INTRODUCTION

Fixed drug eruption (FDE) is diagnosed clinically by linking exposure to a drug with the occurrence of fixed exanthematous reactions. It is a relatively common form of cutaneous adverse drug reaction that has been associated with over 100 medications worldwide. In Nigeria, sulphonamides, particularly sulfadoxine/pyrimethamine and trimethoprim/sulfamethoxazole (co-trimoxazole), are the dominant etiological drugs of FDE. The pathophysiological mechanism of FDE involves a type IV hypersensitivity reaction, mediated by CD8+ memory T lymphocytes of the stratum basale. Classically, FDE requires a few days to 2 weeks to develop after initial exposure and within 48 h for subsequent exposures. Typically, FDE is described as single, well demarcated, red to violaceous, round to oval, patches or plaques that heal with residual hyperpigmentation. There have been several reports of non-pigmenting FDE. Atypical presentations may include multiple/generalized, vesicles/bullae, that rupture into erosions or shallow ulcers that have been misdiagnosed as erythema multiforme, herpes genitalis, Steven–Johnson syndrome, contact dermatitis, and lichen planus. FDE can occur on any skin surface; however, oral mucosa, genitals, and perianal region have received the most attention.
We report a patient with FDE who presented with a prolonged time between re-exposure to co-trimoxazole and the onset of symptoms. The patient had residual hypopigmentation of the genitals, against the conventional hyper- or no pigmentation, as well as recurrent meatal stenosis. These features of FDE are yet to be reported in the literature.

2 | CASE REPORT

A 44-year-old circumcised man was referred to the dermatology clinic in December 2017 on account of 2 years history of recurrent penile ulcers. He has HIV infection and was compliant on Lamivudine/Zidovudine/Nevirapine for 4 years before the onset of lesions. His CD4 count at the time of presentation and throughout the period of evaluation remained above 400 cells/mm³ and a viral load of <20 copies/ml. The recurring ulcers began as solitary papules which progressively increased in size to form a shallow red ulcer that resolved after 2–3 months, leaving behind areas of hypopigmentation (Figure 1). He had variable periods of incomplete and intermittent remission. With time, the lesions became multiple, foul-smelling but limited to the glans penis and penile shaft, and there was no known precipitating or relieving factors. The patient had taken several antibiotics with no improvement. There was no history of multiple sexual partners or urethral discharge. There was an associated history of anejaculation and three recurring episodes of meatal stenosis, linked to the lesions on the glans penis. The last episode resulted in acute urinary retention. The meatal stenosis was treated with meatotomy on all three occasions.

He was referred to the dermatology clinic with a skin biopsy result suggestive of chronic penile ulcer with incomplete features of Kaposi sarcoma. The histology described focal areas of superficial stratified squamous epithelium with pseudoepltheliomatous hyperplasia and mononuclear inflammatory cells infiltrating the subepithelial stroma associated with areas of granulation tissue. For the subsequent 3 years, the patient was investigated and managed for pyogenic granuloma, donovanosis, herpes genitalis, pyoderma granuloma, syphilis, and cutaneous tuberculosis, but the symptoms of recurrent penile ulcers persisted. He had three repeated biopsies. One reported acanthosis, papillomatosis, mild hyperkeratosis and focal ulceration, a mixed inflammatory cell infiltrates in the dermis and proliferating thin-vascular channels (indicated as pyogenic granuloma), while the last two (indicated as condyloma lata) both reported focal epidermal ulceration, psoriasiform hyperplasia and intense superficial and deep perivascular arteritis and dense infiltrates of plasma cells, lymphocytes and histiocytes in the dermis, noticed predominately at the base of the ulcerated area (Figure 2). No caseation, granuloma or neoplastic activity was reported. A wound swab yielded no bacterial growth and was negative for acid fast bacilli. Treponema pallidum hemagglutinin assay and VDRL were both negative. Mycobacterium ulcerans and M. tuberculosis molecular analysis were both negative. He was treated with dapsone, doxycycline, topical mupirocin, azithromycin, systemic and topical corticosteroids, topical streptomycin, and 2 months of empirical antituberculosis drugs, with worsening of symptoms (Figure 3).

