# HIV-related neurocognitive impairment in the era of HAART

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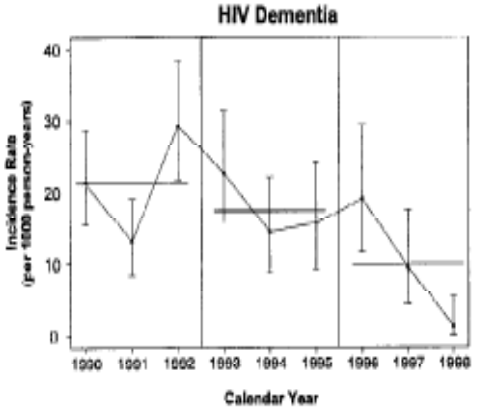
# EPIDEMIOLOGY

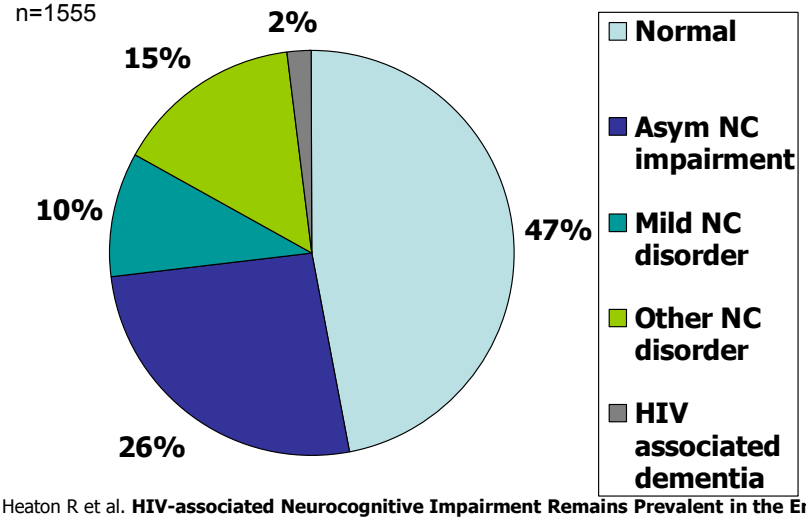
# Decline in HIV associated dementia following introduction of HAART




Sacktor et al. HIV-associated neurologic disease incidence changes:: Multicenter AIDS Cohort Study, 1990-1998 Neurology. 56(2):257-260, January 23, 2001.

# CHARTER STUDY - Results

n=1555




Heaton R et al. **HIV-associated Neurocognitive Impairment Remains Prevalent in the Era of Combination ART: The CHARTER Study** CROI 2009 Abstract 154

| Abstract No. Authors | Location | Sample Size | Prevalence | Correlates |
|---|---|---|---|---|
| Abstract 154 Heaton et al | United States | 1555 | 53% global neuropsychologic impairment | Lower nadir CD4+ counts, detectable HIV RNA in blood, current antiretroviral therapy use |
| Abstract 464 Vassallo et al | France | 107 | 69% HAND or neuropsychologic deficit | Hepatitis C virus coinfection |
| Abstract 474 Bonnet et al | France | 230 | 25% mild neurocognitive disorder | Older age, AIDS, active hepatitis B virus disease |
| Abstract 458 McCutchan et al | United States | 145 | 31% HAND | Diabetes mellitus, higher body mass index and triglycerides, lower high-density lipoprotein cholesterol |
| Abstract 459 Dulioust et al | France | 37 | 51% HAND | Not cardiovascular risk factors |
| Abstract 477 Duiculescu et al | Romania | 43 | 60% HAND | Higher HIV RNA in cerebrospinal fluid |
| Abstract 485 Robertson et al | Various | 293 | 29% neurologic abnormalities | |
| Abstract 920 Ruel et al | Uganda | 218 | HIV-infected performed worse in most measures | |
| Abstract 155 Everall et al | United States | 589 | 17% typical HIV brain pathology, 78% at least 1 central nervous system abnormality | Antiretroviral therapy nonuse, lower nadir CD4+ counts, higher HIV RNA levels in blood |

