

Long-Acting HIV Fusion Inhibitor Albuvirtide is A Safe And Effective Treatment in HIV Patients with Severe Liver Impairment, HBV Co-Infection and High HIV RNA Copies

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Abstract

Introduction : Antiretroviral therapy is recommended promptly after HIV diagnosis to reduce HIV transmission. Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC), Dolutegravir (DTG)/FTC or lamivudine (3TC)/ TAF or tenofovir disoproxil fumarate are the recommended initial treatment. For patients with severe liver impairment, BIC/TAF/FTC and DTG are not recommended. DTG regimens are also not indicated for individuals with HIV RNA >500,000 copies/ml or HBV co-infection. Albuvirtide (ABT) is a novel HIV-1 fusion inhibitor approved in China in 2018. ABT half-life is 10-12 days and can be administered once weekly. ABT is not metabolized by the liver CYP450 system and has minimal drug-drug interactions. ABT had 2.2% mild hepatotoxicity implying its potential use for patients with liver impairments. We reported here seven HIV patients with either liver dysfunction, HBV co-infection or high HIV RNA copies who were successfully treated with ABT/3TC/TDF regimen.

Methods : From November 2019 to November 2020, seven newly diagnosed HIV patients with liver impairments were given intravenous ABT 320 mg daily for 3 days and then weekly together with 3TC /TDF 300 mg daily for 4 weeks followed by DTG/3TC/TDF daily. Mean CD4 counts was 38.4 ± 29.4 cells/ μ L (range 3-82), HIV RNA $558,060 \pm 703,745$ copies/mL (range 39,000-2,090,000) at diagnosis. Four had HBV co-infections, 6 had *Talaromyces Marneffeii* or *Talaromyces Marneffeii* plus *Mycobacteria* co-infections.

Results and Discussion : All showed decrease in HIV RNA at 4 weeks post treatment, mean log reduction -1.04 (0.38-2.22). The HIV RNA copies were less than 20 copies/mL by week 8 to 12 and remained undetectable at subsequent visits. All had CD4 counts above 130 cells/ μ L between week 12 and week 16 of therapy. The treatment was well tolerated and required no dose adjustment.

Conclusions : ABT/3TC/TDF regimen provides a safe and efficacious treatment option for HIV patients with liver dysfunctions, HBV co-infection and high HIV RNA copies.

Keywords: HIV; HBV Co-Infection; Liver Dysfunction; Antiretroviral Therapy

Key Summaries

Currently, there are few treatment regimens for HIV patients with liver impairment, HBV coinfections, high HIV RNA copies numbers or Mycobacteria co-infections.

ABT is long-acting novel HIV-1 fusion inhibitor with low rate of hepatotoxicity. ABT is not metabolized by the liver CYP450 system and has minimal drug-drug interactions.

ABT/3TC/TDF for 4 weeks followed by DTG/3TC/TDF daily in newly diagnosed HIV patients was safe and effective in HIV patients with either severe liver dysfunction, HBV or Mycobacteria co-infection, high HIV RNA copies.

Introduction

Antiretroviral therapy (ART) is recommended promptly after HIV diagnosis to improve virus suppression rate and reduce the risk of HIV transmission [1,2]. Bictegravir (BIC)/tenofovir alafenamide (TAF)/emtricitabine (FTC), Dolutegravir (DTG)/FTC or lamivudine (3TC)/TAF or tenofovir disoproxil fumarate (TDF) are the recommended initial treatment. For patients with severe liver impairment, BIC/TAF/FTC and DTG based regimen are also not recommended. DTG based regimens are also not indicated for individuals with HIV RNA >500,000 copies/ml or HBV co-infection. Albuviride (ABT) is a novel HIV-1 fusion inhibitor registered in China in 2018. It is a 3-Maleimidopropionic acid-modified peptide derived from the N-terminal sequence of HIV-1 gp41 envelope protein [3]. It is active against most circulating and drug-resistant HIV isolates with IC_{50} values ranging from 1.3 to 18.1 nmol/L [4]. ABT has a half-life of 10-12 days and can be administered on a once-weekly basis [5]. ABT is not metabolized by the liver CYP450 enzymes system and has minimal drug-drug interactions [6]. In the TALENT Study, ABT plus lopinavir/ritonavir (LPV/r) was noninferior to LPV/r/3TC/TDF or LPV/r/3TC/zidovudine or LPV/r/3TC/abacavir [7]. 80.4% of the HIV-1 patients in the ABT group had HIV RNA levels below 50 copies/mL at week 48 as compared with 66.0% in the NRTI group. Only 2.2% of the patients in ABT group developed hepatotoxicity and none of them required dose reduction [7].

