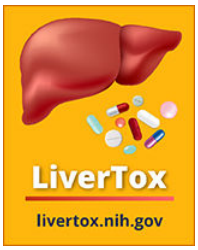
U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Etravirine. [Updated 2018 Feb 20].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Etravirine

Updated: February 20, 2018.

OVERVIEW

Introduction

Etravirine is a nonnucleoside reverse transcriptase inhibitor used in combination with other agents in the therapy of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). Etravirine has been associated with transient serum aminotransferase elevations and with hypersensitivity reactions that can be associated with liver injury including acute liver failure.

Background

Etravirine (e" tra vir' een) is a "second generation" nonnucleoside reverse transcriptase inhibitor that acts by noncompetitive binding to the HIV reverse transcriptase and indirectly inactivating its catalytic site. Etravirine is similar to nevirapine and efavirenz in its mechanism of action, but shares minimal structural features. Etravirine has a higher barrier to development of resistance than nevirapine and efavirenz, at least in vitro. Etravirine was approved for use in the United States in 2007, and current indications are as therapy of HIV infection in combination with other agents in antiretroviral treatment-experienced adult patients. Etravirine is available in tablets of 25, 100 and 200 mg under the brand name Intelence. The recommended dosage in adults is 200 mg orally twice daily. Common side effects include fatigue, dizziness, headache and skin rashes. Less common but potentially serious side effects include peripheral neuropathy, lipodystrophy, immune reconstitution syndrome, and hypersensitivity reactions including erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis.

Hepatotoxicity

Serum aminotransferase elevations occur in a high proportion of patients on etravirine therapy, but increases above 5 times the upper limit of normal occur in only 2% to 3% of patients; this rate may be higher in patients who have hepatitis C coinfection. In most studies, the rate of liver enzyme elevations was no different in etravirine treated than among in comparator arms. In large clinical trials as well as open access studies, there were no reported instances of clinically apparent liver injury attributed to etravirine.

Skin rashes occur in 10% to 20% of patients on etravirine usually during the first 2 to 6 weeks of therapy, and this rate is higher than with other antiretroviral regimens or comparator arms and is the major reason for discontinuation of etravirine because of adverse events. The skin rash during etravirine therapy can be accompanied by other signs of hypersensitivity including Stevens Johnson Syndrome and immunoallergic hepatitis. Clinically apparent hepatotoxicity is rare, but cases of hepatitis accompanying rash and signs of hypersensitivity have been reported to the sponsor, some of which have resulted in fatalities. The clinical features of these cases have not been described in detail. Most cases of hypersensitivity hepatitis due to nonnucleoside

reverse transcriptase inhibitors arise during the first 6 weeks of therapy and are accompanied by immunoallergic manifestations such as rash, fever, lymphadenopathy and eosinophilia. Recovery is usually prompt after discontinuation, but progressive fatal instances of liver injury can occur.

Likelihood score: D (possible cause of clinically apparent liver injury).

Mechanism of Injury

Etravirine is extensively metabolized in the liver via the P450 system (CYP 2C19, 3A4, and 2C9) and hepatotoxicity from etravirine is likely due to a hypersensitivity reaction to an immunogenic intermediate of its metabolism.

Outcome and Management

The severity of the liver injury reported with etravirine has ranged from mild and transient enzyme elevations to clinically apparent liver injury and acute liver failure. Chronic hepatitis and vanishing bile duct syndrome have not been reported. If hypersensitivity hepatic injury does occur, rechallenge should be avoided. However, there is unlikely to be cross sensitivity to the hepatic injury between etravirine and other nonnucleoside reverse transcriptase inhibitors.

Drug Class: Antiviral Agents, Antiretroviral Agents

Other Drugs in the Subclass, Nonnucleoside Reverse Transcriptase Inhibitors: Delavirdine, Doravirine, Efavirenz, Nevirapine, Rilpivirine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Etravirine – Intelence®

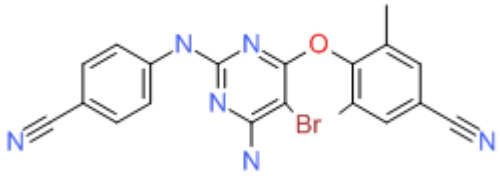
DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Etravirine	269055-15-4	C20-H15-Br-N6-O	

ANNOTATED BIBLIOGRAPHY

References updated: 20 February 2018

Núñez M. Hepatotoxicity of antiviral agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 505-518.

(Review of hepatotoxicity of antiviral agents; etravirine is listed as having been linked to cases of hepatic failure and associated with ALT elevations in ~3% of patients).

Flexner C. Antiretroviral agents and treatment of HIV infection. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1623-1664.

