CNS IRIS – the evil side of cART

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Agenda

Ruxandra Moroti

- IRIS overall
- IRIS physio-pathology
- CNS IRIS histo-pathology
- CNS IRIS imagery
- CNS IRIS risk factors

Adriana Hristea

- Major presentations of CNS IRIS
- CNS IRIS diagnosis
- Management
- Conclusions

IRIS overall

What's **IRIS**?

- Iris: the eye's diaphragm
- Iris: fleur-de-lis, native to both Eurasia and North America
- Iris: the Greek goddess of the rainbow, the gods' messenger

- **IRIS:** Immune Reconstitution Inflammatory Syndrome

IRIS overall

What's **IRIS**?

- An immune hyper-reaction against previously tolerated germs, triggered by antibiotic/antiviral administration

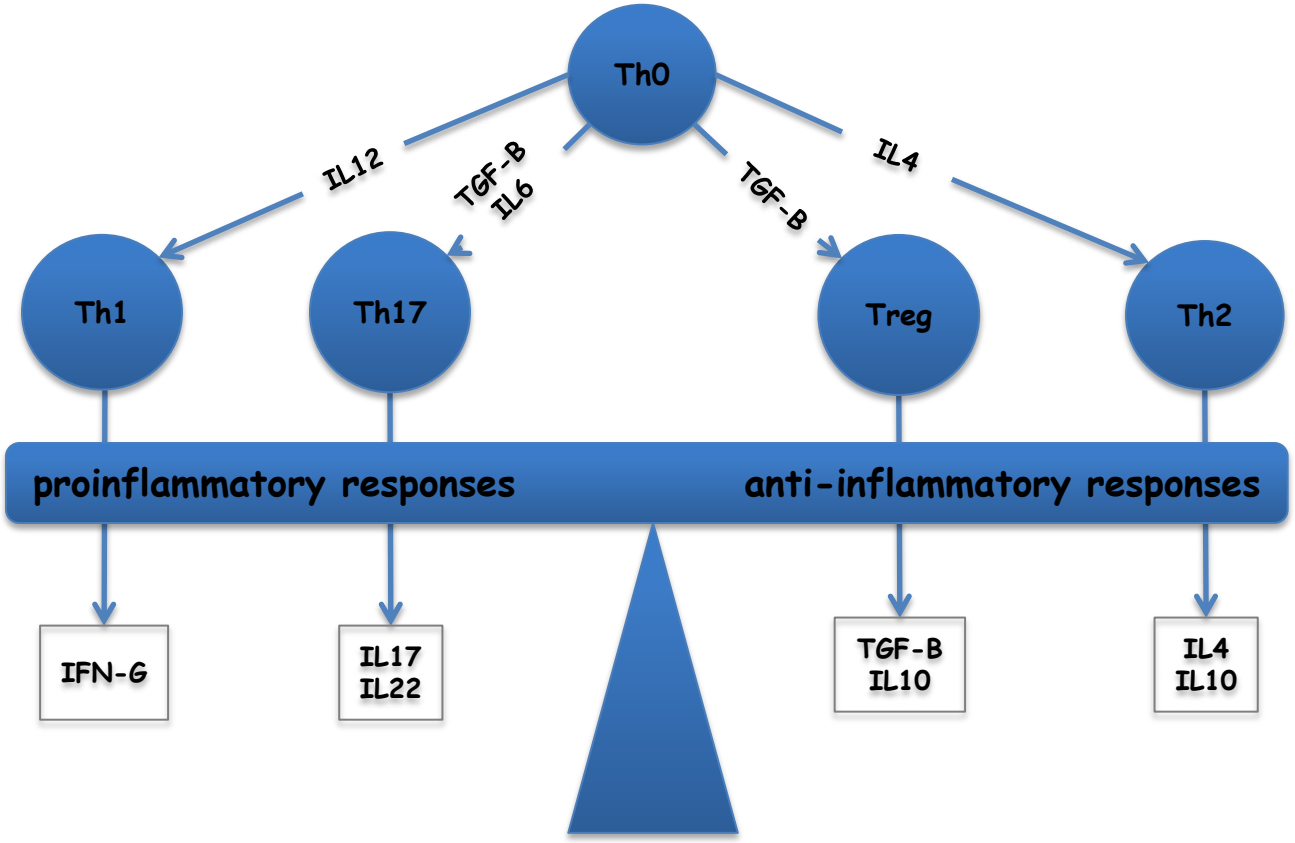
  =a paradoxical illness after the treatment's start and related to!
- Maximal incidence in HIV-positive patients: 25-45%
- When we are chronically infected, our immune system suffers a "paralysis" via germs' different products (e.g.: chronic hepB,TB)

- Acting directly on germs (with antibiotics/ antivirals), we obtain not just dead germs but their paralyzing products' withdrawal too

- In this way, our immune system invigorates and can react (in case of IRIS: over-reacts!) to the antigens (of dead or alive germs (!))

