confirmation of acute hepatic porphyria [8]. Total urinary porphyrins were elevated at 1431.6 nmol/mmol creatinine. Urine porphyrin fractionation by high performance liquid chromatography demonstrated predominantly raised uroporphyrin and heptacarboxylporphyrin [8]. The plasma fluorescence scan did not peak at 626–628 nm (arguing against variegate porphyria), and the faecal profile was not typical of hereditary coproporphyria.

Simultaneously, the faecal porphyrin profile demonstrated markedly increased uroporphyrin, heptacarboxylporphyrin, and isocoproporphyrin, pathognomic of PCT. A plasma fluorescence peak at approximately 618nm, although non-specific, further supported a PCT-like biochemical profile [8]. Given the mixed biochemical pattern, *HMBS* gene sequencing was performed. This confirmed a heterozygous NM_000190.4(HMBS):c.770dup p. (Glu258Glyfs*33) frameshift variant, classified as likely pathogenic, establishing a molecular diagnosis of AIP [9]. The PCT component was attributed to acquired hepatic UROD enzyme inhibition, likely triggered by HIV-related hepatic oxidative stress and cytochrome P450 induction in the absence of iron overload or viral hepatitis. *UROD* gene sequencing is not routinely available and therefore true dual porphyria could not be excluded.

Together, the findings demonstrate AIP with a PCT-like hepatic porphyrin pattern likely due to acquired UROD inhibition. During the acute attack, the patient was managed with non-porphyrinogenic opioid analgesia for pain and intravenous 5% dextrose to suppress hepatic 5-aminolevulinate synthase 1 (ALAS1) transcription. Heme arginate was administered to provide negative feedback on ALAS1, rapidly reducing

production of neurotoxic intermediates (ALA and PBG) and shortening the duration of the attack.

During each episode, her clinical condition improved following heme therapy, pain control, and correction of electrolyte abnormalities.

Because the AIP attacks were thought to be related to the menstrual cycle, a gonadotropin-releasing hormone (GnRH) analogue was initiated for chronic management. GnRH analogues suppress ovarian steroidogenesis by downregulating pituitary GnRH receptors, resulting in suppression of cyclic progesterone surges, which induces ALAS1. In hormonally sensitive AIP, this stabilises hormonal cycling, reduces the high-risk luteal window and helps prevent recurrent neurovisceral attacks.

Table 1: Biochemical investigations of urine, blood, and faeces in the evaluation of porphyria.

Test	Result	Reference interval	Units
Urine porphyria investigations			
Total porphyrins	1431.6 (H)	<300	nmol/mmol creatinine
Uroporphyrin	1120.2 (H)	<40	nmol/mmol creatinine
Heptacarboxylporphyrin	153.5 (H)	<10	nmol/mmol creatinine
Hexacarboxylporphyrin	50.4 (H)	<5	nmol/mmol creatinine
Pentacarboxylporphyrin	67.8 (H)	<5	nmol/mmol creatinine
Coproporphyrin I	21.3	<50	nmol/mmol creatinine
Coproporphyrin III	18.4	<110	nmol/mmol creatinine
Blood porphyria investigations			
Plasma porphyrins	Positive	Negative	
Plasma fluorescence scan	Emission peak at 618 nm		
Faecal porphyria investigations			
Total porphyrins	1840 (H)	<200	nmol/g dry mass
Coproporphyrin I	310 (H)	<200	nmol/g dry mass
Coproporphyrin III	1150 (H)	<200	nmol/g dry mass
Protoporphyrin	380 (H)	<150	nmol/g dry mass
Isocoproporphyrins	Present	Absent	

H = above the reference interval

Figure 1: Heme biosynthesis pathway and relevant enzyme defects [10].

