**Tenofovir-Induced** **Pure Red Cell Aplasia in a Known Patient with HIV/AIDS: A Case Report**

**Abstract**

Anemia in patients diagnosed with HIV/AIDS is attributed to generalized bone marrow failure or to autoimmune hemolytic processes. However, the two most frequent causes of anemia in these groups of patients are related to either the cytopathic effect of HIV or the antiretroviral drugs. This report was of a rare case of Tenofovir-induced Pure Red Cell Aplasia in a known Human Immunodeficiency Virus (HIV) disease patient on highly active antiretroviral therapy HAART, who presented with recurrent generalized body weakness, skin rash, easy fatigability on exertion of four months duration with a history of dizziness and palpitation. Laboratory workups were consistent with persistent anemia on account of which she was transfused with several units of blood since the commencement of Dolutegravir, Lamivudine and Tenofovir (DTG/3TC/TDF). A change in HAART regimen with the removal of Tenofovir was followed by spontaneous gradual and remarkable improvement in packed Cell Volume (PCV).

Conclusion: Although there was a paucity of data on Tenofovir-induced Pure Red Cell Aplasia, this report revealed that Tenofovir is a possible cause of Pure Red Cell Aplasia in patients receiving Tenofovir containing HAART regimen.

**Keywords:** Pure Red Cell Aplasia, Tenofovir, HIV/AIDS, HAART, Nigeria

**Introduction**

Anemia is the most common hematological disorder in people with HIV infection,1 it is almost a universal finding in HIV/AIDS patients and may also be an indicator of disease progression. Most of the time, it is attributed to generalized bone marrow failure or to autoimmune hemolytic processes. There is increased evidence of the risk of anemia with the use of anti-retroviral therapy, especially Zidovudine and lamivudine.2–4 However, Tenofovir-induced anemia in patients on anti-retroviral therapy is rare.

Pure red cell aplasia is a rare clinical disorder characterized by anemia secondary to failure of erythropoiesis, it could be congenital as in the case of Diamond Blackfan anemia DBA; or acquired as in the case of post-infection and drug-induced pure red cell aplasia. DBA usually manifests with pallor, lethargy, congenital bone deformities such as craniofacial and thumb defects, short stature, mental retardation, cancer predisposition, and normochromic, macrocytic/normocytic anemia with severe reticulocytopenia.5,6

Acquired pure red cell aplasia is mostly due to infections such, may be drug-induced, idiopathic or autoimmune-mediated.6,7 While congenital is usually irreversible, acquired forms can sometimes be transient. It manifests as severe anemia (usually normocytic, normochromic), and reticulocytopenia (reticulocyte count of <1%). Common causes of acquired pure red cell aplasia include diseases such as hematological malignancies, infections such as HIV, mumps, viral infections, drugs such as antiepileptic drugs (phenytoin, carbamazepine, sodium valproate) sulfonamides and NRTI such as lamivudine,8 others include rifampicin, and allopurinol.9 Lamivudine, a cytidine analog is an antiretroviral drug of the class nucleotide reverse transcriptase, that inhibits 1 & 2 of HIV reverse transcriptase. It is phosphorylated to active metabolite that compete for incorporation into viral DNA. One of its documented side effects is red cell aplasia due to its suppressive effect in bone marrow cell precursors.

However, several other causes of anemia have been reported in patients with AIDS. The two most frequent causes of anemia in AIDS patients are related to either the cytopathic effect of HIV or the antiretroviral drugs employed in the treatment of these patients. While lamivudine is the antiviral drug known for causing pure red cell aplasia, this study presents a rare case of tenofovir-induced pure red cell aplasia in a known RVD patient on HAART attending a clinic in a tertiary health institute in Nigeria.

**Methods**

The study was a case report of a 15-year-old known female patient diagnosed with HIV and receiving treatment at the Department of Paediatrics and child health of LAUTECH Teaching Hospital, Oyo State Nigeria.

The patient case note folder was retrieved for a detailed retrospective assessment of the reports.

Data obtained were summarized as case presented under utmost confidentiality.