- **IRIS:** **I**mmune **R**econstitution **I**nflammatory **S**yndrome

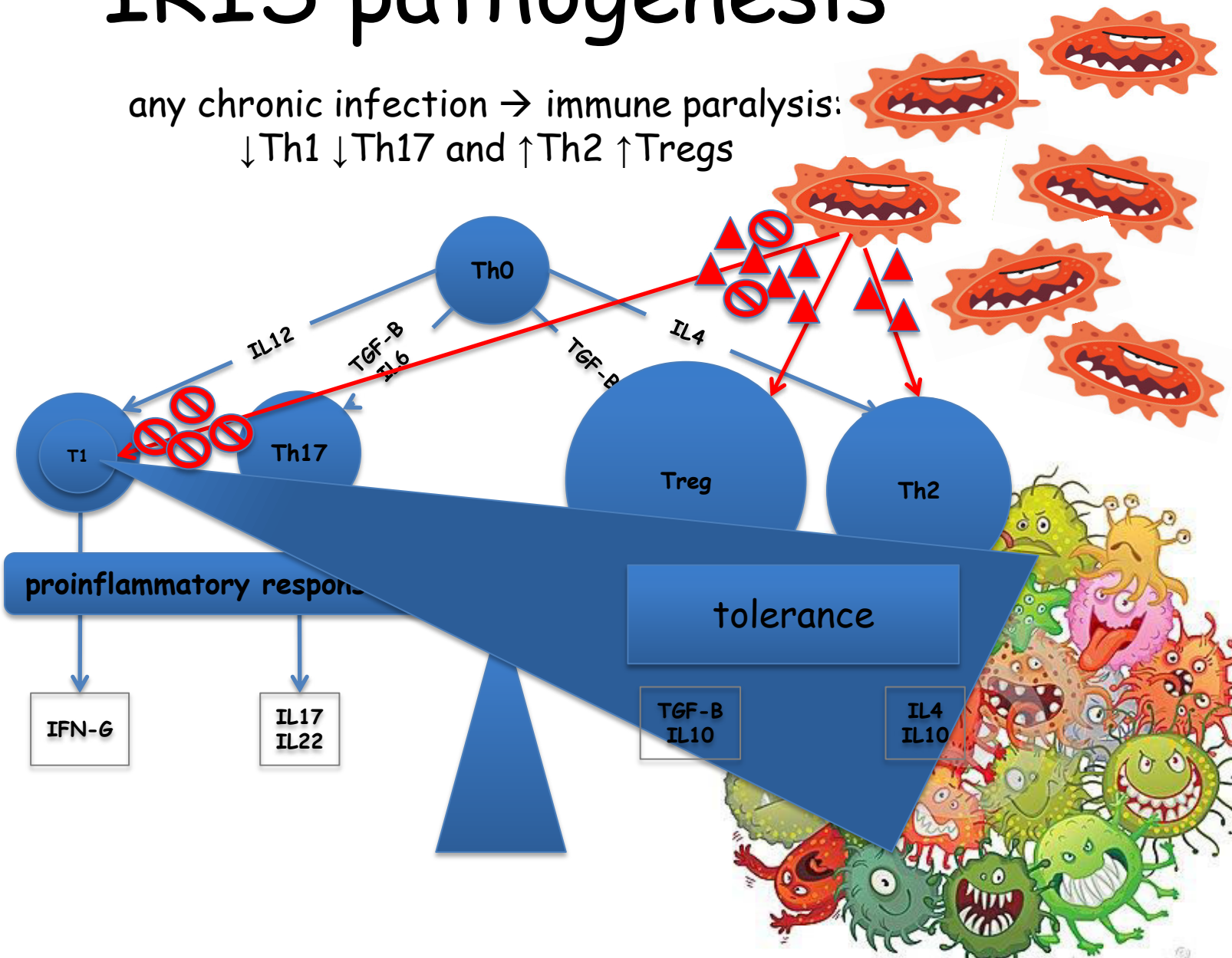
IRIS pathogenesis



Sun and Singh, Current Opinion ID, 2009

IRIS pathogenesis

any chronic infection → immune paralysis:
↓Th1 ↓Th17 and ↑Th2 ↑Tregs



IRIS pathogenesis

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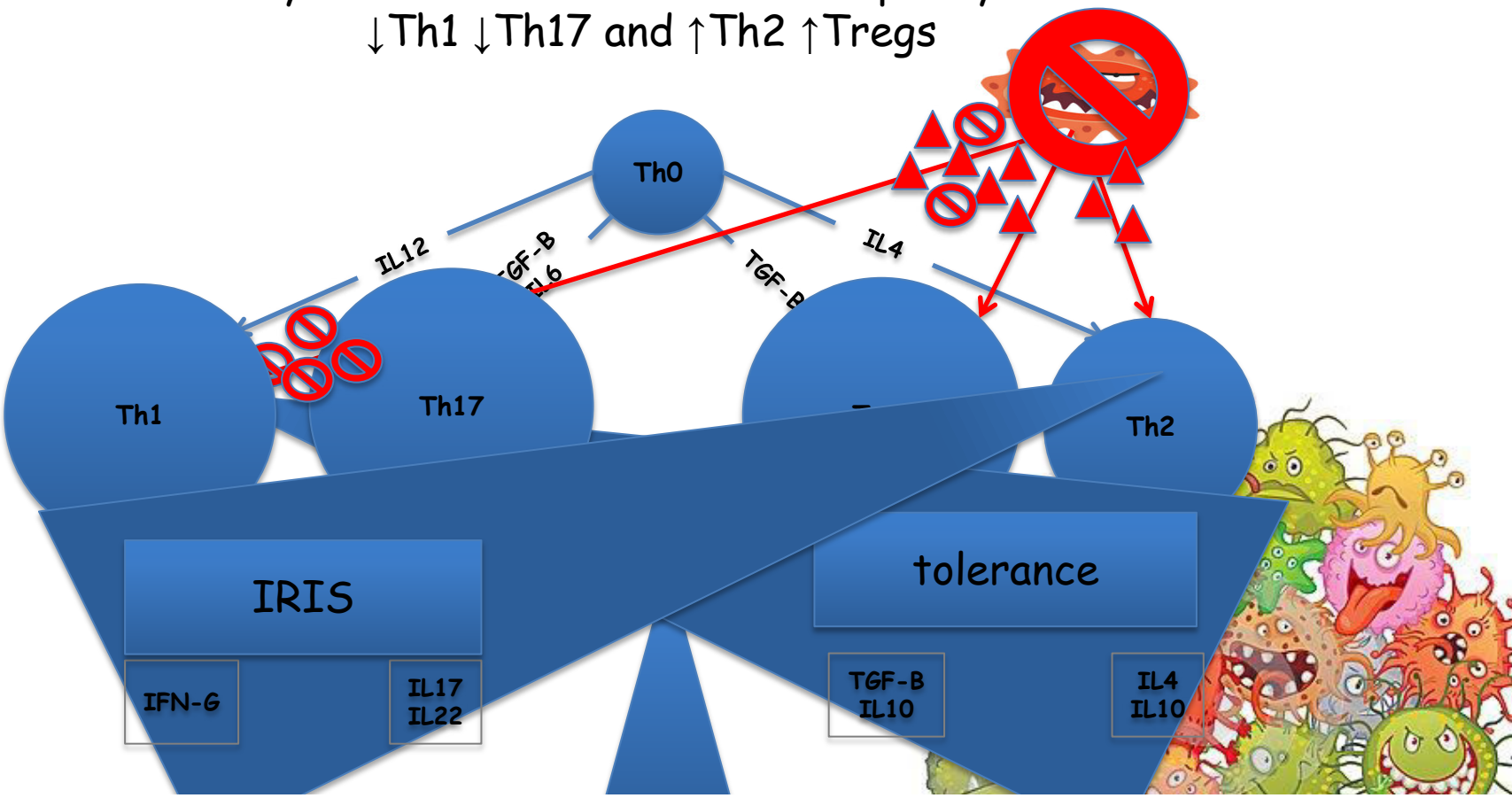
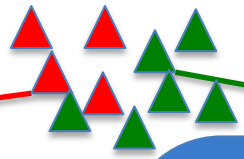


