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UNBOOSTED ATAZANAVIR IN TREATMENT OF HIV INFECTION: CONSIDERATION OF TOLERABILITY AND SAFETY WHILE MAINTAINING EFFICACY – REPORT OF TWO CASES

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CONSIDERATION OF TOLERABILITY AND SAFETY WHILE MAINTAINING  
EFFICACY– REPORT OF TWO CASES**

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**SUMMARY**

**The World Health Organisation anti-retroviral treatment guidelines for resource limited settings rationalise the recommended standard first and second-line regimens on the basis of their efficacy, tolerability, toxicity, availability of fixed-dose combination and cost. Boosted protease inhibitors, recommended as second line agents in combination with a two drug nucleoside analogue backbone may cause diarrhoea and gastrointestinal disturbances and this raises tolerability concerns. Dyslipidaemias and hepatotoxicity are also considerable. Ritonavir contributes significantly to these adverse properties. We report two patients who had had hepatotoxicity and intractable diarrhoea while on a boosted protease inhibitor regimen, treated successfully with unboosted atazanavir in combination with two nucleoside analogues. Liver toxicity and diarrhoea resolved, while the patients maintained immunological and virological response to the unboosted atazanavir based regimen.**

**Unboosted atazanavir is an effective option of therapy in patients with suppressed viral replication and have ritonavir tolerability and safety challenges.**

**CASE 1**

AO, 48 year old female was first seen in our unit three years ago with exfoliative erythroderma and jaundice. She was taking a HAART regimen comprising tenofovir, lamivudine and efavirenz. CD4 + counts done during that presentation was 419/ml. She was also on hydrochlorothiazide for hypertension and co-trimoxazole prophylaxis. Laboratory examination revealed alanine transferase (ALT) of 8 x the upper limit of normal (ULN) and AST 40X ULN. Bilirubins, alkaline phosphatase,  $\gamma$  GT were all elevated. INR was 1.5 and serum albumin was modestly low. The patient had slight pedal oedema and ascites. Both hepatitis B and C markers were negative. Abdominal ultrasound scan reported a normal liver. HAART was stopped and restarted after three months when transaminases had reduced to less than 3 x ULN. The treatment was switched to tenofovir, lamivudine, lopinavir/ritonavir on the premise that the hepatitis

in a background of possible liver disease may have been efavirenz-associated. The liver transaminases rose to x9 ULN after two weeks of therapy. Treatment was once more interrupted and after four weeks of serial follow up of transaminases the enzyme levels had settled to ALT of 1.5 X ULN and AST 2.5 X ULN. At this point ritonavir was considered the potential hepatotoxic agent

The patient was treated with once daily unboosted atazanavir while maintaining a backbone of tenofovir and lamivudine. His CD4 + counts continued showing upward trend at 533cp/ml while viral loads were undetectable after 6 month of therapy.

**CASE 2**

MK was a 39 years old black male who tested positive for HIV infection in December 2008 following admission to hospital for treatment of

severe pneumonia. His CD4 + count were 208/ml. Viral load assay was not done. He was commenced on antiretroviral therapy with a fixed -dose regimen containing tenofovir, emtricitabine and efavirenz.

In March 2009 he was readmitted and treated for smear positive pulmonary tuberculosis. He completed his tuberculosis therapy successfully while maintaining the same HAART regimen.

He was lost to follow up between September 2009 and December 2011 when he was seen with gastroenteritis and acute kidney injury. His serum chemistry during this admission showed a raised creatinine of 946  $\mu\text{mol/l}$ , normal serum transaminases and serum amylase levels. Haemoglobin was 15.0gm/dl with no white cell response. He recorded a CD4+ count of 138/ml and HIV viral load of 100,000copies/ml thus confirming immunological and virological treatment failure.

The patient improved on rehydration and his renal function improved with creatinine levels reducing to 225  $\mu\text{mol/l}$ . His HIV regimen was changed to abacavir, lamivudine and ritonavir-boosted lopinavir and patient was discharged to attend follow up as an outpatient.

Eleven days following discharge, MK presented back with dysentery and progressive weight loss. Examination revealed bleeding haemorrhoids. His haemoglobin was 7.4gm/dl, creatinine 158  $\mu\text{mol/l}$  and serum potassium reduced to 2.9 mmol/l. The patient was treated with blood transfusion, potassium replacement, rehydration, daflon and rectal suppositories. Patient was discharged on the same HAART regimen despite occasional abdominal discomfort and diarrhoea.

At review two months later his viral load was undetectable with CD4+ counts of 252/ml. His weight had dropped from 65 kg to 39 kg. Liver transaminases were modestly raised to x2 normal and diarrhoea had not resolved. On the basis of poor tolerability of boosted protease inhibitor regimen in a patient with previous first line treatment failure while on an efavirenz-based therapy, the patient was switched to unboosted atazanavir 300mg. once, abacavir 300mg. twice daily and lamivudine 150mg once daily.