Patients who are coinfecting with HBV and HIV should receive ART regardless of HBV DNA and serum alanine aminotransferase levels. ART should contain tenofovir-based therapy (TDF or TAF) as lamivudine is insufficient as monotherapy [8]. High baseline HIV viral load is associated with increased risk of viral rebound with non-nucleoside reverse transcriptase inhibitors (NNRTI)-based regimens [9,10]. Therefore, integrase strand transcriptase inhibitors (INSTI)-based regimen are preferred for HIV patients with high viral loads [11]. Most NNRTIs have some degree of hepatotoxicity [12-14]. The greatest risk of NNRTI-associated severe hepatotoxicity is observed in nevirapine (NPV)-based regimen¹⁵. Hepatotoxicity due to efavirenz (EFV) has also been described with some cases leading to liver failure and liver transplantation [15,16]. HIV and TB coinfections are common in some African and Asian countries. INSTIs have interactions with anti-tuberculosis drugs such as rifamycin and rifabutin [17,18]. Dose adjustment is needed when INSTI is taken with rifamycin, where an increase of raltegravir to 800 mg BID and increase of atazanavir to 600 mg QD or 300 mg BID is recommended. BIC is not recommended to be co-administered with rifampicin or rifabutin, since BIC through might drop significantly [18]. Studies have demonstrated that rifamycin could reduce protease inhibitors such as Lopinavir/Ritonavir (LPV/r) and Darunavir systemic concentrations to less than 75% thereby compromising HIV treatment efficacy [19]. Doubling the dose of protease inhibitors may result in adequate protease inhibitor concentrations, but at the expense of increased hepatotoxicity [20,21]. Concomitant use of Nevirapine and anti-TB drugs especially rifamycin could result in overlapping toxicities of skin rash and hepatitis [22].

During treatment of HIV subjects with TB, some experts recommend treatment should be interrupted and, a modified or alternative regimen used for those with ALT elevation more than three times the upper limit of normal in the presence of hepatitis symptoms and/or jaundice, or five times the ULN in the absence of symptoms [23,24]. Therefore, currently for HIV patients with severe liver dysfunction, high viral load, HBV or Mycobacteria co-infection, treatment options are limited.

The low rate of hepatotoxicity of ABT based regimen in the Talent Study suggested its potential use in HIV patients with liver impairment. We initiated a clinical study of ABT/3TC/TDF for 4 weeks followed by DTG/3TC/TDF daily in newly diagnosed HIV patients and highlighted that this regimen was safe and effective in HIV patients with either severe liver dysfunction, HBV co-infection or high HIV RNA copies with a case series of seven patients.

Methods

From November 2019 to November 2020, seven newly diagnosed HIV patients with liver impairments were given ABT 320 mg daily for 3 days and then weekly together with 3TC 300 mg and TDF 300 mg daily. Patients whose liver functions had significantly improved after at least 4 weeks of ABT/3TC/TDF would be switched to DTG 50mg daily plus 3TC/TDF 300 mg daily. Four of them had HBV co-infections. Six patients were infected with *Talaromyces marneffeii* or *Talaromyces marneffeii* plus Tuberculosis-Mycobacterium. One patient had non-TB mycobacteria infection. The four patients with mycobacteria infections were all put on rifabutin containing regimen. *Talaromyces marneffeii* infections were treated with voriconazole/itraconazole.

