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Incidence of Adverse Drug Reactions in First Line Antiretroviral and Antitubercular Drugs

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ABSTRACT

Worldwide, TB is the most common co-infection in subjects infected with HIV-1. The high mortality risk of patients with HIV-associated tuberculosis (TB) is reduced by 64% to 95% by antiretroviral therapy (ART). The authors reviewed the literature for adverse drug reactions of five first line antituberculous medications (isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin). Some ARVs have drug interactions with ATT, therefore appropriate drug choices become imperative. NRTIs like Zidovudine (AZT), Didanosine (ddI), Stavudine (d4t), Lamivudine (3TC) and Abacavir can be safely co-administered with anti-TB drugs.

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INTRODUCTION

Tuberculosis among human immunodeficiency virus (HIV) infected people has become an epidemic within an epidemic. Autopsy of HIV-positive tuberculosis patients frequently reveals old fibrous or calcified lesions of tuberculosis in the thorax that are adjacent to recent active lesions with bacilli. In 87% of cadavers, tuberculosis was disseminated to more than one organ, nearly always involving the lungs, liver, spleen, multiple internal lymph nodes, and bone marrow. The histologic patterns of tuberculosis reflect the integrity of the cellular immune response of the patient. Recent studies of HIV-infected individuals show that Th1 cells are progressively lost, shifting the ratio to a Th2-dominant population. Understanding the timing of Th1 function loss is key to understand the altered host response in tuberculosis and to develop strategies for prophylaxis. Due to the high risk of developing tuberculosis by reactivation or reinfection, trials in Africa and elsewhere are under way to assess the value of antituberculosis prophylaxis in preventing or deferring the development of tuberculosis. The majority were diagnosed as having primary pulmonary or extrapulmonary tuberculosis. The radiographic appearances of advanced pulmonary tuberculosis with or without cavitation are well recognized (1, 2).

The high mortality risk of patients with HIV-associated tuberculosis (TB) is reduced by 64% to 95% by antiretroviral therapy (ART). However, the optimal time to start ART during TB treatment to has for a long time remained unclear. Findings from observational studies and recent randomized controlled trials have demonstrated that delayed ART initiation is associated with increased mortality risk across a wide spectrum of baseline CD4 cell counts. The World Health Organization (WHO) has updated ART guidelines on several occasions between 2002 and 2010, recommending progressively higher CD4 cell count thresholds for ART eligibility and more rapid initiation of ART during TB treatment. Guidelines published in 2010 recommend ART be given to all patients with HIV-associated TB regardless of CD4 cell count and that this be started as soon as possible after TB treatment is tolerated and not later than 8 weeks.

The operational feasibility of early initiation of ART in TB patients under routine programme conditions in resource-limited settings is not known, however. The timing of ART may be influenced by many factors, including delays associated with HIV testing and CD4 cell count measurement, constraints within the health system that contribute to delays in referral and access

to ART clinics, and changes in programmatic efficiency and clinical expertise over time. In this study we quantified and explored factors associated with delays between starting TB treatment and starting ART among TB patients enrolling in three large community based ART services in townships in South Africa (3).

Worldwide, TB is the most common co-infection in subjects infected with HIV-1. Over two-thirds of the 15 million cases of dual HIV/TB infection reported reside in Sub-Saharan Africa. However, as HIV-1 expands in other parts of the world, such as in South-east Asia, the interaction between these two pathogens will continue to expand and compound the health issues related to both infections. In contrast to other HIV-1-associated opportunistic infections (OPI), TB may occur at any level of immunodeficiency, and has clearly been shown to be associated with enhanced HIV-1 morbidity and mortality. OPIs in general and TB in particular are associated with enhanced HIV-1 replication.

TREATMENT

TUBERCULOSIS CONTROL IN INDIA

For patients receiving anti-retroviral treatment

1. Anti-retroviral (ARV) drugs are effective in reducing viral replication and prolonging life.

2. Some ARVs have drug interactions with ATT, therefore appropriate drug choices become imperative. NRTIs like Zidovudine (AZT), Didanosine (ddI), Stavudine (d4t),Lamivudine (3TC) and Abacavir can be safely co-administered with anti-TB drugs.

3. Co-administration of protease inhibitors (PIs) or NNRTIs with Rifampicin is not recommended due to drug interactions. Rifamicin induce cytchrome P-450 and PIs/NNRTIs may induce/inhibit the iso-enzyme resulting in non-reliable serum concentrations of Rifamicin. Rifabutin is a less potent inducer of cytochrome P-450 and thus can be concurrently used with NNRTIs and certain PIs (e.g. Indinavir, Nelfinavir).

Rifabutin is presently not available in India.

4. If a PI or NNRTI is to be started after giving Rifampicin, then at least two weeks should elapse after the last dose of Rifampicin. This time gap is necessary for reduction of the enzyme inducing activity of Rifampicin prior to commencement of ARVs.