Letendre et al. Top HIV Med. 2009 Apr-May;17(2):46-56

# RISK FACTORS & DIAGNOSIS

## Symptoms of Early Stage HIV related cognitive impairment

- Difficulty concentrating
- Difficulty remembering phone numbers or appointments
- Slowed thinking
- Longer time time required to complete complicated tasks
- Reliance on list keeping to help track daily activities
- Mental status tests and other mental capabilities may be normal
- Irritability
- Unsteady gait or difficulty keeping balance
- Poor coordination and a change in handwriting
- Depression

## Risk factors for HAND

- Low CD4 count[1]
- Nadir CD4 count[2]
- Uncontrolled viraemia[1]
- Hepatitis C[3]
- Drug use[4]
- Lower educational achievement[5]
- Anaemia[6]
- Thrombocytopenia[7]
- Aging[8]
- Insulin resistance and diabetes[9]

1.Childs et al. Neurology 1999;52:6073.
2.Moreno-Munoz et al. AIDS Research and Human Retroviruses 24(10): 1301-1307. Oct 2008.
3.Parsons et al. AIDS. 2006 (12):1591-1595.
4.Hauser KF et al. J Neurochemistry (2007) 100 (3), 567–586.
5.De Ronchi et al. Arch Neurol. 2002;59:812–818.
6.McArthur JC et al. Neurology. 1993 Nov;43(11):2245-521.
7.Wachtman LM et al. Arch Neurol 64 (9): 1264-1272, 2007.
8.Valcour et al. Neurology 2004; 63: 822-827.
9.Valcour VG et al. JAIDS 38; 31-36, 2005.

# ARV TREATMENT

# HAART improves cognition

Table 3. Clinical, laboratory, neuropsychological and neuroimaging characteristics of the 26 study patients treated with highly active antiretroviral therapy by month of treatment

| Month since HAART | 0 | 6 | p[a] | 18 | p[a] |
|---|---|---|---|---|---|
| No. of patients examined | 26 | 24 | | 23 | |
| Mean CD4 cell counts (±SD), count/μl | 49 (±15) | 180 (±20) | < 0.001[b] | 173 (±20) | < 0.001[b] |
| Mean plasma HIV RNA (±SD), log copies/ml | 4.7 (0.8) | 1.4 (1.5) | < 0.001[b] | 1.7 (1.9) | < 0.001[b] |
| Patients with undetectable plasma HIV RNA (%) | 0 | 12 (50) | < 0.001[c] | 7 (30.4) | < 0.001[c] |
| Mean haemoglobin (±SD), g/dl | 12.6 (±2.1) | 14.2 (±1.0) | < 0.001[b] | 14.8 (±1.3) | < 0.001[b] |
| Body mass index (±SD), kg/m$^2$ | 23.4 (±2.5) | 24.9 (±2.5) | < 0.001[b] | 25.4 (±3.2) | < 0.001[b] |
| Neuropsychological assessment | | | | | |
| Patients with impaired neuropsychological assessment (%) | 21 (80.8%) | 12 (50.0%) | < 0.05[c] | 5 (21.7%) | < 0.001[c] |
| Patients with impaired concentration and speed of mental processing (%) | 17 (65.4%) | 10 (41.7%) | n.s. | 5 (21.7%) | < 0.05[c] |
| Patients with impaired memory (%) | 13 (50.0%) | 3 (12.5%) | < 0.01[c] | 2 (8.7%) | < 0.01[c] |
| Patients with visuospatial and constructional impairment (%) | 2 (7.7%) | 0 (0%) | n.s. | 0 (0%) | n.s. |
| Patients with impaired fine motor functioning (%) | 3 (11.5%) | 0 (0%) | n.s. | 0 (0%) | n.s. |
| Patients with impaired mental flexibility (%) | 0 (0.0%) | 3 (12.5%) | n.s. | 2 (8.7%) | n.s. |
| SPECT examination | | | | | |
| Patients with agnosic alterations (%) | 5 (19.2) (100%) | 8/23 (34.8%) | | | < 0.05[d] |

[a]Compared to baseline, [b]Paired t-test, [c]Chi square test, [d]Fischer-Tocher test, n.s., not significant.

