Highly Active Antiretroviral Therapy and Anti-tuberculosis Drug Interactions with Associated Clinical Implications: A Review

Karanja JK1*, Kiboi NG2, Nebere SN2 and Achieng HO1

1Department of Zoological Sciences, School of Pure and Applied Sciences, Kenyatta University, Nairobi, Kenya
2Department of Biochemistry and Biotechnology, School of Pure and Applied Sciences, Kenyatta University, Nairobi, Kenya

*Corresponding author: Karanja JK, Department of Zoological Sciences, School of Pure and Applied Sciences, Kenyatta University, Nairobi, Kenya, Tel: +254726721424; E-mail: jkaranja43@yahoo.com

Received date: April 22, 2016; Accepted date: May 06, 2016; Published date: May 20, 2016

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Abstract

Tuberculosis is the most common opportunistic infection associated with HIV/AIDS, and remains a disease of global significance. Co-infection with HIV complicates proper TB diagnosis and therapeutic outcomes. Profound immunosuppression characterizes HIV/TB co-infection prompting early initiation of HAART during TB treatment. Effective management of the co-infection requires concomitant administration of ART and anti-tuberculosis drugs; however, this therapeutic approach has had its fair share of challenges including: overlapping drug toxicities, drug-drug interactions and immune reconstitution reactions. For instance, combination of nevirapine-based ART and rifampicin-based TB treatment is reported to cause hepatotoxicity in healthy volunteers. As such, this review compiles information from multiple studies describing drug interactions associated with co-treatments, with a view to improving management of these co-morbidities.

Keywords: Antiretroviral therapy; Co-infection; Drug interactions; Tuberculosis; HIV

Abbreviations

TB: Tuberculosis; HIV: Human Immunodeficiency Virus; HAART: Highly Active Antiretroviral Therapy; NRTIs: Nucleoside Reverse Transcriptase Inhibitors; NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors; PI: Protease Inhibitors; FI: Fusion Inhibitors; CRAs: Chemokine Receptor Antagonists; AZT: Zidovudine; ABC: Abacavir; NVP: Nevirapine; EFV: Efavirenz; INH: Isoniazid; RMP: Rifampicin; RTV: Ritonavir; CES: Carboxyl Esterase

Introduction

Tuberculosis (TB) and HIV remain the main cause of high infectious disease burden globally. Sub-Saharan Africa is worst hit by the HIV epidemic and accounts for an estimated 24.7 million cases, compared to global reports indicating 35 million people living with HIV (PLWH) [1]. TB is the most common presenting illness among PLWH, with both co-morbidities leading to increased morbidity and mortality worldwide [2]. In 2013, global prevalence of HIV/TB stood at 14 million, with 9 million new cases and 1.5 million reported deaths during the same year (Figure 2) [3].

Human Immunodeficiency Virus (HIV) is a major confounder to proper diagnosis and management of TB [4]. This has necessitated the development of highly sensitive tests, including but not limited to; culture systems and nucleic acid amplification assays that are superior to sputum smear microscopy [5]. Interestingly, patients presenting with HIV are at higher risk of developing Multi-Drug Resistant TB (MDR-TB), arguably due to high pill burden, undesired side effects and poor adherence [6].

Currently, there is no defined drug for the cure of HIV infection. Combined Antiretroviral Therapy (cART), also known as Highly Active Antiretroviral Therapy (HAART) is a regimen that merges at least three antiretroviral drugs from different classes of ART in the treatment of HIV [7]. Atleast six categories of ART exist including; Protease Inhibitors (PIs), Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs, NtRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Fusion Inhibitors (FIs), Integrase Strand Transfer Inhibitors (INSTIs), and Chemokine Receptor Antagonists (CRAs) [8]. Like most other treatment agents HAART is associated with a number of adverse effects including; hepatotoxicity, hypersensitivity rash, lactic acid, osteoporosis, lypodystrophy and metabolic complications (Table 1) [9].

