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Immune reconstitution inflammatory syndrome after commencing antiretroviral therapy in HIV patients with severe immunodeficiency

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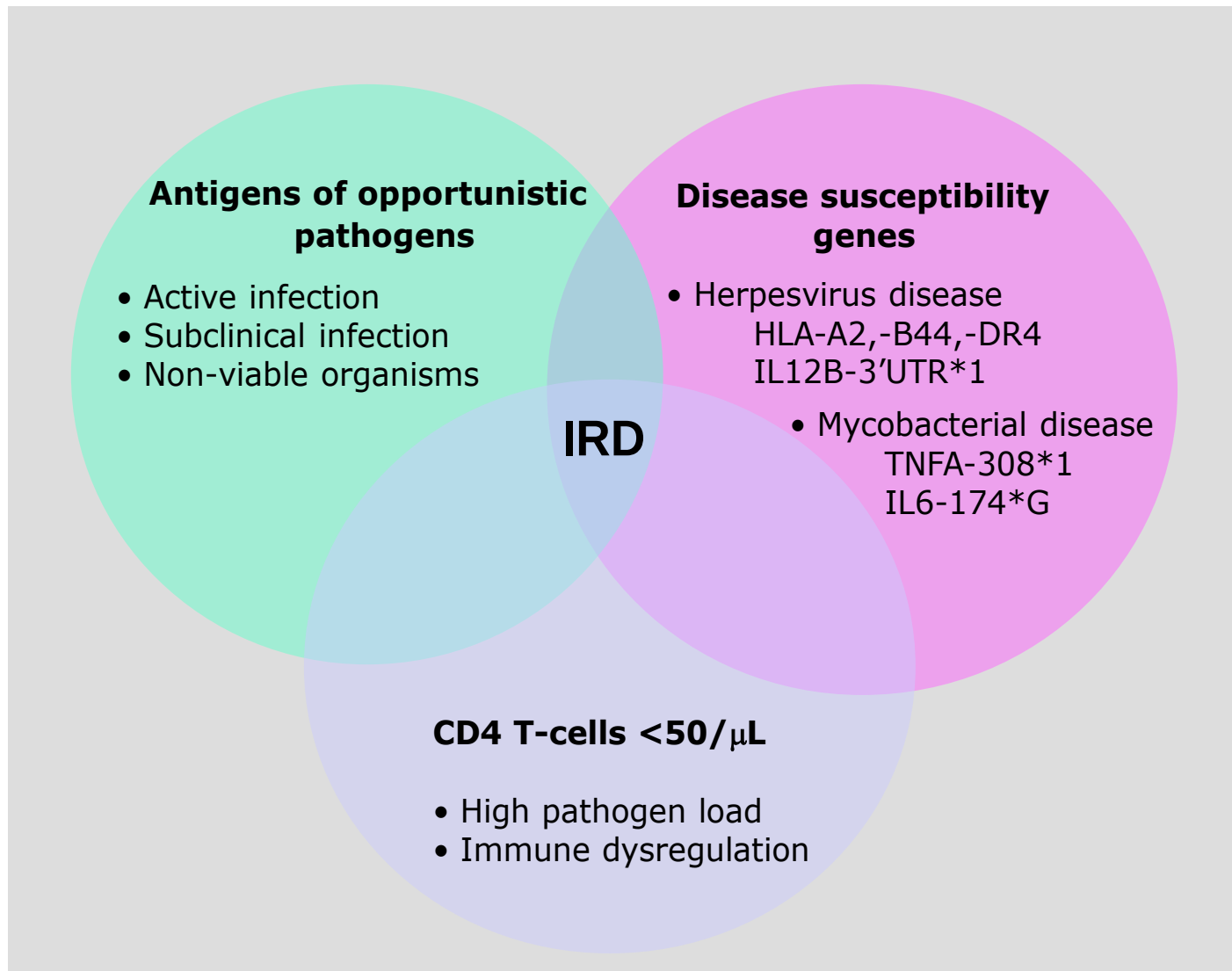
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Pathogens commonly associated with an immune reconstitution inflammatory syndrome (IRIS)

Pathogen	Disease nomenclature
<i>Mycobacterium tuberculosis</i>	Tuberculosis-associated IRIS (TB-IRIS)
<i>Mycobacterium avium</i> complex	MAC-IRIS
Bacille Calmette Guerin (BCG)	BCG-IRIS
<i>Cryptococcus neoformans</i>	C-IRIS
Kaposi's sarcoma herpes virus	KS-IRIS
Cytomegalovirus	CMV retinitis after ART (early) or immune recovery uveitis (late)
Varicella zoster virus	Dermatomal zoster or (rarely) myelopathy or Ramsay-Hunt syndrome after ART
JC polyomavirus	PML-IRIS
Hepatitis B and C viruses	Hepatitis flare after ART

Pathogenesis and risk factors for IRD/IRIS



Prospective international study of incidence and predictors of IRIS and death in people with HIV and severe lymphopenia (NIAID IRIS study)

- Observational study of 506 HIV patients commencing ART with CD4⁺ T cell counts of <100/ μ L (median 29/ μ L)
 - USA (N=206)
 - Kenya (N=200)
 - Thailand (N=100)
- 19.4% developed one or more IRIS event during the first 6 months of ART, with similar rates in all countries
- 6.5% died; IRIS strongly associated with an increased risk of death (HR 3.2, p = 0.031)
- IRIS not associated with CD4⁺ T cell increase post-ART
- Pre-ART, a low Hb level predicted IRIS while high plasma CRP and D-dimer levels predicted death

Risk factors for mycobacterial and cryptococcal IRIS

Risk factor	Retrospective Studies	Prospective Studies
Low pre-ART CD4 ⁺ T-cell count	Yes	Yes
Disseminated infection/high pathogen load	Yes	Yes
Early initiation of ART	Yes	Yes
Rate of CD4 ⁺ T-cell count increase	?	No
Rate of plasma HIV RNA level decrease	?	No

Early ART in HIV patients with treated TB increases rates of TB-IRIS but improves survival

Study	No. of patients	Median baseline CD4 ⁺ T cell count	TB-IRIS (%) Early vs Late ART	Rate of AIDS or death
SAPiT ¹	429	150/ μ L	<u>All patients</u> 20% vs 8.3% (p<0.001) <u>CD4⁺ T cells <50/μL</u> 38.7% vs 11.4% (p=0.01) <u>CD4⁺ T cells >50/μL</u> 16.4% vs 7.7% (p=0.02) Median time = 15 days	Early ART reduced rate by 2/3 in patients with CD4 ⁺ T cells <50/ μ L
ACTG A5221 ²	809	77/ μ L	11% vs 5% (p=0.002) Median time = 15-21 days	Early ART reduced rate by almost 1/2 in patients with CD4 ⁺ T cells <50/ μ L
CAMELIA ³	661	25/ μ L	33% vs 13.7% (p<0.0001) Median time = 14-16 days	Early ART reduced rate by 1/3, irrespective of CD4 ⁺ T cell count

1. Abdool Karim S et al. *New Eng J Med* 2011; 365:1492-501. 2. Havlir D et al. *New Eng J Med* 2011; 365:1482-91.
 3. Blanc F-X et al. *New Eng J Med* 2011; 365:1471-81.