treating the cause → immune restoring
if the restoring is abrupt and pronounced, the unbalanced and exuberant pro-inflammatory response can be harmful

HIV IRIS pathogenesis

ART: CD4+ restoration: Th1 and Th17 recognize and react to **antigens**:



Dead opportunistic agent
Previously recognized and already in treatment OI

Alive opportunistic agent
Silent, thus untreated OI

Paradoxical IRIS

= recurrence/exacerbation/ new symptoms of a previously **recognized and treated OI**

Unmasked IRIS

= unexpected onset (with inflammatory features) of a **hidden OI**

HIV IRIS pathogenesis

- 2 steps:
  - First 2 weeks: prompt release from lymphoid nodes of memory T CD8+ and T CD4+ into circulation (=redistribution)
  - >1-1,5 months→2 years: gradual rise in naïve T from thymus

- unbalanced immune reactions:
  - hyperTh1 and Th17 and
  - hypoTh2 and Treg

- The results:
  - T CD8+ exuberant expansion
  - enhanced macrophages' activation

CNS IRIS histology

Hallmark CD8+ perivascular space infiltration

- Inflammatory reaction with marked inflammatory infiltration of the perivascular space and infiltration of the cerebral cortex and white matter. The immunophenotyping of inflammatory cells demonstrated the presence of a mixed infiltration of CD4+ T lymphocytes, CD20+ B lymphocytes and CD8+ T lymphocytes, along with CD68+ monocytes and activated microglia.

- Paucity of CD4+ in the brain, despite a rising in peripheral T CD4+ count; CD4+/CD8+ abnormal ratio

- MTB: granulomatous reactions: parenchymal infiltration: abscesses
- Viruses (JCV, CMV, …): perivascular infiltration: angeitis & infarcts

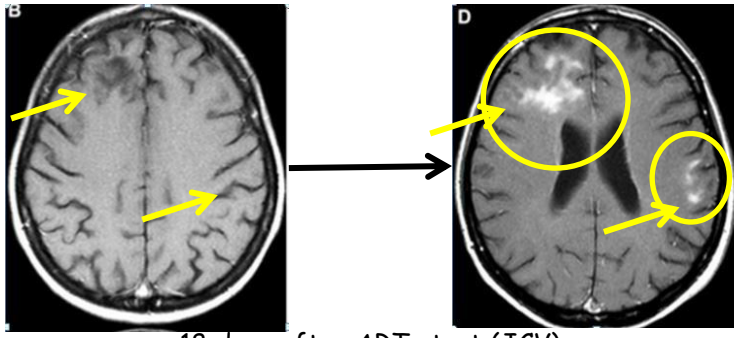
Riedel DJ et al. Nat Clin Pract Neurol, 2006

Post MJD & al, Am J Neuroradiol, 2013

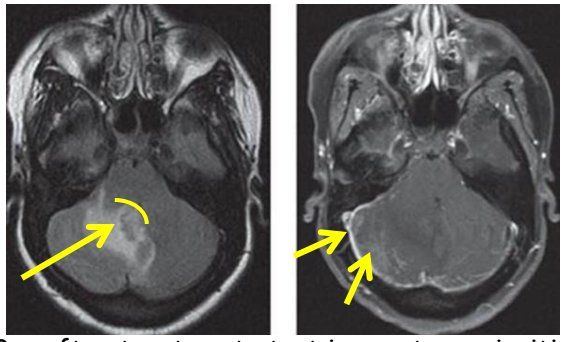
CNS IRIS imagery

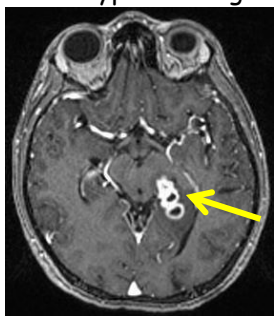
- Parenchymal FLAIR hyper-signal
- Contrast enhancement of the leptomeningeal spaces and/or of the parenchymal lesions; abscesses
- Mass effect
- Restricted diffusion
- Appearing of new images

- Strikingly different in IRIS vs non-IRIS case for:
  - Viruses (**JCV**, CMV, …)
  - **Cryptococcus**
- Slightly or not different in IRIS vs non-IRIS case for:
  - **MTB** (but more frequent: abscesses)
  - Toxoplasma (very rare IRIS! reduced visibility: reduced expression of immunogenic surface proteins; decreased metabolic activity of bradizoites)



18 days after ART start (JCV)


2 w after treatment start in crypto meningitis


3 mo after TB treatment start

Riedel DJ &al, Nat Clin Pract Neurol, 2006 Post MJD & al, Am J Neuroradiol, 2013

CNS IRIS risk factors

- More advanced HIV disease at the time of ART initiation:
  - Low CD4 count (<50/mm3; <10%)
  - High VL >10^5 copies/ml
- Multiple OI and/or high antigenic burden: pathogen type (!)
- Genetic background & particular reactivity:
  - HLA
  - Male gender, younger age
  - Inflammatory markers at ART start: high CRP, IL6
- ART timing and follow up:
  - ART initiation > ART reinforcement or changing to a more potent regimen or switching from a failure regimen
  - Timing: short time interval between initiation of OI therapy and starting ART (early 2w vs late 8w)
  - Rapid rise in CD4 count following ART initiation
  - Rapid decrease of VL (>1 log10) following ART initiation

