Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Efavirenz

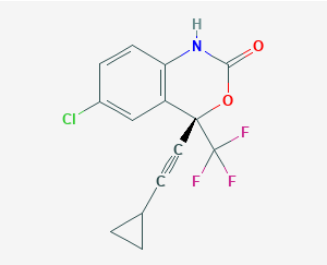
Evidence Summary

At low doses may promote brain cholesterol turnover leading to decreased plaques, but neurotoxicity and 4x increased risk for cognitive impairment observed in HIV patients are major causes for concern.

Neuroprotective Benefit: Low-dose efavirenz increases brain cholesterol turnover in mice and a phase I trial is testing its safety and tolerability in people with MCI; however, preclinical and clinical evidence for its neurotoxicity is overwhelming.

Aging and related health concerns: Significantly increases cholesterol and triglycerides; also associated with sleep abnormalities.

Safety: Adverse events include memory disturbances, insomnia, liver failure, and increased cholesterol and triglyceride levels.

Availability: Rx, approved for HIV infection.	**Dose:** In HIV patients, 600 mg once daily. The clinical trial in mild cognitive impairment is testing doses of 50 and 200 mg/day (NCT03706885).	**Chemical formula:** $C_{14}H_9ClF_3NO_2$ **MW:** 315.676  Source: PubChem
Half life: 40-55 hours	**BBB:** penetrant (probability of 0.91)	
Clinical trials: numerous meta-analyses, e.g., one included 8,466 patients exposed to efavirenz	**Observational studies:** An observational study examined the cause of death in 49,717 people infected with HIV and treated with efavirenz.	

What is it? Efavirenz (brand name, Sustiva®, Bristol-Myers Squibb) is a non-nucleoside reverse transcriptase inhibitor and is used as part of a highly active antiretroviral therapy (HAART) for the treatment of HIV infection. For HIV infection that has not been previously treated, a combination therapy of efavirenz, lamivudine, and zidovudine or tenofovir is the preferred regimen (DrugBank.ca).

Efavirenz has off-target interactions with CYP46A1, which initiates the major pathway of cholesterol removal from the brain and leads to reduced amyloid burden and microglia activation [1]. Based on this rationale, an ongoing clinical trial is testing the safety and efficacy of low-dose efavirenz in people with mild cognitive impairment (NCT03706885).

Neuroprotective Benefit: Low-dose efavirenz increases brain cholesterol turnover in mice and a phase I trial is testing its safety and tolerability in people with MCI; however, preclinical and clinical evidence for its neurotoxicity is overwhelming.

Types of evidence:

- 1 systematic review/expert opinion
- 2 clinical trials
- 3 observational studies
- 3 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

Based on a systematic review (expert opinion piece), efavirenz commonly causes transient neuropsychiatric side effects in HIV-positive patients [2]. HIV infection itself can cause problems in the brain, which affect up to half of people with HIV (Alzheimer's Society UK).Treatment with a combination of antiretroviral drugs often prevents cognitive impairment and can also reverse the cognitive damage caused by HIV. However, there is emerging clinical evidence indicating that efavirenz use may *worsen* neurocognitive impairment or be associated with less improvement in neurocognitive impairment than other antiretrovirals [2].

In a 2016 cohort study that included 445 HIV-positive patients, those who were treated long-term with efavirenz (average, 17.9 months) had worse performance in most cognitive tests than those on the comparator drug, lopinavir-ritonavir (average 16.4 months) [3]. Differences were statistically significant for speed of information processing ($p = 0.04$), verbal fluency ($p = 0.03$), and working memory ($p = 0.03$). In this cohort, clinicians may have prescribed lopinavir-ritonavir to more severely ill patients or as second-line therapy, and despite these differences, efavirenz users had worse cognitive functioning.

In a slightly older and smaller cross-sectional cohort study from 2011 that included 146 HIV-positive patients, efavirenz use (OR=4.00; p=0.008) and non-Italian nationality (OR=3.46; p =0.035) were associated with ~4 times increased risk of cognitive impairment [4]. Furthermore, efavirenz use and age over 65 years independently predicted worse performance on the double barrage and the Stroop test. There were no differences in the main demographic and clinical characteristics of people taking efavirenz versus those on non-efavirenz regimens. No other antiretroviral drug was associated with worse cognitive performance in this study.

Several subsequent studies have examined whether switching from an efavirenz-containing regimen to alternative regimens has any impact on cognitive functions. A small open-label phase IV study of 16 patients with HIV reported that while most subjects (81%) self-reported memory problems on efavirenz, switching to ritonavir-boosted lopinavir regimen did not significantly affect cognitive function, brain metabolites, or brain activity as measured by fMRI [5]. It is not clear if this was because the neurotoxic effects of efavirenz was irreversible in this population. A more recent randomized controlled trial of 49 HIV-infected, cognitively asymptomatic patients reported that switching from efavirenz-containing (Atripla; efavirenz 600 mg/emtricitabine 200 mg/tenofovir 300 mg) to a non-containing regimen (Eviplera; emcitabine/rilpivirine/tenofovir) for 12 weeks resulted in a significant

improvement on attention (p=0.041) and speed of information processing (p=0.014) [6]. In addition, 74% of those who switched to a non-containing regimen opted for this regimen without efavirenz after study completion due to subjective cognitive improvement.

