HIV & the Brain

Dr Simon Rackstraw
Consultant HIV Physician & Medical Director,
Mildmay Hospital
HIV & the Brain

- Direct effect of HIV
- Opportunistic infections
- Tumours
- Vascular lesions
- Metabolic disturbance/drugs
- Mental health
Direct effects of HIV

- Definition
- Epidemiology
- Pathogenesis and clinical features
- Treatment
- Adjunctive treatment
Direct effects of HIV - definition

- Multiple names add to confusion:
  - AIDS dementia complex (ADC)
  - HIV encephalopathy
  - HIV dementia
  - HIV-1-associated cognitive / motor complex
  - HIV encephalitis
CDC definition of HIV encephalopathy (dementia)

- Clinical findings of disabling cognitive or motor dysfunction interfering with occupation or activities of daily living, progressing over weeks to months, in the absence of a concurrent illness or condition other than HIV infection that could explain the findings.

- Methods to rule out such concurrent illness and conditions must include cerebrospinal fluid examination and either brain imaging (computed tomography or magnetic resonance) or autopsy.
### Formal staging of ADC

**Price RW, Brew BJ.**

<table>
<thead>
<tr>
<th>ADC STAGE</th>
<th>CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0: (Normal)</td>
<td>Normal mental and motor function.</td>
</tr>
<tr>
<td>Stage 0.5: (Equivocal/subclinical)</td>
<td>Either minimal or equivocal symptoms of cognitive or motor dysfunction characteristic of ADC, or mild signs (snout response, slowed extremity movements), but without impairment of work or capacity to perform activities of daily living (ADL). Gait and strength are normal</td>
</tr>
<tr>
<td>Stage 1: (Mild)</td>
<td>Unequivocal evidence (symptoms, signs, neuropsychological test performance) of functional intellectual or motor impairment characteristic of ADC, but able to perform all but the more demanding aspects of work or ADL. Can walk without assistance.</td>
</tr>
<tr>
<td>Stage 2: (Moderate)</td>
<td>Cannot work or maintain the more demanding aspects of daily life, but able to perform basic activities of self care. Ambulatory, but may require a single prop.</td>
</tr>
<tr>
<td>Stage 3: (Severe)</td>
<td>Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output), or motor disability (cannot walk unassisted, requiring walker or personal support, usually with slowing and clumsiness of arms as well).</td>
</tr>
<tr>
<td>Stage 4: (End stage)</td>
<td>Nearly vegetative. Intellectual and social comprehension and responses are at a rudimentary level. Nearly or absolutely mute. Paraparetic or paraplegic with double incontinence.</td>
</tr>
</tbody>
</table>
Epidemiology

• Neurological impairment affects approximately 60% of HIV-infected patients\(^1\)

• Before the introduction of HAART, nearly 30% of the infected population developed HIV associated dementia at the late stage of HIV/AIDS.

Neurological disease declines post HAART

Fig. 1. Incidence\(^a\) of central nervous system diagnoses among AIDS cases 1991–2003\(^b\). – All central nervous system causes; ○ dementia; ■ toxoplasmosis; X cryptococcosis; ▲ brain lymphoma; Θ progressive multifocal leukoencephalopathy.
\(^a\)Incidence per 100 individuals living with AIDS per year.
\(^b\)Likelihood ratio for trend, \(P < 0.001\) for all central nervous system diagnoses.

Incidence Of HIV neurocognitive disease with time in a US cohort

Figure 1: Rising incidence rates of different neurological conditions in JHU HIV Clinic. Courtesy of Drs. R. Moore and K. Gebo. (“Other neuropathy” indicates distal sensory polyneuropathy).
Post HAART in Australia

• “A proportional increase in ADC compared with other ADIs and a marked increase in the median CD4 cell count at ADC diagnosis have occurred since the introduction of HAART in Australia. These changes suggest that HAART has a lesser impact on ADC than on other ADIs”

Gregory J. Dore; Patricia K. Correll; Yueming Li; John M. Kaldor; David A. Cooper; Bruce J. Brew. Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. AIDS. 13(10):1249-1253, July 9, 1999
HIV encephalopathy in London

• Royal Free cohort examined from 1992 - 1997
• Overall incidence of AIDS-defining illnesses decreased from 27.4 to 6.9/100 person-years
• However no evidence of a decline in the incidence of HIV-1 related dementia during the same period

Neuro-cognitive impairment in Africa

- Thirty-one percent (24 of 78) of the HIV+ patients had HIV dementia.
- Advanced age and low CD4+ T-lymphocyte count (CD4 count) were the only variables identified as significant risk factors.
- Each additional 10 years of age conferred a greater than twofold risk of HIV dementia.
- Reduced levels of CD4 count (100 cells/µL decrement) was associated with a 60% increase in the odds of having HIV dementia.

