HIV-Related Immune Suppression After Antiretroviral Therapy Predicts Risk of Non-Opportunistic Diseases:

Results from the FIRST study

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for the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA)

Background - 1
Changing HIV Morbidity and Mortality

Antiretroviral therapy (ART) drastically reduces morbidity and mortality

Traditional opportunistic diseases (OD) no longer cause most HIV deaths

‘Non-opportunistic’ (non-OD), end-organ diseases, are increasing in HIV patients

Background - 2
Non-Traditional Outcomes

In SMART, non-fatal and fatal non-opportunistic disease (non-OD) events increased with episodic ART

- **lower CD4 & higher HIV RNA may contribute**

In the D.A.D cohort, non-OD death rates increased with lower CD4+ counts

To date, most studies have focused on fatal non-OD outcomes

Research Question

Among HIV+ patients on ART, do lower CD4 levels contribute to risk of fatal, and non-fatal, diseases not traditionally considered opportunistic ('non-OD')?

FIRST Study Design and Follow-up

1,397 Participants Randomized

PI Strategy	NNRTI Strategy	3-class Strategy
PI + NRTIs (N=470)	NNRTI + NRTIs (N=463)	PI + NNRTI + NRTIs (N=464)

Demographic Characteristics	
Age	38
Women	21%
Non-white	74%

Median Follow-up

60 months

Methods

After ART initiation, clinical endpoints, CD4 count and HIV RNA obtained every 4 months

Hazard Ratios (HR) estimated from Cox models describe OD/non-OD event associations with time updated ('latest') CD4 count (pooled across treatment strategy)

Multivariate analyses adjusted for latest HIV RNA and baseline covariates: age, gender, race, IDU, prior AIDS, hepatitis B/C

Outcomes of Interest: Fatal & Non-Fatal Clinical Events

- **OD = Opportunistic Diseases**

  Adapted from 1993 CDC surveillance criteria for AIDS

- **Non-OD = Non-opportunistic Diseases**

  Liver = cirrhosis, grade 4 elevated liver enzymes (>10x ULN), death from liver failure

  CV (cardiovascular) = myocardial infarction, stroke, coronary intervention, death from chronic ASCVD

  Renal = renal insufficiency, end-stage renal disease, death from chronic kidney disease

  Cancer (non-OD) = all cancers excluding KS, lymphoma and invasive cervical cancer

CD4 Count and HIV RNA Levels During FIRST

	Time Point	CD4 Count Median (cells/μl)	HIV RNA Level Median (log10 copies/ml)	HIV RNA Level % <50 (copies/ml)
FIRST Cohort N=1397	Baseline	**163**	**5.2**	**0.0%**
	Month 32	**399**	**<1.7**	**55%**
OD N=226	Latest	**63**	**4.9**	**16%**
Non-OD N=166	Latest	**239**	**3.1**	**30%**

