

**Supplementary Table 1. VA Original group baseline characteristics.**

Variable		NRTI unexposed N=43493	NRTI exposed N=19685	P value
HIV		6674(15.345%)	14864(75.509%)	<0.001
HBV		37200(85.531%)	6886(34.981%)	<0.001
Age		61.77(9.713)	59.9(9.201)	<0.001
Race	Black	12376(28.455%)	7928(40.274%)	<0.001
	Other/unknown	5661(13.016%)	2173(11.039%)	
	White	25456(58.529%)	9584(48.687%)	
Sex	Female	1189(2.734%)	349(1.773%)	<0.001
	Male	42304(97.266%)	19336(98.227%)	
Charlson comorbidity		1.52(2.081)	0.75(1.598)	<0.001
Smoker		18147(41.724%)	8193(41.621%)	0.814
BMI	<18.5	1028(2.364%)	746(3.79%)	<0.001
	18.5-24.9	12008(27.609%)	7932(40.295%)	
	25-29.9	16006(36.801%)	6643(33.747%)	
	30+	13846(31.835%)	4074(20.696%)	
	Missing	605(1.391%)	290(1.473%)	
Pure hypercholesterolemia		2249(5.171%)	381(1.935%)	<0.001
Hypertriglyceridemia		2126(4.888%)	510(2.591%)	<0.001
Hyperlipidemia		10760(24.74%)	2433(12.36%)	<0.001
Ischemic heart disease		6124(14.08%)	1256(6.38%)	<0.001
Other Heart disease		5688(13.078%)	1043(5.298%)	<0.001
Hypertension		16616(38.204%)	3597(18.273%)	<0.001
T2DM		7428(17.079%)	1543(7.838%)	<0.001
Cerebral infarction		262(0.602%)	51(0.259%)	<0.001
Atrial fibrillation		1104(2.538%)	140(0.711%)	<0.001
Hypothyroidism		1244(2.86%)	193(0.98%)	<0.001
Hyperthyroidism		133(0.306%)	28(0.142%)	<0.001
Depression		7662(17.617%)	1547(7.859%)	<0.001
TBI		195(0.448%)	41(0.208%)	<0.001
Alcohol dependence		5772(13.271%)	924(4.694%)	<0.001
Parkinson's disease		170(0.391%)	16(0.081%)	<0.001
Generalized anxiety disorder		653(1.501%)	137(0.696%)	<0.001
Chronic kidney disease		1735(3.989%)	360(1.829%)	<0.001
Year of HIV/HBV dx		2008.62(6.327)	2008.09(6.71)	<0.001
NRTI use (years)		0(0)	5.8(5.1)	<0.001

HIV, Human immunodeficiency virus. HBV, Hepatitis B virus. BMI, body mass index. T2DM, type 2 diabetes mellitus. TBI, traumatic brain injury. NRTI, nucleoside reverse transcriptase inhibitor.

**Supplementary Table 2. Marketscan Original group baseline characteristics.**

	NRTI unexposed N=136019	NRTI exposed N=63986	P value	Standardized difference	
HIV	44340(32.84%)	50918(79.577%)	<0.001	1.07	
HBV	92534(68.534%)	15786(24.671%)	<0.001	0.977	
Age	59.36(7.23)	56.92(5.1)	<0.001	0.39	
Sex	Male	80013(59.261%)	51424(80.368%)	<0.001	0.472
	Female	55006(40.739%)	12562(19.632%)		0.472
Charlson comorbidity	1.23(2.201)	0.37(1.166)	<0.001	0.486	
Smoker	8316(6.159%)	1164(1.819%)	<0.001	0.226	
Obese	7743(5.735%)	912(1.425%)	<0.001	0.234	
Pure hypercholesterolemia	12808(9.486%)	1483(2.318%)	<0.001	0.309	
Hypertriglyceridemia	9761(7.229%)	1445(2.258%)	<0.001	0.232	
Hyperlipidemia	26873(19.903%)	3852(6.02%)	<0.001	0.423	
Ischemic heart disease	12397(9.182%)	1697(2.652%)	<0.001	0.277	
Other Heart disease	17521(12.977%)	1958(3.06%)	<0.001	0.37	
Hypertension	47902(35.478%)	7751(12.114%)	<0.001	0.571	
T2DM	23601(17.48%)	3831(5.987%)	<0.001	0.363	
Cerebral infarction	1626(1.204%)	173(0.27%)	<0.001	0.104	
Atrial fibrillation	4276(3.167%)	411(0.642%)	<0.001	0.191	
Hypothyroidism	11141(8.251%)	1010(1.578%)	<0.001	0.313	
Hyperthyroidism	1244(0.921%)	146(0.228%)	<0.001	0.095	
Depression	8221(6.089%)	1726(2.697%)	<0.001	0.166	
TBI	596(0.441%)	68(0.106%)	<0.001	0.06	
Alcohol dependence	1332(0.987%)	177(0.277%)	<0.001	0.087	
Parkinson's disease	372(0.276%)	44(0.069%)	<0.001	0.045	
Generalized anxiety disorder	3592(2.66%)	905(1.414%)	<0.001	0.092	
Chronic kidney disease	9115(6.751%)	1127(1.761%)	<0.001	0.248	
Year of HIV/HBV dx	2011.99(3.788)	2012.79(4.301)	<0.001	0.196	
NRTI duration (years)	0(0)	2.4(2.307)	<0.001	1.470	

