



Barcelona May 26-28, 2016

What do psychiatrists need to know when treating HAND – Differential Diagnosis and HAART neurotoxicity

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**HIV associated
neurocognitive disorders
(HAND)**

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graph TD; A[HIV associated neurocognitive disorders (HAND)] --> B[Asymptomatic neurocognitive impairment (ANI)]; A --> C[Mild neurocognitive impairment (MNI)]; A --> D[HIV associated dementia (HAD)];
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**Asymptomatic
neurocognitive
impairment (ANI)**

Mild cognitive impairment that does not interfere with activities of daily living

**Mild
neurocognitive
impairment (MNI)**

Mild cognitive impairment that interferes with activities of daily living

**HIV associated
dementia (HAD)**

Marked cognitive impairment that produces marked interference with activities of daily living

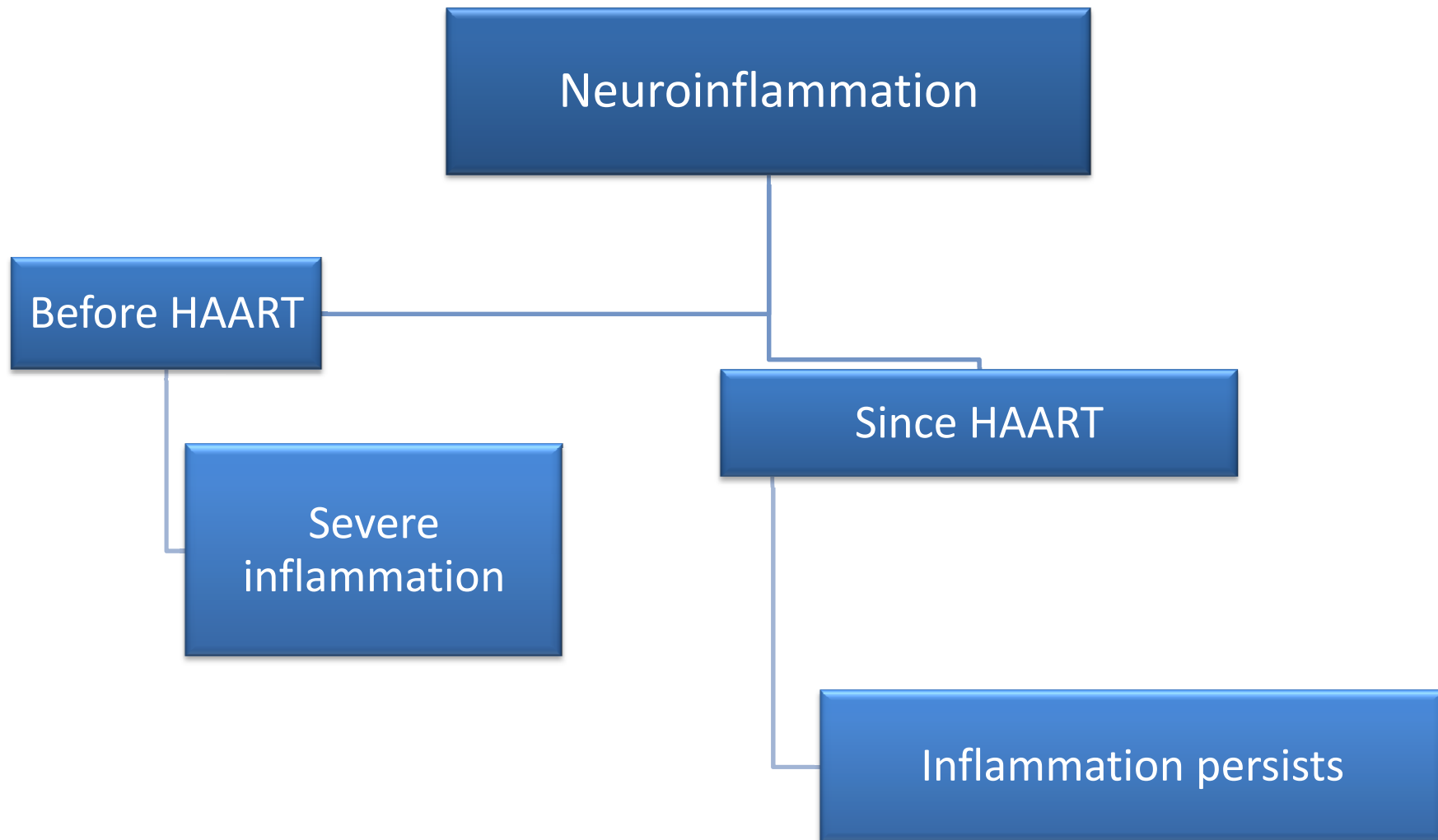
Neuropathogenesis

- Since the advent of HAART: ↓ prevalence of HAD
 - ...but the overall prevalence of HAND and associated morbidity remain high (~50%)*

milder forms of impairment persist in a substantial proportion of patients, with higher levels of immune functioning.

