Central Nervous System Immune Reconstitution Inflammatory Syndrome – CNS-IRIS

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CNS-IRIS LEARNING OBJECTIVES

- Define CNS-IRIS and describes the epidemiology
- Review pathogenesis and classification of CNS-IRIS
- Define diagnosis and Explain the clinical spectrum of CNS-IRIS
- Discuss major pathogens and management of CNS-IRIS

IRIS and CNS-IRIS - definitions

- **IRIS:** Immune reconstitution inflammatory syndrome describes a collection of different inflammatory disorders which are associated with paradoxical deterioration of various pre-existing infectious processes following commencement of HAART in HIV−infected patients.
- **CNS-IRIS**
  - Central nervous System IRIS is a T-cell-mediated encephalitis which is associated with paradoxical neurological deterioration following commencement of HAART in the presence or absence of opportunistic infections.
  - CNS-IRIS may occur in absence of HIV infection, like following MS natalizumab treatment discontinuation, tuberculosis meningitis and autoimmune diseases.

Clifford, D. B. Neurological immune reconstitution inflammatory response. Curr. Opin. Neurol. 28, 295–301 (2015).

CNS-IRIS - introduction and epidemiology

- CNS-IRIS developing after the initiation of HAART is characterized by an intense inflammatory reaction to dead or latent organisms or to self-antigens due to a unregulated immune response.
- While this reaction can range from mild to fulminating, encompassing a very wide clinical spectrum.
- Estimated IRIS incidence ranging from 20–35% of individuals treated with ART.
- The overall incidence of CNS-IRIS inclusive of all patients initiating ART is estimated to be approximately 1%.
- Although CNS-IRIS is a smaller proportion of all IRIS cases, it represents the most debilitating form of IRIS and is associated with death or permanent neurological deficit in an estimated 16–50% of cases.

Singer, E. J., Valdes-Sueiras, M., Commins, D. & Levine, A. Neurologic presentations of AIDS. Neurol. Clin. 28, 253–75 (2010).

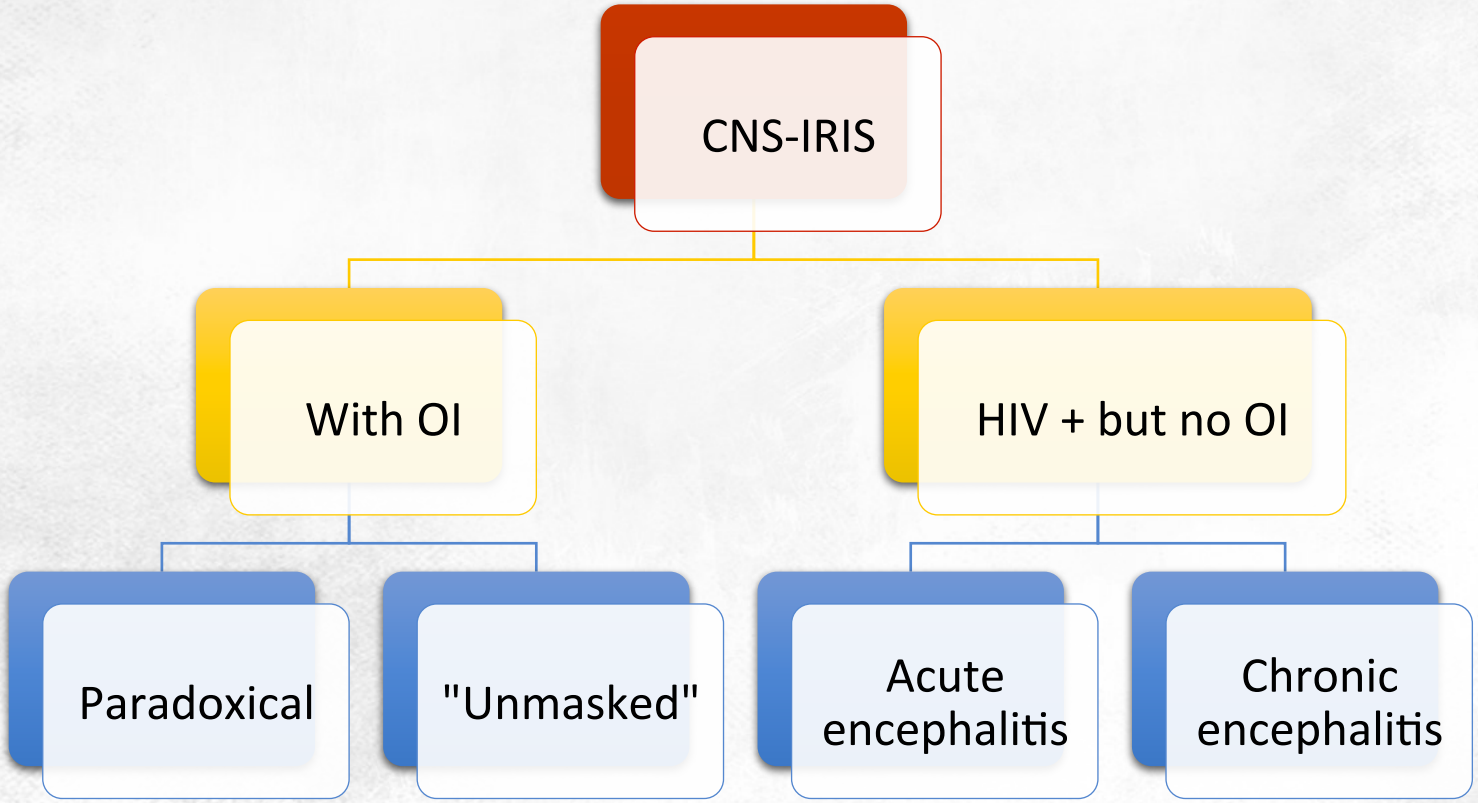
CNS-IRIS – classification and pathogenesis