Tozzi V et al. **Positive and sustained effects of highly active antiretroviral therapy on HIV-1-associated neurocognitive impairment.** *AIDS* 1999, **13**:1889–1897

# Improvement in cognition correlates with CSF viral load reduction

*Table 2 Change in NPZ-4 relative to change in CSF and plasma HIV-1 RNA at each follow-up visit taking into account baseline NPZ-4*

| | Change in NPZ-4 per $\log_{10}$ decrease in HIV-1 RNA concentration | | | |
|---|---|---|---|---|
| Compartment | 4 weeks | *p* Value | 8 weeks | *p* Value |
| In all 25 subjects | | | | |
| CSF | 0.41 ± 0.10 | 0.001 | 0.06 ± 0.18 | 0.75 |
| Plasma | 0.24 ± 0.11 | 0.05 | 0.01 ± 0.13 | 0.93 |
| In 14 subjects who entered on no antiretroviral therapy | | | | |
| CSF | 0.59 ± 0.15 | 0.001 | 0.28 ± 0.18 | 0.02 |
| Plasma | 0.26 ± 0.14 | 0.11 | 0.25 ± 0.18 | 0.04 |

Values are mean ± SD.

Marra CM et al. **Changes in CSF and plasma HIV-1 RNA and cognition after starting potent antiretroviral therapy.** *Neurology* 2003;60:1388–1390

# CNS Penetration-Effectiveness Rank for antiretrovirals

- Rank based on combination of available data using in order of hierarchy:
- Clinical effectiveness studies
- Pharmacokinetic effectiveness studies
- Chemical data

**Letendre S et al. Validation of the CNS Penetration-Effectiveness Rank for Quantifying Antiretroviral Penetration Into the Central Nervous System** *Arch Neurol. 2008;65(1):65-70*

# Cognitive intervention trial

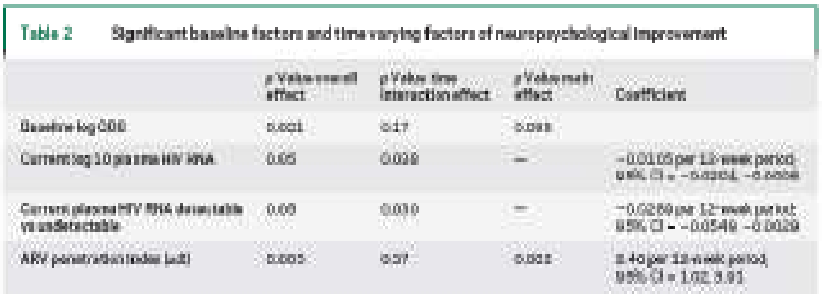


Table 2 Significant baseline factors and time varying factors of neuropsychological improvement

| | p Value overall effect | p Value time interaction effect | p Value main effect | Coefficient |
|---|---|---|---|---|
| Baseline log CD8 | 0.001 | 0.17 | 0.093 | |
| Current log 10 plasma HIV RNA | 0.05 | 0.039 | — | −0.0105 per 12-week period; 95% CI = −0.0205 to −0.0004 |
| Current plasma HIV RNA detectable vs undetectable | 0.03 | 0.010 | — | −0.0269 per 12-week period; 95% CI = −0.0549 to 0.0029 |
| ARV penetration index (all) | 0.005 | 0.57 | 0.003 | 0.40 per 12-week period; 95% CI = 1.02 to 3.91 |

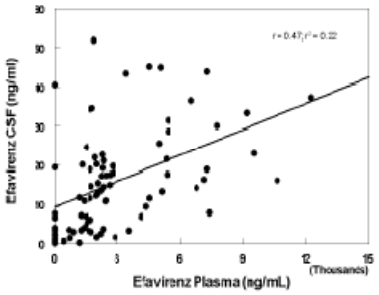
L.A. Cysique et al. Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. ***Neurology*** **2009;73: 342–348**

# CPE ranking table

| CSF Penetration of ARV's | **Good (1)** | **Fair (0.5)** | **Poor (0)** |
|---|---|---|---|
| NRTIs | Abacavir<br>Zidovudine | Emtricitabine<br>Lamivudine<br>Stavudine | Didanosine<br>Tenofovir |
| NNRTIs | Nevirapine | Efavirenz | |
| PIs | Amprenavir/r<br>Indinavir/r<br>Lopinavir/r | Atazanavir+/-r | Nelfinavir<br>Ritonavir<br>Saquinavir/r<br>Tipranavir/r |
| Fusion inhibitors | | | Enfurvitide |

Letendre et al. Arch Neurol **2008**; 65:65–70.

