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Differences in virological and immunological risk factors for non-Hodgkin and Hodgkin lymphoma: The D:A:D study

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On behalf of the D:A:D Study group

D:A:D

UCL

Background

- HIV positive individuals are at higher risk of infection-related malignancies due to immune deficiency [1].
- Since the introduction of combination antiretroviral treatment (cART), a decline in non-Hodgkin lymphoma (NHL) but not Hodgkin lymphoma (HL) incidence has been observed [2].
- Despite this progress for NHL, incidence of NHL and HL remain approximately 10 fold higher than in the HIV negative population [1, 3].
- Previous studies suggest that risk factors for NHL and HL may differ among HIV positive persons.

1. Grulich et al. 2007. The Lancet, 370(9581).
2. Patel et al. 2008. Annals of Internal Medicine, 148(10)
3. Robbins, et al. 2014. AIDS, 28(6)

Objective

To identify risk factors associated with developing NHL or HL in HIV positive people in the D:A:D study.

Methods

- **Two independent outcomes**
  - HL (collected and validated since 2004)
  - NHL (AIDS defining event [1])
- **Baseline:** Latest of study entry, first CD4 cell count, or 1/1/2004
- **D:A:D participants followed from baseline until earliest of**
  - NHL or HL diagnosis
  - Last visit + 6 months
  - Death
  - 1 February 2015
- **Exclusions**
  - History of NHL or HL prior to baseline
  - No CD4 available at baseline

[1] Centers for Disease Control and Prevention. MMWR Recomm Rep 1992;18(41(RR-17))

Methods

Independent risk factors for NHL and HL were identified using Poisson regression

Demographic

- Age
- Gender
- Race
- Mode of HIV infection
- Smoking status
- BMI
- Calendar year

HIV related

HIV treatment

Regimen,Duration

HIV Viral load (VL)

Current HIV-Viral load (HIV-VL)

Area under the curve (AUC) HIV-VL (from first follow-up)

CD4

Current CD4

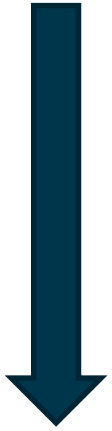
Comorbidities

- AIDS diagnosis (other than cancer)
- AIDS defining malignancy (ADM)
- Non-AIDS defining malignancy (NADM)
- HCV and HBV status
- Hypertension
- Anaemia
- Diabetes
- Cardiovascular events

Area under the curve (AUC)

- A time varying measure of cumulative exposure to HIV replication.
- Calculated since entry into D:A:D.
- Same idea as pack years for smoking.
- Divided into quintiles.

1st quintile: Lowest AUC of HIV-VL
2
3
4
5th quintile: Highest AUC of HIV-VL



Higher AUC-HIV-VL level = More exposure to HIV viral replication

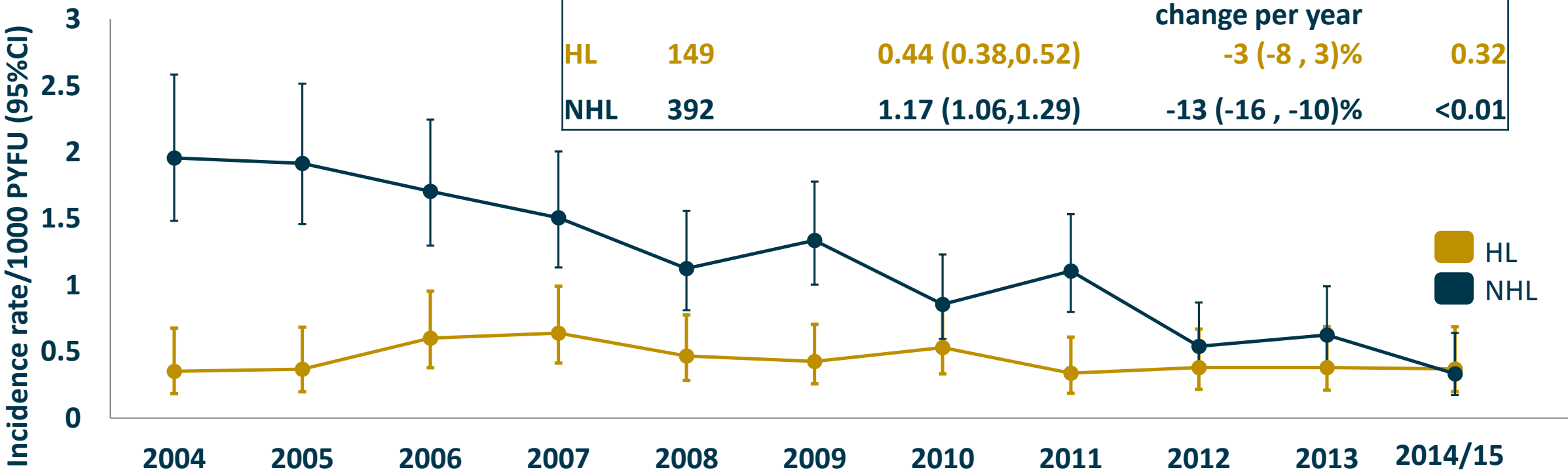
Baseline characteristics

Factor	Total N=40987	%
Median age (years, IQR)	40	34 - 47
Median year of baseline (IQR)	2004	2004 - 2006
Male gender	30214	73
MSM transmission mode	18124	44
Prior AIDS (other than cancer)	8748	21
On cART	21310	51
CD4>350 cells/mm^3	25563	62
HIV-VL <500 copies/mL	21171	51

IQR: Interquartile range, baseline: latest of study entry, first CD4, or 1/1/2004