As the viral load diminishes and the immune system recovers, patients may develop:

1- Paradoxical worsening of a recognized opportunistic infection (OI),

2- Revealing of an underlying opportunistic infection (unmasking IRIS) or

3- Immune disease either in the periphery or in the central nervous system (CNS)

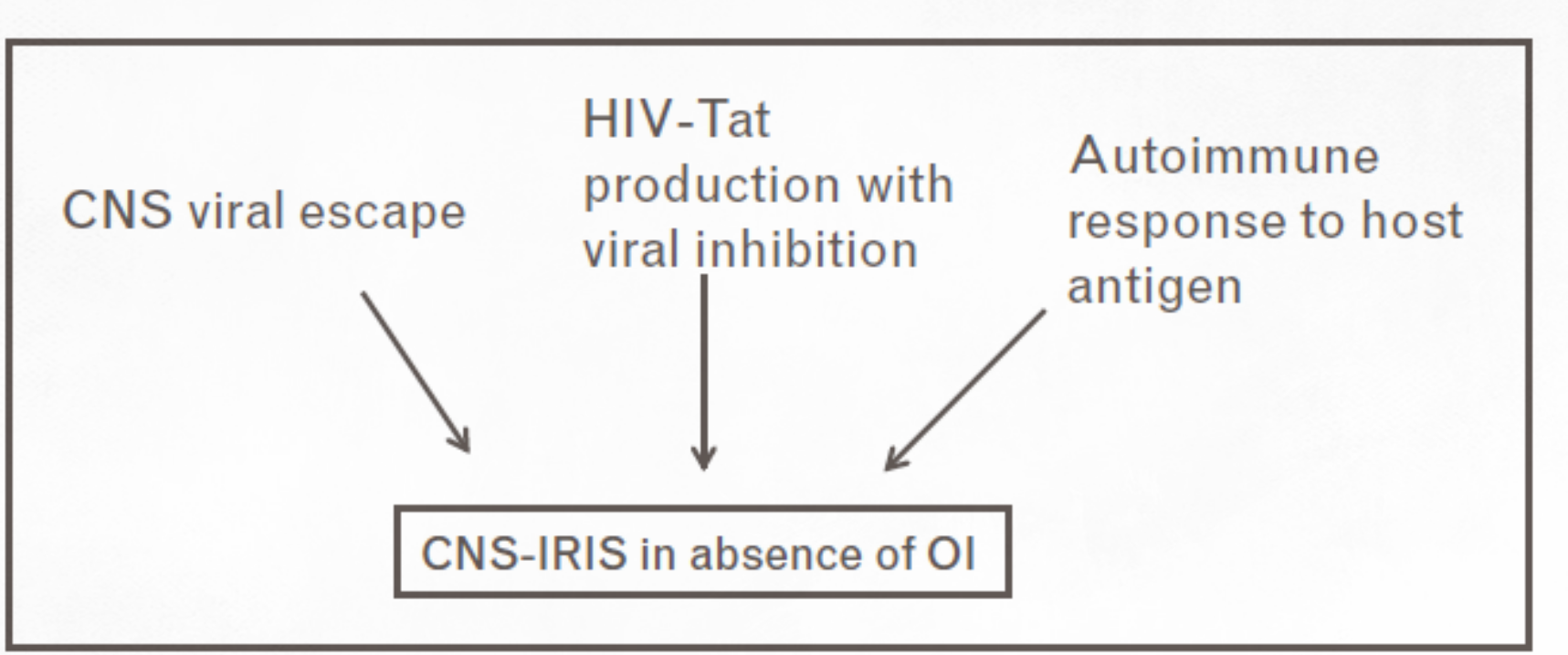


CNS-IRIS – classification and pathogenesis

- CD8 cell infiltration in the leptomeninges, perivascular spaces, blood vessels, and even parenchyma is the pathologic hallmark of CNS-IRIS.
- This may manifest as an acute encephalitis accompanied with neurodegeneration or with demyelination
- One protein with known immune activation capabilities called HIV protein Tat, contributes to immune deregulation and may participate in the development of subacute and chronic forms of CNS-IRIS .
- In the post-antiretroviral therapy era, mild neurocognitive impairment is common which is accompanied with activated lymphocytes in the cerebrospinal fluid. This may represent a form of chronic CNS-IRIS.

Johnson, T. P. & Nath, A. New insights into immune reconstitution inflammatory syndrome of the central nervous system. Curr. Opin. HIV AIDS 9, 572–578 (2014).

