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RESEARCH ARTICLE

Association of nucleoside reverse transcriptase inhibitor use with reduced risk of Alzheimer's disease risk

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Abstract

INTRODUCTION: Inflammasome activation is implicated in Alzheimer's disease (AD). We previously demonstrated that nucleoside reverse transcriptase inhibitors (NRTIs), drugs approved to treat human immunodeficiency virus (HIV) and hepatitis B, also inhibit inflammasome activation.

METHODS: We evaluated the association between NRTI exposure and subsequent development of AD in the United States Veterans Health Administration over a 24-year period and in the MarketScan database over a 14-year period using propensity score-matched multivariate Cox hazards regression and Kaplan–Meier analyses.

RESULTS: We report that in humans, NRTI exposure was associated with a significantly lower incidence of AD in two of the largest health insurance databases in the United States. In contrast, exposure to non-NRTIs, protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs) was not associated with reducing AD incidence.

DISCUSSION: These findings support the concept that inflammasome inhibition could benefit AD and provide a rationale for prospective clinical testing of inflammasome inhibitors such as NRTIs in AD.

KEYWORDS
anti-retroviral, Cox hazards regression, health insurance databases, inflammasome, propensity score matching

Highlights

- Exposure to NRTIs, a class of anti-retroviral drugs that also block inflammasome activation, was associated with a reduction in the risk of developing AD.
- The reduction in risk was observed in two large, diverse health insurance databases after correcting for numerous comorbidities known to be associated with AD.

Joseph Magagnoli and Meenakshi Ambati provided equal contribution to this manuscript and are considered equal first authors.

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- Other anti-HIV therapies such as non-NRTIs, protease inhibitors, and integrase strand transferase inhibitors were not associated with a reduction in the risk of developing AD.
- Our work provides a rationale for randomized clinical trials of inflammasome inhibitors in AD.

1 | BACKGROUND

Alzheimer's disease (AD) is the leading cause of dementia worldwide, and as the global population ages, the prevalence of AD rises, imposing significant burdens on families, societies, and global public health.[1,2] Though considerable progress has been made in discerning the pathogenesis of AD, more effective therapies are needed.[1,2] Acetylcholinesterase and amyloid-beta (Aβ) inhibitors have been foci of AD drug discovery and are mainstay therapies.[3,4] However, emerging evidence suggests that targeting neuroinflammation may offer an alternative or complementary approach to slowing disease progression.

Aβ oligomers and hyperphosphorylated tau fibrils are thought to promote AD by inducing neuroinflammation that leads to neurodegeneration and cognitive decline.[5,6] A critical effector in the pathogenesis of AD is the NLRP3 inflammasome, a multimeric protein complex that responds to aberrant Aβ and tau aggregation by launching a potent inflammatory response characterized by caspase-1 activation, interleukin-1β (IL-1β) release, and neuronal cell death.[7–11] In turn, NLRP3 activation facilitates further deposition of Aβ plaques and tau fibrils, establishing a positive feedback loop that contributes to the development of AD.[12–16]

NLRP3 inflammasome inhibition may protect against AD progression.[13,17] Previously, we discovered that nucleoside reverse transcriptase inhibitors (NRTIs), which are United States Food and Drug Administration (FDA)-approved to treat human immunodeficiency virus (HIV) and hepatitis B infections, also inhibit inflammasome activation independent of their antiretroviral activity.[18] Other groups subsequently confirmed our observation.[19] Prior studies by us and others demonstrated that NRTIs block the NLRP3 inflammatory cascade in a variety of disease states, including models of diabetes, diabetic retinopathy, choroidal neovascularization, and atrophic age-related macular degeneration (AMD).[20–23] We have also shown that NRTI exposure in humans is associated with a reduction in the risk of incident AMD,[24] which shares inflammasome activation as a common pathogenic mechanism with AD.

Given the protective benefits of NLRP3 inflammasome inhibition, we hypothesized that patients with a history of NRTI exposure would be less likely to develop AD. To test this hypothesis, we analyzed health insurance claims for 271,198 individuals across two national databases spanning a maximum of 24 years.