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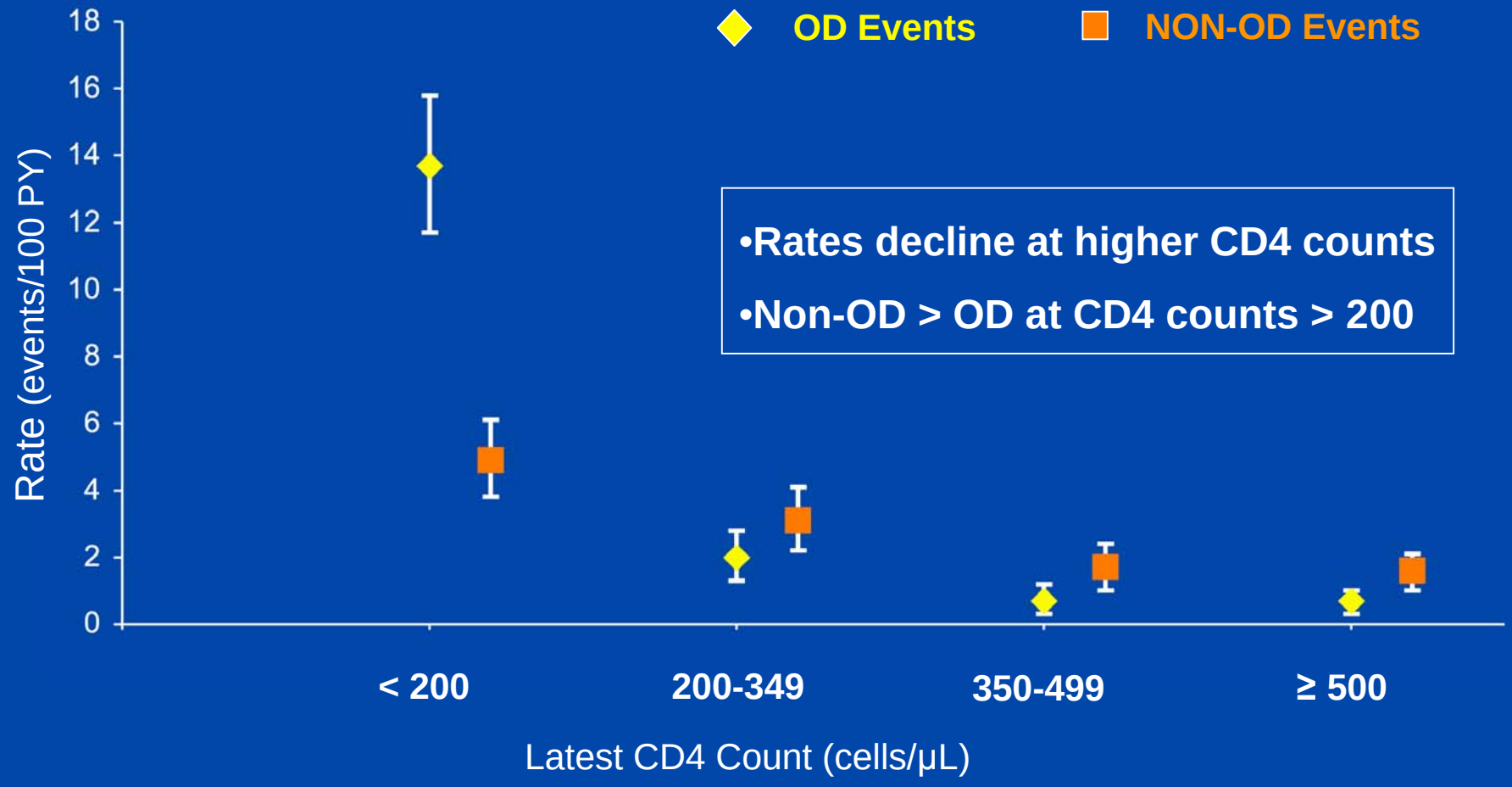
Event Rate by Latest CD4

