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Part VI Opportunistic Infections

Ole Kirk for the Opportunistic Infection EACS guidelines panel

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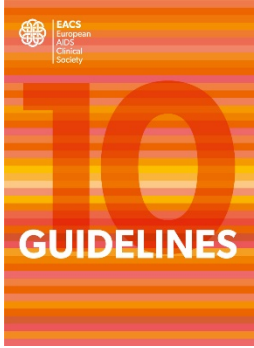

Changes

- Table on when to start ART in PLWH with OIs
- Table on prevention and treatment of IRIS
- Extensive revision of section on treatment of resistant TB
- Table on TB drug doses
- Minor revisions in text for individual OIs

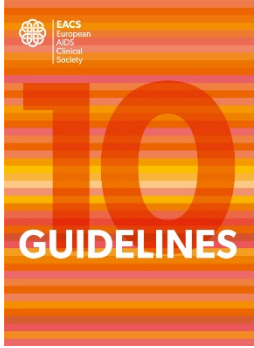

Table on when to start ART in PLWH with OIs

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When to start ART in PLWH with Opportunistic Infections (OIs)

	CD4 count	Initiation of ART	Comments
General recommendation	Any	As soon as possible and within 2 weeks after starting treatment for the opportunistic infection	
Tuberculosis	< 50 cells/µL > 50 cells/µL	As soon as possible and within 2 weeks after starting TB treatment Can be delayed up to 8 weeks after starting TB treatment, especially if difficulties with adherence, drug-drug-interactions or toxicity	A threshold of 100 cells/µL may be more appropriate due to variability in CD4 count assessments CD4 thresholds also apply for TB meningitis – with close monitoring due to increased risk of adverse effects For details, see ART in TB/HIV Co-infection section, page 20
Cryptococcal meningitis	Any	Defer initiation of ART for at least 4 weeks (some specialists recommend a delay of 6-10 weeks in severe cryptococcal meningitis)	
CMV end organ disease	Any	A delay of a maximum of 2 weeks might be considered	Especially for persons with chorioretinitis and encephalitis due to risk of IRIS

IRIS - definition and prevention

Definition	
Paradoxical IRIS	**Paradoxical worsening** symptoms during the ART-induced immune-reconstitution period in association with inflammatory signs (by physical exam, imaging or tissue biopsy), after exclusion of the expected course of a treated/untreated OI or drug toxicities [1]
Unmasking IRIS	**New onset** of symptoms during the ART-induced immune-reconstitution period in association with inflammatory signs (by physical exam, imaging or tissue biopsy), after exclusion of the expected course of a treated/untreated OI or drug toxicities [1]
Prevention	
Cryptococcal meningitis:	
paradoxical IRIS	Start therapy with **amphotericin B plus flucytosine** and defer start of cART for at least 4 weeks.
unmasking IRIS	Determine serum cryptococcal antigen in newly diagnosed PLWH with CD4 counts < 100 cells/µL. If cryptococcal antigen is detected, exclude active cryptococcal disease, and in particular examine CSF to rule out cryptococcal meningitis. If meningitis is ruled out, start pre-emptive therapy. For details, see below the specific section on cryptococcal disease
Tuberculosis	
paradoxical IRIS	Simultaneous initiation of ART and prophylactic prednisone in persons with CD4 cell count < 100 cells/µL, who started anti-TB treatment within 30 days prior to ART, may reduce risk of TB-IRIS by 30%. **Prednisone** dose: 40 mg qd for 2 weeks, followed by 20 mg qd for 2 weeks [2]

IRIS – treatment

Treatment	
In general, OI-IRIS resolve within a few weeks with continuation of specific treatment for the OI, without discontinuing ART and without anti-inflammatory treatment In cases where anti-inflammatory treatment is contemplated by the physician, corticosteroids or non-steroidal anti-inflammatory agents can be used. However, little or no data support their use or specific administration schedules in the specific conditions	
TB-IRIS	Start of systemic corticosteroids is recommended (e.g., oral prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg/day for 2 weeks) [3]
Life-threatening CNS-IRIS:	
TB-meningitis	Oral **prednisone** (1.5 mg/kg/day for 2 weeks, then tapering) [4]
PML	iv **methylprednisolone** (1 g/day for 3-5 days or iv dexamethasone 0.3 mg/kg/day for 3-5 days), then oral tapering

Individual OIs

PCP/cerebral toxoplasmosis:

- Primary prophylaxis:
  - Stop: if CD4 count >100 cells/µL and HIV-VL undetectable over 3 months
  - Typo in booklet: atovaquone dose should be **1500 mg qd**

- PCP treatment:
  - 'Some experts recommend adding caspofungin or other echinocandins to standard treatment in persons with severe PcP (requiring intensive care unit admission)'

Individual OIs

MAC:

- Primary prophylaxis (CD4 count <50 cells/µL) is not recommended if ART is started

Herpes Simplex:

- Initial and recurrent genital and mucocutaneous HSV -> Section on Sexual and Reproductive Health

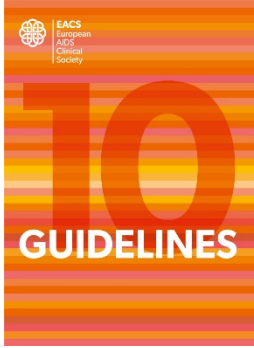
Individual OIs

Talaromycosis

Talaromycosis (*Talaromyces* (former *Penicillium marneffei*))

Treatment [7]			
Consider diagnosis in PLWH who lived in Asia. **Diagnosis:** antigen detection in blood, urine or broncho-alveolar fluid, OR positive microscopy, OR mycological culture of blood, urine, broncho-alveolar fluid, CSF or tissue biopsy or PCR in blood OR other clinical samples. *Aspergillus* galactomanan assays may be helpful to diagnose disseminated infections as cross reactivity occurs.			
	Drug	**Dose**	**Comments**
Severe disseminated talaromycosis	**Induction therapy:** **liposomal amphotericin B**	3 mg/kg qd iv	For 2 weeks or until clinical improvement
	Consolidation therapy: **itraconazole**	200 mg tid po for 3 days, then 200 mg bid po	For at least 10 weeks (followed by secondary prophylaxis)
Moderate talaromycosis	**itraconazole**	200 mg tid po for 3 days, then 200 mg bid po	For 8 weeks (followed by secondary prophylaxis)
Secondary prophylaxis / Maintenance therapy			
Secondary prophylaxis: itraconazole 200 mg qd po **Stop:** if CD4 count > 100 cells/µL and HIV-VL undetectable over 6 months, negative fungal blood cultures or negative PCR/ negative antigen			

MDR-TB – new recommendation



- EACS Guidelines in agreement with new WHO Guidelines:
  - 4 drugs for 6 months,
  - followed by 3 drugs for 12-14 months

- 'Treatment of MDR-/XDR-TB is a specialist area…. Other specialists have different views and practice may vary'

Group A: **Include all three medicines**	• levofloxacin (LFX) or moxifloxacin (MFX) • bedaquiline(BED) • linezolid (LZD)
Group B: **Add one or both medicines**	• clofazimine (CFX) • cycloserine (CS) or terizidone (TRD)
Group C: **Add to complete the regimen and when medicines from Groups A and B cannot be used**	• ethambutol (E) • delamanide (DLM) • pyrazinamide (Z) • amikacin (AMK) (or streptomycin (S) – only if susceptible) • imipenem–cilastatin (IPM-CLN) or meropenem (MPM) with amoxicillin/clavulanic acid (AMX) • ethionamide (ETO) or prothionamide (PTO) • p-aminosalicylic acid (PAS)

TB Drug Doses

- Doses of all TB drugs and common adverse events – e.g.:

Moxifloxacin	400 mg qd	Max 800 mg qd (used in the standardized shorter MDR-TB regimen) Monitor ECG in respect of QT prolongation
Bedaquiline	400 mg qd for 2 weeks 200 mg qd three times weekly for 22 weeks	EFV, ETV: potential reduction of bedaquiline exposure and activity. Not recommended Boosted regimens: increase in bedaquiline exposure. Potential risk of QT interval prolongation, ECG monitoring recommended. Avoid coadministration > 14 days
Linezolid	600 mg qd	Max 1200 mg qd Caution: hematological side effects and neurotoxicity, including optic neuropathy
Clofazimine	100 mg qd	Alternative: 200 mg for 2 months then 100 mg qd Caution: skin toxicity Monitor ECG in respect of QT prolongation

Acknowledgements

Opportunistic Infections

Chair: Ole Kirk	**Copenhagen, Denmark**
Vice-Chair: Paola Cinque	**Milan, Italy**
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