(Textbook of pharmacology and therapeutics).

http://aidsinfo.nih.gov/drugs/398/etravirine/0/patient.

(Summary of clinical information on etravirine for the public).

Rivero A, Mira JA, Pineda JA. Liver toxicity induced by non-nucleoside reverse transcriptase inhibitors. J Antimicrob Chemother 2007; 59: 342-6. PubMed PMID: 17255142.

(Review of liver toxicity of nevirapine and efavirenz, ALT elevations above 5 times ULN were reported in 1-8% of efavirenz compared to 4-16% of nevirapine recipients; no mention of etravirine).

Lazzarin A, Campbell T, Clotet B, Johnson M, Katlama C, Moll A, Towner W, et al.; DUET-2 study group. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007; 370: 39-48. PubMed PMID: 17617271.

(Trial of etravirine vs placebo combined with an optimized antiretroviral regimen for 24 weeks in 591 treatment experienced patients with HIV infection; little difference found in frequency of adverse reactions except for rash [14% vs 9%]; ALT elevations above 5 times ULN occurred in 2% on etravirine and 1% on placebo; no mention of clinically apparent liver injury, hepatitis or death from liver disease).

Madruga JV, Cahn P, Grinsztejn B, Haubrich R, Lalezari J, Mills A, Pialoux G, et al.; DUET-1 study group. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007; 370: 29-38. PubMed PMID: 17617270.

(Trial of etravirine vs placebo combined with a stable antiretroviral regimen for 24 weeks in 612 patients with HIV infection; adverse events were comparable except for rash in 20% on etravirine vs 10% in controls; ALT increase above 5 times ULN in 3% of etravirine vs 2% of controls; no mention of clinically apparent liver injury, hepatitis or death from liver disease in list of adverse events).

Soriano V, Puoti M, Garcia-Gascó P, Rockstroh JK, Benhamou Y, Barreiro P, McGovern B. Antiretroviral drugs and liver injury. AIDS 2008; 22: 1-13. PubMed PMID: 18090386.

(Review of hepatotoxicity of antiretroviral drugs with recommendations on management, stopping therapy if symptoms arise, with overt jaundice [direct bilirubin], evidence of mitochondrial toxicity, ALT above 10 times ULN, ALT at lower levels if newly marketed agent; important to rule out other causes; problematic agents include didanosine, stavudine and zidovudine; nevirapine and efavirenz, full dose ritonavir and tipranavir).

No hepatotoxicity found for etravirine. AIDS Patient Care STDS 2008; 22 (12): 1022. PubMed PMID: 19097262.

(New report of results of controlled trials of etravirine vs placebo for 48 weeks in 1203 patients with HIV infection; there were no differences in rates of serum enzyme elevations between etravirine vs placebo therapy and most were attributable to underlying chronic HBV or HCV coinfection).

Hughes CA, Robinson L, Tseng A, MacArthur RD. New antiretroviral drugs: a review of the efficacy, safety, pharmacokinetics, and resistance profile of tipranavir, darunavir, etravirine, rilpivirine, maraviroc, and raltegravir. Expert Opin Pharmacother 2009; 10: 2445-66. PubMed PMID: 19678794.

(Review of the efficacy and safety of tipranavir, darunavir, etravirine, rilpivirine, maraviroc and raltegravir; the incidence and severity of adverse events were similar between etravirine and placebo groups except for rash [19% vs 11%], generally arising in the first few weeks and resolving even with continuing therapy, requiring discontinuation in 2%; no mention of hepatotoxicity).

Hammer SM, Eron JJ Jr, Reiss P, Schooley RT, Thompson MA, Walmsley S, Cahn P, et al.; International AIDS Society-USA. Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. JAMA 2008; 300: 555-70. PubMed PMID: 18677028.

(Updated recommendations on use of antiviral therapy in adults with HIV infection, including use of recently approved agents raltegravir, maraviroc and etravirine).

Etravirine (Intelence) for HIV infection. Med Lett Drugs Ther 2008; 50 (1288): 47-8. PubMed PMID: 18551091.

(Concise review of the clinical efficacy and safety of etravirine published shortly after its approval in the US; mentions that rash is common and can be severe and serum aminotransferase elevations can occur).

Portilla J. [Safety and tolerability of etravirine]. Enferm Infecc Microbiol Clin 2009; 27 Suppl 2: 21-6. Spanish. PubMed PMID: 20116624.

(Review of tolerability of etravirine; skin rash occurs in 19% of patients, but severe skin rash in <1%; in clinical trials, ALT elevations were reported in 5% of etravirine treated patients, but similar rates were found with comparator regimens and acute liver failure was not reported).