CNS-IRIS – classification and pathogenesis

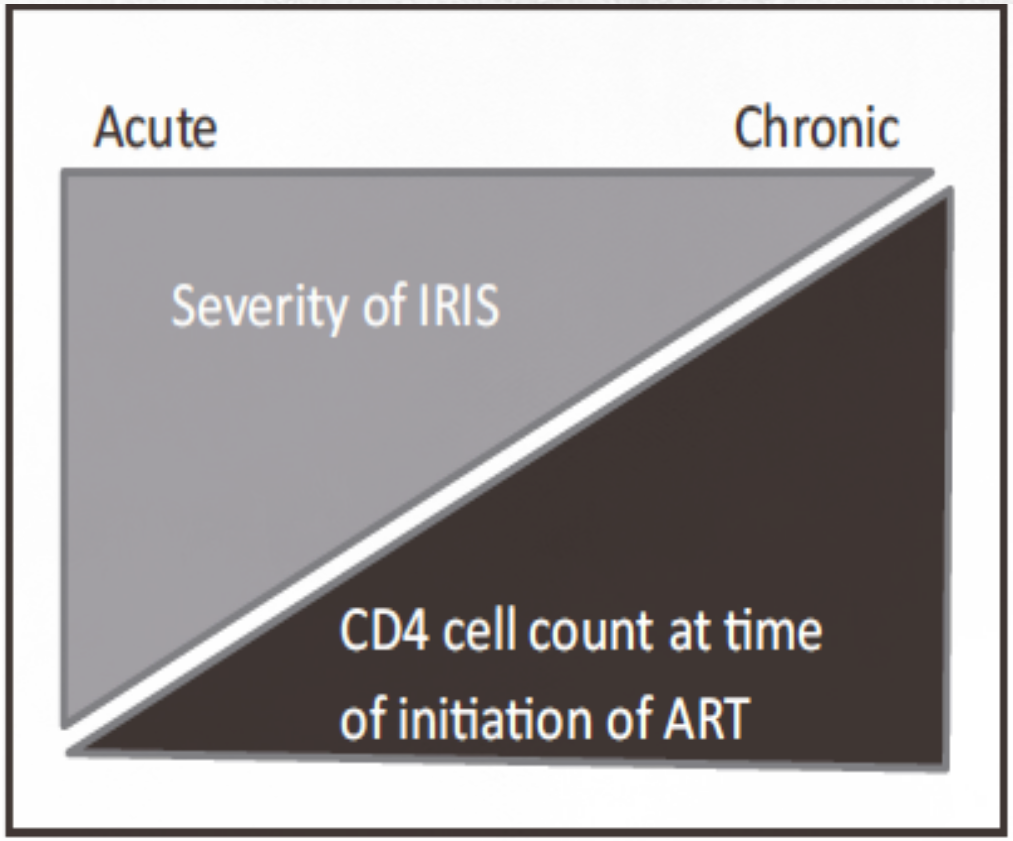


In the absence of an opportunistic infection, central nervous system-immune reconstitution inflammatory syndrome may be driven by multiple antigenic stimuli.

CNS, central nervous system; IRIS, immune reconstitution inflammatory syndrome; OI, opportunistic infection.

CNS-IRIS – diagnosis and clinical spectrum

- CNS-IRIS typically occurs within 2 months after the initiation of ART; however, IRIS may occur as late as 2 years after ART initiation
- A positive virologic and immunological response to ART and a temporal association between initiation and the onset of clinical features.
- The main risk factors for CNS-IRIS in HIV-infected individuals are as follows:
  1. low CD4 nadir (<100 cells/ml);
  2. rapid decline in viral load following initiation of ART;
  3. underlying opportunistic infection;
  4. genetic factors.



Johnson, T. P. & Nath, A. New insights into immune reconstitution inflammatory syndrome of the central nervous system. Curr. Opin. HIV AIDS 9, 572–578 (2014).

CNS-IRIS – diagnosis and clinical spectrum

OI Major Pathogens

- Mycobacterium tuberculosis
- Cryptococcus neoformans
- JC Virus

OI Minor Pathogens

- varicella zoster virus - VZV
- Cytomegalovirus - CMV
- Candida species
- Toxoplasma gondii

No OI – Acute / Subacute

- Neurodegeneration with demyelination
- Neurodegeneration without demyelination
- Inflammatory Syndrome and hiv encephalitis
- Peripheral nervous system

No OI - Chronic

- HAND
- Stroke
- Premature aging

CNS-IRIS – opportunistic infection

Tuberculous Meningitis

- Neurological tuberculosis IRIS occurs in a substantial proportion (12%) of tuberculosis IRIS cases. Mortality is high (up to 30%) in those affected
- Tuberculous meningitis in the setting of IRIS is characterized by high CSF neutrophil counts and CSF culture positivity at presentation
- Manifestations of neurological tuberculosis IRIS include
  1. meningitis
  2. intracranial tuberculomata
  3. brain abscesses
  4. Radiculomyelitis
  5. spinal epidural abscesses
- In the case of tuberculosis meningitis delaying ART reduced the most severe adverse clinical events but did not impact mortality
- It is currently recommended that in the case of tuberculosis meningitis ART be delayed 2-4 weeks

Marais S, Meintjes G, Pepper DJ, et al. Frequency, severity and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. Clin Infect Dis. 2012;56:450-460.