Results

The clinical characteristics and responses of these seven cases were summarised in Table 1 and Figure 1. All subjects

Table 1: HIV patients with severe liver impairment treated with ABT/3TC/TDF regimen

Case	Age	Sex	HBV DNA (IU/mL)	Other infection	Bilirubin (umol/L)		HIV RNA (copies/mL)			CD4 counts/(cells/ μ L)		
					Pre	Week 4	Pre	Week 4 Log (reduction)	Week 8*-12	Pre	Week 4	Week 28
1	52	F	Negative	Non-TB, mycobacteria	61.5	6.9	59,200	2,160 (-1.44)	<20*	3	29	139
2	30	M	129,000	T Marneffeii	40	6.3	80,200	33,100 (-0.38)	<20*	39	86	178
3	47	M	45,500	T Marneffeii	134	48.7	39,000	234 (-2.22)	<20*	37	170	218
4	38	M	738,000	T Marneffeii	23.6	4.8	999,000	56,000 (-1.25)	<20	4	19	164
5	71	M	56,000	TB plus T Marneffeii	52.6	18.9	139,000	46,200 (-0.48)	<20	82	92	217
6	29	M	Negative	TB plus T Marneffeii	75.4	5.78	2,090,000	376,000 (-0.74)	<20	65	176	284
7	39	M	Negative	TB plus T Marneffeii	48.6	5.99	500,000	88,800 (-0.75)	<20*	4	134	220