Incidence rate of NHL and HL by year

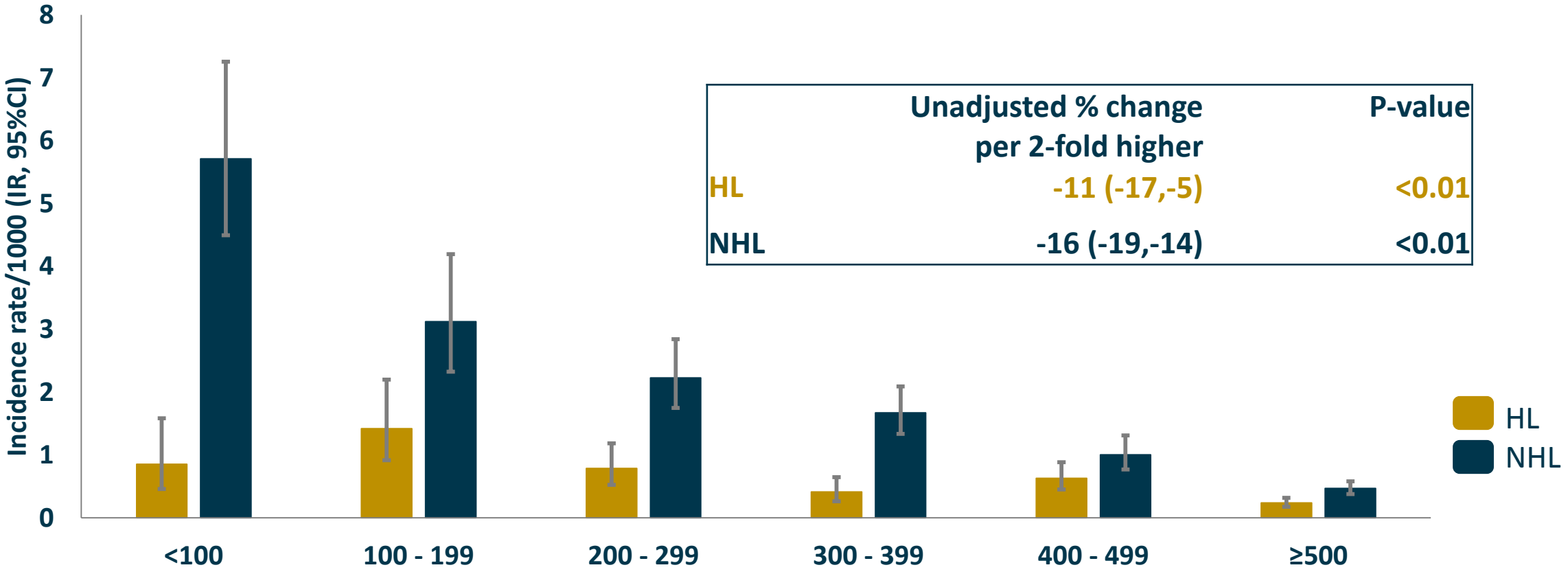
	N	IR/1000 PYFU (95%CI)	Unadjusted % change per year	P-value
HL	149	0.44 (0.38,0.52)	-3 (-8 , 3)%	0.32
NHL	392	1.17 (1.06,1.29)	-13 (-16 , -10)%	<0.01



Number of events per year

HL	9	10	17	21	15	15	18	11	12	11	10
NHL	50	52	50	48	36	45	29	34	17	18	8

Incidence rate of NHL and HL by CD4 count



	Unadjusted % change per 2-fold higher	P-value
HL	-11 (-17,-5)	<0.01
NHL	-16 (-19,-14)	<0.01

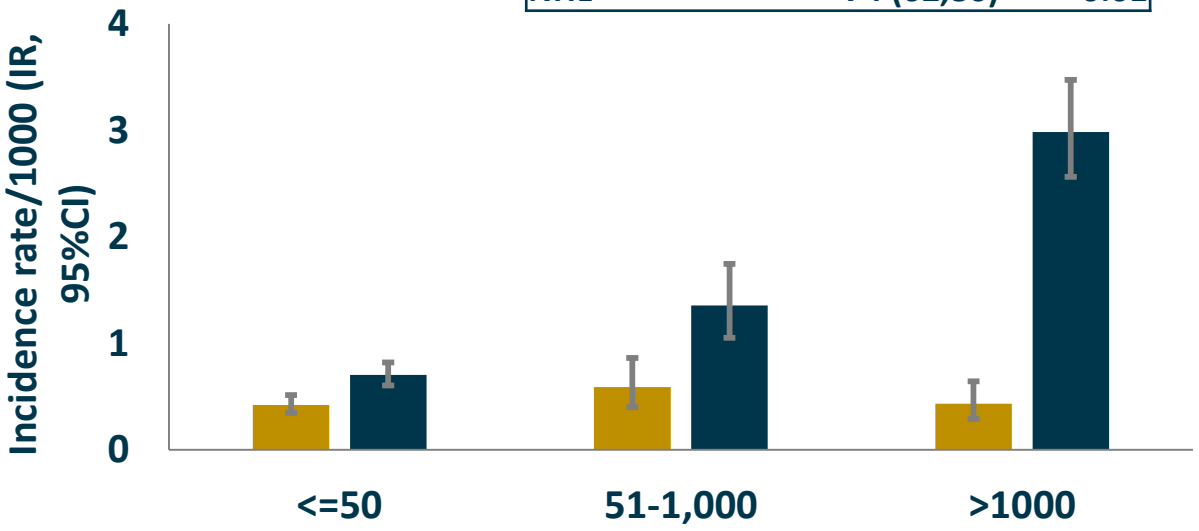
Number of events

	CD4 cell count (cells/mm3)					
HL	8	20	22	19	33	42
NHL	63	40	64	72	54	80

Incidence rate of NHL and HL by current and AUC of HIV-VL

Current HIV Viral-load

	Unadjusted % change per 10-fold higher	P-value
HL	5 (-10,22)	0.56
NHL	74 (62,86)	<0.01



Number of events

HL[1]	98	26	24
NHL[2]	164	60	166

Missing: [1]N=1, [2]N=2, [3]N=2, [4]N=29

Incidence rate of NHL and HL by current and AUC of HIV-VL

Current HIV Viral-load

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HL	5 (-10,22)	0.56
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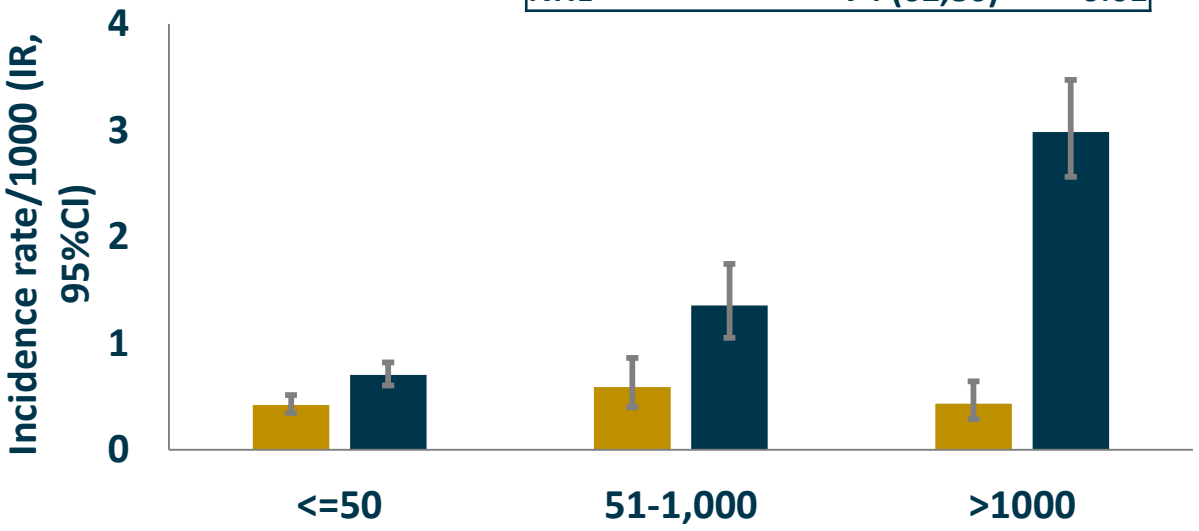
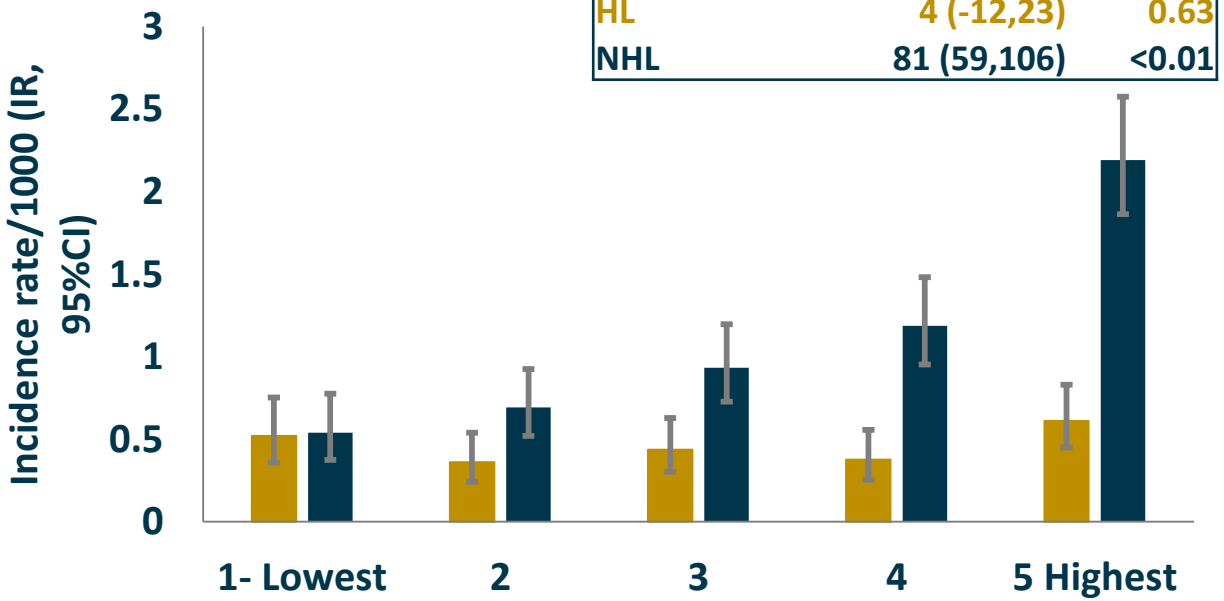