TB-IRIS of the central nervous system causes substantial morbidity

Paradoxical TB-IRIS, N=190

CNS TB-IRIS, 12%
(Meningitis, Tuberculoma, Radiculomyelitis)

81% were hospitalised
91% required corticosteroid therapy
13-30% died
37.5% had neurological disability at 6 months

HIV-related PML-IRIS

(Published reports 1998-2016)

- Unmasking in 45% and paradoxical in 55%
- Median CD4⁺ T cell count: 45/ μ l (0–301) before ART and 101/ μ l (20–610) after ART
- Death in 28% of cases
- Corticosteroid therapy may be effective if commenced early¹

Fournier A et al. *Front Immunol* 2017; 8:577

1. Also see: Tan K et al. *Neurology* 2009; 72:1458-64

Sainz-de-la-Maza S et al. *Eur J Neurol*. 2016; 23:919-25

Immunopathogenesis of mycobacterial IRIS

- Activation of monocytes/macrophages and neutrophils before and after commencing ART^{1,2}
 - Inflammasome activation³, especially in monocytes⁴
 - Increased production of pro-inflammatory cytokines, particularly IL-6, TNF, IFN- γ and IL-18⁵⁻⁹
- Expansion of effector memory CD4⁺ T cells after commencing ART, especially mycobacterial antigen-specific cells with a Th1 phenotype⁹⁻¹⁶
- Impaired recovery of naïve CD4⁺ T cells after ART^{5,16}

1) Andrade BB *et al. PLoS Pathog* 2014; 10:e1004433

3) Lai RP *et al. Nat Commun* 2015; 6:8451

5) Antonelli LR *et al. Blood* 2010; 116:3818-27

7) Barber DL *et al. J Immunol* 2014; 192:676-82

9) Ravimohan S *et al. Clin Infect Dis* 2016; 62:795–803

11) Meintjes G *et al. AJRCCM* 2008; 178:1083-9

13) Mahnke YD *et al. Blood* 2012; 119:3105-12

15) Hsu DC *et al. Clin Infect Dis* 2018; 67:437-446

2) Nakiwala JK *et al. JAIDS* 2018; 77:221-9

4) Tan HY *et al. J Immunol* 2016; 196:4052-63

6) Tadokera R *et al. Eur Respir J* 2011; 37:1248-1259

8) Tan HY *et al. AIDS* 2015; 29:421-431

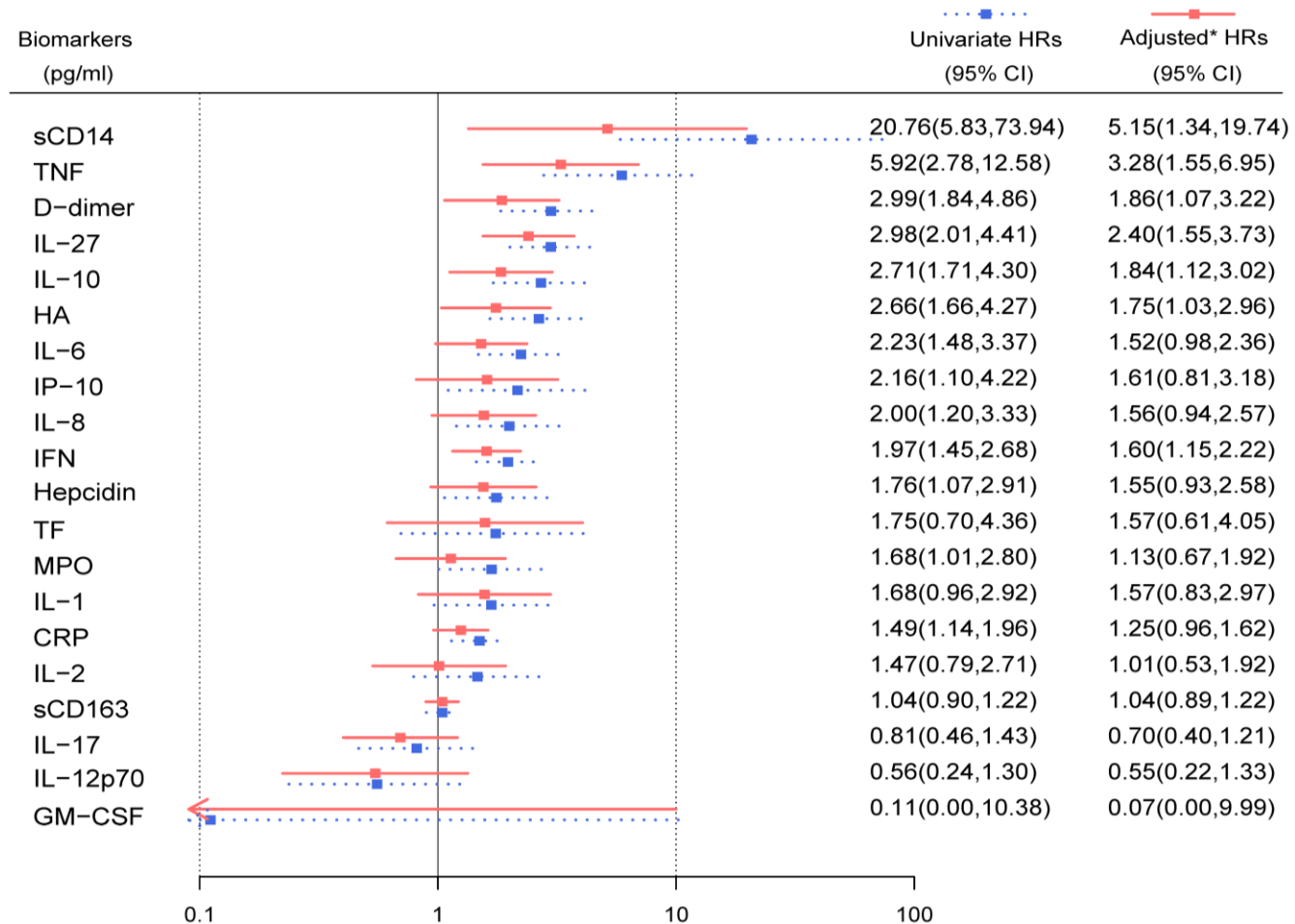
10) Bourgarit A *et al. AIDS* 2006; 20: F1-7

12) Bourgarit A *et al. J Immunol* 2009; 183:3915-23

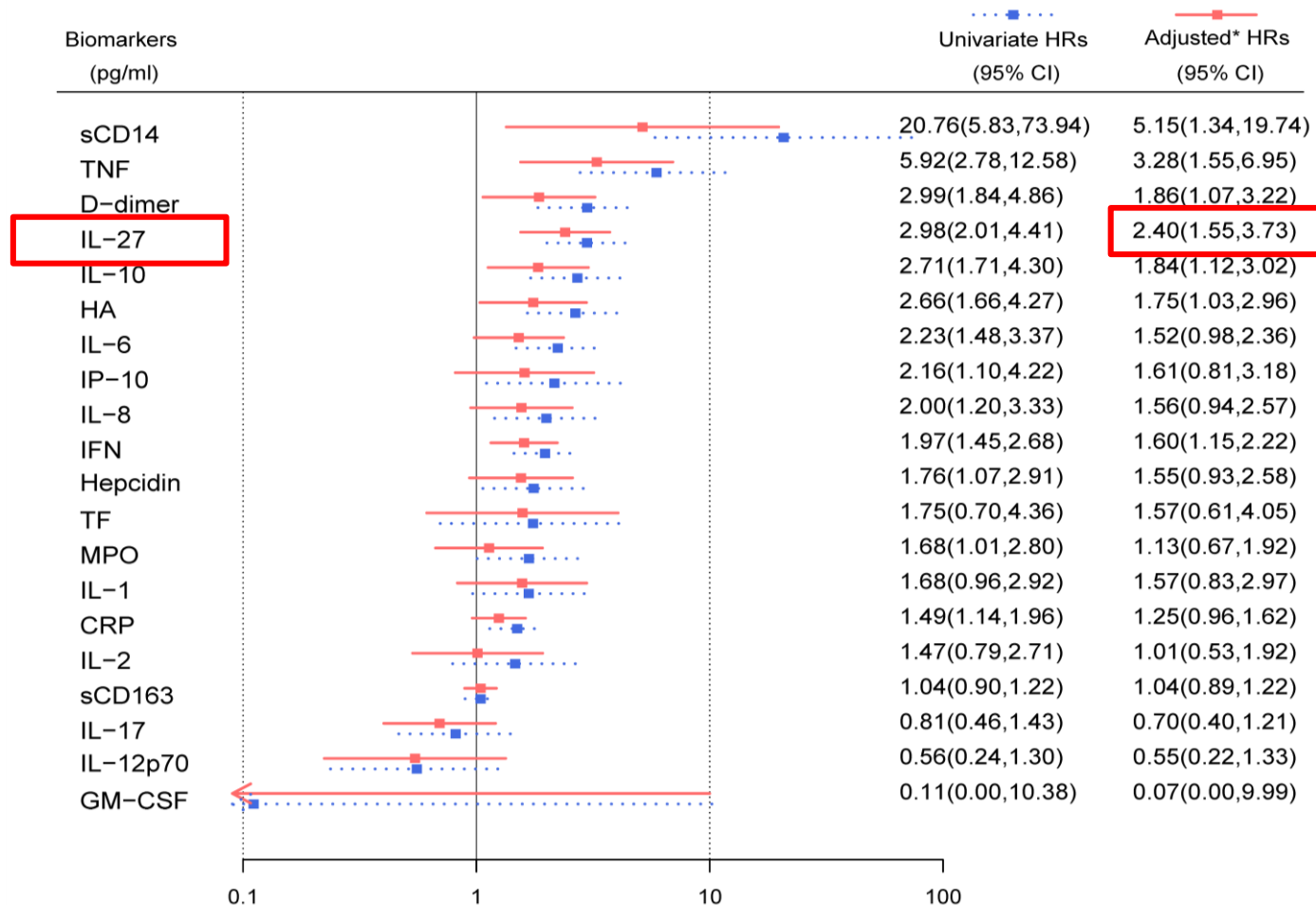
14) Vignesh R *et al. JAIDS* 2013; 64:241-248