Other information was obtained from online literature using the search such as Pure red cell aplasia, Anaemia in HIV/AIDS, Tenofovir, Lamivudine, and Causes of Anaemia in HIV/AIDS using articles from Google Scholar, National Library of Medicine and Researchgate.

**Case Presentation**

A 15-year-old female patient diagnosed with retroviral disease (HIV) with a history of recurrent
generalized body weakness, skin rash, easy fatigability on exertion of 4 months duration and a positive history of dizziness and increased awareness of heartbeats. Skin rash was noticed first on the legs but spread progressively to the buttocks and the upper limbs, it was pruritic with hyperpigmentation of affected skin. Productive cough and fever were noticed at presentation but denied any complaint of excessive sweating, loss of consciousness, fainting attacks, blood loss or blood in stool. The patient was diagnosed with HIV 5 years earlier when she presented with a dry cough and fast breathing. She was subsequently commenced on HAART (Dolutegravir, Tenofovir and Lamivudine) and has been regular with clinic appointments and medications. There was a history of sharing sharp objects with her parents (both parents are known patients living with retroviral disease), however, none of her siblings tested positive for HIV infection on testing. In the past 2 months, she had been admitted twice to the hospital and was transfused severally with whole blood on each occasion.

On physical examination, she was acutely ill, febrile (380C), severely pale, with generalized
hyperpigmented patches and maculopapular rash. Respiratory rate of 30 cycles/minute with reduced air entry especially on the left hemithorax, breath sounds were vesicular. Her heart rate was 120 beats/minute with a blood pressure of 99/60 mmHg (supine). The abdomen was full and moves regularly with respiration. The liver is palpably enlarged, 4cm below the right coastal margin, firm and tender. The spleen is 3cm palpable below the left costal margin, firm and not tender.

Laboratory hematology workup showed a packed cell volume of PCV 9% (normal: 37-47%) and a reticulocyte count of 0.4% (normal: 0.5-3%) with some polychromasia, large and giant platelets which was normal in count, relative lymphocytosis, which was normal in size and form. Peripheral blood film revealed normochromic, normocytic anaemia. Bone marrow aspirate revealed erythroid hyperplasia with nucleo-cytoplasmic asynchrony, megaloblast with large nucleus having sieve-like chromatin and deep blue cytoplasm.

Chest x-ray showed a normal cardiothoracic ratio (50%), widespread reticular opacities in both lung fields, and the bony thorax and overlying soft tissue were preserved. Impression is that of pneumonic changes.

Skin biopsy showed Psoriasis form-like dermatitis and skin scrapping for fungal studies yielded mixed growth of: *Coccidioides immitis, Trichoptyorrubrum,* and *Aspergillus niger*. Rapid diagnostic test and microscopic for malaria was for malaria were positive.

The patient was given IV Cefuroxime and Gentamicin and also treated for malaria with oral Arthemeter Lumefantrine. She had several units of blood transfused on account of severe anemia.
Repeat chest X-ray after three weeks still shows normal costophrenic sulci, bony thorax and overlying soft tissue with persevered lung fields. No obvious active focal lung lesion and CTR 12.5/26

She was discharged after three weeks of admission with a PCV of 24%. However, on suspicion of Lamivudine induced Red Cell Aplasia. A new HAART regimen was constituted in which Lamivudine was removed while on this new HAART regimen (without Lamivudine) the PCV declined from 24% to 11% over 4 weeks, warranting transfusion. This prompted a suspicion of Tenofovir as a likely culprit. A reconstitution of the HAART regimen in which Lamivudine was retained and Tenofovir was replaced with Abacavir was commenced. The PCV improved within two weeks of the commencement of this regimen and further improvements were observed over the subsequent 6 months to a remarkable PCV of 42%, the patient remains stable and was regular on the reconstituted HAART regimen. Detailed PCV pattern is shown on Table 1 below.

