# Association Between Herpes Simplex Virus Type 1 and the Risk of Alzheimer's Disease

# Introduction

- There is a significant unmet need of novel therapeutics for Alzheimer's disease (AD) and AD-related dementia (ADRD)<sup>1</sup>
- A growing body of evidence suggests a role for herpesviruses in the development of AD/ADRD and reduced risk of AD/ADRD among patients receiving antiviral<sup>2-6</sup>
- We investigated the association between herpes simplex virus type 1 (HSV-1) and AD/ADRD, and the effect of antiviral medications using real-world data

# Objectives

### **Primary:**

- To describe the demographic and clinical characteristics of patients with AD/ADRD
- To assess the association between HSV-1 infection and AD/ADRD

### **Secondary:**

To assess if antiviral use reduces risk of AD/ADRD in patients with HSV-1 infection

# Methods

- A matched case-control study design was used; patients with AD aged  $\geq 50$  y diagnosed between 2006 and 2021 were identified from the IQVIA® PharMetrics<sup>®</sup> Plus (Durham, NC) claims database using International Classification of Disease (ICD) codes (ICD-9 331.0; ICD-10 G30.x)
- Controls without any history of neurologic disorders were matched in a 1:1 ratio with patients with AD on age, sex, region, database entry year, and healthcare visit numbers
- HSV-1 diagnoses were identified using relevant ICD codes
- Multivariate conditional logistic regression was used to evaluate the association between HSV-1 and AD
- The association between antiviral use and AD was assessed by multivariate Cox proportional hazards model in patients with HSV-1 diagnosis
- A parallel analysis was conducted including all patients with ADRD and matched controls

# Results



### **Patient Clinical Characteristics** Char Datab

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ADRD patients n=1,039,683

**IQVIA claims database** 

n=206,550,245

Control pool witho

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n=171,499,232

# **Study Flow: Attrition and Matching**

#### Inclusion/Exclusion

- Definition of case (AD/ADRD)
  - 1) ≥2 AD/ADRD diagnosis codes ≥30 d apart or 2)  $\geq$ 1 AD/ADRD diagnosis code and  $\geq$ 1 ADRD
  - medication prescribed after 1st AD/ADRD diagnosis
- Aged ≥50 y at 1st AD/ADRD diagnosis date (index date) Patients with AD/ADRD or other neurologic disorders anytime
- in database history were excluded from control pool



AD

patients

n=395,654

#### **Patient Demographic Characteristics**



acteristics	AD Case n=344,628	Control n=344,628	p-Valı
base entry year, n (%)			1.00
2006–10	285,085 (82.7)	285,085 (82.7)	
2011–15	45,850 (13.3)	45,850 (13.3)	
2016–21	13,693 (4.0)	13,693 (4.0)	
atient visit #			1.00
Mean (SD)	13.32 (10.10)	13.32 (10.10)	
Median (Q1, Q3)	11 (6, 18)	11 (6, 18)	
ient visit #			1.00
Mean (SD)	3.36 (4.88)	3.36 (4.88)	
Median (Q1, Q3)	2 (1, 4)	2 (1, 4)	
orbidities, n (%)			<0.00
None	101,458 (29.4)	119,351 (34.6)	
1	69,603 (20.2)	69,552 (20.2)	
≥2	173,567 (50.4)	155,725 (45.2)	
Charlson)			<0.00
Mean (SD)	2.61 (2.89)	2.41 (2.93)	
Median (Q1, Q3)	2 (0, 4)	1 (0, 4)	
w-up time, mo			<0.00
Mean (SD)	47.86 (46.24)	53.98 (39.97)	
Median (Q1, Q3)	33 (9, 74)	48 (24, 72)	
1, n (%)	1507 (0.4)	823 (0.2)	<0.00
morbidity Index: Q. quartiles: SD. standard deviation.			



		OR (95% CI)			
Overall (344,628 pairs)	HSV-1 vs no HSV-1	1.80 (1.65, 1.96)			
	1 comorbidity vs none	1.30 (1.28, 1.32)			H
	≥2 comorbidities vs none	1.60 (1.57, 1.62)			
50–70 y (84,820 pairs)	HSV-1 vs no HSV-1	1.14 (0.91, 1.44)		H	
	1 comorbidity vs none	1.34 (1.31, 1.38)			H≡H
	≥2 comorbidities vs none	1.54 (1.50, 1.59)			
71–74 y (118,603 pairs)	HSV-1 vs no HSV-1	1.51 (1.27, 1.80)			F
	1 comorbidity vs none	1.34 (1.31, 1.37)			H≡H
	≥2 comorbidities vs none	1.45 (1.42, 1.49)			H
≥75 y (141,205 pairs)	HSV-1 vs no HSV-1	2.10 (1.88, 2.35)			
	1 comorbidity vs none	1.23 (1.20, 1.27)			<b>⊦</b> ∎-1
	≥2 comorbidities vs none	1.77 (1.73, 1.81)			
			0.50	1	OR (95% CI

I. confidence interval: OR. adjusted odds ratio

# Effects of Antiviral Medications in Patients With HSV-1 Diagnosis

	_	HR (95% CI)			
Age group	50–64 y (n=705)	Reference			
	65–74 y (n=920)	1.24 (1.08, 1.42)	⊢∎	⊢I	
	≥75 y (n=705)	2.62 (2.28, 3.01)			
Sex	Woman (n=1552)	Reference			
	Man (n=778)	0.94 (0.85, 1.05)	<b>⊢−</b> 1		
Region	Northeast (n=469)	Reference			
	Midwest (n=610)	0.87 (0.75, 1.02)	I∎I		
	South (n=705)	1.00 (0.86, 1.16)	<b>⊢</b>		
	West (n=546)	0.96 (0.82, 1.12)	<b>⊢⊞</b> I		
Comorbidities	0 (n=216)	Reference			
	1 (n=357)	1.16 (0.91, 1.48)		I	
	2 (n=1757)	1.22 (0.99, 1.51)		I	
Antiviral use after infection	No (n=1399)	Reference			
	Yes (n=931)	0.83 (0.74, 0.92)	<b>⊢−−−</b> ∎−−−−1		
			1	1.5 HR (95% CI)	2

HR. adjusted hazard ratio

#### Limitations

- Real-world data could be missing or incomplete, the extent of which could not be ascertained
- Commercial claims data don't capture patients insured solely by Medicare; therefore, patients aged  $\geq 65$  y were underrepresented in this study
- Asymptomatic HSV-1 infection may not be captured by claims data

#### **Conclusions**

HSV-1 and risk of AD/ADRD and the possible protective role of antiviral drugs

References: 1. 2021 Alzheimer's disease facts and figures. Alzheimers Dement 2021;17:327-406; 2. James C, et al. Alzheimers Dement 2021;7:e12119; 5. Tzeng NS, et al. Neurotherapeutics 2018;15:417-29; 6. Young-Xu Y, et al. Neurotherapeutics 2018;15:417-29; 7. Et al. Neurotherapeutics 2018;15:41 2021;18:2458. Acknowledgments: We extend our thanks to the patients and their families. This study was funded by Gilead. Disclosures: L. Liu, N. Jarousse, S.P. Fletcher, and S. Iqbal: Gilead; C. Johnston: Gilead, AbbVie, GSK.



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Findings from this large real-world data study are consistent with emerging literature on the association between