Ageing Research Reviews 112 (2025) 102878

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Nucleoside reverse transcriptase inhibitors as a therapeutic opportunity to counteract inflammaging and age-related diseases: New evidence from epidemiological data

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ARTICLE INFO

Keywords:
Nucleoside Reverse Transcriptase Inhibitors
NRTIs
Inflammaging
Alzheimer's disease
Type 2 diabetes
Reverse Transcriptase

ABSTRACT

Nucleoside Reverse Transcriptase Inhibitors (NRTIs), widely used to treat HIV and hepatitis B, have recently been shown to possess anti-inflammatory properties by inhibiting inflammasome activation. Epidemiological studies have revealed a significantly reduced incidence of age-related diseases, such as Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM), among patients chronically treated with NRTIs, but not with other classes of antiretroviral drugs. In this short review, we explore the mechanistic and clinical evidence linking NRTIs to reduced inflammaging, with particular attention to their effects on endogenous retroelements such as LINEs, SINEs and human endogenous retroviruses (HERVs). These elements, increasingly active with age, contribute to sterile inflammation and disease progression. NRTIs may mitigate this process by blocking reverse transcriptase-dependent formation of RNA:DNA hybrids and other immunostimulatory nucleic acid species. Although mitochondrial toxicity has been a concern, it mainly applies to older NRTIs and is much less pronounced with newer, safer compounds. NRTIs thus represent a compelling case for drug repurposing in the context of age-related diseases. Efforts should be devoted to developing new drugs that overcome NRTIs side effects and retain the anti-inflammaging properties of the parent drugs.

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and age-related diseases

Nucleoside Reverse Transcriptase Inhibitors (NRTIs), primarily prescribed for the treatment of HIV and hepatitis B, interfere with the reverse transcriptase enzyme, which is essential for the replication of these viruses by enabling the transcription of RNA into DNA (Holec et al., 2017). While traditionally known for their antiviral effects through reverse transcriptase inhibition, NRTIs have recently garnered attention for an additional property: their "anti-inflammatory activity" (Fowler et al., 2014). Mechanistically, NRTIs inhibit inflammasome activation independently of their antiviral activity, by directly targeting the P2X7 receptor-mediated pathway, when present in their inactive, unphosphorylated nucleoside form (reviewed in Brochard et al., 2023). This phosphorylation-independent anti-inflammatory effect was demonstrated using modified nucleoside analogs (known as Kamuvudines), which cannot be converted into active triphosphate metabolites (Narendran et al., 2021). Specifically, NRTIs were shown to block caspase-1 activation and IL-1β release in response to multiple triggers of the NLRP3 inflammasome, including extracellular ATP. The inhibition occurs without affecting upstream priming events or cell viability, indicating a selective blockade of inflammasome assembly or function (Fowler et al., 2014). Ongoing clinical trials with Kamuvudine derivatives (NCT06467435, NCT06781255) may help clarify the relative importance of RT-independent inflammasome inhibition in mediating the anti-inflammatory effects of NRTIs.

Further evidence comes from in vitro studies showing that the NRTI stavudine significantly reduces NLRP3 inflammasome activation and modulates amyloid-β autophagy, suggesting a direct interference with innate immune signaling pathways beyond antiviral activity (La Rosa et al., 2019). Taken together, these findings reinforce the idea that the anti-inflammatory effects of NRTIs converge on the NLRP3

