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Immediate ART initiation reduces risk of infection-related cancer during HIV infection

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* no financial relationships with commercial entities to disclose. 

Background

- HIV and cancer have been closely linked since the beginning of the AIDS epidemic.
- HIV infection is associated with increased risk for infection-related and AIDS-defining cancers, as well as infection-unrelated cancers.
- Cancer has emerged as a major cause of morbidity and death among HIV+ persons in the post-ART era.

Haymes Lancet 1981

Grulich Lancet 2007

Silverberg AIDS 2009

Shiels JAIDS 2009

Shiels JNCI 2011

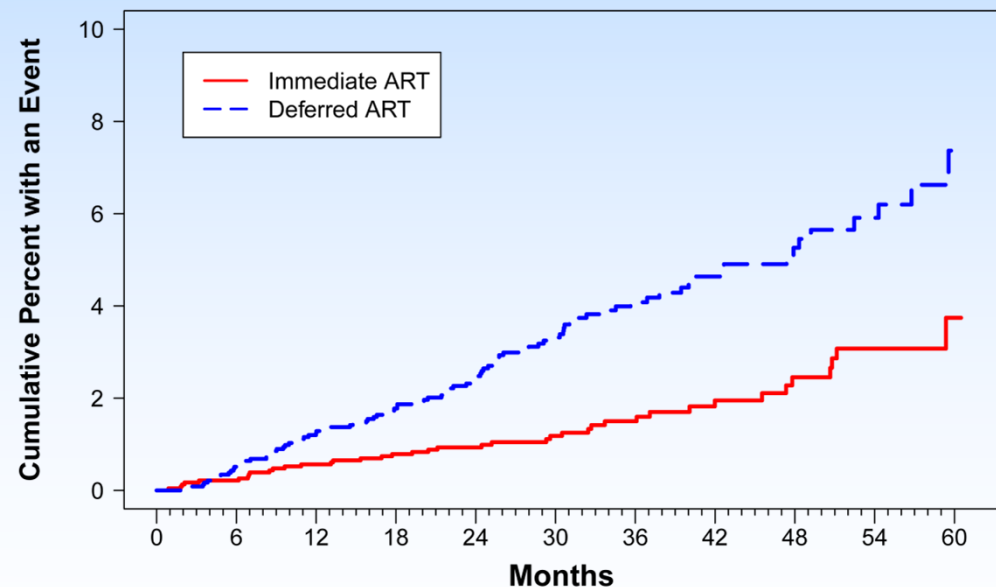
Borges Curr Opin HIV AIDS 2014



Background: START study; composite primary endpoint

	Immediate ART	Deferred ART
No. with Event (%)	42 (1.8%)	96 (4.1%)
Rate/100PY	0.60	1.38
HR (Imm/Def)	0.43 (95% CI: 0.30 to 0.62, p <0.001)	

	No. of Participants	
Type of event	Imm. ART	Def. ART
Serious AIDS	14	50
Serious non-AIDS	29	47
Total*	42	96