**Table 1: Serial PCV while on HAART**

|  |  |  |  |
| --- | --- | --- | --- |
| Day | PCV  | Transfusion/unit | Post-transfusion PCV |
| 1 | 8% | Yes/1 | 12% |
| 3 | 12% | Yes/1 | 17% |
| 5 | 17% | Yes/2 | 27% |
| 10 | 24% | No | - |
| 25 | 16% | Yes /2 | 24% |

**Table 2: Serial PCV after discontinuation of HAART**

|  |  |  |  |
| --- | --- | --- | --- |
| Durations | PCV  | Transfusion | Post -transfusion PCV |
| 2 weeks  | 23% | No | - |
| 4 weeks  | 16% | Yes/2 | 23% |
| 5 weeks  | 11% | Yes/1 | 20% |

**Table 3: Serial PCV after reconstitution of new HAART regimen**

|  |  |  |
| --- | --- | --- |
| Durations | PCV | Transfusion |
| 2 weeks  | 28% | No |
| 4 weeks  | 40% | No |
| 3 months  | 43% | No |
| 6 months  | 42% | No |

While on Dolutegravir, Tenofovir and Lamivudine combination, she has received nine (9) units of whole blood transfusion on account of persistent anemia. Consequently, a new HAART regimen of Abacavir, Lamivudine and Dolutelgravir was instituted to replace the earlier regimen. (Abacavir substituted for Tenofovir) There was a spontaneous gradual increase in the level of the hematocrit and an optimal level of 40% was attained within 4 weeks of the commencement of the new regimen. The patient was monitored subsequently over six months with a sustained normal hematocrit level ranging between 40 and 43% and there was a complete resolution of initial symptoms of general body weakness, palpitations and easy fatigability. The patient was followed on the out-patient Haart clinic for 12 months with stable PCV values.

**Discussion**

Pure Red Cell Aplasia is a rare syndrome characterized by normochromic, normocytic anemia and severe reticulocytopenia, as well as marked reduction or absence of erythroid precursors from otherwise normal bone marrow.8

Treatment of patients with HIV/AIDS with Lamivudine monotherapy has not been known to show anemia to be a frequent side effect. However, a combination of Lamivudine and Zidovudine increases the likelihood of the development of Drug-induced Pure Red Cell Aplasia. The patient in this index case report was on Lamivudine containing an anti-retroviral regimen, a drug that has been implicated in PRCA. It was a treatment modification replacing Tenofovir with Abacavir that resulted in the resolution of the anemia over the following 4 weeks. Resolution of the refractory anemia shortly after the withdrawal of Tenofovir while the patient was still on Lamivudine suggested that the anemia was Tenofovir induced. Lamivudine in this case would have been a cause despite the withdrawal of Tenofovir, however, the patient showed a remarkable improvement with abacavir replacement.

In comparison to our findings, several other antiretroviral regimens have been documented as drug-induced causes of PRCA. It has been reported that Lamivudine induced Pure Red Cell Aplasia in a study involving five male patients on a lamivudine-containing antiretroviral regimen who recovered five weeks after withdrawal of Lamivudine.10 Similarly, Kakubu et al4 reported a case of lamivudine-induced pure red cell aplasia in a 44-year-old female HIV-positive patient which resolved after withdrawal of lamivudine from the anti-retroviral therapy. Nithendra et al11 reported Emtricitabine-induced pure red cell aplasia in HIV-positive patients on treatment with a fixed drug combination consisting of Tenofovir, Emtricitabine and Efavirenz. Complete resolution of anemia was noticed with the replacement of Emtricitabine with Abacavir. Also, Hassan et al12 reported Zidovudine-induced pure red cell aplasia in a 27-year-old HIV-positive widow who has been on HAART (Zidovudine, Lamivudine and Nevirapine). She made remarkable improvement with the replacement of Zidovudine with Stavudine.

**Conclusion**

In this case report, there was a significant decline in the PCV after the removal of lamivudine from HAART. The subsequent substitution of Tenofovir with Abacavir and restoring Lamivudine in the regimen was followed with remarkable clinical improvement and spontaneous gradual and progressive improved PCV to a stable value of 42%. This made us implicate Tenofovir to be likely an Antiretroviral drug responsible for this persistent anemia in this reported index patient.

**COMPETING INTERESTS**

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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