Wong M H; Robertson K; Nakasujja N; Skolasky R; Musisi S; Katabira E; McArthur J C; Ronald A; Sacktor N. Frequency of and risk factors for HIV dementia in an HIV clinic in Sub-saharan Africa. Neurology. 2007 Jan 30;68(5):350-5.
Neuro-cognitive impairment in Asia

- Study involved 658 HIV-positive patients and 161 HIV-negative control patients in Thailand, Indonesia, China, Malaysia and the Asia-Pacific region.
- Median age of the patients was 36 years, 59% were male, just under two-thirds had been diagnosed with AIDS, median CD4 cell count was 203 cells/mm³, and 65% were receiving HAART.
- 12% assessed as suffering serious neurocognitive impairment.

Risk factors for HIV encephalopathy

• Low CD4 count
• Drug use
• Hepatitis C
• Insulin resistance
• Anaemia

Neuroinvasion by HIV
AIDS-related Dementia: Pathology

HIV-infected microglial nodules, and multinucleated giant cells, with reactive astrocytosis, characterize HIV encephalopathy. Here, mononuclear cells, stained in brown, form a perivascular infiltrate. In HIV encephalopathy, there is no infection of neurons or oligodendrocytes.

Source: R. Dupasquier
Symptoms of Late Stage ADC

- Loss of bladder or bowel control
- Spastic Gait, making walking increasingly difficult
- Loss of initiative or interest
- Withdrawal
- Psychosis or mania
- Confinement to bed
Symptoms of Middle Stage ADC

- Symptoms of motor dysfunction, such as muscle weakness
- Poor performance on regular tasks
- More concentration and attention required
- Reversing of numbers or words
- Slow response and frequently dropping objects
- General feelings of indifference or apathy
- Slowness in normal activities, such as eating and writing
- Walking, balance, and coordination requires a great deal of effort
Symptoms of Early Stage ADC

- Difficulty concentrating
- Difficulty remembering phone numbers or appointments
- Slowed thinking
- Longer 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
T2-weighted brain MRI showing:
- diffuse, symmetrical hyperintensity of the white matter of both fronto-parietal lobes
-- sub-cortical atrophy as revealed by the increased size of the ventricles.
The differential diagnosis with progressive multifocal leuco-encephalopathy (PML) can be difficult. In HIV encephalopathy, extensive lesions of the white matter on brain MRI often contrast with the paucity of neurological deficits.

Source: R. Dupasquier
This patient presented with early signs of Aids-related-dementia; a CT scan was essentially normal (left). 11 months later, marked brain atrophy is evident (right).
Treatment of HIV encephalopathy

- Antiretroviral therapy
- Adjuvant medical therapy
- Rehabilitation
Influence of AZT on ADC incidence