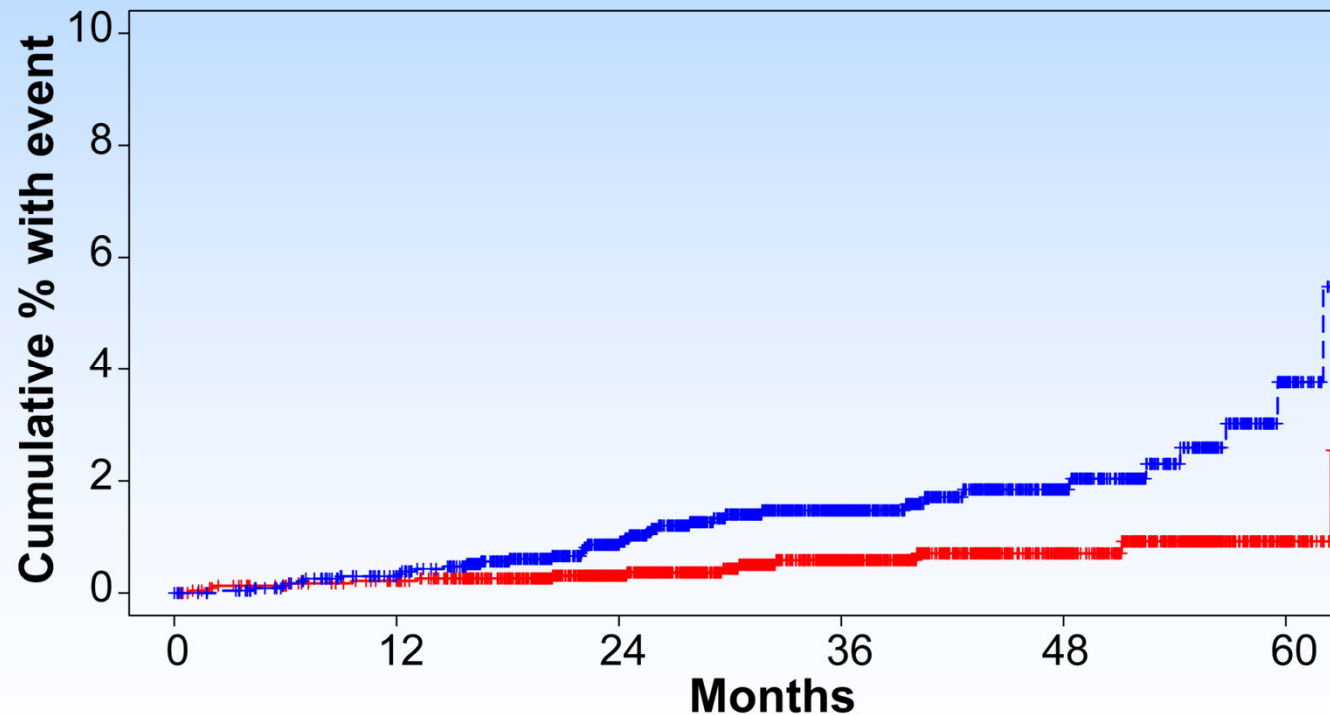
* One participant in each group had both a Serious AIDS and a Serious Non-AIDS Event

INSIGHT START Study Group NEJM 2015



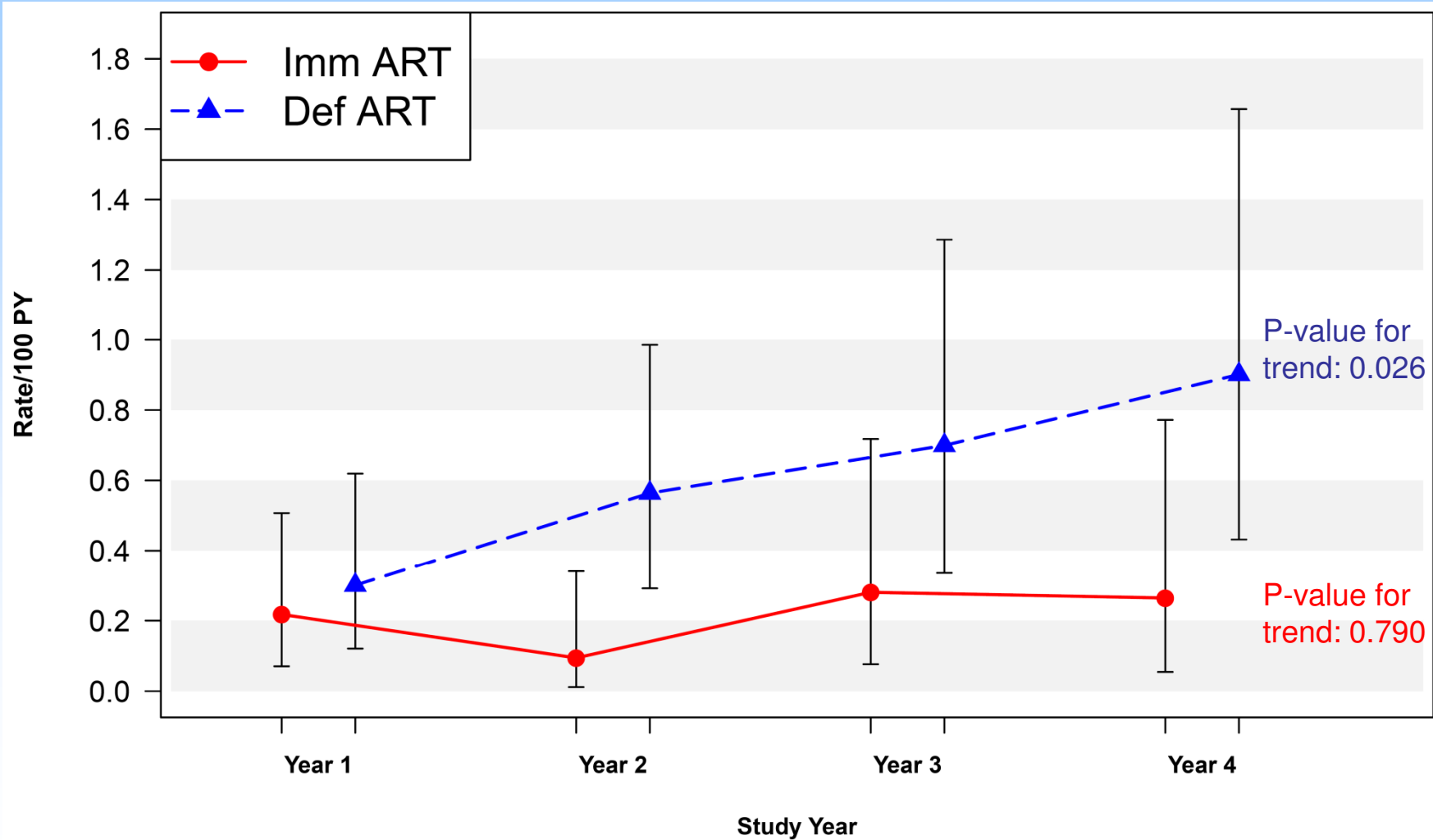
Background: Immediate ART reduces cancer risk

