A frailty-related phenotype and death: Investigating inflammatory markers as potential mediators among men with HIV in the modern HAART era

Interleukin 6 (IL-6)
C-reactive protein (CRP)
Tumor necrosis factor-receptor 2 (TNFαR2)

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Derek Ng, PhD ScM
Assistant Scientist
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
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Co-authors and Disclosures

- Kristine M. Erlandson (University of Colorado)
- Lisa P. Jacobson (Johns Hopkins Bloomberg School of Public Health)
- Joseph Margolick (Johns Hopkins Bloomberg School of Public Health)
- Adrian S. Dobs (Johns Hopkins University School of Medicine)
- Frank J. Palella (Northwestern University Medical Center)
- Jordan E. Lake (UCLA Medical Center)
- Lawrence A. Kingsley (University of Pittsburgh)
- Todd T. Brown (Johns Hopkins University School of Medicine)

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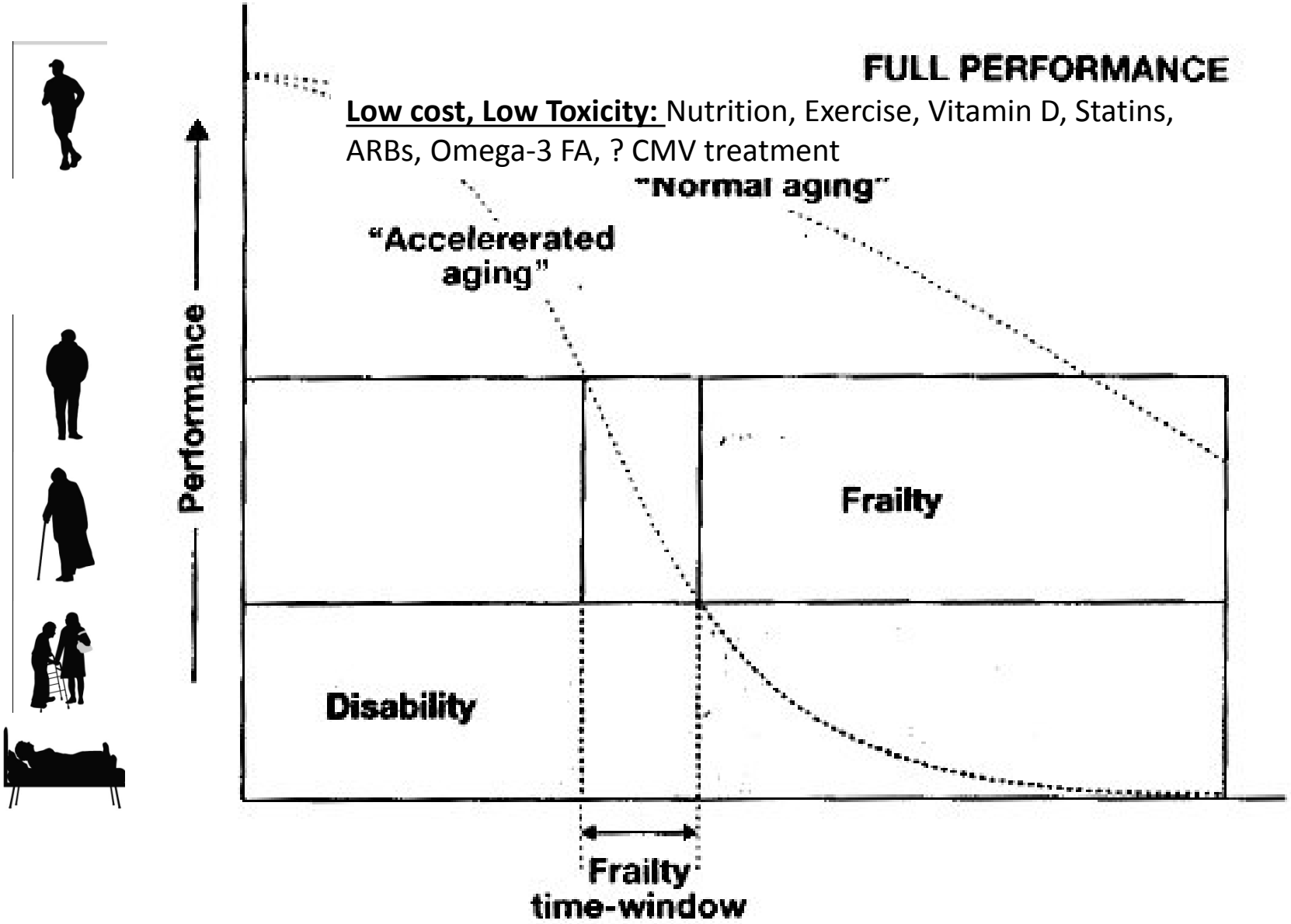
Frailty and frailty-related phenotype

