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.

Maraviroc

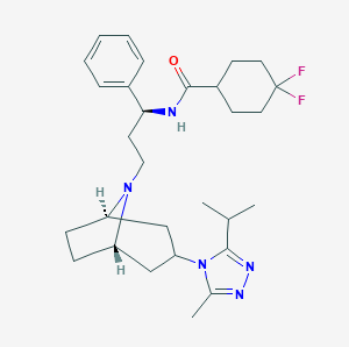
Evidence Summary

Based on limited clinical evidence, maraviroc may be beneficial for atherosclerosis and cancer. However, it is associated with many side effects including infection and has a boxed warning for hepatotoxicity.

Neuroprotective Benefit: Some cognitive benefits have been observed in patients with HIV whose therapy was intensified with maraviroc; however, the clinical evidence is inconsistent and based on open-label designs.

Aging and related health concerns: Small clinical studies suggest that maraviroc may be beneficial for atherosclerosis and cancer, but all studies to date have been small pilot studies without placebo controls.

Safety: Most clinical data are from patients with HIV. Maraviroc has a boxed warning for hepatotoxicity. Common side effects include infection, cough, fever, and vomiting.

Availability: Rx; approved for slowing HIV/AIDS.	**Dose**: In HIV patients, doses range from 150 mg twice daily to 600 mg twice daily, depending on whether concomitant medications are CYP450 3A inducers or inhibitors.	**Chemical formula:** $C_{29}H_{41}F_2N_5O$ **MW**: 513.7  Source: PubChem
Half life: 14-18 hours	**BBB**: likely penetrant	
Clinical trials: very few trials have been carried out in people without HIV/AIDS. One proof-of-concept study enrolled 110 people with rheumatoid arthritis.	**Observational studies**: N/A	

What is it? Maraviroc is a chemokine co-receptor 5 (CCR5) antagonist developed by Pfizer that is designed to act against the human immunodeficiency virus (HIV) by interfering with the interaction of HIV and CCR5 that is necessary for CCR5-tropic HIV-1 to enter cells. It was approved by the FDA for use in the US in 2007. Maraviroc is used with other medications to treat CCR5-tropic HIV type 1.

As a chemokine receptor, CCR5 helps to initiate immune responses and to distribute effector immune cells to sites of inflammation (Telenti and Egger, 2007). CCR5 plays a complex role in innate immunity against a number of pathogens, including Toxoplasma gondii, West Nile virus, and other infectious agents. CCR5 inhibition could be protective against some pathogens (e.g., HIV) while deleterious in others (e.g., tick-borne encephalitis, West Nile virus).

Neuroprotective Benefit: **S**ome cognitive benefits have been observed in patients with HIV whose therapy was intensified with maraviroc; however, the clinical evidence is inconsistent and based on open-label designs.

Types of evidence:

- 4 open-label clinical trials
- A few laboratory studies

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

No studies have examined whether maraviroc can prevent dementia or cognitive decline. All studies examining the potential effects of maraviroc on cognitive functions have been carried out in people with HIV.

In a randomized open-label prospective controlled trial of 60 treatment-naïve HIV positive individuals without overt cognitive complaints, maraviroc-intensified (150 mg) antiretroviral regimen was compared to a standard regimen (tenofovir-emtricitabine [300/200 mg] and atazanavir/ritonavir [300/100 mg])(Mora-Peris et al., 2018). Cognitive function improved over 48 weeks for both standard and maraviroc-intensified therapy, but no statistically significant differences between the study groups were observed for overall cognitive score change from baseline to week 24 or to week 48. Regarding individual tasks, only the Groton maze learning task showed statistically significant differences between the study arms in the mean score difference with greater improvements in maraviroc-intensified therapy. Groton maze learning task was the only cognitive test out of 12 that showed a significant group effect; p-values were corrected using Sidak/Bonferroni corrections to account for multiple analyses. A greater increase in frontal grey matter neuronal metabolite (N-acetyl aspartate/creatine ratio) was observed in standard therapy versus maraviroc-intensified therapy, although this was not associated with changes in cognitive function. No statistically significant associations were observed between changes in global cognitive scores and changes in cerebral imaging markers, cerebrospinal fluid antiretroviral drug exposure or cerebrospinal fluid infectivity measures.

In contrast, in an open-label pilot randomized controlled trial of 17 people with HIV-associated neurocognitive disorder reported that medium-to-large effect sizes were observed in favor of improved global neurocognitive performance with maraviroc-intensification (150, 300, or 600 mg, twice daily) compared to the traditional combined antiretroviral therapy (Gates et al., 2016). However, no treatment-related changes were detected for MRS metabolites or cerebrospinal fluid biomarkers.