16) Silveira-Mattos PS *et al. Scientific Reports* 2019; 9:1502

Plasma biomarkers of inflammation pre-ART predict the development of IRIS (NIAID IRIS study)

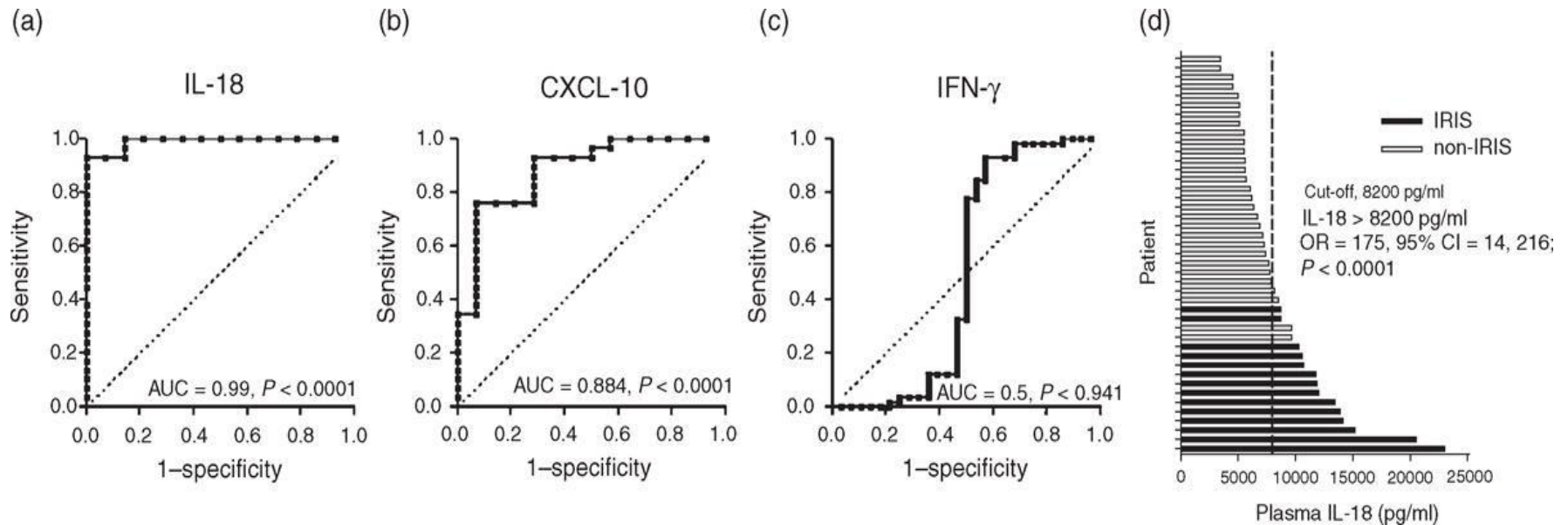


Plasma biomarkers of inflammation pre-ART predict the development of IRIS (NIAID IRIS study)



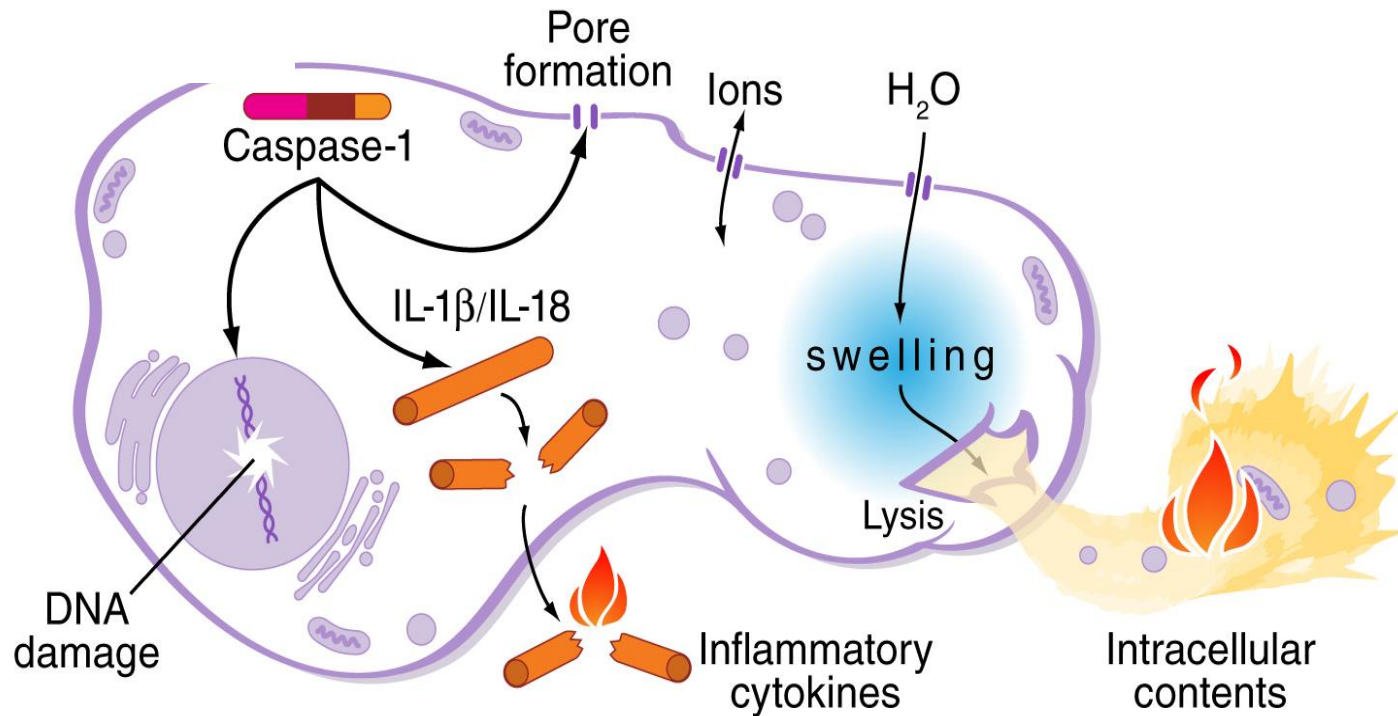
IL-27 is a promoter of Th1 CD4⁺ T cell differentiation

Plasma IL-18 levels predict occurrence of TB-IRIS after commencing ART in HIV patients with TB

