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.

Lamivudine

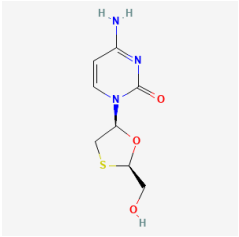
Evidence Summary

Based on some preclinical and observational work, lamivudine may be an interesting target to reduce transposition events, inflammation, and SASP. Actual efficacy and safety in healthy populations is unclear.

Neuroprotective Benefit: Preclinical work suggests that lamivudine may be neuroprotective, such as by reducing SASP or inflammation. Antiretroviral therapy may reduce dementia in patients with HIV and lamivudine may benefit ALS patients.

Aging and related health concerns: Preclinical and some observational evidence indicate that lamivudine may have efficacy in senescence, diabetes, and cancer, potentially through regulating transposition, SASP, and/or inflammation.

Safety: Lamivudine is typically well-tolerated. However, rare but serious side effects including pancreatitis and liver dysfunction have been seen in patients. Most data is in the context of serious viral infection and/or combination therapy.

Availability: Rx	**Dose**: For adult patients with HIV and post-exposure prophylaxis: 300 mg daily by mouth. For adult patients with hepatitis B: 100 mg daily. Ongoing trials in ALS and AD are testing 300 mg daily doses.	**Chemical formula:** $C_8H_{11}N_3O_3S$ **MW**: 229.26 Source: PubChem 
Half-life: 2 – 4 hours	**BBB**: Penetrant	
Clinical trials: Tested in numerous studies of 100-1000 people	**Observational studies**: Largest observational study specifying antiretroviral medication included 3398 patients	

What is it?

Lamivudine, also called 3TC or by its brand name, Epivir, is a nucleoside reverse transcriptase inhibitor (NRTI), a class of drugs that has been discussed in the report on LINE1 inhibition. This report will focus specifically on lamivudine. Where relevant, this report will refer back to the LINE1 inhibition as delineated by citations, or expand on the literature published since that report was completed.

As reviewed by Pray, 2008, transposable elements (TEs), sometimes referred to as 'jumping genes', are sequences of nucleic acids that can be removed and/or copied from one site in the genome and relocated to another. Some transposons, known as class II transposons, move through a "cut and paste" activity such that the DNA is excised from one location and moved to another. These transposons are a minority in the human genome. The vast majority of transposons in humans are retrotransposons, or class I transposons. There are further subdivisions of retrotransposons based on their nucleic acid sequences, such as non-long terminal repeat (non-LTR) retrotransposons like LINE1 retrotransposons, or long terminal retrotransposons like endogenous retroviruses (ERVs).

Retrotransposons 'jump' by being transcribed from DNA into RNA, reverse transcribed from RNA back to DNA, and then being inserted back into the genome. This insertion can interrupt genes or regulatory regions, which can lead to novel and useful combinations or deleterious mutations (Pray, 2008). Transcription and retrotranscription both involve enzyme(s) using a template nucleic acid and building a complementary strand of nucleic acids by linking nucleotides together in a specific sequence. The enzyme reverse transcriptase is necessary for this reverse transcription from RNA back to DNA (Coffin et

al., 1997). There are a variety of cell mechanisms designed to regulate transposition, such as chromatin or histone modifications, siRNA, and piRNA (Yushkova & Moskalev, 2023).

There are also several medications that can disrupt the transposition process, such as by inhibiting viral reverse transcriptase. Lamivudine, as an NRTI, is one such medication that inhibits HIV and hepatitis B virus reverse transcriptases. NRTIs are analogs of nucleotides. Unlike nucleotides, NRTIs cannot be linked to other nucleic acids, thus halting the transcription process (Garcia-Trejo et al., 2021).

Lamivudine is an analog of cytidine. It is a prodrug that requires transport into a cell and subsequent phosphorylation to an active form. Lamivudine lacks the 3' OH that is required to link to the subsequent nucleotide base (Else et al., 2012). It is the (-) enantiomer of BCH-189. Originally BCH-189 was tested as a racemic mixture, but the (-) isomer now known as lamivudine was found to be more potent and less toxic (Shinazi et al., 1992, Taylor et al., 2023).

Increased transposition is thought to be a consequence of aging, as many mechanisms that usually suppress transposon activity become less efficient over time. This de-repression of transposition may then contribute to aging or age-related diseases including cancer and neurodegeneration (Yushkova & Moskalev, 2023).