*Evaluation at week 8 after initiation of ABT/3TC/TDF regimen

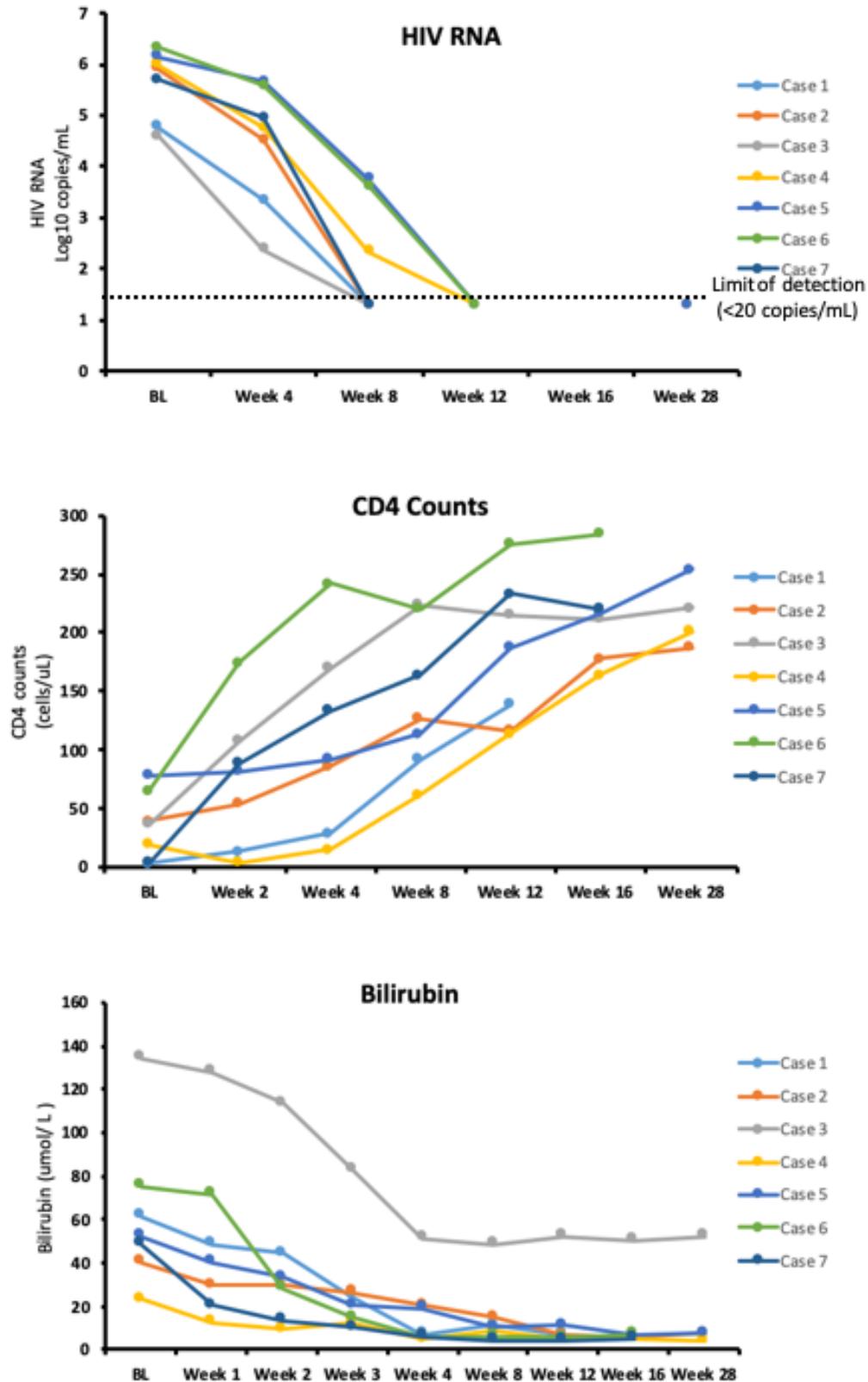


Figure 1: Dynamic changes of HIV RNA (A), CD4 counts (B) and Bilirubin (C) at baseline and different time points

All showed significant decrease in HIV RNA at 4 weeks post treatment and were less than 20 copies/mL by week 8 to 12 and remained undetectable at subsequent visits. All had CD4 counts above 130 cells/ μ L between week 12 and week 16 of therapy. All but one patients had normalization of bilirubin by week 12.

showed decrease in HIV RNA at 4 weeks post treatment, mean log reduction -1.04 (0.38-2.22). The HIV RNA copies were less than 20 copies/mL by week 8 to 12 and remains undetectable at subsequent visits. All had CD4 counts increased to greater than 130 cells/ μ L between week 12 and week 16 after initiation of antiretroviral therapy. The treatment was well tolerated, and no dose adjustment was required. All patients showed decreased or normalisation of elevated serum bilirubin and transaminase. The four patients with mycobacteria infections had negative sputum cultures by week 4.

Case 1

52 years old female presented with fever 38.5-39.8 °C, sore throat and cough. CT-scan showed bilateral pneumonitis. Sputum culture was positive for non-tuberculosis Mycobacterium. HIV-RNA copies 59000/ml, CD4 counts 3 cells/ μ L, bilirubin 61.5 μ mol/L, AST 61.3 IU/mL, ALT 26.4 IU/mL. The patient was started on ABT/3TC/TDF regimen together with rifabutin 0.3g qd, ethambutol 0.75g qd, azithromycin 0.5g qd. She became afebrile, bilirubin returned to normal level, HIV RNA decreased to 2160 copies/mL and CD4 counts increased to 29 cells/ μ L by day 28. Sputum culture for non-tuberculosis Mycobacterium was negative. She was discharged on DTG/3TC/TDF, ethambutol, azithromycin and rifabutin on day 45. HIV RNA was <20 copies/mL by week 8 and remained < 20 copies/mL at follow-up visits. CD4 counts was 139 cells/ μ L at week last follow-up at 12 weeks of HIV treatment.