A) RMP-based TB regimen

<table>
<thead>
<tr>
<th></th>
<th>Recommended dose</th>
<th>Nucleoside backbone*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV</td>
<td>600 or 800 mg/qd</td>
<td>2 NRTI/NtRTIs</td>
</tr>
<tr>
<td>NVP</td>
<td>200 mg bid</td>
<td>2 NRTI/NtRTIs</td>
</tr>
<tr>
<td>PI</td>
<td>SQV/r</td>
<td>LPV/r</td>
</tr>
<tr>
<td>----------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td>400/400 mg bid or 1000/100 mg bid</td>
<td>400/400 mg bid</td>
</tr>
</tbody>
</table>

**B) RBT-based TB regimen**

<table>
<thead>
<tr>
<th></th>
<th>Recommended dose</th>
<th>Nucleoside backbone*</th>
<th>Recommended RBT dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDV</td>
<td>1000 mg tid</td>
<td>2 NRTI/NtRTIs</td>
<td>150 mg qd or 300 mg 3×/week</td>
</tr>
<tr>
<td>NFV</td>
<td>1000 mg tid</td>
<td>2 NRTI/NtRTIs</td>
<td>150 mg qd or 300 mg 3×/week</td>
</tr>
<tr>
<td>APV</td>
<td>1200 mg bid</td>
<td>2 NRTI/NtRTIs</td>
<td>150 mg qd or 300 mg 3×/week</td>
</tr>
<tr>
<td>ATV</td>
<td>400 mg qd</td>
<td>2 NRTI/NtRTIs</td>
<td>150 mg qd or 300 mg 3×/week</td>
</tr>
<tr>
<td>LPV/r</td>
<td>400/100 mg bid</td>
<td>2 NRTI/NtRTIs</td>
<td>150 mg qd or 300 mg 3×/week</td>
</tr>
<tr>
<td>FPV</td>
<td>1040 mg bid</td>
<td>2 NRTI/NtRTIs</td>
<td>150 mg qd or 300 mg 3×/week</td>
</tr>
<tr>
<td>RTV combined with ATV,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APV, IDV, FPV, SQV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVP</td>
<td>200 mg bid</td>
<td>2 NRTI/NtRTIs</td>
<td>300 mg qd or 300 mg 3×/week</td>
</tr>
<tr>
<td>EFV</td>
<td>600 mg qd</td>
<td>2 NRTI/NtRTIs</td>
<td>600 mg qd or 600 mg qod</td>
</tr>
</tbody>
</table>

**C) Non-rifamycin-based TB regimen**

<table>
<thead>
<tr>
<th></th>
<th>Usual dose</th>
<th>Nucleoside backbone*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDV</td>
<td>800 mg tid</td>
<td>2 NRTI/NtRTIs</td>
</tr>
<tr>
<td>NFV</td>
<td>1250 mg bid or 750 mg tid</td>
<td>2 NRTI/NtRTIs</td>
</tr>
<tr>
<td>APV</td>
<td>1200 mg bid</td>
<td>2 NRTI/NtRTIs</td>
</tr>
<tr>
<td>ATV</td>
<td>400 mg qd</td>
<td>2 NRTI/NtRTIs</td>
</tr>
<tr>
<td>LPV/r</td>
<td>400/100 mg bid</td>
<td>2 NRTI/NtRTIs</td>
</tr>
<tr>
<td>FPV</td>
<td>1400 mg bid</td>
<td>2 NRTI/NtRTIs</td>
</tr>
<tr>
<td>SQV (soft gel capsule)</td>
<td>1200 mg tid</td>
<td>2 NRTI/NtRTIs</td>
</tr>
<tr>
<td>RTV boosted PI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV/r</td>
<td>300/100 mg bid</td>
<td>2 NTRI/NtRTIs</td>
</tr>
<tr>
<td>AMP/r</td>
<td>600/100 mg bid or 1200/200 mg qd</td>
<td>2 NTRI/NtRTIs</td>
</tr>
<tr>
<td>IDV/r</td>
<td>400/400 or 800/100 or 800/200 mg bid</td>
<td>2 NTRI/NtRTIs</td>
</tr>
<tr>
<td>FPV/r</td>
<td>700/100 mg bid or 1400/200 mg qd</td>
<td>2 NTRI/NtRTIs</td>
</tr>
<tr>
<td>SQV/r</td>
<td>400/400 mg or 1000/100 bid or 1600/200 qd</td>
<td>2 NTRI/NtRTIs</td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVP</td>
<td>200 mg bid</td>
<td>2 NTRI/NtRTIs</td>
</tr>
</tbody>
</table>
Table 1: Recommended doses of antiretroviral and RBT-based regimens that can be co-administered in HIV-1 and TB combined therapy.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>NTRIs/NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>600 mg bid</td>
<td>2</td>
</tr>
</tbody>
</table>