Neuroprotective Benefit: Preclinical work suggests that lamivudine may be neuroprotective, such as by reducing SASP or inflammation. Antiretroviral therapy may reduce dementia in patients with HIV and lamivudine may benefit ALS patients.

Types of evidence:

- 4 observational studies
- 1 open label study
- 3 review articles
- 1 conference presentation
- 8 laboratory studies

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

As discussed in the LINE1 report, TE activity has been associated with different dementias, including AD (LINE1 Report). While no human studies have shown a preventative activity of lamivudine in healthy populations or a preventative activity of lamivudine alone, there are some studies that indicate that combination antiretroviral therapy may help prevent dementia, decline or improve cognitive function in patients with HIV.

Patients with HIV may experience HIV-associated neurocognitive disorder (HAND). HAND includes asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia, the latter of which has become less common now that combination antiretroviral therapy (ART) is widely used. A 2020 paper examined the associations between antiretroviral medication use and neurocognitive impairment in populations. The authors investigated this by looking at healthcare data from patients with HIV and compared those who took antiretroviral medication to those who did not. The authors included 47,862 patients; 30,828 treated with antiretrovirals, and 17,034 who were not. Antiretroviral use was associated with reduced risk of cognitive impairment (HR=0.46; 95% CI: 0.42--0.50); HAND (HR=0.75; 95% CI: 0.63--0.88); Alzheimer's disease (HR=0.38; 95% CI: 0.27--0.56); Parkinson's disease (HR=0.45; 95% CI: 0.33--0.62), multiple sclerosis (HR=0.26; 95% CI: 0.19--0.35); and other dementias (HR=0.57; 95% CI: 0.52--0.63). This study did not compare different antiretroviral medications, and this patient population's use of these medications may not inform the use of the medications in non-HIV populations (Siangphoe et al., 2020).

A cross-sectional study published in 2021 assessed the association of certain NRTI plasma concentrations and cognitive function as assessed by a computerized CogState battery in people with HIV. The study included 554 people with HIV on combination antiretroviral therapy, 83 of whom were on lamivudine/abacavir. The authors found that higher plasma exposures of lamivudine was associated with greater cognitive performance, though maximum lamivudine plasma concentrations were associated with poorer cognitive performance. Some limitations of this study included the smaller number of people on lamivudine and the fact that they examined plasma concentrations of the drugs rather than CSF levels or intracellular levels of the active NRTI metabolites which are more direct readouts of CNS efficacy (De Francesco et al., 2021).

Human research to suggest benefits to patients with dementia:

No completed studies have assessed the utility of lamivudine in dementia patients. An ongoing study, NCT04552795, is testing lamivudine in 12 patients with early AD. This study reached its primary completion date on May 4, 2023. Results have not yet been published. For more information, see the 'Research Underway' section.

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

The inhibition of transposition by lamivudine may be neuroprotective through a variety of mechanisms. Some of the mechanisms include, among others: decreased gene de-regulation, mutation, or duplication of genes such as *APP* caused by transposons; decreased senescence-associated secretion phenotype (SASP); and decreased type-1 interferon (IFN-1) response. Yushkova & Moskalev reviewed the potential role(s) of transposons in aging in 2023.

Sun et al., 2018 reported aberrant expression of transposable elements (50 upregulated, 60 downregulated) in a Drosophila tau transgenic model at day 10. The most common transposable elements that were differentially expressed were class 1 long terminal repeat (LTR) retrotransposons. In another transgenic Drosophila model that increases transposable element mobilization (flamenco), there was an increase in neuronal death in tau transgenic Drosophila. There was also a reduction of piRNAs (a group of regulatory RNAs that inhibit transposon activity) in tau Drosophila and a decondensation of heterochromatin. Overexpression of piwi (a regulatory protein of piRNA biogenesis) also reduced neuronal death. Finally, treatment with lamivudine (a nucleoside reverse transcriptase inhibitor) reduced transposable element mobilization and neuronal death (LINE1 Report).

A 2021 experimental study tested the effects of lamivudine in senescence-prone 8 (SAMP8) mice, a mouse model of aging. SAMP8 mice have upregulations in mRNAs for genes related to TEs, type 1 interferon responses, and senescence-associated secretion phenotype (SASP) factors. The authors treated SAMP8 mice with lamivudine for 4 weeks, starting at 44 weeks of age. They found that treatment with lamivudine reversed weight loss seen in SAMP8 mice and improved spatial memory as measured by Morris Water Maze and senescence scores as compared to vehicle treated SAMP8 mice. Lamivudine treatment mitigated neurodegeneration and neuronal morphology defects in vitro and in vivo as compared to vehicle treatment, and partially reversed the upregulation in mRNA related to SASP, TEs, and type-1 interferon responses (Li et al., 2021).