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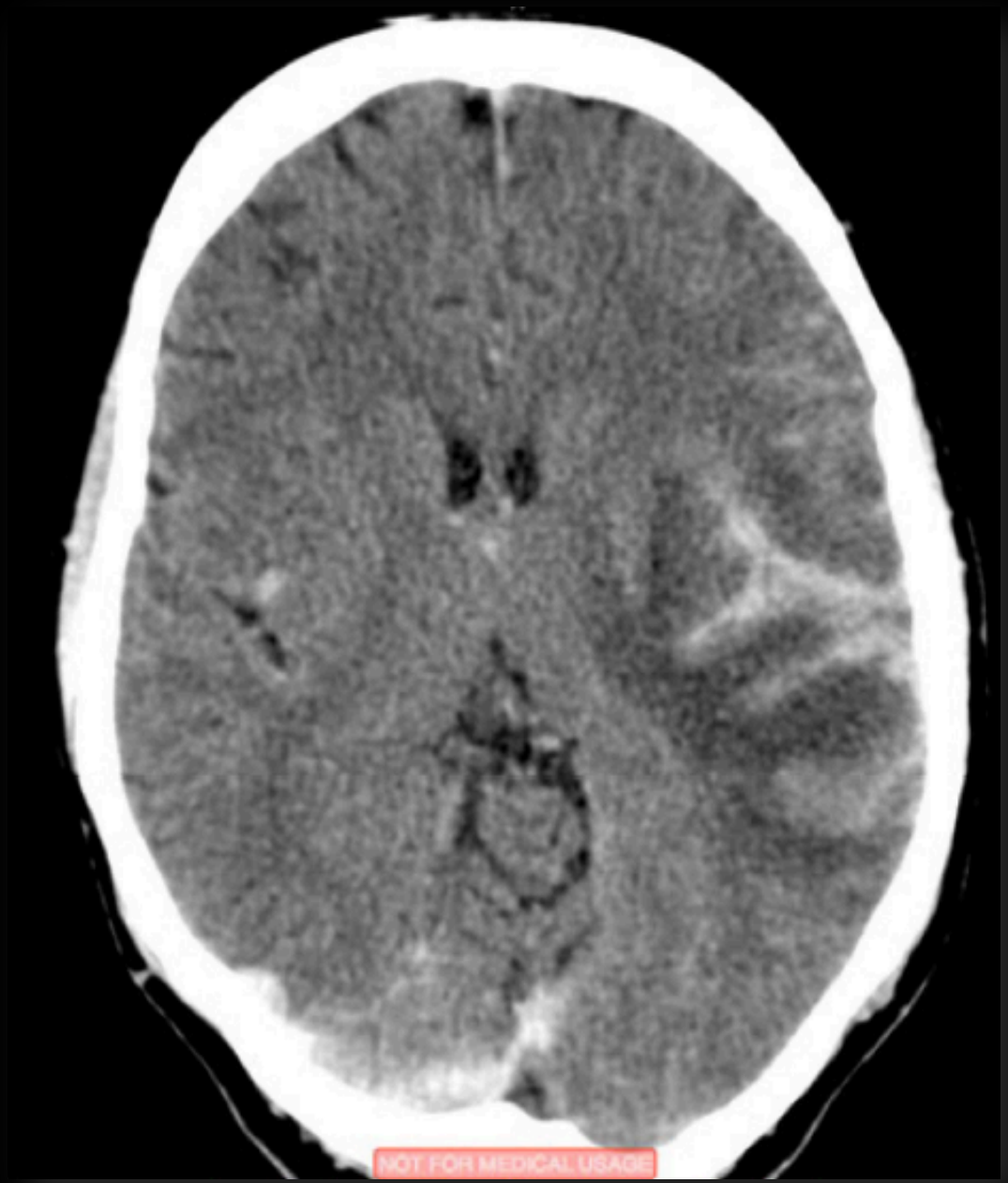

TB-IRIS pachymeningitis

Postcontrast TC, shows focal leptomeningeal enhancement involving the left sylvian fissure with adjacent cerebral edema in a patient with tuberculous meningitis immune reconstitution inflammatory syndrome

Bahr N, Boulware DR, Marais S, Scriven J, Wilkinson RJ, Meintjes G. Central Nervous System Immune Reconstitution Inflammatory Syndrome. Curr Infect Dis Rep. 2013;15(6):583-593. doi:10.1007/s11908-013-0378-5.