AUC of HIV Viral-load

	Unadjusted % change per 10-fold higher	P-value
HL	4 (-12,23)	0.63
NHL	81 (59,106)	<0.01

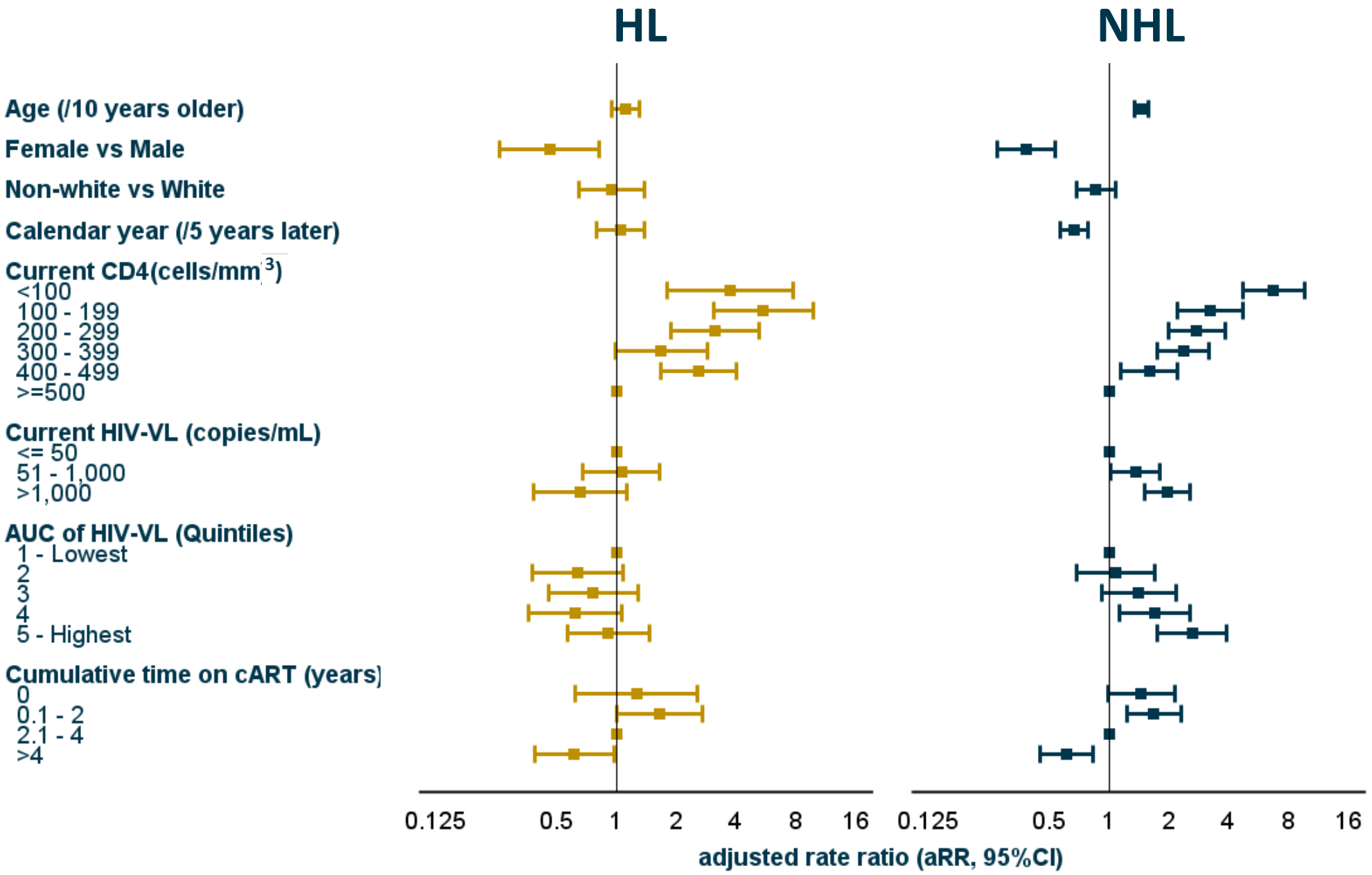


Number of events

HL[1]	98	26	24	HL[3]	28	24	29	25	41
NHL[2]	164	60	166	NHL[4]	29	46	62	79	147

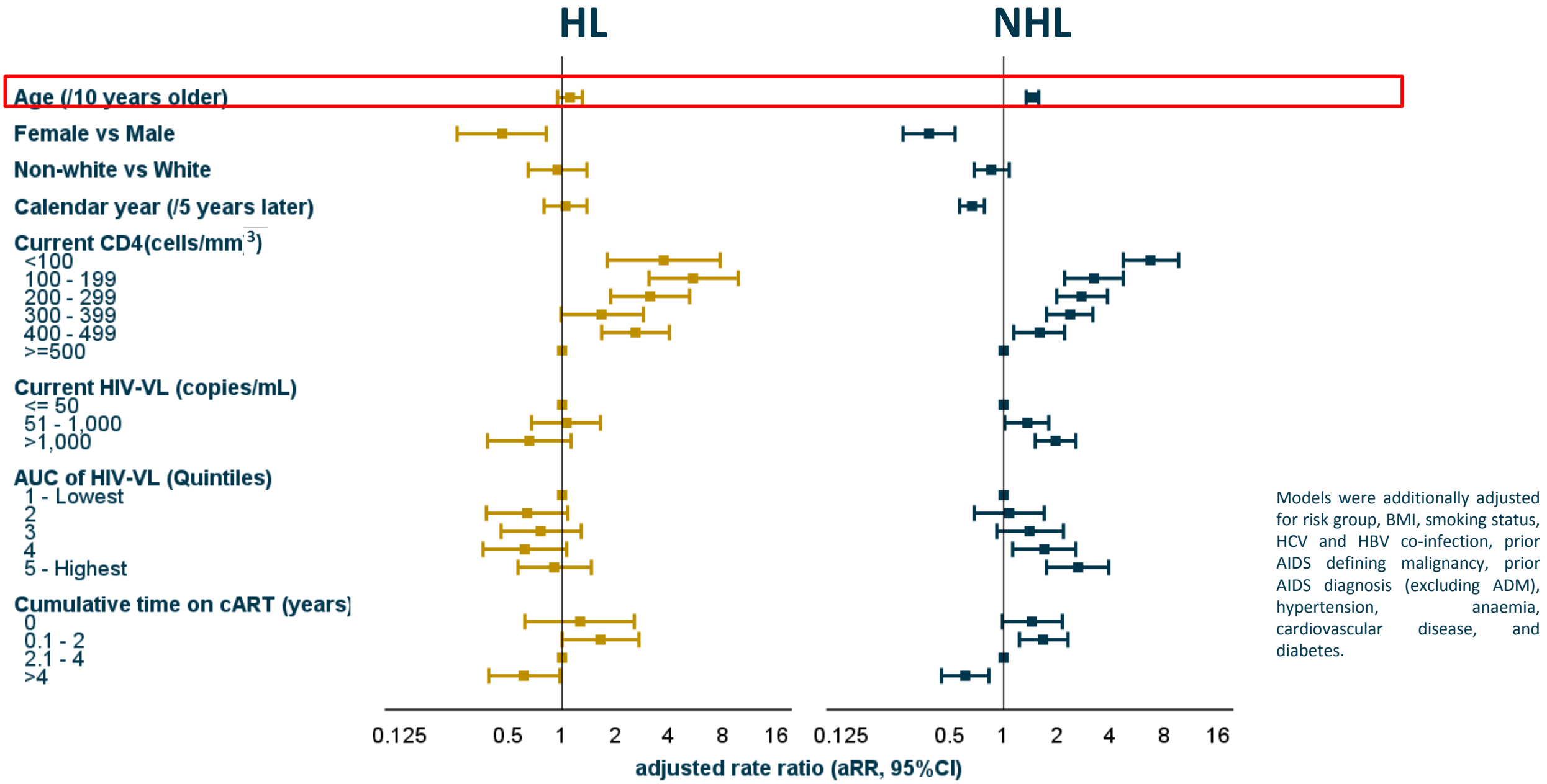
Missing: [1]N=1, [2]N=2, [3]N=2, [4]N=29

Adjusted incidence rate ratios



