Among African HIV-infected patients with Kaposi's sarcoma, do plasma concentrations of interleukin 6 at antiretroviral therapy initiation predict subsequent mortality?

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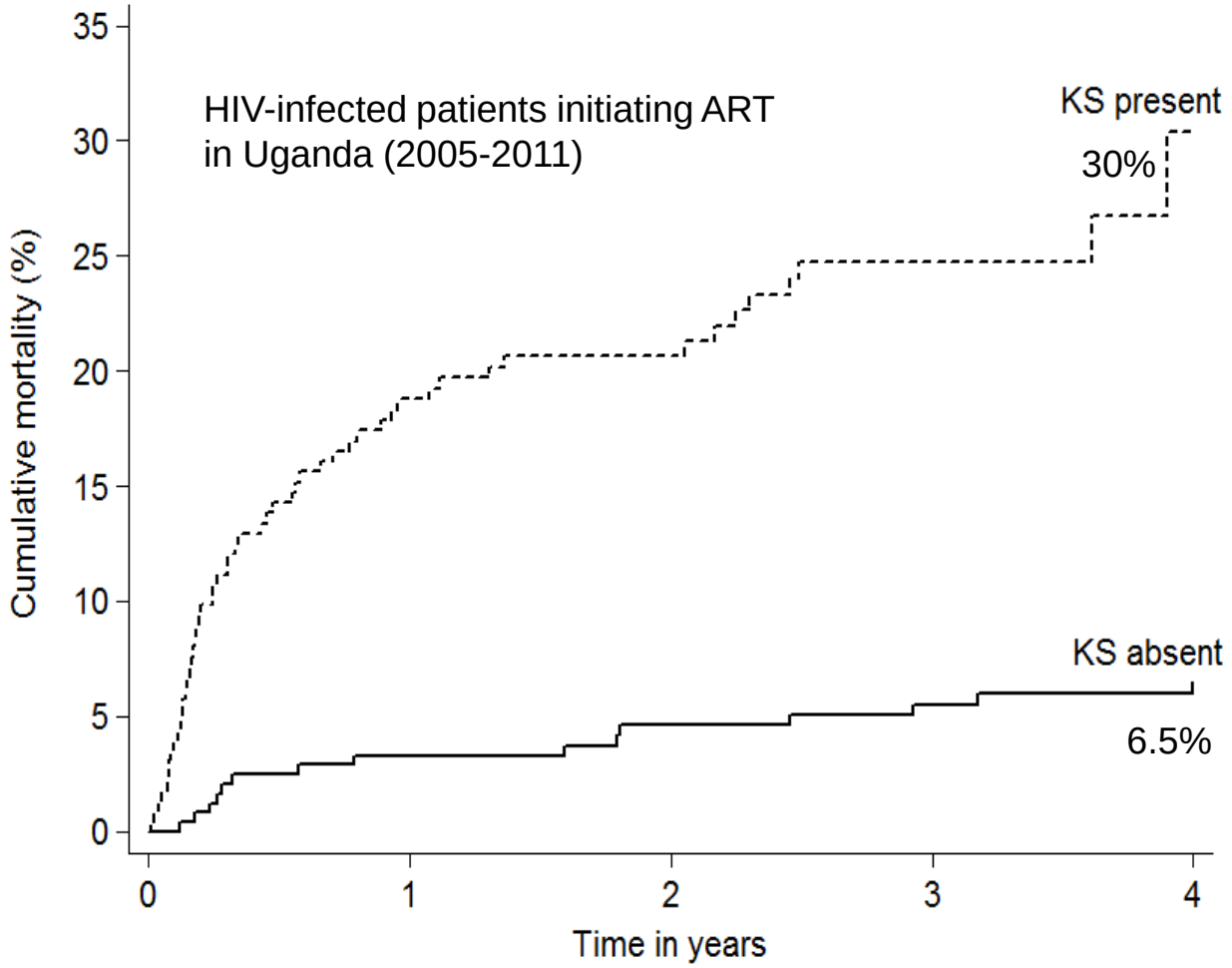
In sub-Saharan Africa, HIV-infected patients with KS initiating ART have excess mortality