HIV, Human immunodeficiency virus. HBV, Hepatitis B virus. BMI, body mass index. T2DM, type 2 diabetes mellitus. TBI, traumatic brain injury. NRTI, nucleoside reverse transcriptase inhibitor.

**Supplementary Table 3. VA Cox models, hazard of AD: Time-dependent NRTI exposure**

	Original group HR(95% CI)	PS matched HR(95% CI)
NRTI use per year	0.915 (0.89-0.94)	0.907 (0.862-0.955)
Age	1.027 (1.025-1.03)	1.033 (1.027-1.038)
Race	Black vs. white	0.934 (0.793-1.099)
	Other/Unknown vs. white	0.912 (0.717-1.159)
Sex	Female vs. male	0.445 (0.23-0.862)
Charlson comorbidity		0.542 (0.132-2.227)
BMI	18.5-24.9 vs. missing	1.184 (1.137-1.234)
	25-29.9 vs. missing	1 (0.513-1.952)
	30+ vs. missing	3.143 (0.433-22.82)
	<18.5 vs. missing	0.83 (0.426-1.614)
Smoker		0.63 (0.322-1.235)
Pure hypercholesterolemia		1.039 (0.448-2.409)
Hypertriglyceridemia		0.427 (0.361-0.505)
Hyperlipidemia		0.426 (0.295-0.614)
Ischemic heart disease		1.245 (0.958-1.618)
Other Heart disease		1.14 (0.583-2.228)
Hypertension		0.913 (0.637-1.307)
T2DM		1.208 (0.56-2.606)
Cerebral infarction		0.916 (0.763-1.099)
Atrial fibrillation		0.892 (0.595-1.335)
Hypothyroidism		1.142 (0.694-1.88)
Hyperthyroidism		1.217 (0.946-1.565)
Depression		1.21 (1.027-1.426)
TBI		1.378 (0.976-1.945)
Alcohol dependence		1.097 (0.894-1.345)
Parkinson's disease		1.081 (0.686-1.703)
Generalized anxiety disorder		1.955 (1.035-3.693)
Chronic kidney disease		7.49 (2.662-21.073)
		1.232 (0.811-1.872)
		0.359 (0.072-1.784)
		1.205 (0.825-1.761)
		1.391 (0.55-3.52)
		0.953 (0.303-2.992)
		1.955 (0.251-15.222)
		1.099 (0.898-1.346)
		0.999 (0.612-1.632)
		1.805 (0.746-4.367)
		-
		0.87 (0.665-1.139)
		0.707 (0.333-1.502)
		-
		-
		1.207 (0.718-2.029)
		-
		0.599 (0.395-0.909)
		0.566 (0.218-1.473)

HIV, Human immunodeficiency virus. HBV, Hepatitis B virus. BMI, body mass index. T2DM, type 2 diabetes mellitus. TBI, traumatic brain injury. NRTI, nucleoside reverse transcriptase inhibitor.