Down Syndrome (DS) is a genetic form of AD. As increased retrotransposition is also implicated in neurodevelopmental disorders, a group examined the effects of lamivudine on a mouse model of DS. They found that compared to placebo treatment, lamivudine treatment mitigated behavioral and cognitive deficits in this mouse model of DS. Lamivudine treatment may have increased some anxiety-like behavior in the WT mice (Martinez de Lagran et al., 2022).

In an open-label study, 40 patients with ALS were treated with Triumeq (abacavir, lamivudine, and dolutegravir) for 24-weeks after a 10-week lead-in period. Patients declined 32% less on the ALSFRS-R (ALS-functional rating score) than would be expected from the lead-in period. There was less decline on other functional outcome measures than would be expected. There was also a reduction in transcription levels of human endogenous retroviruses. There were no changes in neurofilament light, a marker of neurodegeneration. A model of survival probability predicted a median of 5 deaths with an interquartile range of 2-8; 1 patient died 5 months after stopping treatment due to disease progression (Gold et al., 2019) (LINE1 Report).

There is an ongoing Phase 3 randomized controlled trial, NCT05193994 testing a combination therapy that includes lamivudine in 390 ALS patients. For more information, see the 'Research Underway' section.

APOE4 interactions:

No studies were found that explored or found a relationship between APOE4 status and the effects of lamivudine.

Aging and related health concerns: Preclinical and some observational evidence indicate that lamivudine may have efficacy in senescence, diabetes, and cancer, potentially through regulating transposition, SASP, and/or inflammation.

Types of evidence:

- 2 meta-analyses
- 1 observational study
- 4 reviews
- 1 conference presentation
- 2 laboratory studies

TEs are thought to potentially play a role in senescence, and treatment with lamivudine or other NRTIs have shown some preclinical efficacy in addressing senescent phenotypes. The LINE1 inhibition report covered several papers on this topic up until 2020 (LINE1 Report).

SIRT6 knock out (SIRT6-KO) mice have a shortened lifespan and growth retardation. They are also characterized by elevated L1 activity. In vitro, cells from SIRT6-KO animals have high levels of L1 retrotransposition events, increased L1 DNA copy numbers, and high levels of DNA damage compared to wild type cells. These phenotypes are repressed by treatment with nucleoside reverse-transcriptase inhibitors (NRTIs – lamivudine and stavudine), drugs which can inhibit L1 retrotransposition. Similarly, in SIRT6-KO mice NRTI treatment reduces the level of genomic L1 DNA and cytoplasmic L1 DNA in multiple organs (though not significantly in the brain). Old mice also have elevated cytoplasmic L1 at levels similar to SIRT6-KO mice in multiple organs (though in the brain levels are only slightly significantly elevated compared to young mice, and not nearly as elevated as SIRT6-KO mice). SIRT6-KO mice also have elevated levels of IFN-α and IFN-β, which are repressed with NRTI treatment. Finally, NRTI treatment extended lifespan in SIRT6-KO mice (image right) and reverses several age-related phenotypes (body weight, mobility, behavior, bone density, muscle mass, muscle fiber thickness, apoptosis in the thymus and spleen, and a reduction of sterile inflammation and SASP proteins). However, NRTI treatment did not completely reverse aging, as treated mice still died by 60 days of age (Simon et al, 2019) (LINE1 Report).

Further in vitro studies suggested that SIRT6 binds to the 5'-UTR of the L1 locus. It interacts with KAP1 and facilitations KAP1 interaction with the heterochromatin factor, HP1α, packaging L1 elements into

heterochromatin and suppressing transcription. In vitro, SIRT6 is depleted from the L1 loci in old or senescent cells, thereby derepressing L1 elements (Van Meter et al, 2014). Another study suggested that during cellular senescence L1 is depresressed and accumulates in the cytoplasm, triggering a type-1 interferon (IFN-1) response. IFN-1 contributes to the maintenance of the senescence-associated secretory phenotype (SASP), and treatment with lamivudine repressed the L1 response (but not expression) and downregulated inflammaging in vivo. In aged human dermal fibroblasts, senescent cells were increased and 10.3% had evidence of L1 activation. Notably, none of the non-senescent cells had evidence for L1 activation (De Cecco et al, 2019) (LINE1 Report).