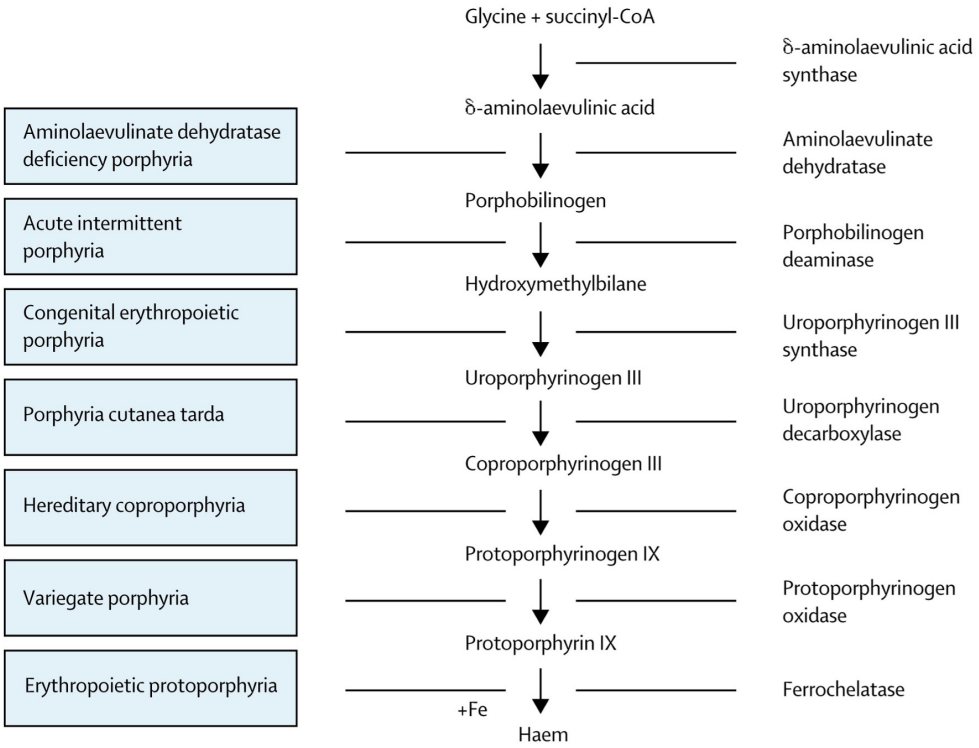

Figure 1 illustrates the heme biosynthesis pathway. AIP results from reduced HMBS activity, leading to accumulation of ALA and PBG and acute neurovisceral attacks. Inhibition of UROD activity produces a PCT-like porphyrin pattern with increased uroporphyrins and isocoproporphyrins, as observed in this patient.

Discussion

The markedly elevated urinary porphobilinogen during the acute neurovisceral episodes, together with the absence of a plasma fluorescence peak at 623–626 nm and the lack of increased faecal coproporphyrins, strongly supported an acute hepatic porphyria consistent with AIP rather than Variegate Porphyria or Hereditary Coproporphyria [1,8]. Identification of a pathogenic variant in the HMBS gene confirmed the diagnosis of AIP in this patient [9].

At the same time, the faecal porphyrin profile showed a dominant uroporphyrin and heptacarboxylporphyrin pattern with clear formation of isocoproporphyrins. This profile is characteristic of PCT or a PCT-like hepatic porphyrin pattern and reflects decreased activity of the enzyme uroporphyrinogen decarboxylase [6]. PCT arises when hepatic UROD activity falls below roughly 20%, often due to oxidative conversion of uroporphyrinogen into inhibitor porphyrinogens under conditions of hepatic stress [6,8].

The simultaneous presence of an AIP profile and a PCT-like biochemical pattern raises two possible explanations. The first is true dual porphyria caused by inherited defects in both the HMBS and UROD genes. Figure 1 illustrates the heme biosynthesis pathway, highlighting the enzymatic blocks relevant to AIP and the downstream porphyrin accumulation observed in this case [8]. The second is a functional dual pattern in which a single inherited defect in the HMBS gene combines with acquired suppression of uroporphyrinogen decarboxylase due to hepatic stress.