By September 2020, the patient re-presented after being lost to follow-up for 1 year. He presented with a 2- and 4-month history of ulcers on the penile shaft. The ulcers had reoccurred on the same site as past ulcers. It began as a single blister which eventually ruptured into an ulcer. He admitted to having a tingling sensation just before the eruption of the blister. The drug history of the patient at this point included oral Augmentin, Cefuroxime, Doxycycline, vitamin C, his ARV drugs, and co-trimoxazole. Further probing revealed that the co-trimoxazole, which is part of the drugs he receives from the HIV clinic as prophylaxis against Pneumocystis jiroveci pneumonia, was not as consistent as the ARV drugs. Every 3 months, the patient returned to the clinic to renew his prescription, but occasionally, co-trimoxazole will be out of stock. He had not, however, observed a connection between his intake of co-trimoxazole and the eruption of the lesions. Nevertheless, this additional information suggested differentials of...
either FDE or herpes genitalis. He was told to stop taking co-trimoxazole and to continue with his ARV drugs since co-trimoxazole is one of the most commonly prescribed medications in Nigeria connected with FDE and herpes genitalis infection had earlier been ruled out. 2,3 We observed that the ulcers healed over 3 months (Figure 4) and did not re-occur for the next 8 months of follow-up of the patient.

Following the recommendations by the European Network on Drug Allergy, 8 a patch test and subsequent provocation test with co-trimoxazole were carried out 8 months after the ulcers had healed in order to confirm the likelihood of FDE associated with the drug. The co-trimoxazole tablet was crushed and prepared at 20% in petrolatum and applied for 48 hours in Finn Chambers (SmartPractice) on the upper back’s normal skin and the region of persistent hypopigmentation on the penile shaft (Figure 5). On reading Days (D) 2, 5, and 7, there was no
reaction seen. An oral provocation test for co-trimoxazole was then done after obtaining informed consent from the patient. On D1, the patient received half of the therapeutic dose of co-trimoxazole. There was no reaction after 24 h, and he was then given the full therapeutic dose and observed for 3 days; there was still no reaction. At this point, the test was considered negative. However, the patient was asked to continue with the therapeutic dose of co-trimoxazole and to avoid all forms of antimalarial or antibiotics and to report any changes immediately. Seven weeks after, the patient reported the formation of a single irritating papule on the residual hypopigmented area of previous lesions (Figure 6). Co-trimoxazole was immediately stopped and topical steroids were applied with prompt healing within 2 weeks. The patient remained symptom-free during 18 months of follow-up.

3 | DISCUSSIONS

Genital FDE is quite challenging to diagnose in the general population and more difficult in patients with background HIV infection. Often times, it is mistaken for herpes genitalis, syphilis, or donovanosis. In reviews of 29 and 60 patients with genital FDE, respectively, Sehgal et al.9 and Pandhi et al.10 found that the typical clinical variant of genital FDE includes a solitary, well-defined edematous, superficial ulceration, pigmented macule/patch or bullae surrounded by an erythematous halo. Lesions are located commonly on the glans penis or preputial skin. Rarely do patients present with multiple lesions. This is probably due to the early presentation of patients with genital lesions as compared to those with cutaneous lesions.7 Our patient presented with multiple ulcers on the glans and penile shaft, 2 years after onset and several weeks after recurrence. Residual hyperpigmentation is one of the hallmarks of FDE, aside from similar lesions recurring at the same sites. This hyperpigmentation is seen as an indicator of site recognition.11 Non-pigmenting FDE (NPFDE) is considered the non-classical form of FDE. There have been fewer than 40 NPFDE case reports in the literature. The causative drugs of NPFDE are similar to those associated with classical FDE. Both forms of FDE have similar clinical characteristics of same-site recurrence except that there is no residual pigmentation in NPFDE. The absence of pigmentary incontinence and epidermal necrosis in NPFDE’s histology findings further demonstrate this distinction.7 The residual hypopigmentation and multiple ulcerations observed in our patient and the patient’s inability to link lesions with drug intake contributed to the delay in his diagnosis. To our knowledge, this is the first reported case of residual hypopigmentation in FDE in the literature.