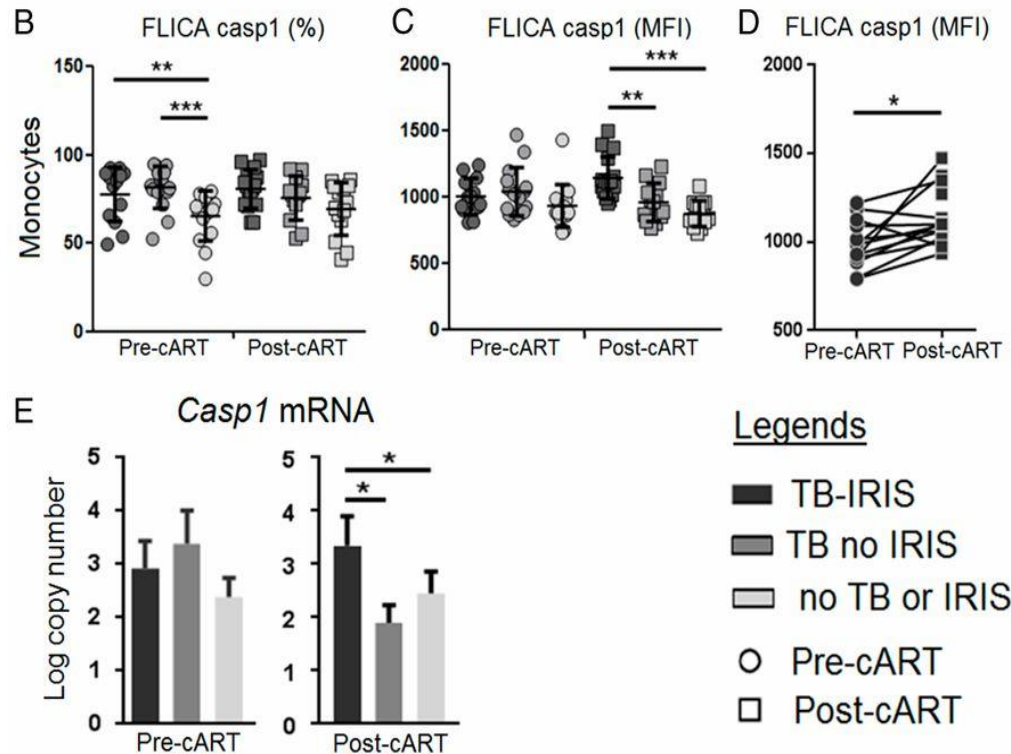


Tan HY et al. *AIDS* 2015; 29:421-31

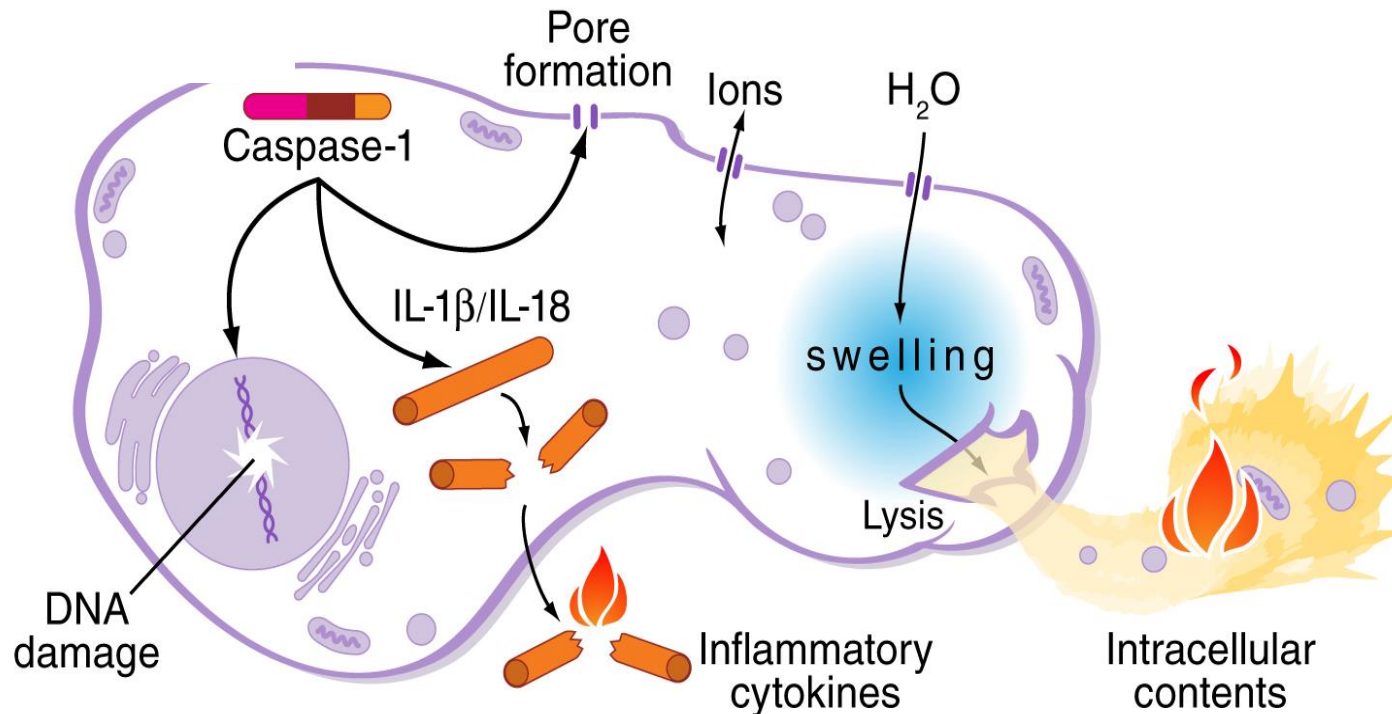
IL-18 is produced after activation of caspase-1 during inflammasome activation and pyroptosis



Monocytes expressing activated caspase 1 are higher in HIV patients with TB and caspase 1 expression is greatest in TB-IRIS patients

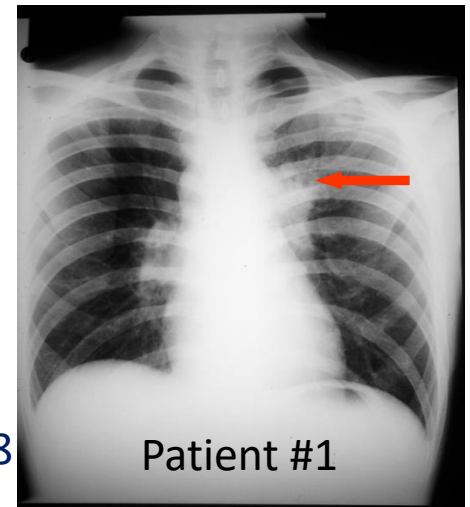
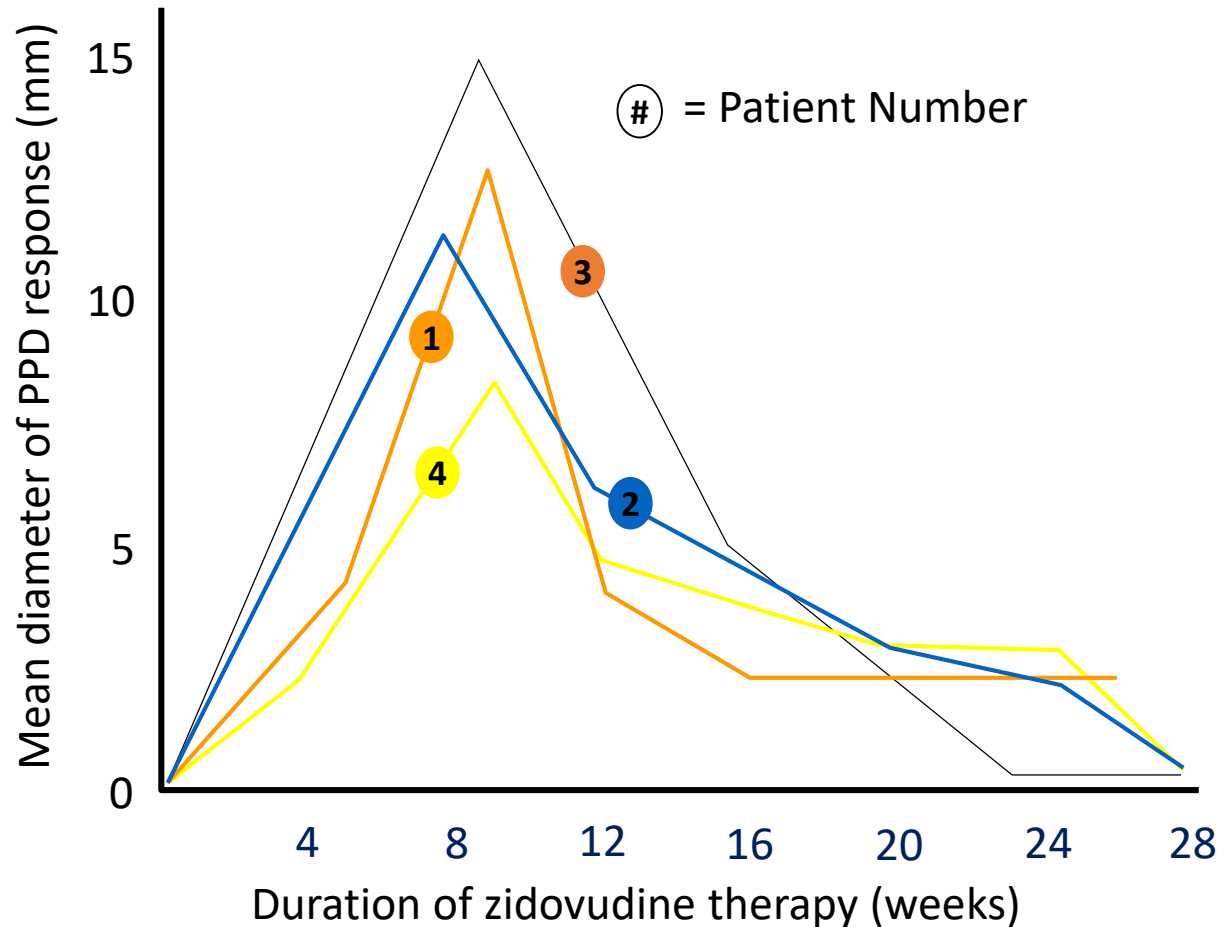