# Efavirenz in the CSF




- Efavirenz CSF concentrations were only 0.5% of plasma concentrations, consistent with the unbound fraction in blood and suggesting limited active transport out of the CSF.
- Plasma concentrations have higher peaks and a greater decline over 24 hours, while CSF concentrations remain relatively stable.
- Concentrations of efavirenz in CSF exceed the wild-type IC50 in most individuals and may inhibit HIV replication in the nervous system.

**Best B et al. Efavirenz and Emtricitabine Concentrations Consistently Exceed Wild-type IC50 in Cerebrospinal Fluid: CHARTER Findings. CROI 2009 Abstract 702**

## Total CSF and plasma Darunavir concentrations

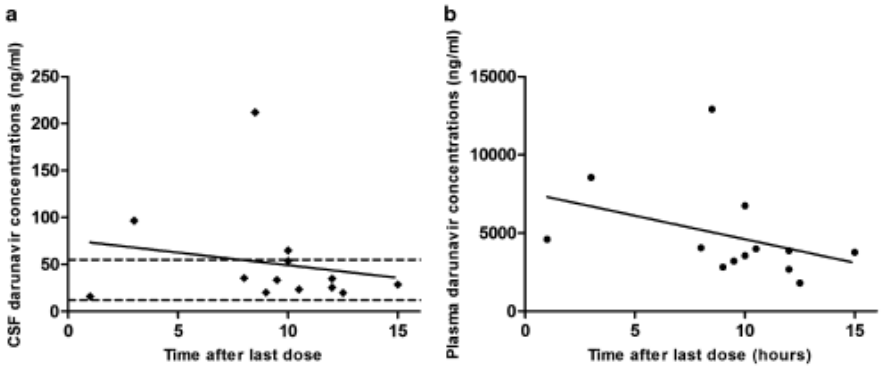
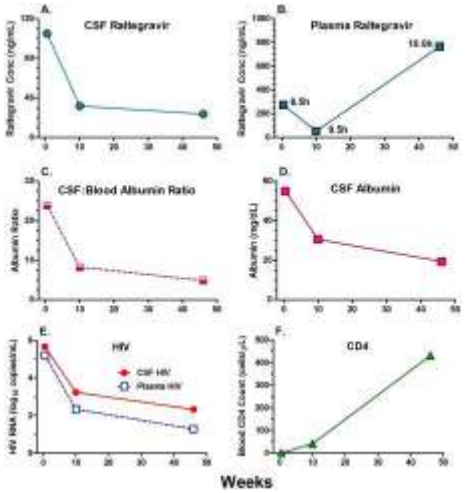



FIG. 1. Darunavir cerebrospinal fluid (CSF) (a) and plasma (b) concentrations by postdose time for the 13 paired specimens with known sampling time. The solid lines are linear regression lines for CSF and plasma. The dotted lines in (a) indicate the estimated range of the $IC_{50}$ in CSF (12–55 ng/ml).

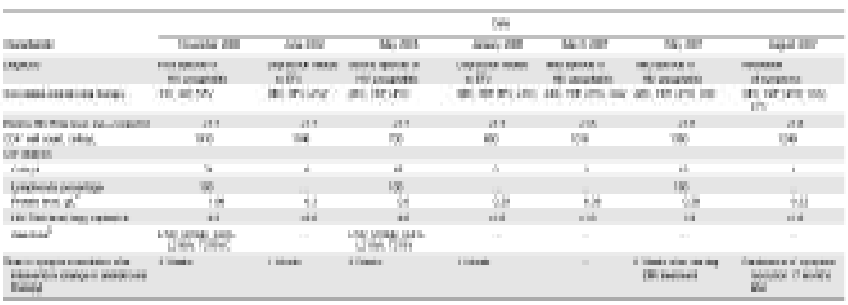
Yilmaz, *et al.* AIDS Res Hum Retroviruses 2009: Vol25, No 4

# Raltegravir in the brain




Yimaz et al. PLoS One. 2009

# Etravirine in the brain



**Couzigou et al. CID 2009:48**

Presence of HIV-1 R5 Viruses in Cerebrospinal Fluid Even in Patients Harboring R5X4/X4 Viruses in Plasma.