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CNS IRIS

- 9% (Spanish cohort) to 47% (South African study-TB)
  - depending on the incidence and types of infections that patients have at the time of ART initiation
- Mortality rate: 20%–30%
  - depending on the underlying infection and individual circumstances
  - due to increased intracranial pressure that may ultimately cause brain herniation and death and/or dysfunction in vital brain structures

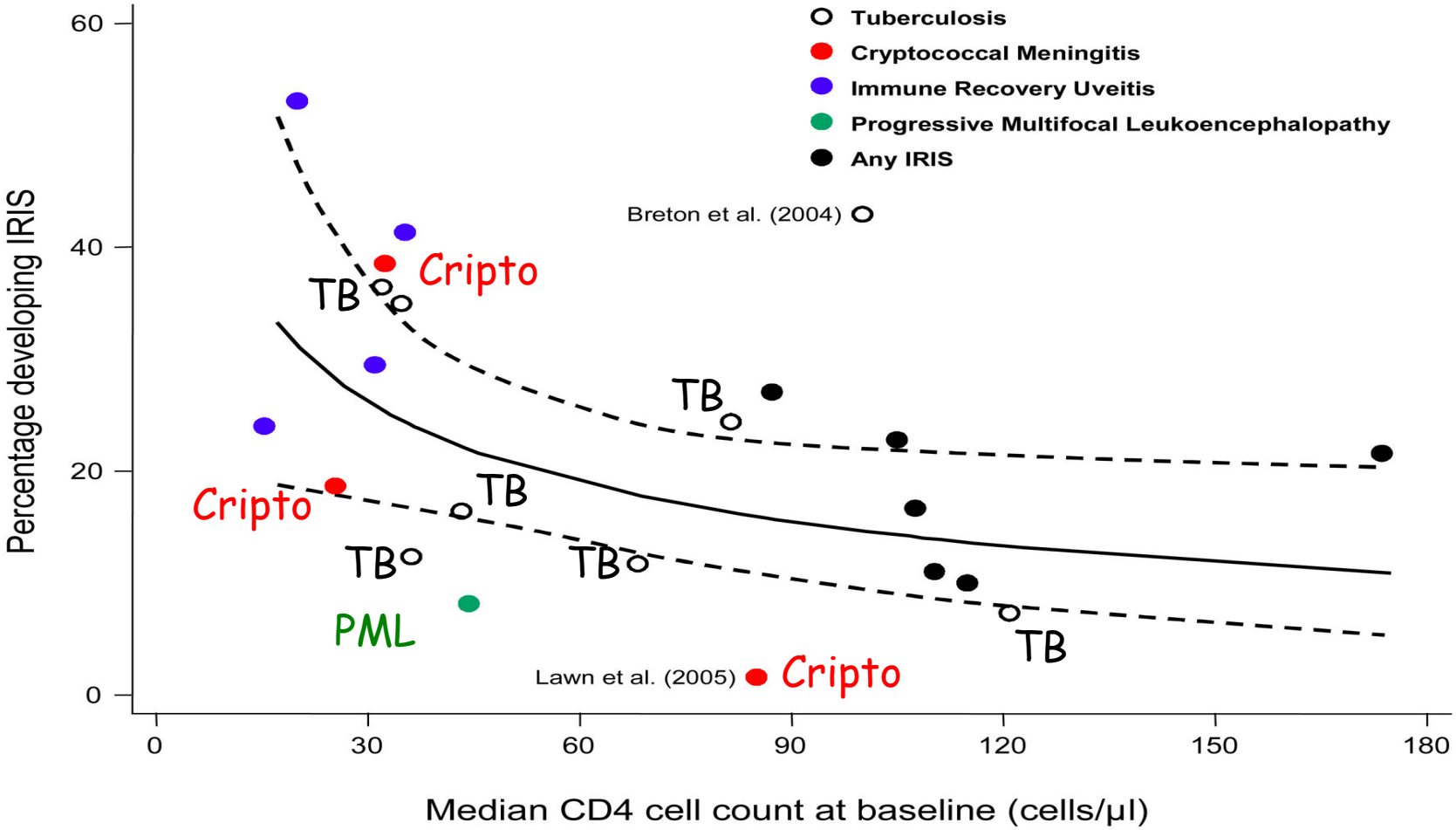
Riveiro-Barciela M, et al HIV Medicine. 2013
Asselman V, et al AIDS. 2010
Marais S, et al Clin Infect Dis. 2013

Neurological IRIS

Underlying Infection	Neurological Manifestation(s)
Cryptococcus neoformans	Meningitis
	Intracerebral cryptococoma/abscess
	Cerebellitis
Coccidiomycoses	Meningitis
Candida	Meningitis
Sporothrix schenckii	Meningitis
Mycobacterium tuberculosis	Meningitis
	Intracerebral tuberculoma
	Radiculopathy
	Epidural abscess
Mycobacterium avium complex	Mass lesion
Varicella zoster virus	Encephalitis
	Transverse myelitis
	Vasculopathy
Cytomegalovirus	Ventriculitis
	Vasculitis
	Encephalitis
Human immunodeficiency virus	Encephalitis/encephalopathy
Herpes simplex virus	Encephalitis
JC virus	Progressive multifocal leukoencephalopathy
Epstein–Barr virus	Cerebral lymphomatoid granulomatosis
Parvovirus B19	Encephalitis
Toxoplasma	Encephalitis

Bahr N et al Curr Infect Dis Rep. 2013

IRIS incidence in 22 cohort studies according to median CD4 count at the start of ART



The solid line shows the predicted percentage from the meta-regression model, the dotted lines indicate the 95% confidence intervals

Muller M et al Lancet Infect Dis.2010

Timing of CNS IRIS

Cryptococcus meningitis (CM)

Median time
paradoxical CM-IRIS: **12-16 weeks**

M.tuberculosis meningitis (TBM)

