Update on CNS-OIs in HIV infection

Paola Cinque

Unità di Malattie Infettive

IRCCS Ospedale San Raffaele | Milano

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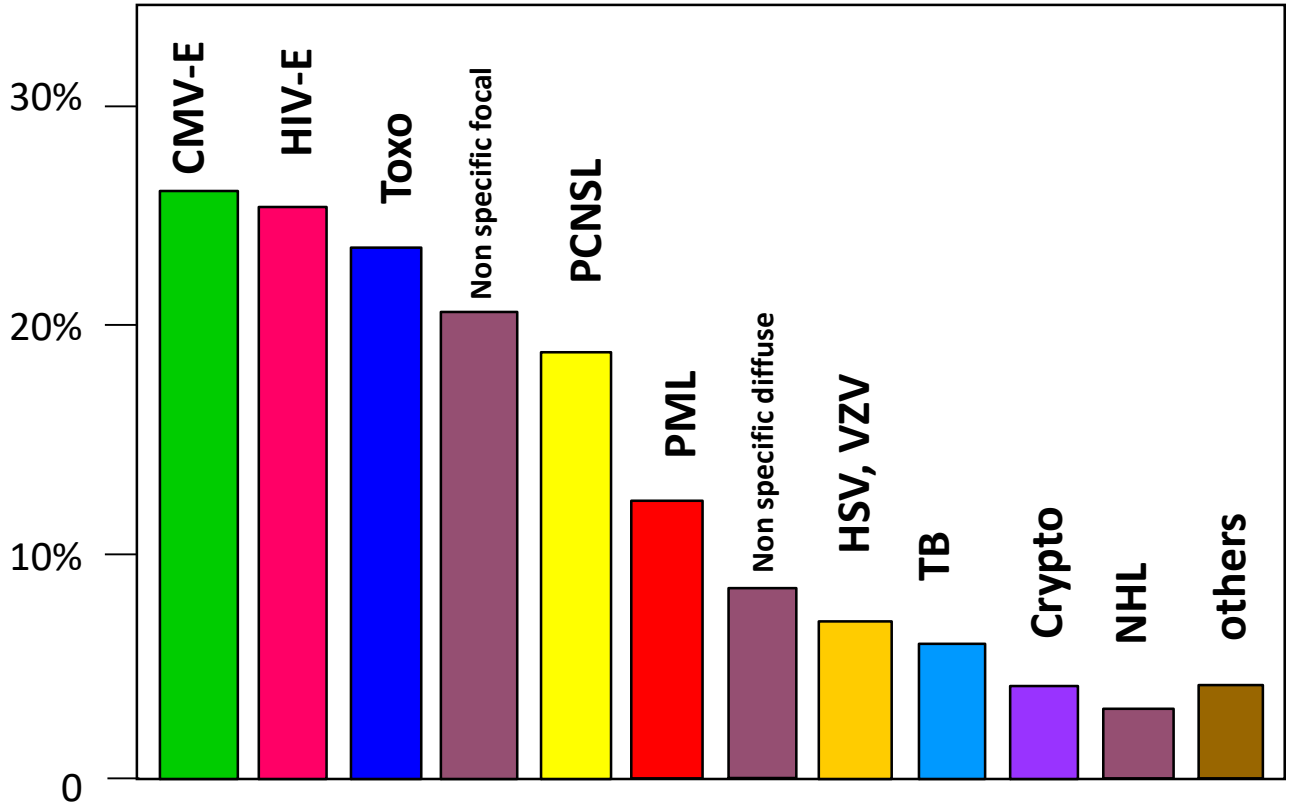
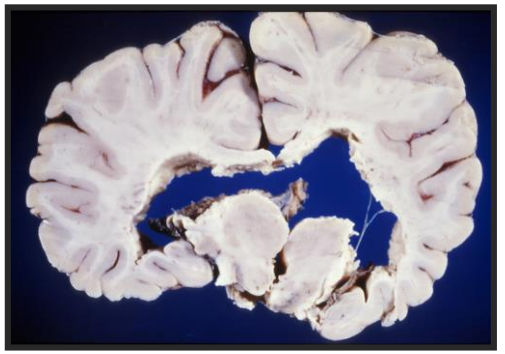
Frequency of HIV-related CNS diseases at post-mortem examination (1985-1995)

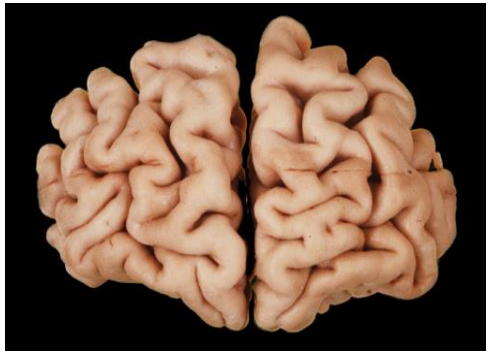


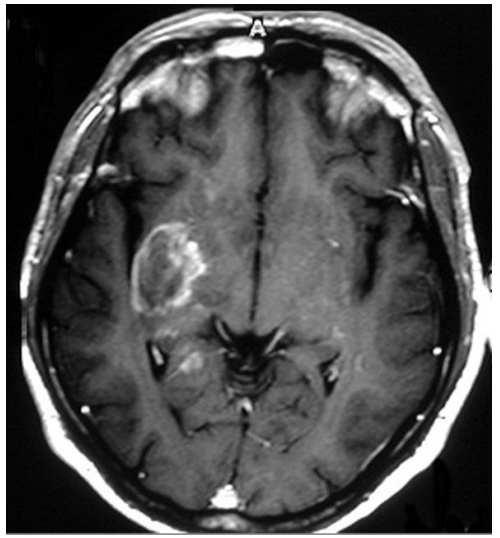
L. Vago and P. Cinque, 1998

CMV-E

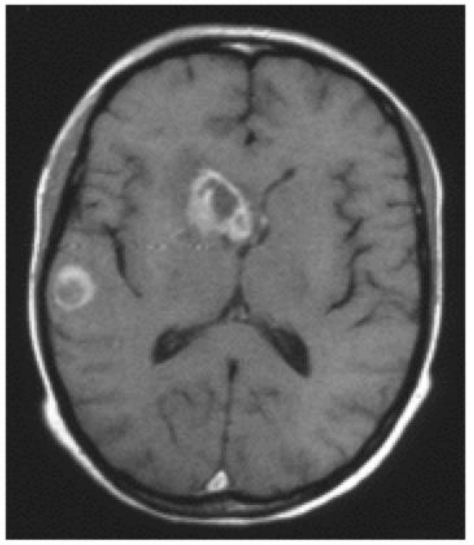


HIV-E



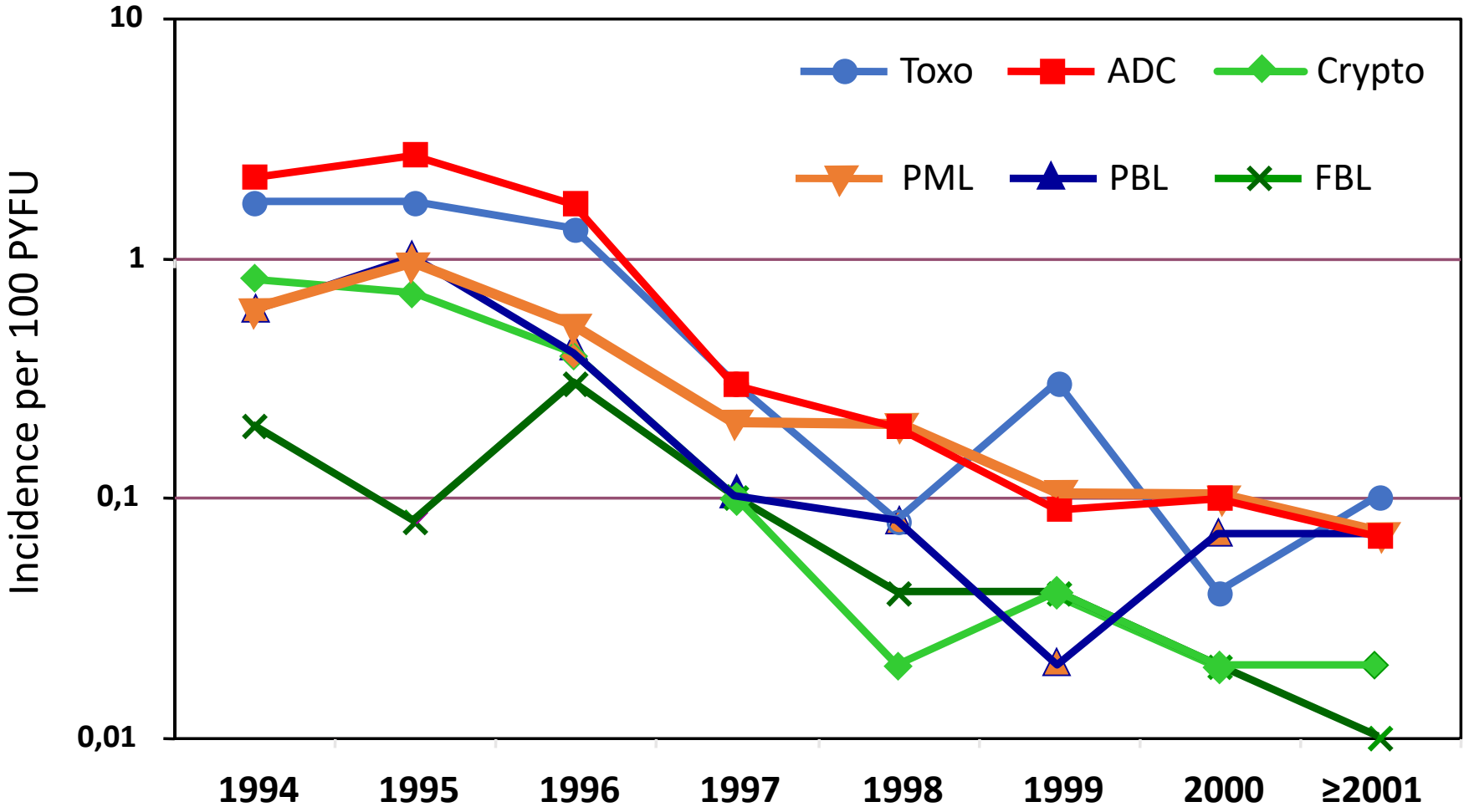


Toxo



PCNSL

Reduced incidence of CNS-D in the EuroSIDA cohort



D'Arminio Monforte et al, Ann Neurol 2004

Mortality Hazard Risk of AIDS-associated events (ADE) during cART

31,620 patients from 15 cohorts
2880 ADE; 377 ADE-related deaths

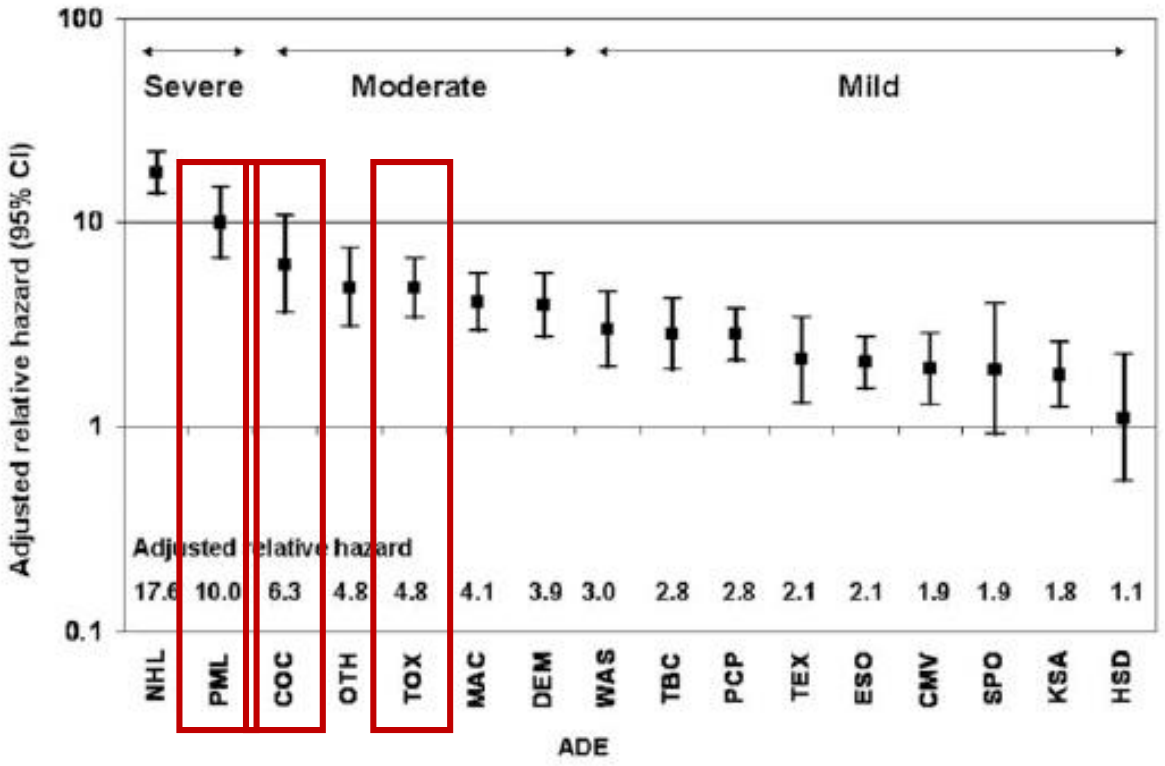


Table 2. Ranking and classification of AIDS-defining events (ADEs) according to severity (impact on subsequent mortality) in antiretroviral-naive patients initiating combination antiretroviral therapy.