**Supplementary Table 4. Marketscan Cox models, hazard of AD: Time-dependent NRTI exposure**

	Original group HR (95% CI)	PS matched HR (95% CI)
NRTI use per year	0.894 (0.845-0.947)	0.877 (0.821-0.936)
Age	1.145 (1.138-1.152)	1.163 (1.149-1.177)
Sex Male vs. Female	0.876 (0.764-1.005)	0.897 (0.689-1.169)
Smoker	1.188 (0.902-1.563)	1.995 (1.063-3.746)
Obesity	0.956 (0.682-1.34)	0.962 (0.353-2.621)
Charlson comorbidity	1.047 (1.011-1.084)	1.095 (1.006-1.191)
Pure hypercholesterolemia	0.882 (0.713-1.09)	1.119 (0.648-1.93)
Hypertriglyceridemia	0.965 (0.736-1.267)	0.566 (0.224-1.431)
Hyperlipidemia	0.962 (0.812-1.14)	0.953 (0.639-1.42)
Ischemic heart disease	1.163 (0.964-1.403)	1.135 (0.748-1.724)
Other Heart disease	1.225 (1.019-1.474)	0.958 (0.632-1.452)
Hypertension	1.014 (0.855-1.201)	0.839 (0.6-1.173)
T2DM	1.383 (1.163-1.644)	1.288 (0.872-1.9)
Cerebral infarction	1.499 (1.066-2.109)	2.879 (1.197-6.925)
Atrial fibrillation	0.657 (0.505-0.854)	0.799 (0.352-1.814)
Hypothyroidism	1.036 (0.834-1.287)	1.177 (0.615-2.254)
Hyperthyroidism	0.876 (0.425-1.803)	0.886 (0.112-6.994)
Depression	1.709 (1.359-2.149)	1.685 (0.98-2.897)
TBI	1.396 (0.706-2.761)	0.674 (0.055-8.199)
Alcohol dependence	1.673 (0.934-2.995)	0 (0-0)
Parkinson's disease	4.987 (3.4-7.313)	9.43 (4.904-18.133)
Generalized anxiety disorder	1.21 (0.801-1.828)	1.079 (0.365-3.189)
Chronic kidney disease	1.06 (0.851-1.321)	0.778 (0.42-1.44)
Year of diagnosis	0.957 (0.936-0.978)	0.972 (0.934-1.011)

HIV, Human immunodeficiency virus. HBV, Hepatitis B virus. BMI, body mass index. T2DM, type 2 diabetes mellitus. TBI, traumatic brain injury. NRTI, nucleoside reverse transcriptase inhibitor.

**Supplementary Table 5. VA: Propensity Score-Matched cohorts baseline characteristics.**

	Variable	NRTI unexposed N=8214	NRTI exposed N=8214	P value	Standardized difference
HIV		3693(44.96%)	3695(44.98%)	0.987	0
HBV		4714(57.39%)	4693(57.13%)	0.752	0.005
Age		61.54(9.21)	61.91(9.25)	<0.001	0.04
Race	Black	2692(32.77%)	2851(34.71%)	<0.001	0.041
	Other/unknown	1154(14.05%)	1310(15.95%)		
	White	4368(53.18%)	4053(49.34%)		
Sex	Female	178(2.17%)	175(2.13%)	0.914	0.002
	Male	8036(97.83%)	8039(97.87%)		
Charlson comorbidity		1.12(1.83)	1.25(1.99)	0.001	0.068
Smoker		2992(36.43%)	2993(36.44%)	1	0
BMI	<18.5	227(2.76%)	303(3.69%)	<0.001	0.052
	18.5-24.9	2551(31.06%)	2755(33.54%)		
	25-29.9	2971(36.17%)	2769(33.71%)		
	30+	2327(28.33%)	2239(27.26%)		
	Missing	138(1.68%)	148(1.80%)		
Pure hypercholesterolemia		192(2.34%)	236(2.87%)	0.035	0.034
Hypertriglyceridemia		286(3.48%)	327(3.98%)	0.1	0.026
Hyperlipidemia		1501(18.27%)	1665(20.27%)	0.001	0.051
Ischemic heart disease		727(8.85%)	822(10.00%)	0.012	0.04
Other Heart disease		561(6.83%)	602(7.33%)	0.224	0.019
Hypertension		2099(25.55%)	2153(26.21%)	0.345	0.015
T2DM		916(11.15%)	937(11.41%)	0.622	0.008
Cerebral infarction		31(0.377%)	28(0.34%)	0.794	0.006
Atrial fibrillation		58(0.71%)	61(0.74%)	0.854	0.004
Hypothyroidism		133(1.62%)	108(1.32%)	0.119	0.025
Hyperthyroidism		19(0.23%)	14(0.17%)	0.486	0.014
Depression		831(10.12%)	866(10.54%)	0.383	0.014
TBI		23(0.28%)	28(0.34%)	0.575	0.011
Alcohol dependence		545(6.64%)	444(5.41%)	0.001	0.052
Parkinson's disease		4(0.049%)	8(0.097%)	0.386	0.018
Generalized anxiety disorder		65(0.79%)	75(0.91%)	0.445	0.013
Chronic kidney disease		196(2.39%)	213(2.59%)	0.423	0.013
Year of HIV/HBV dx		2009.27(6.67)	2009.65(6.74)	0.001	0.057
NRTI use (year)		0(0)	4.44(4.48)	<0.001	NA