Median time
paradoxical TBM IRIS: **2 weeks**

PML

Median time
paradoxical PML IRIS: **4 weeks** (8 weeks unmasking PML IRIS)

Bahr N et al Curr Infect Dis Rep. 2013

Cryptococcal meningitis-IRIS

- **Incidence:**
  - Paradoxical CM-IRIS: 13%–30%
  - Unmasking CM-IRIS: 0.4%–1.7%

- **Risk stratification for development for CM-IRIS may be possible:**
  - High antigen burden (CrAg) titer or by quantitative culture
  - Low CSF lymphocytes count
  - Paucity of pro-inflammatory cytokines and chemokines (lower levels of IL-6, IL-8, TNF-**α** , and IFN-**γ**) at CM diagnosis

- **Mortality:** rates range from 7.7% to 36%

Chang CC AIDS 2013
Boulware DR PLoS Med. 2010
Bahr N et al Curr Infect Dis Rep. 2013

Cryptococcal meningitis-IRIS

Is the prevention possible ?

Paradoxical CM-IRIS

- optimal timing of ART after CM
- COAT trial (177 ART-naïve persons with a first episode of CM),
  - lower mortality when deferring ART for approximately 5 weeks, as compared with initiation of ART in the first 1–2 weeks after CM diagnosis.

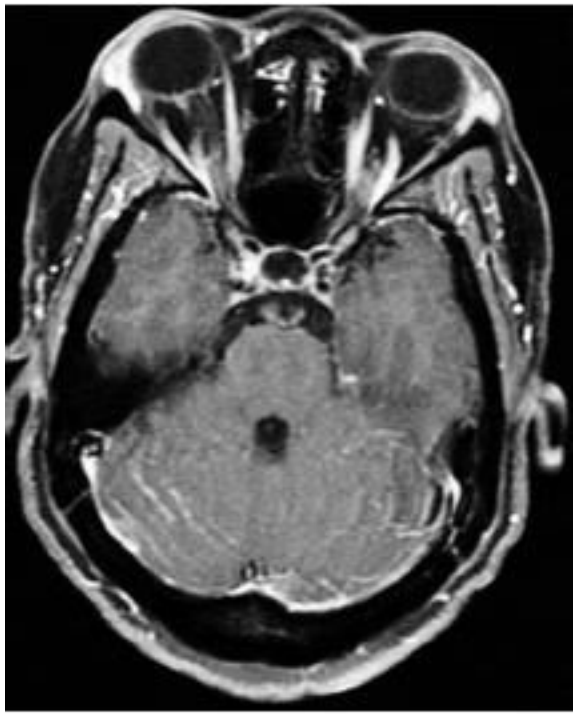
Unmasking CM-IRIS

- Pre-ART CrAg screening with preemptive fluconazole therapy for those positive has recently been recommended for patients with CD4+ counts <100 cells/μL

Boulware, DB CROI 2013

Cryptococcal meningitis-IRIS

- **Clinical picture**
  - **recurrent meningitis,** with sterile CSF fungal cultures.
  - **intracranial space occupying lesions**
  - **extension beyond the CNS** (lymphadenitis, pneumonitis, and ophthalmologic complications)
- **Management**
  - Therapeutic LP is essential
  - Corticosteroids/ hydroxychloroquine, azathioprine, adalimumab, or thalidomide
  - Intensification of antifungal therapy
  - Interruption of ART is rarely necessary



Meintjes G, et al Curr HIV/AIDS Rep. 2012
Boulware DR PLoS Med. 2010
Haddow LJ Lancet Infect Dis. 2010

Tuberculous meningitis-IRIS

- **Incidence:**
  - 47% of TBM patients after starting ART (high TB endemic setting)
  - 12-20% of TB-IRIS = neurological TB- IRIS

- **Risk factors for paradoxical TBM-IRIS:**
  - High baseline CNS bacillary load (CSF *M.tuberculosis* culture positivity
  - Higher CSF concentrations of inflammatory cytokines such as TNF-**α** , IFN-**γ** , and IL-6,
  - Higher CSF neutrophil counts
  - Extrameningeal TB

- **Mortality:** 13-75%, disability 25%

Marais S et al Clin Infect Dis. 2013
Bahr N et al Curr Infect Dis Rep. 2013

Tuberculous meningitis-IRIS

Is prevention possible ?

Paradoxical TBM-IRIS

- optimal timing of ART after TBM diagnosis

- 3 RCTs (2011), (CD4+ count <50 cells/μL), showed a **mortality benefit for starting ART early**, as compared with later (2–4 weeks vs. 8 weeks) after TB treatment
- study of TBM found **no difference between early (within 7 days)** and **delayed (8 weeks)** after TB treatment initiation) ART, but more severe IRIS with early ART

- **our practice is to start ART at 4 weeks in TBM patients**

Unmasking TBM-IRIS

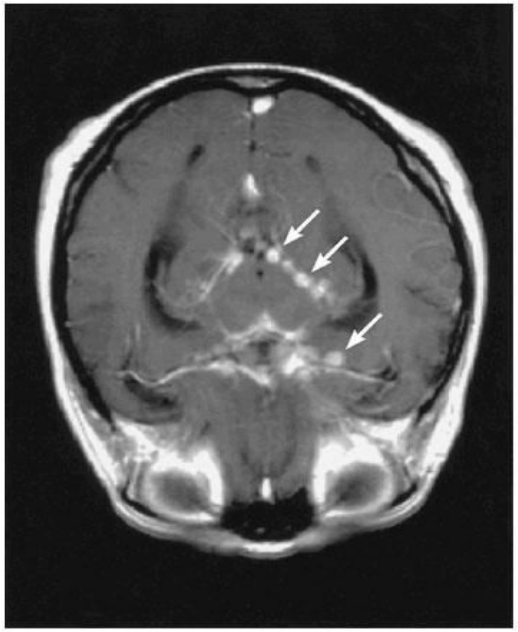
- Pre-ART screening for TB

Bahr N et al Curr Infect Dis Rep. 2013

CNS tuberculosis-IRIS

- **Clinical picture**
  - **meningitis,**
  - brain tuberculomas/abscesses
  - radiculomyelitis, spinal epidural abscesses