ADE	Median rank (2.5th and 97.5th percentiles)	ADE severity category
Non-Hodgkin's lymphoma	16 (15–16)	Severe
Progressive multifocal leukoencephalopathy	15 (13–16)	Severe
Cryptococcosis	14 (8–15)	Moderate
Cerebral toxoplasmosis	12 (6–14)	Moderate
Rare ADE[a]	12 (8–14)	Moderate
AIDS dementia complex	11 (6–14)	Moderate
Disseminated *Mycobacterium avium* disease	11 (6–14)	Moderate
HIV wasting syndrome	8 (2–13)	Mild
Pulmonary tuberculosis	7 (3–12)	Mild
Pneumocystis jiroveci (carinii) pneumonia	7 (3–11)	Mild
Extrapulmonary tuberculosis	5 (1–10)	Mild
Esophageal candidiasis	5 (2–9)	Mild
Cryptosporidiosis	4 (1–12)	Mild
Cytomegalovirus infection	4 (1–9)	Mild
Kaposi sarcoma	3 (1–8)	Mild
Herpes simplex disease	1 (1–8)	Mild

The Antiretroviral Therapy Cohort Collaboration, CID 2009

CNS-OIs are highly prevalent and associated with high mortality in low-income and middle-income countries (LMICs)

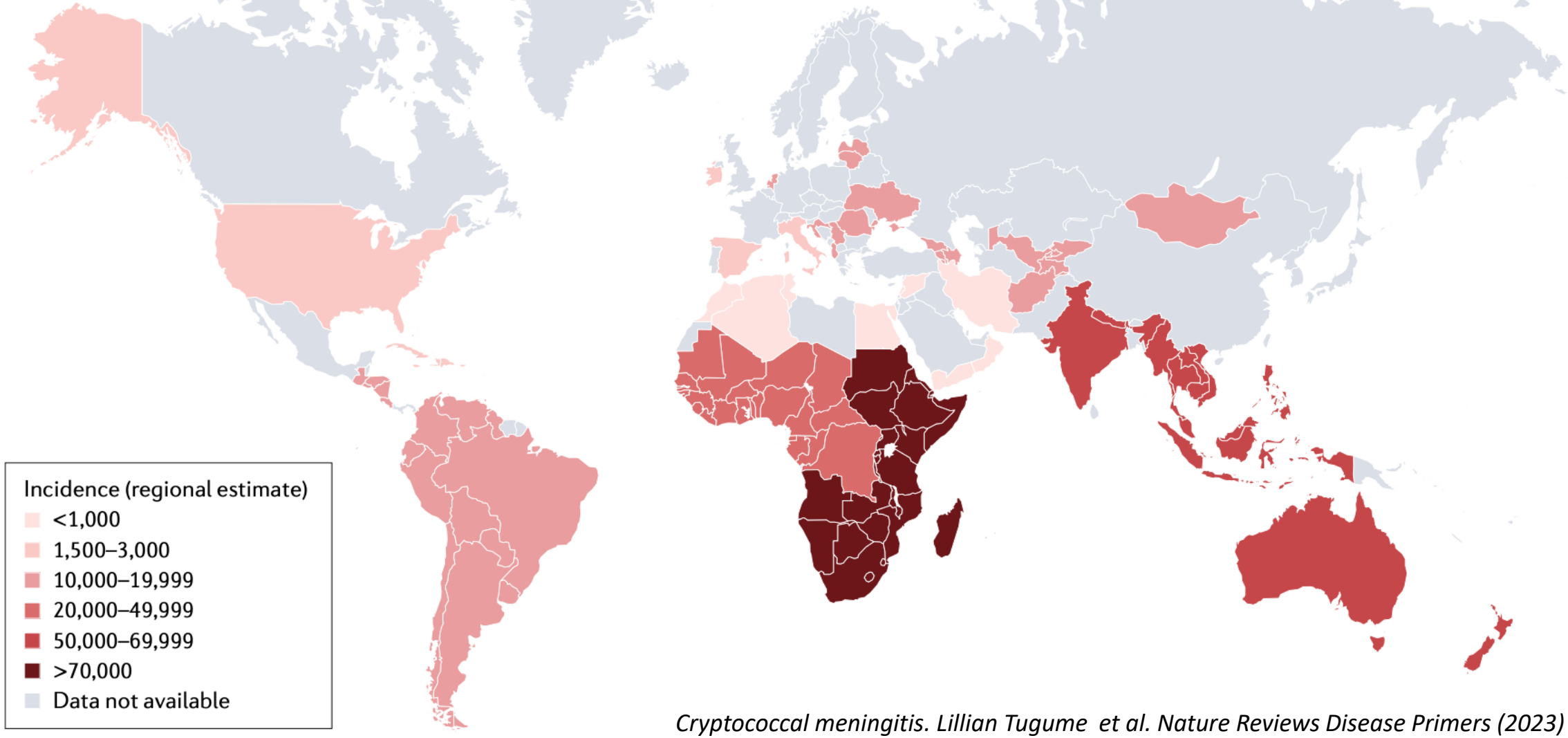
- The precise burden of CNS infections in LMICs in Africa remains unknown, but these Ois might contribute **up to a third of HIV-related deaths**
- **Cryptococcal meningitis** remains a leading cause of HIV-related CNS infection, contributing up to 20% of HIV-related mortality despite ART roll-out
- **Tuberculous and bacterial meningitis, and cerebral toxoplasmosis** are also common causes of HIV-related death
- Substantial numbers of PWH continue to present or re-present to care with advanced HIV disease, and over half of patients with cryptococcal meningitis are either non-adherent ART or on a failing regimen

*Rajasingham R, et al. Lancet Infect Dis 2022; **22:** 1748–55*

Global incidence of cryptococcal meningitis

25-30% mortality in trial settings (up to 70% in clinical practice)

15-20% contribution to HIV-related mortality



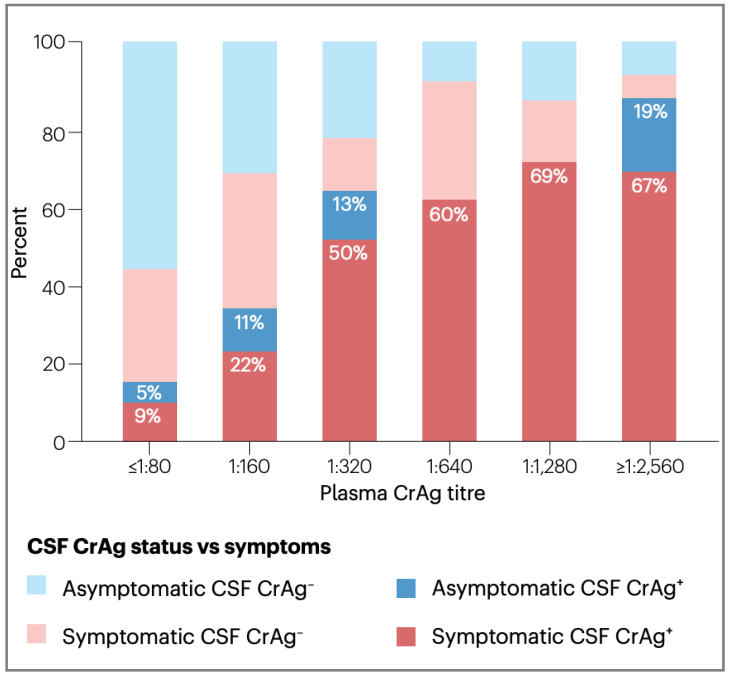
Cryptococcal meningitis. Lillian Tugume et al. Nature Reviews Disease Primers (2023) 9:62

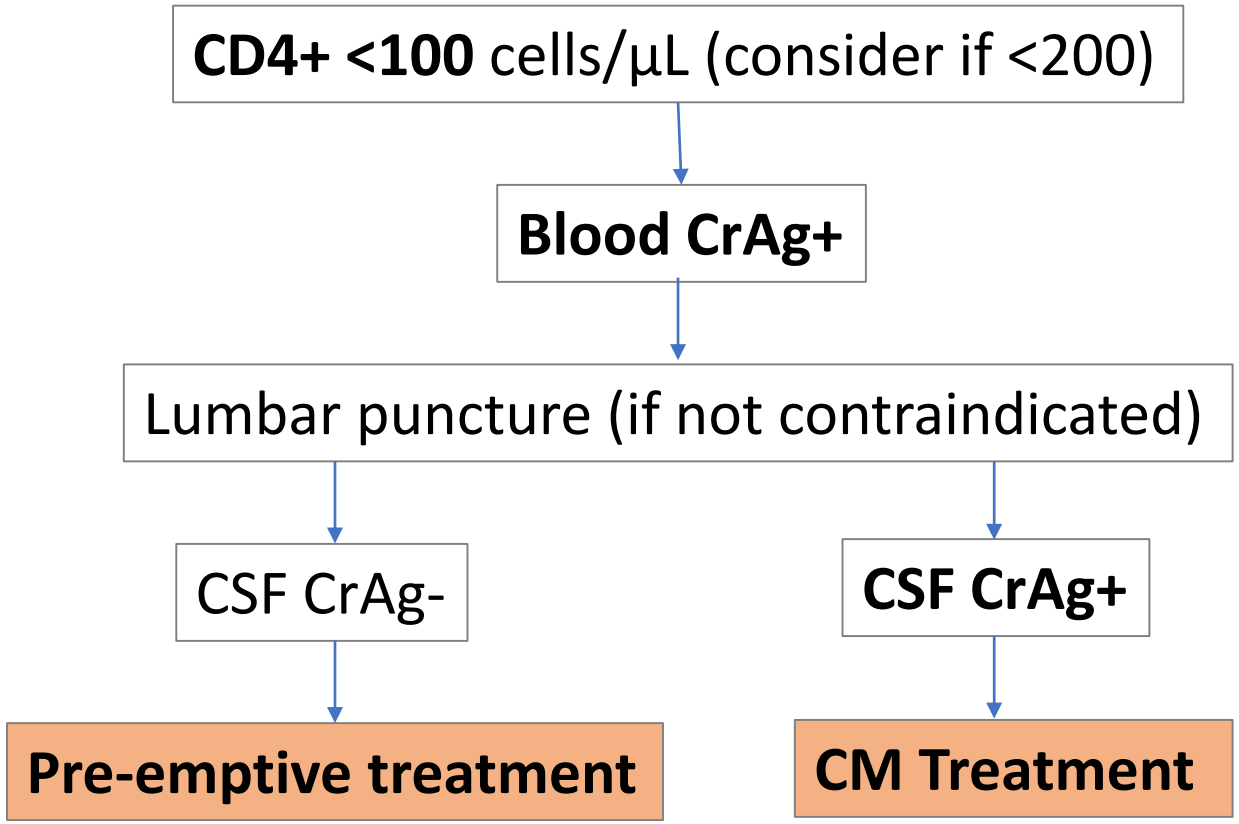
Cryptococcal meningitis: algorithm for screening, diagnosis and therapy

Lab diagnostics of Cryptococcosis

Assay	Sensitivity (%)	Specificity (%)
CSF fungal culture[a]	82.4–94.2	100
CrAg lateral flow assay	99.3	99.1
CrAg latex agglutination[a]	97.0–97.8	85.9–100
Indian ink microscopy[a]	86.1	97.3
Multiplex PCR[b]	82	98

Plasma vs. CSF Ag status





Tugume L et al. Nature Reviews Disease Primers (2023) 9:62

The 2022 WHO treatment guidelines for HIV-CM

Induction phase *

A single high dose (10 mg/kg) of liposomal amphotericin B with 14 days of flucytosine (100 mg/kg per day divided into four doses per day) and fluconazole (1,200 mg per day in adults; 12 mg/kg per day in children and adolescents up to a maximum of 800 mg per day).

Alternative therapy in the induction phase

- If liposomal amphotericin B is not available: a 7-day course of amphotericin B deoxycholate (1 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) followed by 7 days of fluconazole (1,200 mg per day in adults and 12 mg/kg per day in children and adolescents up to a maximum of 800 mg per day).
- If no amphotericin B deoxycholate is available: 14 days of fluconazole (1,200 mg per day, 12 mg/kg per day in children and adolescents) and flucytosine (100 mg/kg per day, divided into four doses per day).
- If flucytosine is not available: 14 days of liposomal amphotericin B (3–4 mg/kg per day) and fluconazole (1,200 mg per day, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg per day).
- If liposomal amphotericin B and flucytosine are not available: 14 days of amphotericin B deoxycholate (1 mg/kg per day) and fluconazole (1,200 mg per day, 12 mg/kg per day in children and adolescents up to a maximum of 800 mg per day).

Consolidation phase

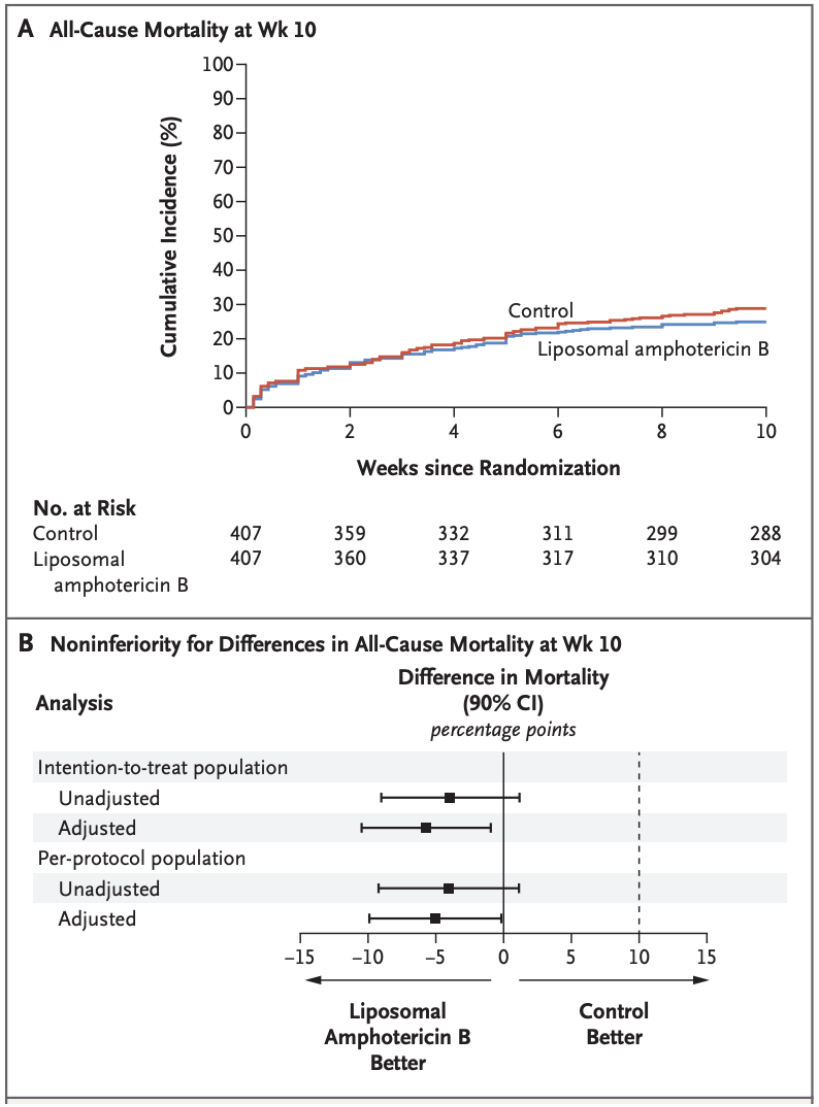
- Fluconazole (800 mg per day in adults or 6–12 mg/kg per day in children and adolescents up to a maximum of 800 mg per day) is recommended for the consolidation phase (for 8 weeks following the induction phase to 10 weeks).
- Start antiretroviral therapy (ART) between week 4 and week 6 from initiation of antifungal treatment.

Maintenance phase

Fluconazole (200 mg per day in adults or 6 mg/kg per day in children and adolescents) until immune reconstitution ($CD4^+$ T cell counts >200/μl) and suppression of viral loads on ART.