Cancer: THEORETICAL BENEFIT

HIV drugs have long been examined for their potential use as anti-cancer therapies after showing that highly active retroviral therapies (HAART) could reduce the risk of HIV-related Kaposi's sarcoma (Chow et al., 2009). L1 insertions could be a cause of cancer as they have been reported to interrupt tumor suppressor genes, and cancer cells could have increased L1 activity. For instance, a meta-analysis of six studies of patients with chronic hepatitis C found that patients taking lamivudine had a reduced risk of developing hepatocellular carcinoma (HCC) versus those taking no therapy (OR = 0.48; 95%CI 0.38 – 0.61) (a caveat, Hepatitis C affects the liver) (Singal et al., 2013) (LINE1 Report).

Lamivudine or other NRTIs may have other efficacy as cancer treatments, as reviewed by Garcia-Trejo et al., 2021. Based on in vitro studies in cancer cells, lamivudine and other NRTIs may act as sensitizers to radiotherapy by inhibiting telomerase; inhibit viral replication that contributes to cancer progression; or increase apoptosis and decrease cell migration.

The effect on telomerase, while useful in cancer treatment, is a potential concern as telomerase activity and telomere length are linked to aging. However, lamivudine does not appear to affect either aspect of telomere biology at therapeutic doses in PBMCs from patients with HIV infection. Moreover, no NRTI appeared to affect telomerase activity or telomere length in HIV negative PBMCs from patients given NRTIs for 4 weeks. Whether this is due to the length of NRTI treatment or an effect of HIV itself is not clear (Leeansyah et al., 2013).

Type 2 Diabetes: POTENTIAL BENEFIT

A 2020 study examined health insurance claim database records to assess the association, if any, between NRTI treatment and subsequent type-2 diabetes (T2D) diagnosis in 128,861patients with HIV or HBV. The authors investigated this possibility because TE regulatory machinery may be downregulated in T2D and TEs may activate the inflammasome. NRTIs can reduce transposition events. The authors found that NRTI exposure in these patients compared to no NRTI exposure was associated with a significantly lower hazard rate of T2D diagnosis (adjusted HR=0.673; 95% CI 0.638–0.710, $p < 0.0001$). The authors also investigated the effects of lamivudine on insulin resistance and inflammasome

activation in human cells and animals. They found that lamivudine treatment improved insulin sensitivity in human primary cells, and reduced insulin resistance and inflammasome activation in a mouse model of T2D. Importantly, this was not due to weight loss in the mice, as weight loss can be a side effect of NRTI treatment in humans (Ambati et al., 2020).

Safety: Lamivudine is typically well-tolerated. However, rare but serious side effects including pancreatitis and liver dysfunction have been seen in patients. Most data is in the context of serious viral infection and/or combination therapy.

Types of evidence:

- 1 meta-analyses or systematic reviews
- 4 randomized controlled clinical trials
- 2 observational studies
- 1 open label study
- 3 reviews
- 3 educational sources
- 2 laboratory studies

Lamivudine is typically given as a combination therapy; the side effect profile of lamivudine alone is therefore less well studied. Common side effects include nausea, vomiting, weight loss, diarrhea, abdominal pain, headache, cough, nasal symptoms, and fever. Serious side effects are rare but can include serious liver problems, pancreatitis, peripheral neuropathy, muscle pain, weakness, aplastic anemia, lactic acidosis, immune reconstruction syndrome, or fat redistribution (Taylor et al., 2023; Ambati et al., 2020).

An open-label dose-escalation study in 1995 of lamivudine monotherapy in 104 patients with asymptomatic or mildly symptomatic HIV reported that nausea, diarrhea, abdominal pain, headache, and fatigue were among the most common side effects. Two cases of mild peripheral neuropathy were reported after treatment. The cases did not progress during continuous treatment and were therefore not considered to be drug related. They were reported to be mild and transient, and no side effect was dose-dependent. In less than 5% of subjects there were occasional events of neutropenia, thrombocytopenia, and elevations of bilirubin and liver enzymes less than or equal to 5 times the normal limit. These events were transient and did not result in dose changes or withdrawal from the study (Leeuwen et al., 1995).