- **Management** (no treatment trials in neuro-TB-IRIS)
  - prednisone (starting dose, 1.5 mg/kg/day or equivalent) tapering the dose after 2–4 weeks according to the individual patient's response (3-4 months)
  - continue ART during the IRIS episode



Tuberculous Meningitis

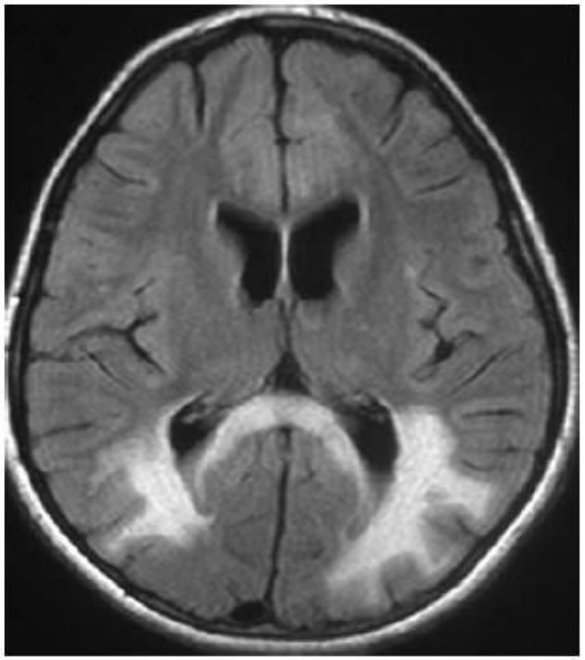
Meintjes G,et al Curr HIV/AIDS Rep. 2012
Marais S et al Clin Infect Dis. 2013
AJNR Am J Neuroradiol

PML-IRIS

- **Incidence:**
  - 18 % of patients with PML diagnosed pre-ART
  - 40% of patients with PML in a mixed cohort of patients (HIV and other causes of immunosuppression)
- **Risk factors** for PML IRIS: few studies
- **Mortality**:
  - paradoxical PML-IRIS 53%
  - unmasking IRIS was 31%.

Tan K, et al Neurology 2009

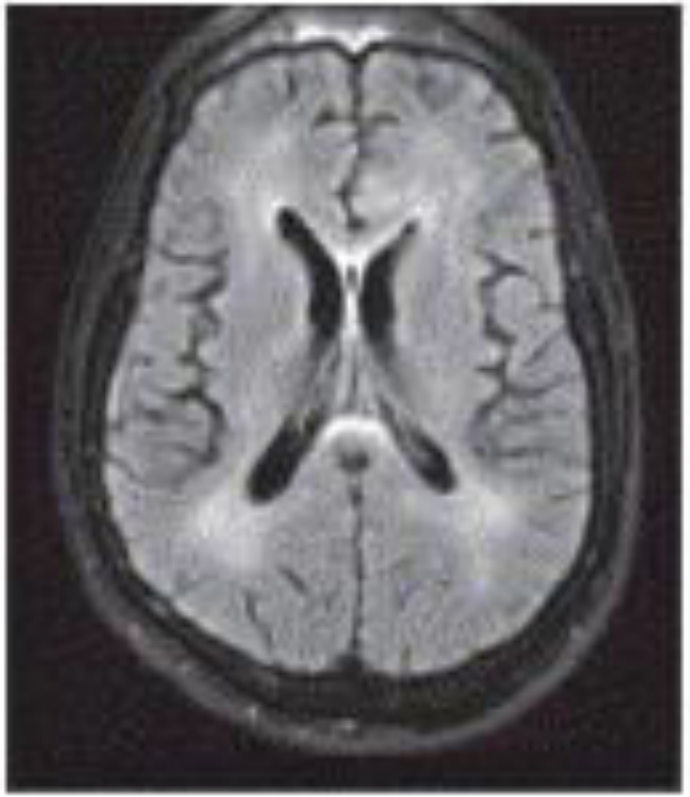
Bilateral symmetrical hyperintensity in the periventricular white matter of the parieto-occipital lobes



Rapid clinical deterioriation and death soon after starting HAART

HIV Associated Neurocognitive Disorder (HAND) IRIS

- IRIS has been reported to complicate HAND as an encephalitic process in patients initiating ART
- HAND-IRIS has been described
  - as worsening of preexisting HAND,
  - as the cause of new onset HAND
- Fulminant disease complicated by cerebral edema = the most severe form of HAND-IRIS



HAND: symmetrical hyper-signal of white-matter, especially periventricular (FLAIR); no mass effect or contrast enhancement; U fibers not involved

Research priorities in CNS-IRIS

- further characterization of IRIS pathogenesis,
- risk factors for the development of PML-IRIS,
- more rapid diagnostic tools for CNS-IRIS
- role and timing of amphotericin B and corticosteroid use in CM-IRIS,
- further characterization of HAND-IRIS
- the role of IRIS in the development of HAND in patients on ART

Unanswered questions about HAND IRIS

HIV itself or a component of HIV is the antigenic target?