* Following the results of the Ambition trial

Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis (Ambition)



Treatments

- Single high dose of liposomal amphotericin B (10 mg/Kg) on day 1 + 14 days of flucytosine (100 mg/Kg) and fluconazole (1200 mg)

- Current WHO-recommended treatment: amphotericin B deoxycholate (1 mg/Kg) plus flucytosine (100 mg/Kg) for 7 days, followed by fluconazole (1200 mg) for 7 days (control)

Outcome

Single-dose liposomal amphotericin B + flucytosine + fluconazole = noninferior to the WHO-recommended treatment and associated with fewer adverse events

Cost-effectiveness

The AmBisome regimen was cost-effective at a low incremental cost-effectiveness ratio. It might be even less costly and potentially cost-saving in real-world implementation given lower drug-related toxicity and potential for shorter hospital stays.

J.N. Jarvis et al for the Ambition Study Group. N Engl J Med 2022;386:1109-20

The 2022 WHO treatment guidelines for HIV-CM

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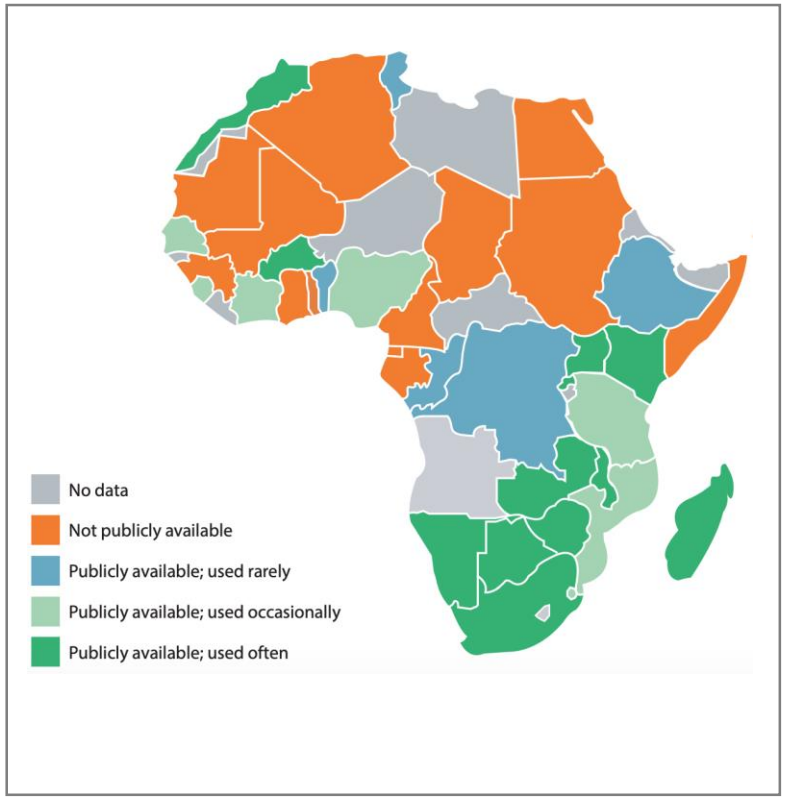
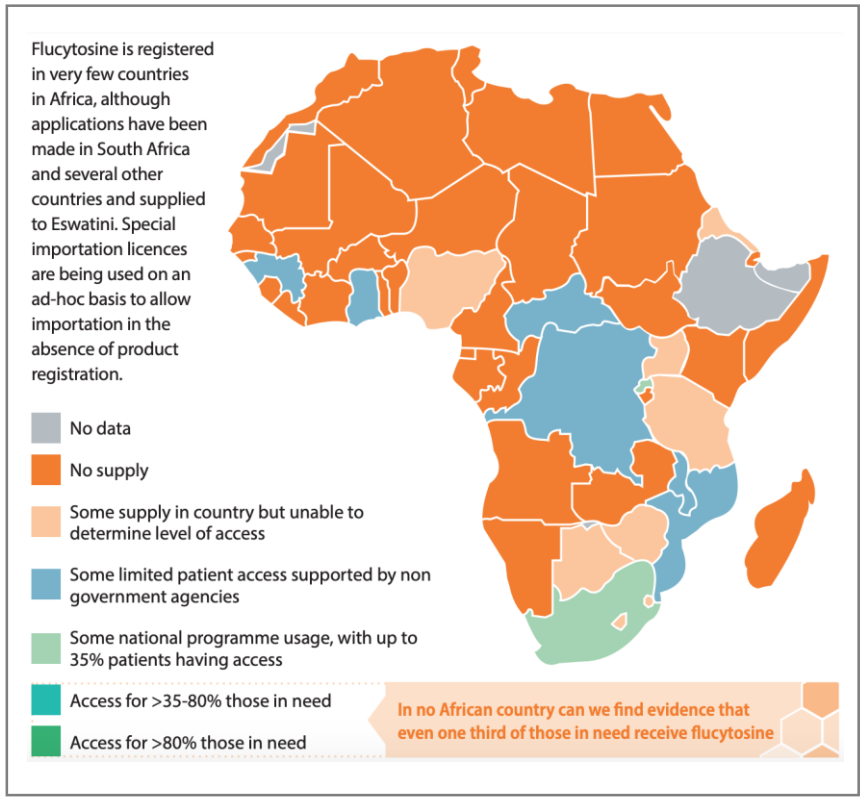
* Following the results of the Ambition trial

Screening, diagnosis and treatment opportunities for cryptococcal meningitis in African countries

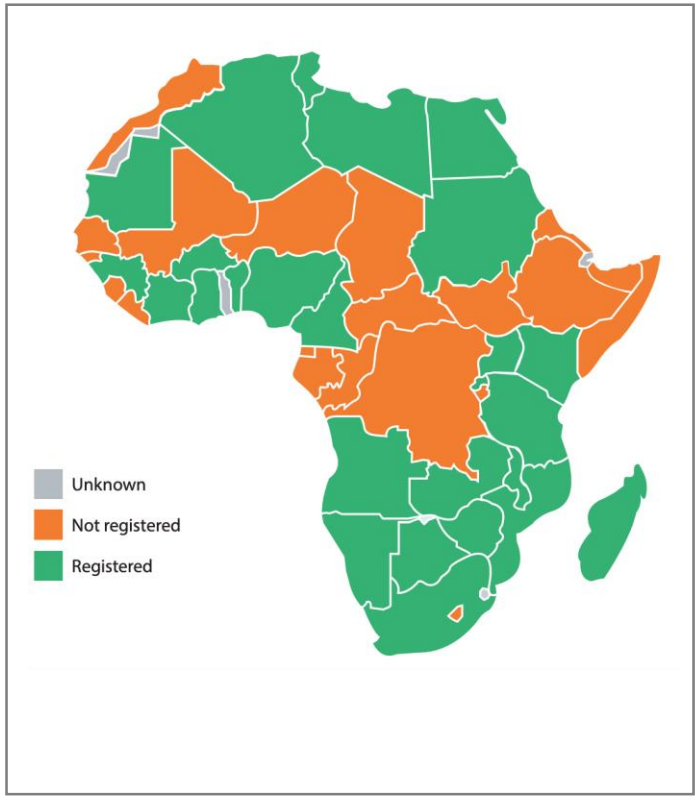
CrAg test access (2020)



Access to flucytosine (March 2021)



Registration of amphotericin B deoxycholate (2020)



Ending Cryptococcal meningitis deaths by 2030 Strategic Framework

The 2023 EACS treatment guidelines for HIV-CM

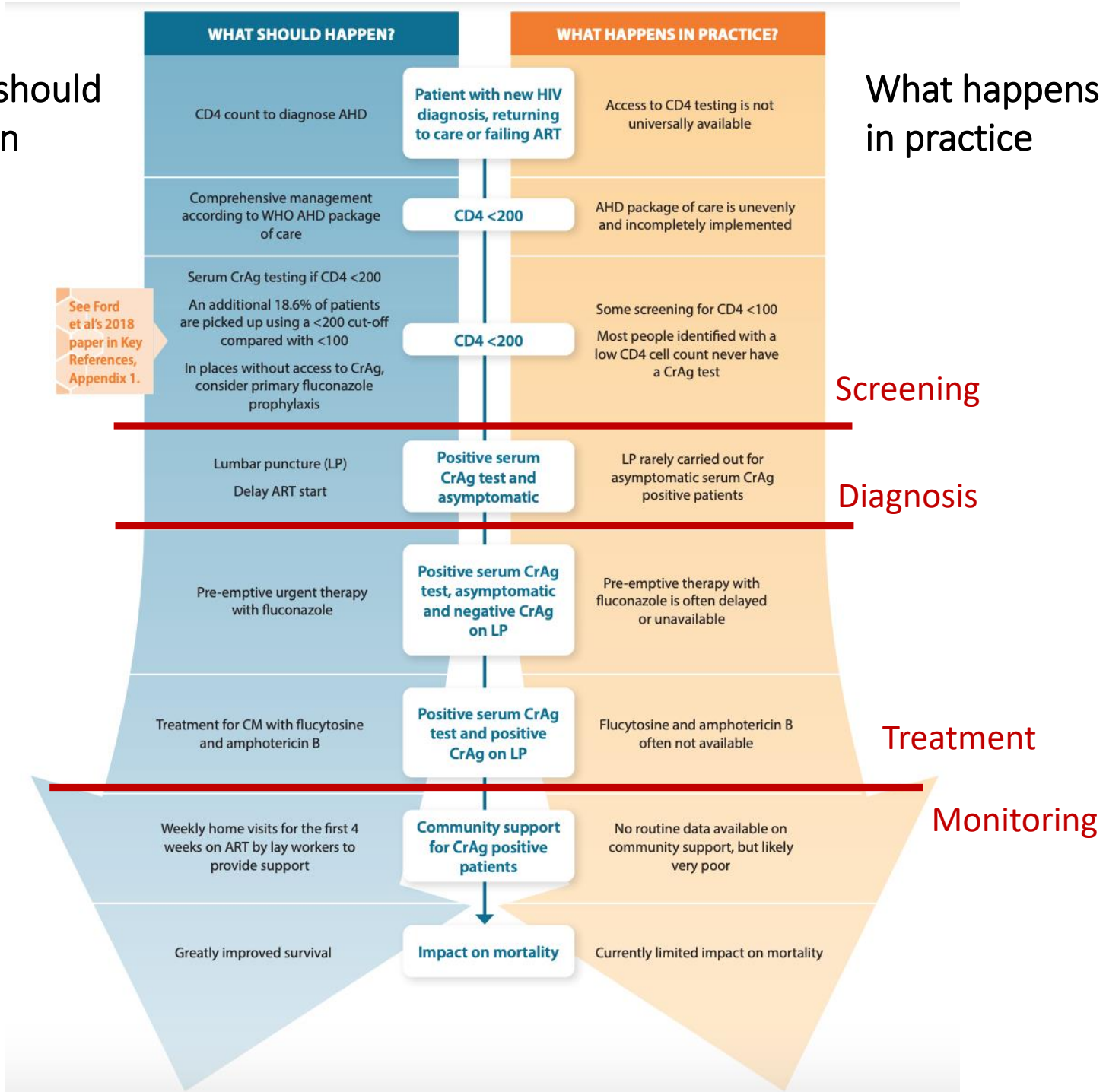
Induction therapy	**liposomal amphotericin B** **+ flucytosine**	3 mg/kg qd iv 25 mg/kg qid po	**14 days** - Perform repeated lumbar puncture (LP), until opening pressure is < 20 cm H_20: - If CSF culture is sterile, switch to oral regimen - Repeated LPs or CSF shunting are essential to effectively manage in-creased intracranial pressure which is associated with better survival - Corticosteroids have no effect in reducing increased intracranial pressure, could be detrimental and are contraindicated - **Flucytosine** dosage must be adapted to renal function - Defer start of ART for at least 4 weeks, since early initiation of ART has been associated with decreased survival. Where very close monitoring and optimal treatment are available, earlier ART start can be considered in selected, low-risk cases - Due to substantial nephrotoxicity **amphotericin B deoxycholate** should only be used if **liposomal amphotericin B** is not available - **Flucytosine** may not be available in all European countries. Consider replacing it by **fluconazole** 800 mg qd during the induction phase
	or **amphotericin B deoxycholate** **+ flucytosine**	0.7 mg/kg qd iv 25 mg/kg qid po	
	or **single-dose liposomal amphotericin B** **+ flucytosine** **+ fluconazole**	10 mg/kg IV single-dose 25 mg/kg qid po for 2 weeks 1200 mg/die for 2 weeks	- Preferred WHO-2022 regimen in resource limited settings - In resource-limited settings, alternative induction regimens may include: i) one week of **amphotericin B** + **flucytosine** followed by one week of **fluconazole** 1200 mg qd (the 2018 WHO-recommended treatment) or ii) two weeks of **fluconazole** 1200 mg qd plus **flucytosine**
Consolidation therapy	**fluconazole**	400 mg qd po (single loading dose of 800 mg on 1st day)	8 weeks See Drug-drug Interactions between ARVs and Non-ARVs

Limited impact of the algorithm on Cryptococcal meningitis mortality in low-income countries

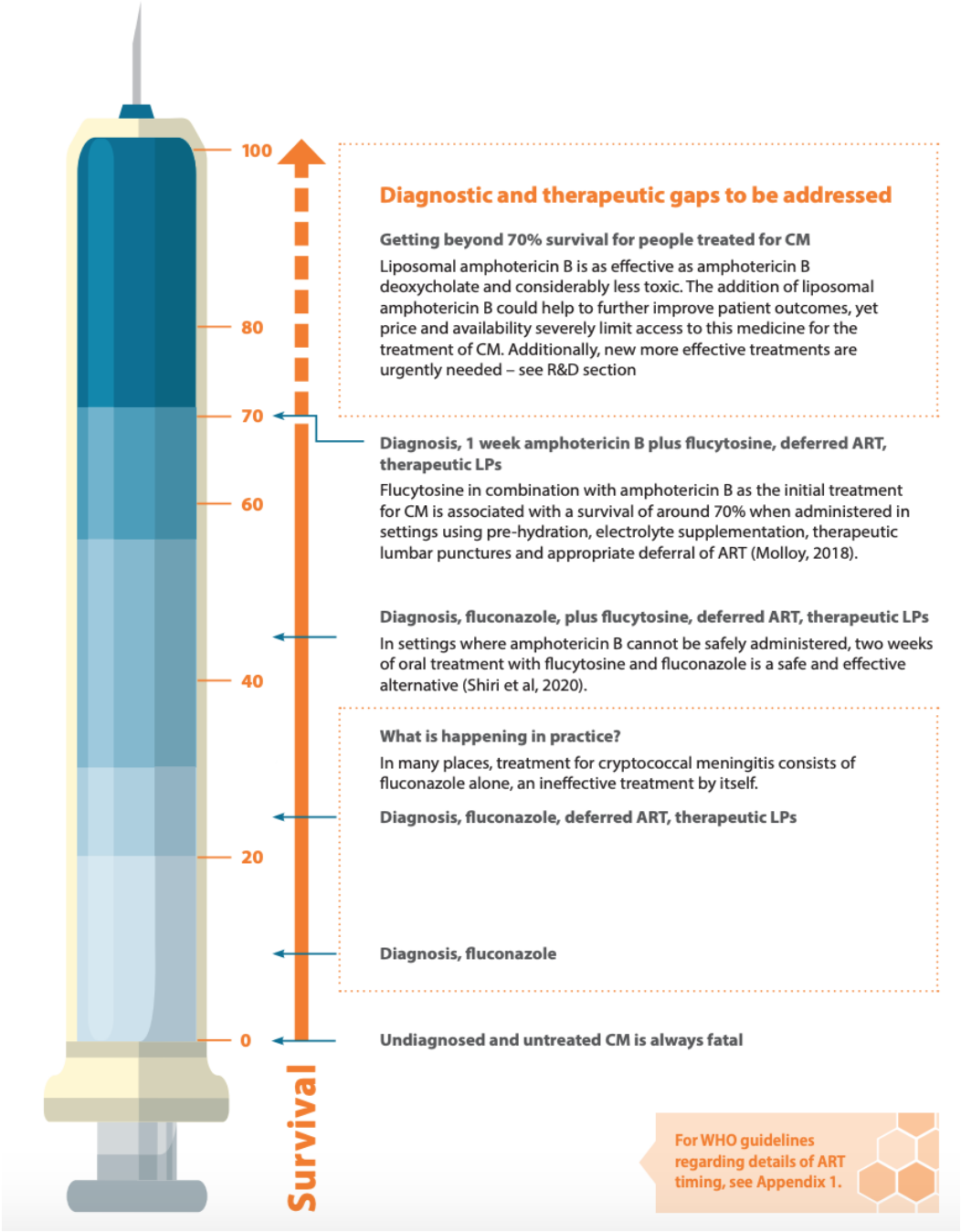
25-30% mortality in trial settings, and up to 70% in clinical practice