*Sacktor et al., 2002; McArthur et al., 2004; Nath et al., 2008; Heaton et al. 2010; Gannon et al., 2011; Akay et al., 2013

Neuropathogenesis



How to diagnose HAND?

Problems:

1. Frascati Criteria is a classificatory system, not a clinical diagnosis...
 - So, how to interpret cognitive function in the context of comorbidities?
2. Comorbid and differential diagnostic considerations for HAND pathogenesis have shifted away...

How to diagnose HAND?

- Comorbid and differential diagnostic considerations for HAND pathogenesis have shifted away... **Co-factors for exacerbation of persistent neuroinflammation in HAND:**
 - substance abuse;
 - hepatitis C co-infection;
 - effects of aging on brain vulnerability;
 - long-term CNS toxicity of HAART.

Substance abuse

- Drugs of abuse are a major comorbidity risk for neurocognitive dysfunction:
 - *Delirium*;
 - Exacerbation of neuronal injury induced by HIV (additive, if not synergistic, effect);
 - ↑ risk in intravenous drug abusers (30% of HIV-positive individuals in developed countries);

Substance abuse

- Major drugs of abuse contributing to HIV pathogenesis:
 - Opiates (morphine, methadone);
 - Stimulants (cocaine, METH).
 - ↑ Enhanced HIV replication;
 - ↑↑ production of neurotoxic factors;
 - Alterations in BBB integrity

Hepatitis C co-infection

- Hepatitis C (independent of HIV co-infection):
 - Multiple neuropsychiatric complaints;
 - The pattern of cognitive impairment associated with hepatitis C is similar to that of HIV;
- Comorbid HIV and hepatitis C increase the risk of cognitive impairment:
 - risk is twice as high compared to HIV patients without hepatitis C;

Aging

- The long-term prognosis for HIV+ patients with HAART continues to improve and by 2015 more than 50% of the HIV+ population in the United States will be over 50 years of age.*