2 | METHODS

2.1 | Data sources

Data were evaluated from two health insurance claims databases: The United States Veterans Health Administration database (which includes healthcare claims from the Veterans Health Administration (VA) Informatics and Computing Infrastructure [VINCI] for approximately 11 million individuals) for the years 2000–2024, and MarketScan (which includes employer-based health insurance claims of approximately 158 million individuals) for the years 2006–2020. Codes from the International Classification of Diseases, 9th and 10th Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM, respectively) were used to identify individuals with diagnoses of interest. This drug disease cohort study was conducted using data from the U.S. Department of Veterans Affairs. VINCI was utilized to obtain individual-level information on demographics, administrative claims, and pharmacy dispensation. The study was conducted in compliance with the Department of Veterans Affairs requirements and received Institutional Review Board (IRB) and Research and Development approval. All data within the MarketScan database are Health Insurance Portability and Accountability Act-compliant and thus were deemed exempt from IRB approval by the University of Virginia IRB.

2.2 | Study population

Patients were included in analyses if they had a medical claim for HIV/AIDS (ICD-9/10-CM codes 042, V08/B20-B24, Z21) or hepatitis B (ICD9/10-CM codes V02.61, 070.20, 070.21, 070.22, 070.23, 070.30, 070.31, 070.32, 070.33/B16, B18.0, B18.1, B19.1) during the study period and were at least 50 years old at the study index (the first date of HIV/hepatitis B per database). Patients that had a prior diagnosis of AD (ICD-9/10-CM codes 331.0/G30) were excluded. Eligible patients were followed until death (VA), incident AD (VA and MarketScan), or end of eligibility (MarketScan). The date of death was determined by the VA vital status file, which was sourced from the Social Security Administration Death Master File and Veterans Benefits Administration (VBA) Beneficiary Identification Records Locator Subsystem Death File.

2.3 | Exposure and outcome definitions

Individuals were classified as receiving NRTIs (i.e., lamivudine, zidovudine, abacavir, didanosine, stavudine, tenofovir, emtricitabine, entecavir, adefovir, telbivudine, entecavir), if at least one pharmacy prescription for these medications was filled. Pharmacy records were filtered by either text search (VA) or by national drug code (MarketScan database). The primary outcome was incident AD. The primary analysis tracked NRTI medication exposure over time by measuring cumulative years of use as calculated from the days' supply. At the start of the study, patients who had never taken NRTIs were coded as having 0 years of exposure, and this continued until their first NRTI prescription. After the first prescription, each additional NRTI prescription exposure was increased based on the additional days' supply, which was annualized.

2.4 | Statistical analyses

The key predictor was NRTI exposure. To account for immortal time bias, exposure was coded time-dependently and entered the model as cumulative annualized NRTI exposure. Cox regression was used to estimate the hazard of developing AD in relation to NRTI exposure, with adjustment for baseline covariates including age, race (available for the VA), sex, Charlson comorbidity score, pure hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, ischemic heart disease, other heart disease, hypertension, type II diabetes mellitus, cerebral infarction, atrial fibrillation, hypothyroidism, hyperthyroidism, depression, traumatic brain injury, alcohol dependence, Parkinson's disease, generalized anxiety disorder, and chronic kidney disease. 95% confidence intervals were constructed for hazard ratios based on standard errors derived from the model. All covariates were flagged during the period between 1 year prior to the study index and the study index date. *t*-tests and chi-square tests were used to compare continuous variables (age, Charlson comorbidity index) and categorical variables (race, sex), respectively. Given that death would preclude a diagnosis of AD, a Fine and Gray competing risk model was fit to the VA sample, with corresponding sub-distribution hazard ratios and 95% confidence intervals. Given that NRTI treatment was not randomized, we also used propensity score (PS) matching using all available covariates from the study (accounting for both the demographic and clinical factors above) to minimize potential selection bias. We then transformed the PS into its logit (log-odds) form, which was used as the basis for creating matched cohorts. To create the matched cohorts, we used greedy nearest neighbor 1:1 PS matching. Kaplan–Meier survival curves are reported for both the original and matched cohorts.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature on anti- human immunodeficiency virus (HIV) medications and inflammasome biology and their relevance to Alzheimer's disease (AD) using traditional (e.g., PubMed) sources and meeting abstracts and presentations. These relevant citations are appropriately cited.
2. **Interpretation**: Our findings suggest that nucleoside reverse transcriptase inhibitors (NRTIs), a class of antiretroviral drugs, may reduce the risk of developing AD, potentially through their additional ability to inhibit inflammasome activation.
3. **Future directions**: Our manuscript provides a rationale for testing the hypothesis that inflammasome inhibition could be beneficial for AD. Examples of such testing could include (a) prospective, randomized clinical trials of NRTIs or less toxic derivatives; and (b) mechanistic studies of such inflammasome inhibitors in animal models of AD.