Multivariate drug factors and HIV/TB co-infections have confounded the management of both diseases resulting in various clinical implications including; liver impairment, renal failure and cardiovascular disorders. Therefore, this review summarizes data on HAART and anti-tuberculous drug interactions, adverse reactions and host toxicity.

Metabolism of Antiretroviral Drugs

Nucleoside reverse transcriptase inhibitors constitute the backbone of ART regimens. Some commonly used NRTIs including Abacavir (ABC) and Zidovudine (AZT) are metabolized via hepatic glucuronidation and are phosphorylated into their active triphosphate form [12,13]. These drugs are substrates for phase II metabolizing enzymes that do not involve the CYP450 system, thus, they are less prone to interactions with CYP450 substrates such as isoniazid [14].

Non-nucleoside reverse transcriptase inhibitors are usually co-administered with NRTIs for HIV treatment in resource-limited settings. Unlike NRTIs, NNRTIs are not activated by phosphorylation but are metabolised by the CYP450 system, leading to various drug-drug interactions form [15]. Efavirenz (EFV), an NNRTI is metabolized to inactive hydroxylated metabolites by CYP3A4 and CYP2B6 [16]. Studies have shown EFV to be both an inducer and inhibitor of CYP3A4, thus affects metabolism of many other drugs metabolized by the same isoenzyme [17]. Another NNRTI, Nevirapine (NVP) is eliminated via CYP3A4 and CYP2B6 isoenzymes and induces CYP3A4 [18].

Protease inhibitors are recommended as second-line ARV regimens in some resource-constrained setups. All PIs are extensively metabolized by CYP3A4 isoenzyme, with Ritonavir (RTV) having the most pronounced inhibitory effect and Saquinavir (SQV) the least [19]. The potent CYP3A4 inhibitory properties of RTV have been pharmacologically used to boost the concentrations of other PIs when used in combination [20]. Thus, when used as a booster, RTV acts as a therapeutic enhancer rather than as antiviral agent.

Despite integrase inhibitors being limited in developing countries, this review highlights their metabolism and subsequent drug interactions with anti-TB agents. Enfuvirtide, a synthetic peptide fusion inhibitor is shown to be metabolized by proteolytic hydrolysis without involvement of the CYP450 system, thus is less prone to interactions with CYP450 substrates [21]. On the other hand, Maraviroc (MVC) is a substrate of CYP3A4, and dosage adjustments have been recommended in presence of drugs that alter action of this isoenzyme. For instance, the dosage of maraviroc should be increased if combined with CYP3A4 inducers such as Rifampicin (RMP) [22]. The only well characterized integrase strand transfer inhibitor is Raltegravir (RAL) that is reported to be metabolized by glucuronidation and does not interact with CYP450 enzymes [23]. As such, RAL is expected to have minimal drug-drug interactions. However, recent studies indicate potential drug-drug interactions with strong CYP450 inducers such as RMP [24]. Therefore, raltegravir is recommended not to be co-administered with RMP since it lowers raltegravir plasma concentrations.