A 1996 RCT assessed the safety and efficacy of zidovudine, another NRTI, alone or with low or high dose of lamivudine. This study randomized 223 patients with HIV to one of three groups: zidovudine alone, zidovudine + 150 mg lamivudine, or zidovudine + 300 mg lamivudine. Most side effects were seen in all

three groups and thus ascribed to zidovudine or to the disease itself. The only adverse effects that occurred more in a zidovudine + lamivudine group both occurred in the higher dose lamivudine group: decreased hemoglobin (0% of zidovudine; 1% of zidovudine + 150 mg lamivudine; 4% of zidovudine + lamivudine) and decreased neutrophil count (3% of zidovudine; 3% of zidovudine + 150 mg lamivudine; 11% of zidovudine + 300 mg lamivudine) (Staszewski et al., 1996).

A 1998 study randomized 358 patients to placebo treatment, 25 mg lamivudine, or 100 mg of lamivudine daily for 1 year. There were no significant differences in adverse events or laboratory values, and no serious adverse event was considered to be drug related (Lai et al., 1998).

A 1999 randomized study of 143 patients with chronic hepatitis B assessed the effects of 100 mg daily of lamivudine as compared to placebo treatment for 52 weeks, with an additional 16 weeks of monitoring for durability of response and safety. They found that lamivudine was well-tolerated with similar adverse events to placebo group. They found that post-treatment self-limited elevations in serum alanine aminotransferase were more common in the lamivudine treated group as compared to control (Dienstag et al., 1999).

A 2012 open-label crossover study examined doses of 150 mg or 300 mg of lamivudine daily in 24 healthy volunteers. The study involved 10 days on one dose of the medication, a 10 day wash out period, and then 10 days on the other medication dose. The focus of the study was pharmacokinetics, but the authors noted that there were no grade 3 or grade 4 adverse events and that lipid profiles were normal at both baseline and after treatment end (Else et al., 2012).

NRTIs have also been associated with cases of myopathy and neuropathy. For instance, in clinical trials lamivudine was associated with elevated creatine kinase in 9% of patients (vs 5% in placebo) (Fleischer and Lok, 2009) (LINE1 Report). This myopathy and/or neuropathy is thought to stem from off-target inhibition of mitochondrial DNA (mtDNA). Lamivudine is not as studied as other NRTIs, but is thought to be less associated with peripheral neuropathy (Dalakas et al., 2001), and some papers state that lamivudine is 'not generally associated with peripheral neuropathy' (Moyle & Sandler, 1998).

Drug interactions:

There are 42 drugs known to interact with lamivudine. 11 are major, 30 are moderate, and 1 is minor. The major interactions include: betibeglogene autotemcel and elivaldogene autotemcel, as lamivudine can interfere with their metabolism; bexarotene, as the two medications can increase the risk of pancreatitis; leflunomide, levoketoconazole, lomitapide, mipomersen, pexidartinib, and teriflunomide, as the combination of medications can increase risk of hepatotoxicity; and emtricitabine and zalcitabine, two other antiretrovirals that may be less effective when used in this particular combination (Drugs.com).

Lamivudine can also interact with, exacerbate, or cause hepatotoxicity, pancreatitis, or renal dysfunction. Patients with a history of or risk factor for these conditions, including patients with pre-existing liver disease, past or present alcohol abuse, high triglycerides, or renal impairment should be carefully monitored while taking lamivudine (Drugs.com).

Research underway:

There are 177 ongoing clinical trials involving lamivudine in the US and EU. The vast majority of these trials are for patients with HIV, with a smaller number for patients with hepatitis B. There are some studies investigating lamivudine as a cancer treatment. There is one ongoing trial assessing the use of lamivudine in AD, and one exploring the use of a combination medication that includes lamivudine in ALS. Secondary outcomes are adverse events and cognition as measured by CDR Sum of Boxes.

NCT04552795 is a study assessing the potential use of lamivudine in AD. This is an open label study that plans to enroll 12 patients with early stage AD and treat with lamivudine for 24 weeks. Their primary outcome is target engagement as measured by reverse transcriptase activity in CSF and the extent to which lamivudine crosses the blood-brain barrier as assessed by concentration of lamivudine in CSF.

NCT05193994 is a trial exploring the use of Triumeq in ALS patients. Triumeq is a combination antiretroviral medication that includes three compounds: dolutegravir 50mg, abacavir 600mg, and lamivudine 300mg. The randomized double-blinded trial began in 2022 and plans to enroll a total of 390 participants, and to treat them for a maximum of 2 years. Their primary outcome is survival; they are also looking at safety, tolerability, disease progression, and quality of life. They plan to collect biomarkers for post-trial exploratory analyses.

Search terms:
Pubmed, Google: lamivudine, transposon

- Dementia, APOE4, peripheral neuropathy, cancer

Websites visited for lamivudine:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

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