Despite the lack of genetic sequencing, clinical evidence suggests this case represents a secondary PCT-like pattern rather than a primary defect. Notably, the patient exhibited iron deficiency, which contradicts the classic PCT phenotype of iron overload. However, localized hepatic oxidative stress can impair UROD enzyme function regardless of systemic iron status. Furthermore, iron deficiency may exacerbate the underlying AIP by limiting substrate availability for ferrochelatase, thereby further reducing the regulatory heme pool and upregulating ALAS1 activity [11]. We propose that chronic HIV infection served as the primary driver; HIV-induced oxidative stress and mitochondrial impairment likely facilitated the formation of oxidized porphyrinogens [5,6]. These molecules inhibit UROD activity, effectively producing a biochemical phenotype of PCT [5].

The patient was receiving a tenofovir disoproxil fumarate, lamivudine, and dolutegravir–based antiretroviral regimen, with documented adherence challenges and virological non-suppression. While this regimen is generally well tolerated, both chronic HIV infection and antiretroviral exposure have been associated with mitochondrial dysfunction, and hepatic oxidative stress, even in the absence of overt biochemical liver injury. In this context, subclinical hepatic metabolic stress may plausibly contribute to secondary suppression of uroporphyrinogen decarboxylase activity, providing a mechanistic explanation for the observed PCT-like biochemical profile despite normal liver enzymes and the absence of classical iron overload.

Pathophysiologically, both HIV infection and antiretroviral therapy can promote hepatic oxidative stress and metabolic

dysfunction that may secondarily inhibit UROD [5,6,12]. Chronic HIV infection has been associated with increased generation of reactive oxygen species, altered iron handling, and CYP450 induction, all of which favour oxidative conversion of uroporphyrinogen to inhibitory porphyrinogens within hepatocytes [5,6,11]. Several ART agents may further contribute through mitochondrial toxicity, steatotic liver change and disruption of hepatic redox pathways, even when conventional liver biochemistry is normal [5,12]. When hepatic UROD activity is sufficiently reduced, a PCT-like porphyrin pattern emerges with excess uroporphyrins and isocoproporphyrins, as seen in this case [4,6,8]. In this context, poor virological control may lower the threshold for secondary UROD inhibition and modify the biochemical expression of underlying AIP [5,13].

True dual porphyria was considered but deemed less likely due to the absence of persistent biochemical features across multiple sample types and the lack of confirmatory genetic evidence [9].

Drug-induced pseudoporphyria and antiretroviral-associated photosensitivity were also considered in the differential diagnosis [5]. However, pseudoporphyria is typically characterised by cutaneous blistering in the absence of porphyrin over-production, whereas this patient demonstrated marked increases in urinary uroporphyrin and heptacarboxylporphyrin together with faecal isocoproporphyrins, which are regarded as pathognomonic for hepatic UROD inhibition [4,6,7]. Furthermore, the patient was receiving a dolutegravir-based regimen, and antiretroviral-related photosensitivity is both uncommon with this regimen and not associated with the porphyrin excretion pattern observed [5]. These findings support a true PCT-like biochemical phenotype rather than drug-induced pseudoporphyria.

From the perspective of laboratory medicine, this case shows that accurate porphyria diagnosis cannot rely on a single specimen type [7,10,14]. Interpretation depends on integrating information from several sample types, including urine for early pathway precursors, plasma for fluorescence patterns that separate acute porphyrias, and faeces for downstream porphyrins [8,10,14]. A PCT- type faecal porphyrin pattern should therefore be regarded as evidence of reduced hepatic uroporphyrinogen decarboxylase activity even in the absence of skin findings [4,6].

This case also illustrates the value of careful attention to pre analytical factors, particularly in settings with limited resources. Protection of samples from light, appropriate timing of specimen collection during clinical attacks and thoughtful review of concurrent medications, iron status and hormonal influences all contribute to accurate interpretation of porphyrin studies.