3 | RESULTS

3.1 | NRTI exposure associated with reduced risk of developing AD

We evaluated the association between NRTI exposure and subsequent development of AD in the VA, one of the largest integrated healthcare systems in the United States, over a 24-year period. In this database, 72,193 patients (Table S1) were identified that met the study criteria (at least 50 years of age, diagnosis of HIV or hepatitis B, and no prior diagnosis of AD). Kaplan–Meier survival estimates revealed better survival (higher probability of no AD diagnosis) across study follow-up for individuals exposed to NRTIs (Figure 1A, log-rank $p < 0.001$). In the MarketScan database, which encompasses individuals with employer-based health insurance, a total of 199,005 patients over the years 2006–2020 met the study inclusion criteria (Table S2). Kaplan–Meier survival estimates revealed better disease-free survival probability throughout study follow-up in NRTI-exposed individuals compared to those unexposed (Figure 1B, log-rank $p < 0.001$).

Multivariate models were adjusted for important sociodemographic and clinical factors. Demographic data include age at index, race, sex, and smoking status. The Charlson comorbidity score was included as a composite measure of overall health burden. Importantly, we also adjusted for comorbidities previously reported to be associated

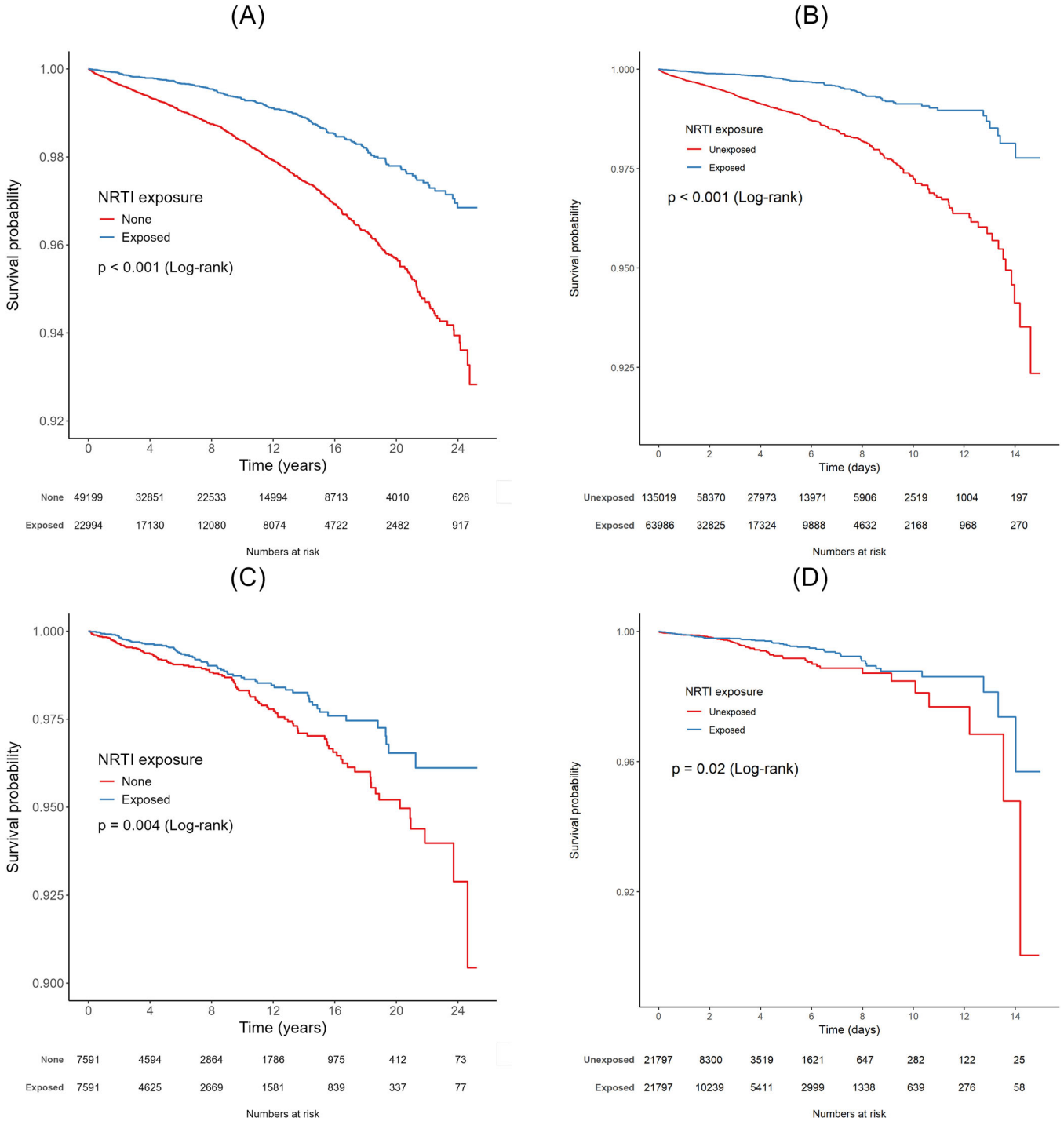

FIGURE 1 Improved disease-free survival of AD among NRTI users in the VA and MarketScan populations. (A—D) AD-free survival curves are presented for the VA (A, C) and MarketScan (B, D) database populations, calculated for each level of NRTI exposure in the original (A, B) and propensity-score matched (C, D) populations. Log-rank *p* values displayed. AD, Alzheimer's disease; NRTI, nucleoside reverse transcriptase inhibitors; VA Veterans Health Administration.

with AD (Table 1) including pure hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, ischemic heart disease, other heart disease, hypertension, type 2 diabetes, cerebral infarction, atrial fibrillation, hypothyroidism, hyperthyroidism, depression, traumatic brain injury, alcohol dependence, Parkinson's disease, generalized anxiety disorder, and chronic kidney disease.

In both databases, each additional year of NRTI exposure was associated with a reduced hazard of developing AD (Tables 1, S3, and S4). In the VA sample, each additional year of NRTI exposure was associated with a 4% reduced hazard of AD (adjusted hazard ratio [aHR], 0.96; 95% confidence interval [CI], 0.93–0.99; Table S3). In the MarketScan database, there was a 10.3% reduced hazard of AD with each

TABLE 1 Hazard of AD with NRTI time-dependent exposure, Cox models in original and PS-matched populations.