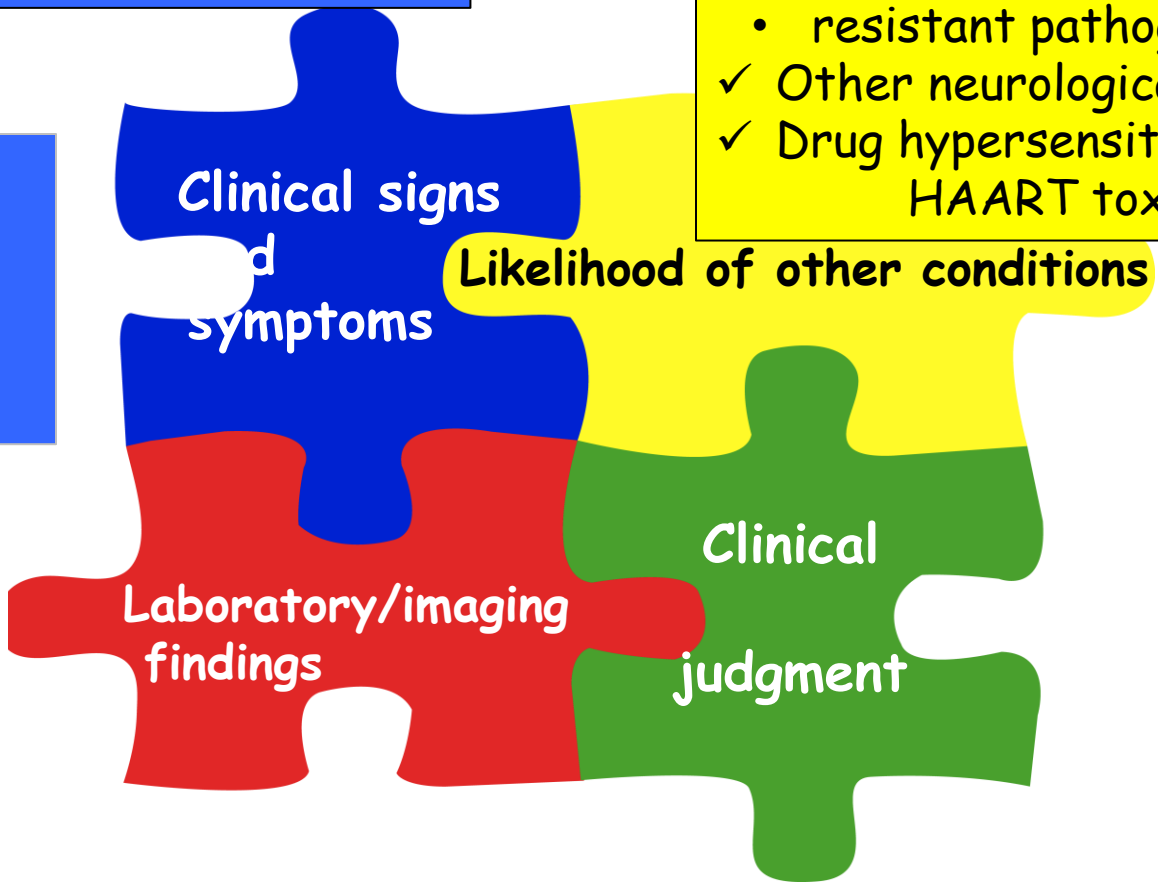
Autoimmune CNS process in the context of ART occurring on the background of chronic HIV damage and immune dysregulation in the CNS?

Miller RF,et al Acta Neuropathol. 2004

IRIS: a challenging diagnosis

Clinical deterioration under adequate antimicrobials targeting at least one specific germ.

- Fever
- Headache
- Vomiting
- Focal signs
- Coma



- ✓ Uncontrolled disease
  - inadequate treatment,
  - low adherence,
  - resistant pathogen
- ✓ Other neurological infection
- ✓ Drug hypersensitivity (ARs)/ HAART toxicity

CNS IRIS

Patient (recently started) on ART

Risk factors

- ✓ More advanced HIV disease at the time of ART initiation
- ✓ Multiple OI and/or high antigenic burden; depend on pathogen(!)
- ✓ Genetic background & particular reactivity
- ✓ ART timing and follow-up (rapid T CD4+ rise, rapid VL drop)

Clinical deterioration IRIS symptoms often mimic the original infection
Laboratory and imaging supporting a CNS OI

Excluding:

- ✓ Uncontrolled disease (inadequate treatment, low adherence, resistant pathogen)
- ✓ Other conditions (concomitant diseases due to other pathogens)
- ✓ Drug hypersensitivity or other medication's adverse reactions

CNS-IRIS management

- "unmasking" IRIS: antimicrobial therapy to reduce the antigen load of the triggering pathogen

- "paradoxical" IRIS: generally no new antimicrobial therapy; short term corticosteroids therapy (NSAIs)

NB: consider if the initial antimicrobial therapy was effective and appropriate

CNS-IRIS management

- Most challenging form of IRIS to manage
- No clear evidence based guidelines
- Most cases: self-limited course and will resolve with continuing treatment with little or no change in overall management
- Centers on decreasing inflammation and reducing raised intracranial pressure
- Local surgical procedures (brain abscesses)

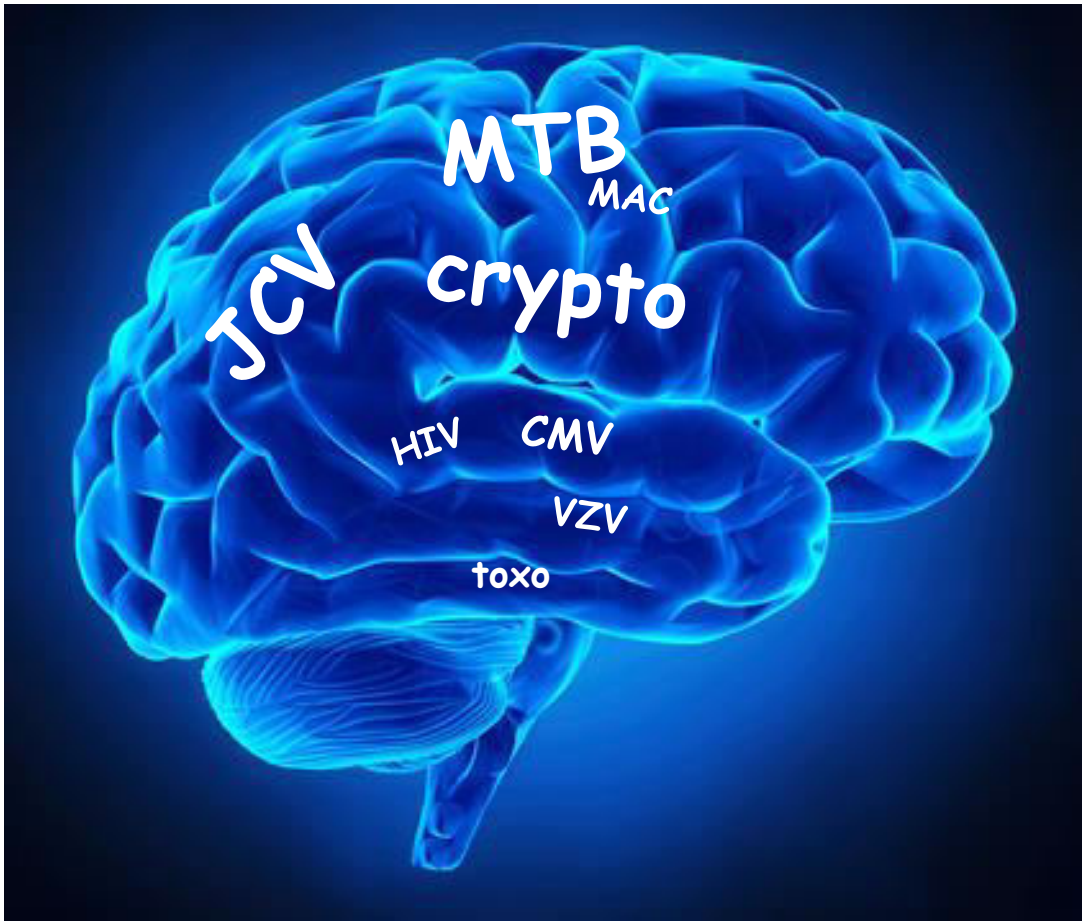
Discussion - Diagnosis and Management of TB-IRIS - Resource-Limited Settings - Global HIV Web Study
http://depts.washington.edu/ghivaids/reslimited/case3/discussion.html