- **Frailty is a syndrome associated with aging and death, including loss of muscle mass, decreased energy and reserves resulting in weight loss, and a decline in strength**
- **Frailty related phenotype (FRP) is a self-reported indicator**
- **FRP is defined as the presence of at least 3 of 4 self-reported characteristics:**
  - ❑ **Unintentional weight loss of 10+ lbs in past year**
  - ❑ **Work/activity difficulty due to physical health**
  - ❑ **Health limits walking several blocks**
  - ❑ **Health limits vigorous activities**
- **Closely related to Frailty Phenotype but without quantitative walk speed test and grip strength test**



Low cost, Low Toxicity: Nutrition, Exercise, Vitamin D, Statins, ARBs, Omega-3 FA, ? CMV treatment

Slide source: Todd T. Brown

FRP among men with HIV

- **HIV infection is associated with an earlier occurrence of FRP**
  - **3.4% of men age 55 with ≤ 4 years HIV infection have FRP; the same as uninfected men aged 65+ years in pre-HAART era[a]**
- **FRP is associated with decreased CD4+ T-cells (likely caused by diminished immune function)[b]**
- **FRP prior to HAART initiation is a predictor of AIDS/death (adjusted HR= 3.8)[c]**
- **FRP is associated with hormonal dysfunction and higher levels of inflammation (Erlandson et al., in progress)**

[a] Desquilbet L, et al. **HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty**. *J. Gerontol. A Biol. Sci. Med. Sci.* 62: 1279–1286, 2007.

[b] Desquilbet L, et al. **Relationship between a frailty-related phenotype and progressive deterioration of the immune system in HIV-infected men**. *J Acquir Immune Defic Syndr* 50: 299–306, 2009.

[C] Desquilbet L, et al. **A frailty-related phenotype before HAART initiation as an independent risk factor for AIDS or death after HAART among HIV-infected men**. *J. Gerontol. A Biol. Sci. Med. Sci.* 66: 1030–1038, 2011.

FRP and inflammatory dysfunction

- **FRP has been linked to abnormal hormone levels and markers of inflammation among men with HIV**
  - **DHEA (↓), free testosterone (↓), HOMA-IR (↑)**
  - **IL-6 (↑), CRP (↑), TNFαR2 (↑),**
- **Purpose of this study is to investigate the extent to which the FRP and death relationship is mediated by inflammatory markers, a potentially modifiable factor in HIV management**

Data

- Multicenter AIDS Cohort Study (MACS)
- All HIV infected men receiving HAART
  - In the modern HAART era (after January 1, 2001 through March 31, 2010)
  - ≥ 50 years of age (n= 761 contributing 8277 person-visits of FRP status)
- Inflammatory markers
  - IL-6 from ARRA1 substudy (central laboratory)
  - CRP (local laboratory)
  - TNFαR2 from ARRA1 substudy (central laboratory)

Missing inflammatory marker data

- **761 men contributed 8277 person-visits for FRP**

	IL-6	CRP	TNFαR2
Person-visits	1468	1471	1473
ICC	0.400	0.522	0.726

- **Multiple imputation to account for missing data**
  - **Assumed MAR conditional on CD4, detectable VL, age, FRP, outcome (death), age at infection, duration of infection, duration from ART, previous AIDS diagnosis, nadir CD4+, recruitment cohort**