*Deeks et al. 2009

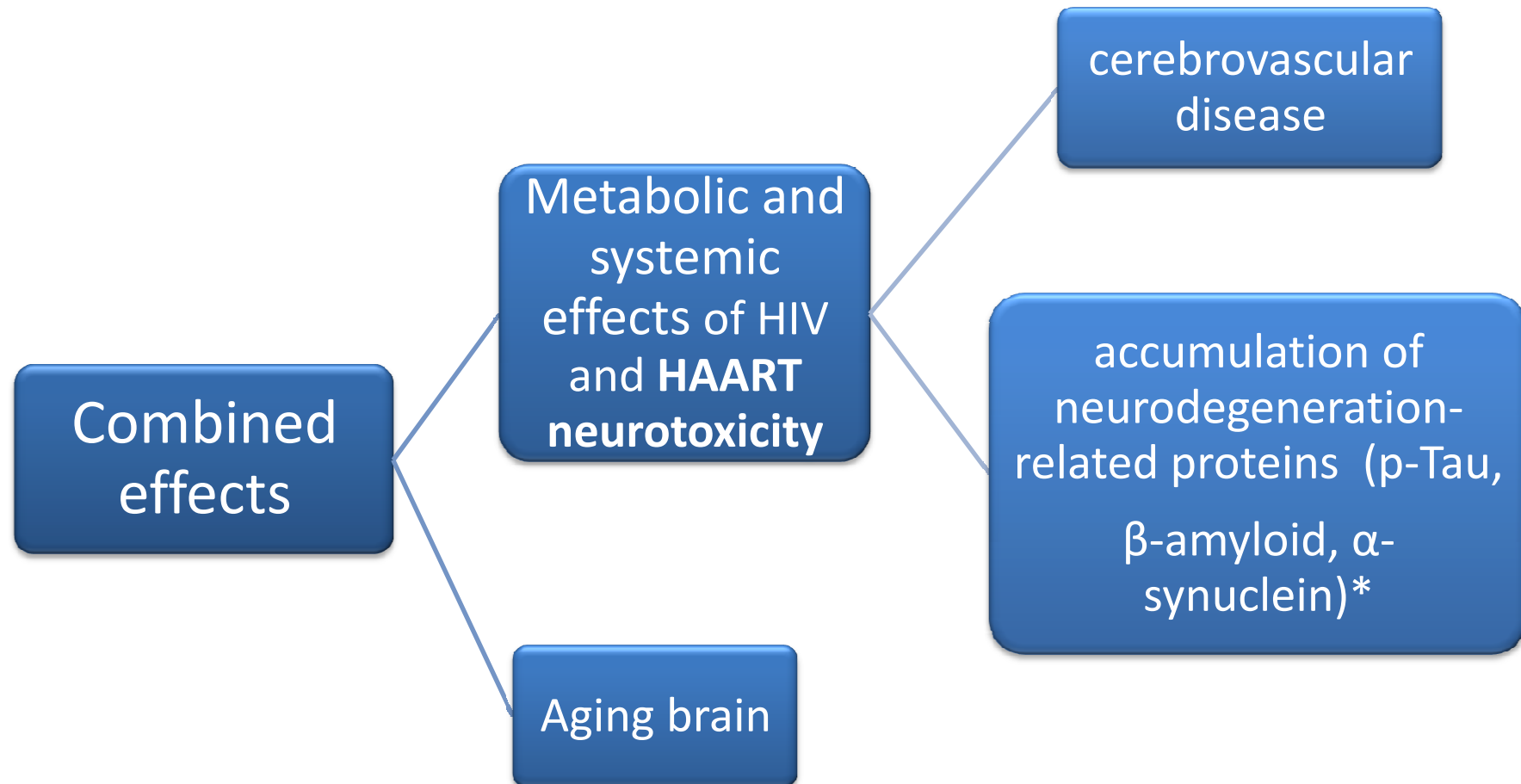
Aging

- But, life expectancy remains 10–30 years less than that of uninfected individuals:
 - HIV+ patients treated with HAART have ↑ risk for systemic and CNS diseases associated with aging: renal failure, osteoporosis, cancer, cardiovascular disease and cognitive decline, which can be associated with Alzheimer's disease and Parkinson's disease-like pathology.

Aging

- Age related brain vulnerability:
 - Independent of HIV infection – neurodegenerative disorders (Alzheimer's disease and Parkinson's disease);
 - Combined effects – HIV+ serostatus associated with a greater than five-fold acceleration of aging effects.

Aging



p-Tau: hyperphosphorylated Tau; * Similarities between the pathogenesis of HAND and other neurodegenerative disorders (Alzheimer's and Parkinson's disease)

HAART

- There is emerging evidence that high CNS concentrations of some HAART are potentially neurotoxic and may be associated with the development of HAND.

Evidence linking CNS Penetration Effectiveness (CPE) scores with cognitive performance has been mixed...

HAART

- CNS Penetration Effectiveness (CPE) score:
 - Hierarchy of drug distribution (or penetration) into the CNS;
 - High CPE: ↑ suppression in HIV replication within the CNS:
 - Better neurocognitive performance;
 - Neuroprotective effect.

So, some HAART is more effective in reducing HIV replication in the brain than other.

HAART

| | 4 | 3 | 2 | 1 |
|---------------------------------------|--------------|---|--|---|
| NRTI | → Zidovudine | Abacavir Emtricitabine | → Didanosine Lamivudine Zalcitabine Stavudine | Tenofovir Zalcitabine |
| NNRTI | Nevirapine | Delavirdine Efavirenz | Etravirine | .. |
| Protease inhibitors | Indinavir* | Darunavir* Fosamprenavir* Indinavir Lopinavir* | Atazanavir Atazanavir* Fosamprenavir | Nelfinavir Ritonavir Saquinavir Saquinavir* Tipranavir* |
| Cell fusion and cell entry inhibitors | .. | Maraviroc | .. | Enfuvirtide |
| Integrase inhibitor | .. | Raltegravir | .. | .. |

CPE score is the sum of the individual scores of all drugs in the ART regimen. NNRTI=non-nucleoside reverse transcriptase inhibitor. *Ritonavir boosted. NRTI=non-nucleoside reverse transcriptase inhibitor.

Table 2: CNS penetration effectiveness (CPE) 2010 ranking scale⁷

NRTIs (Nucleoside Reverse Transcriptase Inhibitors) : Zidovudine; Didanosine; Abacavir; NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) : Nevirapine; Efavirenz ; **Neuropsychiatric effects**; Zidovudine was effective in the treatment of HIV associated dementia (monotherapy); Didanosine monotherapy effective in improving psychomotor function.

Nightingale et al., 2013

HAART

- So ...
 - The relation between the drug concentration needed to inhibit HIV replication in the CNS and that needed to cause neurotoxicity probably differs according to the drug used;
 - The drugs that have the greatest penetration into and distribution within the CNS are not necessarily the most neurotoxic.

Messages to take home

1. Comorbidity in HIV patient is changing over time;
2. HAND is diagnosed accordingly to the Frascati criteria, that lacks simplicity and it's not a good screening method;
3. The primary concern of the psychiatrist must be do a correct clinical differential diagnosis in the presence of cognitive impairment, having in to account other contributors for HAND pathogenesis: drugs of abuse, hepatitis C co-infection, aging and HAART neurotoxicity;
4. It's important to psychiatrists to have knowledge of the specific HAART used.

Thanks for your attention!