IL-18 is produced after activation of caspase-1 during inflammasome activation and pyroptosis



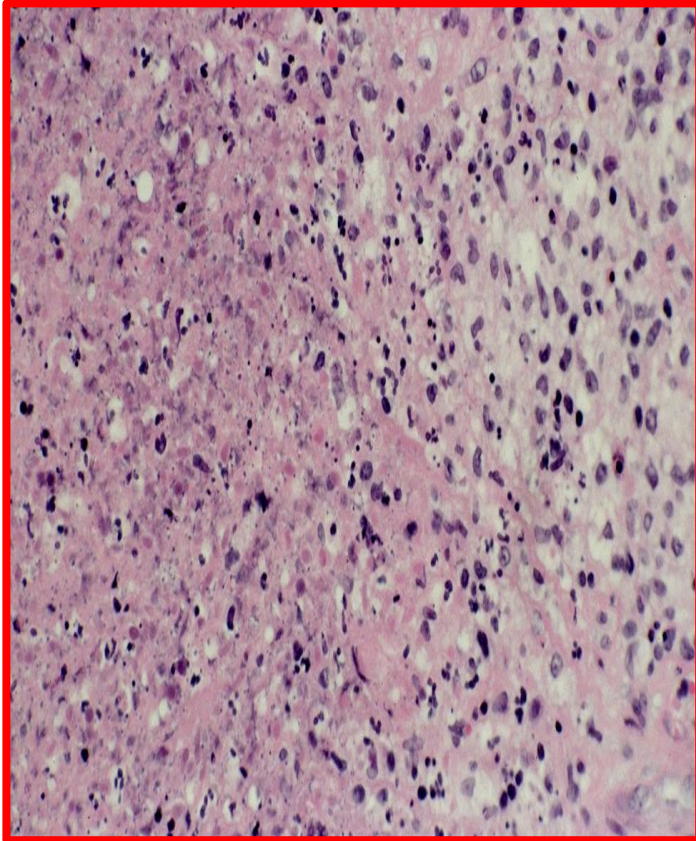
IL-18 is a promoter of Th1 CD4⁺ T cell differentiation

MAC disease associated with restoration of DTH skin test responses to PPD after zidovudine monotherapy



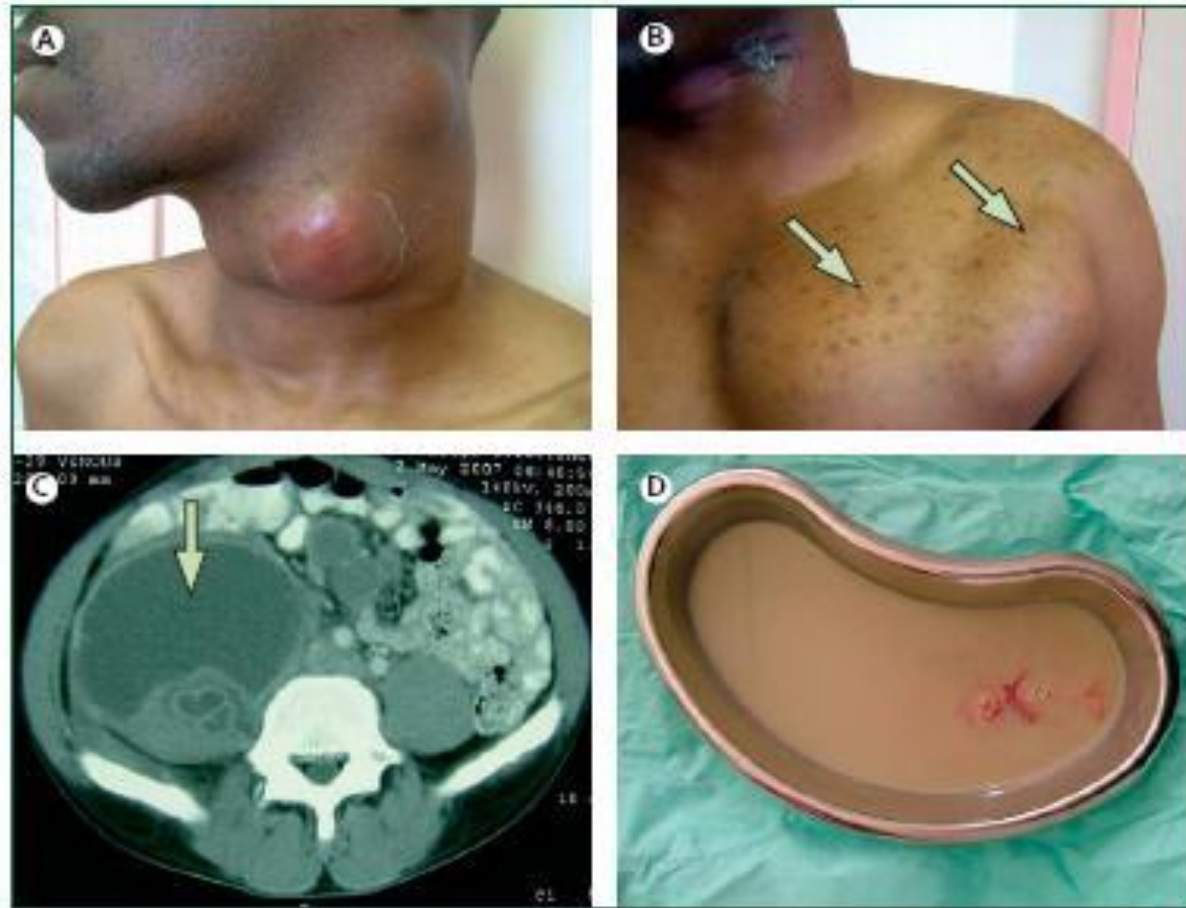
Data from: French M et al. *AIDS* 1992; 6:1293

Necrotising granulomatous lymphadenitis in BCG-IRIS



Sharp M & Mallon D. *Ped Inf Dis J* 1998; 17:660

Suppurative lymphadenitis in TB-IRIS



Meintjes G et al. *Lancet Infect Dis.* 2008; 8:516-23

Pathogenesis of cryptococcal IRIS meningitis (The Durban C-IRIS Study)

Pre-ART	Early C-IRIS (first 3 months of ART)	Late C-IRIS (after 3 months of ART)
Persistent cryptococcal infection in CSF ¹		
Lower CD4 ⁺ T cell counts ¹ and CD4 ⁺ T cell dysfunction (Th2 skewing and defective IL-7R signalling in T cells) ^{2,3}	Smaller increase in total CD4 ⁺ T cell counts ¹	Smaller increase in total CD4 ⁺ T cell counts ¹
Lower Cryptococcus-specific T cell and antibody responses ^{4,5}		
Higher monocyte and neutrophil activation ^{3,6} and chemokine gradient for trafficking to CSF ⁷	Molecular signatures of innate immune responses, including inflammasome activation ⁶	Molecular signatures of T cell, B cell and NK cell activity ⁶

1) Chang CC et al. *AIDS* 2013; 27:2089-99

3) Akilimali NA et al. *JAIDS* 2019 (E-pub)