Changes to neuropsychological function with antiretroviral therapy


<table>
<thead>
<tr>
<th>Variable</th>
<th>1 (n = 141)</th>
<th>2 (n = 135)</th>
<th>3 (n = 141)</th>
<th>4 (n = 141)</th>
<th>5 (n = 136)</th>
<th>6 (n = 117)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count (cells/µL)</td>
<td>249 (228)</td>
<td>213 (191)</td>
<td>287 (231)</td>
<td>299 (137)</td>
<td>330 (238)</td>
<td>371 (241)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log_{10} viral load</td>
<td>4.9 (0.9)</td>
<td>4.5 (0.9)</td>
<td>4.1 (1.1)</td>
<td>3.8 (1.0)</td>
<td>3.7 (1.1)</td>
<td>3.6 (1.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Number of HIV symptoms</td>
<td>1.5 (1.4)</td>
<td>1.6 (1.5)</td>
<td>1.4 (1.4)</td>
<td>1.7 (1.7)</td>
<td>1.2 (1.3)</td>
<td>1.1 (1.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Physical Limitations score</td>
<td>14.1 (3.0)</td>
<td>14.6 (3.4)</td>
<td>14.3 (3.0)</td>
<td>14.2 (3.1)</td>
<td>14.4 (3.4)</td>
<td>14.1 (2.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Antiretroviral potency category, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>96 (68)</td>
<td>58 (43)</td>
<td>38 (27)</td>
<td>22 (15)</td>
<td>21 (15)</td>
<td>19 (16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2</td>
<td>38 (27)</td>
<td>44 (33)</td>
<td>28 (20)</td>
<td>28 (20)</td>
<td>18 (13)</td>
<td>6 (5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3</td>
<td>5 (4)</td>
<td>16 (12)</td>
<td>12 (9)</td>
<td>10 (7)</td>
<td>9 (7)</td>
<td>6 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>4</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>6 (4)</td>
<td>6 (4)</td>
<td>9 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>5</td>
<td>1 (1)</td>
<td>16 (12)</td>
<td>62 (44)</td>
<td>75 (53)</td>
<td>83 (61)</td>
<td>79 (66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neuropsychologically impaired, n (%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>87 (62)</td>
<td>74 (54)</td>
<td>39 (33)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Taking Antidepressants or anxiolytics, n (%)</td>
<td>41 (29)</td>
<td>38 (24)</td>
<td>37 (23)</td>
<td>34 (24)</td>
<td>23 (19)</td>
<td>29 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>Beck Depression Inventory score</td>
<td>9.6 (7.6)</td>
<td>9.1 (7.8)</td>
<td>8.2 (7.2)</td>
<td>8.5 (7.0)</td>
<td>8.0 (6.9)</td>
<td>8.9 (7.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: Values shown are mean (SD) unless otherwise indicated. NS = not significant.
Cerebral blood volumes (CBV) as assessed by MRI. The colour scale going from white to red represents low to high relative blood volume.

(a) Healthy control (left) and an HIV+ patient (right) with moderate dementia (ADC Stage 2). Increase in the cortical and deep gray dynamic CBV in the patient with dementia is apparent.

(b) Functional MRI images from the same patient obtained before and after 6 months of treatment with zidovudine. Improvement in dementia with treatment coincided with a reduction in the cortical and deep gray matter dynamic CBV.

ARV penetration into CSF

<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF Penetration Index*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside reverse transcriptase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>0.2</td>
</tr>
<tr>
<td>Didanosine</td>
<td>0.05</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>0.04[^51]</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>0.06</td>
</tr>
<tr>
<td>Stavudine</td>
<td>0.5</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>&lt; 0.0[^51]</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>0.03</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Nonnucleoside reverse transcriptase inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>0.001</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Amprenavir/fosamprenavir</td>
<td>&lt; 0.05[^21]</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>0.0021-0.0226[^21]</td>
</tr>
<tr>
<td>Indinavir</td>
<td>0.14</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>0.07</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>0.07</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>&lt; 0.05[^21]</td>
</tr>
<tr>
<td>Ritonavir (full-dose)</td>
<td>0.07</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>0.02</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>No studies to date</td>
</tr>
<tr>
<td><strong>Fusion inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No studies to date</td>
</tr>
</tbody>
</table>

*CSF penetrance index, ratio of mean CSF level and the mean plasma level. High figures represent good CSF penetration. The mean daily dosage is given in parentheses.
Proportion of patients with cerebrospinal fluid (CSF) and plasma HIV-1 RNA levels below 200 and 20 copies/mL in a retrospective cross-sectional study with various antiretroviral treatment regimens

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>n</th>
<th>Mean Treatment Time in Months</th>
<th>CSF &lt;200 copies/ml (%)</th>
<th>CSF&lt;20 copies/ml (%)</th>
<th>Plasma &lt;200 copies/ml (%)</th>
<th>Plasma &lt;20 copies/ml (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 NRTI</td>
<td>27</td>
<td>13.5</td>
<td>11</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>2 NRTI</td>
<td>27</td>
<td>26.7</td>
<td>59</td>
<td>41</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>HAART</td>
<td>45</td>
<td>21.6</td>
<td>87</td>
<td>69</td>
<td>76</td>
<td>47</td>
</tr>
</tbody>
</table>