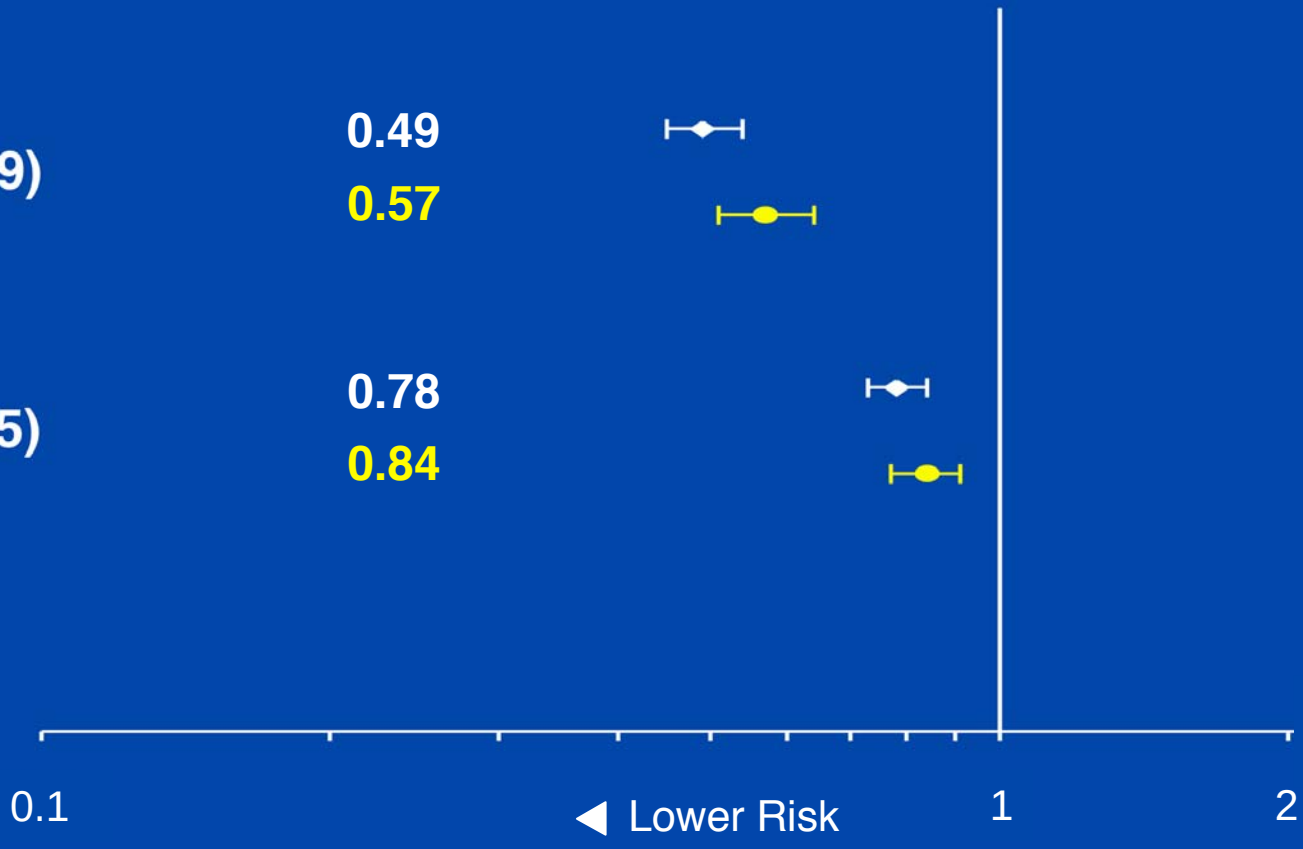


Person-Years:	1288 | 1442	1324 | 1343	1238 | 1232	1940 | 1900

* Error bars represent 95% CL

Event Risk Predicted by Latest CD4

Category	# Events (Deaths)	*Hazard Ratio (95% CI) per 100 cell higher CD4 count
OD	226 (89)	0.49
		0.57
Non-OD	166 (25)	0.78
		0.84