Human research to suggest benefits to patients with dementia:

No clinical trials have tested efavirenz in people with dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Efavirenz increases the activity of cytochrome P450 46A1 (CYP46A1 or cholesterol 24-hydroxylase), which initiates the major pathway of cholesterol turnover in the brain (without altering the levels of brain cholesterol) [7]. Efavirenz induces the conversion of cholesterol to 24(S)hydroxycholesterol, which in turn is a ligand for liver X receptors (LXRs) and a positive allosteric modulator of glutamate NMDA receptors. The doses of efavirenz (0.09 and 0.22 mg/kg/day) required for stimulation of cerebral cholesterol turnover in mice were a hundred times lower than those prescribed to HIV patients. In a follow-up study in a mouse model of Alzheimer's (5xFAD mice), efavirenz treatment (0.1 mg/kg/day) activated CYP46A1, promoted cerebral cholesterol turnover, while also reducing amyloid burden, decreasing microglia activation in the cortex and subiculum, improving long-term spatial memory, and decreasing mortality rate among male mice [1].

Based on the rationale above, an ongoing clinical trial is testing the safety and efficacy of low-dose efavirenz in people with mild cognitive impairment (NCT03706885). This trial will include 36 participants and two different doses of efavirenz will be tested: 50 mg or 200 mg per day (for 20 weeks). These doses are significantly lower (1/12th or 1/3rd) than the dose commonly used in HIV patients. The study is expected to be completed in September 2020.

Despite these potential benefits with efavirenz on cholesterol turnover and decreased plaques, animal data indicate that efavirenz, especially its major metabolite 8-hydroxyefavirenz, is directly toxic to neurons at concentrations reached in the cerebral spinal fluid of HIV-infected patients [2; 8]. Several potential mechanisms underlie efavirenz's neurotoxicity, including mitochondrial damage, increased proinflammatory cytokines, and involvement of the cannabinoid system.

In vitro studies have also shown that efavirenz decreases neural stem cell proliferation by decreasing intracellular ATP stores, disrupting the mitochondrial membrane potential, and increasing pro-

apoptotic signaling (e.g. increased Bax and caspase 3) [9]. In mice, efavirenz treatment (20 mg/kg) for 30 days also reduced proliferating neural stem cells in the subventricular zone.

APOE4 interactions: Unknown.

Aging and related health concerns: Significantly increases cholesterol and triglycerides; also associated with sleep abnormalities.

Types of evidence:

- 2 clinical trials

Cardiovascular: INCREASED CHOLESTEROL AND TRIGLYCERIDES. Efavirenz may increase cardiovascular disease risk as it increases total cholesterol and triglyceride levels (Drugs.com). In healthy volunteers receiving efavirenz, total cholesterol increased from baseline by 10 to 20%. In patients treated with Efavirenz + zidovudine + lamivudine, non-fasting total cholesterol and HDL increased from baseline by approximately 20% and 25%, respectively. In a 2015 comparative analysis of 4 phase II-III trials, people treated with efavirenz (n=355) had significantly elevated total cholesterol (by 24.1 mg/dL), LDL (by 13.1 mg/dL), HDL (by 8.0 mg/dL), and triglycerides (by 18.6 mg/dL) [10].

Sleep: HARM. HIV patients taking efavirenz have a high baseline rate of sleep disordered breathing and abnormalities in sleep architecture [11]. However, in a clinical trial of 32 HIV-positive subjects, discontinuation of efavirenz therapy (switch to comparator drug for 12 weeks) did not significantly improve sleep parameters. Thus, efavirenz discontinuation does not appear to readily reverse the sleep and neuropsychological disturbances.

Safety: Adverse events include memory disturbances, insomnia, liver failure, and increased cholesterol and triglyceride levels.

Types of evidence:

- 6 meta-analyses or systematic reviews
- 1 clinical trial
- 2 observational studies
- Numerous laboratory studies

Efavirenz may cause serious psychiatric symptoms including confusion, sadness, suicidal thoughts, anxiety, paranoia, hallucinations, trouble speaking or moving, or unusual behavior (Drugs.com). Efavirenz also affects the immune system and may increase risk of new infections or swelling in the neck or throat (enlarged thyroid). Common side effects include nausea, vomiting, dizziness, rash, headache, and insomnia. Based on a large meta-analysis of 34 clinical studies in HIV-positive patients, efavirenz-based treatment was associated with a higher risk of therapy discontinuation due to adverse events [12].

Neuropsychiatric events: HARM. In a large meta-analysis of 42 clinical trials including 8,466 patients exposed to efavirenz (and 9,631 patients exposed to the comparator drug), severe neuropsychiatric adverse events were more common for efavirenz compared with atazanavir/r (RR: 2.4, 95% CI: 1.5 to 3.8), dolutegravir (RR: 16.7, 95% CI: 2.0 to 137.8), and maraviroc (RR: 5.3, 95% CI: 1.6 to 18.1), and absolute differences were also higher for efavirenz compared with abacavir (RD: 6.0, 95% CI: 2.4 to 9.6) [13].