15-20% contribution to HIV-related mortality

Ending Cryptococcal meningitis deaths by 2030 Strategic Framework



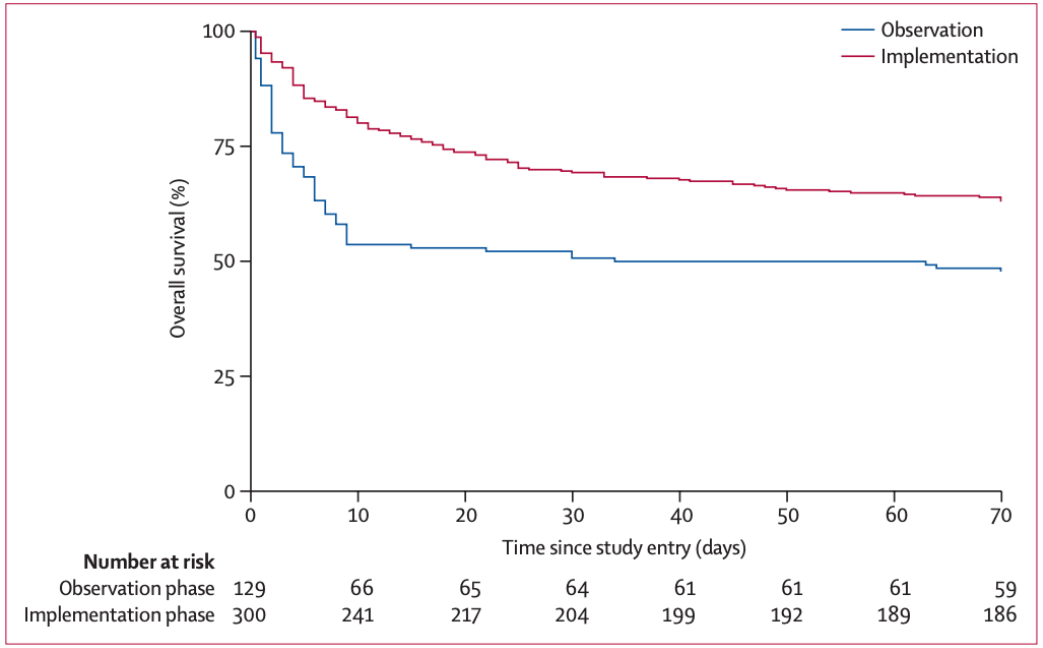
END CRYPTOCOCCAL MENINGITIS DEATHS by 2030



Ending Cryptococcal meningitis deaths by 2030
Strategic Framework

Reduction in mortality from HIV-related CNS infections* in routine care in Africa (DREAMM): a before-and-after, implementation study

* Cryptococcal meningitis, tuberculous and bacterial meningitis, cerebral toxoplasmosis



	Died within 10 weeks, n/N (%)	Adjusted for site		Adjusted for site, age, sex, mental status, and ART exposure	
		Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Overall					
Observation phase	71/129 (55%)	1 (ref)	..	1 (ref)	..
Implementation phase	103/265 (39%)	0·58 (0·43–0·79)	0·001	0·60 (0·44–0·82)	0·002
Tanzania					
Observation phase	43/67 (64%)	1 (ref)	..	1 (ref)	..
Implementation phase	47/98 (48%)	0·56 (0·37–0·85)	0·006	0·55 (0·36–0·84)	0·006
Malawi (Lilongwe only)					
Observation phase	13/35 (37%)	1 (ref)	..	1 (ref)	..
Implementation phase	26/70 (37%)	0·96 (0·49–1·86)	0·89	0·85 (0·42–1·71)	0·64
Cameroon					
Observation phase	15/27 (56%)	1 (ref)	..	1 (ref)	..
Implementation phase	30/97 (31%)	0·40 (0·21–0·74)	0·003	0·51 (0·26–1·00)	0·05

All patients, excluding Zomba and patients lost to follow-up. ART=antiretroviral therapy.

Table 4: **Time-to-death analysis in the observation and implementation phases, all cases**

Implementation of an algorithm to rapidly identify, triage, diagnose, and treat PWH who presented with suspected CNS infections lead to significant reduction in mortality

Of note, 173 (65%) of 268 participants with CNS infections were exposed to ART = **almost half participants did not adhere to ART or had disengaged from care**, which limited the efforts to prevent advanced HIV disease deaths.

Mfinanga et al. Lancet HIV 2023; 10: e663–73

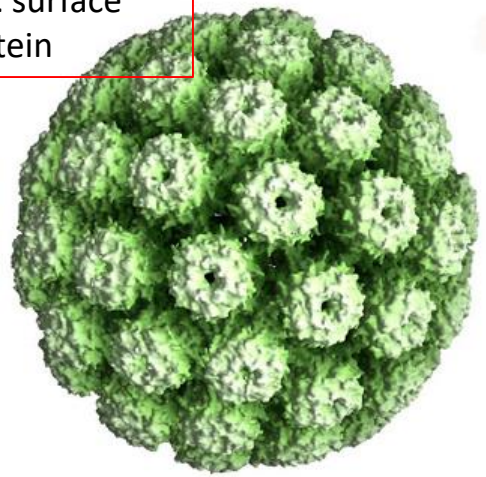
Update on cryptococcal meningitis in PWH: Key messages

- Highly prevalent in LMIC countries (AIDS presenters and PWH with low adherence or who disengaged from care)
- In high-income countries: still observed in AIDS presenters and in PWH with low adherence or who disengaged from care
- Unacceptable high mortality, especially in LMIC, for limited access to screening, diagnosis and treatments, including with old and newer drugs

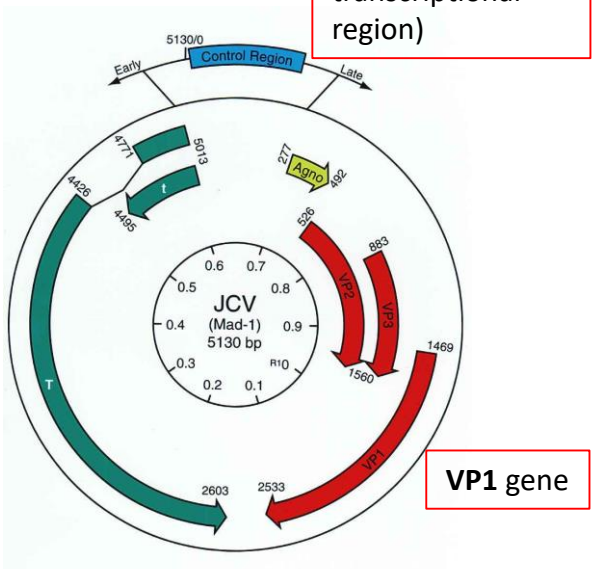
Progressive Multifocal Leukoencephalopathy (PML)

- Progressive (fatal) demyelinating encephalitis
- Caused by reactivation of the papovavirus JC (JCV)
- Occuring in persons with immune dysfunction
- Upon development of VP1 mutations
- Diagnosis not difficult to achieve nowadays
- Neither cure nor vaccine available today

VP1 surface protein



NNCR (non coding transcriptional region)

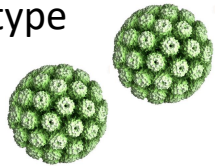


VP1 gene

Double-stranded DNA (5130 bp)

The natural history of JCV infection and PML

Wild-type JCV



Immune competence

Loss of immune control

Primary JCV infection

Persistent / Latent JCV infection

JCV reactivation

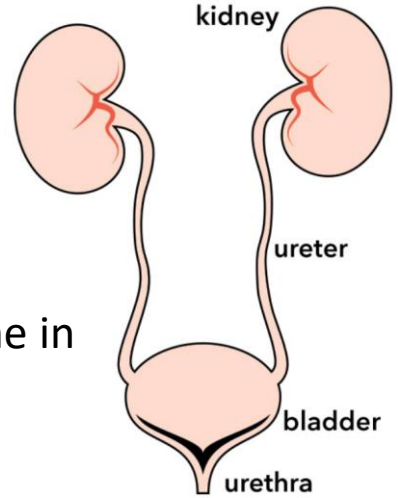
CNS seeding ?

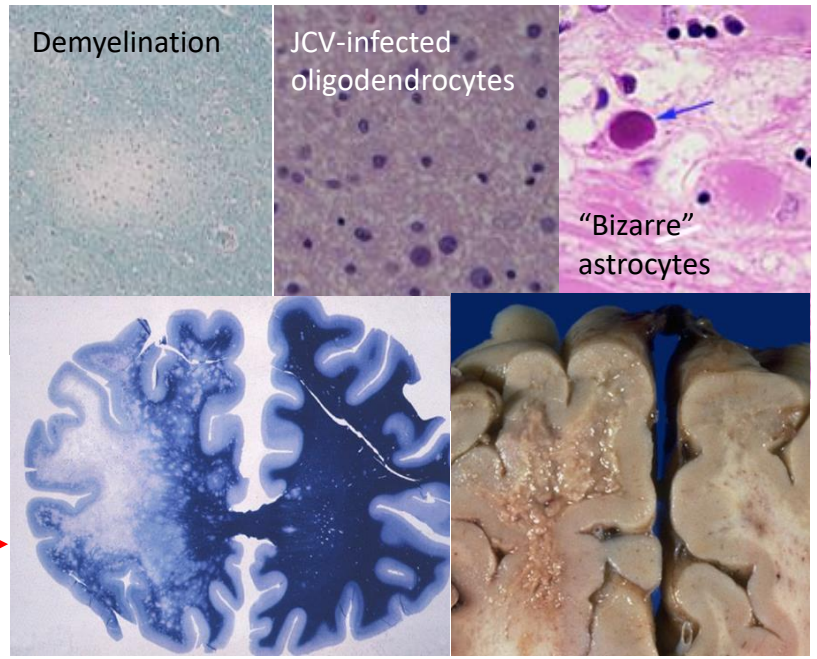
JCV replication in CNS - PML

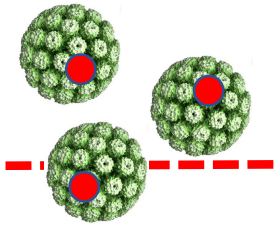
50-80% seroprevalence in healthy adults

- Urinary tract
- Bone marrow ?
- CNS ?

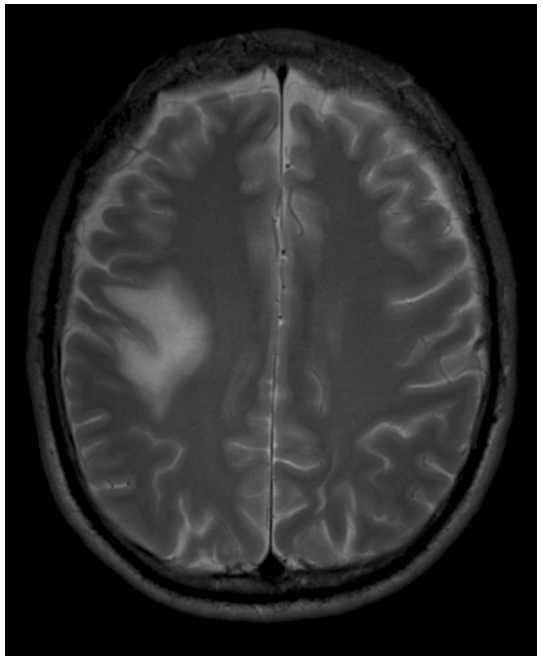
20% JCV DNA excretion in urine in healthy adults





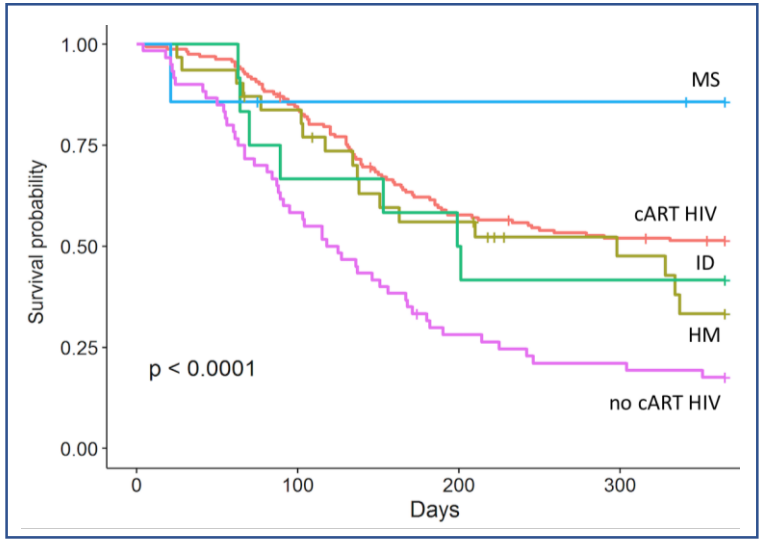


VP1 mutants
NCCR rearrangements

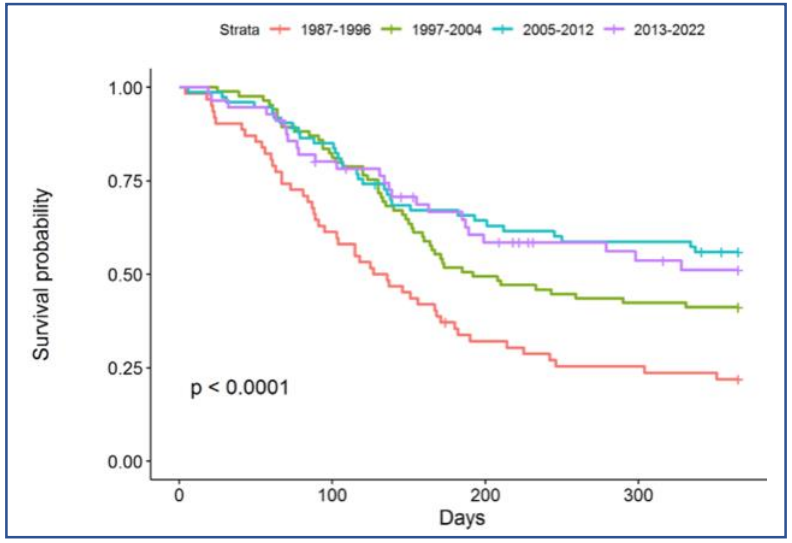


PML one-year survival from time of diagnosis (1987-2022, n=423)