	Immediate ART	Deferred ART
No. with event	14	39
HR (Imm/Def)	0.36 (95%CI: 0.19 to 0.66, p=0.001)	



START study

Any Cancer Event Rates (95% CI) by Year of Follow-up



Methods

- Hypothesis: The reduction in cancer risk is higher for infection-related vs infection-unrelated cancers and is mainly driven by differences in CD4 counts and HIV RNA levels between the study arms
- Cancers were classified into infection-related and infection-unrelated after individual review of case report forms and source documentation
- Multivariable Cox models identified factors associated with infection-related and infection-unrelated cancers
- Cox models with a indicator for treatment group were adjusted sequentially for baseline covariates, cancer risk factors and HIV-specific variables

Results: Types of infection-related cancers by treatment group

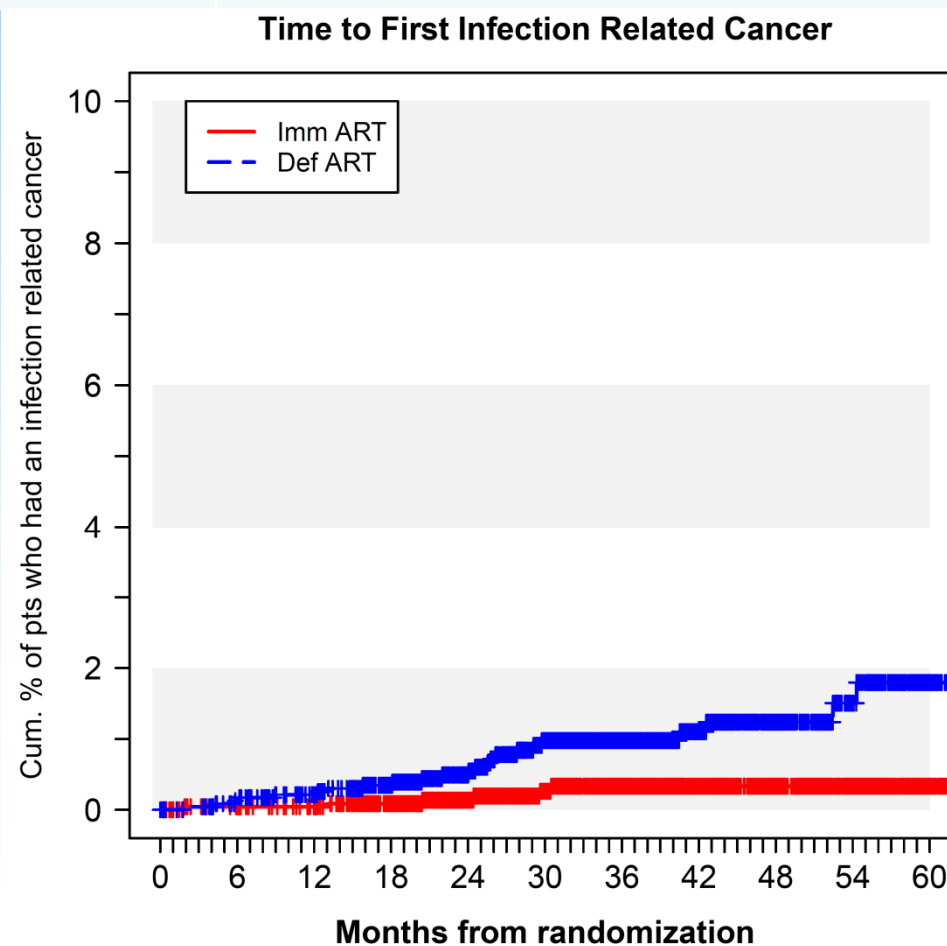
Infection-related	Immediate ART (n=6)	Deferred ART (n=23)
<i>Human herpes virus 8</i> Kaposi sarcoma	1	11
<i>Epstein-Barr virus</i> Non-Hodgkin lymphomas	2	9
Hodgkin lymphomas	1	1
<i>Human papilloma virus</i> Anal cancer	1	2
Cervical cancer	1	0