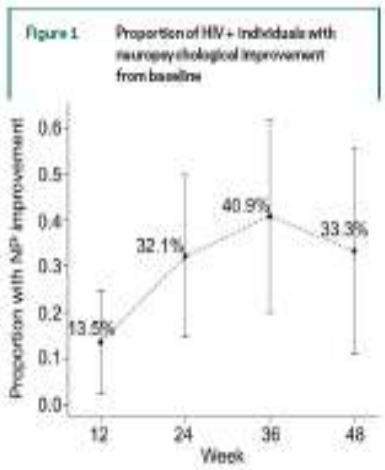
| Subject No. | Tropism | | Age, yrs | Sex | CD4 T-Cell Count (Cells/mm$^3$) | Nadir CD4 Count (Cells/mm$^3$) | HIV RNA Level ($log_{10}$ Copies/mL) | | Subtype | Antiretroviral Treatment | Neurological Disorder |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | CSF | Plasma | | | | | CSF | Plasma | | | |
| 1 | R5 | R5 | 63 | M | 137 | 137 | 4.4 | 3.2 | B | Y | HIV encephalitis |
| 2 | R5 | R5 | 47 | M | 190 | 190 | 3.3 | 2.6 | B | Y | HIV encephalitis |
| 3 | R5 | R5 | 43 | F | 38 | 12 | 5.4 | 4.2 | B | Y | HIV encephalitis |
| 4 | R5 | R5 | 28 | F | 194 | 33 | 5.0 | 2.3 | CRF02_AG | Y | HIV encephalitis |
| 5 | R5 | R5 | 44 | M | 511 | 511 | 3.8 | 5.3 | B | N | HIV encephalitis |
| 6 | R5 | R5 | 51 | F | 273 | 45 | 3.7 | 2.8 | B | Y | HIV encephalitis |
| 7 | R5 | R5 | 35 | M | 381 | 381 | 4.5 | 5.7 | B | Y | Bacterial meningitis |
| 8 | R5 | R5 | 49 | M | 592 | 249 | 4.1 | 5.3 | B | N | HIV encephalitis |
| 9 | R5 | R5 | 67 | F | 512 | 167 | 3.0 | 3.9 | B | Y | Bacterial meningitis |
| 10 | R5 | R5 | 61 | M | 204 | 35 | 5.6 | 4.3 | CRF02_AG | Y | Bacterial meningitis |
| 11 | R5 | R5 | 65 | M | 179 | 49 | 4.8 | 2.6 | CRF02_AG | Y | HIV encephalitis |
| 12 | R5 | R5 | 24 | M | 527 | 462 | 5.2 | 5.7 | CRF02_AG | N | Neurosyphilis |
| 13 | R5 | R5 | 31 | F | 34 | 34 | 4.1 | 5.4 | CRF02_AG | N | Cerebral toxoplasmosis |
| 14 | R5 | R5 | 49 | M | 432 | 173 | 2.9 | 2.7 | B | Y | HIV encephalitis |
| 15 | R5 | R5 | 46 | M | 1088 | 969 | 3.8 | 2.7 | B | Y | HIV encephalitis |
| 16 | R5 | R5 | 42 | F | 184 | 151 | 5.7 | 5.5 | Undetermined | Y | HIV encephalitis |
| 17 | R5 | R5 | 41 | M | 390 | 67 | 3.3 | 5.9 | B | Y | HIV encephalitis |
| 18 | R5 | R5X4/X4 | 56 | M | 121 | 4 | 4.8 | 3.1 | B | Y | HIV encephalitis |
| 19 | R5 | R5X4/X4 | 41 | F | 415 | 51 | 2.5 | 3.9 | G | Y | HIV encephalitis |
| 20 | R5 | R5X4/X4 | 35 | M | 13 | 3 | 3.2 | 3.8 | B | N | Bacterial meningitis |
| 21 | R5X4/X4 | R5X4/X4 | 36 | M | 37 | 1 | 3.8 | 5.2 | Undetermined | Y | HIV encephalitis |
| 22 | R5X4/X4 | R5X4/X4 | 49 | F | 409 | 404 | 5.4 | 4.7 | CRF10_CD | N | HIV encephalitis |

