Effective prolonged suppression of HIV-1 viral load using tenofovir alafenamide, emtricitabine and efavirenz in an adult with BMI >59 kg/m^2

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Abstract

Limited information is available regarding the efficacy of antiretrovirals in people with HIV-1 and high or very high Body Mass Index (BMI). This is especially the case for the alafenamide salt of tenofovir as clinical trials have only enrolled patients with BMI ≤30 kg/m^2. Lower concentrations of some antiretrovirals are expected in patients with BMI >30 kg/m^2 due to potential changes in clearance and distribution of medication. This report describes an individual taking tenofovir alafenamide, emtricitabine and efavirenz in whom HIV-1 viral load was consistently undetectable (<50 copies/ml) over a 2.5 year period. During this period the patient's BMI ranged between 59.8 and 68.1kg/m^2. Further data is required to support the efficacy of antiretrovirals in individuals with high and very high BMI.

Introduction

An increase in weight has been observed among people living with HIV, attributed to a combination of diet, exercise, behavioural eating patterns and antiretroviral therapy (ART)[1-3]. ART-associated increases in body mass, as well as serum glucose and lipid levels, are associated with protease inhibitors, integrase strand inhibitors, efavirenz, tenofovir alafenamide (TAF) and emtricitabine[1,4-5]. Drug pharmacokinetics can also vary in individuals with high Body Mass Index (BMI) compared to those with a normal BMI[6-7]. This highlights the importance of accruing data on the use of ART in individuals with elevated BMI. Previous studies have shown efavirenz, emtricitabine and tenofovir disoproxil (TDF) plasma concentrations to be lower in individuals with elevated BMI, but this has not been associated with treatment failure as measured by HIV viral load or immune status through CD4 count measurements[6,8-9].

Tenofovir alafenamide (TAF) is an alternative tenofovir prodrug to TDF. Current British HIV Association treatment guidelines recommend switching from TDF to TAF in patients with osteoporosis, a high risk of fragility fracture, established renal disease or patients at risk of

renal disease[10]. There is a lack of information available regarding use of TAF in those with high BMI. Moreover, in trials, only participants with BMI ≤30 were enrolled, or BMI parameters for the patient population were not provided to enable subgroup analysis[11-13]. This case report describes a person with HIV-1 and a very high BMI, treated with TAF, emtricitabine and efavirenz with maintained virological suppression for over 2.5 years.

Case report

A 59-year-old African female acquired HIV-1 with a baseline viral load of 279000 copies/ml and CD4 count of $0.070x10^9$ cells/L. No baseline genotype test was done. She commenced ART in 2002 (abacavir, lamivudine, zidovudine and TDF) and was switched to abacavir, lamivudine plus efavirenz in 2006. In 2019 the patient was switched to TDF, emtricitabine and efavirenz to minimise the risk of cardiotoxicity due to abacavir. Her HIV viral load was undetectable while she was treated with efavirenz, TDF and emtricitabine. She did not take any other medication that could affect the pharmacokinetics of the antiretrovirals, with no over the counter, herbal or recreational drug use.

The TDF component of ART was switched to TAF, after the patient presented with acute kidney injury and diabetic ketoacidosis. She remained on this treatment for 30 months to reduce the risk of further renal impairment and was then switched to bictegravir, emtricitabine and TAF to avoid a drug interaction between efavirenz and clopidogrel, which was started after a suspected stroke. She has remained on this regimen with good adherence and engagement, to date.

The patient had a documented weight of 147.5kg 4 months prior to switching to TAF and 168kg 22 months after the switch. Being 157cm tall, the BMI was 59.8–68.1kg/m^2. She had an undetectable HIV viral load (<50 copies/ml) throughout the treatment period and her latest CD4 count was $1.25x10^9$ cells/L, confirming virological and immunological treatment success was maintained. HIV viral load remained undetectable when measured approximately 16 months and 29 months after switching TDF to TAF and 2 months after subsequent switch to the bictegravir based regimen.

Discussion

Use of standard adult doses of efavirenz and emtricitabine in this person living with HIV-1 and a very high BMI, whilst maintaining immunological and virological treatment success as measured by CD4 count and HIV-1 viral load respectively, is consistent with previous publications[6,8-9]. Efavirenz has a reported volume of distribution of 252L, despite being approximately 99.5% plasma protein bound, as it is highly lipophilic[14-15]. This allows efavirenz to distribute into body tissue, including adipose tissue, thus prolonging its half-life and could explain why treatment success is achieved in individuals with very high BMI despite previously reported lower plasma levels. Use of 400mg daily efavirenz was previously shown to be non-inferior to standard 600mg daily dosing when combined with TDF and emtricitabine in individuals with a mean BMI of 24[16]. This could suggest that the therapeutic range of efavirenz

is wide enough to support use of standard dosing in those with very high BMI despite reduced plasma levels.

TDF and TAF are both prodrugs that are metabolised intracellularly by cathepsin A to the active compound tenofovir diphosphate[17]. TAF achieves higher intracellular concentrations of active tenofovir diphosphate than TDF as it is more stable in plasma[18-19]. This could explain how TAF can remain efficacious despite potentially reduced plasma concentrations in those with high BMI.

TAF is a substrate of p-glycoprotein and breast cancer resistance protein drug efflux transporters, which are both induced by rifampicin leading to decreased TAF plasma concentrations and therefore tenofovir disphosphate intracellular levels. Despite this, one study demonstrated greater than four times higher intracellular concentrations of tenofovir diphosphate in patients administered rifampicin with TAF compared to TDF[20]. Current practice does not recommend increasing TDF or TAF doses despite this interaction with rifampicin as efficacy is considered to be maintained despite reduced plasma concentrations[21]. This suggests that TAF has a high therapeutic range which is likely to explain why treatment success was achieved in this case.

To the best of our knowledge, this is the first report of use of a TAF containing regimen to manage HIV-1 in an individual with a very high BMI. Switching to TAF-based regimens has been shown to lead to increased weight gain compared to patients switched to non-TAF containing regimens[22]. Because of this, more evidence to demonstrate long-term efficacy of TAF in individuals with high and very high BMI is required. TAF plasma levels and intracellular levels were not measured in this case as virological and immunological treatment success was maintained, thus these tests were not clinically indicated. Future pharmacokinetic studies of TAF use in those with high BMI are required to ensure treatment efficacy.

Ethics Statement

The patient provided informed, written consent to the publication of this anonymised case report.

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