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# EFV/FTC/TDF-Associated Hepatotoxicity: A Case Report and Review

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## Abstract

The fixed-dose combination efavirenz, emtricitabine, and tenofovir (EFV/FTC/TDF) is a first-line agent for the treatment of HIV. We report the case of a 40-year-old female with a history of HIV acquired through heterosexual contact who initiated EFV/FTC/TDF. Hepatitis B and C serologies were negative, CD4 cell count was 253 cells per cubic millimeter (15.8%), and HIV viral load was 67,373 copies per milliliter. Eight months later she developed transaminitis and severe right upper quadrant pain. Neither illicit drug abuse nor hepatotoxic medication such as acetaminophen was reported. After evaluation including negative acute viral hepatitis studies, EFV/FTC/TDF was discontinued; both her transaminitis and pain resolved. Hepatotoxicity is most often associated with efavirenz. Rarely, fulminant hepatic failure occurs. Efavirenz-related hepatotoxicity is thought to result from a cellular self-digestion process known as autophagy. This is the first report to our knowledge of EFV/FTC/TDF-related hepatotoxicity.

## Introduction

The introduction of the fixed-dose combination efavirenz, emtricitabine, and tenofovir (EFV/FTC/TDF, commercially known as Atripla) has significantly altered regimens for treatment naïve and experienced patients alike with human immunodeficiency virus (HIV). Guidelines from the International AIDS Society-USA Panel and the US Department of Health and Human Services endorse this combination for the first-line treatment of patients. Among combination antiretroviral therapies (cART), EFV/FTC/TDF is associated with fever adverse symptoms and associated with improved quality of life.[1] In one survey, EFV/FTC/TDF accounts for 85% of first-line regimens.[2] The components are among the most highly studied antiretroviral therapies with regards to their efficacy, safety profiles, and adverse drug effects of the individual agents. Not surprisingly, combination therapy is considered bioequivalent to administration of its individual components.[3] We present a case of antiretroviral therapy-related hepatotoxicity, and review the literature concerning this adverse drug effect.

## Case Presentation

A 40-year-old Hispanic female with a history of HIV acquired by sexual contact from her husband presented for evaluation of right upper quadrant pain. She was diagnosed in October 2005 and followed routinely in clinic until June 2010 when her CD4 cell count fell to a nadir of 179 cells per cubic millimeter. At this point, her HIV-1 RNA level was 3866 copies per mL. On August 22, 2010, she was started on cART with ritonavir, darunavir, emtricitabine/tenofovir, but she experienced emesis refractory to antiemetics and thus therapy was discontinued. Thereafter on September 11, 2010, she began a regimen of ritonavir/atazanavir and emtricitabine/tenofovir, but once more discontinued therapy after unremitting emesis. Ritonavir was felt to be the likely cause. Treatment options were offered. As she was neither sexually active nor desired future pregnancy, efavirenz and its teratogenicity were discussed. She elected to begin an efavirenz-containing regimen.

In September 2011, she was started on efavirenz, tenofovir, and emtricitabine combination, or EFV/FTC/TDF. Past medical history was otherwise unremarkable. She took no other medications, including no over-the-counter medications such as acetaminophen or herbal supplements at this nor any point thereafter.

She suffered no immediate subjective adverse drug effects and tolerated the new regimen well. However, on May 10, 2012, surveillance laboratory analyses showed new transaminitis. She was otherwise asymptomatic, and denied history of a history of drug and alcohol use, as well as any prior history of hepatic disease. In follow-up a week later, she noted

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new, unremitting right upper quadrant pain. Her exam was remarkable for mild right upper quadrant tenderness, negative for Murphy's point tenderness, and absence of a rash. Aspartate aminotransferase and alanine aminotransferase remained persistently elevated, felt to represent a predominantly hepatocellular injury. A hepatitis panel was negative. Immune reconstitution inflammatory syndrome was thought to be unlikely as the patient's CD4 cell counts were never persistently below 200 cells per cubic millimeter. After discussion with the patient, her EFV/FTC/TDF was discontinued. By May 23, her values began to trend towards normalization, and her symptoms resolved (Table 1).

In September 2012, she was re-initiated with a treatment regimen consisting of rilpivirine/emtricitabine/tenofovir combination fixed dose tablet. In June 2013, she continues to tolerate this regimen without reported adverse drug effects, with an undetectable viral load.

