Workshop. Practical Training on diagnosis and management of clinical CNS problems in HIV-positive individuals

Treatment

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10th International Symposium on Neuropsychiatry & HIV

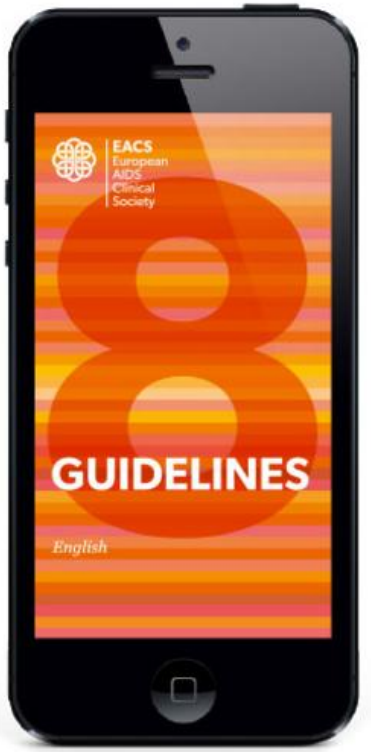
Treatment Considerations for HIV associated cognitive impairment

(after ruling out other causes including depression and drug abuse)

Detectable HIV RNA in plasma or CSF	Plasma HIV RNA detectable: • Optimise ART, reinforce compliance CSF escape • Optimise ART based on plasma and CSF genotype results, CSF effective drugs?

Undetectable HIV RNA in plasma and CSF	No evidence of neuroinflammation
	• Consider ART toxicity
	• Review co-morbidity management
	
	Evidence of ongoing neuroinflammation:
	• Progressive WM lesions on MRI, or raised CSF inflammatory biomarkers
	• No proven strategy
	  • Maraviroc intensification
	  • ART modification based on pharmacokinetic scoring systems
	  • Research into adjunctive therapies

Management of HIV-associated cognitive impairment



HIV-positive person-self or their relatives complaining of, or care giver noting cognitive problems - without obvious confounding conditions[i]

→ Initial assesments[ii]

↓ Problems confirmed

↓ Evaluation for depression and possible treatment[iii]

↓ Problems persisting but depression excluded or optimally managed

↓ NP examination[iv]

↓ Abnormal

↓ Neurological examination
Brain MRI
CSF examination[v]

↓ Additional causes of NCI other than HIV excluded

↓ Diagnosis: **HIV-associated NCI**[vi]

- Off ART
  - ↓ Start ART (refer to general guidelines) *Consider inclusion of potentially CNS-active drugs*[ix]
- On ART
  - CSF viral escape[vii]
    - ↓ Optimise ART by CSF and plasma GDR testing *Include potentially CNS-active drugs*[ix]
    - ↓ Repeat CSF examination and other evaluations after ≥ 4 weeks
  - Other situations[viii]
    - ↓ Continue or switch ART (refer to general guidelines) *Reconsider other causes of NCI*

- Drugs with demonstrated clear CSF penetration:
  - —NRTIs: ZDV, ABC*
  - —NNRTIs: EFV**, NVP
  - —PI/r: IDV/r, LPV/r, DRV/r*
  - —INSTI: DTG
  - —Other classes: MVC
- Drugs with proven clinical efficacy:
  - —NRTIs: ZDV, ABC
  - —PI/r: LPV/r

EACS Guidelines, January 2017

Detectable CSF HIV RNA

Definition
- Lack of plasma virological suppression
- Lack of CSF virological suppression
  - No consensus definition
  - Generally considered CSF HIV RNA 1log greater than plasma HIV RNA if plasma detectable
  - Or CSF detectable if plasma undetectable

How common is this?