Abacavir in the CSF

- The peak concentration of abacavir in CSF ranged from 0.6 to 1.4 microg/ml - 8 to 20 times the mean 50% inhibitory concentration for HIV clinical isolates in vitro (0.07 microg/ml)
- Abacavir showed significant penetration into CSF

Penetration of nucleoside analogues in the CSF

- 28 antiretroviral-naive individuals free of neurological symptoms
- CD4 cell counts > 200/µL or more
- HIV-1-RNA concentrations > 10,000 copies/mL
- Randomly assigned lamivudine plus either stavudine (n = 17) or zidovudine (n = 11).
- After 12 weeks of treatment HIV-1-RNA concentrations were undetectable in the cerebrospinal fluid.
- The highest drug concentration in the cerebrospinal fluid was for lamivudine followed by stavudine and zidovudine.
- Concentrations were consistent over time, unlike plasma concentrations.

Foudraine, NA, Hoetelmans, RMW, Lange, JMA  Cerebrospinal-fluid HIV-1 RNA and drug concentrations after treatment with lamivudine plus zidovudine or stavudine. 1998; 1547–1551
AZT in the CSF

- 50 samples from 39 patients stable on AZT
- CSF concentrations of AZT showed little fluctuation 1-8 h after the last dose of AZT.
- Plasma levels displayed large variability in this period and decreased exponentially over time.
- Penetration of ZDV into the CSF was independent of the dose (range, 200-1250 mg daily)
- The CSF/plasma ratio of ZDV concentrations is not an appropriate marker for drug penetration into CSF

Burger, DM, Kraaijeveld, CL, Meenhorst, PL. Penetration of zidovudine into the cerebrospinal fluid of patients infected with HIV. 1993; , 1581-1587
Efavirenz in the CSF

- Efavirenz levels and HIV-1 RNA levels were measured in cerebrospinal fluid (CSF) and plasma of 10 HIV-1-infected patients taking efavirenz, 600 mg daily.
- Efavirenz was detected in the CSF at a mean concentration of 35.1 nM (range, 6.6-58.9 nM), which was above the IC95 for wild-type HIV-1.
- The mean CSF-to-plasma ratio was 0.61% (range, 0.26%-0.99%).
- CSF HIV-1 RNA levels <400 copies/mL after a mean of 26 weeks on therapy.

Tashima, KT, Caliendo, AM, Ahmad, M Cerebrospinal fluid human immunodeficiency virus type 1 (HIV-1) suppression and efavirenz drug concentrations in HIV-1-infected patients receiving combination therapy. 1999; 862–864
Protease inhibitors in the CSF

- $n = 24$
- Strong correlation was found between plasma and CSF HIV RNA levels ($r = 0.870; p < .001$).
- Plasma HIV RNA levels undetectable (80 copies/ml)
- CSF HIV RNA levels undetectable
- CSF levels of saquinavir ($<2$ ng/ml) and ritonavir ($<25$ ng/ml) were low.
- CSF:plasma drug concentration ratio of 0.005 (0.5%) ($n = 11$)

Kravcik, S, Gallicano, K, Roth, V  Cerebrospinal fluid HIV RNA and drug levels with combination ritonavir and saquinavir. 1999; , 371–375
Protease inhibitors in the CSF

• In this study, only four of 14 patients treated with a dual-PI regimen with saquinavir and ritonavir decreased their CSF levels below 400 HIV-1 RNA copies/mL after 12 weeks

Diversity of CSF & plasma strains

Changing trends in HIV encephalopathy

• There appears to be a “new” HIV encephalopathy that is more aggressive.\textsuperscript{1,2}

• Uncertainty about its aetiology

1. Langford DT et al. Severe, demyelinating leukoencephalopathy in AIDS patients on antiretroviral therapy AIDS 2002, 16:1019±1029
Adjuvant treatment trials

<table>
<thead>
<tr>
<th>Table: Placebo controlled trials of neuroprotective therapy in HIV dementia</th>
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</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
</tr>
<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Nimodipine</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Peptide T</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>OPC-14117</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
</tr>
<tr>
<td>Transdermal system</td>
</tr>
<tr>
<td>Lexispant</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Memantine (Navia B, submitted)</td>
</tr>
<tr>
<td>CPI-1189</td>
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</tbody>
</table>

*P= placebo, D=drug.; NP= neuropsychological tests*
Current ideas about adjuvant treatments

- Ceftriaxone
- Ibuprofen
Glycogen synthase kinase-3 beta inhibitors

- Most promising work is looking at glycogen synthase kinase-3 beta inhibitors
- Two currently used medicines have this activity in vitro & in a mouse model \(^1,2\)


Sodium valproate

- A pilot 10-week placebo-controlled study of sodium valproate 250 mg twice daily in 22 HIV-infected individuals
- n = 16 with cognitive impairment
- n = 6 without cognitive impairment
- Sodium valproate was safe and well tolerated, with trends toward improved neuropsychological performance and brain metabolism in the impaired subjects.