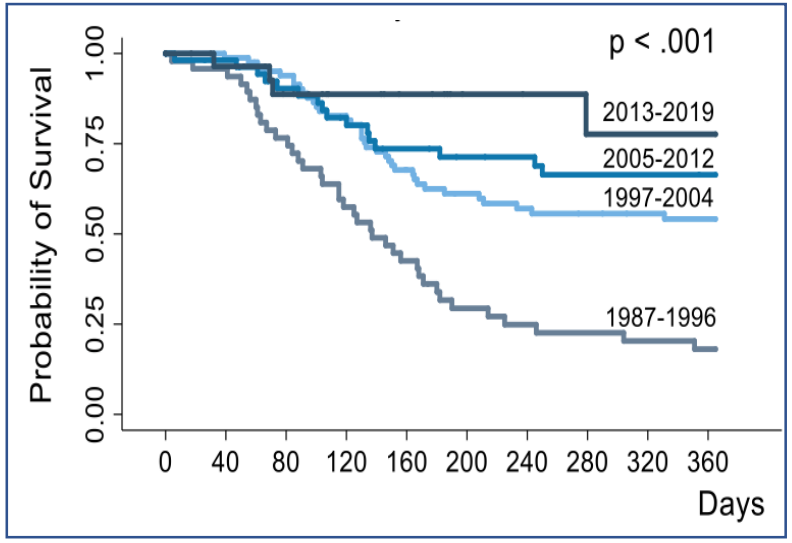
According to underlying conditions



According to calendar year (all)

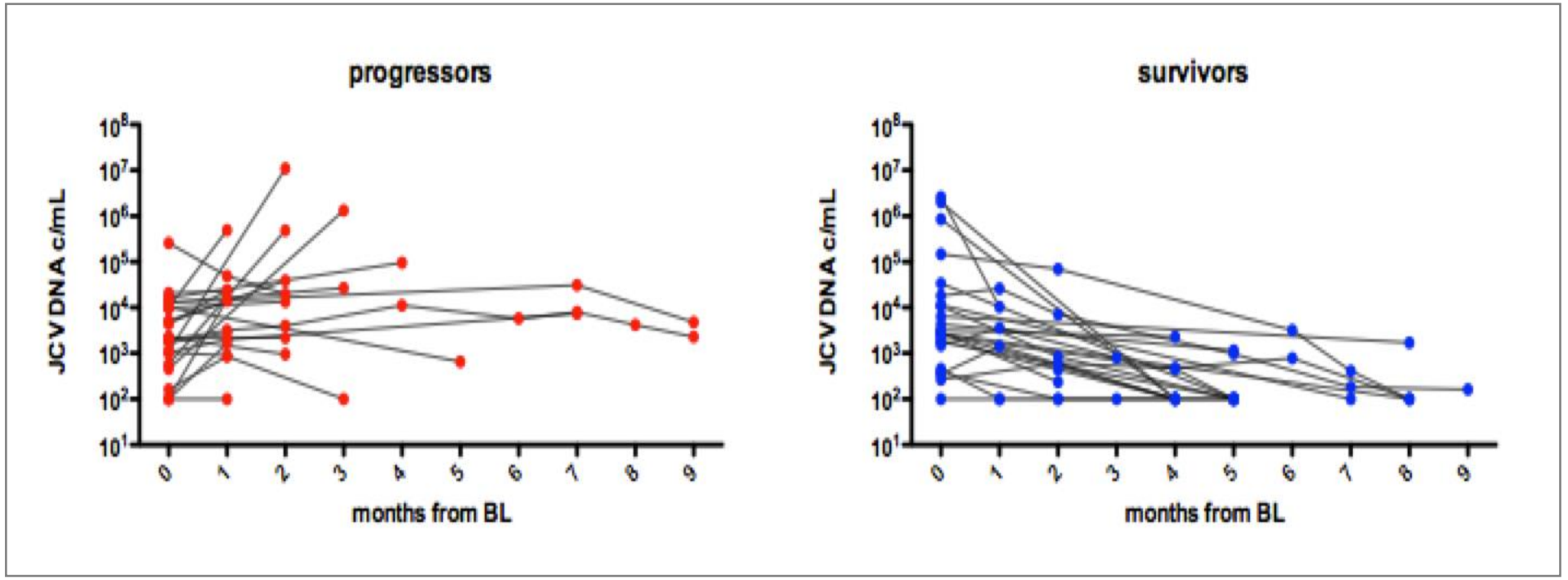


According to calendar year (HIV)



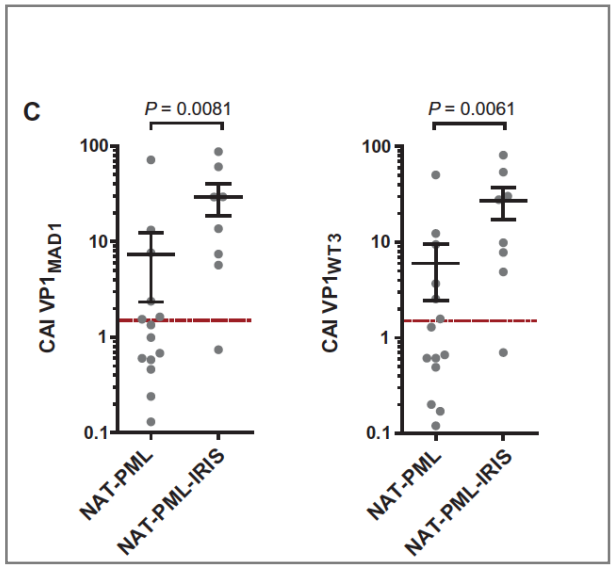
Mainardi I., ms in preparation

PML outcome depends on the balance between viral replication and JCV-specific immunity: JCV-DNA in CSF



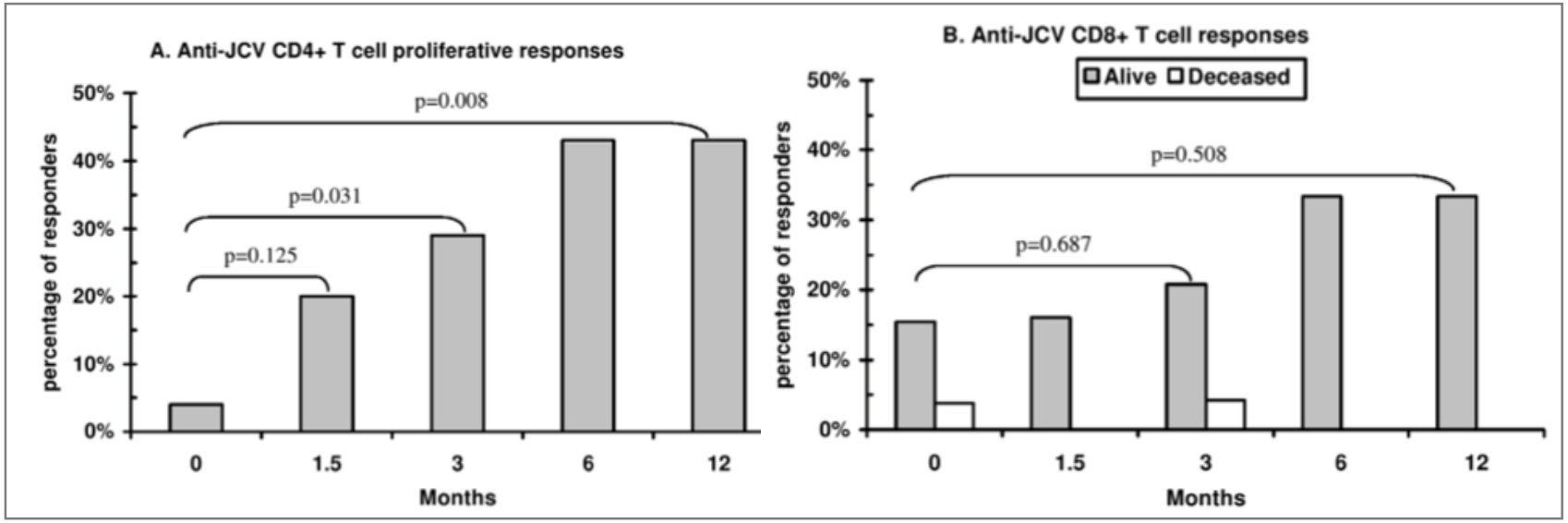
PML outcome depends on the balance between viral replication and JCV-specific immunity: T-cell and B-cell specific responses

Intrathecal Ab production



Jelcic et al., Science Transl Med 2015

JCV-specific CD4 T-cell responses



JCV-specific CD8 T-cell responses

Gasnault J et al., PLOS One 2011

Current management of PML

→ PML outcome depends on the balance between viral replication and JCV-specific immunity

Antiviral drugs

- JCV-specific antiviral drugs neither available nor on the horizon

Reduction of immunosuppression

- Start anti-HIV treatment (cART) in HIV infection or stop immunosuppressive/modulant drugs
- Additional immune-based interventions

Drug Repurposing in PML: a collection of disappointment stories

Based on in vitro findings and anecdotical case reports:

- Topotecan (topoisomerase inhibitor; 1995 → 2003) *
- Cytarabine (polymerase inhibitor; 1977 → 1998) *
- Cidofovir (polymerase inhibitor; 1998 → 2008) *
- Brincidofovir (polymerase inhibitor; 2010-2020)
- 5HT2a inhibitors (entry inhibitors; 2004 → …) **
- Mefloquine (mechanism unknown)(2009 → 2013) **

CDC, NIH, HMA-IDSA guidelines for HIV-OIs, 2018

* Non-recommended, based on results of controlled trials or meta-analysis (AII)

** Use not justified in routine (BIII)

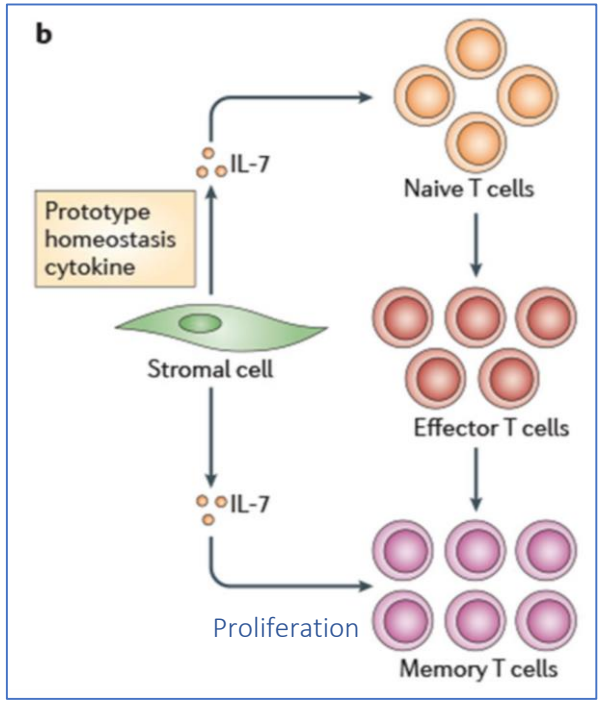
Additional host-directed interventions as potential PML treatment

Treatment	Type of sudy, nr. of treated pts (PubMed)
• PD-1 inhibitors	Retrospective survey (n=79)
• Interleukin-7	Retrospective survey (n=64)
• Adoptive cell transfer*	Case series, single case reports (n=34)
• VP-1	Case series (n=3)

*either using BKV- or JCV-specifci T-cells

Interleukin-7 (IL-7)

Functions and effects



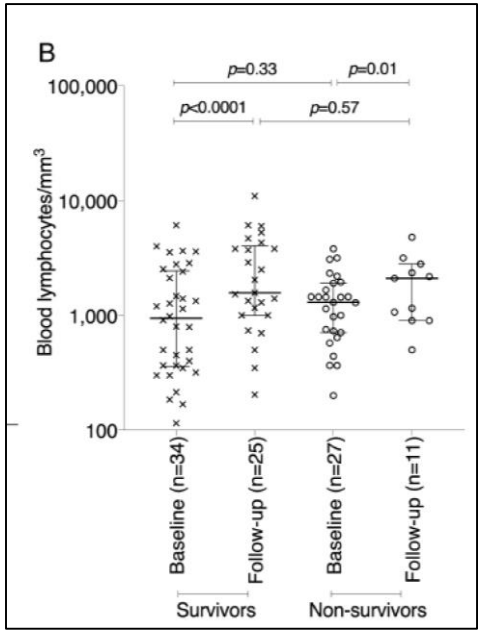
Mackall CL. et al., Nat Rev Immunol 2011

Required for T-cell development

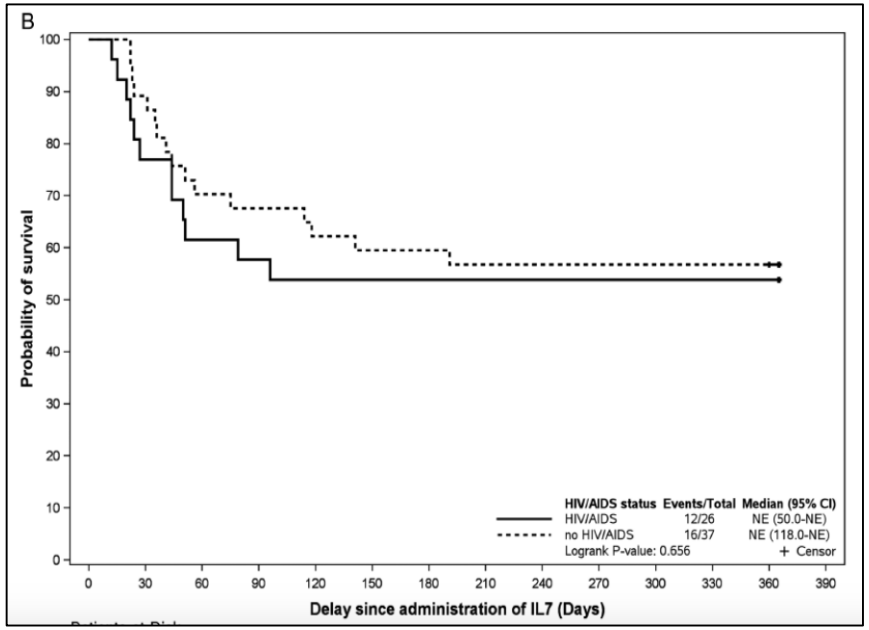
Required for maintaining and restoring homeostasis of mature T-cells