HIV infected patients with TB generally respond well to anti-TB therapy, as long as the regimen contains INH and a rifamycin for the duration of TB treatment. As for HIV-uninfected individuals, the standard recommendation for HIV-coinfected individuals with pulmonary TB is a 6-month course of treatment, with extension to 9 months for patients with cavitary lung disease and culture positivity at 2 months of TB treatment. A 2010 meta analysis found a trend toward increased risk of relapse with 6 months of TB treatment compared with ≥8 months of treatment. However, most of the studies included in the meta analysis were not randomized and most did not distinguish reinfection from relapse. Randomized trials will be needed to establish whether ≥8 months of treatment is indeed more efficacious than 6 months in HIV/TB coinfection. Longer courses of TB treatment are required for central nervous system (CNS) TB and for drug-resistant TB (5).

The authors reviewed the literature for adverse drug reactions of five first line antituberculous medications (isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin).

ADVERSE DRUG REACTIONS

Summary points:

- They are diagnosed adverse drug reactions are a common clinical problem on clinical grounds from the temporal relation between the start and finish of drug treatment and the onset and offset of the reaction.
- Pharmacological adverse reactions are generally dose dependent related to the pharmacokinetic properties of the drug, and resolve when the dose is reduced.
- Idiosyncratic adverse reactions are not related to the known pharmacology of the drug, do not show any simple dose response relation, and resolve only when treatment is discontinued.
- Vigilance by clinicians in detecting, diagnosing, and reporting adverse reactions are important for continued drug safety monitoring (4).

ADVERSE DRUG REACTIONS OF DRUGS USED IN TREATMENT OF HIV:

1) Lamivudine	• Headache, • Dizziness, • Nausea, • Diarrhea, • Trouble sleeping • Unexplained weight loss, • Persistent muscle aches/weakness, joint pain, • Numbness/tingling of the hands/feet/arms/legs, • Severe tiredness, • Vision changes, • Severe/persistent headaches, • Signs of infection (such as fever, chills, trouble breathing, cough, non-healing skin sores), • Signs of anoveractive thyroid (such as irritability, nervousness, • Heat intolerance, fast/pounding/irregular heartbeat, • Bulging eyes, • Unusual growth in the neck/thyroid known as a goiter), • Signs of a certain nerve problem known as guillain-barre syndrome (such as difficulty in breathing/swallowing/moving your eyes (5)
2) Efavirenz	• Depression • Skin rash or itching • Blood in the urine • Difficult or painful urination • Pain in the lower back or side • Abdominal or stomach pain • Blistering • Changes in vision

	• Clumsiness or unsteadiness • Confusion • Convulsions (seizures) • Cough • Dark urine • Delusions • Double vision • Fainting • Fast or pounding heartbeat • Fever or chills • Headache (severe and throbbing) • Hives • Inappropriate behavior • Loss of appetite • Mood or mental changes (severe) • Muscle cramps or pain • Nausea or vomiting • Nerve pain • Open sores • Pain, tenderness, bluish color, or swelling of the leg or foot • Rapid weight gain • Seeing, hearing, or feeling things that are not there • Sense of constant movement of self or surroundings • Sores, ulcers, or white spots in the mouth or on the lips • Speech disorder • Swelling or tenderness in the upper abdominal or stomach area • Swelling of the hands, arms, feet, or legs • Thoughts of suicide or attempts at suicide • Tightness in the chest • Tingling, burning, numbness, or pain in the hands, arms, feet, or legs • Tingling, burning, or prickling sensations

	• Tremor • Troubled breathing • Unusual tiredness • Weight loss • Yellow eyes or skin (6)
3) Zidovudine	**Nervous system** • Headache • Insomnia • Neuropathy • Wernicke's syndrome **Hematologic** • Bone marrow suppression • Granulocytopenia • Neutropenia • Severe anemia **Gastrointestinal** **Nausea** • Anorexia • Vomiting • Constipation • Dyspepsia **Hepatic** • Hyperbilirubinemia • Fulminate hepatitis • Hepatic failure. **Other** • Malaise • Asthenia • Fatigue chills

	• Fever **Musculoskeletal** • Arthralgia • Myalgia • Musculoskeletal pain • Myopathy **Psychiatric** • Depression • Mania • Anxiety • Grandiosity • Anxiety • Depression **Dermatologic** • Nailbed hyperpigmentation • Nail hyperpigmentation • Hypertrichosis **Cardiovascular** • Reversible congestive heart failure • Vasodilation • Cardiomyopathy • Vasculitis • Hypersensitivity: **Skin rash** • Angioedema **Metabolic** • Hyperlipidemia • Obesity • Dorsocervical • Fat enlargement

	• Peripheral wasting • "Cushingoid appearance" **Respiratory** • Cough • Dyspnea • Rhinitis • Sinusitis **Immunologic** • Immune reconstitution syndrome • Autoimmune disorders (e.g., graves' disease, polymyositis, and guillain-barre syndrome) **Ocular** • Amblyopia • Macular edema • Photophobia **Genitourinary** • Gynecomastia • Urinary frequency • Urinary hesitancy (7)
4. Stavudine	• Burning, numbness, tingling, or painful sensations • Chills with fever • Tingling, burning, numbness, or pain in the hands or feet • Unsteadiness or awkwardness • Weakness in the arms, hands, legs, or feet • Cough • Difficulty with swallowing • Dizziness • Fast heartbeat • Hives • Itching