Data structure and analysis

- **Primary exposure: frailty-related phenotype (FRP; absorbent exposure)**
- **Primary outcome: all-cause mortality (death, censored 0.75 years after last visit)**
- **Potential mediator: inflammatory markers (iL6, CRP, TNFαR2)**
- **Confounders: detectable viral load, CD4+ < 350, black race, HCV infection, BMI categories**
- **Time updating inflammatory markers and confounders**
- **Time scale is age after 50 years (incorporating late entries)**
- **Analysis:**
  - **Kaplan-Meier plots**
  - **Cox proportional hazards model with FRP and biomarkers**

Baseline characteristics

Characteristic	First MACS visit after age 50 N= 761 (39 FRP prevalent)	First FRP visit N= 173
Age, years	50.6 [50.3, 53.7]	54.6 [52.0, 59.3]
Black race	25% (190)	29% (51)
Overweight	32% (243)	20% (19)
Obese	11% (80)	13% (22)
Hypertension	52% (393)	68% (118)
Diabetes	11% (87)	20% (34)
Hepatitis C infection	12% (87)	22% (35)
eGFR < 60 ml/min	8% (44)	19% (27)
Current smoker	27% (203)	34% (58)

Median [25th percentile, 75th percentile] or % (n)

Baseline characteristics, cont.

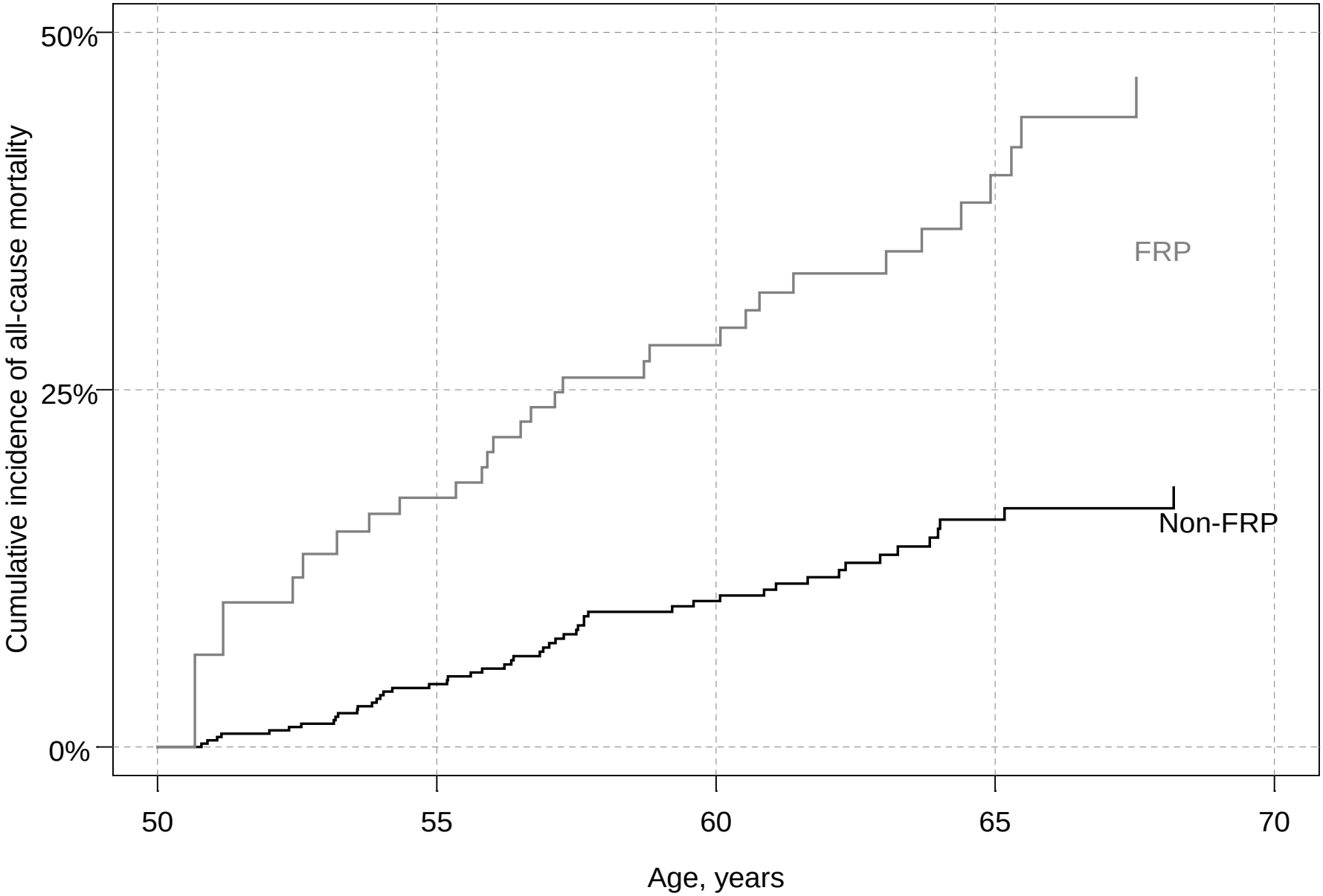
Characteristic	First MACS visit after age 50 N= 761 (39 FRP prevalent)	First FRP visit N= 173
Years since HAART initiation, years	6.4 [4.4, 10.6]	9.5 [5.9, 12.1]
Nadir CD4+ count/µL	269 [149, 374]	215 [113, 378]
Nadir CD4+ < 350/µL	70% (521)	72 %(123)
Current CD4+ count/µL	513 [336, 697]	443 [277, 650]
Current CD4+ < 350/µL	26% (163)	35% (45)
Detectable viral load	33% (207)	36% (47)
Previous AIDS diagnosis	17% (133)	28% (49)
Any FRP	23% (173)	NA
Deaths	11% (84)	20% (35)