In another single-arm, open-label study of 15 HIV patients (of whom 12 were evaluated), maraviroc addition to existing antiretroviral therapy resulted in a decreased proportion of circulating intermediate and nonclassical CD16-expressing monocytes (Ndhlovu et al., 2014). This change was associated with a significant improvement in neuropsychological performance among six subjects who entered the study with evidence of mild to moderate cognitive impairment. Although there was no significant change from entry (week 0) to week 24 in global composite scores or any neuropsychological subdomain scores, there was a trend for improvement in executive function ($p = 0.08$). When the six subjects who entered

the study with impairment (NPZglobal ≤ −0.5) were analyzed separately, they showed significant improvements in global functioning (median change=0.57; p = 0.03), learning and memory (median change=0.66; p = 0.03), and executive function (median change=0.89; p = 0.046).

In a single-arm open-label study of 12 HIV patients with neurocognitive impairment, treatment switching to a maraviroc-containing regimen for 48 weeks resulted in a trend towards improvement in neurocognitive status and reduced TNF-α concentrations (median, 0.51 to 0.35 pg/mL) in the cerebral spinal fluid (Tiraboschi et al., 2015). No changes in other inflammatory markers were observed.

Human research to suggest benefits to patients with dementia: None.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Cognitive dysfunction is prevalent in people living with HIV, and the degree of HIV DNA in monocytes appear to be linked to cognitive outcomes. Although the underlying pathogenesis is unclear, several factors likely play a role, including antiretroviral toxicities, neuronal damage from untreated HIV-disease, and lifestyle factors such as smoking, alcohol, and recreational drug use. It has also been hypothesized that the pathogenesis involves trafficking of circulating bone marrow-derived monocytes, some of which are HIV-infected, through the blood-brain barrier into the brain parenchyma, triggering neuroimmune activation and inflammation, ultimately leading to neuronal degeneration and death (Ndhlovu et al., 2014). As maraviroc is a small molecule, it is thought to enter the cerebral spinal fluid and exert antiretroviral and/or anti-inflammatory activity in the CNS compartment (Mora-Peris et al., 2018).

Not many preclinical studies have tested maraviroc for its neuroprotective potential in conditions other than HIV-related cognitive impairment.

In a study of rat cortical and striatal nerve terminals, maraviroc treatment showed a concentration-dependent *impairment* of striatal nerve terminal maximal mitochondrial respiration and spare respiratory capacity as well as a reduction of intraterminal ATP levels (Stauch et al., 2017). Because of the *in vitro* nature of this study and the high concentration of maraviroc used, it is not clear how these results translate to the clinic.

APOE4 interactions: Unknown.

Aging and related health concerns: Small clinical studies suggest that maraviroc may be beneficial for atherosclerosis and cancer, but all studies to date have been small pilot studies without placebo controls.

Types of evidence:

- 5 clinical trials, 3 in HIV patients, 1 in rheumatoid arthritis, and 1 in colorectal cancer
- Numerous laboratory studies

Atherosclerosis: POTENTIAL BENEFIT. In HIV patients, atherosclerosis is accelerated due to chronic inflammatory processes including insulin resistance, hepatic steatosis, microbial translocation, and immune activation. A few clinical studies have evaluated potential benefits of maraviroc in slowing atherosclerosis. In a 2019 randomized crossover pilot study of 21 HIV-positive patients at high cardiovascular risk, maraviroc treatment (300 mg/day) for 24 weeks significantly improved brachial flow-mediated dilation, carotid-femoral pulse wave velocity, and carotid intima-media thickness by 66%, 11%, and 13%, respectively (p= 0.002, p=0.022, and p=0.038, respectively)(Francisci et al., 2019). There was also a beneficial effect of maraviroc on the endothelial microparticles to endothelial progenitor cell ratio, a measure of vascular competence (p< 0.001), and platelet/leukocyte aggregates (p=0.013). No significant changes in markers of systemic inflammation, monocyte activation, or microbial translocation were observed. Maraviroc treatment led to significant improvements in several markers for cardiovascular risk, endothelial dysfunction, arterial stiffness, and early carotid atherosclerosis, which were accompanied by an increase in vascular competence without affecting systemic inflammation.

In a 2017 pilot prospective study of 12 HIV-1/HCV co-infected patients, switching to a maraviroc-including therapy for 48 weeks resulted in a decrease in intima media thickness in two patients (from 1.1 and 1.0 mm to 0.9 and 0.76 mm), and 4 out of 9 patients with plaques showed a reduction of plaque, while 5 out of 9 showed no modifications; no patients got worse (Maggi et al., 2017). No significant changes in inflammatory or endothelial adhesion biomarkers, Veterans Aging Cohort Study index or Framingham risk score were reported.