Metabolism of anti-tuberculosis drugs

First-line anti-tubercular drugs include isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin, with isoniazid and rifampicin identified as the most active agents [3]. Following instances of resistance to first-line agents and serious drug reactions, second line
drugs including fluoroquinolones, cycloserine and kanamycin may be administered [11,25].

Isoniazid (INH), a highly potent anti-tubercular agent, undergoes metabolism in the liver by acetylation through the genetically polymorphic N-acetyltransferase 2 (NAT2) enzyme. INH is metabolized internally to acetylisoniazid, and then undergoes hydrolysis to isonicotinic acid and acetylhydrazine [26,27]. The drug is a substrate for phase II metabolic enzymes and does not interact with CYP450 system, thus, is not prone to cross-reactions with the CYP450 substrates [28].

Rifampicin, an anti-TB drug is metabolized by human carboxyl esterase (CES) via deacetylation within liver microsomes [29]. Hence, the drug is an N-acetylation transferase inhibitor that causes decreased acetylation ratio in fast acetylators. Additionally, both RMP and rifabutin are known potential inhibitors of β-subunit-dependent DNA-RNA polymerase which limits DNA formation by M. tuberculosis [30]. As a strong inducer of most CYP450 isoforms including CYPs 1A2, 2C9, 2C19, 2D6, and 3A4, RMP is reported to hasten elimination of many drugs such as protease inhibitors and some NNRTIs that are also substrates of CYP450 enzymes [20,31].

Pyrazinamide and ethambutol also make up essential medications in TB therapy. The former is primarily eliminated by hepatic metabolism and involves two pathways that differ by the order of succession of enzymatic sequences but yields similar end products comprising 5-hydroxyprazinoic acid and pyrazinoic acid [32]. Antimicrobial potency of pyrazinamide has been suggested to be mediated through its conversion to pyrazinoic acid by the amidase activity of intracellular tubercle bacilli and subsequent entrapment in phagosomes [33]. On the other hand, ethambutol is poorly metabolized and upto 80% undergoes renal clearance [34], but during instances of renal insufficiency it may accumulate in patients thus heightening nephrotoxicity [35].

### Potential Clinical Risks of Drug Interactions

#### Drug-drug interactions

Most clinically important drug-drug interactions occur during metabolism of drugs. Numerous phase I metabolic processes take place in the hepatic microsomes via Cytochrome P450 (CYP450) family of heme-containing mono-oxygenases [36]. Previous reports indicate that drugs inducing or inhibiting CYP450 enzymes may either decrease or increase concentrations of concurrently administered drugs [37]. Therefore, changes in drug concentrations resulting from drug interactions may bring about treatment failure or toxicities.

For instance, RMP-based anti-tubercular therapy induces multiple genes that control drug metabolism and transport including: cytochrome P450 isoenzymes and the drug efflux pump p-glycoprotein [38]. Thus, RMP has the potential to reduce plasma concentrations of concomitantly administered antiretroviral agents that eventually results in inadequate plasma levels and poor ART outcomes. Previous studies documented marked reduction in EFV concentrations following RMP-based TB therapy due to induction of CYP2B6 and CYP3A5 isoenzymes [39,40]. Similarly, plasma NVP levels decline significantly following concomitant use with RMP in treatment of HIV-1 and TB co-infection [41]. Hence co-administration of NVP/EFV and RMP during combined therapy requires utmost consideration in order to avoid lowering treatment efficacy.

Efavirenz, a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) that is also used alongside TB therapy has been implicated with teratogenic effects during pregnancy [42]. As a result, EFV is substituted with alternative regimen if available, especially in resource-constrained settings. On the other hand, cytochrome P450 2B6 516 G>T gene polymorphism exhibits dominance among Africans and impairs metabolism of EFV thereby maintaining high concentrations at EFV standard doses even during co-treatment of TB [41,43].