Parameter	Original group HR (95% CI)	PS matched HR (95% CI)
VA Time-dependent exposure: NRTI use per year	0.96 (0.93, 0.99)	0.94 (0.89, 0.999)
MarketScan time-dependent exposure: NRTI use per year	0.90 (0.84, 0.96)	0.87 (0.78, 0.97)
VA Competing risk of mortality: NRTI use per year	0.68 (0.55, 0.85)	0.63 (0.46, 0.85)
Model covariates		
Age	Race	Sex
Charlson comorbidity index	Body mass index	Smoker
Pure hypercholesterolemia	Hypertriglyceridemia	Hyperlipidemia
Ischemic heart disease	Other heart disease	Hypertension
Type 2 diabetes mellitus	Cerebral infarction	Atrial fibrillation
Hypothyroidism	Hyperthyroidism	Depression
Traumatic brain Injury	Alcohol dependence	Parkinson's disease
Generalized anxiety disorder	Chronic kidney disease	

Note: Hazard ratios (HR) based on a Cox proportional hazards model for the original and PS-matched populations in the VA and MarketScan databases, adjusted for the confounding variables listed under Model covariates. Hazard ratios for covariates are presented in Tables S3 and S4.
Abbreviations: AD, Alzheimer's disease; CI, confidence interval; HR, hazard ratio; NRTI, nucleoside reverse transcriptase inhibitor; PS, propensity score; VA, Veterans Health Administration.

additional year of NRTI exposure (aHR, 0.897; 95% CI, 0.84–0.959; Table S4).

3.2 | PS-matched analysis

Given that NRTI treatment was not randomized, we used PS matching to minimize potential selection bias and differences in baseline characteristics. This process yielded patient cohorts with similar baseline demographic and clinical characteristics. The standardized difference was used to quantify similarities between cohorts. In the VA sample, each cohort contained 7591 patients all standardized differences were 0.1 or below, indicating excellent balance between cohorts (Table S5). In the MarketScan data, each cohort contained 21,797 patients, with all standardized differences less than 0.1 (Table S6). As with the original unmatched group results, Kaplan–Meier plots of PS-matched populations revealed protective estimates for those exposed to NRTIs compared to those unexposed in both the VA (log-rank $p = 0.004$, Figure 1c) and MarketScan (log-rank $p < 0.001$, Figure 1d) databases.

We also adjusted for all of the sociodemographic factors, overall health, and comorbidities known to alter the risk of AD development that were employed for the original unmatched group analyses in order to control for any residual covariate imbalance. After PS matching and adjustment for potential confounders, time-dependent Cox models in each database revealed that each additional year of NRTI exposure was associated with reduced hazard of developing AD (Table 1) (VA: 6% reduced hazard per year of NRTI use; aHR, 0.94; 95% CI, 0.89–0.999; Table S3; MarketScan: 13% reduced hazard per year of NRTI exposure; aHR, 0.87; 95% CI, 0.779–0.972; Table S4). The small differences in hazard ratio estimates between unmatched and PS-matched analyses suggest that residual bias in the unmatched analyses was likely minimal.

3.3 | Competing risk of mortality analysis

In chronic diseases such as AD, mortality can preclude the diagnosis of AD. Thus, we performed a competing risk regression analysis, which was possible in the VA cohort as the VA contains mortality records. We estimated a Fine and Gray model to account for the competing risk of death. In this analysis, data were organized cross-sectionally, and NRTI exposure was indicated if there was any NRTI use over the study period. After adjusting for potential confounding variables and the competing risk of death, NRTI exposure was associated with 32% reduced hazard of developing AD (sub-distribution aHR, 0.68; 95% CI, 0.55–0.85; Tables 1 and S7). We also performed the competing risk of mortality analysis in the PS-matched population. After adjusting for potential confounding variables and the competing risk of death, NRTI exposure was associated with a 37% reduced hazard of developing AD (sub-distribution aHR, 0.63; 95% CI, 0.46–0.85; Tables 1 and S7). These protective findings, similar to risk reduction observed in the primary analysis, suggest that the differential mortality rates are not responsible for the observed risk reduction of incident AD among NRTI users in the VA cohort.

3.4 | Subanalysis

After observing an overall association between NRTI exposure and a reduced risk of AD, we conducted two post hoc analyses to examine

this effect separately in patients with HIV but without hepatitis B infection and those with hepatitis B infection but without HIV. Kaplan–Meier survival plots from both databases demonstrate that NRTI exposure was associated with a lower risk of incident AD in both HIV-positive patients (Figure S1A, B) and hepatitis B-positive patients (Figure S1C, D) (all p values < 0.05).