Asymptomatic subjects:
- 10-15% of subjects with suppressed plasma viraemia [1,2]
- 10% in those not on ART
- Higher rates if ultrasensitive assays used [3]
- Associated with markers of inflammation

Symptomatic subjects:
- Reported 20-100% subjects (depending on symptoms)
- Canestri syndrome[4]
- Resistance mutations well described in CSF when not apparent in the plasma compartment / resistance associated with lower plasma HIV RNA [5]

Management
- Optimise ART guided on current and historical plasma and CSF resistance testing

1. J Infect Dis. 2010 Dec 15;202(12):1819-25,
2. J Infect. 2012 Sep;65(3):239-45.
3. AIDS. 2014 Jul 14.
4 Clin Infect Dis. 2010 Mar 1;50(5):773-8
5 AIDS. 2010 Sep 24;24(15):2412-4.

ART neurotoxicity

- Several mechanisms proposed
- *In vitro* less neurotoxic: emtricitabine, tenofovir, darunavir, maraviroc
- Efavirenz associated with neurological symptoms and, less clearly, with cognitive disorders
- Dolutegravir associated with *in vitro* neurite overgrowth and with *in vivo* mild and reversible neuropsychological disturbances

- Efavirenz switch studies to date have not reported cognitive benefits
- Guidelines recommend avoiding efavirenz in individuals with cognitive impairment

Underwood J, et al.AIDS 2015; Robertson K, et al. JNV 2012; Hinckley S, et al. CROI2916 #395; De Boer MG, AIDS 2016; Hoffman C, et al. HIV Medicine 2017; Fettiplace A, et al. JAIDS 2016; Bonfanti P, et al. AIDS 2017

Comorbidities

- CV risk factors, Central obesity, Insulin, resistance, Diabetes (elderly) and Higher IMT have been associated with cognitive disorders

No study assessed so far the impact of an improved cardiovascular profile in patients with HIV associated cognitive impairment

Wright EJ, et al. Neurology 2010; Valcour V, et al. AIDS Res and Hum Retrov 2011; McCutchan A, et al. Neurology 2012; Fabbiani M, et al. HIV Medicine 2013; Sattler FR, et al. JAIDS 2015; Jake LE, et al. Antiv Ther 2015; Haddow L, et al. AIDS Patient Care and STDs 2014; Bladowska J, et al. PlosOne 2014

Pharmacokinetic scoring systems

- High CPE
  - 4: AZT, NVP, IDV/r
  - 3: ABC, FTC, EFV, DRV/r, LPV/r, MVC, RAL
  - new drugs? DTG, EVG/c, RPV
- High Inhibitory Quotients
  - single study: DRV/r, EFV, ETV
- High Monocyte Efficacy score
  - single study, several drugs missing: ddC, 3TC, TDF, AZT, EFV, APV, ENF

Hammond ER, et al. Am J Epidemiology 2014; Calcagno A, et al. CID 2014; Shikuma C, et al. Antiviral Therapy 2012

Maraviroc intensification

- Maraviroc intensification
  - Improved CSF markers and MRS
  - Better cognition, small RCT (7 vs. 7)

Li G-H, et al. AIDS 2015; Garvey L, et al. JAC 2012; Vera JH, et al. HIV Clin Trials 2012; Ndhlovu LC, et al. JNV 2014; Gates TM, et al. AIDS 2016

Adjunctive strategies for future research

- Paroxetine
  - *In vitro* and animal study support its use
  - Small randomized placebo-controlled trial (n= 24, stable HAART, >90% adherence)

- Rivastigmine
  - Small (17 aviremic pts with HAND) Randomized, double-blind, crossover using oral rivastigmine (up to 12 mg/day for 20 weeks) vs. placebo

  Improved processing speed and executive functioning

Sacktor N, et al. CROI 2016 #146; Simioni S, et al Neurology 2013

Neuro-rehabilitation

- Very limited data
- Small (16 vs. 16), randomized controlled trial with an intense cognitive rehabilitaion protocol

Significant improvement in five domains (Learning and memory, Abstraction/executive functioning, Verbal fluency, Attention/working memory, and Functional) that persisted for 6 months after rehabilitation

Weber E, et al. Neuropsychol Rev. 2013; Livelli A, et al. Front Behav Neurosci. 2015

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