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https://doi.org/10.1016/j.arr.2025.102878
Received 23 May 2025; Received in revised form 20 August 2025; Accepted 21 August 2025
Available online 23 August 2025

inflammasome, a key multiprotein complex in the inflammatory cascade, positioning it as a principal target of these compounds (Fowler et al., 2014; La Rosa et al., 2019). The NRTIs' dual functionality has sparked growing interest in repurposing NRTIs for the treatment of chronic inflammatory conditions, including type 2 diabetes (T2DM) and neurodegenerative diseases (Ambati et al., 2020; Magagnoli et al., 2025, 2023). A recent study reported that NRTI exposure was associated with a significantly reduced incidence of Alzheimer's disease (AD) in two of the largest U.S. health insurance databases (Magagnoli et al., 2025). In contrast, no such association was observed for other antiretroviral drug classes - i.e., protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs) - suggesting that the reduced incidence of AD in patients receiving anti-HIV therapy is specifically related to the reverse transcriptase-inhibitory activity of NRTIs, rather than to a more general antiviral effect (Magagnoli et al., 2025). In addition to NRTIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs) are also widely used in antiretroviral therapy. Unlike NRTIs, they inhibit reverse transcriptase via allosteric binding. While some studies suggest they may influence systemic inflammation, mechanistic data are scarce and inconsistent (Hileman and Funderburg, 2017; Hullahalli et al., 2025). However, given the limited evidence and lack of a clear link to cytoplasmic nucleic acid sensing, NNRTIs will not be further discussed in this review.

These findings are consistent with previous results from a retrospective cohort study based on data from the U.S. Veterans Health Administration, which showed that NRTI therapy in HIV-positive patients was linked to a reduced risk of developing prediabetes and a slower progression to T2DM (Magagnoli et al., 2023). This aligns with earlier data from an analysis of five large health insurance databases, which found that among 128,861 patients with HIV-1 or hepatitis B, those exposed to NRTIs had a 33 % lower adjusted risk of incident diabetes (Ambati et al., 2020). The anti-inflammatory potential of NRTIs was previously validated in preclinical models of geographic atrophy, choroidal neovascularization, graft-versus-host disease, and sterile liver inflammation (Fowler et al., 2014; Wilhelm et al., 2010). Tissues from patients with geographic atrophy showed pathological features, including amyloid-β, complement, transposable sequences, and iron, all associated with inflammasome activation (Narendran et al., 2021).

2. NRTIs and misplaced nucleic acids

Recent mechanistic insights have revealed that a key driver of inflammasome activation is the abnormal presence of nucleic acids in the cytoplasm - such as RNA:DNA hybrids, cDNA, and double-stranded DNA - which are normally confined to the nucleus or mitochondria (Kong et al., 2023). When these molecules accumulate in the wrong cellular compartment, whether derived from pathogens or endogenous sources, they are sensed by cytosolic pattern recognition receptors, triggering inflammation. Indeed, at least 14 cytoplasmic nucleic acid sensors have been identified to date, each with distinct roles in initiating inflammation and/or cell death (Chen et al., 2025). It was demonstrated that bacterial RNA:DNA hybrids and other nucleic acid species can access the cytosol under various conditions, including cellular stress and infection, where they are sensed by inflammasome complexes such as NLRP3. Notably, synthetic RNA:DNA hybrids delivered into the cytosol have been shown to trigger NLRP3-dependent responses, whereas RNase H treatment, which degrades these hybrids, abolishes inflammasome activation (Kailasan Vanaja et al., 2014).

Based on current knowledge of the molecular mechanisms underlying inflammasome activation, the inhibitory effect of antiretroviral drugs on inflammasome activity should not be considered separate from their suppression of reverse transcription (Ambati et al., 2020; Magagnoli et al., 2025, 2023).