HIV, Human immunodeficiency virus. HBV, Hepatitis B virus. BMI, body mass index. T2DM, type 2 diabetes mellitus. TBI, traumatic brain injury. NRTI, nucleoside reverse transcriptase inhibitor.

**Supplementary Table 6. Truven: Propensity Score Matched cohorts baseline characteristics.**

	NRTI unexposed N=48297	NRTI exposed N=48297	P value	Standardized difference
HIV	35073(72.619%)	35229(72.942%)	0.263	0.007
HBV	14799(30.642%)	14671(30.377%)	0.375	0.006
Age	57.5(5.67)	56.64(5.446)	<0.001	0.155
Sex				
Male	35513(73.53%)	36497(75.568%)	<0.001	0.047
Female	12784(26.47%)	11800(24.432%)	<0.001	0.047
Charlson comorbidity	0.5(1.295)	0.49(1.314)	<0.001	0.008
Smoker	1082(2.24%)	1158(2.398%)	0.109	0.01
Obese	932(1.93%)	908(1.88%)	0.588	0.004
Pure hypercholesterolemia	1541(3.191%)	1476(3.056%)	0.236	0.008
Hypertriglyceridemia	1372(2.841%)	1415(2.93%)	0.419	0.005
Hyperlipidemia	3775(7.816%)	3816(7.901%)	0.632	0.003
Ischemic heart disease	1635(3.385%)	1651(3.418%)	0.79	0.002
Other Heart disease	2014(4.17%)	1955(4.048%)	0.347	0.006
Hypertension	7851(16.256%)	7581(15.697%)	0.0182	0.015
T2DM	3844(7.959%)	3796(7.86%)	0.575	0.004
Cerebral infarction	158(0.327%)	172(0.356%)	0.473	0.005
Atrial fibrillation	422(0.874%)	407(0.843%)	0.625	0.003
Hypothyroidism	1079(2.234%)	1008(2.087%)	0.121	0.01
Hyperthyroidism	133(0.275%)	146(0.302%)	0.472	0.005
Depression	1391(2.88%)	1641(3.398%)	<0.001	0.03
TBI	62(0.128%)	68(0.141%)	0.661	0.004
Alcohol dependence	152(0.315%)	175(0.362%)	0.223	0.008
Parkinson's disease	48(0.099%)	44(0.091%)	0.754	0.003
Generalized anxiety disorder	693(1.435%)	875(1.812%)	<0.001	0.03
Chronic kidney disease	1106(2.29%)	1101(2.28%)	0.931	0.001
Year of HIV/HBV dx	2011.93(3.924)	2012.43(4.13)	<0.001	0.124
NRTI duration (years)	0(0)	2.43 (2.33)	<0.001	NA

HIV, Human immunodeficiency virus. HBV, Hepatitis B virus. BMI, body mass index. T2DM, type 2 diabetes mellitus. TBI, traumatic brain injury. NRTI, nucleoside reverse transcriptase inhibitor.