Diarrhoea resolved and patient maintained virologic suppression and immunologic reconstitution with weight gain to 59 kg in the subsequent six months of follow up.

## DISCUSSION

The World Health Organisation guidelines identify the most potent, effective and feasible first-line and second-line applicable to the majority of population and address the criteria of switching highly active antiretroviral therapy (1). The 2013 consolidated guidelines on HIV therapy in treatment naive adults and adolescents recommend a fixed-dose combination of tenofovir with either lamivudine or emtricitabine and efavirenz as a preferred first-line (2, 3). The choice of efavirenz as a preferred NNRTI over nevirapine is based on its lower propensity to cause severe adverse events. Compared to nevirapine, efavirenz is associated with lower frequency of severe hepatotoxicity, skin reaction and hypersensitivity reaction (4).

The second-line treatment recommends use of heat-stable fixed-dose combination of ritonavir boosted atazanavir or ritonavir boosted lopinavir as preferred protease inhibitor options (2, 3). The recommendations for first and second line therapy take cognisance of efficacy, tolerability, safety and option of sequencing therapy.

Molina *et al* demonstrated non-inferiority of ritonavir boosted atazanavir to ritonavir boosted lopinavir both using a backbone of tenofovir and emtricitabine in antiretroviral-naïve patients (5). Better gastrointestinal tolerability and less metabolic toxicity was seen in fixed-dose combination of atazanavir a combination that has 100mg. of ritonavir as compared to higher ritonavir in other boosted protease inhibitor formulations that require 200mg. of ritonavir (5). In patients with multiple virologic failures boosted atazanavir has been comparable to boosted lopinavir in efficacy (6).

If ritonavir contributes significantly to toxicity and tolerability concerns of use of boosted protease inhibitors, then unboosted protease inhibitors could be used in patients who are unable to tolerate boosted protease inhibitors or in patients who manifest toxicities attributable to ritonavir. Baril *et al* conducted a meta-analysis of the efficacy and safety of unboosted atazanavir compared with ritonavir boosted protease inhibitor maintenance therapy in HIV-infected adults with established virologic suppression. This systematic review of randomised controlled trials evaluating the efficacy

and safety in patients with established virologic suppression upon treatment simplification involving the replacement of boosted protease inhibitor with unboosted atazanavir found that switching patients with virologic suppression from ritonavir boosted protease to atazanavir leads to improvement in safety without sacrificing virologic efficacy (7). The treatment simplification strategy provides for improved lipid profiles and overcomes unfavourable adverse events like diarrhoea and lipodystrophy (8, 9, 10).

Severe hepatotoxicity has been seen in 5-10% of patients on HAART with major risk factors being advanced liver disease, hepatitis co-infection and elevated liver transaminases at initiation of therapy. The dideoxynucleoside analogues stavudine and didanosine, nevirapine and tipranavir and full dose ritonavir have been the main culprits (11). Studies indicate an association of ritonavir with higher rates of severe hepatotoxicity and cholestasis than regimens not containing ritonavir (12,13,14) A pilot study on the efficacy, pharmacokinetics and safety of unboosted atazanavir in patients with end-stage liver disease documented no worsening of liver disease. Patients in this study were able to gain or maintain immunovirological eligibility with a limited effect on unconjugated bilirubin (15, 16).

The two case reports illustrate the use of unboosted atazanavir in situations where NNRTI or ritonavir boosted protease inhibitors cannot be used. Poor tolerability and associated intractable diarrhoea in one patient and severe hepatotoxicity in another necessitated withdrawal of ritonavir. Both patients maintained reasonable immune-reconstitution and virologic suppression on a once daily unboosted atazanavir therapy. Work done in Senegal on the efficacy and safety of unboosted atazanavir in combination with two nucleoside analogues conclude that with its high genetic barrier of resistance, unboosted atazanavir could be valuable alternative for NNRTI in resource limited countries in some HIV-infected patients where adherence, resistance and intolerance to NNRTI, and concern for use of efavirenz in women with child bearing potential is a consideration (17). We must however be quick to point out that more data on optimal dosing is still required. Where treatment with unboosted protease inhibitor is considered, care must be taken to use optimal doses so as to avoid rapid evolution of resistance. A Pharmacokinetic and pharmacodynamic modeling of unboosted atazanavir in a cohort of stable HIV-infected patients suggest that twice daily dosing may

optimise drug therapy (18).

Care must be exercised in selecting eligible patients. Good treatment outcomes are likely if patient has virological suppression at the point of switch to unboosted atazanavir, have no history of previous virologic failure and not on rifampicin based TB therapy. Both these patients represent switch to unboosted atazanavir due to likely ritonavir based adverse events. Simplification studies appear to show sustained viral suppression in patients who switch to unboosted atazanavir upon viral suppression. It is however important to note that current guideline recommend boosted protease inhibitor therapy for second line treatment in resource limited settings and there treatment with unboosted protease inhibitors should be limited on to these special circumstances.

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