It is important to note that only the triphosphate forms of nucleoside analogs are capable of inhibiting reverse transcriptase activity, whether viral or endogenous. These active metabolites are formed via sequential phosphorylation by host kinases (Rando and Nguyen-Ba, 2000). By blocking reverse transcription, NRTIs can reduce the cytoplasmic accumulation of RNA:DNA hybrids or cDNA, which are potent inflammasome activators. However, the inhibition of viral reverse transcription alone is unlikely to fully explain the observed reduction in the risk of age-related diseases. Endogenous sources must also be considered. Indeed, the nuclei of eukaryotic cells contain retrovirus-like sequences known as transposable elements (TE), including Long Interspersed Nuclear Elements-(LINEs) and Short Interspersed Nuclear Elements (SINEs), the latter group including the subtype Alu Elements (Schmidleithner et al., 2025). These non-LTR retroelements coexist in the human genome with endogenous Long Terminal Repeat (LTR) retroviruses (HERVs), remnants of ancient retroviral infections that also encode reverse transcriptase (Mao et al., 2021). TEs are mobile genetic elements that contribute to genomic variation, as their transposition can disrupt gene expression, alter chromosome structure, and reshape the epigenetic landscape. To limit TE-induced genomic instability, cells employ various epigenetic silencing mechanisms, such as DNA methylation, histone modifications, and small RNAs, to repress their activity. However, these mechanisms become less effective with age, leading to increased TE activation and potential genomic damage (Merenciano et al., 2025).

Retrotransposition of these elements leads to DNA and RNA:DNA hybrid localization in the cytoplasm of a cell, activating an innate immune response through the interaction with cytosolic nucleic acid sensors, such as cGAS-STING, AIM2 and NLRP3 inflammasome (Burlet et al., 2024; Di Micco et al., 2016; Motwani and Fitzgerald, 2017). Interestingly, the transfection of synthetic RNA:DNA hybrids into human cells activates the NLRP3 inflammasome (Kailasan Vanaja et al., 2014). Although initial studies focused primarily on pathogenic activation of these pathways, more recent work has uncovered endogenous cytoplasmic DNA (cytoDNA) as a major contributing factor in chronic inflammation and age-related pathology (Miller et al., 2021). Experimental models further support this link, showing that NRTIs enhance insulin sensitivity and suppress inflammasome activation in both human insulin-resistant cells and high-fat diet-fed mice (Ambati et al., 2020). At the mechanistic level, diabetic models exhibited increased levels of SINE transcripts and decreased expression of DICER1, an enzyme involved in their degradation, suggesting that the accumulation of endogenous retroelements may play a key role in driving inflammation in T2DM (Ambati et al., 2020).

3. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and inflammaging

We previously discussed how elevated cytoplasmic levels of misplaced nucleic acids can promote inflammation, thus fueling inflammaging, the phenomenon characterized by the chronic, low-grade, systemic activation of the innate immune system that accompanies human aging and predisposes individuals to diseases (Franceschi et al., 2000; reviewed in Storci et al., 2018). Treatment of aged mice with NRTIs was able to downregulate inflammaging in several tissues, suggesting that the activation of TEs is an important component of sterile inflammation that is a hallmark of aging, and that endogenous reverse transcriptase is a relevant target for the treatment of age-associated disorders (De Cecco et al., 2019). Extensive data have provided insights into two key underlying mechanisms through which TEs may cause disease: (1) nuclear insertional mutagenesis and resultant genomic havoc, and (2) cytosolic sensing of the products of endogenous reverse transcription fueling inflammation (Baldwin et al., 2024). Much of our knowledge of the evolution of retrotransposons reflects their activity in the germline and is evident from genome sequence data. Recent research has provided a wealth of information on the activity of retrotransposons in somatic tissues during an individual's lifespan, the molecular mechanisms that underlie this activity, and the way these processes intersect with our own physiology, health, and well-being