5) Yoon HA et al. *J Infect Dis.* 2019; 219:420-428

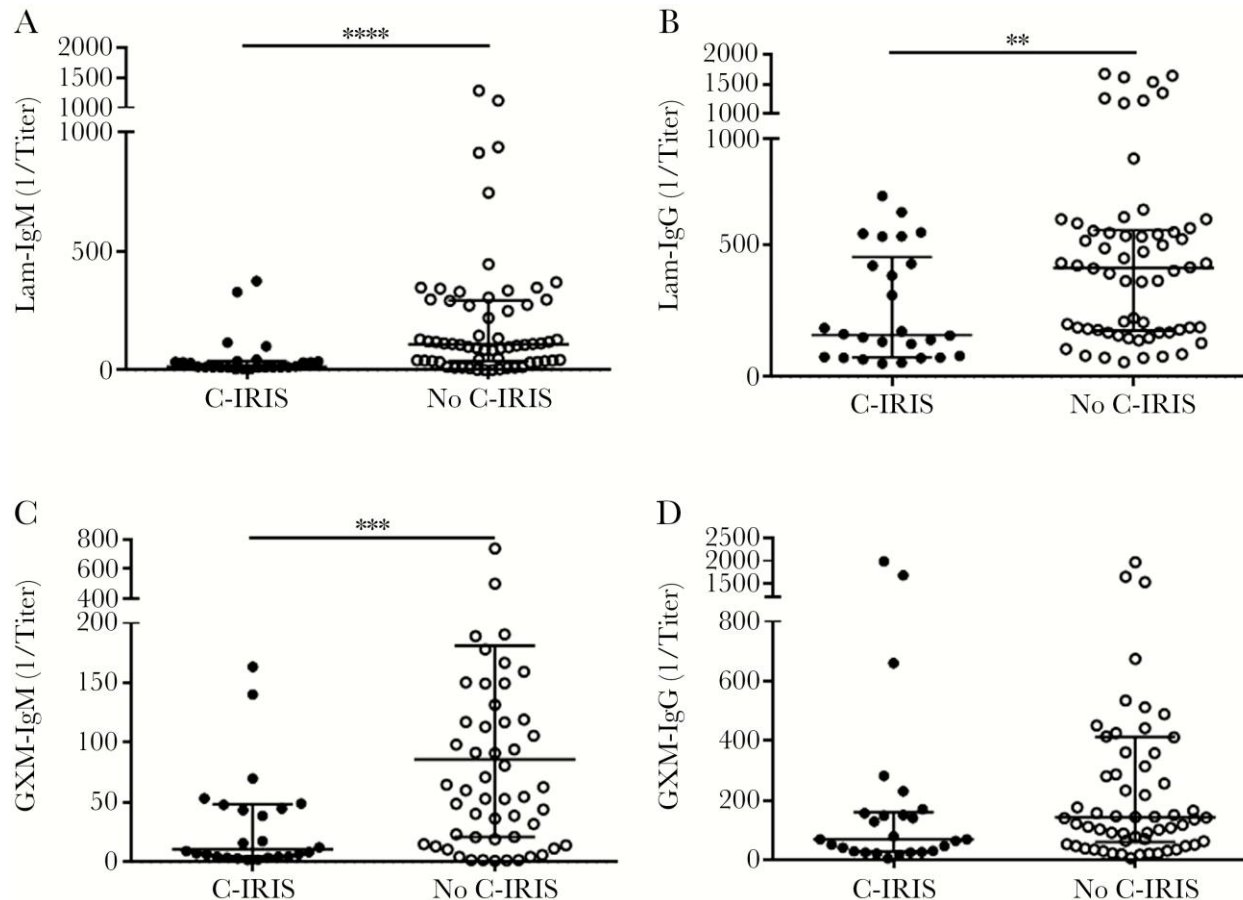
7) Chang CC et al. *J Infect Dis.* 2013; 208:1604-12

2) Akilimali NA et al. *Clin Infect Dis.* 2017; 65:1551-9

4) Chang CC et al. *J Infect Dis.* 2013; 208:898-906

6) Vlasova-St Louis I et al. *Open Forum Infect Dis.* 2018; 5:ofy157

Plasma titres of IgM and IgG anti-laminarin and IgM anti-glucuronoxylomannan are lower pre-ART in patients who develop paradoxical C-IRIS meningitis



Predictors of IRIS and/or death in immunodeficient HIV patients starting ART

Pathogen (load)	Inflammation (immune dysregulation)
Cryptococcal infection • Serum CrAg <i>M. tuberculosis</i> infection • Urine lipoarabinomannan (LAM)	Increased plasma levels of 'inflammation biomarkers': • D-dimers^{1,2,5,6} • sCD14⁵ • IL-6²⁻⁴ • CRP^{1-4,6} Low Hb^{3,6}

1) Porter BO et al. *Clin Immunol* 2010; 136:42-50

3) Narendran G et al. *PLoS One* 2013; 8:e63541

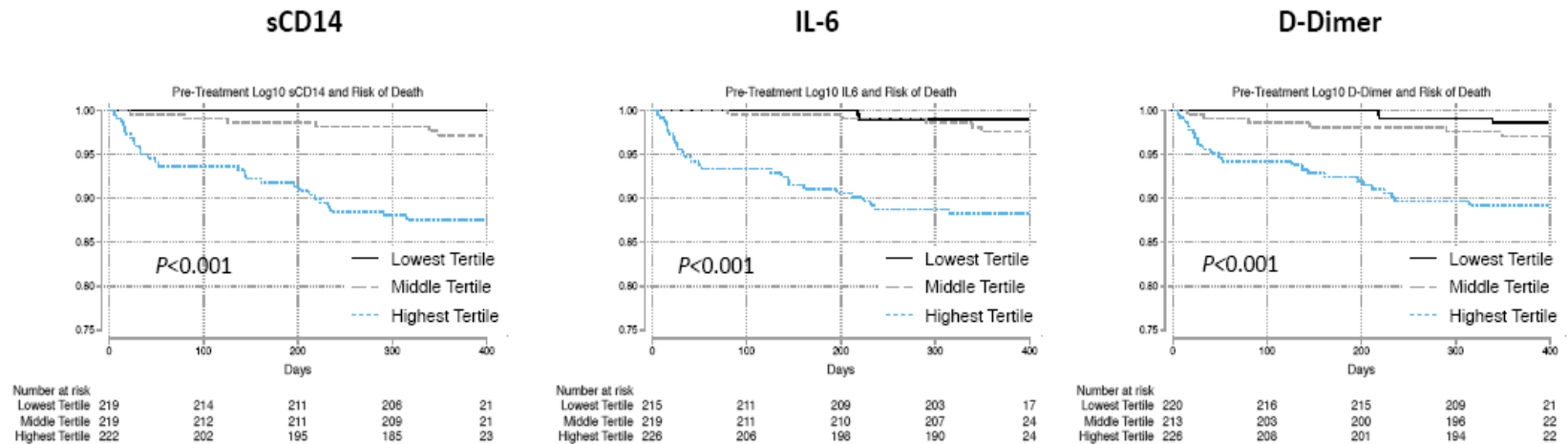
5) Musselwhite LW et al. *EBioMedicine* 2016; 4:115-23

2) Boulware DR et al. *J Infect Dis* 2011; 203:1637-46

4) Andrade BB et al. *PLoS Pathog* 2014; 10:e1004433

6) Sereti I et al. *Clin Infect Dis* 2019, doi: [10.1093/cid/ciz877](https://doi.org/10.1093/cid/ciz877)

Pre-ART biomarkers of inflammation predict early mortality after ART more effectively than CD4⁺ T cell counts and HIV viral load