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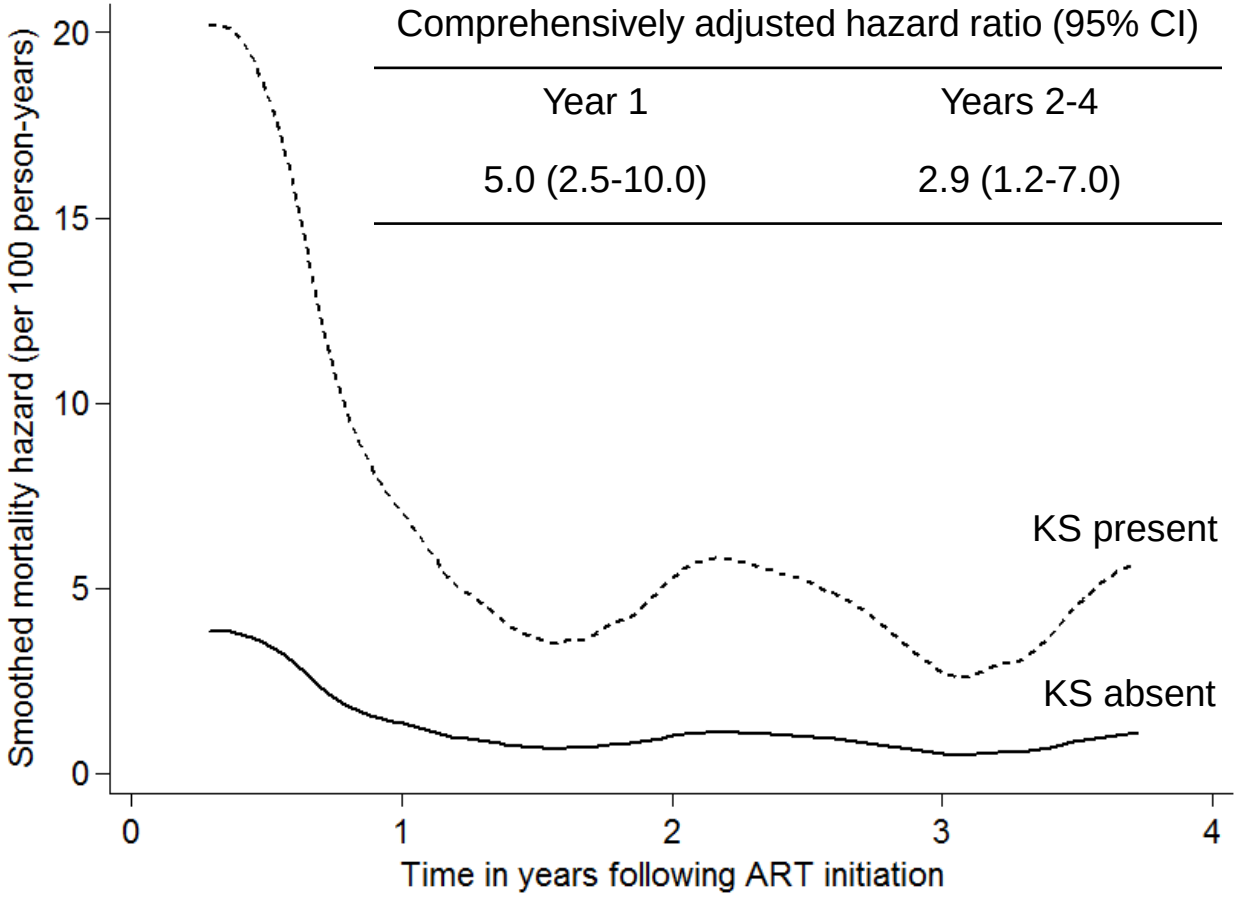
Mortality hazard is highest immediately following ART initiation and decreases thereafter



Asiimwe et. al., CROI 2014

Why might patients with KS die immediately after initiating ART; and how can we determine the cause?