Case 2

30 years old male presented with jaundice and cough. CT-scan showed multiple bilateral patchy infiltrates. MRI showed liver cirrhosis. HBV DNA was 129,000 IU/mL. Bone marrow cultures was positive for Talaromyces marneffei. HIV RNA was 80,200 copies/mL, CD4 counts 39 cells/ μ L, bilirubin 40 μ mol/L, AST 59.5 IU/mL, ALT 58 IU/mL. The patient was started on ABT/3TC/TDF regimen together with voriconazole 200mg qd. His symptoms improved, bilirubin returned to normal level, HIV RNA copies decreased to 33,100 copies/mL and CD4 counts increased to 86 cells/ μ L by week four and repeat bone marrow cultures were negative. Patient discharged on DTG/3TC/TDF and itraconazole 200mg daily on day 42. HIV RNA was < 20 copies/mL by week 8 and remained < 20 copies/mL at follow-up visits. His HBV DNA was undetectable by week 16 post treatment. CD4 counts was 178 cells/ μ L at week 28 of HIV treatment.

Case 3

47 years old male presented with jaundice, abdominal distention, dyspnea and cough. CT scan showed multiple bilateral patchy infiltrates, liver cirrhosis and splenomegaly. HBV DNA was 45,500IU/mL. Blood and bone marrow cultures was positive for Talaromyces marneffei. HIV RNA 39000 copies/mL, CD4 counts 37 cells/ μ L, bilirubin 134 μ mol/L, AST 52.9 IU/mL, ALT 50 IU/mL. The patient was started on ABT/3TC/TDF regimen together with voriconazole 200mg qd. His symptoms improved, bilirubin decreased to 48.7 μ mol/L, HIV RNA copies decreased to 234 copies/mL and CD4 counts increased to 170 cells/ μ L by week four and repeat bone marrow cultures were negative. He was discharged on DTG/3TC/TDF and itraconazole 200mg daily on day 58. HIV RNA was <20 copies/mL by week 8 and remained < 20 copies/mL at follow-up visits. His HBV DNA was undetectable by week 16 post treatment. CD4 counts was 218 cells/ μ L at week 28 of HIV treatment.

Case 4

38 years old male presented with, abdominal distention, dyspnea and cough. CT scan showed multiple bilateral patchy infiltrates and liver cirrhosis, HBV DNA was 738,000 IU/mL. Bone marrow cultures was positive for Talaromyces marneffei. HIV RNA 999,000 copies/mL, CD4 counts 4 cells/ μ L, bilirubin 23.6 μ mol/L, AST 130 IU/mL, ALT 90.8 IU/mL. The patient was started on ABT/3TC/TDF regimen together with voriconazole 200mg qd. He developed hallucinations and voriconazole was switched to liposomal amphotericin B. His symptoms improved, bilirubin decreased to 4.87 μ mol/L, HIV RNA decreased to 56,000 copies/ml and CD4 counts increased to 19 cells/ μ L by week four and repeat bone marrow cultures were negative. Liposomal amphotericin B was switched to itraconazole 200mg daily. He was discharged on DTG/3TC/TDF and itraconazole 200mg daily on day 39. HIV RNA was <20 copies/ml by week 12 and remained <20 copies/ml at 6 months follow-up visit. His HBV DNA was undetectable by week 16. CD4 counts was 164 cells/ μ L at week 28 of HIV-treatment.

Case 5

71 years old male presented with jaundice, dyspnea and cough. CT-scan showed multiple bilateral cavitating lesions, mediastinal lymphadenopathy. HBV DNA was 56,000 IU/mL. Sputum was positive for Tuberculosis Mycobacterium. Bone marrow cultures was positive for Talaromyces marneffei. HIV RNA 139,000 copies/mL, CD4 counts 82 cells/ μ L, bilirubin 52.6 μ mol/L, AST 84 IU/mL, ALT 20 IU/mL. The patient was started