(Gorbunova et al., 2021). Endogenous retroelements are typically silenced by DNA methylation at their genomic loci, but during aging these sequences become derepressed and resume transcriptional activity (Gorbunova et al., 2021). Recent data from large human studies assessing the expression levels of 795 blood retrotransposable (RTE) subfamilies in 2467 participants of the population-based Rhineland Study, confirmed that the expression of more than 98 % of RTE subfamilies increased with both chronological and biological age (Della Valle et al., 2025; Talevi et al., 2025). The complex involvement of SINE elements in a wide range of age-related diseases, including neurodegenerative disorders, heart failure, hypertension, atherosclerosis, type 2 diabetes mellitus, osteoporosis, visual system dysfunctions, and cancer, is increasingly recognized. Recent studies have investigated the anti-aging potential of therapies targeting SINE activity, with a particular focus on the ability of SINE antisense RNAs to counteract age-associated cellular and molecular changes, highlighting promising avenues for the development of novel interventions against age-related pathologies (Shah et al., 2024). In addition, HERV-derived reverse transcriptases have also emerged as contributors to different disease states (Kury et al., 2018; Levet et al., 2019), and have been shown to be sensitive to inhibition by NRTIs (Baldwin et al., 2022).

Although the precise interaction between NRTIs and the RNA and/or RNA:DNA hybrids formed during reverse transcription remains to be fully clarified, it is now plausible that NRTIs inhibit endogenous reverse transcriptase activity analogously to their well-established effect on HIV reverse transcriptase, i.e., through chain termination (Ghanim et al., 2025; Singh and Das, 2022). In this way, NRTIs reduce the cytoplasmic burden of RNA:DNA hybrids or cDNA, strongly limiting inflammasome activation.

We recently demonstrated in endothelial cells (ECs) that exposure to high glucose induces senescence-like features, including telomere shortening and the release of proinflammatory cytokines (Ramini et al., 2024). These changes were accompanied by the cytoplasmic accumulation of telomeric DNA, double-stranded DNA, and RNA (dsDNA, dsRNA), as well as RNA:DNA hybrid molecules. Senescent ECs exhibited the activation of the dsRNA sensors RIG-I and MDA5, and the DNA sensor TLR9, without concomitant activation of the STING pathway via either the canonical cGAS or non-canonical IFI16 mechanisms (Ramini et al., 2024). Additionally, our study revealed that replicative senescence in human endothelial cells is associated with significant hypomethylation of LINE-1 elements and increased expression of both LINE-1 and Alu sequences, leading to the accumulation of transposable element-derived DNA in the cytoplasm (Ramini et al., 2022). We also previously reported that the anti-inflammatory molecular make-up of centenarian fibroblasts, characterized by low levels of IL-6, type I interferon β, and pro-inflammatory microRNAs, is coupled with low levels of DNA damage, preserved telomere length, and high levels of the RNAseH2C enzyme subunit, and low amounts of RNAseH2 substrates, i.e., cytoplasmic RNA:DNA hybrids (Storci et al., 2019). Moreover, RNAseH2C locus was hypomethylated and RNAseH2C knockdown upregulated IL-6 and type I interferon β in centenarian fibroblasts, as well as in in vitro senescent cells and in tissues from atherosclerotic plaques and breast tumors (Storci et al., 2019).

Remarkably, NRTIs can inhibit the synthesis of RNA:DNA hybrids and cDNA not only in viral replication, but also in the presence of endogenous retroelement expression. Alu elements are non-coding retrotransposons that, like HIV, rely on reverse transcriptase for propagation (Dewannieux et al., 2003). Importantly, Alu RNA has been shown to activate the NLRP3 inflammasome via the purinergic receptor P2X7, and several clinically approved NRTIs have been shown to prevent caspase-1 activation, an essential effector of NLRP3 inflammasome signaling, induced by Alu RNA. Since increased inflammasone is a major driver of inflammaging – acting in concert with the NF-κB pathway - it is plausible to hypothesize that the NRTI-associated reduction in the risk of developing inflammatory diseases such as T2DM and AD may be, at least in part, attributable to a decrease of inflammaging levels.