Mechanism	Suspected entity	Nature of instrument	Suggested instrument	Hypothetical patterns	Intervention
Adverse response to ART with propensity to act immediately but not later	IRIS	Inflammatory biomarker	Interleukin-6 (IL-6)	Elevated or normal pre-ART, levels increase post-ART	Add anti-inflammatory prophylaxis to ART, Treat IRIS
Mortality is already high before ART initiation; ART just needs time to work	Advanced KS/HIV at ART initiation	Inflammatory/ HIV /KS markers	Viral load, IL-6, KSHV DNA, HMGB1	Elevated pre-ART, levels decrease post-ART	Earlier diagnosis of KS
	Sepsis	Biomarker of microbial translocation	LPS, Soluble CD14, D-Dimer	Elevated pre-ART, levels decrease post-ART	Add antibiotic prophylaxis to ART
	Pre-ART KSAID	Inflammatory biomarker	IL-6, KT ratio, HMGB1	Elevated pre-ART, levels decrease post-ART	Earlier diagnosis of KS, and anti-inflammatories to ART

IRIS = Immune reconstitution inflammatory syndrome, LPS = lipopolysaccharide, K/T ratio = kynurenine to tryptophan ratio, HMGB1 = High mobility group box 1, KSAID = unknown KS-associated inflammatory disorder

Previous studies

Author	Population	Outcome	Predictor and findings
Letang, 2013	436 ART initiators with KS, 221 UK, 215 SSA	IRIS	Advanced KS (T1), AHR, 3.0 (1.3-7.0) Viral load ≥5 log10 copies/ml, 2.1 (1.3-2.3) Being on ART + KS-specific chemo protective, 0.33 (0.12-0.93)
		Mortality (median follow-up = 8 months)	KS IRIS versus no, 33% vs 11%, unadjusted HR 19.2 (7.6-48.6)
Boulware, 2011	189 ART initiators N with KS small (3)	IRIS	Baseline IL-6 concentrations , AOR, 2.0 (0.9-4.5) 1 month post-ART, AOR, 11.5 (2.1-62.8)
		1 year mortality	Baseline IL-6 concentrations, AOR, 1.8 (1.1-2.7) 1-month post-ART, 4.9 (2.2-10.8)

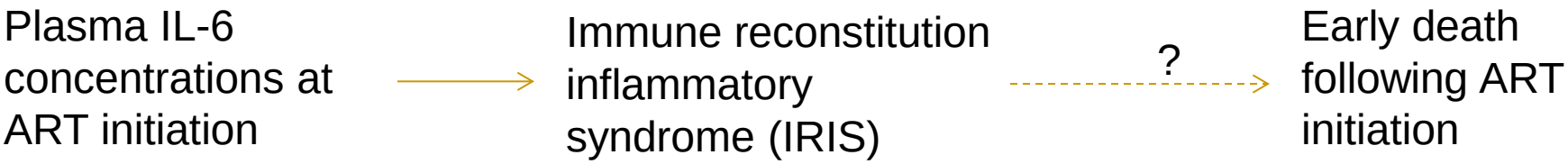
Summary: plasma IL-6 concentrations may predict IRIS, and both IL-6 and IRIS predict early death after ART initiation. KS-specific studies measuring IL-6 are lacking.

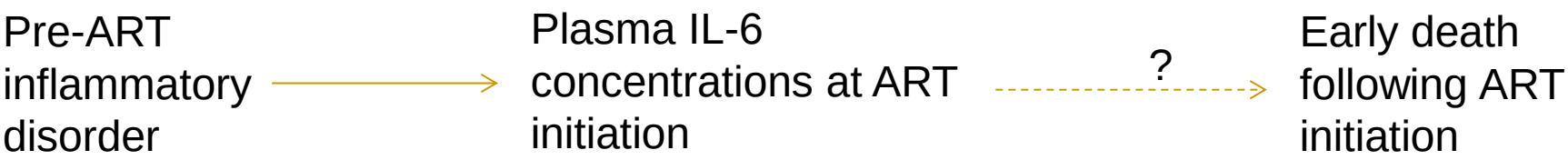
Study population

Study feature/activity	Description
Source	Antiretroviral for KS (ARKS) clinical trial (Uganda)
N	224
Enrollment period	2007 - 2011
Inclusion	Biopsy-confirmed KS, no urgent chemo indications
Exclusion	Other cancers, ongoing OIs, ongoing fevers
ART regimens	TDF/FTC + a PI or EFV