Nevirapine, a potent NNRTI and RMP, a first line anti-tubercular drug are both used in HIV and TB co-infected patients [44]. However, concurrent use of both therapeutic agents is not recommended because RMP is a potent inducer of hepatic CYP450, which in turn, interferes with metabolism of NVP [45]. Prior studies suggest that oxidative metabolism of NVP is mediated primarily by CYP isozymes from the CYP3A4 family [46]. By inducing the expression of CYP3A4 isoenzyme in the liver, RMP greatly reduces the plasma concentration of NVP upon concurrent administration [45].

Protease inhibitor-based antiretroviral regimens such as Lopinavir-Ritonavir (LPV/r) and Darunavir (DRV) are important option for the treatment of HIV infection [47]. However, studies have demonstrated that co-administration of PIs with RMP reduces PIs systemic concentration to less than 75% thereby compromising HIV treatment efficacy [48]. In order to evaluate how to boost the PIs plasma concentrations when concurrently administered with RMP, several studies have been conducted to assess either higher doses of the PI or of the pharmacologic boosting agent, RTV, or both [48,49]. These studies indicate that PIs plasma concentrations could be boosted by two methods; super-boosting, (administering PI with higher dose of RTV) and double dosing, (doubling the dose of both the PI and RTV). Although these strategies may result in adequate protease inhibitor concentrations, clinical reports have documented increased hepatotoxicity [49,50].

Among the rifamycins, the drug RMP has earlier been shown to be the most powerful inducer of CYP3A4 [51], hence responsible for clinically important interactions with PIs and NNRTIs. However, other than RMP, the anti-tubercular agent RBT also induces CYP3A4 isoenzyme but to a lesser magnitude [52]. Interestingly though, RBT is also a substrate of the enzyme unlike RMP [53]. As such, inhibitors of CYP3A4 including PIs and NNRTIs will essentially elevate plasma concentrations of RBT, with no effect on RMP metabolism. For instance, concomitant administration of RBT with NVP (NNRTI) or RTV (PI) results in elevated systemic levels of RBT [54]. Thus dose adjustments of RBT are required in order to control toxicity [55].

Antiretroviral backbone regimen that comprises of NNRTIs including: AZT, TDF, 3TC, ABC and d4T among others, have been described not to elicit major clinically significant drug interactions with various anti-TB regimen specifically RBT and the commonly used RMP [12]. However, previous studies conducted by Burger et al. documented notable drug interactions between RMP and AZT. The continuous administration of both AZT and RMP regimens concurrently, lead to marked clearance of plasma AZT levels with subsequent therapeutic implications [56]. This activity may result from RMP CYP450 powerful inducing capacity. Contrastingly, other reports document AZT substantially lowering systemic levels of pyrazynamide, also an anti-tuberculosis agent [57], which may be owed to the fact that pyrazinamide is a less potent inducer of CYP450 as compared to RMP.
Complex toxic effects

Toxicity profiles of antiretrovirals and anti-tuberculosis drugs overlap making it complex to identify the exact causative agent [58]. More importantly, concomitant administration of NNRTIs and boosted PIs, with TB treatment has been shown to accelerate drug induced liver injury (DILI), which may heighten drug resistance and ultimate treatment failure [59-61]. Similarly, co-administration of aminoglycosides such as: kanamycin and amikacin used for drug-resistant TB, and tenofovir (TFV) an NRTI aggravates nephrotoxicity [62,63].

Among the identified predictors of anti-tubercular and antiretroviral associated DILI include; slow acetylation status, increased baseline liver aminotransferases, reduced haemoglobin and albumin levels, marked elevation of plasma efavirenz concentration and also CYP2B6*6/*6 and ABCB13435TT genotypic characterization [59]. On the whole, impaired liver functions greatly complicate the management of the co-epidemic and may necessitate withdrawal of hepatotoxic antiretrovirals and TB drugs [64], a clinical practice which though necessary in case of severe toxicities, tends to worsen prognosis.