## Discussion

No reports of EFV/FTC/TDF-associated hepatotoxicity were found in our PubMed literature search. Among its components, this disorder has rarely been associated with tenofovir,[4,5] and there are no reports with emtricitabine. In contrast, efavirenz-associated hepatotoxicity is a recognized clinical entity.[6–8] Nevirapine is also associated with this occurrence,[7,9–11] although it is not necessarily a class effect amongst the non-nucleoside reverse-transcriptase inhibitors (NNRTIs).[12,13] Severe hepatotoxicity, defined as grade 3 to 4 elevations in transaminases, is varyingly reported in comparing efavirenz and nevirapine.[8] A meta-analysis addressed adverse events in efavirenz versus nevirapine-based first-line regimens, confirming central nervous system side effects as the major treatment limiting effect of the former.[14] While nevirapine was more likely to experience any grade hepatotoxicity and severe hepatotoxicity, the absolute risk of hepatotoxicity for the two agents was not described.

Severe hepatotoxicity occurs most frequently in patients co-infected with hepatitis B or C virus, and in those with a baseline elevated alanine aminotransferase level or hepatic dysfunction.[6,7,15,16] Other groups have found an association with female sex and antiretroviral-naïve patients undergoing their first regimen,[11] or if their regimen contains a protease inhibitor.[17] Lamivudine and ritonavir have also been implicated.[11] Most of the increases in transaminases are mild-to-moderate and asymptomatic[7,8] and appear to occur predominantly in the first year of therapy.[13] In some instances, efavirenz-hepatotoxicity has been associated with necessitating transplantation and death.[18]

The mechanism of efavirenz-related hepatotoxicity is incompletely understood. The most widely accepted model implicates autophagy, a cellular self-digestion process that is distinct from apoptosis.[19,20] The former is a rescue mechanism that promotes cell survival through cell differentiation, regulating organelle turnover, nutrients, and the removal of misfolded or damaged proteins.[20,21] Autophagy thus mitigates damage from oxidative stress, and promotes survival, but to a certain point. If this damage is excessive, a phenomenon known as autophagic stress occurs, which limits the viability of cells.[20] *In vitro*, clinically relevant concentrations of efavirenz were toxic to the mitochondria of human cells.[22] Furthermore, up to 20% of patients exhibit plasma levels of efavirenz that exceed the therapeutic range.[15,23,24]

Table 1. Patient Laboratory Data

| | *10/15/2010*[a] | *4/28/2011* | *9/3/2011* | *10/6/2011* | *1/12/2012* | *3/10/2012* | *5/10/2012* | *5/16/2012* | *5/23/2012* | *6/6/2012* |
|---|---|---|---|---|---|---|---|---|---|---|
| Protein (g/dL) | | | | | 7.9 | 7.9 | 8.1 | 7.5 | 7.4 | 7.9 |
| Albumin (g/dL) | | | | | 4.2 | 4.4 | 4.3 | 4.2 | 4 | 4.1 |
| AST (IU/L) | 26 | 45 | 34 | 63 | 33 | 27 | 290 | 230 | 166 | 155 |
| ALT (IU/L) | 23 | 84 | 37 | 81 | 39 | 35 | 442 | 184 | 184 | 214 |
| Total bilirubin (mg/dL) | 0.4 | 0.6 | 0.2 | 0.2 | | | | | | |
| Direct bilirubin (mg/dL) | <0.1 | <0.1 | <0.1 | <0.1 | | | | | | |
| Alkaline phosphatase (IU/L) | 47 | 49 | 46 | 66 | 83 | 93 | 451 | 563 | 569 | 619 |
| CD4 (cells per cubic millimeter) | 381 | 466 | 253 | 291 | 343 | | 370 | | | 395 |
| Percent CD4 (%) | 25.4 | 19.4 | 15.8 | 18.2 | 24.5 | | 26.4 | | | 28.2 |
| HIV viral load PCR (copies/mL) | 342 | 31498 | 67373 | 160 | TND[b] | | | | | TND |
| Hepatitis B surface antigen | Nonreactive | | | | | | | Nonreactive | | |
| Hepatitis B surface antibody (mIU/mL) | <1.0 | | | | | | | | | |
| Hepatitis B core IgM antibody (mIU/mL) | Nonreactive | | | | | | | Nonreactive | | |
| Hepatitis C virus antibody (mIU/mL) | Nonreactive | | | | | | | Nonreactive | | |
| Hepatitis C virus qualitative assay | | | | | | | | Nonreactive | | |
| Anti-nuclear antibody (mIU/mL) | | | | | | | | Nonreactive | | |
| Anti-smooth muscle antibody (mIU/mL) | | | | | | | | | <1:20 | |
| Serum protein electrophoresis | | | | | | | | Normal pattern | | |

[a]Exact dates altered to ensure patient confidentiality.
[b]TND: target not detected, threshold <40 copies.