Recombinant Human IL-7 (rhIL-7) in PML

Meta-analysis of 64 published and unpublished cases, 2007 - 2020



Total lymphocytes increase in both survivors and non-survivors

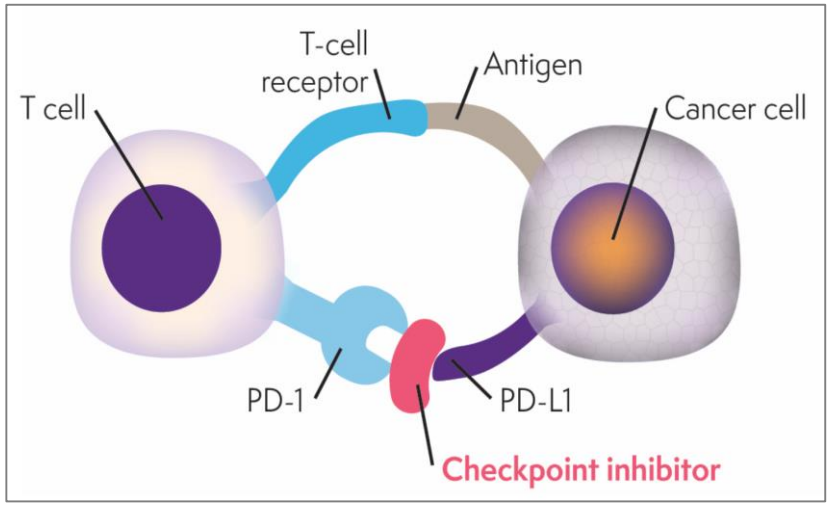


Lajaune et al. Ann Neurol 2022

54.7% one-year survival

Immune check-point inhibitors (anti-PD1: pembrolizumab, nivolumab)

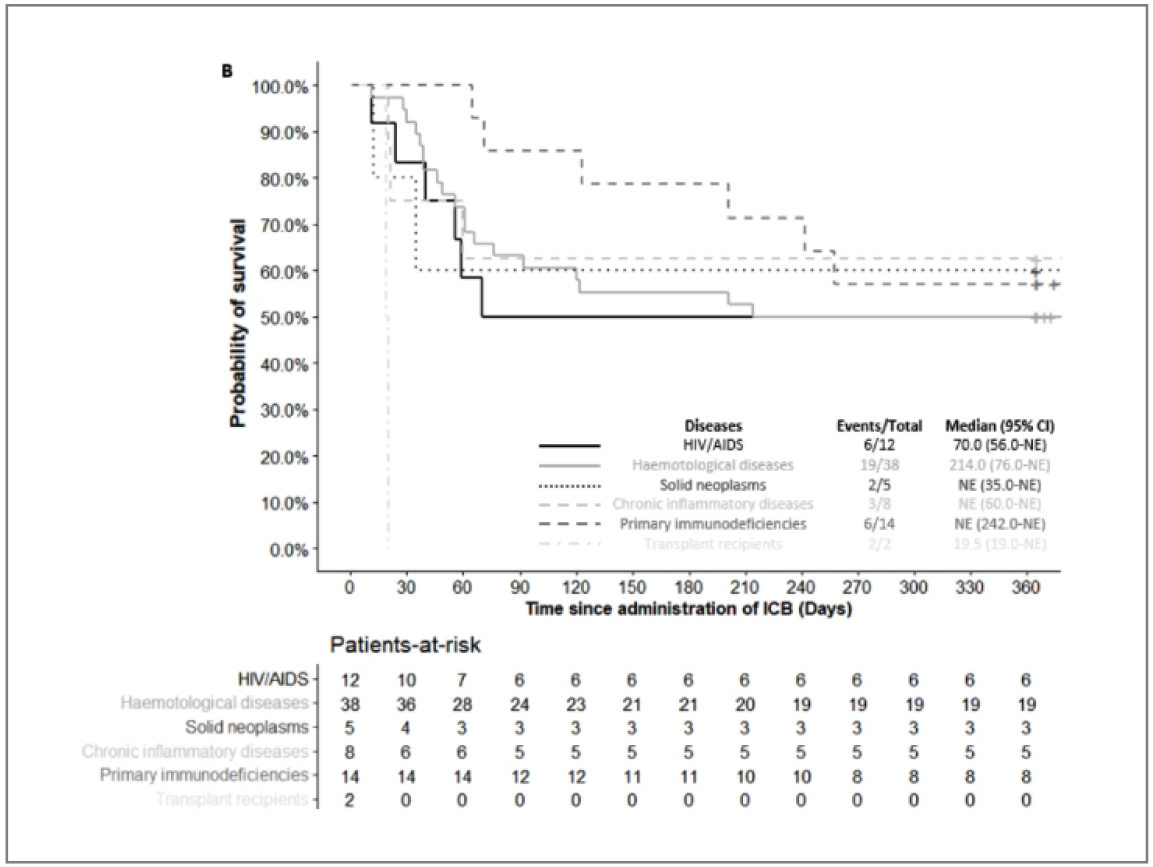
Functions and rationale for use in PML



- Inhibition of immune check-point, which control T-cell proliferation and activation (e.g., PD-1/PDL-1)

- High PD-1 expression in CD4 and CD8 T cells from PML patients (JCV-specific CD8 cells)

Meta-analysis of 79 published and unpublished cases, 2007 – 2020

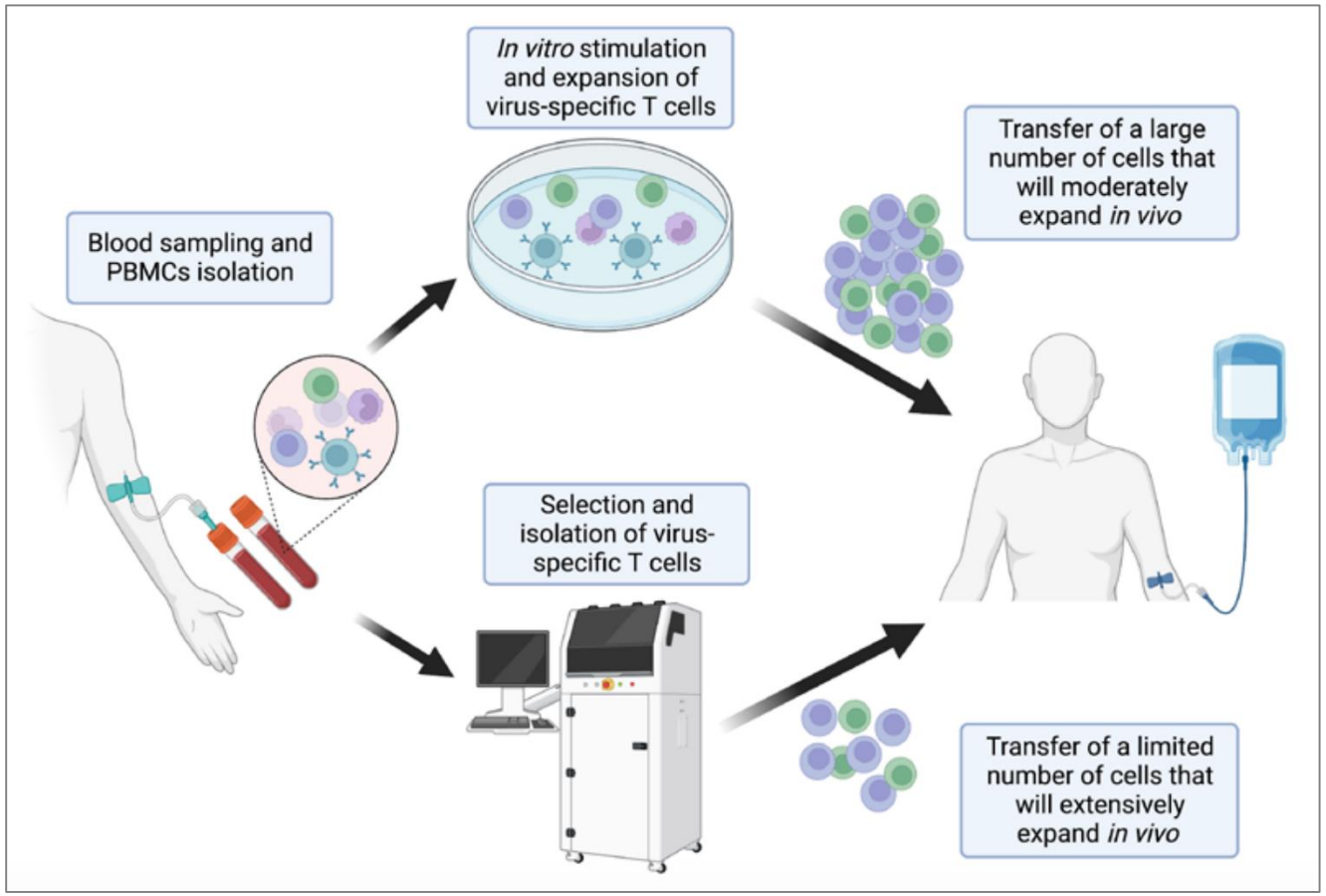


Boumaza et al. Ann Neurol 2022

One-year survival 51.9%

32 adverse events in 24 patients (30.4%), treatment discontinuation in 7

Virus-specific T-cell transfer



- Autologous
- Allogeneic
  - Transplant donor (hematopoietic stem cell donor)
  - Third-party (cryopreserved cells)
  - Relatives

  - Minimum HLA matching required (e.g., at least one HLA-A and one HLA-DRβ1 allele matched)

Lambert et al., Viruses 2023

Patients with PML treated using polyomavirus-specific T-cells reported in the literature (*Lambert et al., Viruses 2023*)

Article	Age (Years), Sex	Underlying Immune Deficiency	Virus Targeted by the Cells	Autologous or Allogeneic Cells	Number of Infusions	HLA Matching	Associated Treatments	Complications	Clinical Outcome Regarding PML
Balduzzi et al., 2011 [34]	14, M	Acute lymphoblastic leukemia	HPyV2	Allogeneic (HSCT donor)	2	10/10	Cidofovir, citalopram	None	Improvement
Muftuoglu et al., 2018 [35]	32, F	Acute myeloblastic leukemia	HPyV1	Allogeneic	3	5/10	Mirtazapine (stopped)	None	Improvement
Muftuoglu et al., 2018 [35]	73, F	Polycythemia rubra	HPyV1	Allogeneic	2	4/10	None	IRIS	Stabilization
Muftuoglu et al., 2018 [35]	35, M	HIV	HPyV1	Allogeneic	5	5/10	ART	None	Improvement
Steinhardt et al., 2020 [44]	59, M	Multiple myeloma	HpyV2	Allogeneic (HSCT donor)	1	10/10	Cidofovir, mirtazapine, DLI	None	Stabilization
Berzero et al., 2021 [41]	59, F	Non-Hodgkin lymphoma	HpyV2	Allogeneic	4	Unknown	None	None	Stabilization
Berzero et al., 2021 [41]	55, M	Multiple myeloma	HpyV2	Autologous	3	Not appropriate	Mirtazapine (stopped)	None	Improvement
Berzero et al., 2021 [41]	70, F	Non-Hodgkin lymphoma	HpyV2	Autologous	1	Not appropriate	None	None	Deterioration and death
Berzero et al., 2021 [41]	50, M	Hodgkin lymphoma	HpyV2	Allogeneic	3	Unknown	Cidofovir (stopped)	None	Unknown (death due to VZV infection)
Berzero et al., 2021 [41]	68, M	Non-Hodgkin lymphoma	HpyV2	Autologous	6	Not appropriate	None	None	Improvement
Berzero et al., 2021 [41]	54, M	Non-Hodgkin lymphoma	HpyV2	Allogeneic	2	Unknown	None	None	Deterioration and death
Berzero et al., 2021 [41]	66, M	Chronic lymphocytic leukemia	HpyV2	Allogeneic	4	Unknown	None	None	Deterioration and death
Berzero et al., 2021 [41]	54, F	Idiopathic CD4 lymphocytopenia	HpyV2	Autologous	6	Not appropriate	None	None	Improvement
Berzero et al., 2021 [41]	17, M	Wiskott–Aldrich syndrome	HpyV2	Allogeneic (HSCT donor)	5	Unknown	None	None	Improvement
Hopfner et al., 2021 [43]	55, F	Hodgkin lymphoma	HPyV1	Allogeneic	4	6/10	None	None	Improvement
Hopfner et al., 2021 [43]	71, F	Breast cancer, dermatomyositis	HPyV1	Allogeneic	3	6/10	None	None	Improvement
Cortese et al., 2021 [40]	62, F	Idiopathic lymphocytopenia, cyclic neutropenia	HPyV1	Allogeneic (two different donors)	3	6/10 (1st) 1/10 (2nd)	Pembrolizumab (stopped), mefloquine	None severe	Deterioration and death
Cortese et al., 2021 [40]	61, F	Microscopic polyangeitis	HPyV1	Allogeneic	3	5/10	Mirtazapine	None severe	Improvement
Cortese et al., 2021 [40]	53, F	Chronic lymphocytic leukemia	HPyV1	Allogeneic	2	10/10	Mirtazapine	None severe	Deterioration and death
Cortese et al., 2021 [40]	71, M	Non-Hodgkin lymphoma	HPyV1	Allogeneic	2	5/10	Cidofovir (stopped), mirtazapine	None severe	Improvement
Cortese et al., 2021 [40]	40, F	Systemic lupus erythrematosus	HPyV1	Allogeneic	3	5/10	None	None severe	Improvement

Patients with PML treated using polyomavirus-specific T-cells reported in the literature (*Lambert et al., Viruses 2023*)