Models were additionally adjusted for risk group, BMI, smoking status, HCV and HBV co-infection, prior AIDS defining malignancy, prior AIDS diagnosis (excluding ADM), hypertension, anaemia, cardiovascular disease, and diabetes.

Adjusted incidence rate ratios



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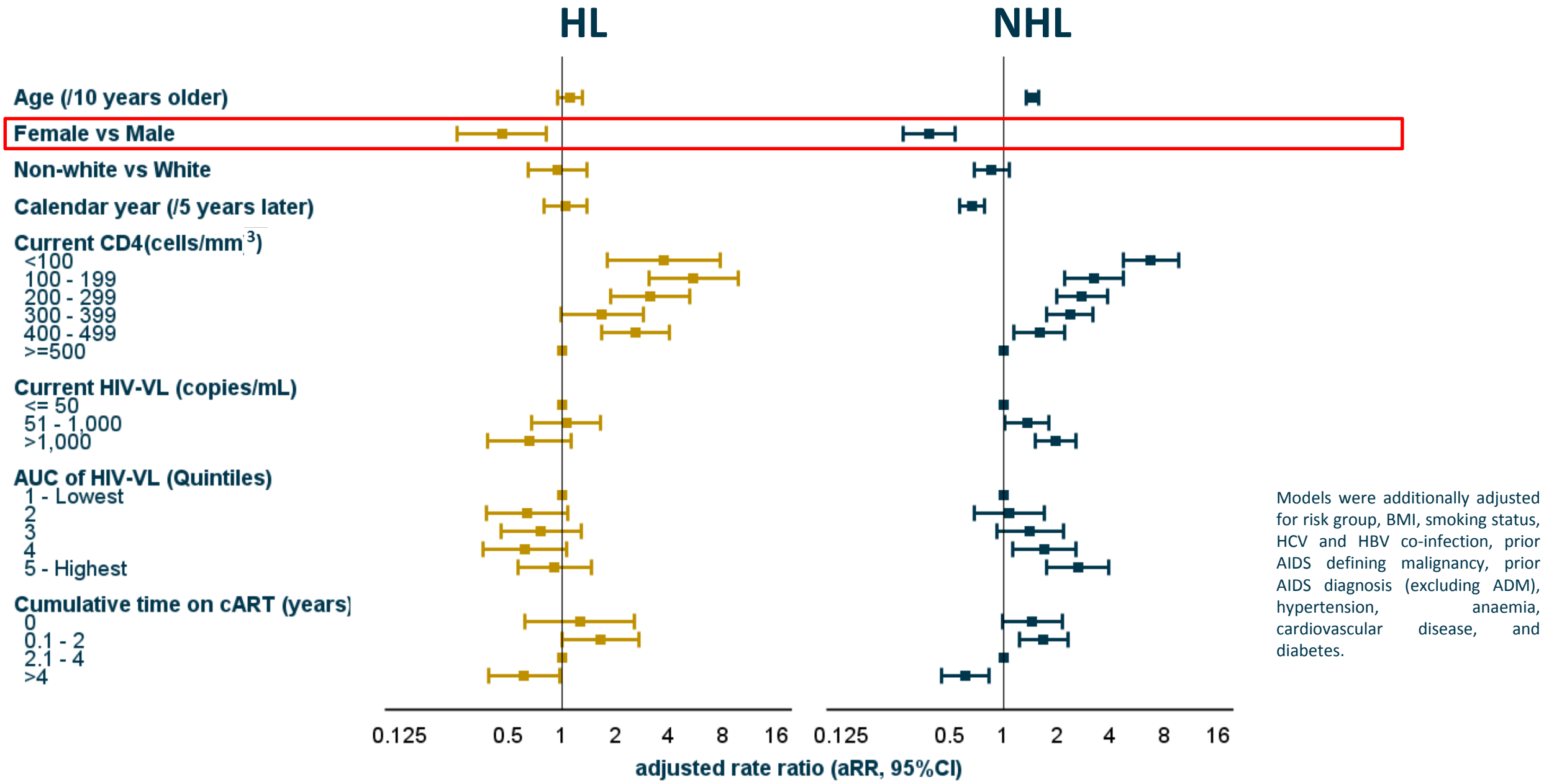