Results: Types of infection-unrelated cancers by treatment group

Infection-unrelated	Immediate ART (n=8)	Deferred ART (n=16)
Prostate	2	3
Lung	2	2
Testicular	0	2
Multiple myeloma	1	0
Fibrosarcoma	1	0
Breast	0	1
Bladder	1	0
Ureteral	0	1
Malignant melanoma	0	1
Myeloid leukemia	0	1
Thyroid	0	1
Leiomyosarcoma	0	1
Squamous cell carcinoma of the skin	1	0
Squamous cell carcinoma of the head & neck	0	1
Gastric adenocarcinoma	0	1
Liver	0	1

Results: Hazard ratio for infection-related cancer

	Immediate ART	Deferred ART
No. with event	6	23
HR (Imm/Def)	0.26 (95%CI: 0.11 to 0.64, p=0.003)	

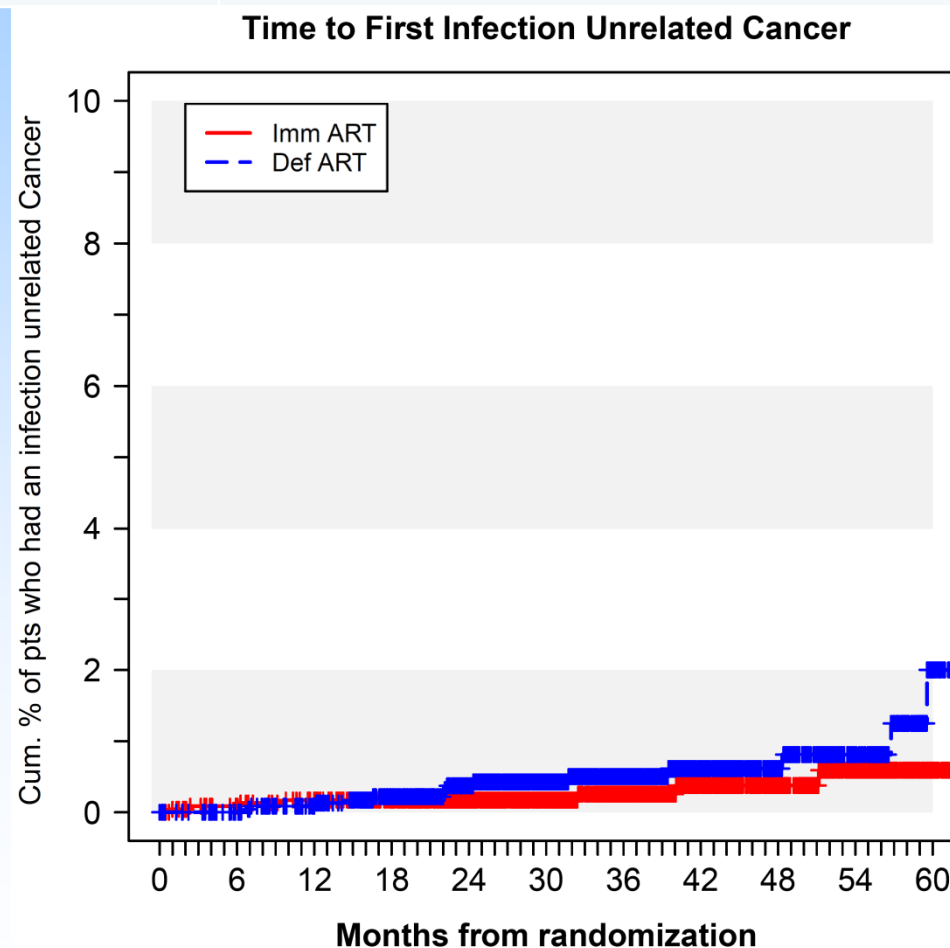


No. at risk:

Imm	2326	2302	2282	2168	1805	1441	1035	762	546	338	111
Def.	2359	2333	2296	2152	1822	1437	1040	743	532	343	106

Results: Hazard ratio for infection-unrelated cancer

	Immediate ART	Deferred ART
No. with event	8	16
HR (Imm/Def)	0.49 (95%CI: 0.21 to 1.15, p=0.103)	

