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Early virological response of zidovudine/lamivudine/abacavir for patients co-infected with HIV and tuberculosis in Uganda

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Abstract

Triple nucleoside reverse transcriptase inhibitors are recommended as an alternative regimen for HIV-infected patients undergoing tuberculosis treatment in resource-limited settings. Few data exist on the efficacy of such regimens in tuberculosis patients. In 34 tuberculosis/HIV-co-infected patients treated with zidovudine/lamivudine/abacavir, 76% achieved HIV RNA less than 50 copies/ml at 24 weeks. No cases of hypersensitivity or immune reconstitution syndrome were observed. These data support the continuing evaluation of nucleoside-based antiretroviral regimens as an alternative treatment for this population.

Current World Health Organization guidelines for resource-limited settings recommend the initiation of antiretroviral therapy (ART) for individuals with HIVand active tuberculosis at CD4 cell counts below 350 cells/μl [1]. The use of first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART regimens during the management of tuberculosis is complicated by significant drug interactions between rifamycins and nevirapine or efavirenz [2], an increased risk of hepatotoxicity with the use of nevirapine at CD4 cell counts above 250 cells/μl [3], and safety concerns with efavirenz in early pregnancy [4].

Nucleoside-based regimens represent alternative ART options for patients co-infected with tuberculosis and HIV in resource-limited settings, and have the advantages of being compatible with rifamycin-based tuberculosis regimens, carrying a lower risk of hepatic toxicity at higher CD4 cell counts than nevirapine-based regimens, and remaining safe to use in early pregnancy. These regimens remain largely untested in the treatment of tuberculosis patients. Among tuberculosis/HIV co-infected patients in Africa, we evaluated the early virological and CD4 cell response to zidovudine/lamivudine/abacavir, and examined the development of immune reconstitution syndrome (IRS) and abacavir hypersensitivity reaction.

HIV-infected, ART-naive adults with acid-fast bacillus sputum smear or culture-positive pulmonary tuberculosis and CD4 cell counts of 350 cells/μl or greater were recruited from the Mulago Tuberculosis Research Unit in Kampala, Uganda. Consenting individuals were initiated on short-course antituberculous therapy (2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin). Clinically stable patients were initiated on oral zidovudine 300 mg/lamivudine 150 mg/abacavir 300 mg (as fixed-dose Trizivir) twice a day 2–4 weeks after starting tuberculosis therapy. Subjects received directly observed ARTand antituberculous therapy for 6 months, and were clinically evaluated monthly and at patient-initiated visits.

Adverse events were graded using standard NIAID/ACTG criteria (www.nih.gov). Abacavir hypersensitivity reaction was suspected if a subject reported two or more of fever, rash, gastrointestinal symptoms, non-tuberculosis respiratory symptoms, myalgia, arthralgia, headache, or parasthesia; and was confirmed when other possible etiologies were excluded and there was symptom resolution with abacavir discontinuation. Tuberculosis-associated IRS was defined as more than one week of new persistent fevers after ART initiation without other identifiable etiology, or a marked worsening of pulmonary infiltrates, intrathoracic or cervical lymphadenopathy, or other tuberculosis lesions on serial examination. Complete blood count and liver function tests were performed at baseline, 2, 4, 8, 12, and 24 weeks. Urine β-human chorionic gonadotrophin was performed at baseline and monthly for female subjects of childbearing potential, and female subjects were required to use two forms of contraception. CD4 cell counts and plasma HIV-RNA levels were quantified [Roche Amplicor 1.5, limit of detection (LOD) 400 copies/ml; Roche Diagnostic Systems Inc., Branchburg, New Jersey, USA] at baseline, 12, and 24 weeks. Twenty-four week HIV RNA was also quantified using the Roche Amplicor 1.5 Ultra-sensitive assay, LOD 50 copies/ml.

