

Safety and Early Virologic Response of Zidovudine/Lamivudine/Abacavir for Patients Co-infected with HIV and Tuberculosis (TB) in Uganda

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Background

- WHO recommends antiretroviral therapy (ART) for patients with TB and HIV at CD4 cell counts below 350 cells/mm³
- Treatment with standard first-line ART for HIV-TB is complicated by
 - Increased risk of Nevirapine (NVP) hepatotoxicity at CD4 count >250 cells/mm³
 - Efavirenz (EFV) not safe in early pregnancy
 - Logistical and access issues with protease inhibitors (HIV-2)
 - Drug interactions between NVP, EFV, and rifamycins
- Select triple nucleoside regimens are alternative ART for co-infected patients
 - Can be used at higher CD4 cell counts
 - Compatible with rifamycin-based TB regimens
 - Safer in early pregnancy than EFV-based regimens
- Limited data on tolerability and virologic response to triple nucleoside regimens among co-infected patients in Africa

Study Objectives

- Among TB-HIV co-infected patients, evaluate the following:
 - 24-week virologic and CD4 count response of Zidovudine/Lamivudine/Abacavir (ZDV/3TC/ABC)
 - Development of ABC hypersensitivity (HSR)
 - Tolerability of ZDV/3TC/ABC regimen
 - Development of Immune Reconstitution Syndrome



Study Methods

Study Site

Mulago TB Research Unit, Mulago Hospital, Kampala, Uganda

Study Population

- Age ≥18 years
- HIV positive, ART naïve
- CD4 cell count ≥350 cells/mm³
- AFB sputum-smear positive pulmonary TB
- Enrolled in an ongoing prospective clinical trial

Antiretroviral and Anti-Tuberculous Therapy

- Standard 6-month, 4-drug TB therapy: INH-Rifampin-PZA-Ethambutol
- Fixed-dose ZDV/3TC/ABC initiated 2–4 weeks after starting TB therapy
- Directly observed ART and TB therapy for six months

Laboratory Assessments

- CD4 cell count: Baseline, 12 weeks, 24 weeks
- HIV RNA (Roche Amplicor Assay)
 - Limit of detection 400 c/mL: Baseline, 12 and 24 weeks
 - Limit of detection 50 c/mL: Available week-24 specimens with VL <400 c/mL
- Complete blood count and liver function tests: Baseline, 2, 4, 8, 12, 24 weeks
- Urine β-HCG (for women of childbearing potential only): Baseline, 2, 4, 8, 12, 16, 20, 24 weeks

Clinical Assessments

History, examination, adverse event survey: Baseline and monthly

Case Definitions

- **Adverse events graded using NIAID/ACTG Toxicity Tables**
- **ABC HSR:**
 - Suspected:* ≥2 of fever, rash, GI symptoms, respiratory symptoms (non-TB related), myalgia, arthralgia, headache, paresthesia
 - Confirmed:* Suspected HSR, exclusion of other etiologies, and resolution of symptoms with ABC discontinuation
- **Immune Reconstitution Syndrome:** >1 week new persistent fevers (≥38.6°C) after ART initiation without identifiable etiology *or* New or marked worsening of pulmonary infiltrates, intrathoracic or cervical lymphadenopathy, or other TB lesions on serial exam

Results

Baseline Characteristics

Characteristic	N=34 (%/range)
Male sex	19 (56%)
Median age, years	28 (20–45)
Median CD4 cell count, cells/mm ³	541 (356–852)
Median HIV RNA, log copies/mL	4.67 (3.23–5.87)
Chest radiograph	
Minimal disease	5 (15%)
Moderate disease	11 (33%)
Advanced disease	17 (52%)

Virologic Response

Characteristic	n/N (%)
HIV RNA <400 copies/mL	
12 weeks	29/34 (85%)
24 weeks	31/34 (91%)
HIV RNA <50 copies/mL at 24 weeks	14/16 (88%)*

* Remainder of specimens undergoing evaluation

Immunologic Response

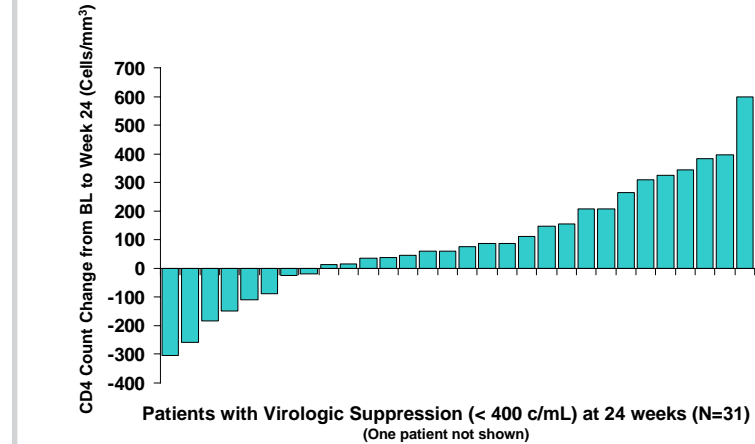
Characteristic	Cells/mm ³ (Range)
Median CD4 cell count at 24 weeks	628 (325–1370)
Median CD4 cell count increase	
12 weeks	65 (-567–559)
24 weeks	81 (-303–841)

CD4 Response: Patients with Viral Suppression at 24 Weeks

Characteristic	N=31 (%)
CD4 cell count increase > 50 cells/mm ³	18 (58)
CD4 cell count increase < 50 cells/mm ³	13 (42)
CD4 cell count decline from baseline	8 (26)*

* Would meet WHO criteria for Treatment Failure
Not predicted by age, sex, baseline CD4 count, or baseline HIV-RNA

Heterogeneity of CD4 Response



Clinical Outcomes (N=34)

Hematologic toxicity

- Grade 3 or 4 neutropenia: 4/34 (12%)
- Grade 4 anemia in 1/34 (3%)
 - Resolved in all 4 patients with ZDV dose reduction

ABC HSR

- Suspected in 3/34 (9%) patients, none met criteria for confirmed HSR
 - Determined to be TB medication-related in 1 of 3 patients
 - Determined to be ZDV-related side effect in 2 of 3 patients
 - Symptoms resolved in all 3 patients

- None required ABC discontinuation

Immune Reconstitution Syndrome

- No observed cases

Pregnancy

- Detected in 1/34 (3%), continued to tolerate ART

Conclusions

- Potent 24-week antiviral response with ZDV/3TC/ABC among TB-HIV co-infected patients with CD4 count >350 cells/mm³ in Uganda
- ZDV/3TC/ABC well tolerated
 - No ABC hypersensitivity or ABC discontinuation
 - Well tolerated in one pregnant patient
 - ZDV dose reduction needed in 4 patients due to hematologic toxicity
- Heterogeneous CD4 cell response despite virologic success

Discussion

- Data support continued evaluation of nucleoside-based regimens as alternative ART for TB-HIV co-infection
- ZDV dose reduction primarily for neutropenia not anemia. However, clinical guidelines to determine threshold for ZDV dose reduction for neutropenia still in evolution
- Heterogeneity of CD4 cell response suggests TB may alter ability to predict virologic failure based on immunologic response in this setting

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