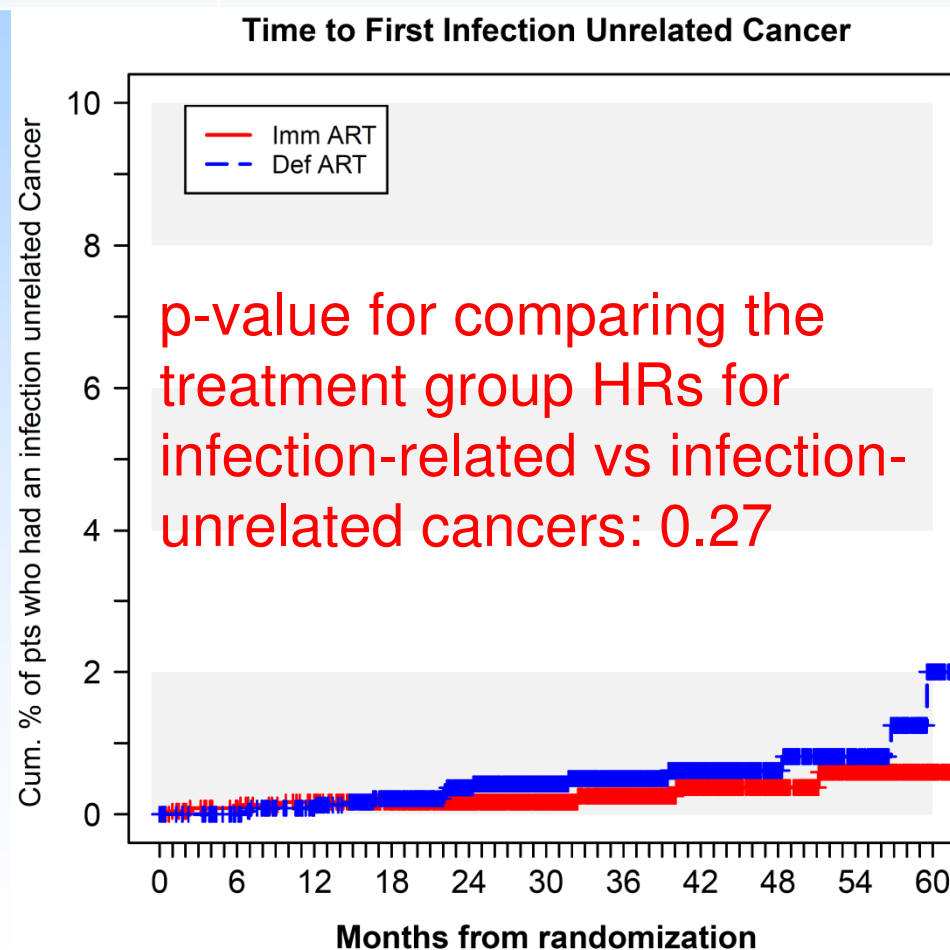


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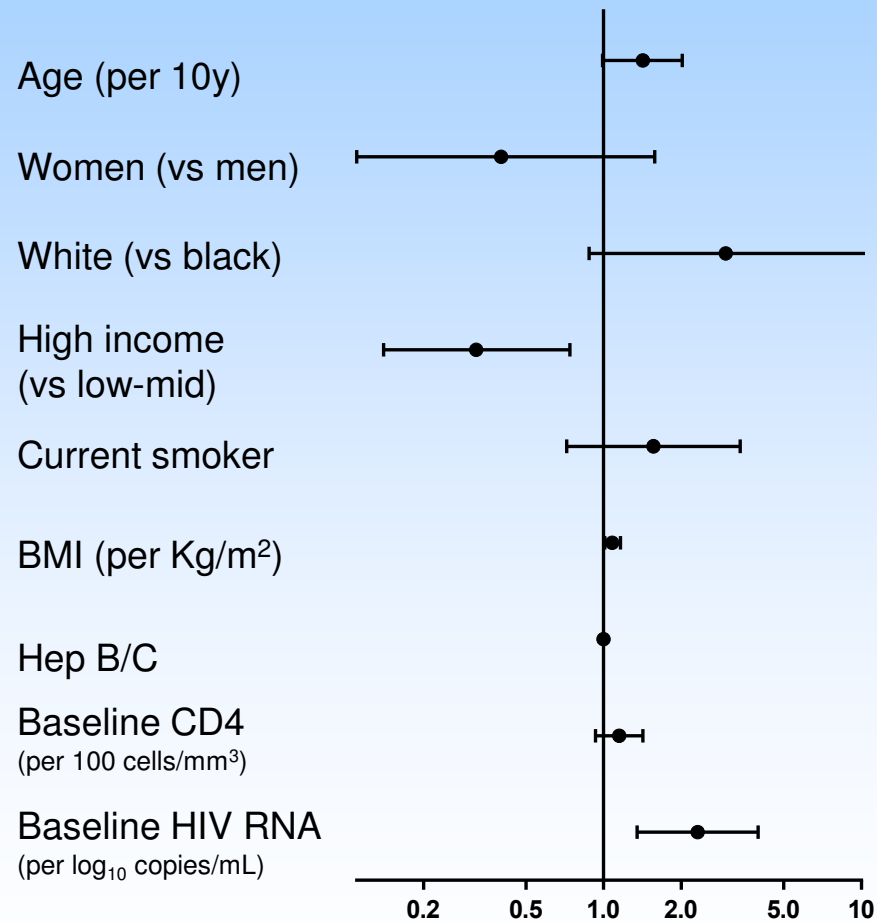