Among 34 tuberculosis/HIV-co-infected subjects who completed 24 weeks of fixed-dose zidovudine/lamivudine/abacavir, the median age was 28 years (range 20–45), and 56% were men. The median baseline CD4 cell count among subjects was 541 cells/μl (range 356– 852 cells/μl) and HIV RNA was 4.57 log copies/ml (range 3.23–5.87 log copies/ml). Of the 34 subjects, 29 (85%) and 31 (91%) achieved virological suppression to less than 400 copies/ml HIV RNA at 12 and 24 weeks, respectively (Table 1). Twenty-six subjects (76%) demonstrated virological suppression at less than 50 copies/ml HIV RNA at 24 weeks. The median CD4 cell count increase at 24 weeks was 81 cells/μl (−303–841 cells/μl). Despite virological suppression, 13 of 31 (42%) subjects had CD4 cell count increases of less than 50 cells/μl at 24 weeks, of whom eight had CD4 cell count declines below baseline. A poor CD4 cell response was not associated with age, sex, baseline CD4 cell count, or baseline HIV RNA.

NIAID grade 3 or 4 neutropenia was detected in four patients, one of whom also had grade 4 anemia. Hematological toxicities resolved in all four patients with dose reduction of zidovudine. Abacavir hypersensitivity reaction was suspected in three of 34 (9%) subjects, but none met the criteria for confirmed hypersensitivity reaction. Suspected hypersensitivity reaction symptoms were determined to be related to zidovudine (n = 2) or tuberculosis medications (n = 1), and resolved in all patients without abacavir discontinuation. There

were no cases of tuberculosis-associated IRS. Pregnancy was detected in one subject, who continued to tolerate zidovudine/lamivudine/abacavir.

We present the first data on short-term virological and clinical outcomes of zidovudine/lamivudine/abacavir among HIV-infected patients with active tuberculosis in Africa. Published reports of efavirenz or nevirapine-based ART in tuberculosis/HIV-co-infected patients in Thailand and South Africa have shown 24-week on-treatment viral suppression rates ranging from 66 to 88% [5–9]. Subjects in our study achieved comparable early viral suppression (76%) to less than 50 copies/ml HIV-RNA. The heterogeneous CD4 cell response to ART in our study, even among patients with viral suppression, further confirms other African data that suggest that the immunological response to ART is a poor predictor of virological suppression [10,11].

Zidovudine/lamivudine/abacavir was well tolerated among study subjects, with no confirmed episodes of abacavir hypersensitivity reaction. Very low rates of hypersensitivity reaction were also reported among HIV-infected African individuals receiving zidovudine/lamivudine/abacavir in the DART trial [12]. Our study extends these data to the tuberculosis/HIV co-infection setting, in which interactions with tuberculosis medications and the potential development of IRS are additional concerns that complicate the management of suspected hypersensitivity reaction in a resource-limited country. Although zidovudine dose reduction was required in four patients for neutropenia, dosing changes in the study were dictated by NIAID/ACTG toxicity criteria, which may not be applicable to the African setting where normal immunological reference values can differ considerably from those in the United States [13]. Notably, even in a clinical trial setting one subject became pregnant, underscoring the importance of safe ART options for tuberculosis/HIV-co-infected women of childbearing potential in Africa.

At present, alternatives to NNRTI-based ART regimens are either very limited or non-existent in most resource-constrained countries. Nucleoside-based ART regimens represent a possible option for select populations, such as HIV-infected individuals receiving concurrent tuberculosis treatment, who may be unable to tolerate NNRTI. Concerns remain about the potency of such regimens, given the demonstrated inferior virological response to zidovudine/lamivudine/abacavir in comparison with an efavirenz-based regimen in AACTG 5095 [14]. Although our sample size is limited, our preliminary data on safety and efficacy suggest that the development and continued evaluation of potent nucleoside reverse transcriptase inhibitor-based regimens as alternative ART for tuberculosis/HIV co-infection is warranted.

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Table 1

Virological and immunological response to zidovudine/lamivudine/abacavir among patients from Uganda co-infected with tuberculosis and HIV.

Characteristic	
Viral response	*N* =34 (%)
HIV RNA < 400 copies/ml	
12 weeks	29 (85)
24 weeks	31 (91)
HIV RNA < 50 copies/ml	
24 weeks	26 (76)
Immune response	Cells/μl (range)
Median CD4 cell count at 24 weeks	628 (325–1370)
Median CD4 cell count change at 24 weeks	81 (−303–841)
CD4 cell count response in patients with viral suppression at 24 weeks	*N* = 31 (%)
Increase > 50 cells/μl	18 (58)
Increase < 50 cells/<μl	13 (42)
CD4 cell decline from baseline	8 (26)