Median [25th percentile, 75th percentile] or % (n)

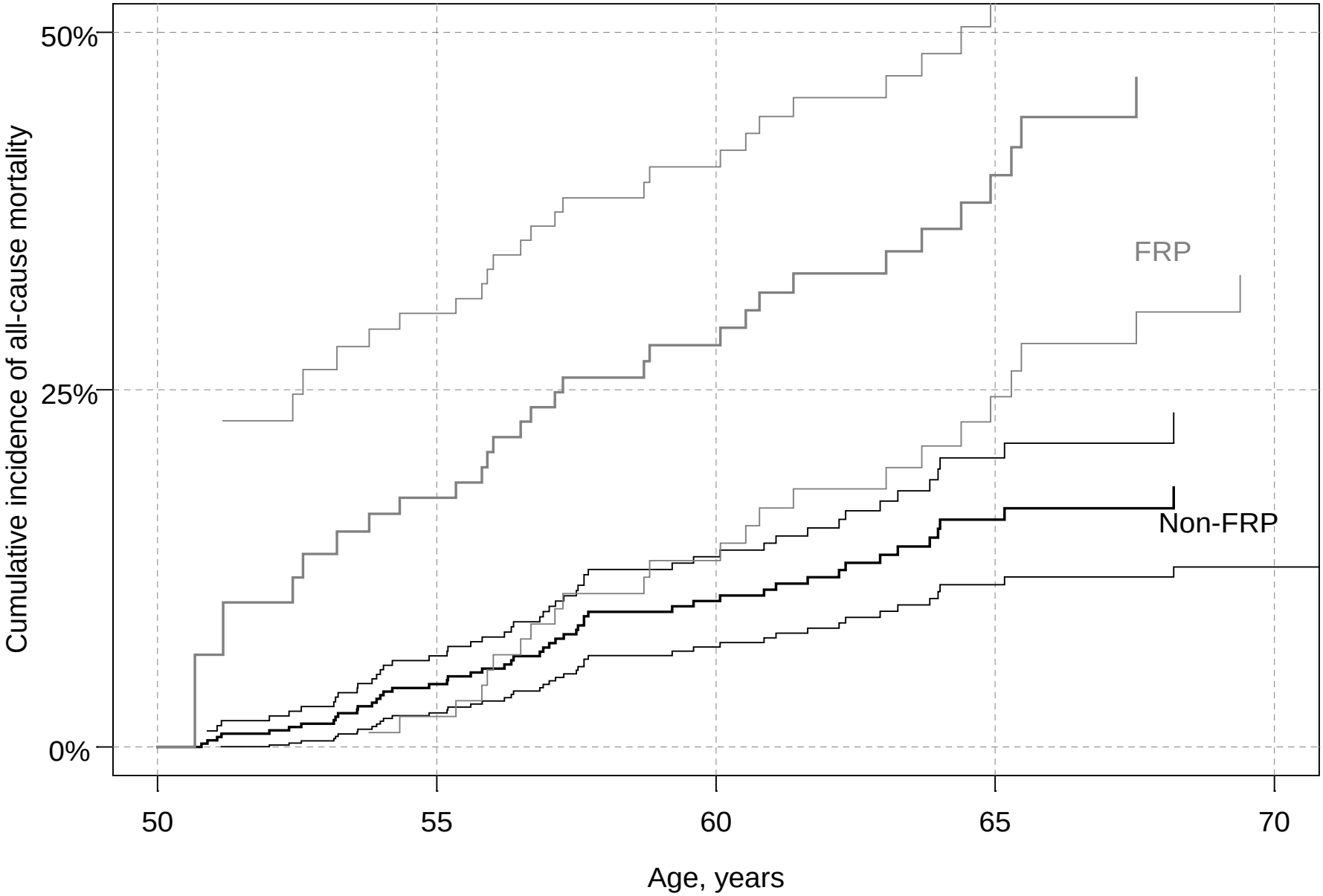
Characteristics of FRP and death

	FRP free n= 588	FRP n= 173
Number of visits reporting FRP		
1	NA	16% (27)
2	NA	6% (11)
3	NA	8% (14)
4+	NA	70% (121)
Deaths	8% (49)	20% (35)
AIDS-related death	3% (17)	7% (12)
Non-AIDS-related death	4% (26)	7% (13)
Unknown cause of death	1% (6)	5% (10)

Kaplan-Meier of all cause mortality, by FRP status