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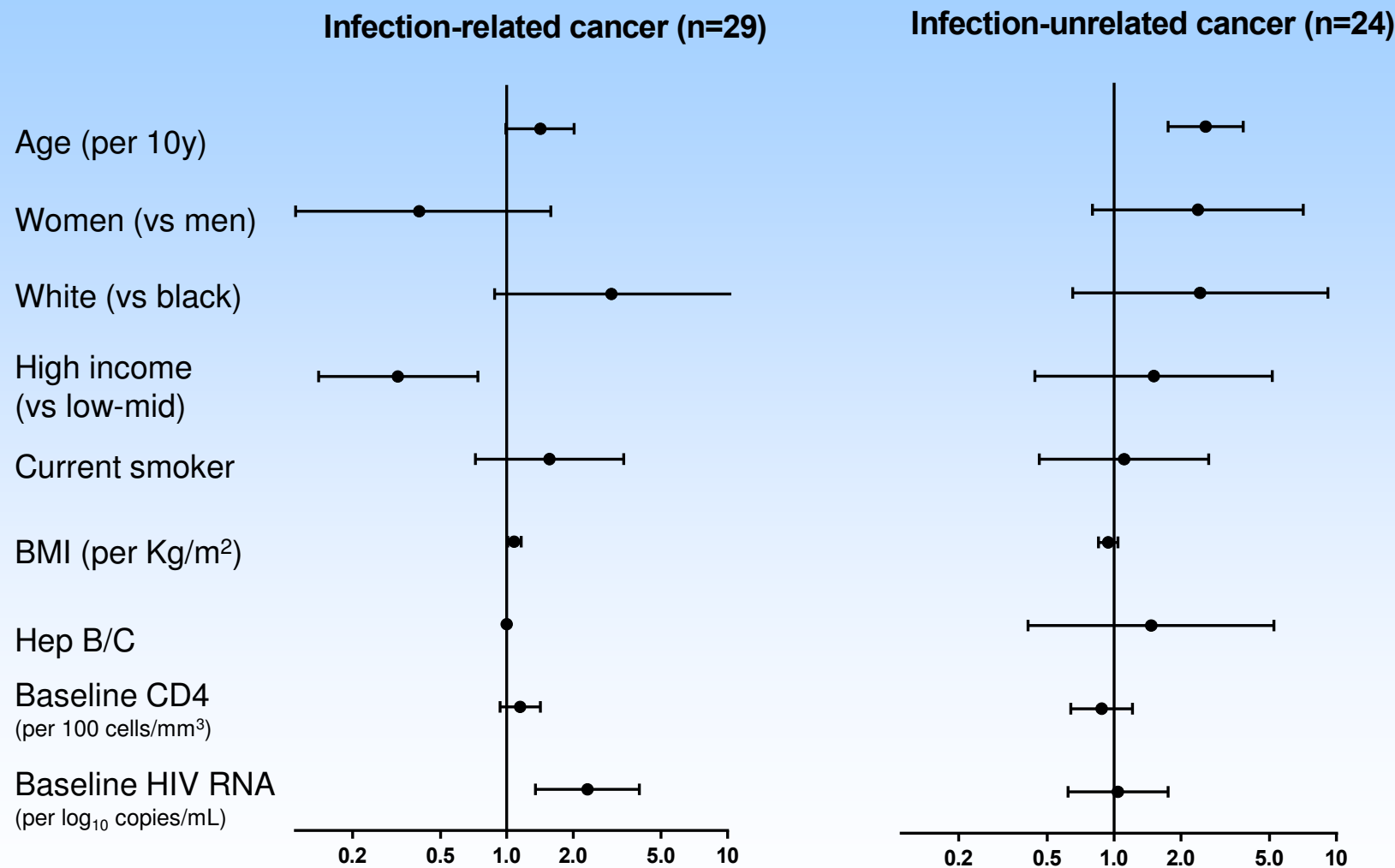
Results: Factors independently associated with infection-related and infection-unrelated cancers