CNS-IRIS – opportunistic infection

Cryptococcal meningitis

- Cryptococcal-IRIS can be manifested in many different ways— as lymphadenitis, pneumonitis, cryptococcal meningitis (CM-IRIS), or cryptococcomas.
- CM-IRIS mortality rates have ranged between 8% and 30%
- Patients with CM-IRIS can be recognized clinically by the development of headache, fever, malaise, altered mental status, raised intracranial pressure, and cranial nerve palsies in the setting of lymphadenopathy and new pulmonary infiltrates.
- Higher fungal burden in the blood, higher opening pressures in the CSF, and sometimes culture-negative CSF are diagnostic clues that may differentiate CM-IRIS from pre-HAART cryptococcal infection
- The major risk factors for paradoxical CM-IRIS are related to high antigen burden and severity of pre-ART immune dysfunction. Antigen burden can be assessed either by cryptococcal antigen (CrAg) titer or by quantitative culture
- HAART initiation should be delayed until completion of induction therapy with an objective to start HAART within 4–5 weeks.

Vidal, J. E., Penalva de Oliveira, A. C., Dauar, R. F. & Boulware, D. R. Strategies to reduce mortality and morbidity due to AIDS-related cryptococcal meningitis in Latin America. *Braz. J. Infect. Dis.* **17,** 353–62 (2013).

CNS-IRIS – opportunistic infection

HIV progressive multifocal leukoencephalopathy –PML-IRIS

- Progressive multifocal leucoencephalopathy (PML), a demyelinating disease of the brain caused by the JC polyomavirus, occurs in 3 %–5 % of persons with AIDS worldwide.
- Both paradoxical (also termed PML-delayed IRIS) and unmasking (also termed PML simultaneous IRIS) PML-IRIS have been described.
- the median time to PML-IRIS was 4 weeks from starting ART with paradoxical IRIS and 7–8 weeks with unmasking IRIS
- CSF PCR for JC virus in patients not on ART is >95 % sensitive, but the PCR is less sensitive in patients on ART (sensitivity 58 %)
- Brain MRI shows enhancement more often with PML-IRIS than with PML
- It is essential to begin ART immediately if JCV infection is detected within the CNS regardless of the risk of IRIS as the immune system is the only current defense against this pathogen
- Corticosteroids have shown some benefit if CNS-IRIS does occur

Bahr N, Boulware DR, Marais S, Scriven J, Wilkinson RJ, Meintjes G. Central Nervous System Immune Reconstitution Inflammatory Syndrome. Curr Infect Dis Rep. 2013;15(6):583-593. doi:10.1007/s11908-013-0378-5.