Kaplan-Meier of all cause mortality, by FRP status (95%CI)



Comparison of inflammatory markers, by FRP status

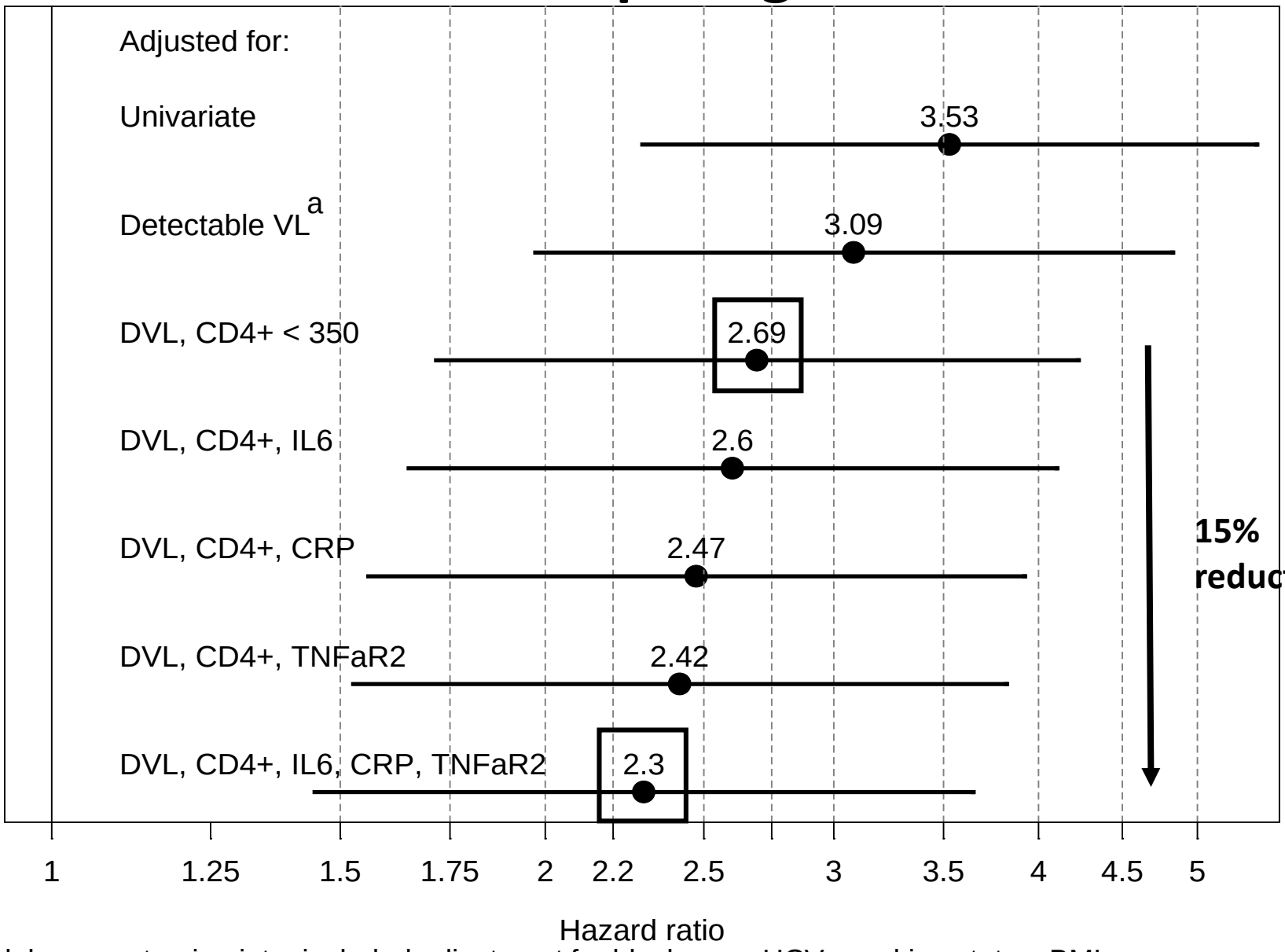
- **Linear regression of inflammatory markers in the log scale with an indicator for FRP (absorbent state)**
- **Participant contributes to FRP-free prior to incident FRP**
- **GEE to account for repeated measures**
- **Multiple imputation to account for missing data**