A variety of mechanisms have been proposed for the interpatient variability in efavirenz drug levels. Cytochrome P450 enzyme variants and other metabolism genes, drug-transporter genes, transcription factor genes, and protein–protein interactions are all implicated in affecting the metabolism in some form. CYP2B6 has been proposed as the best but not exclusive predictor of variance in efavirenz clearance.[25–31] The specific CYP2B6*6 haplotype (among its two non-synonymous variants, CYP2B6:516G>T) and high efavirenz levels both independently predict hepatic injury.[32] Other haplotypes, particularly CYPB6*9, CYPB6*16, and CYPB6*18 are associated with decreased production of the corresponding cytochrome protein, diminished clearance of efavirenz, and thus higher drug levels.[33,34] The CYP2B6 polymorphisms vary among populations, but also significantly within them. With this caveat, CYP2B6 single nucleotide polymorphisms (SNPs) associated with diminished clearance of efavirenz appear to predominate in African and Hispanic groups more so than in European and Asian populations.[25,33]

The UGT2B7 SNP, which similarly affects efavirenz metabolism, also shows marked population variability, although this has been less extensively investigated.[23,25,33,35] Other accessory pathways for efavirenz metabolism and their associated polymorphisms include CYP3A5 and ABCB1 (MDR1) transporter, but to date the associations are less robust.

Concomitant medications of particular relevance include rifamycin, levonorgestrel, artemether/lumefantrine, as these can impact efavirenz concentrations varyingly, and vice versa.[36–42]

Optimal strategies have not yet been outlined. These may include empiric dose adjustments based on genotypes or therapeutic drug level monitoring with dose reductions, but further prospective investigation is necessary; the latter strategy has so far proven to be feasible to some extent.[26,43–46] Application of these strategies to resource-limited settings is a further concern. Of course, adjustments to efavirenz dosages, at least based on present formulations, would not allow use of the presently available fixed-dose combination EFV/FTC/TDF tablet.

In our patient, her symptoms and laboratory abnormalities appeared 8 months after beginning her treatment regimen, and improved rapidly with cessation of such therapy, both consistent with efavirenz-hepatotoxicity. In AIDS Clinical Trials Group A5095, patients who experienced an efavirenz-related reaction such as skin symptoms or virologic failure were permitted to substitute efavirenz for nevirapine. Elevated transaminase levels were noted in one patient among 384 who initially reported a targeted toxicity, and patients with any history of liver disease were further excluded—the remaining group of 239 patients was analyzed. When switched to nevirapine regardless of cause, grade 3 to 4 hepatotoxicity was noted in 10 of 70 patients (14%), compared to 6% in non-substituting cohorts.[47] Substitution was felt to be safe and efficacious, but the post-hoc analysis was not powered for this specific examination. Ultimately patient history, concomitant medications, and additional risk factors may be a better determinant if such a trial should be attempted.

Adverse effects are a significant factor behind the alteration of first-line ART regimens, and the risk of adverse effects appears to increase over time.[48,49] Shifting to an individualized pharmacogenomic regimen offers the opportunity to pursue treatment regimens without the apparent trial and error exposure to side effect profiles based upon medical comorbidities, concomitant medications, and available therapeutic agents. It is not clear if accounting for isolated variables (such as CYP2B6*6 haplotypes) correlates with mitigation of adverse drug effects. In addition to differences in medication cost and therapeutic monitoring, there may be further unintended consequences in healthcare utilization that require further investigation.[50]

Fixed-dose combination of efavirenz, emtricitabine, and tenofovir, or EFV/FTC/TDF, is a first-line agent for treatment-naïve patients. It is bioequivalent to its individual agents, and it stands to reason that the adverse effects associated with its use will be equivalent as well. In our case of EFV/FTC/TDF-associated hepatotoxicity, cessation of therapy was associated with quick improvement of symptoms and improvement in laboratory values. As such, we echo recommendations for the continued routine surveillance for adverse drug effects and consideration for this diagnosis in events of otherwise unexplained transaminitis. Incorporation of efavirenz drug-level monitoring and analysis of cytochrome p450 haplotypes are not routinely recommended, but may be of value in managing medication side effect profiles or in selecting alternate regimens.

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## Author Disclosure Statement

The authors declare that they have no competing interests.

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