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FDA-Approved HIV Medicines

| Drug Class | Generic Name (Other names and acronyms) | |
|--|---|--|
| Nucleoside Reverse Transcriptase Inhibitors (NRTIs) | | |
| NRTIs block reverse transcriptase, an enzyme HIV needs to make copies of itself. | abacavir (abacavir sulfate, ABC) | |
| | didanosine (delayed-release didanosine, dideoxyinosine, enteric-coated didanosine, ddl, ddl EC) | |
| | emtricitabine (FTC) | |
| | lamivudine (3TC) | |
| | stavudine (d4T) | |
| | tenofovir disoproxil fumarate (tenofovir DF, TDF) | |
| | zidovudine (azidothymidine, AZT, ZDV) | |
| | Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) | |
| | NNRTIs bind to and later alter reverse transcriptase, an enzyme HIV needs to make copies of itself. | delavirdine (delavirdine mesylate, DLV) |
| | | efavirenz (EFV) |
| etravirine (ETR) | | |
| nevirapine | | |
| | | |

| | | |
|---|---|-----------------------|
| | (extended-release nevirapine, NVP) | |
| | rilpivirine (rilpivirine hydrochloride, RPV) | |
| Protease Inhibitors (PIs) | | |
| PIs block HIV protease, an enzyme HIV needs to make copies of itself | atazanavir (atazanavir sulfate, ATV) | |
| | darunavir (darunavir ethanolate, DRV) | |
| | fosamprenavir (fosamprenavir calcium, FOS-APV, FPV) | |
| | indinavir (indinavir sulfate, IDV) | |
| | nelfinavir (nelfinavir mesylate, NFV) | |
| | ritonavir (RTV) | |
| | saquinavir (saquinavir mesylate, SQV) | |
| | tipranavir (TPV) | |
| | Fusion Inhibitors | |
| | Fusion inhibitors block HIV from entering the CD4 cells of the immune system. | enfuvirtide (T-20) |
| Entry Inhibitors | | |
| Entry inhibitors block proteins on the CD4 cells that HIV needs to enter the cells. | maraviroc (MVC) | |

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|--|--|
| Integrase Inhibitors | |
| Integrase inhibitors block HIV integrase, an enzyme HIV needs to make copies of itself. | dolutegravir (DTG) elvitegravir (EVC) raltegravir (raltegravir potassium, RAL) |
| Pharmacokinetic Enhancers | |
| Pharmacokinetic enhancers are used in HIV treatment to increase the effectiveness of an HIV medicine included in an HIV regimen. | cobicistat (COBI) |
| Combination HIV Medicines | |
| Combination HIV medicines contain two or more HIV medicines from one or more drug classes. | abacavir and lamivudine (abacavir sulfate / lamivudine, ABC / 3TC) abacavir, dolutegravir, and lamivudine (abacavir sulfate / dolutegravir sodium / lamivudine, ABC / DTG / 3TC) abacavir, lamivudine, and zidovudine (abacavir sulfate / lamivudine / zidovudine, ABC / 3TC / ZDV) atazanavir and cobicistat (atazanavir sulfate / cobicistat, ATV / COBI) darunavir and cobicistat (darunavir ethanolate / cobicistat, DRV / COBI) efavirenz, emtricitabine, and tenofovir disoproxil fumarate (efavirenz / emtricitabine / tenofovir, efavirenz / emtricitabine / tenofovir DF, EPV / FTC / TDF) elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide |

| | |
|--|---|
| <p>fumarate (elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide, EVG / COBI / FTC / TAF)</p> | <p>elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (QUAD, EVG / COBI / FTC / TDF)</p> |
| <p>emtricitabine, rilpivirine, and tenofovir alafenamide (emtricitabine / rilpivirine / tenofovir AF, emtricitabine / rilpivirine / tenofovir alafenamide fumarate, emtricitabine / rilpivirine hydrochloride / tenofovir AF, emtricitabine / rilpivirine hydrochloride / tenofovir alafenamide, emtricitabine / rilpivirine hydrochloride / tenofovir alafenamide fumarate, FTC / RPV / TAF)</p> | <p>emtricitabine, rilpivirine, and tenofovir disoproxil fumarate (emtricitabine / rilpivirine hydrochloride / tenofovir disoproxil fumarate, emtricitabine / rilpivirine / tenofovir, FTC / RPV / TDF)</p> |
| <p>emtricitabine and tenofovir alafenamide (emtricitabine / tenofovir AF, emtricitabine / tenofovir alafenamide fumarate, FTC / TAF)</p> | <p>emtricitabine and tenofovir disoproxil fumarate (emtricitabine / tenofovir, FTC / TDF)</p> |
| <p>lamivudine and zidovudine (3TC / ZDV)</p> | <p>lopinavir and ritonavir (ritonavir-boosted lopinavir, LPV/r, LPV / RTV)</p> |