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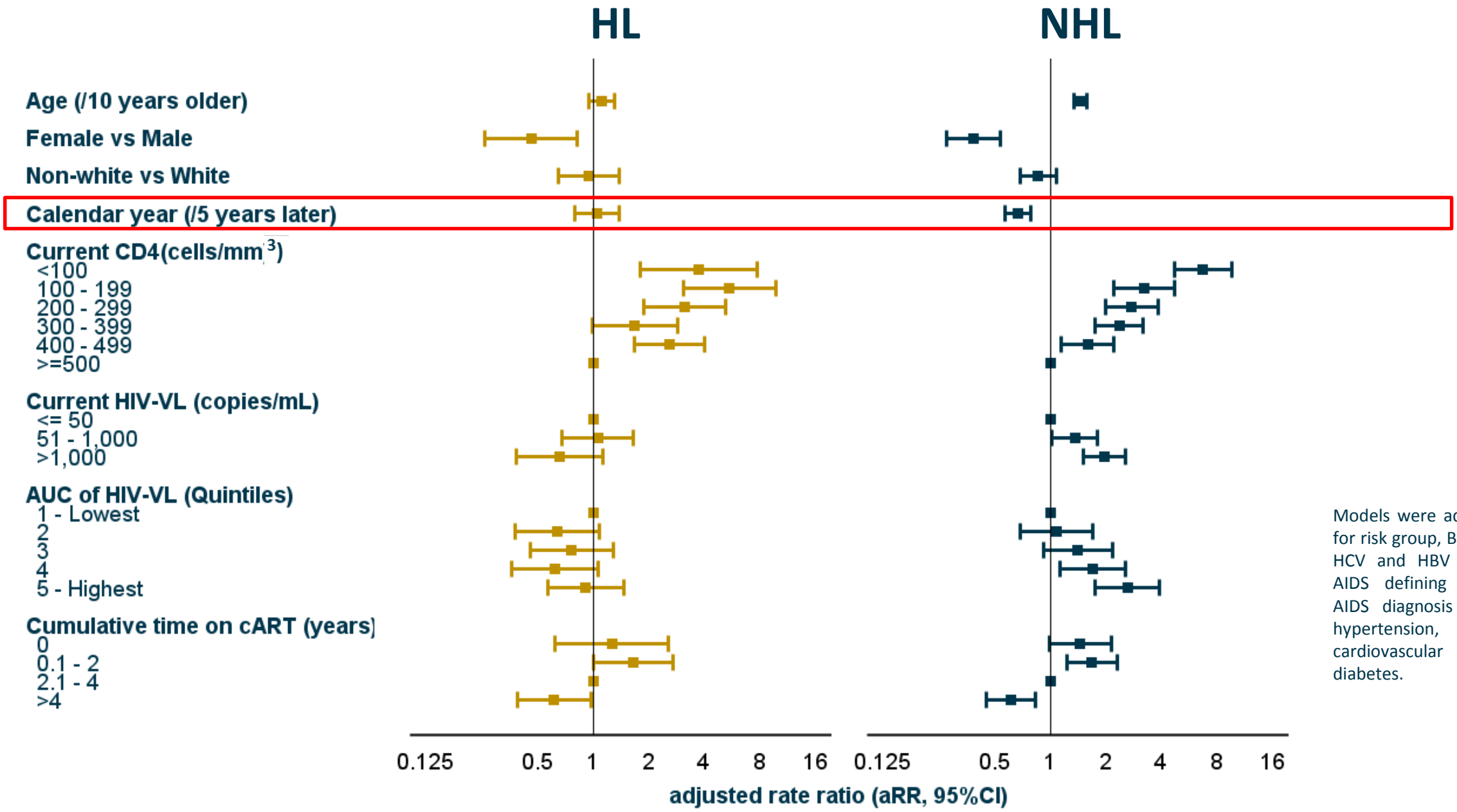

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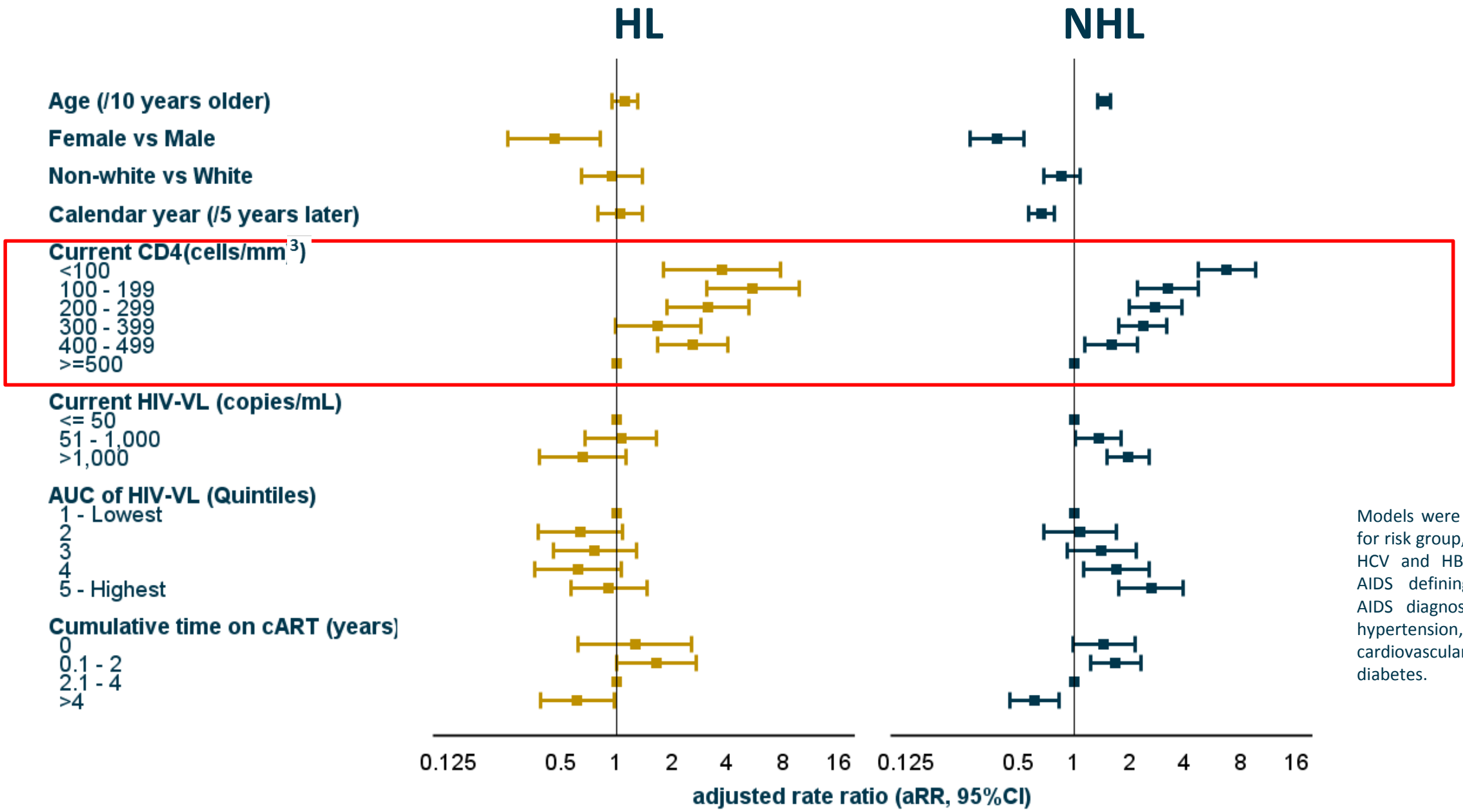