Infection-related cancer (n=29)



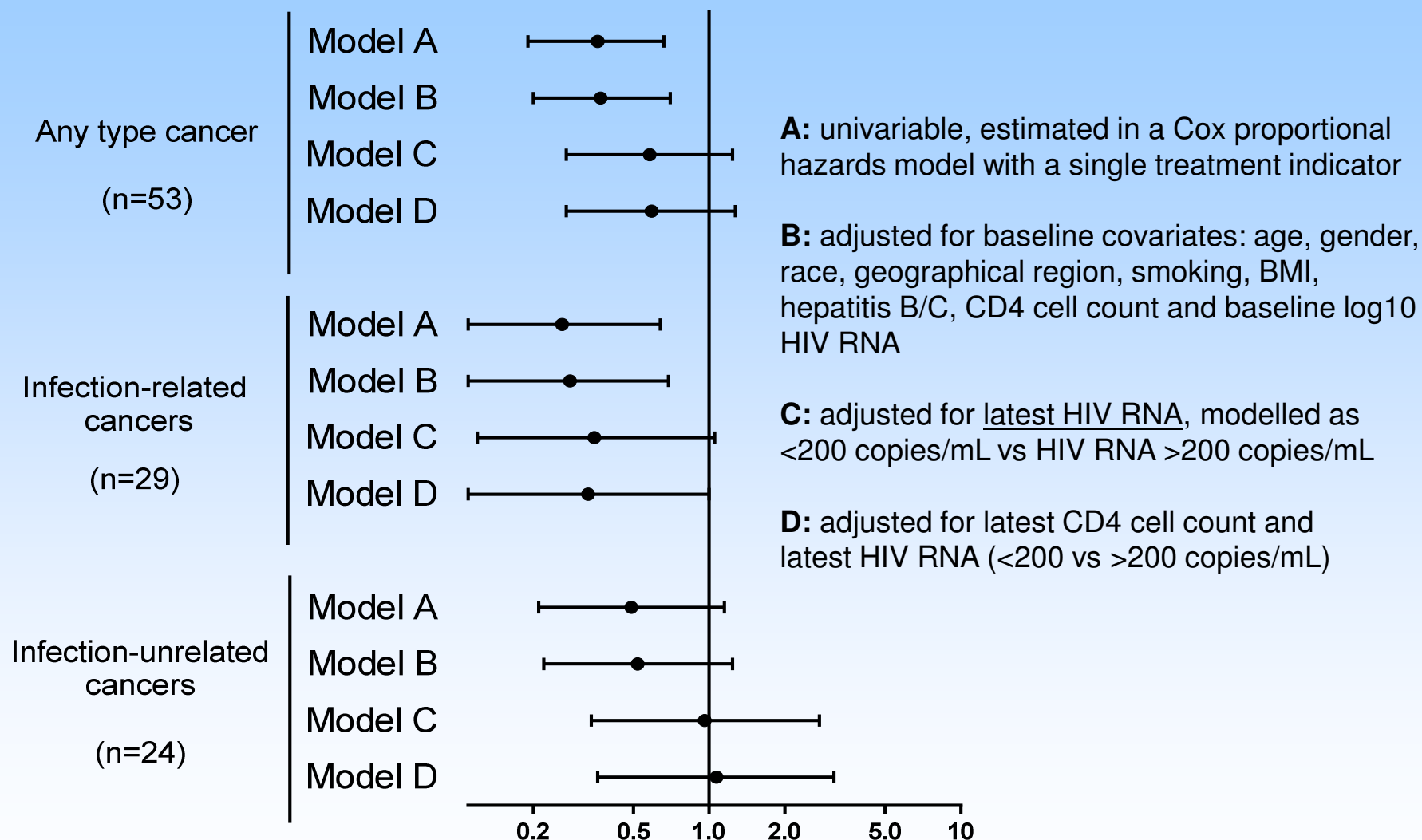
Hazards Ratios (95% CI) from unstratified Cox models adjusting for all variables listed: time to first event. Both treatment arms grouped (n=4,685)