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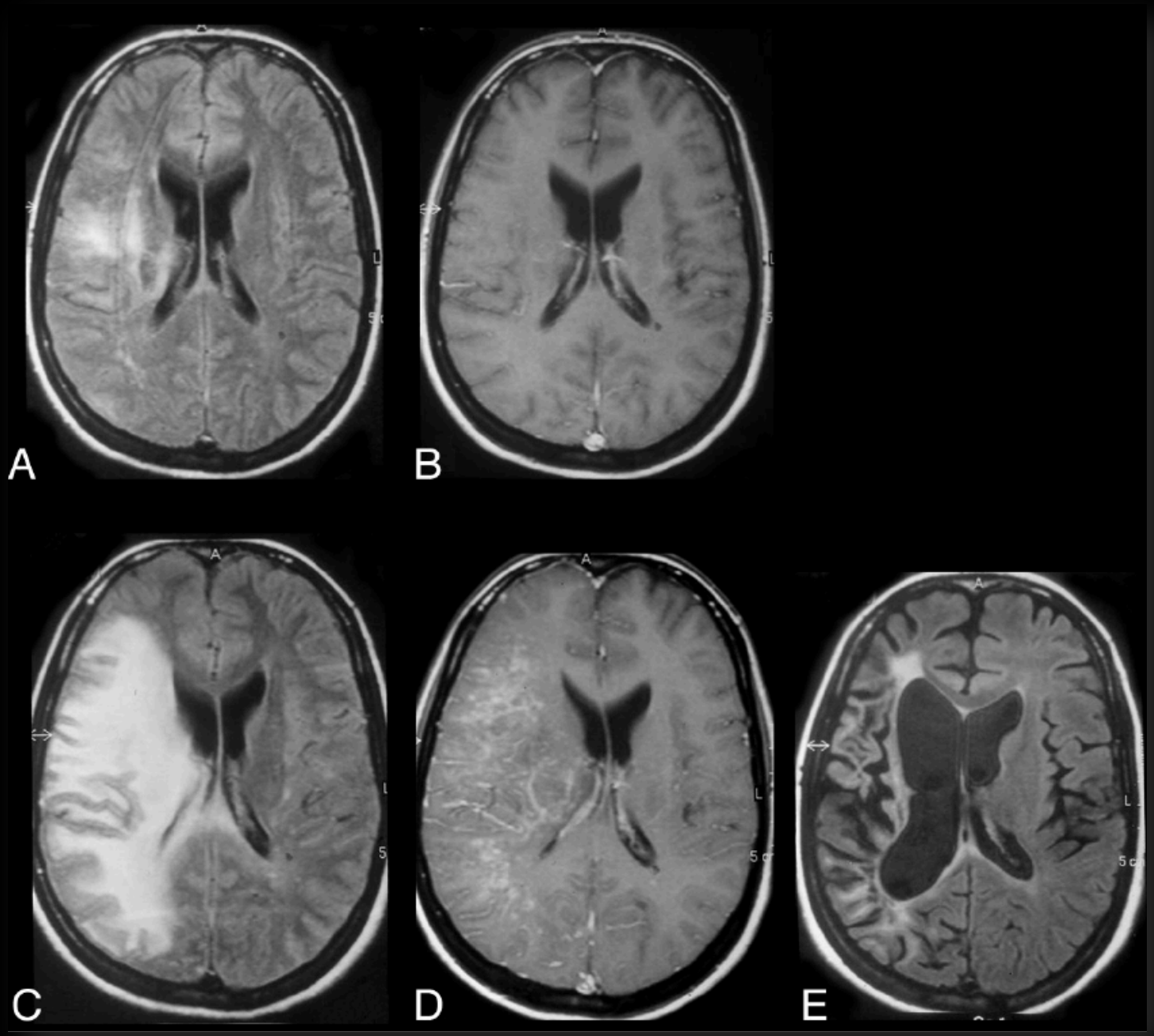


PML-IRIS. Patient with AIDS and PML

Riveiro-Barciela, M. *et al.* Neurological opportunistic infections and neurological immune reconstitution syndrome: impact of one decade of highly active antiretroviral treatment in a tertiary hospital. *HIV Med.* **14,** 21–30 (2013).