Based on a questionnaire of 174 HIV-infected adult outpatients treated with efavirenz, neuropsychiatric adverse reactions included cognitive, sleep, and mood disturbances: abnormal dreams (24.7%), memory disorders (23.0%), nocturnal waking (19.6%), sadness (19.3%), impaired concentration (18.9%), trouble falling asleep (17.8%), anxiety (15.5%), and suicidal ideations (9.2%) [14]. Global neuropsychic discomfort was moderate to severe in 23% of patients after a 3-month treatment period.

Liver functions: HARM. Postmarketing cases of hepatitis, including fulminant hepatitis progressing to liver failure (requiring transplantation or resulting in death) have been reported in patients treated with efavirenz (Drugs.com). Efavirenz is not recommended in patients with moderate or severe hepatic impairment. Monitoring of liver enzymes before and during treatment is recommended for all patients.

Lipids: INCREASED CHOLESTEROL AND TRIGLYCERIDES. Efavirenz may increase total cholesterol and triglyceride levels (Drugs.com). In healthy volunteers receiving efavirenz, total cholesterol increased from baseline by 10 to 20%. In patients treated with Efavirenz + zidovudine + lamivudine, non-fasting total cholesterol and HDL increased from baseline by approximately 20% and 25%, respectively. In a 2015 comparative analysis of 4 phase II-III trials, people treated with efavirenz (n=355) had significantly elevated total cholesterol (by 24.1 mg/dL), LDL (by 13.1 mg/dL), HDL (by 8.0 mg/dL), and triglycerides (by 18.6 mg/dL) [10]. The increase in total cholesterol was numerically higher in efavirenz-treated patients compared with dolutegravir-treated patients.

Mortality: SOME DEATHS POSSIBLY RELATED TO DRUG. In a large meta-analysis of 42 clinical trials including 8,466 patients exposed to efavirenz (and 9,631 patients exposed to the comparator drug), 10 deaths reported by 5 trials were considered to be at least possibly related to study drug [13]. Efavirenz was associated with 7 deaths: 3 deaths were attributed to severe lactic acidosis among 3 overweight women, 1 patient died of hepatotoxicity 14 weeks after treatment initiation; 1 patient died of sepsis 5 weeks after treatment initiation that was considered possibly related to the study drug; 1 patient died of lactic acidosis; and 1 patient died of hepatic steatosis associated with hepatitis C coinfection.

In a large study of 49,717 HIV-infected people (D:A:D study), death rates from suicide among those taking efavirenz were not higher than those on other anti-retroviral therapy regimen [15]. There were no differences in suicide risk across current anti-retroviral therapy regimens.

Stroke: POTENTIAL HARM IN PRECLINICAL MODEL. In a mouse model of stroke (middle cerebral artery occlusion), efavirenz exposure increased the severity of stroke, increased endothelial permeability, and disrupted blood-brain barrier integrity [16].

Congenital anomalies: NO HARM. In a meta-analysis of 23 studies that included HIV-infected pregnant women, no differences were found in overall risks of congenital anomalies between those on efavirenz during the first trimester or those on non-efavirenz regimens (relative risk 0.78, 95% CI 0.56-1.08) [17]. The incidence of neural tube defects was low (0.05%; 95% CI <0.01-0.28), and comparable to the incidence in the general population.

Drug interactions: There are 272 major drug interactions and 684 moderate drug interactions with efavirenz (Drugs.com). The list of 272 major drug interactions can be found here. Efavirenz plasma concentrations may be altered by substrates, inhibitors, or inducers of the liver enzyme CYP3A.

Sources and dosing: Efavirenz (brand names Sustiva® and Stocrin®), usually in combination with several other antiretroviral agents, is approved for the treatment of HIV. The usual adult dose for HIV infection is 600 mg orally once daily (Drugs.com). The ongoing clinical trial (described below) is testing lower doses of 50 mg or 200 mg daily in people with mild cognitive impairment (NCT03706885). Based on a pharmacokinetics study in 334 healthy volunteers, efavirenz clearance was lower in Asians and Blacks relative to Caucasians [18]. A slightly lower clearance was observed in women compared to men.

Research underway: Numerous clinical trials testing efavirenz are ongoing, though the vast majority are in HIV-positive patients. There is one ongoing clinical trial in people with mild cognitive

impairment. A phase I placebo-controlled blinded clinical trial will test whether efavirenz (Sustiva®) is safe and tolerable in people with mild cognitive impairment or early dementia due to Alzheimer's (NCT03706885). This trial will include 36 participants and two different doses of efavirenz will be tested: 50 mg or 200 mg per day (for 20 weeks). These doses are significantly lower (1/12th or 1/3rd) than the dose commonly used in HIV patients. The study is expected to be completed in September 2020.

Search terms:

Pubmed, Google: efavirenz

- + meta-analysis, + cognitive, + Alzheimer, + ApoE4, + cardiovascular, + lifespan

Websites visited for efavirenz:

- Clinicaltrials.gov
- Examine.com (0)
- Treato.com
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharma
- Pharmapro.com (0)

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