In a 2016 clinical study of 6 patients with HIV (who were compared to 9 people from an out-patient control cohort), maraviroc intensification (150 mg twice daily) for 6 months resulted in a significant reduction in intima media thickness (Piconi et al., 2016). A notable reduction of arterial stiffness, as evaluated by pulse wave velocity, compared to the baseline values was also seen at months 3 and 6 in the maraviroc intensification group. These data indicate that maraviroc intensification may have

beneficial effects on atherosclerotic burden. Plasma IL-6 (p = 0.029) and MCP-1 concentrations were reduced after 6 months of maraviroc treatment compared to what was observed at baseline.

Some studies have shown that people with a deletion (CCR5delta32) in the CCR5 gene have reduced susceptibility to coronary artery disease, reduced early onset of coronary heart disease in women, and protection against myocardial infarction (Jones et al, 2011). Though findings are not consistent and other studies have found no effect of the CCR5delta32 polymorphism on coronary artery disease or myocardial infarction in other populations.

In a mouse model of genetic dyslipidemia, maraviroc reduced atherosclerosis progression by lowering macrophage infiltration and expression of adhesion molecules and RANTES (regulated on activation, normal T-cell expressed, and secreted) inside the plaques (Cipriani et al., 2013).

Breast cancer: POTENTIAL BENEFIT IN MOUSE MODELS. No clinical studies have tested maraviroc in breast cancer; however, several preclinical studies have been carried out. In nude rats implanted with breast cancer cells (MDA-MB-231 cells), maraviroc treatment (25 mg/kg, i.p.) for 3-4 weeks attenuated proliferation, colony formation, and migration of metastatic breast cancer cells, and induced apoptosis and arrest in the G1 phase of the cell cycle (Pervaiz et al., 2019). In a xenograft mouse model of triple-negative breast cancer (MDA-MB-231-LN, SUM149, and SUM159), the combination of maraviroc (8 mg/kg, oral) and cMR16-1 (mouse version of anti-IL6R antibody) significantly reduced tumor growth compared to each agent alone (Jin et al., 2018). The combination of maraviroc and cMR16-1 also abrogated thoracic metastasis.

In mice implanted metastatic mammary tumors, maraviroc treatment (31 mg/kg, oral gavage) for 24 days significantly reduced the level of CCR5-positive Tregs and metastatic tumor burden in the lungs (Halvorsen et al., 2016). C-C chemokine ligand 8 (CCL8), an endogenous ligand of CCR5, is produced by macrophages in the lungs of mice with metastatic primary tumors. However, migration of Tregs toward CCL8 was reduced in the presence maraviroc.

CCL5 and CCR5 expression are increased in breast cancer cells and correlate with poor prognosis (Woollard and Kanmogne, 2015).

Colorectal cancer: POTENTIAL BENEFIT. In a pilot phase I trial (MARACON) of maraviroc (300 mg, twice daily) in patients with liver metastases of advanced refractory colorectal cancer, clinical effects included an induction of central tumor necrosis and a partial remission of lung metastases (Halama et al., 2016).

Histological analysis showed that all tumor samples had reduced proliferation (as evidenced by Ki67 staining) and increased tumor cell death. In most clinical samples, marked reductions in key cytokines and growth factors promoting tumor growth, chemotherapy resistance, or angiogenesis were seen. In an *in vitro* study of patient-derived organotypical culture, CCR5 inhibition resulted in macrophage repolarization with anti-tumoral effects. CCR5 blockade induced a phenotypic shift mediated by STAT3/SOCS3, referred to as a switch from an M2 (anti-inflammatory) to an M1 (inflammatory) phenotype.

In a study in mice that were orthotopically injected with human colon cancer cell lines, maraviroc treatment (30 mg/kg every 2 days) for 15 days reduced tumor formation and reduced the intratumor number of α-smooth muscle actin-positive fibroblasts, which express epidermal growth factor (EGF), a growth factor for colon cancer cell growth (Tanabe et al., 2016).

In a cell culture study of colorectal cancer cells (SW480 and SW620 cells), maraviroc significantly reduced proliferation and induced an arrest in G1 phase of the cell cycle, while promoting apoptosis and increasing cleaved caspases (Pervaiz et al., 2015).

Other cancers: POTENTIAL BENEFIT IN PRECLINICAL STUDIES.
In a mouse model of lymphoblastic leukemia, maraviroc suppressed the growth of SUP-B15 xenograft tumors in athymic mice (Zi et al., 2017). Maraviroc induced SUP-B15 cells to undergo apoptosis by increasing cleaved caspase-3, cleaved caspase-9, and PARP.