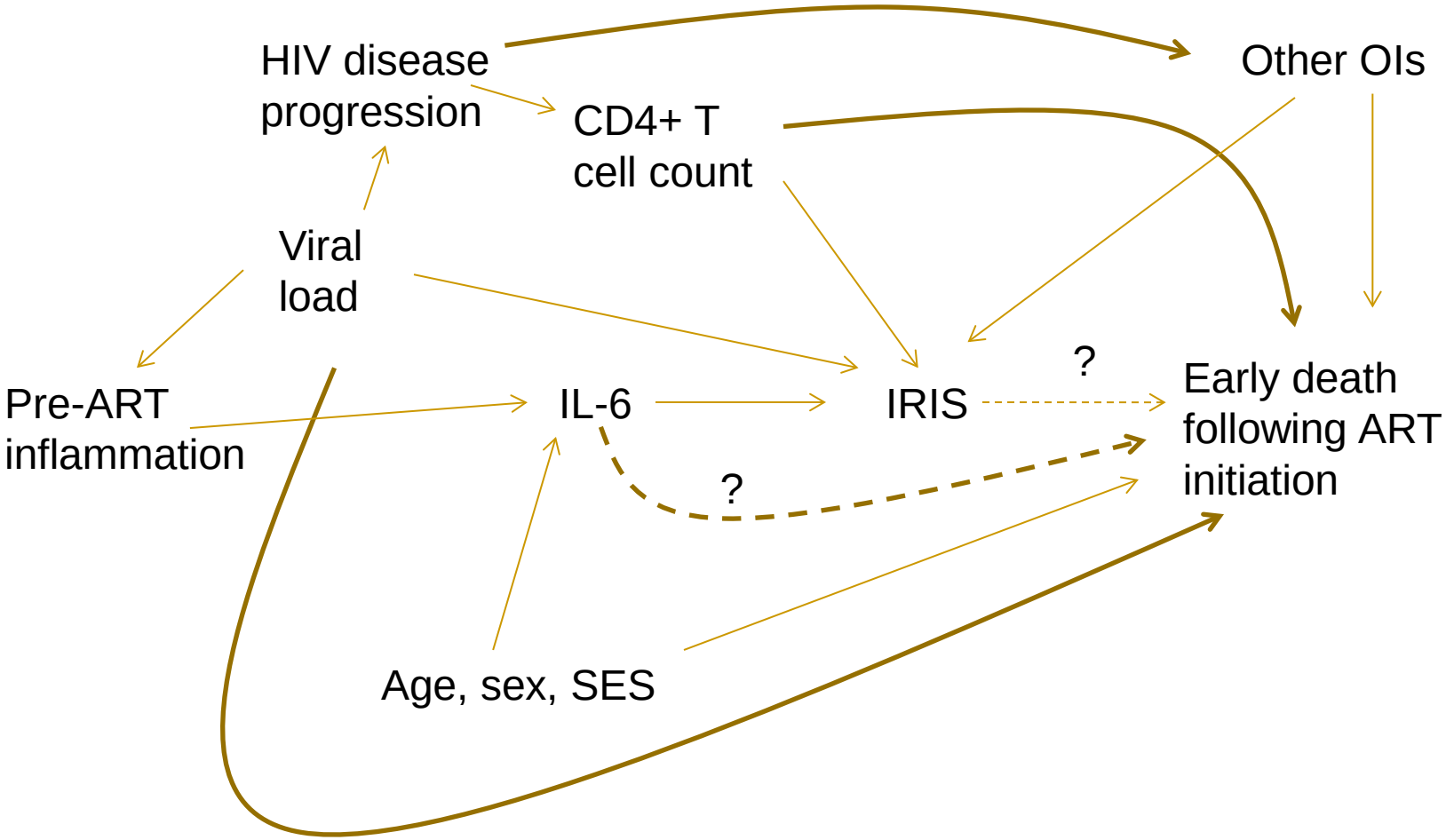
TDF = Tenofovir, FTC = Emtricitabine, PI = Protease inhibitor, EFV = Efavirenz

Does plasma IL-6 concentration at ART initiation predict early death after ART initiation?





Probable DAG



Question: Elevated IL-6 may predict death because it is a marker of pre-ART inflammation (unmeasured) or because it is a predictor of IRIS (also unmeasured). How can we draw this DAG in a more acceptable way?