CNS-IRIS management

- **Mild** cases:
  - observation,
  - continue HAART
- **Moderate** cases:
  - NSAI drugs,
  - continue HAART
- **Severe** cases:
  - corticosteroids,
  - consider stopping HAART if life-threatening

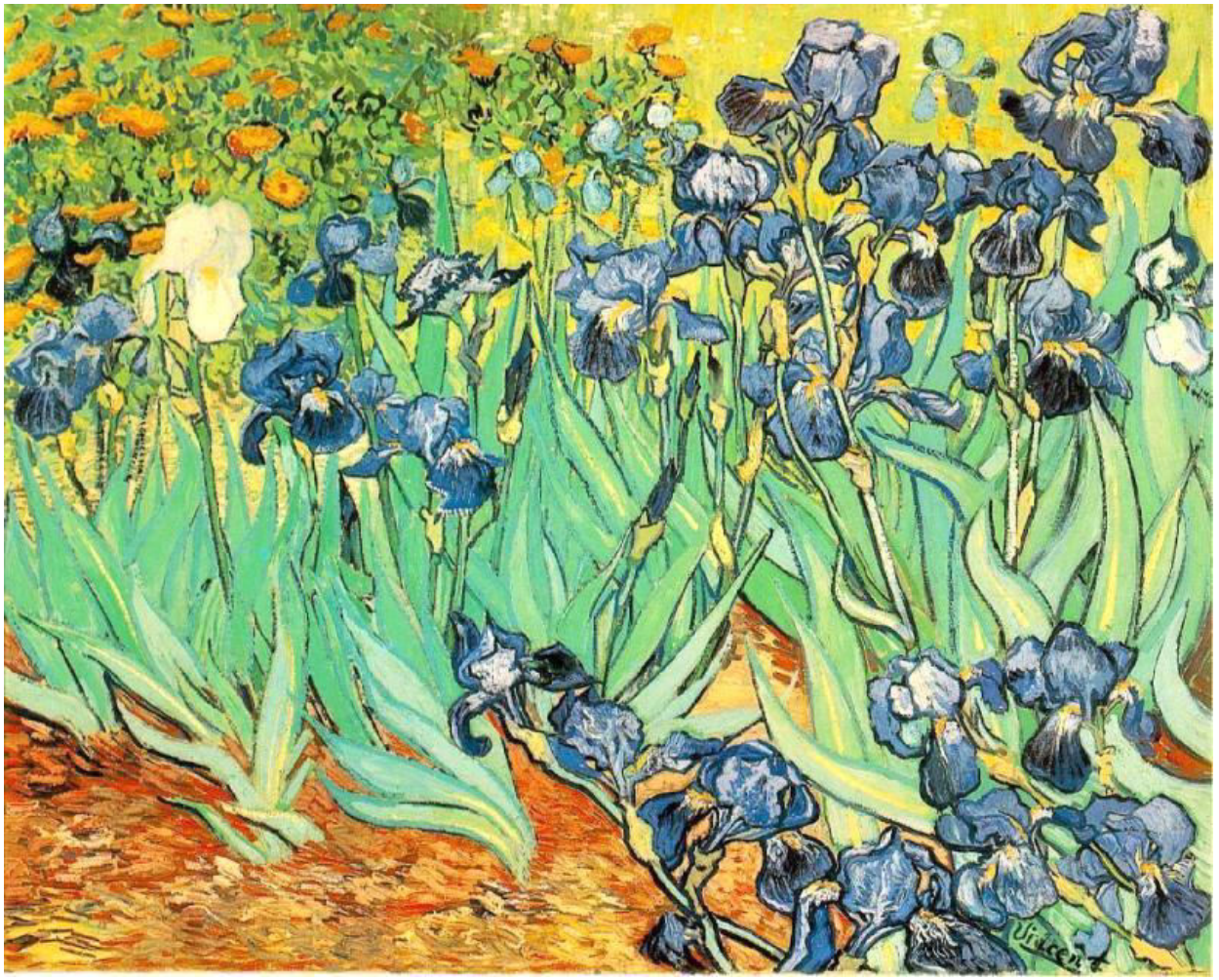
Conclusions

- CNS-IRIS is a significant cause of morbidity and mortality
- CNS-IRIS related to TB, Cryptococcus and PML are most frequent
- Advances in diagnosis and prediction have been made in the past few years
- Very few evidence based guidelines for the management


MTB
MAC
JCV
crypto
HIV
CMV
VZV
toxo

in the IRIS' field…

…a brighter light!



Thank you!