A comprehensive analysis of health claims data from U.S. databases revealed that patients treated with NRTIs for HIV or hepatitis B had a significantly reduced risk of developing AD, T2DM, geographic atrophy, and multiple sclerosis compared to matched controls not receiving these drugs (Ambati et al., 2020; Magagnoli et al., 2025, 2023). These epidemiological insights have spurred clinical investigation of NRTIs in AD. A Phase 2a open-label trial (NCT04552795) tested lamivudine (300 mg/day for 24 weeks) in 12 individuals with early-stage AD, reporting good tolerability, stable cognition, reduced cerebrospinal fluid GFAP, and increased plasma Aβ42/40 ratios, suggesting decreased neuroinflammation and amyloid burden. Another trial (NCT04500847) is evaluating emtricitabine (200 mg/day) in patients with AD or mild cognitive impairment. These epidemiological and early clinical findings strengthen the rationale for repurposing NRTIs as preventive therapies targeting inflammaging and age-related diseases.

4. Conclusion

We could never have imagined having access to longitudinal epidemiological data confirming the anti-aging effects and the delay in the onset of the most common age-related diseases induced by drugs that prevent the accumulation of misplaced nucleic acids in the cytoplasm. This extraordinary opportunity has been made possible with the use of NRTIs for the treatment of patients with HIV and hepatitis B, who have been chronically treated with these drugs for 10–20 years, providing an unprecedented chance to advance scientific understanding in a highly complex field. In our view, the protective effects observed in antiretroviral-treated patients may stem, at least in part, from the inhibition of endogenous reverse transcriptases, such as LINE-1, which become derepressed during aging.

Overall, NRTIs exert their anti-inflammatory effects through two distinct but co-occurring mechanisms, both of which may contribute simultaneously to reducing chronic inflammation: (1) inhibition of P2X7 receptor-mediated inflammasome activation via the nucleoside form of NRTIs, and (2) suppression of LINE-1 reverse transcription and downstream RNA:DNA hybrid formation via the phosphorylated triphosphate form of NRTIs. While these mechanisms operate independently, they may synergistically contribute to the reduction of inflammaging and age-related pathology (Fig. 1).

These findings reinforce the idea that drug repurposing is a concrete and promising strategy to address chronic age-related diseases. NRTIs, long used and well-characterized in virology, are now emerging as unexpected candidates in the field of sterile inflammation and inflammaging. Although NRTIs are widely and effectively used in the treatment of HIV and hepatitis B, their potential repurposing for non-infectious, chronic age-related conditions might raise concerns about mitochondrial toxicity. This toxicity is primarily associated with older NRTIs, such as stavudine (d4T), didanosine (ddI), and zidovudine (AZT), which exhibit low selectivity for mitochondrial DNA polymerase γ (Lee et al., 2003). In contrast, more recent compounds, such as lamivudine (3TC) and emtricitabine (FTC) show markedly improved safety profiles, with substantially reduced mitochondrial effects (Margolis et al., 2014). While some degree of mitochondrial interaction cannot be entirely excluded, the overall risk-benefit balance of these newer agents remains favorable, particularly in long-term therapeutic contexts.

There is therefore a compelling rationale to develop next-generation NRTI derivatives that retain both the anti-inflammatory effects mediated by P2X7 inhibition and the suppression of reverse transcriptase activity, while minimizing mitochondrial toxicity. Optimizing the pharmacological profile of these compounds could enable effective inflammaging-targeted therapies with improved safety for long-term use.