Lithium carbonate

- Single-arm, open-label, 12-week pilot study
- n=8. Diagnosed with HIV-associated neurocognitive impairment and had been on stable antiretroviral therapy for at least 12 weeks
- Given lithium 300 mg daily & titrated to maintain 12-h trough concentrations between 0.4 and 0.8 mEq/l.
- Lithium resulted in improved neuropsychological performance as assessed by the global deficit score.

Other medical factors

- Co-existent sepsis
- Anaemia
- Epilepsy
- Renal failure/metabolic insults
- Co-existent psychiatric morbidity
  - Psychotic features
  - Depression
Adherence interventions

- Use of PEG as delivery mode
- Liquid/tablet formulations
- Once daily therapy (max BD)
- Minimisation of pill burden
- Staged adherence programme
- Dossette boxes
Rehabilitation

• Structure is important
• Multidisciplinary approach

• “Specialist rehabilitation for people with HIV-related cognitive impairment, following assessment of suitability for this intervention, can result in improvements in cognitive function.” Medfash Recommended standards for NHS HIV services - Standard 12

Opportunistic infections

- Toxoplasma
- TB
- HSV, CMV, VZV
- Cryptoccocus
- PML
HIV diagnoses, AIDS case reports and deaths in HIV-infected individuals, UK

1 Numbers will rise, for recent years, as further reports are received.

Data Source: HIV/AIDS reports. Reports received by the end of September 2005.
Percentage of HIV infected adults diagnosed late: with CD4 count at HIV diagnosis less than 200 cells per mm$^3$; England & Wales 1995-2004

(CD4 count reported within one month of HIV diagnosis)

Data source: CD4 surveillance
Toxoplasmosis
Toxo case 1, slide #1

59 year old man with left-sided weakness after a convulsion.

Unique annular lesion, with contrast enhancement, in the right occipital lobe. Note peri-lesional edema (arrows).

Dpt of Radiology, Geneva University Hospital. Personal collection, B. Hirschel and C. Renold
Toxoplasmosis treatment

- 1st Line: Sulpahdiazine + Pyrimethamine + Calcium Folinate¹
- 2nd line: Clindamycin + Pyrimethamine + Calcium Folinate²
- 3rd Line: Atovaquone + Pyrimethamine + Calcium Folinate³
- 4th Line: Azithromycin + Pyrimethamine + Calcium Folinate⁴
- 5th Line: Fansidar

# Toxoplasmosis treatment - monitoring

<table>
<thead>
<tr>
<th>TREATMENT and DOSING</th>
<th>MONITORING PARAMETERS</th>
<th>COMMENTS</th>
<th>COMMON INTERACTIONS &amp; ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREFERRED REGIMEN</strong></td>
<td>Renal function FBC LFTs Fluid intake &gt;2L daily Urine pH&gt;7 to prevent crystalluria G6PD status</td>
<td>Can desensitise to sulphadiazine if necessary. Patient should drink at least 2L daily of fluid to prevent crystalluria – also watch for excessive fluid loss. Caution in G6PD deficiency Should see a response within 2 weeks of treatment.</td>
<td>A large number of patients may develop significant adverse effects, including rash, nausea and vomiting, crystalluria, nephrotoxicity, and haematological abnormalities. These can occur in up to 40% of patients but does not often warrant discontinuation</td>
</tr>
<tr>
<td>Sulphadiazine 2g qds for 100mg/kg/day given QDS if pt &lt; 70kg] (max. 8g daily) iv/ po</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrimethamine 200mg on day 1 then 75mg OD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium folinate 15 mg OD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALTERNATIVE REGIMEN</strong></td>
<td>U&amp;Es LFTs FBC</td>
<td>Should see a response within 2 weeks of treatment.</td>
<td>Nausea, vomiting, diarrhoea (check c.diff), jaundice, liver and haematological abnormalities reported, rash.</td>
</tr>
<tr>
<td>Clindamycin 1.2g iv QDS initially, changing to 600mg po QDS after 3/52</td>
<td>Investigate diarrhoea immediately for clostridium difficile infection.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrimethamine 200mg on day 1 then 75mg OD</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Calcium folinate 15mg OD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atovaquone 750mg bd</td>
<td>LFTs U&amp;Es FBC</td>
<td>Take with food (particularly high fat to increase absorption. This regimen has only been studied in patients who have been intolerant to or have not responded to other treatments.</td>
<td>Diarrhoea, nausea, vomiting, headache, rash, elevated liver enzymes, anaemia, hyponatraemia. Rifamycins reduce plasma concentration of atovaquone.</td>
</tr>
<tr>
<td>Pyrimethamine 200mg on day 1 then 75mg OD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium folinate 15mg OD</td>
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</tr>
</tbody>
</table>
CMV Encephalitis
Periventricular contrast enhancement is suggestive of CMV encephalitis (fine arrows), in a patient with a calcified lesion of cerebral toxoplasmosis (thick arrow).
CMV Treatment