Although skin biopsy is not done routinely for FDE since the diagnosis is basically clinical and no specific histopathological guidelines have been described, histological findings differ between bullous FDE and non-bullous FDE. An epidermal necrolysis pattern was significantly reported by Perron et al.12 for bullous and erosive FDE. Essentially, there is epidermal detachment, superficial and deep perivascular and interstitial infiltration of lymphocytes, neutrophils, and eosinophils (as was observed in our patient), as well as accumulation of melanophages or melanin incontinence in the superficial dermis.13 However, in our patient, we observed loss of pigmentation in the superficial dermis (Figure 2). Meanwhile, these features of bullous FDE are seen as potential diagnostic pitfalls, as they mimic other bullous dermatoses.2,3,13 Since most FDE present acutely, and thus, are usually biopsied early, histology of normal basket-weave cornified layer with spongiosis or hydrops of the basal keratocytes is often observed. The first biopsy, which was taken before the ulceration of the lesion, reported a pseudoepitheliomatosus hyperplasia. This is defined as a reactive epithelial proliferation in response to various skin conditions, which does not include FDE.14 This epidermal hyperplasia was consistent in all four biopsies, in addition to epidermal detachment and infiltration of the subepidermis by inflammatory cells. According to the general criteria proposed by Weyers et al.15 marked epithelial hyperplasia is a sign of a chronic drug eruption that was biopsied after many months. The epidermal hyperplasia reported on the biopsy

![FIGURE 6](image-url) Papule (black arrow) developed 7 weeks after re-commencing oral intake of co-trimoxazole at healed site of past ulcers.
of our patient could be due to the chronicity of the lesions and this probably led to the inconsistent histopathological diagnosis.

It is common in our clime for FDE patients to not associate their skin lesions with an offending drug. This makes the identification of the causative drug often difficult. Since FDE becomes increasingly severe with continuous intake, the identification and avoidance of the offending medication, as well as of cross-reacting substances, is the mainstay of management. Diagnostic tests to identify the etiological drug are sometimes required.

Drug provocation test (DPT) is the gold standard for diagnosing FDE, though patch testing can occasionally suffice. Patch testing for bullous/ulcerative FDE has a generally poor sensitivity and specificity. It was not surprising that we obtained a negative result. DPT is typically performed under strict supervision by the physician by beginning at a sub-therapeutic dose and re-assessing for recurrence of lesions. If the lesion has not returned, the full therapeutic dose is then administered; this dose may be continued and stopped as soon as the first objective symptom is observed. Depending on the drug, DPT may be completed within hours, days, or weeks, although a maximum of 7 days is generally recommended. However, a DPT for delayed cutaneous drug reactions such as FDE that is carried out for more than 7 days is controversial, especially if the drug is an antibiotic. This is because of the fear of inducing drug resistance.

Seven weeks, as was observed in our patient, is quite a long time to observe for the recurrence of lesions in FDE, being that it is a delayed-type hypersensitivity reaction. It is unclear if this prolonged delay is due to the phenomena called the “refractory period,” first described by Chagrin et al. a period in an already sensitized individual when subsequent exposure to the offending drug does not elicit any reaction. The period varies from weeks to months and has been reported with exposure to phenolphthalein, arsenic, and antipyrine in 1940, in Nigerians by Brown et al. and more recently to a yellow dye used in an oral contraceptive by Ritter et al. Although Chargin et al. suggested that the refractory period might be due to use of sub-therapeutic dosing, (this was not observed with our patient), the mechanism remains unknown. The recurrent meatal stenosis seen in this patient is due to a chronic inflammatory reaction from the FDE on the glans penis, a very rare cause of meatal stenosis. According to a theory put forth by Nabavizadeh et al. circumcised males with persistent inflammation in the meatal region may develop scarring and urethral meatus stenosis. However, the commonest non-infectious cause of meatal stenosis, lichen sclerosus of the glans (balanitis xerotica obliterans), was ruled out in this patient, both clinically and histologically.

Besides, lichen sclerosus is mostly reported in middle-aged uncircumcised males.

4 | CONCLUSION

We report a novel case of genital FDE with residual hypopigmentation in a HIV patient with a high CD4 count (>400 cells/mm³) and an undetectable viral load of <20 copies/ml; who had recurrent meatal stenosis as a result of the affectation of his glans penis. Histopathology and DPT were unhelpful in making a diagnosis. However, the patient’s lesion recurred 7 weeks after recommencement of the prophylactic dose of co-trimoxazole marking a probable refractory period phenomenon. A refractory period in FDE may delay early diagnosis and prompt treatment of FDE.

AUTHOR CONTRIBUTIONS

PU Ibekwe have made substantial contributions to the conception, design, obtaining of information and in the drafting of the manuscript. HO Ajibola and BA Ukonu have made substantial contributions to the design, obtaining of information and in the drafting of the manuscript. Z Babba, G Otokpa, and R Solomon have made substantial contributions to the obtaining of information and in the drafting of the manuscript.

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CONFLICT OF INTEREST

This publication is self-funded. Each author does not have any conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated, or the article describes entirely theoretical research.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

ORCID

Perpetua U. Ibekwe https://orcid.org/0000-0003-1827-1362

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