CNS-IRIS – opportunistic infection

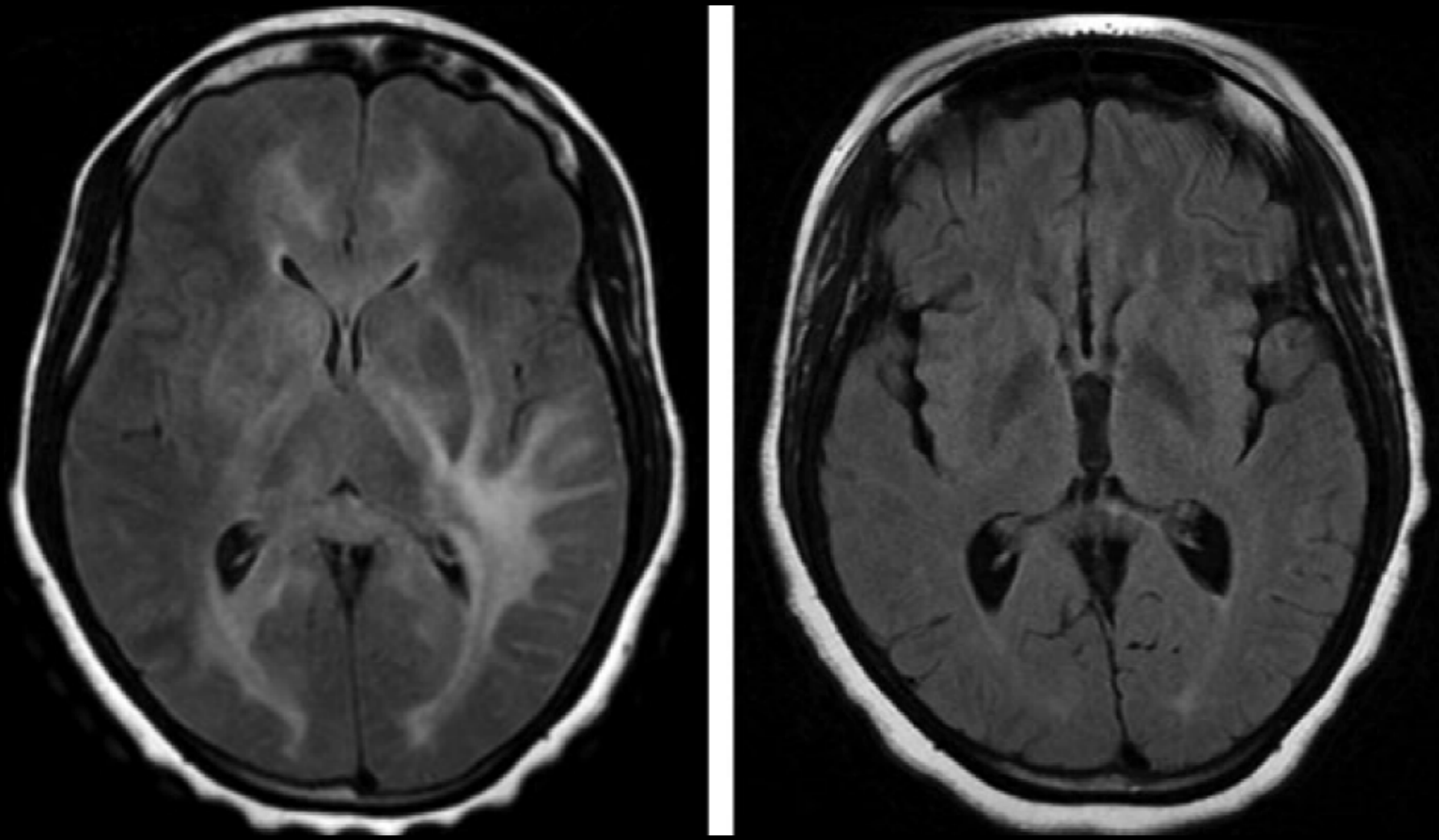
natalizumab-associated progressive multifocal leukoencephalopathy IRIS

- Natalizumab is a humanized monoclonal antibody directed against the cellular adhesion molecule a4-integrin and is used in the treatment of multiple sclerosis (MS). By inhibiting the egress of lymphocytes from the blood vessels, it markedly reduces inflammation in the CNS.
- Plasma exchange has been used to remove natalizumab, thus restoring lymphocyte trafficking into the brain in patients who developed PML.
- Paradoxically, the effective removal of natalizumab and sudden restoration of cellular immunity may cause worsening of neurologic deficits, consistent with the development of IRIS
- PML developed in all cases of natalizumab-associated PML. Patients appeared to be differentiated by the time course and patterns of clinical worsening and contrast enhancement relative to PLEX after the diagnosis of PML into early and late IRIS.
- The PML-IRIS developing in this particular setting is said to be more severe than that observed in the HIV patient with PML-IRIS because of the restored immune surveillance

Hellwig, K., Kleiter, I. & Gold, R. Immune reconstitution inflammatory syndrome in natalizumab-associated PML. *Neurology* **78,** 371; author reply 371 (2012).

CNS-IRIS – neurocognitive impairment

- Similar to IRIS, the risk of neurocognitive impairment is also tightly correlated with a lower CD4 nadir suggesting that immune depletion then restoration plays an important role in the development of HAND
- Chronic form of CNS-IRIS may be an important component of HAND and they may have similar disease mechanisms with differing acute severity



T2 fluid attenuated inversion recovery (FLAIR) image (A) from a patient with worsening cognitive function nearly 2 years after initiation of combination antiretroviral therapy

Lyons, J., Venna, N. & Cho, T. a. Atypical nervous system manifestations of HIV. Semin. Neurol. 31, 254–65 (2011).

CNS-IRIS – conclusions

- CNS-IRIS is a serious complication, particularly associated with HAART

- The syndrome has varied clinical presentation and maybe unrecognized

- Treatment strategies may vary depending on the pathophysiological mechanism