4 | DISCUSSION

Innate immune signaling through the NLRP3 inflammasome has been implicated in the pathogenesis of AD.[8–16] A therapy that inhibits inflammasome activation could thus be neuroprotective and improve clinical outcomes in AD. In the present study, we demonstrate that exposure to inflammasome-inhibiting NRTIs[18,20–23] is associated with a significantly lower incidence of AD in two of the largest health insurance databases in the United States.

Throughout our health insurance database analyses, steps were taken to mitigate potential biases and promote internal validity. At baseline, we adjusted for an extensive number of demographic and clinical variables by including them as fixed risk factor covariates. Given that NRTI treatment was not randomized, we also used PS matching to minimize potential selection bias and differences in baseline characteristics. To account for immortal time bias, we studied NRTI exposure as a cumulative, time-dependent variable. We also estimated a Fine and Gray model in the VA sample to account for the competing risk of death. In addition, we also corrected nearly 20 other comorbidities that have been previously reported to alter AD risk. Altogether, these measures support the validity and conclusions of database analyses.

The VA and MarketScan populations differ in key demographic and clinical characteristics. The VA cohort primarily consists of older, predominantly male individuals with a higher burden of comorbid conditions, whereas the MarketScan cohort includes a broader, commercially insured population with a more balanced age and sex distribution. Given these differences, we analyzed the two datasets separately to account for potential heterogeneity and assess the consistency of findings across diverse populations. While differences in baseline characteristics could impact generalizability, the concordance of results between these distinct cohorts strengthens the robustness of our findings.

The use of these two distinct databases also provides a broader perspective on the relationship between NRTI exposure and AD risk. These databases also represent vastly different patient populations. The VA population tends to be older and includes veterans, who may have distinct socioeconomic profiles. In contrast, MarketScan, comprises commercially insured individuals through employer-sponsored coverage, likely reflecting a different socioeconomic spectrum. The consistent effects we observed across these two disparate populations suggest that socioeconomic status, while potentially influential, is unlikely to be a dominant confounder in the observed association.

Post hoc analyses also revealed protective associations of NRTI use in both HIV patients and hepatitis B patients, further suggesting that our conclusion is generalizable. Future research specifically designed to investigate additional potential subgroup effects (e.g., by age, sex, or underlying condition) could be informative.

Importantly, we found that exposure to other classes of anti-HIV drugs, that is, non-NRTIs, protease inhibitors (PIs), or integrase strand transfer inhibitors (INSTIs), was not associated with a reduced incidence of AD (Tables S3 and S4). These findings further buttress the concept that inflammasome inhibition by NRTIs in particular is protective against the development of AD rather than a generic result of anti-HIV therapy effect.

Despite our efforts to mitigate bias by accounting for important AD risk factors and using PS analysis, residual or unmeasured confounding may still result. Additionally, the administrative claims nature of the data lacked information such as genetic variants that may increase AD risk. AD outcome was coded using diagnosis codes; however, we were unable to assess progression of AD with clinical measures such as cognitive or neurologic assessments or assess functioning in day-to-day living because such details are unavailable in the databases. Differences in healthcare access and diagnostic practices between the VA and MarketScan cohorts also are potential sources of bias. Prospective randomized clinical trials can overcome these limitations and help ascertain causality.