CRediT authorship contribution statement

Fabiola Olivieri: Writing – original draft. **Angelica Giuliani** and

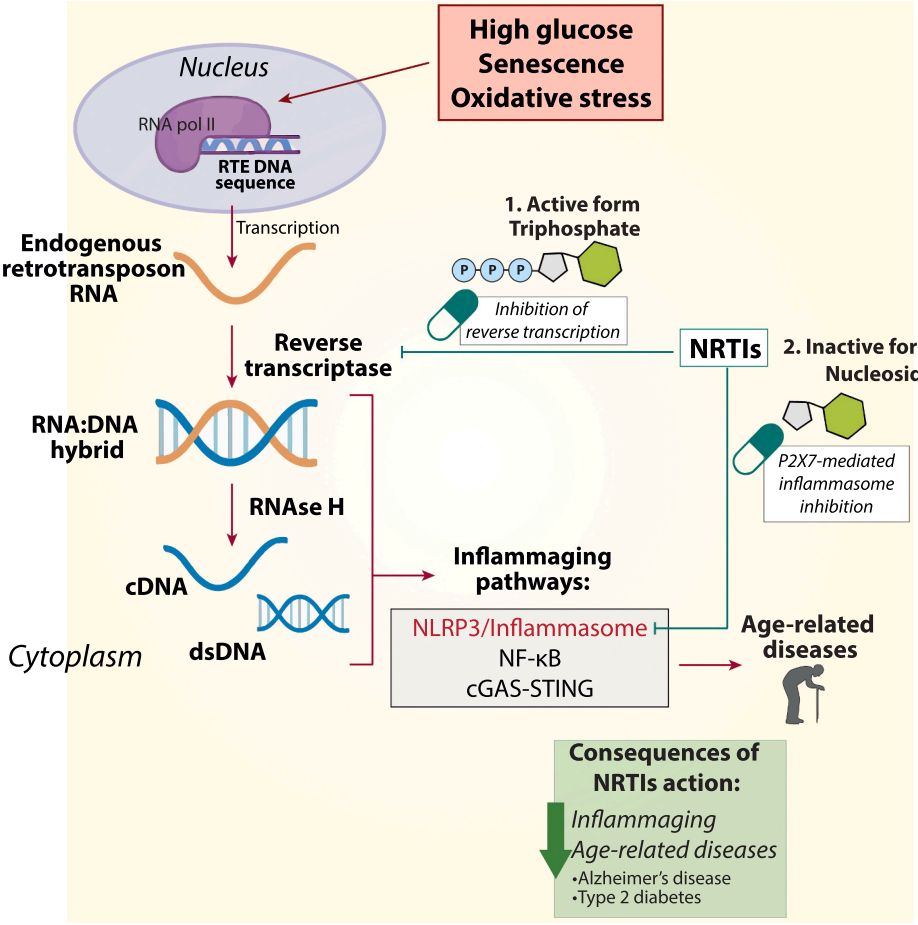

Fig. 1. Dual anti-inflammatory mechanisms of NRTIs in the context of inflammaging and age-related disease. 1. Cellular stressors such as high glucose, oxidative stress, and senescence enhance the transcription of endogenous retrotransposons (e.g., LINE-1, Alu elements). The resulting RNA is exported to the cytoplasm, where it is reverse transcribed into RNA:DNA hybrids and cDNA. These nucleic acid species activate cytosolic innate immune sensors, including the NLRP3 inflammasome, cGAS–STING, and NF-κB, promoting inflammaging and contributing to age-related pathology. Red arrows indicate stress-induced processes leading to nucleic acid accumulation and immune activation, while green elements represent drug-mediated protective effects. Nucleoside reverse transcriptase inhibitors (NRTIs), once phosphorylated by endogenous cellular kinases, become active in their triphosphate form. These active metabolites can be incorporated by reverse transcriptase into the nascent DNA strand, leading to chain termination. In this way, NRTIs block reverse transcriptase activity (green line), reducing the accumulation of proinflammatory nucleic acids and dampening downstream immune activation. 2. In parallel, NRTIs in their unphosphorylated nucleoside form directly inhibit the P2X7 receptor, thereby preventing activation of the NLRP3 inflammasome and the release of IL-1β. Together, these mechanisms limit the chronic inflammatory signaling that underlies inflammaging. Epidemiological and clinical studies suggest that NRTI use is associated with a reduced risk of age-related diseases, particularly Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM). *Red arrows indicate stress-induced, proinflammatory processes; green lines represent NRTI-mediated protective actions.*

Massimiliano Bonafè: Writing – review & editing.

Ethics approval and consent to participate

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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