- 1st line: Ganciclovir
- 2nd line: Foscarnet
- Third line: Cidofovir

- In CNS disease, dual therapy may be preferred with a combination of IVI Ganciclovir and IVI Foscarnet therapy being used for an extended period (4 weeks).
- Toxicity is a real risk in this scenario – monitoring of FBC, U&Es, Mg, urinalysis

Progressive multifocal leukoencephalopathy (PML)
Case 1, slide # 1

T2-weighted sequences showing hyperintensities in the white matter of the right parietal lobe

8 weeks later, extension into the right internal capsule and to the white matter of the left parietal lobe through corpus callosum

T1-weighted images without gadolinium show extensive hypodensities corresponding to loss of myelin

Picture credit: R. Dupasquier
PML & Cidofovir

- Thirty-five cases of PML were identified. The diagnosis was made by histology (9 cases), detection of JCV in CSF (17 cases), and by radiologic findings (9 cases).
- Upon manifestation of PML, 15/35 patients had never received HAART, and 11/35 were on HAART for >6 months.
- In 12 patients who were treated concomitantly with cidofovir, cumulative survival was significantly shorter than in patients without cidofovir (P = 0.03).
- Patients in whom PML was diagnosed while on HAART demonstrated a trend toward a shorter survival than HAART-naive patients (P = 0.15).

Drugs

- Efavirenz
- Other ARVs
- Interactions
Neuropsychiatric Adverse Effects in Patients Treated for HIV

- Both neurologic and psychiatric adverse effects not uncommon in patients receiving antiretroviral therapy

- Diagnosis and management often hampered by overlap with neuropathology caused by HIV infection itself
  - Particularly in patients with advanced disease

- Problem further complicated by
  - Higher prevalence of preexisting neurologic and psychiatric disease in HIV-infected patients
  - Higher rates of drug abuse in HIV-infected population
Outcomes in ACTG 5097s – comparison of EFV v non-EFV containing regime

- CNS effects more frequent with EFV at Day 7
- Symptoms generally self-resolved by Week 4
- Higher serum EFV levels → poorer neuropsychological performance at Weeks 4, 12
- EFV plasma levels not associated with mood changes
- Limitations of study
  - Low frequency of substance abuse at baseline (10%)
  - Prevalence of preexisting psychiatric disorders unknown
  - Low percentage of women in study
Long-term Effects of EFV in Study 5097s

- 117 patients treated with EFV-based therapy for 184 weeks
- Median score of neuropsychologic function improved from baseline by +0.56 \((P < .001)\)
  - Median score changes greatest in following components
    - Trailmaking Test A: +0.81
    - Trailmaking Test B: +0.39
    - Digit Symbol Test: +0.49 (all \(P < .001\) compared with baseline)
- Median change in overall symptom scores unchanged (median: 0; \(P = .42\))
  - Symptoms associated with EFV increased (median: +1; \(P = .03\))
- Bad dream sleep scores \((P = .0002)\) and anxiety scores \((P = .03)\) increased
- Global depression and global sleep scores unchanged
Pharmacogenetic Analysis of Patients in Study 5097s