R5X4- or X4-tropic viruses are grouped together.
F, female; M, male; N, no; Y, yes.

Soulie et al; JAIDS Journal of Acquired Immune Deficiency Syndromes. 51(1):60-64, May 2009.

3

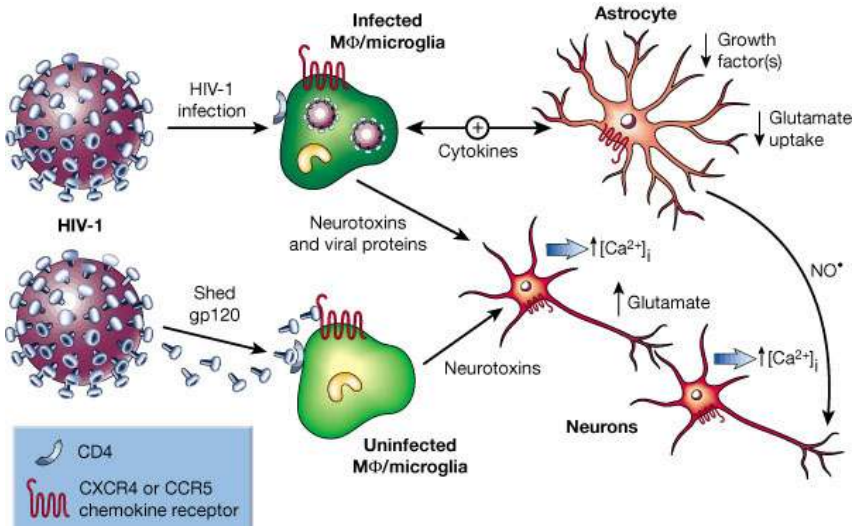
# Neurocognitive improvement increases with time




L.A. Cysique et al. Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. ***Neurology*** **2009;73: 342–348**

# OTHER TREATMENT OPTIONS

## HIV neurocognitive impairment – disease pathogenesis




Kaul, Garden & Lipton (2001). Pathways to neuronal injury and apoptosis in HIV-associated dementia. *Nature* 410, 988-994.

# Adjunctive therapy

- No randomised control trial evidence[1]
- Promising small scale studies of sodium valproate & lithium[2,3]
- Trial A5235 (Trial of Minocycline for HIV-Associated Cognitive Impairment) is currently recruiting in Uganda
- Treatment with antidepressants can have good results

1Uthman et al. Cochrane Database of Systematic Reviews 2008, Issue 3.
2Schifitto et al Neurology. 2006;66:919–921
3Letendre et al. AIDS 2006, 20:1885–1888

# Rehabilitation

- Additive effect on neurocognitive improvement over HAART alone
- Multidisciplinary approach

Stephenson J, Woods S & Scott B et al (2000) HIV-related brain impairment: from palliative care to rehabilitation. International Journal of Palliative Nursing 6: 6-11.

# Rehabilitation outcomes

| | **Year 2004/2005** | **Year 2005/2006** | **Year 2006/2007** |
|---|---|---|---|
| Number of admissions | 52 | 63 | 38 |
| Average length of stay | 95 days | 82 days | 87 days |
| Discharged to community | 23% | 37% | 45% |
| Discharged to residential care | 19% | 14% | 18% |
| Self discharged | 2% | 3% | 3% |
| Transferred to acute hospital services | 29% | 21% | 16% |
| Died | 2% | 2% | 0% |

Rackstraw S. Poster 130 14th BHIVA Conference 2008