Inflammatory marker	**FRP-free** **N= 588** **Estimate (95%CI)**	**FRP** **N= 173** **Estimate (95%CI)**
IL-6	1.35 (1.26, 1.44)	**+34% (+15%, + 56%)**
CRP	1.60 (1.46, 1.75)	**+26% (+1%, +57%)**
TNFaR2	3007 (2864, 3158)	**+15% (+5%, +25%)**

Cox models

- Cox models to summarize the risk associated with FRP
- Age after 50 years as the time scale (late entries)
- Compare univariate relative hazard to relative hazards adjusted for:
  - Detectable viral load, black race, smoking status, HCV infection, BMI
  - CD4+ cell count <350
  - DVL, CD4+, IL-6 (<0.6pg/mL, ≥0.6 and < 2; ≥2pg/ml)
  - DVL, CD4+, CRP (<0.6mg/L, ≥0.6 and < 3.5; ≥3.5mg/L)
  - DVL, CD4+, TNF-aR2 (<2000pg/mL, ≥2000 and < 4000; ≥4000pg/mL)
  - DVL, CD4+, IL-6, CRP, TNF-aR2
- Decreasing HR with inclusion of inflammatory markers suggest role of (at least partial) mediation of the effect of FRP on mortality

Relative hazards comparing FRP to FRP-free



[a] All models, except univariate, included adjustment for black race, HCV, smoking status, BMI

Conclusions

- **FRP is strongly associated with death, including with adjustment for CD4+ cell count and detectable viral load and other confounders**
- **Inflammatory markers IL-6 and CRP may mediate the effect of FRP to a small degree**
- **Systemic inflammation may play a modest role in the FRP and mortality relationship**
- **Efforts to decrease inflammation in ART-treated HIV-infected persons with frailty may only have a marginal benefit on adverse outcomes**

Comparison of inflammatory markers, by FRP status, complete data

- **Linear regression of inflammatory markers in the log scale with an indicator for FRP (absorbent)**
- **Participant contributes to FRP-free prior to incident FRP**
- **GEE to account for repeated measures**
- **Complete case analysis**

Inflammatory marker	**FRP-free N= 588**	**FRP N= 173**
IL-6	1.28 (1.19, 1.37)	**+39% (+14%, +71%)**
CRP	1.58 (1.43, 1.74)	**+36% (+.3%, +83%)**
TNFaR2	3076 (2954, 3202)	**+22% (+9%, +37%)**