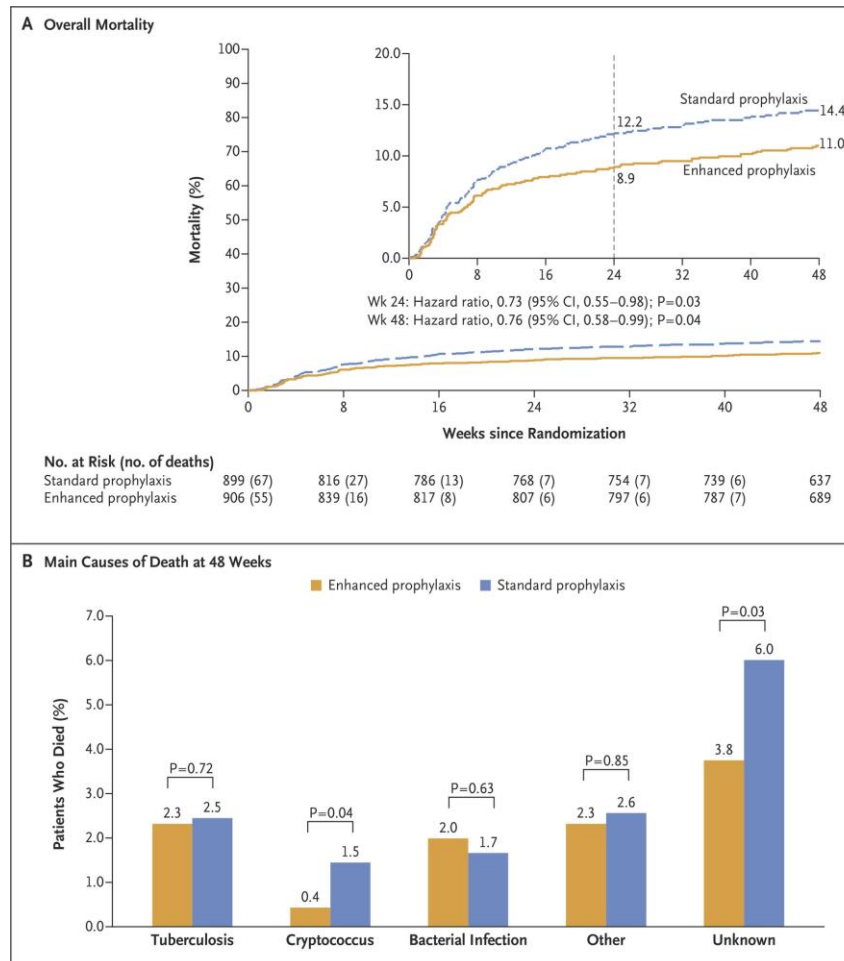


High plasma biomarkers of systemic inflammation pre-ART predicted a 300-500% increased risk of early mortality, in South Africa and Uganda

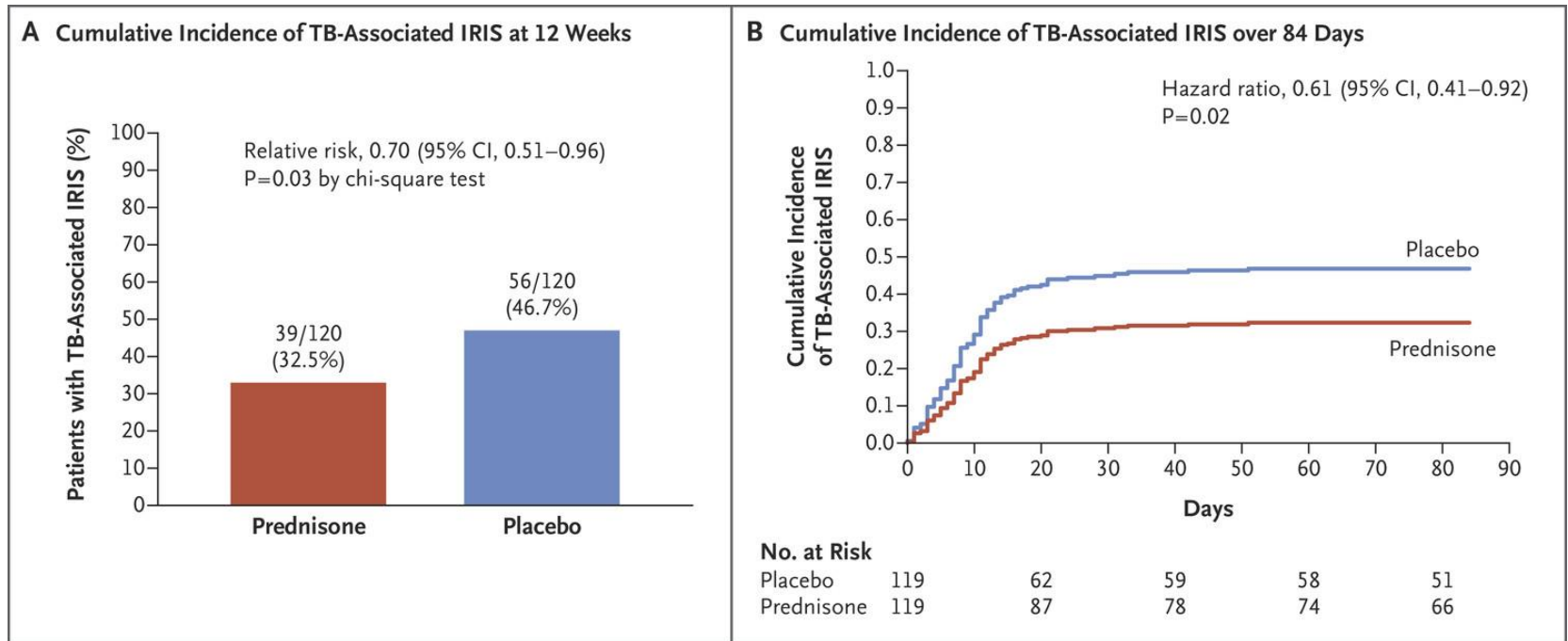
Siedner MJ et al. *AIDS*, in press (DOI: 10.1097/QAD.0000000000002305)

Also see: Ledwaba L et al. *PLoS One* 2012; 7:e24243.

Enhanced anti-microbial prophylaxis reduces early mortality in immunodeficient HIV patients commencing ART: REALITY study



Prophylactic prednisolone therapy decreases the risk of paradoxical TB-IRIS



Meintjes G et al. *N Engl J Med* 2018; 379:1915-1925

Summary

- IRIS causes substantial morbidity and mortality in HIV patients commencing ART with CD4⁺ T cells <100/μL
- Higher risk of IRIS related to activation of innate immune responses (monocytes/macrophages in TB-IRIS and C-IRIS) pre-ART rather than changes in CD4⁺ T cell counts or HIV viral load post-ART
- In TB-IRIS, monocyte/macrophage activation likely drives expansion of Mtb-specific Th1 CD4⁺ T cells and activation of neutrophils
- Pre-ART, low Hb and high CRP and D-dimers indicate a high risk of IRIS and/or death
- Prophylactic corticosteroid therapy decreases the risk of paradoxical TB-IRIS

