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CASE REPORT

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HIV-1/HIV-2 Dual Co-infection: The Need to Tame both Viruses

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In October 2019, the British HIV Association (BHIVA) commissioned an audit to look at diagnosis, prevalence and management of HIV-2 infection in clinical care across the UK. We in Milton Keynes University Hospital NHS Foundation Trust (MKUH) looked at all our 700+ HIV positive patients who have previously attended and currently attending our *Blood Borne Virus* (BBV) clinics to date. We found 4 patients who were diagnosed with HIV-2 and would like to present an unusual case of a dual HIV-1 and HIV-2 case co-infection which led to HIV-2 multi-drug resistance.

A 56-year-old Ghanaian Health Care Assistant lady DB was initially diagnosed with HIV-1 and HIV-2 in August 2003 in pregnancy at 12 weeks gestation. This was her second pregnancy with a new partner who was HIV negative at the time. Her first child, a daughter was born in Ghana in 1990 as a vaginal delivery. DB has never disclosed her HIV status to her daughter who now lives in the UK and reassured us that she has tested negative for HIV subsequently. At that time, due to incineration of all paper records in 2006 and no electronic storage of blood results, there was no documented HIV-1 or HIV-2 antibody test. The referral letter from the obstetrician to the HIV team did state that 'HIV 1 and 2 infection was detected'. Her CD4 count was 590 and her HIV-1 RNA viral load was 27,000copies/ml.

From the second trimester of pregnancy, she commenced Combivir (Zidovudine and Lamivudine) 1 tablet, twice daily and Nelfinavir 250mg twice daily where she successfully reached an undetectable HIV-1 viral load at 34 weeks' gestation (viral load less than 400copies/ml) and delivered a healthy baby son who was subsequently HIV-1 and HIV-2 negative after 18 months. At the time, a Protease Inhibitor (PI) Nelfinavir was commenced rather than Nevirapine due to a Hepatitis B surface antigen positive status. PIs may be more potent in preventing hepatic fibrosis rather than a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI). Unfortunately, DB did not attend for further follow up care post-partum and did not attend any further HIV clinic appointments for 10 years until June 2014 where she was referred back to us by the hematology team who had picked up a polyclonal hypergammaglobulinaemia secondary to HIV infection. In June 2014, a repeat HIV test was reported as:

'HIV 1+2 antibody and p24 antigen detected with the presence of both gp41 reactivity and gp36 peptide indicates that dual infection is likely, and DNA PCR is recommended.'

It is unclear why an HIV 'DNA PCR' rather than an HIV RNA PCR was suggested but no further investigations on HIV-2 was carried out at this point. DB fully admitted to not wanting to engage with HIV care for 10 years but was ready to do so at that point. Her HIV-1 viral load came back as 27,000Copies/ml and her CD4 count had dropped to 190. DB had now developed natural immunity to hepatitis B with core Antibodies present with no surface Antigen. She had IgG antibodies to *Toxoplasmosis* and *Cytomegalovirus* and was negative for Hepatitis C and Syphilis. DB had hypertension and was on standard anti-hypertensive treatment for this. As she did night shifts and had HIV-1 *wild type virus*, she declined an Efavirenz based regimen and opted for Eviplera (Tenofovir Disoproxil Fumarate, Lamivudine and Rilpivirine) and remained on this regimen as her HIV-1 viral load dropped to less than 50copies/ml and her CD4 count rose to 590 in January 2020.

When we realized that this lady was dual infected as a result of the BHIVA audit, she was recalled in February 2020 where an HIV-2 viral load was shown to be 2,300copies/ml. A subsequent HIV-2 resistance assay showed extensive nucleoside reverse transcriptase mutations (V21V, L21Q, K35KR, M184V, D195G, R200K, V201A, F214FL, Y227F, Q228R, V251T, K65R, N69ST, R104K and V111I) as well the K65R mutation which meant resistance to tenofovir. There was a natural resistance to NNRTIS with some PI mutations (G17D, N41D, S43V, E65K, 668N) which suggested natural resistance to Fosamprenavir and Tipranavir. Understandably, DB was quite upset and understood that the presence of dual HIV-1 and HIV-2 infection was rare. We discussed our U=U (Undetectable = Untransmissable)

campaign and thankfully, DB had always used condoms with previous partners and was currently single. As there was full susceptibility to Integrase inhibitors and most PIs, DB was offered dual therapy of Rezolsta (Cobicistat boosted darunavir) with Dolutegravir as a switch from Eviplera and was undetectable for both HIV-1 and HIV-2 a month later. Several lessons were learnt from this case.

We need to be more vigilant of HIV-2 diagnoses both as a mono and dual infection with HIV-1 and a look back exercise is needed for existing HIV patients to ensure no other cases are missed. It is imperative that all HIV-1 and HIV-2 results are documented and checked in patient records by the attending clinician and we would suggest an 'Alert' system for any HIV-2 result by the virology laboratory system involved so that appropriate HIV-2 viral load and HIV-2 Resistance assays can be implemented. With HIV-2 having natural resistance to NNRTIs [1], this class of drugs should not have been offered or given as it was clearly sub-therapeutic with dual therapy of the same class. The implications of U=U and HIV-2 is not to be understated as although HIV-2 is thought to be less pathogenic than HIV-1 [2] and most remain long term non-progressors [3], the rate of HIV-2 transmission and indeed transmitted drug resistant HIV-2 is unknown. Although the HIV-2 viraemia is at relatively low levels [4] and likely to be less infectious than HIV-1 [5], it is unclear in whether this has slowed concomitant HIV-1 progression [6] in this lady and what potential systemic disorders could arise from this eg., risk of HIV related malignancies. It is also unclear in whether HIV-2 mono-infected individuals have protection against an HIV-1 'super' infection [7] as it is uncertain in whether this lady was infected simultaneously or separately by both strains of HIV. Diagnosis, surveillance and monitoring of dual HIV-1 and HIV-2 are crucial for effective antiretroviral therapy management. This case further highlights the importance of clinical services engaging in regional and national audits to ensure evidence-based guidelines and ensuring good medical practice.

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