Despite these limitations, this analysis using large-scale human data show that NRTI exposure is associated with significant and substantial reductions in the risk of developing AD among two diverse cohorts of patients increases confidence in the successful outcome of clinical trials of such drugs in this neurodegenerative disease, given the concordance between well-designed insurance claims database studies and the results of randomized clinical trials.[25]

Work from others also supports the notion that NRTIs could protect against AD development. Chow et al.[26] conducted a retrospective claims analysis using the IQVIA Inc. database. Over a 2.75-year follow-up period, and after adjusting for age and sex, Chow et al. found that patients exposed to NRTIs had a lower incidence of AD. Our analysis and our previous version, published on medRxiv[27] prior to Chow et al., present a more robust analysis. We adjusted for a wider range of demographic and clinical variables, used PS matching to reduce selection bias, and accounted for immortal time bias by examining NRTI exposure as both a binary and time-dependent variable. Additionally, we employed a Fine and Gray model to consider competing risks and corrected for numerous comorbidities affecting AD risk. These measures collectively strengthen the validity and reliability of our findings.

Mechanistically, Chow et al. suggest that the reverse transcriptase activity of NRTIs could prevent somatic brain gene recombination implicated in AD pathogenesis. In contrast, and perhaps in addition, we propose that the inflammasome-inhibitory activity of NRTIs that is independent of their reverse transcriptase activity,[18] might be responsible for their association with reduced AD risk. Future research with K-9, an NRTI derivative that lacks reverse transcriptase inhibition but retains the ability to inhibit inflammasome activation[28,29] and is now in clinical trials (NCT06467435, NCT06781255), could help clarify the relative importance of these mechanisms of action. Indeed, our preliminary study of K-9 in an animal model of AD published on medRxiv[27]

identified a complete reversal of the functional impairment in spatial memory formation and learning.

As the prevalence of AD rises, so does the demand for quality, disease-modifying therapies.[1,2] The repurposing of existing, approved therapies could accelerate drug development. Prospective randomized controlled trials in humans are warranted to gain better insight into the effects of NRTIs or suitable derivatives on clinical outcomes in AD. Indeed, two NRTIs have been recently tested in AD clinical trials: lamivudine (NCT04552795; recently completed) and emtricitabine (NCT04500847; ongoing). The 24-week pilot clinical study of lamivudine in AD reported a reduction in some neurodegeneration- and neuroinflammation-related biomarkers, supporting the concept that NRTIs could be beneficial in AD.[30] Although lamivudine was well tolerated in this small 12-patient 6-month trial, NRTIs can induce mitochondrial toxicity via off-target inhibition of mammalian DNA polymerases.[31] As a result, they can induce serious adverse effects including lactic acidosis, which can be fatal.[32] However, lamivudine is considered a new-generation nucleoside reverse transcriptase inhibitor and is associated with a substantial reduction in the incidence of lactic acidosis when compared with other medications in the same class.[33] Serious adverse events such as lactic acidosis are rare and managed with biannual laboratory tests in patients who take lamivudine for hepatitis B or HIV. Apart from such toxicity, isolated administration of NRTIs can potentially induce retroviral resistance.[34] Thus, NRTI derivatives such as K-9, which inhibits inflammasome activation without inducing the aforementioned toxicity of NRTIs,[18,20,28,29] might be more suitable for chronic administration, where patient tolerance is critical.

The key considerations for translating the results of our study into clinical trials, particularly for prevention, include identifying patients who would have a sufficiently high risk of developing during the course of the trial and identifying a dosage regimen that exhibits target knockdown yet minimizes adverse events.

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CONFLICT OF INTEREST STATEMENT

J.A. is a co-founder of iVeena Holdings, iVeena Delivery Systems, and Inflammasome Therapeutics and, unrelated to this work, has been a board member for Theragen and consultant for Abbvie/Allergan, Retinal Solutions, and Saksin Life Sciences. S.S. has received research grants from Boehringer Ingelheim, Coherus Bioscience, EMD Serono, and Alexion Pharmaceuticals, all for projects unrelated to the study. J.A. and B.D.G. are named as inventors on matter-related patent applications filed by the University of Virginia or the University of Kentucky. All other authors declare no competing interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The study was conducted in compliance with the Department of Veterans Affairs requirements and received Institutional Review Board (IRB) and Research and Development approval. All data within the MarketScan database are Health Insurance Portability and Accountability Act-compliant and thus were deemed exempt from IRB approval by the University of Virginia IRB.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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