on ABT/3TC/TDF regimen together with voriconazole 200mg qd, isoniazid 0.3g qd, ethambutol 0.75g qd, rifabutin 0.3g qd and pyrazinamide 1.5g qd. His symptoms improved, bilirubin decreased to 48.7 $\mu\text{mol/L}$, HIV RNA decreased to 46,200 copies/mL and CD4 counts increased to 92 cells/ μL by week four and repeat bone marrow cultures were negative. Sputum culture was negative for Tuberculosis Mycobacterium. He was discharged on DTG/3TC/TDF, isoniazid, ethambutol, rifabutin, pyrazinamide and itraconazole 200mg daily on day 41. HIV RNA was <20 copies/mL by week 12 and remained <20 copies/mL at 6 months follow-up visit. His HBV DNA was undetectable by week 16. CD4 counts was 217 cells/ μL at week 28 of HIV-treatment.

Case 6

29 years old male presented with fever, jaundice, fatigue and cough. CT-scan showed military pattern. Sputum was positive for Tuberculosis Mycobacterium and bone marrow cultures was positive for *Talaromyces marneffi*. HIV RNA was 2,090,000 copies/mL, CD4 counts 65 cells/ μL , bilirubin 75.4 $\mu\text{mol/L}$, AST 243 IU/mL, ALT 80 IU/mL. The patient was started on ABT/3TC/TDF regimen together with voriconazole 200mg qd, isoniazid 0.3g qd, ethambutol 0.75g qd, rifabutin 0.3g qd and pyrazinamide 1.5g qd. His symptoms improved, bilirubin decreased to 5.8 $\mu\text{mol/L}$, HIV RNA decreased to 376,000 copies/mL and CD4 counts increased to 176 cells/ μL by week 4 and repeat bone marrow cultures were negative. Sputum culture was negative for Tuberculosis Mycobacterium. He was discharged on DTG/3TC/TDF, isoniazid, ethambutol, rifabutin, pyrazinamide and itraconazole 200mg daily on day 45. HIV RNA was <20 copies/mL by week 12 and remained <20 copies/mL at 6 months follow-up visit. CD4 counts was 284 cells/ μL at week 28 of HIV treatment.

Case 7

39 years old male presented with fever, headache, fatigue and cough. CT-scan showed multiple bilateral cavitating lesions and lymphadenopathy. Sputum was positive for Tuberculosis Mycobacterium and bone marrow cultures was positive for *Talaromyces marneffi*. HIV RNA was 500,000 copies/mL, CD4 counts 4 cells/ μL , bilirubin 48.6 $\mu\text{mol/L}$, AST 128 IU/mL, ALT 13.4 IU/mL. The patient was started on ABT/3TC/TDF regimen together with voriconazole 200mg qd, isoniazid 0.3g qd, ethambutol 0.75g qd, rifabutin 0.3g qd and pyrazinamide 1.5g qd. His symptoms improved, bilirubin decreased to 5.99 $\mu\text{mol/L}$, HIV RNA decreased to 88,800 copies/mL and CD4 counts increased to 134 cells/ μL by week four and repeat bone marrow cultures were negative. Sputum culture was negative for Tuberculosis

Mycobacterium. He was discharged on DTG/3TC/TDF, isoniazid, ethambutol, rifabutin and pyrazinamide. HIV RNA was <20 copies/mL by week 8 and remained <20 copies/mL at follow-up visit. CD4 counts was 220 cells/ μL at week 28 after initiation of HIV treatment.