Shared adverse drug effects

Adverse drug reactions resulting from concurrent treatment of HIV and TB are common among the dual infections, and predispose patients mainly to liver damage due to shared metabolic pathways [65,66]. A high incidence of peripheral neuropathy (55%) has been documented in patients undergoing both d4T and INH treatment [67], that may be as a consequence of additive toxic effects from both therapeutic agents. To add further, individuals on INH treatment should closely be monitored and require administration of supplemental pyridoxine therapy in order to minimize risk of INH-related CNS/neurotoxicity) [68]. On the other hand, concomitant use of both NVP and anti-TB drugs especially RMP subjects multiple overlapping toxicities including hypersensitivity skin rash and hepatitis [44,69,70].

The risk of hepatotoxicity is up-regulated during antiretroviral and anti-TB therapy, hence the need to screen for pre-existing liver diseases including; hepatitis B and C before HAART or anti-TB commencement [71]. In individuals exhibiting abnormal baseline hepatic transaminases, an elevation of two-to three fold above abnormal baseline levels should be adopted as threshold for hepatotoxicity [72]. On the other hand, AZT administration has been discouraged in patients with low haemoglobin levels (<8 g/dl) due to likelihood of developing AZT associated anaemia [73]. The antiretroviral drug is also implicated with inducing myelosuppression in HIV positive patients [74]. Finally, gastrointestinal disturbances including malabsorption are reported with all first line anti-TB drugs and various antiretroviral regimen including NVP, that may possibly be attributed to presence of gastrointestinal disease (Tables 2 and 3) [75].

<table>
<thead>
<tr>
<th>Toxicity/side effect</th>
<th>Antiretroviral drugs</th>
<th>Anti-tuberculosis drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>ABC, NVP, EFV, APV, FPV</td>
<td>INH, RMP, pyrazinamide, quinolones</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>d4T, ddI, ddC</td>
<td>INH, cycloserine, ethambutol</td>
</tr>
<tr>
<td>CNS toxicity</td>
<td>EFV</td>
<td>INH, streptomycin, quinolones, cycloserine</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>EFV, NVP, all PIs and NRTIs</td>
<td>RMP, RBT, INH, pyrazinamide</td>
</tr>
<tr>
<td>Anaemia, neutropenia</td>
<td>AZT</td>
<td>RMP, INH</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>AZT</td>
<td>RBT, RMP</td>
</tr>
<tr>
<td>Ocular effects</td>
<td>ddI</td>
<td>RBT, ethambutol</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>RTV, IDV, AZT</td>
<td>RMP, quinolones, ethionamide, pyrazinamide</td>
</tr>
<tr>
<td>GIT side effects</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>NVP, PIs</td>
<td>RMP, INH, ethinamide, pyrazinamide</td>
</tr>
</tbody>
</table>

Note: NVP: Nevirapine; EFV: Efavirenz; ABC: Abacavir; APV: Amprenavir; FPV: Fosamprenavir; d4T: Stavudine; ddI: Didanosine; ddC: Zalcitabine; AZT: Zidovudine; INH: Isoniazid; RMP: Rifampicin; RBT: Rifabutin; PIs: Protease inhibitors; NRTIs: Nucleoside reverse transcriptase inhibitors; GIT: Gastrointestinal tract [44,70].

Table 2: Overlapping or additive adverse effect profiles due to antiretroviral and anti-tuberculosis agents.
Transient deterioration of signs and symptoms of tuberculosis established on TB treatment prior to ART, and they present with examination for clinical features are liver enlargement, liver functional derangements usually. Features frequently occur in about 21-56% of TB-IRIS patients, and is features comprise: recurrent TB symptoms, lymph node enlargement, and include intestinal lesions, splenic and hepatic derangements, systemic lesions [77]. Abdominal manifestations have also been reported and include intestinal lesions, splenic and hepatic derangements, peritonitis, ascites as well as lymphadenopathy [77,80]. Hepatic features frequently occur in about 21-56% of TB-IRIS patients, and is usually difficult to differentiate with drug-induced hepatitis. Major clinical features are liver enlargement, liver functional derangements and granulomatous hepatitis [81,82].