◆ Univariate

● Multivariate

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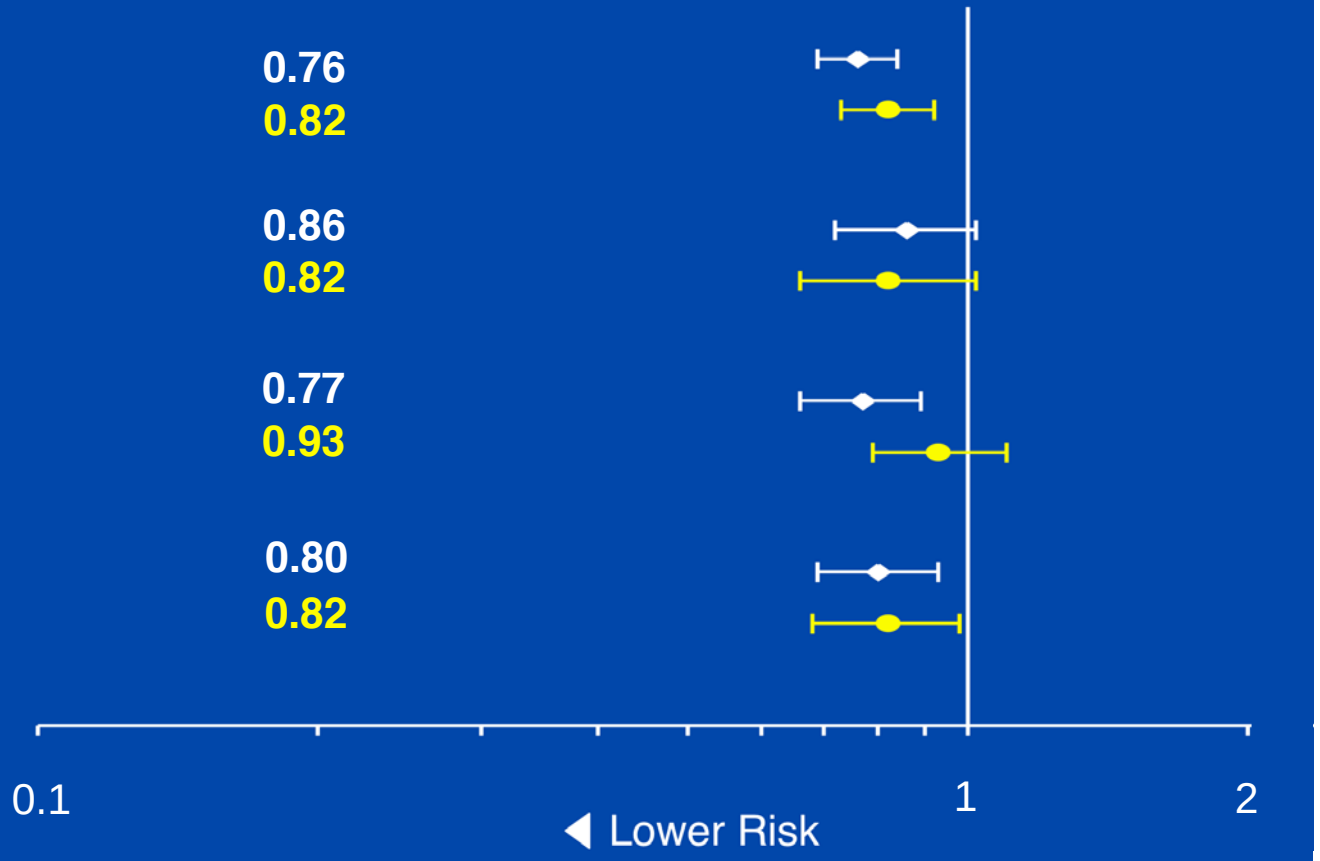
‘Non-OD’ Event Risk Predicted by Latest CD4

Category	# Events	*Hazard Ratio (95% CI) per 100 cell higher CD4 count
Liver	84	0.76 0.82
CV	21	0.86 0.82
Renal	38	0.77 0.93
Cancer (Non-OD)	32	0.80 0.82