Discussion

For adults, the World Health Organization recommended first-line regimens comprise two nucleoside reverse transcriptase inhibitors (NRTIs), such as TDF and 3TC, and a NNRTI, principally efavirenz/nevirapine or the INSTI dolutegravir. Current recommended second-line regimens for adults include two NRTIs such as zidovudine with 3TC, and a boosted protease inhibitor, such as lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir [2,25]. However, there are few treatment regimens for HIV patients with liver impairment, HBV coinfections, high HIV-RNA copies numbers or Mycobacteria co-infections. All NNRTIs with the exceptions of etravirine can cause some degree of hepatotoxicity including hepatic necrosis [12,13]. Nevirapine (NPV) can cause hepatic necrosis and severe liver impairment [14]. In a study of 758 treatment-naïve HIV patients in China treated with 2NRTIs + NNRTI as their initial regimen, rates of virological suppression in subjects with $\geq 500,000$ copies/ml was only 63.8%, as compared with 94.1% in subjects with copies < 100,000/ml, $P < 0.001$ and odd ratios of viral rebound was 3.671 (95% CI: 1.009–13.355, $P = 0.048$) [10]. INSTI based regimen is the treatment choice for patients with high HIV viral loads, however, certain guidelines recommend that elvitegravir and bicittegravir should not be co-administered with rifabutin. When efavirenz (EFV) is not chosen due to resistance or intolerance, integrase inhibitor (INSTI)-based ART with raltegravir (RAL) or dolutegravir (DTG) has been assessed as an alternative to EFV-based regimen for treatment of patients co-infected with HIV and TB. Pharmacokinetic analyses showed that using a double dose of RAL or DTG compensates for their drug-drug interaction with rifampicin. Thus, when RAL is used, a dosage of 800mg twice daily is preferred over 400mg twice daily with a rifampicin-containing TB regimen. If a DTG-based regimen is considered, doubling the dosage from 50mg daily to 50mg twice daily is needed with a rifampicin-containing regimen whereas standard dose is required with rifabutin [17,18]. However, DTG and RAL are more expensive than EFV in many third world countries where mycobacteria infections are also very prevalent. Doubly the doses of RAL or DTG could result in great financial burden. Tenofovir alafenamide (TAF), bicittegravir (BIC) and doravirine (DOR) are contraindicated with rifampicin since their AUC is decreased by 55%, 75% and 82% respectively. While

TAF and BIC are also not recommended with rifabutin due to reduction in drug level that might potentially affect their treatment efficacy [18]. About 85% of the commonly used first line and second line antiretroviral agents, including all NNRTs and PIs are metabolized by the liver CYP450 enzyme CYP3A4 [24]. CYP2B6 constitutes the major metabolic pathway for EFV and an alternative pathway for NPV. Therefore, the availability of an effective antiretroviral drug that is not metabolized by the liver CYP450 enzymes system would be helpful for HIV patients with liver impairment, HBV coinfections, or Mycobacteria co-infections. Our study suggested that ABT/3TC/TDF regimen is a safe and effective treatment option for such patients. The major advantage of Albuvirtide over enfuvirtide, the only viral fusion inhibitor approved by the Food and Drug Administration, is the long half-life of Albuvirtide allows it to be administered on a weekly basis, while enfuvirtide is given twice daily. Therefore, Albuvirtide based regimen can potentially be given on an outpatient basis, and more cost-effective. The once weekly visit also allows closer monitoring of patient's drug compliance. In our cases series, we initiated treatment with ABT/3TC/TDF, and for patients who had shown improvement in liver functions and decrease in HIV RNA copies after at least 4 weeks of ABT, we would switch them to oral DTG/3TC/TDF at discharge. ABT is not metabolised by the CYP450 enzymes system and has minimal drug-drug interactions, no dose adjustment is needed in HIV patients who require therapy for mycobacteria infections.

Conclusions

ABT/3TC/TDF regimen provides a safe and effective option for HIV patients with liver dysfunction, HBV co-infection and high HIV RNA copies. A 4-week regimen can be a bridging therapy to DTG/3TC/TDF in these patients.

Competing Interests

All authors of this study declare they have no competing interests.

Authors' Contributions

XC and FX lead the project, collected the epidemiological and clinical data, conducted the data analysis and wrote the manuscript, and all co-authors (NP, KH, YK, YA and QL) commented on and edited earlier versions. All authors (XC, FX, NP, KH, YK, YA and QL) critically reviewed the manuscript and approved the final version.

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