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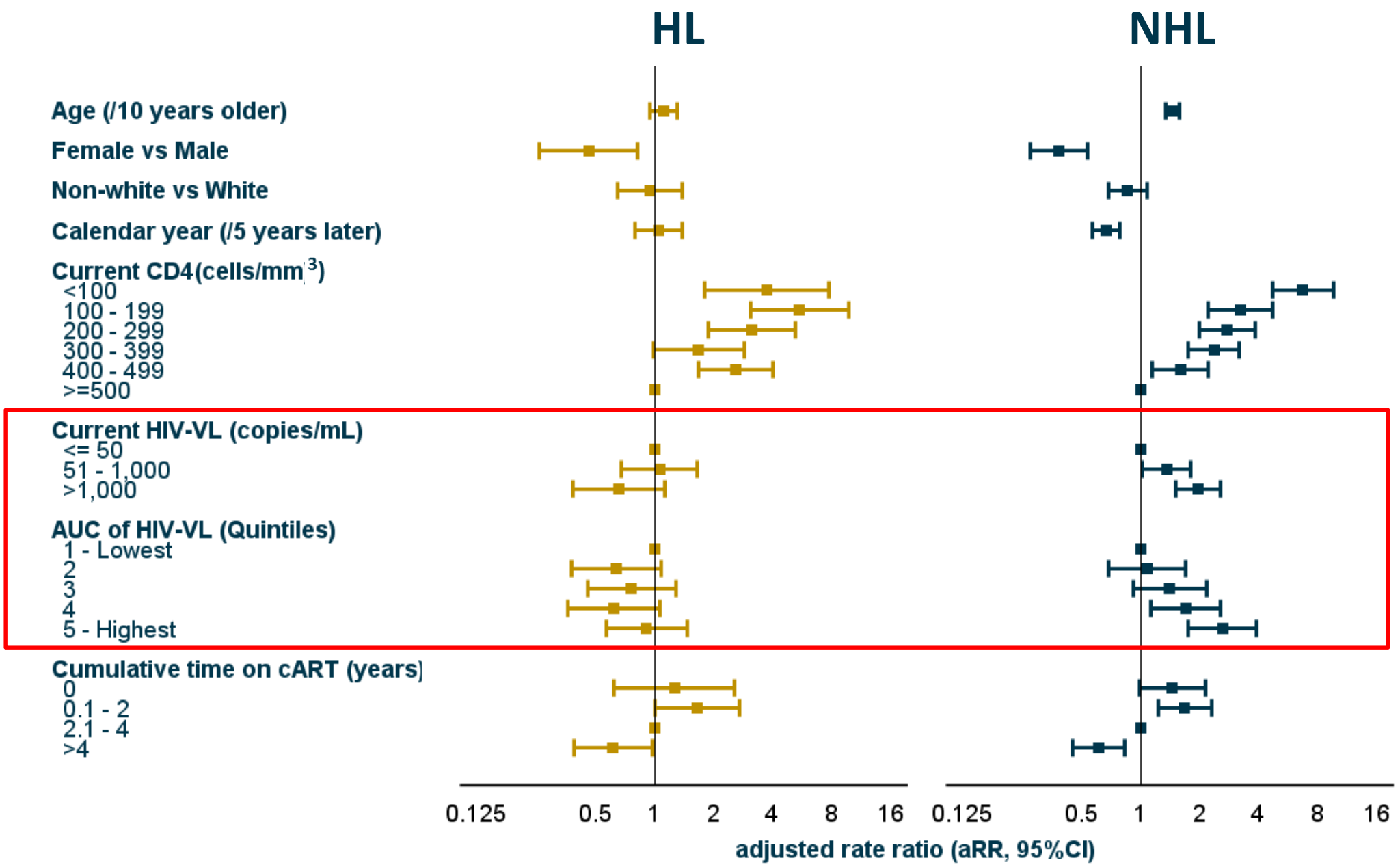

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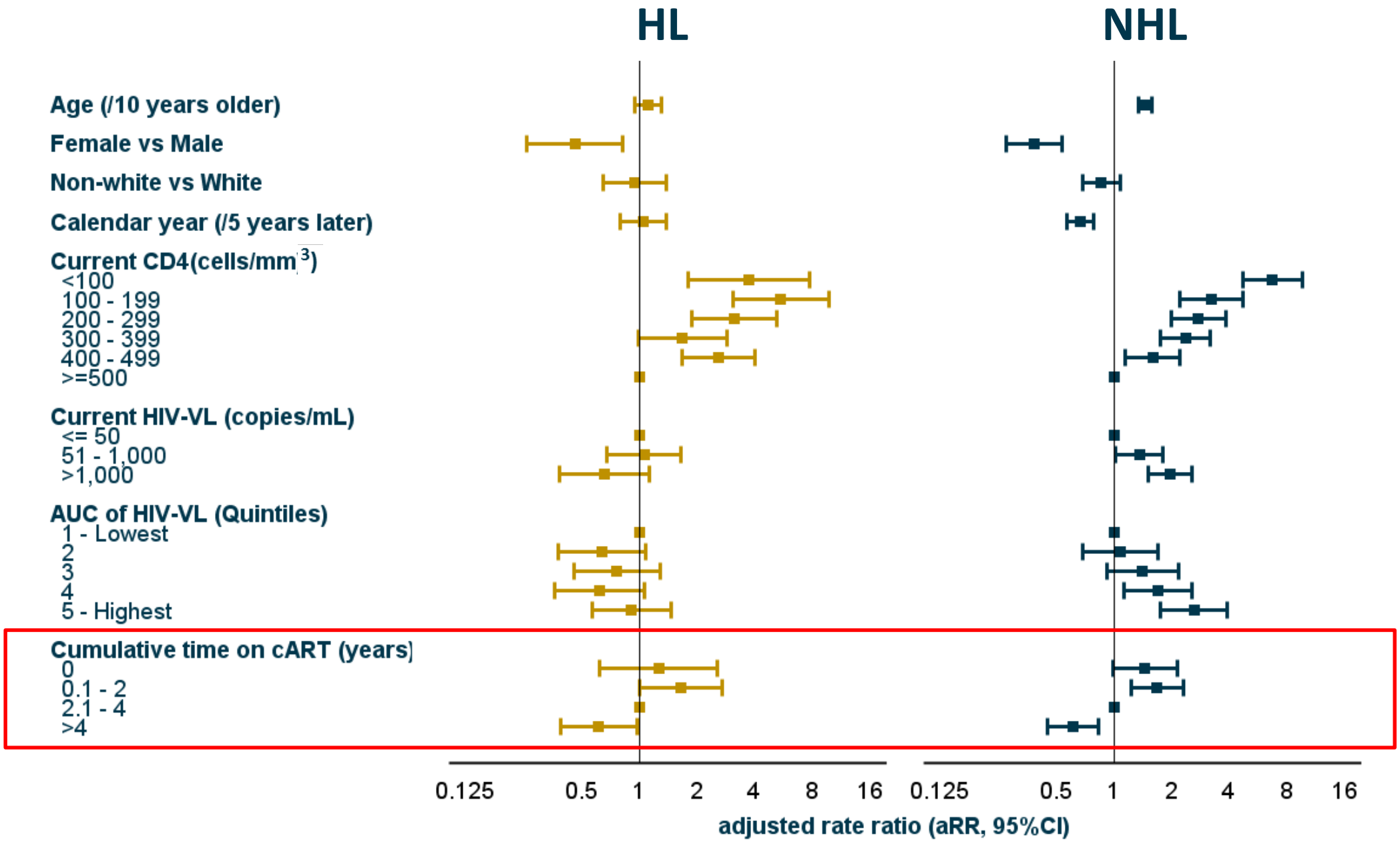