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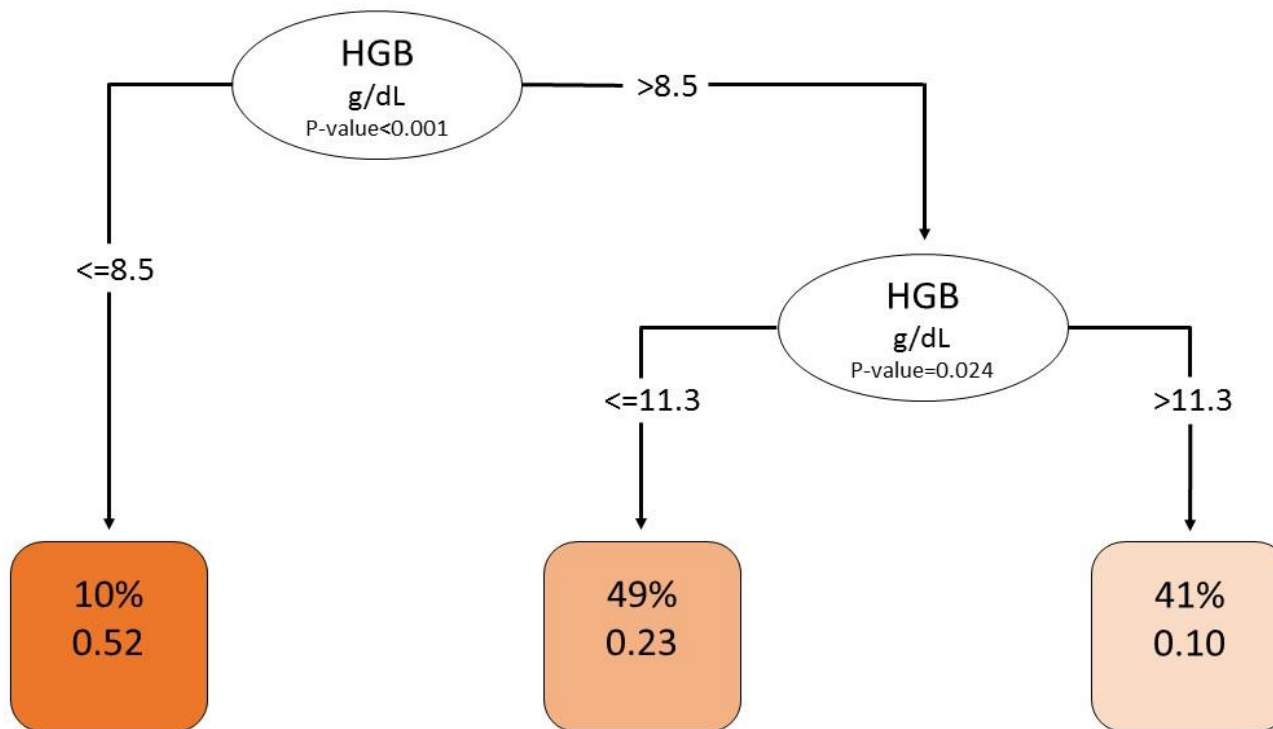
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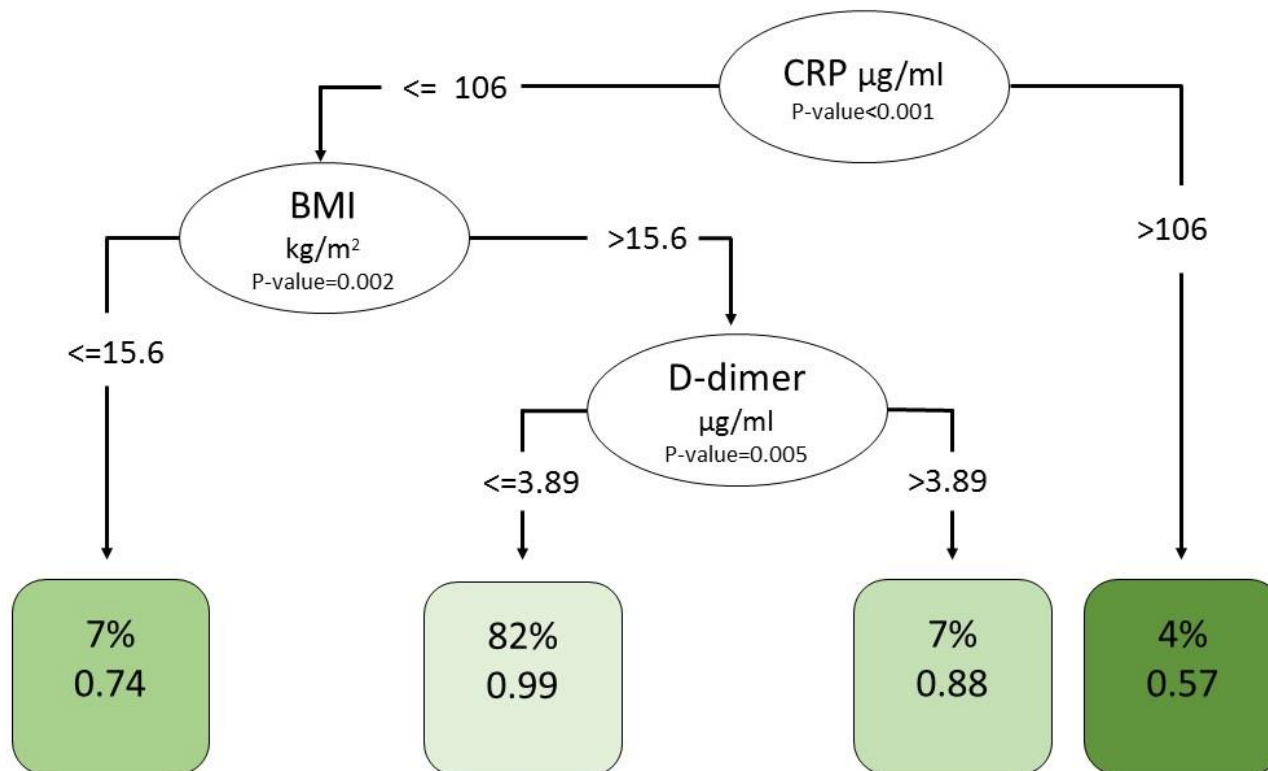
Pre-ART Hb level predicts IRIS after commencing ART

Figure 4. Decision Tree displaying baseline biomarkers as predictors of IRIS after ART initiation

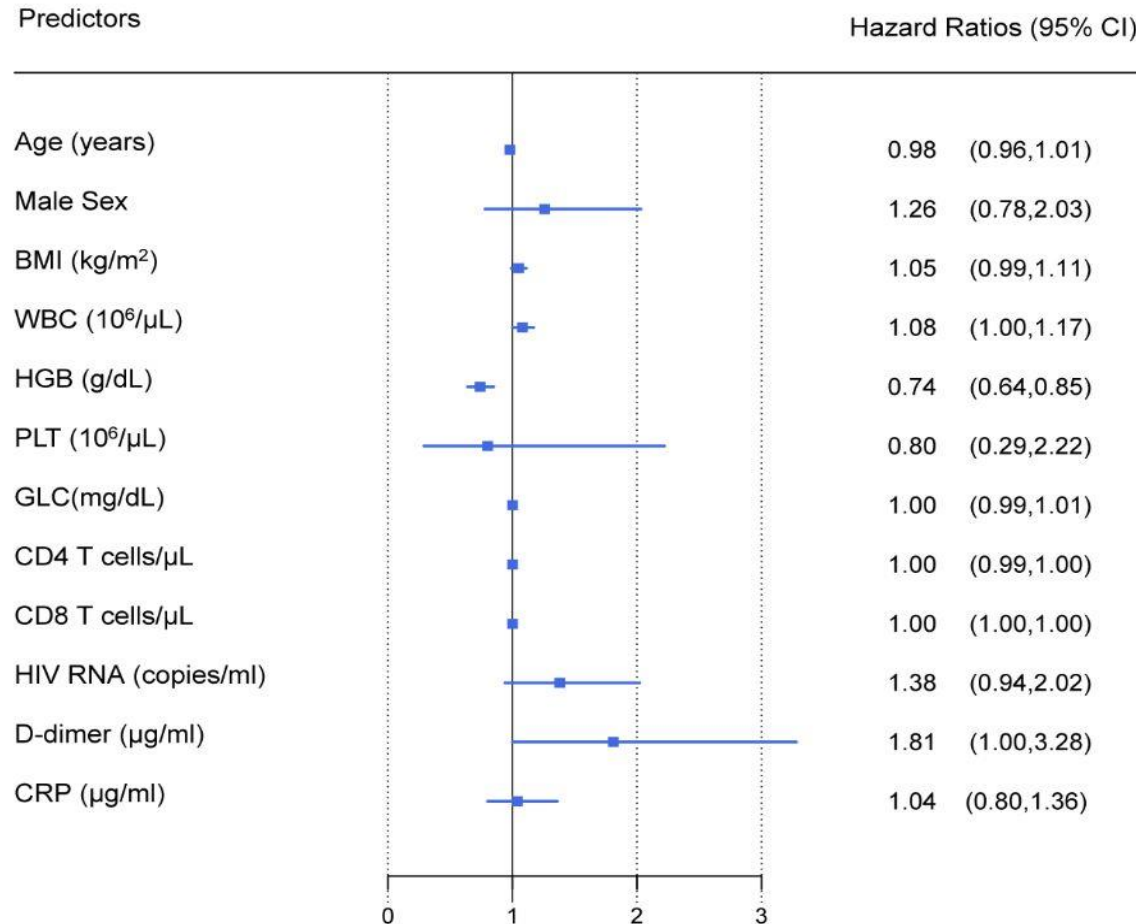


Pre-ART BMI, CRP and D-dimer predict death after commencing ART

Figure 5. Decision Tree displaying baseline biomarkers as predictors of death after ART initiation



Low Hb and high D-dimers predict IRIS in a large prospective multicenter international study



A higher pathogen load prior to ART is a risk factor for an IRIS

Disease	Marker of pathogen load	Reference
TB-IRIS	Urine LAM level	Conesa-Botella A et al. <i>JAIDS</i> 2011; 58:463-8.
Cryptococcal IRIS	CSF quantitative cryptococcal culture	Chang C et al. <i>AIDS</i> 2013; 27:2089-99.
KS-IRIS	Detectable plasma KSHV DNA	Letang E et al. <i>JAIDS</i> 2010; 53:589-97. Letang E et al. <i>AIDS</i> 2013; 27:1603-13.
HBV hepatitis flare	Plasma HBV DNA level	Crane M et al. <i>JID</i> 2009; 199:974-81. Andrade B et al. <i>JID</i> 2013; 207:1379-88.
HCV hepatitis flare	Plasma HCV RNA level	Andrade B et al. <i>JID</i> 2013; 207:1379-88.