Article	Age (Years), Sex	Underlying Immune Deficiency	Virus Targeted by the Cells	Autologous or Allogeneic Cells	Number of Infusions	HLA Matching	Associated Treatments	Complications	Clinical Outcome Regarding PML
Cortese et al., 2021 [40]	40, F	Non-Hodgkin lymphoma	HPyV1	Allogeneic	3	6/10	Mirtazapine	None severe	Deterioration and death
Cortese et al., 2021 [40]	60, M	B and D hepatitis	HPyV1	Allogeneic	3	5/10	None	None severe	Stabilization
Cortese et al., 2021 [40]	71, M	Chronic lymphocytic leukemia	HPyV1	Allogeneic	1	2/10	Mirtazapine, mefloquine	None severe	Unknown (withdrew from study)
Cortese et al., 2021 [40]	40, F	Severe combined immunodeficiency	HPyV1	Allogeneic	1	5/10	None	None severe	Deterioration and death
Cortese et al., 2021 [40]	35, F	Common variable immunodeficiency	HPyV1	Allogeneic	2	5/10	Interleukin-7 (stopped), mirtazapine, mefloquine	None severe	Deterioration and death
Cortese et al., 2021 [40]	57, M	Chronic lymphocytic leukemia	HPyV1	Allogeneic	3	10/10	Mirtazapine	None severe	Improvement
Cortese et al., 2021 [40]	72, M	Chronic lymphocytic leukemia	HPyV1	Allogeneic	3	7/10	Mirtazapine	None severe	Stabilization
Wicklein et al., 2021 [42]	57, M	Non-Hodgkin lymphoma	HPyV1	Allogeneic	2	5/10	Pembrolizumab	None	Improvement
Rubinstein et al., 2022 [45]	64, F	Acute myeloblastic leukemia	HPyV1	Allogeneic	6	3/10	None	None	Improvement
Rubinstein et al., 2022 [45]	59, M	Non-Hodgkin lymphoma	HPyV1	Allogeneic (two different donors)	3	2/10 (1st) 3/10 (2nd)	Pembrolizumab (stopped)	None	Deterioration and death
Rubinstein et al., 2022 [45]	62, M	Non-Hodgkin lymphoma	HPyV1	Allogeneic	2	4/10	Unknown	IRIS	Deterioration and death
Rubinstein et al., 2022 [45]	67, F	Non-Hodgkin lymphoma	HPyV1	Allogeneic	1	5/10	Unknown	None	Deterioration and death
Peghin et al., 2022 [46]	29, F	Lung transplantation	HPyV2	Allogeneic	Unknown	5/10	Mirtazapine, mefloquine	None	Improvement

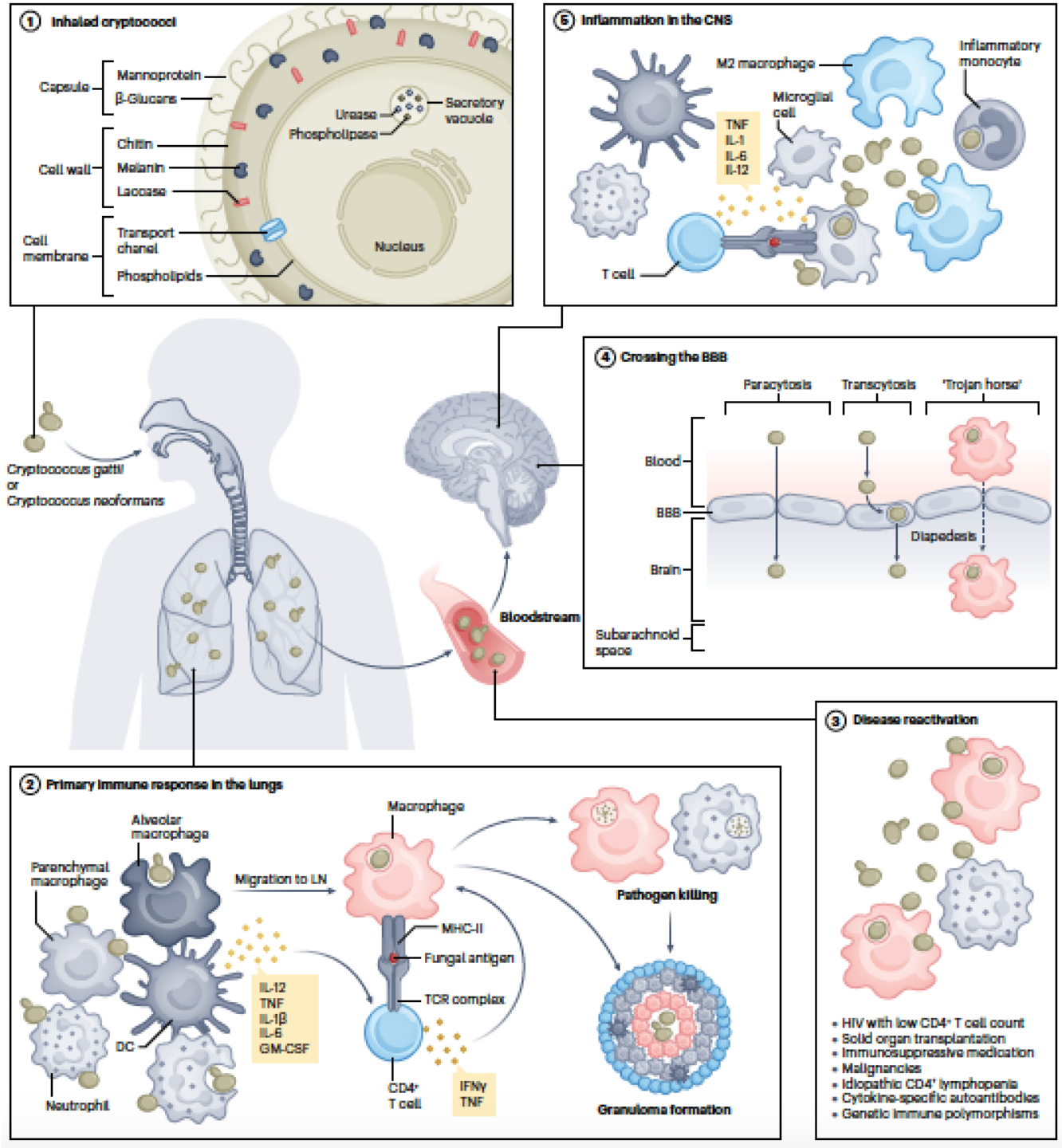
Total: **34 published cases** + unpublished cases

BKV-specific T-cells: 22; JCV-specific T-cells: 12
autologous T-cells: 4; allogeneic T-cells from their HSCT donor: 3; patients received third-party allogeneic T-cells: 7
Hematological malignancy: 23 (67%; among which 26% allogeneic HSCT and 30% autologous HSCT); primary immunodeficiency: 5 (14.7%), autoimmune disease: 3 (8.8%), **HIV infection: 1 (3%);** SOT :1 (3%), chronic HBV/HDV infection: 1 (3%).

Update on PML in PWH: Key messages

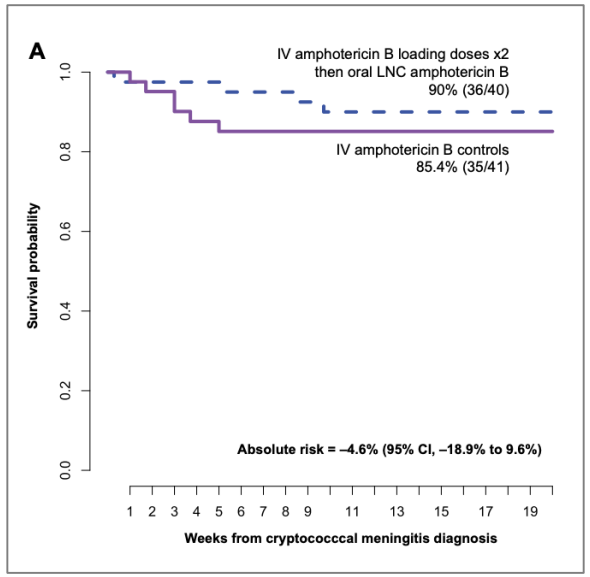
- Reduced incidence and prevalence of PML in HIV infection
- Early diagnosis is essential to attempt therapeutic interventions
- Still no direct antiviral treatment available
- Regaining the JCV-specific immune function is key to halt disease progression (but takes time!)
- Clinical trials should be the way to test the efficacy of immune-based (and possibly other) approaches, but these are difficult (impossible?) to implement

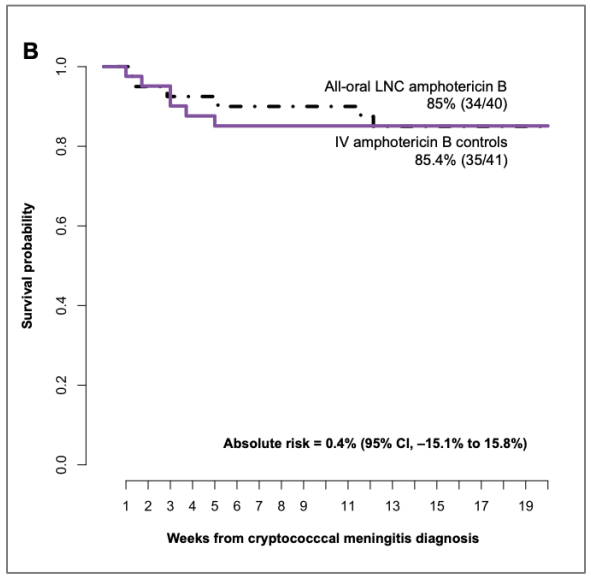
Cryptococcal meningitis



Tugume L et al. Nature Reviews Disease Primers (2023) 9:62

Oral lipid nanocrystal amphotericin B for cryptococcal meningitis: a randomized clinical trial





Treatments

Oral LNC amphotericin B (MAT2203; Matinas Biopharma) vs IV amphotericin B for 2 weeks, then fluconazole 1200 mg/d through day 14

Vs.

Liposomal amphotericin B (n = 22) at 3 mg/kg/d or amphotericin B deoxycholate (n = 19) 1 mg/kg/d for 7 days, with (A) or without (B) 2 IV amphotericin loading doses, with flucytosine then fluconazole 1200 mg/d through day 14. Oral LNC amphotericin B regimens were given with oral flucytosine 100 mg/kg daily for 2 weeks

Outcome

- 2-week CSF sterility in 63% (44 of 70) of LNC amphotericin groups vs 68% (23 of 34) of controls.
- 18-week survival in 85% (34 of 40) with all-oral LNC amphotericin, 90% (36 of 40) with oral LNC amphotericin given IV loading doses, and 85% (35 of 41) with IV amphotericin.
- Grade 3–4 lab adverse events occurred less frequently in LNC amphotericin groups (41%) than the IV amphotericin group (61%, P = .05), particularly for anemia (21% vs 44%; P = .01) and potassium (5% vs 17%; P = .04).

Boulware, D. R. et al. Clinical Infectious Diseases 2023;77(12):1659–67

IRIS development in patients with previous OIs

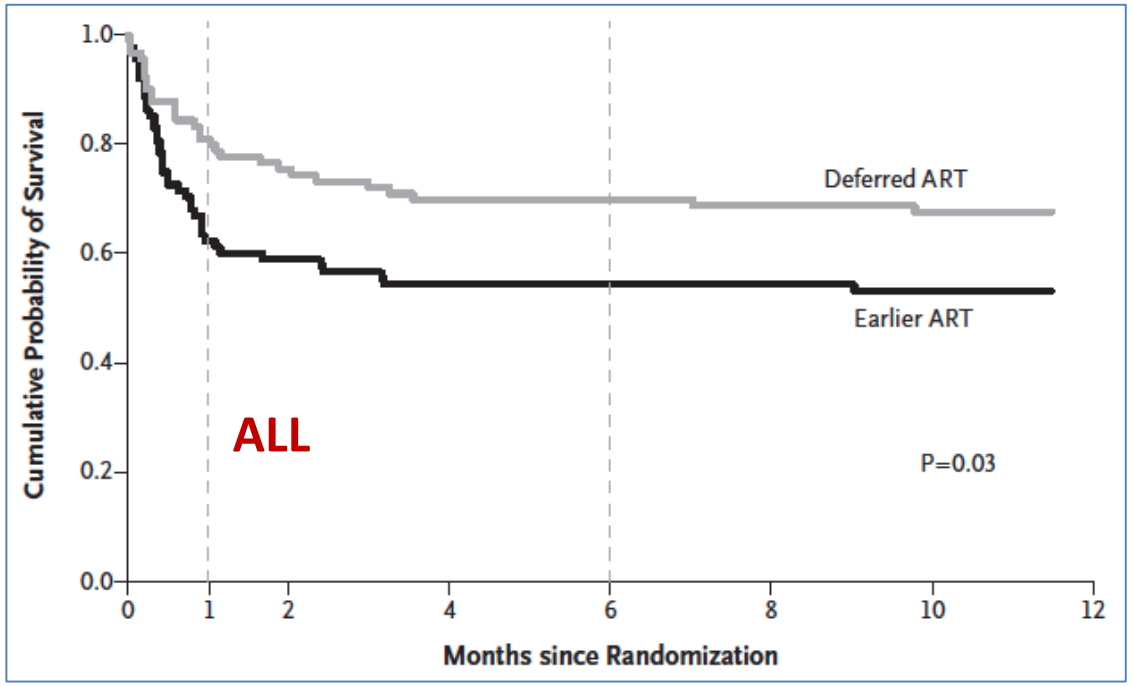
Meta-analysis of data from 54 cohorts
involving > 13,000 patients

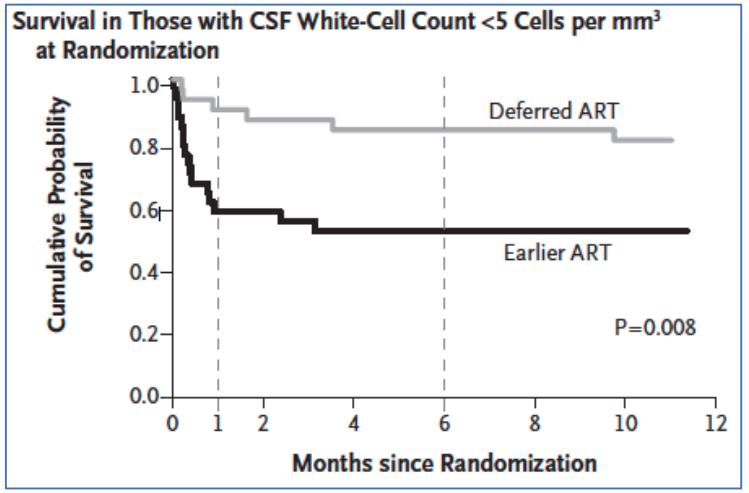
Previous OI	Pooled %	95% CI
TB	15.7	9.7 – 24.5
Crypto meningitis	**19.5**	**6.7 - 44.8**
CMV retinitis	37.7	26.6 - 49.4
Kaposi's sarcoma	6.4	1.2 - 24.7
PML	16.7	2.3 - 50.7

Adapted from Muller et al., Lancet ID 2010, and Lawn SD and Meintjes G, Exp Rev Anti Infect Ther 2011

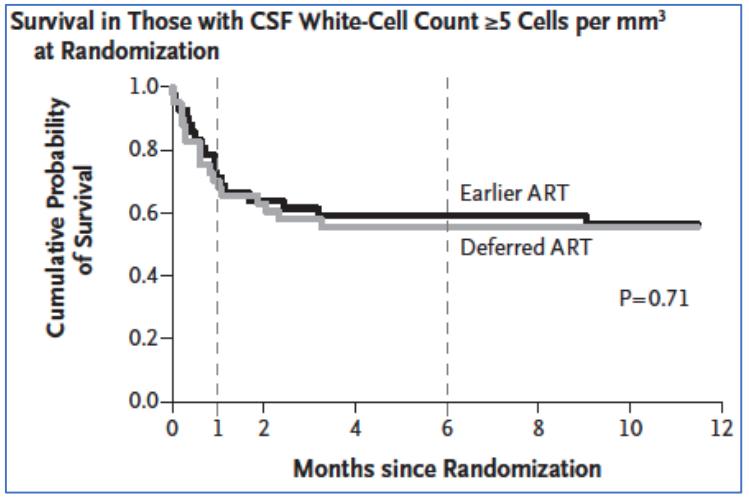
Timing of ART after diagnosis of Cryptococcal meningitis (Cryptococcal Optimal ART Timing - COAT) Trial: longer survival after deferred ART