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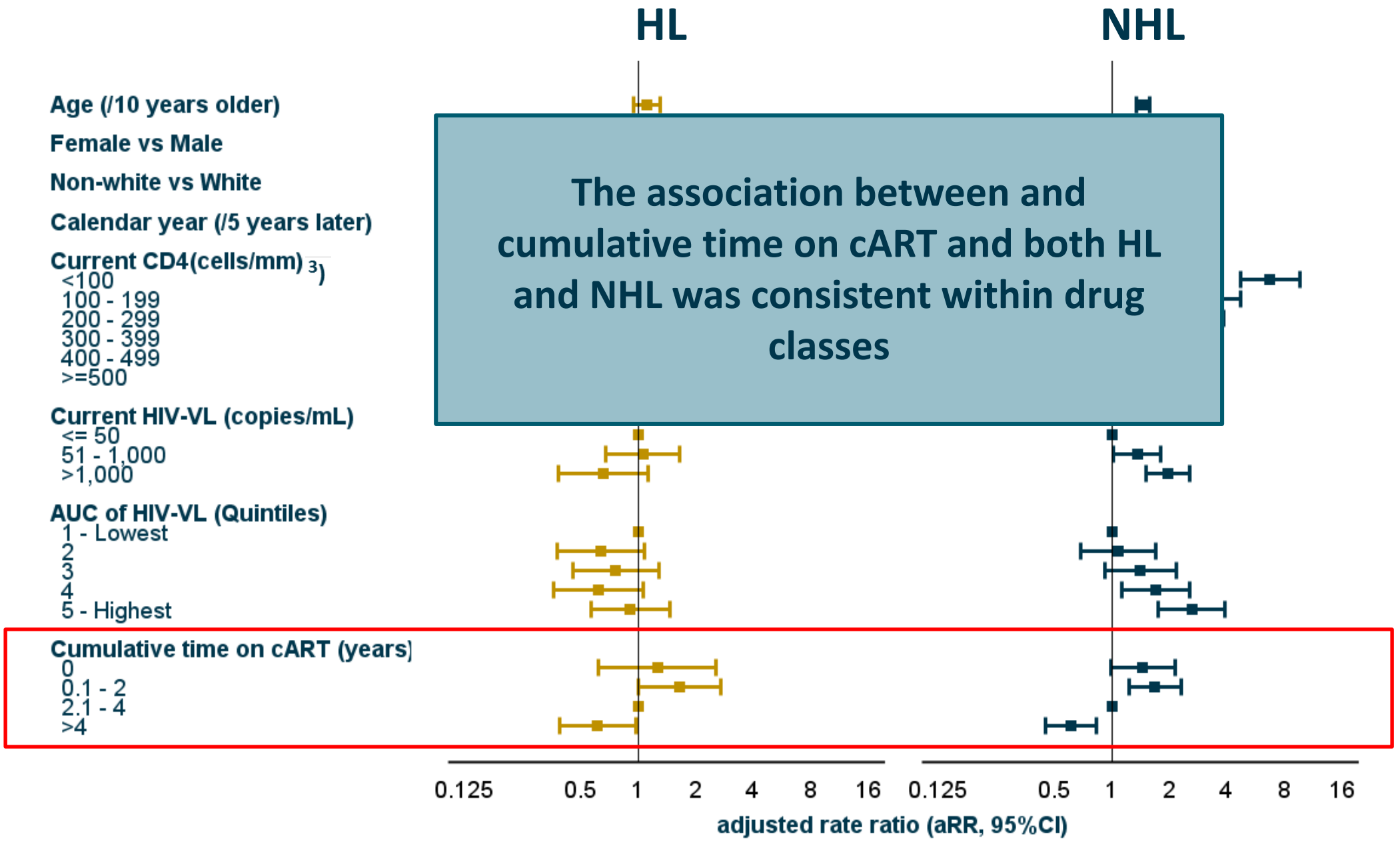
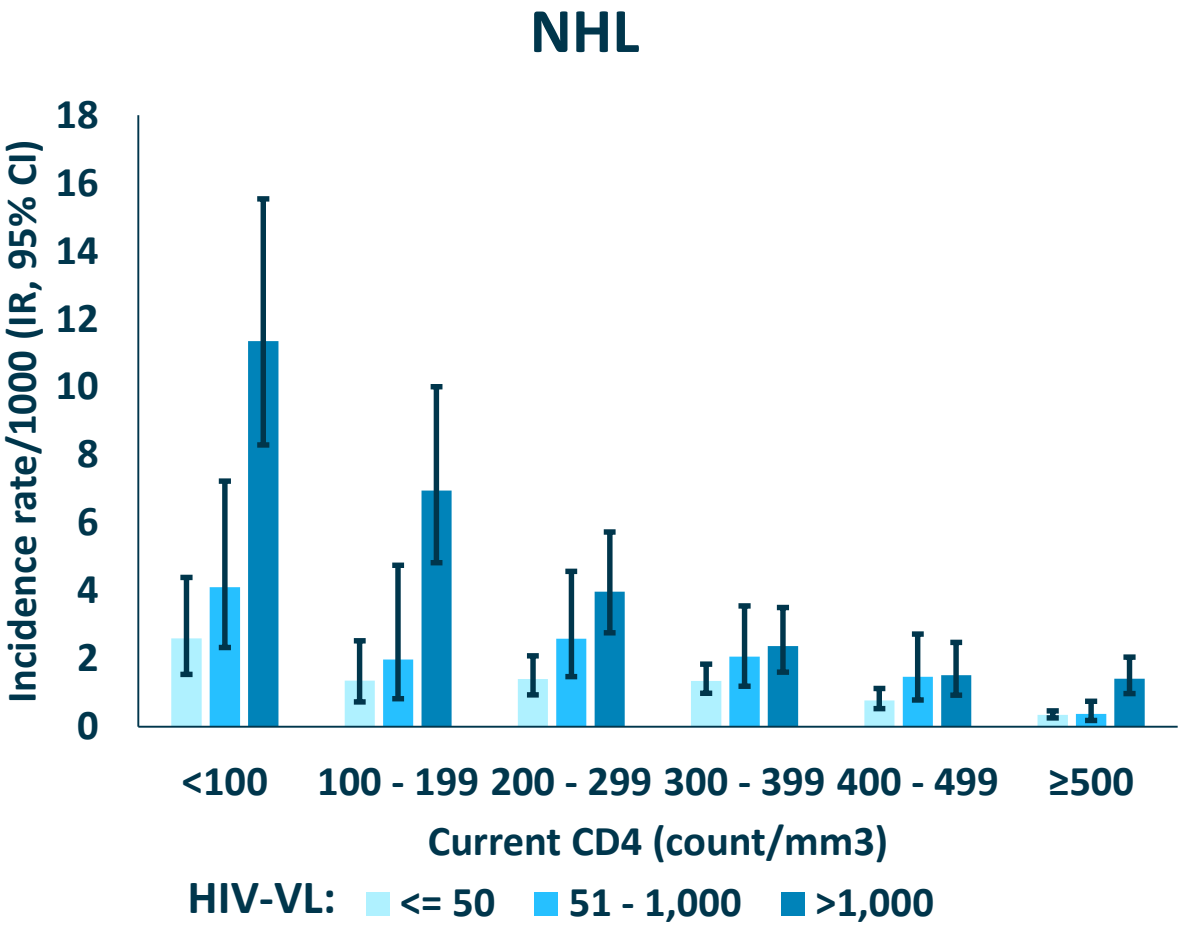
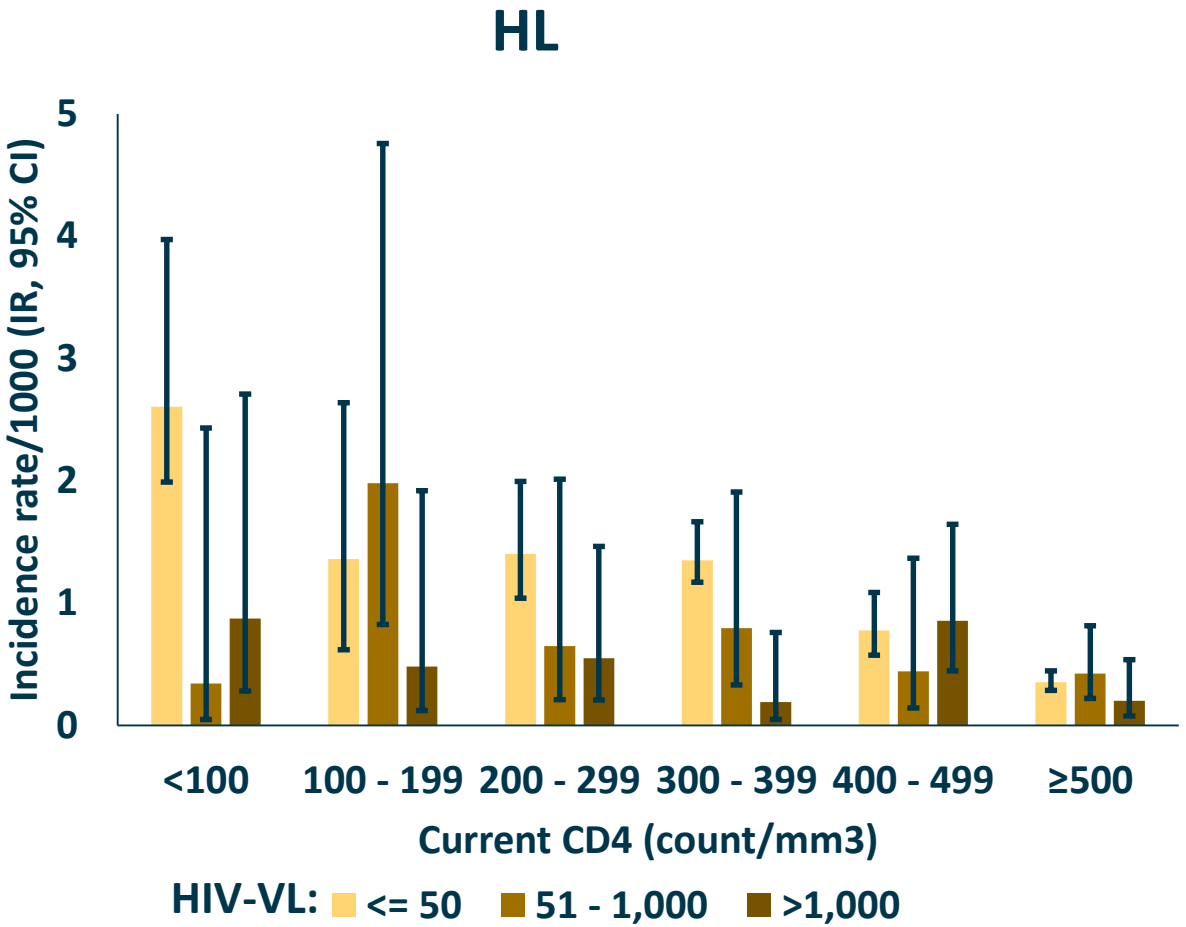