**Supplementary Table 7. VA Competing risk model, death as a competing risk. Sub-distribution hazard ratios (sHR).**

	Original group sHR(95% CI)	PS matched sHR(95% CI)
NRTI use per year	0.456 (0.371-0.56)	0.514 (0.374-0.706)
Age	1.027 (1.024-1.03)	1.032 (1.023-1.04)
Race		
Black vs. white	1.027 (0.869-1.213)	0.9712 (0.994-0.706)
Other/Unknown vs. white	0.692 (0.539-0.888)	0.8962 (1.03-0.664)
Sex		
Female vs. white	0.522 (0.261-1.046)	0.6246 (0.699-0.167)
Charlson comorbidity	1.016 (0.975-1.059)	1.002 (0.918-1.095)
BMI		
18.5-24.9 vs. missing	1.241 (0.631-2.443)	3.613 (0.497-26.251)
25-29.9 vs. missing	1.235 (0.63-2.421)	3.142 (0.432-22.875)
30+ vs. missing	0.979 (0.496-1.929)	2.213 (0.3-16.329)
<18.5 vs. missing	0.904 (0.387-2.108)	1.961 (0.202-19.032)
Smoker	0.509 (0.43-0.603)	0.49 (0.333-0.72)
Pure hypercholesterolemia	1.462 (1.118-1.911)	1.47 (0.721-2.997)
Hypertriglyceridemia	0.977 (0.675-1.415)	1.33 (0.628-2.82)
Hyperlipidemia	0.996 (0.832-1.193)	1.002 (0.678-1.48)
Ischemic heart disease	0.939 (0.746-1.183)	0.99 (0.59-1.66)
Other Heart disease	0.948 (0.729-1.232)	1.313 (0.711-2.427)
Hypertension	1.151 (0.973-1.363)	1.377 (0.944-2.009)
T2DM	1.146 (0.936-1.403)	1.099 (0.687-1.758)
Cerebral infarction	1.93 (1.003-3.712)	6.054 (2.028-18.069)
Atrial fibrillation	1.207 (0.787-1.852)	0.435 (0.061-3.123)
Hypothyroidism	1.15 (0.783-1.69)	1.456 (0.571-3.713)
Hyperthyroidism	1.095 (0.345-3.469)	2.139 (0.242-18.92)
Depression	1.129 (0.916-1.393)	1.159 (0.695-1.934)
TBI	1.587 (0.65-3.876)	-
Alcohol dependence	0.727 (0.555-0.953)	0.621 (0.272-1.421)
Parkinson's disease	3.662 (2.088-6.423)	-
Generalized anxiety disorder	1.273 (0.748-2.166)	-
Chronic kidney disease	0.562 (0.367-0.862)	0.576 (0.214-1.549)

HIV, Human immunodeficiency virus. HBV, Hepatitis B virus. BMI, body mass index. T2DM, type 2 diabetes mellitus. TBI, traumatic brain injury. NRTI, nucleoside reverse transcriptase inhibitor.

**Supplementary Table 8. Morris Water Maze, Mixed effect model results.**

<i>Predictors</i>	<i>Estimates</i>	<b>Time</b>	
		<i>CI</i>	<i>p</i>
(Intercept)	56.59	50.24 – 62.95	< <b>0.001</b>
24-week 5xFAD	8.42	1.81 – 15.02	<b>0.013</b>
36-week 5xFAD – K-9	-10.84	-18.48 – -3.20	<b>0.006</b>
36-week 5xFAD - PBS	9.21	1.57 – 16.85	<b>0.018</b>
WT	-9	-16.63 – -1.37	<b>0.021</b>
day	-8.37	-9.71 – -7.02	< <b>0.001</b>
<b>Random Effects</b>			
$\sigma^2$	278.98		
$\tau_{00}$ Mouse.ID	20.24		
ICC	0.07		
$N_{\text{Mouse.ID}}$	30		
Observations	478		
Marginal $R^2$ / Conditional $R^2$	0.345 / 0.389		

\*All groups compared to reference level of 13-week 5xFAD mice



**Supplementary Table 9. Morris Water Maze, Contrast estimates**

<i>Contrast</i>	<i>Estimates</i>	<b>Time</b>	
		<i>CI</i>	<i>p</i>
36-week 5xFAD – K-9 vs. 36-week 5xFAD - PBS	-20.05	-28.66, -11.44	<b>&lt;0.001</b>
36-week 5xFAD – K-9 vs. 18-week wild-type	-1.842	-10.44, 6.76	0.85