Results: Factors independently associated with infection-related and infection-unrelated cancers



Hazards Ratios (95% CI) from unstratified Cox models adjusting for all variables listed: time to first event. Both treatment arms grouped (n=4,685)

Results: Immediate versus deferred ART initiation and the risk of any type cancer, infection-related and infection-unrelated cancers in the START study



Hazard ratios for cancer events: immediate versus deferred ART initiation;
START (N=4,685)

Conclusions

- Immediate ART initiation significantly reduces risk of infection-related cancer during HIV infection.
- Adjustment for latest HIV RNA level attenuated the HR (Imm/Def) for infection-unrelated cancers more than infection-related cancers.
- The benefit of immediate ART doesn't appear to be solely attributable to HIV RNA suppression and may also be mediated by other mechanisms, such as a curb on oncogenic virus coinfection and reduction of inflammation.
- Further research is needed to identify mediators of the benefit of immediate ART initiation in reducing cancer risk.

Acknowledgments

START Study Team

Protocol Team: James D Neaton (INSIGHT PI), Abdel G Babiker (cochair), Sean Emery (cochair), Fred M Gordin (cochair), Jens D Lundgren (cochair), Brian K Agan, Jose R Arribas, John Baxter, William Burman, David A Cooper, Richard T Davey Jr, Guy De La Rosa, Eileen T Denning, Greg Dore, Ezekiel Emanuel, Alexia Exarchos, Gerd Fätkenheuer, Linda Fischer, Hansjakob Furrer, Daniela C Gey, Birgit Grund, Sally Hodder, Bruno Hoen, Margaret A Johnson, Karin L Klingman, Alan Landay, Gregg Larson, Bruno Ledergerber, Eric Lefebvre, Sandra N Lehrman, Ana Martinez, Marisol Martinez-Tristani, Sue Meger, Ronald T Mitsuyasu, Amanda Mocroft, Jean-Michel Molina, David Munroe, Michael Norton, Ines M Otegui, Nick Paton, Sarah L Pett, Andrew Phillips, Deenan Pillay, Michael Proschan, Claire Rappoport, Peter Reiss, Jurgen Rockstroh, James F Rooney, Michael J Ross, Mauro Schechter, Siegfried Schwarze, Daniel Seekins, Shweta Sharma, Wendy Snowden, Jeff Tryon, Michael J Vjecha, Scott A Wegner, William Woodward.

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