The association between and cumulative time on cART and both HL and NHL was consistent within drug classes

Models were additionally adjusted for risk group, BMI, smoking status, HCV and HBV co-infection, prior AIDS defining malignancy, prior AIDS diagnosis (excluding ADM), hypertension, anaemia, cardiovascular disease, and diabetes.

Incidence rate of NHL and HL by current HIV-VL, stratified by current CD4





	P for interaction
NHL	0.02
HL	0.36

Strengths and limitations

Strengths

- Large dataset > 40,000 HIV positive individuals
- Large number of NHL and HL
- HL events centrally validated, NHL diagnosed as AIDS defining event [1]
- Detailed data collection on several important and specific HIV-related risk factors

Limitations

- HL collected and centrally validated from 2004 only
- Observational study
- Residual confounding may remain and reverse causality cannot be ruled out
- Limited data on dissemination/stage of disease

[1] Centers for Disease Control and Prevention. MMWR Recomm Rep 1992;18(41(RR-17))

Conclusions

- NHL incidence was associated with lower current CD4 and higher current and historical exposure to viral replication.
- This indicates that ongoing viral replication may play a part in NHL development along side current-immunodeficiency.
- HL incidence was elevated in those with current-immunodeficiency, but current and historical exposure to uncontrolled HIV replication were not associated.
- Factors involved in the pathology of HL are less clear.

Conclusions

- Preventive measures should include identification and management of persons with HIV to minimise exposure to uncontrolled viremia and advanced immunodeficiency. Our results highlight the importance of early diagnosis and early cART initiation.

Acknowledgements

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