In a mouse model of gastric cancer, administration of maraviroc reduced the extent of peritoneal disease and increased survival (Mencarelli et al., 2013). Maraviroc treatment also reduced the tumor burden in a xenograft model. CCR5 antagonism modulated the expression of genes known for their role in cancer growth, including IL-10 receptor B; hepatocyte growth factor receptor (MET); the homolog of the atypical cadherin gene, FAT1; Nm23-H1; and lymphotoxin β receptor. Median survival time increased from 30 to 46 days in mice administered maraviroc.

In a mouse model of hepatocellular carcinoma, those treated with maraviroc showed longer survival, less liver fibrosis, lower levels of liver injury markers and chemokines, less apoptosis, lower proliferation index, and lower tumor burden than their control counterparts (Ochoa-Callejero et al., 2013). In addition, maraviroc inhibited hepatic stellate cell activation markers such as phospho-p38 and ERK, and increased hepatocyte survival.

Rheumatoid arthritis: NO BENEFIT. CCR5 ligands and other chemokines are increased in synovial fluids during rheumatoid arthritis, resulting in tissue and joint damage (Woollard and Kanmogne, 2015). Theoretically, blocking CCR5 could reduce inflammation at synovial joints and reduce symptoms. However, in a double-blind randomized controlled trial, maraviroc treatment (300 mg twice daily) was ineffective in treating rheumatoid arthritis (Fleishaker et al., 2012). The study was terminated after the planned interim futility analysis due to lack of efficacy.

Safety: Most clinical data are from patients with HIV. Maraviroc has a boxed warning for hepatotoxicity. Common side effects include infection, cough, fever, and vomiting.

Types of evidence:

- 3 clinical trials
- 3 reviews

Common side effects of maraviroc include infection (55%), upper respiratory tract infection (23-32%), cough (14%), fever (13%), vomiting (12%), and skin rash (11%)(see full list here: Drugs.com). There is also a US Boxed Warning for liver toxicity with use of maraviroc. Severe rash or evidence of a systemic allergic reaction may occur prior to hepatotoxicity. Contraindications include patients with severe renal impairment or end-stage renal disease who are taking concomitant potent CYP3A inhibitors or inducers.

In a randomized open-label prospective controlled trial of 60 treatment-naïve HIV positive individuals without overt cognitive complaints, maraviroc-intensified (150 mg) antiretroviral regimen was not associated with any safety, laboratory, or serious adverse events (Mora-Peris et al., 2018).

In a single-dose placebo-controlled five-way crossover trial of 61 healthy subjects, a single dose of maraviroc (100, 300, or 900 mg) did not result in serious adverse events or discontinuations due to treatment-related adverse events (Davis et al., 2008). The most frequent treatment-related adverse event was dizziness, followed by headache, nausea and postural hypotension. A similar number of subjects in all treatment groups, including placebo, experienced laboratory abnormalities, but none were considered clinically significant. Maraviroc was not associated with clinically relevant effects on QT interval.

In a double-blind randomized controlled trial of 16 patients with rheumatoid arthritis, the most common adverse events associated with maraviroc treatment (300 mg twice daily) was constipation (7.8%),

nausea (5.2%), and fatigue (3.9%)(Fleishaker et al., 2012). No serious or severe adverse events, temporary discontinuations, or dose reductions due to adverse events were reported.

Drug interactions: A total of 286 drugs are known to interact with maraviroc, including 39 major interactions, 245 moderate interactions, and 2 minor interactions (Drugs.com).

Sources and dosing: Maraviroc is marketed by Pfizer as Selzentry and is used with other medications to treat CCR5-tropic HIV type 1. In HIV patients, doses range from 150 mg twice daily to 600 mg twice daily, depending on whether concomitant medications are CYP450 3A inducers or inhibitors (Drugs.com).

Research underway: As of 12/4/2019, there are currently 20 ongoing clinical trials testing maraviroc (ClinicalTrials.gov). Most trials are in HIV/AIDS patients, but a few are testing maraviroc in patients with stroke, endothelial dysfunction, graft-versus-host disease, and metastatic colorectal cancer.

Search terms:
Pubmed, Google: maraviroc

- + cognitive, + Alzheimer, + dementia, + APOE4, + meta-analysis, + clinical trial, + cancer, + atherosclerosis

Websites visited for maraviroc:

- Clinicaltrials.gov (20)
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharma (0)
- Pharmapro.com (0)

***Disclaimer**: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the **Terms & Conditions**.*

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.