Katlama C, Haubrich R, Lalezari J, Lazzarin A, Madruga JV, Molina JM, Schechter M, et al.; DUET-1, DUET-2 study groups. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. AIDS 2009; 23: 2289-300. PubMed PMID: 19710593.

(Abstract only: Combined results of registration trials of etravirine for HIV treatment-experienced patients; rash occurred in 19% of etravirine treated vs 11% of controls).

Drugs for HIV infection. Treat Guidel Med Lett 2011; 9 (106): 29-40. PubMed PMID: 21617596.

(Concise summary of status of therapies for HIV infection states that etravirine is effective in combination with other agents in achieving virologic control in treatment-experienced patients with documented resistance to other agents; mentions that it can cause rash and increases in serum aminotransferase levels).

Vispo E, Fernández-Montero JV, Labarga P, Barreiro P, Soriano V. Low risk of liver toxicity using the most recently approved antiretroviral agents but still increased in HIV-hepatitis C virus coinfected patients. AIDS 2013; 27: 1187-8. PubMed PMID: 23739226.

(Among 1982 patients starting antiretroviral therapy between 2010-2011, liver enzyme elevations occurred in 9% overall [17% vs 6% in those with or without HCV coinfection], but were above 5 times ULN in only 0.4%; no patient developed jaundice and only 6 required change in agents; the lowest rates were with etravirine).

Casado JL. Liver toxicity in HIV-infected patients receiving novel second-generation nonnucleoside reverse transcriptase inhibitors etravirine and rilpivirine. AIDS Rev 2013; 15: 139-45. PubMed PMID: 24002197.

(Review of hepatotoxicity of etravirine and rilpivirine from controlled trials and expanded access studies during which 1.7% of 2578 patients on etravirine had ALT elevations above 5 times ULN [3.7% in those with HBV or HCV coinfection]; no mention of clinically apparent liver injury with jaundice).

Surgers L, Lacombe K. Hepatoxicity of new antiretrovirals: a systematic review. Clin Res Hepatol Gastroenterol 2013; 37: 126-33. PubMed PMID: 23522569.

(Review of literature on the hepatotoxicity of newer antiretroviral agents used to treat HIV infection mentions that etravirine therapy is accompanied by a low rate of transient serum enzyme elevations and has not been linked to cases of severe hepatotoxicity).

Casado JL, Bañón S, Rodriguez MA, Moreno A, Moreno S. Efficacy and pharmacokinetics of the combination of etravirine plus raltegravir as novel dual antiretroviral maintenance regimen in HIV-infected patients. Antiviral Res 2015; 113: 103-6. PubMed PMID: 25460844.

(Among 25 patients with HIV infection and previous exposure to multiple antiretroviral agents who were treated with raltegravir and etravirine for an average of 2 years, there were no virologic breakthroughs and no ALT elevations requiring dose modification or interruption).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 12 [1.3%] cases were attributed to antiretroviral agents, but none to etravirine).

Casado JL, Mena A, Bañón S, Castro A, Quereda C, Moreno A, Pedreira J, Moreno S. Liver toxicity and risk of discontinuation in HIV/hepatitis C virus-coinfected patients receiving an etravirine-containing antiretroviral regimen: influence of liver fibrosis. HIV Med 2016; 17: 62-7. PubMed PMID: 26122981.

(Among 211 patients with HIV infection treated with an etravirine containing antiretroviral regimen and followed for a median of 1.8 years, only one had an ALT elevation above 5 times ULN [who had HCV coinfection] and there was no association between preexisting hepatic fibrosis [assessed by elastography] and any degree of ALT elevation during therapy).

Fabbri G, Mastrorosa I, Vergori A, Mazzotta V, Pinnetti C, Grisetti S, Zaccarelli M, et al. Reactivation of occult HBV infection in an HIV/HCV Co-infected patient successfully treated with sofosbuvir/ledipasvir: a case report and review of the literature. BMC Infect Dis 2017; 17: 182. PubMed PMID: 28249574.

(54 year old woman with HIV and HCV coinfection as well as anti-HBc and anti-HBs [without HBsAg] was treated for HIV with darunavir/r and etravirine [without nucleoside analogues] and with sofosbuvir and ledipasvir for HCV, and shortly thereafter developed acute HBV reactivation [bilirubin 7.1 mg/dL, ALT 435 U/L, HBV DNA 1 million IU/L, HBsAg and HBeAg positive], resolving with addition of entecavir but remaining HBsAg positive).

http://www.aidsinfo.nih.gov/guidelines

(Current and regularly updated guidelines on therapy of HIV infection in adults, adolescents and children).

(Current and regularly updated guidelines on therapy of HIV infection in adults, adolescents and children).