	• Joint pain • Muscle pain • Puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue • Shortness of breath • Skin rash • Tightness in the chest • Unusual tiredness or weakness • Wheezing • Nausea and vomiting • Stomach pain (severe)
5. Nevirapine	• Black, tarry stools • Blistering, peeling, or loosening of the skin • Chills • Clay-colored stools • Cough • Dark urine • Diarrhea • Fever • General tiredness and weakness • Itching • Joint or muscle pain • Light-colored stools • Lower back or side pain • Nausea and vomiting • Painful or difficult urination • Pale skin • Red, irritated eyes • Red skin lesions, often with a purple center • Shortness of breath

	• Skin rash • Sore throat • Sores, ulcers, or white spots in the mouth or on the lips • Troubled breathing with exertion • Unusual bleeding or bruising • Unusual tiredness or weakness • Upper right abdominal or stomach pain • Yellow eyes and skin • Decreased appetite • Hives • Loss of appetite • Swelling of the feet or lower legs • Abdominal or stomach pain • Pain, numbness, or tingling of the hands, arms, legs, or feet • Sleepiness or unusual drowsiness • Tingling, burning, or prickly sensations (9)

ADVERSE DRUG REACTIONS OF DRUGS USED IN TREATMENT OF TB:

6) Isoniazid	• Clumsiness or unsteadiness • Dark urine • Loss of appetite • Nausea or vomiting • Numbness, tingling, burning, or pain in hands and feet • Unusual tiredness or weakness • Yellow eyes or skin • Blurred vision or loss of vision, with or without eye pain • Convulsions (seizures) • Fever and sore throat • Joint pain • Mental depression

	• Mood or other mental changes • Skin rash • Unusual bleeding or bruising (14)
7) Streptomycin	• Black, tarry stools • Burning, crawling, itching, numbness, prickling, "pins and needles", or tingling feelings • Chest pain • Chills • Clumsiness • Cough • Dizziness or lightheadedness • Feeling of constant movement of self or surroundings • Fever • Large, hive-like swelling on the face, eyelids, lips, tongue, throat, hands, legs, feet, or sex organs • Nausea • Painful or difficult urination • Sensation of spinning • Shortness of breath • Sore throat • Sores, ulcers, or white spots on the lips or in the mouth • Swollen glands • Unsteadiness • Unusual bleeding or bruising • Unusual tiredness or weakness • Vomiting • Back, leg, or stomach pains • Bleeding gums • Bloody or cloudy urine • Blurred vision

	• Change in vision • Dark urine • Deafness • Difficulty with breathing • Difficulty with swallowing • Dry mouth • Fast heartbeat • General body swelling • Headache • Hives • Impaired vision • Itching • Loss of appetite • Muscle weakness • Nosebleeds • Pain in lower back or side • Pale skin • Pinpoint red spots on the skin • Puffiness or swelling of the eyelids or around the eyes, face, lips, or tongue • Skin rash • Thirst • Tightness in the chest • Wheezing • Yellowing of the eyes or skin • Change in the frequency of urination or amount of urine • Drowsiness • Increased thirst • Swelling of the feet or lower legs • Weakness (15)

8) Ethambutol	**Ocular** • Irreversible blindness • Optic neuritis • Optic neuropathy **Metabolic** • Joint arthralgias • Gouty arthritis • Hyperuricemia • Acute gout **Hepatic** • Liver toxicities (including fatalities). • Jaundice • Hepatitis **Hypersensitivity** • Hypersensitivity syndrome • Nephritis • Pericarditis • Lymphadenopathy • Hematologic • Thrombocytopenia • Leukopenia • Neutropenia. • Eosinophilia **Respiratory** • Pulmonary infiltrates • Pneumonitis **Nervous system** • Headache • Dizziness,

	• Numbness • Psychiatric • Mental confusion • Disorientation, • Hallucinations • Dermatologic • Dermatitis • Erythema multiforme • Pruritus **Other** • Fever • Malaise • Musculoskeletal • Joint pain (11)
9) Rifampicin	**Nervous system** • Headache • Paresthesias • Weakness • Fatigue • Ataxia • Dizziness **Hypersensitivity** • Urticaria • Rash • Pruritus • Pemphigoid reaction **Endocrine** • Menstrual disturbance • Rare reports of adrenal insufficiency

	• Musculoskeletal • Myopathy • Muscular weakness. • Psychiatric • Psychoses • Respiratory • Flu syndrome (12)
10) Pyrazinamide	**General** • Fever, • Porphyria • Dysuria • Gout **Gastrointestinal** • Hepatotoxicity • Nausea, • Vomiting • Anorexia • Hematologic and Lymphatic: • Thrombocytopenia • Anemia • Hyperplasia **Other** • Arthralgia • Myalgia • Urticaria • Pruritis (13)

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