◆ Univariate

● Multivariate

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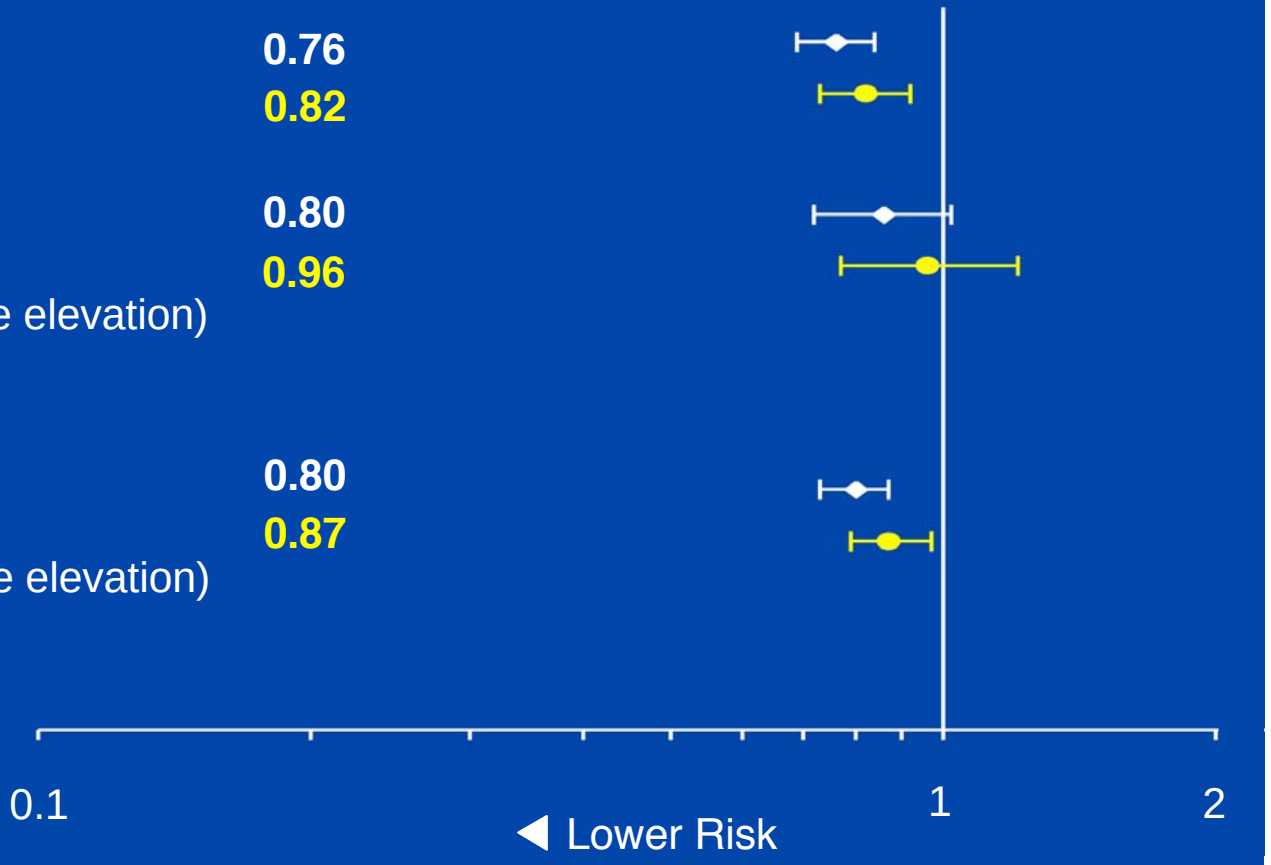
Liver Related Event Risk

Category	# Events	*Hazard Ratio (95% CI) per 100 cell higher CD4 count
All Liver	84	0.76 0.82
Liver (excluding grade4 liver enzyme elevation)	14	0.80 0.96
Non-OD (excluding grade4 liver enzyme elevation)	99	0.80 0.87



◆ Univariate

● Multivariate

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Limitations

Inadequate power to reliably estimate risk of *individual* non-OD events

- **Increased risk of liver, CV, renal and cancer (non-OD) events at lower CD4 counts**

FIRST cohort had advanced disease (low CD4) at initiation of ART

- **Limits risk assessment at higher CD4 counts**

Summary

Rates of non-OD decline at higher CD4 counts, though less than for traditional OD

Liver, CV, renal and cancer events account for more morbidity and mortality than OD events at CD4 counts >200

Latest CD4 count predicts risk of non-OD events after adjusting for other factors

Acknowledgements

1397 Study Participants

CPCRA Investigators

Mentors

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- Donald Abrams
- Michael Silverberg
- Winston Cavert