- 177 pts, Uganda and South Africa
- **Early ART**: 1-2 weeks after dx
- **Deferred ART**: 5 weeks after dx
- Rx: amphotericin B + fluconazole
- Outcome: survival at 26 weeks





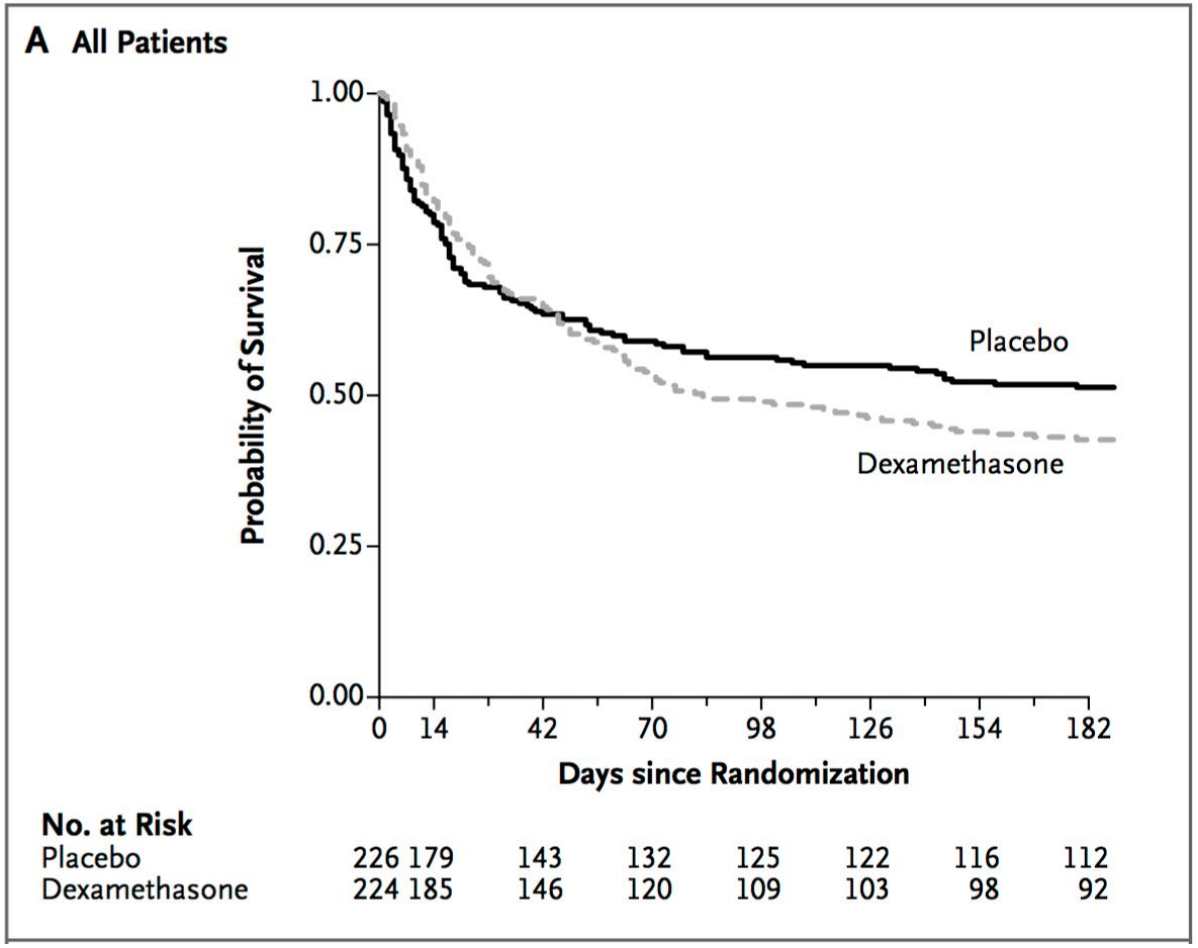
CSF WBC < 5/µL



CSF WBC > 5/µL

Boulware DR, N Engl J Med 2014

The Crypto-Dex Study: A randomised, double-blind, placebo-controlled phase III trial of adjunctive dexamethasone in HIV-CM



Deaths at 10 weeks:

- 106 of 224 (47%) in the dexamethasone group
- 93 of 226 (41%) in the placebo group

J. Beardsley, NEJM 2016

- Dexamethasone (0.3 mg/kg/day, reducing weekly over 6 weeks) did not reduce mortality among patients with HIV-CM
- It was associated with more adverse events (infections, renal and cardiac) and disability than placebo

Risk factors for cryptococcal IRIS following ART

Microbiological

- Higher fungal burden or antigen titre at diagnosis
- Positive residual culture at the end of induction therapy when starting fluconazole 400 mg for consolidation therapy. Excess risk was not observed when using fluconazole 800 mg for consolidation therapy.

Immunological

- Lower pre-ART CD4+ T cell count
- Robust immunological response to ART (> 4-fold CD4+ T cell increase)
- Elevated blood values of CRP
- Low levels of IgM, laminarin-binding IgM, glucuronoxylomannan-specific IgM in plasma
- Low CSF inflammation (WBC<25/µL, total protein <50 mg/dl)
- Trafficking of inflammatory monocytes, activated CD4+ T cells, natural killer cells into the CNS compartment
- Low levels of interferon-γ, tumour necrosis factor, IL-2, IL-6, IL-8 and IL-17 in CSF

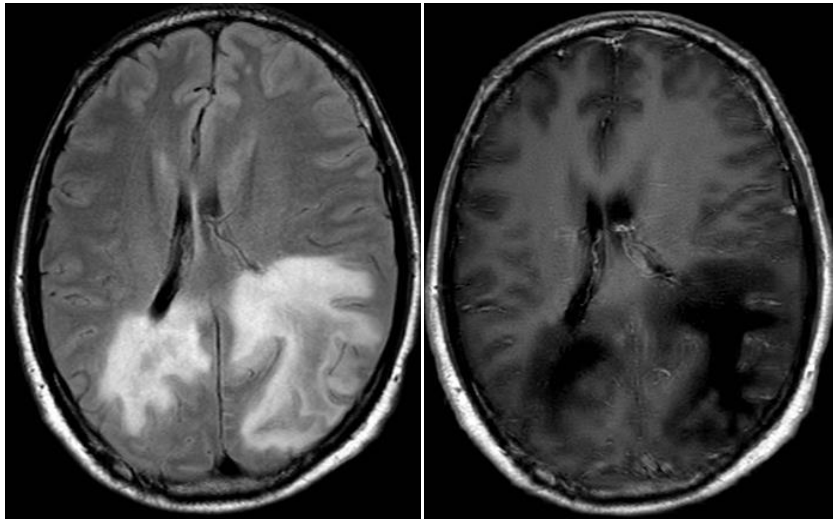
Inflammatory PML

1. New onset or sudden worsening of neurological symptoms and signs
2. In low immunocompromised persons, or during immune reconstitution
3. Associated with signs of inflammation at MRI

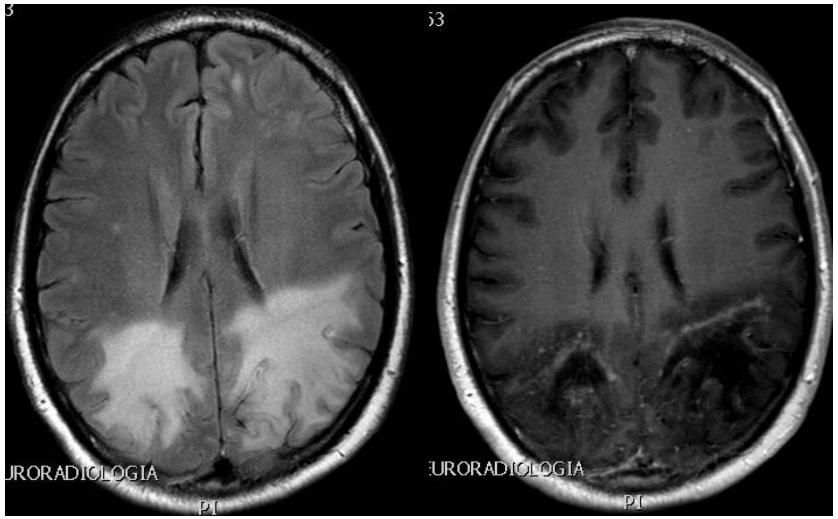
Relevance

→ Can be fatal

→ Improvement or resolution with steroids



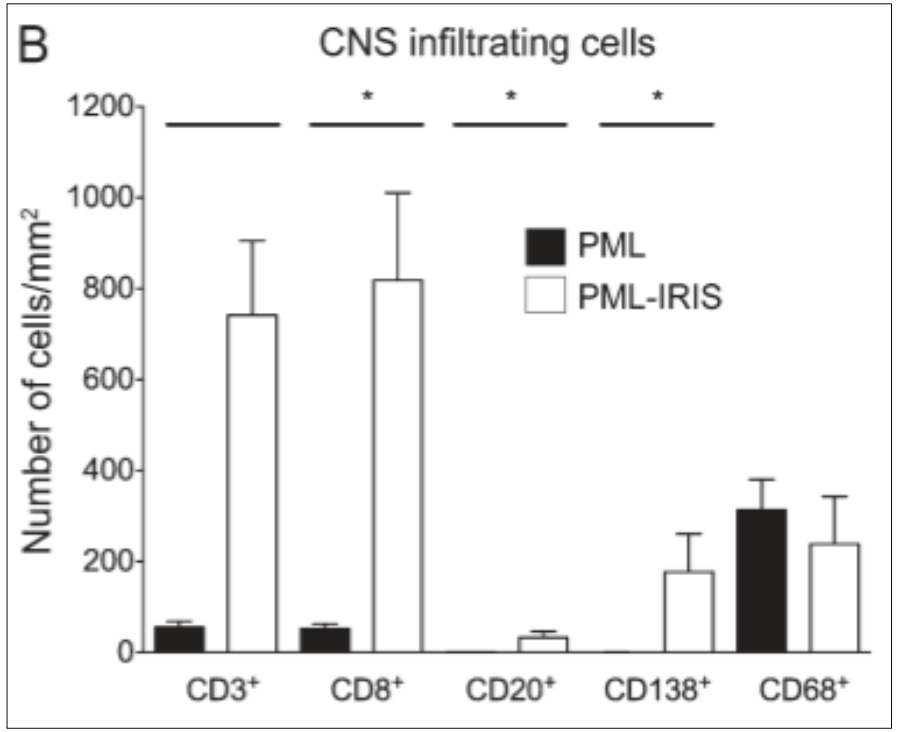
Edema with mass effect

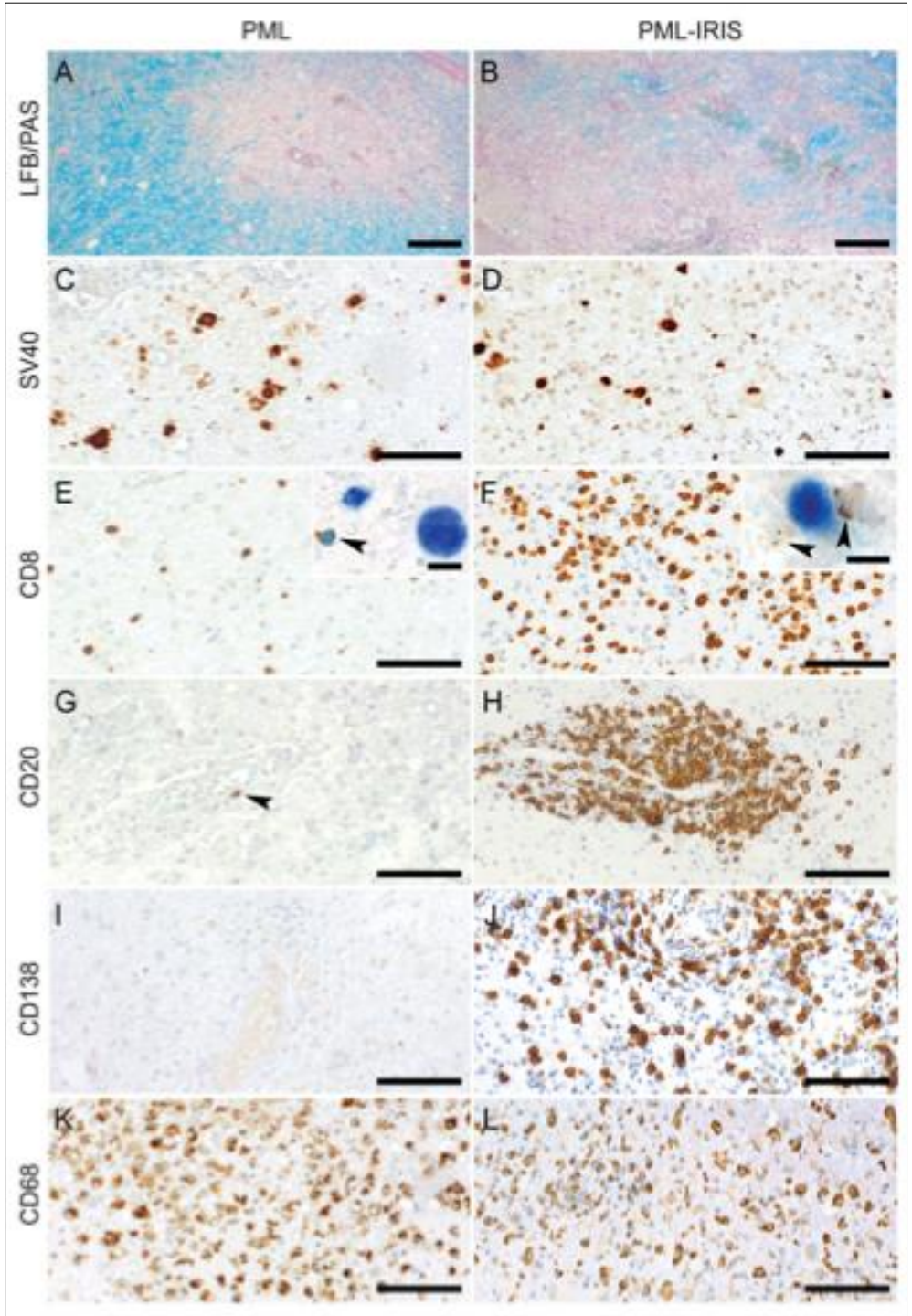


Peripheral contrast enhancement

CD8+ T-cells in HIV-related PML-IRIS

PML-IRIS (n=5) vs. classical PML (n=4)





Martin-Blondel, Ann Neurol 2013