New cases of paradoxical TB-IRIS account for 8-43% among patients who initiate ART while on TB therapy. Key risk factors for this condition are low CD4+ T cell counts, disseminated TB and short interval between starting TB treatment and ART [83,84]. Contrastingly, a study carried out among Ugandan patients found no significant association between interval of starting treatment of the dual infections and the development of TB-IRIS. The study reported that delaying ART until 2 months of TB treatment did not appear to deter paradoxical TB-IRIS [85]. These observed variations may results in distinct mechanisms of immune activation that are differentially affected by antiretroviral treatment. On the other hand, fatalities associated with paradoxical TB-IRIS are rare, only exceptionally reported in cases where central nervous system is affected [86].

Diagnosis of paradoxical TB-IRIS is complicated by the lack of confirmatory diagnostic tests [87]. Opportunistic infections, malignancies and drug resistance have to be excluded during assessment. However, in resource-challenged settings, a diagnosis of TB-IRIS can also be performed based on case definition as recommended by the International Network for the Study of HIV-associated IRIS (INSHI) [78]. On the other hand, management of paradoxical TB-IRIS can be done using non-steroidal anti-inflammatory drugs (NSAIDs) and steroids [83] (Table 4).

### Table 3: Summarized management recommendations for ART use in HIV and TB co-infected patients.

<table>
<thead>
<tr>
<th>Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS)</th>
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| **Immune Reconstitution Inflammatory Syndrome (IRIS):** The transient deterioration of signs and symptoms of tuberculosis after initiation of ART, despite reduction in HIV viral load and immunological recovery [77,78]. Two forms of IRIS exist: Paradoxical TB-IRIS which occurs in patients diagnosed with TB and already established on TB treatment prior to ART, and they present with recurrent or new TB; unmasking TB-IRIS occurring in patients not on TB treatment when they initiate ART, a form characterized by an unusually high inflammatory response of TB [78,79]. Pronounced IRIS features comprise: recurrent TB symptoms, lymph node enlargement, fever, cold abscess, worsening respiratory signs and central nervous system lesions [77]. Abdominal manifestations have also been reported and include intestinal lesions, splenic and hepatic derangements, peritonitis, ascites as well as lymphadenopathy [77,80]. Hepatic features frequently occur in about 21-56% of TB-IRIS patients, and is usually difficult to differentiate with drug-induced hepatitis. Major clinical features are liver enlargement, liver functional derangements and granulomatous hepatitis [81,82].

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### Table 4: Incidences of tuberculosis-immune reconstitution inflammatory syndrome (IRIS) in HIV-TB co-infection.

**Conclusions and Future Directions**

This review compiles data from various sources on multiple adverse drug effects stemming from concomitant use of ART and antituberculosis drugs. These include; d4T and INH-induced peripheral neuropathy, NVP and RMP associated hypersensitivity rash and AZT induced myositisuppression among others. However, these adverse effects require to be ascertained through appropriate clinical examination for specific signs and symptoms that will eventually aids in improved patient management. Equally, although ART and antituberculosis regimen improves patient outcomes, several drug-drug interactions have been documented during the concurrent use of both therapeutic agents. Nonetheless, these interactions subject patients to overlapping toxicities with associated clinical implications. As such, more investigations on actual pharmacokinetic mechanisms behind drug interaction is necessitated, while also factoring in patient safety and treatment efficacy. Several clinical trials may generate answers to these concerns.
Authors’ Contributions

All authors contributed in drafting, review of article and revising the manuscript. Final version of the manuscript was approved by all authors.

Acknowledgment

The authors thank Kenyatta University library for facilitating space and accessibility to online databases used to gather relevant information for this review. This work received no specific grant from any funding agency whatsoever.

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