Patient Outcome

At present, the patient continues to experience acute porphyria attacks, though their frequency and severity have decreased since the initiation of GnRH analogue therapy. She remains under the care of the endocrine outpatient department, where management is focused on maintaining virological suppression and minimizing hormonal triggers. Long-term follow-up aims to determine if the secondary PCT-like biochemical profile is transient or persistent; this will be assessed through serial porphyrin studies performed during periods of clinical stability.

Limitations

UROD gene sequencing was not available. Although the biochemical pattern strongly suggests secondary hepatic UROD inhibition rather than hereditary PCT, the absence of UROD sequencing means that true dual porphyria (co-existence of pathogenic HMBS and UROD variants) cannot be completely excluded.

Secondly, although we propose that HIV-mediated oxidative stress was the primary driver of the PCT-like profile, the lack of independent assessment for liver fibrosis or steatosis is a limitation. Without this data, we cannot fully exclude the presence of underlying structural liver disease as a synergistic factor in impairing UROD function.

A further limitation is that repeat porphyrin studies were only performed during subsequent acute attacks, rather than in the period of clinical stability immediately following therapy. While these follow-up results confirmed the persistence of the underlying AIP, the lack of testing during a stable, asymptomatic interval precludes an assessment of whether the secondary PCT-like biochemical profile resolved with improved HIV infection control.

Conclusion

This patient's biochemical porphyria pattern is most likely due to a primary HMBS deficiency causing acute attacks, while oxidative stress from uncontrolled HIV infection and hormone-driven ALAS1 induction probably caused secondary UROD inhibition.

This case shows the need for planned and consistent monitoring in HIV-positive patients with porphyria, especially when the viral load is not well controlled. The key goals are to achieve viral suppression, assess liver function and iron status at intervals, and avoid medicines that are hepatotoxic or porphyrin-inducing. To help distinguish ongoing secondary UROD inhibition from true PCT, clinicians should consider serial urine, stool and plasma porphyrin profiles. It is also important to address other causes of oxidative stress, such as alcohol use, oestrogen exposure, or viral hepatitis.

Learning points

- In settings with limited resources, reliable diagnosis depends on strict sample handling and careful clinical correlation because repeat sampling, full porphyrin profiles, and genetic confirmation may not be readily accessible.
- Isocoproporphyrins detected in faeces are a defining marker of hepatic UROD inhibition and confirm a PCT-type biochemical pattern.
- Hepatic oxidative stress, mitochondrial dysfunction, and cytochrome P450 induction associated with HIV infection and ART can secondarily suppress UROD activity, producing a PCT-like phenotype despite normal UROD genotype.
- PCT-like profiles occur when hepatic UROD activity falls below ~20%, typically due to oxidative conversion of uroporphyrinogen into inhibitory porphyrinogens.
- Progesterone-driven ALAS1 up-regulation during the luteal phase increases precursor production and can trigger cyclical neurovisceral attacks in hormonally sensitive AIP.

Author Disclosures and contributions

Ethical Clearance

Written informed consent was obtained from patient for publication of this case. Ethical clearance was obtained from the Medical Human Research Ethics Committee, University of the Witwatersrand - clearance certificate no. M250766.

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Author contributions

Conceptualization: KM Masemola, KR Masemola, M Dintshi, T Pillay.
Investigation and data curation: KM Masemola, T Pillay.
Supervision: M Dintshi, T Pillay.
Writing – original draft: KM Masemola.
Writing – review and editing: KR Masemola, M Dintshi, T Pillay.
All authors approved the final version of the manuscript.

AI disclosure

The manuscript was edited using ChatGPT (OpenAI) to improve wording and clarity. No AI tools were used to generate, change, or analyze any clinical data, laboratory results, figures, or interpretations. All scientific content and conclusions reflect the authors' own work and judgement.

Competing interests

The authors declare that they have no competing interests.

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