- CYP2B6 T/T genotype at position 516 (Gln → His substitution) more common in blacks (20%) than in whites (3%)
  - Associated with greater EFV plasma exposure ($P < .0001$) and decreased clearance of EFV

- CYP2B6 G516T genotype also associated with increased CNS symptoms at Week 1 ($P = .036$)

Management of EFV-Related CNS Adverse Effects

- Most patients experience spontaneous improvement in symptoms within 2-4 weeks despite ongoing therapy\(^1\)
- \(~10\% of patients have persistent or worsening symptoms\(^2\)\)

- Nonpharmacologic techniques
  - Pretreatment education

- Pharmacologic techniques
  - Adjust dosing schedule relative to sleep time
  - Medical treatment

Neuropsychiatric reactions with other antiretrovirals

Neuropsychiatric Disorders in Patients With HIV

• Depression rates (22% to 45%) up to 5 times that of general population

• Rates of anxiety disorders: 10% to 18%

• HIV infection may be linked to new-onset psychosis (0.5% to 15.0%)[^1]

• Substance abuse, addiction prevalent[^2]

• Serious neuropsychiatric adverse effects in 0.4% to 2.4% of patients receiving Efavirenz[^3]

## Selected Interactions Between ART and Psychotropic Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (possibly other SSRI s)</td>
<td>Increases plasma concentrations of PIs</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Decreases plasma concentrations of IDV</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Decreases concentrations of PIs</td>
</tr>
<tr>
<td></td>
<td>Decreases concentration of EFV</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Increases concentrations of LPV</td>
</tr>
<tr>
<td>Methadone</td>
<td>Increases concentrations of ZDV</td>
</tr>
<tr>
<td></td>
<td>Decreases concentrations of ddI</td>
</tr>
<tr>
<td>RTV (possibly other PIs)</td>
<td>Increases concentrations of tricyclic drugs, nefazodone, benzodiazepines, trazodone, bupropion, antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Decreases concentrations of lamotrigine</td>
</tr>
<tr>
<td>NFV, EFV</td>
<td>Increases concentrations of bupropion</td>
</tr>
<tr>
<td>EFV, NVP, RTV</td>
<td>Decreases concentrations of methadone</td>
</tr>
<tr>
<td>EFV</td>
<td>Decreases concentration of carbamazepine</td>
</tr>
</tbody>
</table>
Case 1

- 54 year old White British MSM
- Diagnosed HIV+ in 1995, following a number of minor skin problems
Medical history

- Idiopathic epilepsy developed in early 1990s
- History of alcohol use
- Pulmonary TB 1997
Presentation

- Complained of “forgetfulness”
- Poor self care noted by sister in December 1999
- Landlady broke down door in Feb 2000: “found semi-conscious in bed with 2 dead puppies”
Admission

- Admitted to hospital Feb 2000
- Absconded on 2 occasions
- Detained under Section 2 MHA 10/03/00 for assessment
- MRI, LP & Neuropsychological assessment
- Diagnosis: HIV encephalopathy
On admission to Mildmay

- Admitted Mildmay HRBI unit 31/05/00
- CD4 count 17
- Viral load 464,376 copies/ml
- Multidrug resistance virus
Clinical picture

• Mute

• Extreme motor retardation
  - e.g. eating lunch 2 hrs+

• Poor short term memory
  - e.g. would forget intent in-between steps

• Poor orientation

• Doubly incontinent
  - e.g. defaecating in staff room
Drugs on admission

- Co-trimoxazole 480mg OD
- Aciclovir 400mg BD
- Gabapentin 400mg BD
- Thioridazine 25mg TDS
Initial medical management

- Settling in period & orientation
- Decreasing thioridazine slowly, then stopped – led to increasing psychomotor speed
- Empirical commencement of citalopram 20mg daily
Settling in

• Improvement in awareness of surroundings

• Some return of speech, improvement in eating

• No adherence problems
Mega HAART

• Liaison about restarting HAART
• Started on: (03/11/01)
  – Lamivudine 150mg BD
  – Abacavir 300mg BD
  – Nevirapine 200mg BD
  – Amprenavir 750mg BD
  – Lopinavir/r 4 tablets BD
Response to HAART

• Increasing cognitive improvement globally
  - E.g. appearance of spontaneous humour
  - E.g. arithmetical abilities resurface

CD4 count 171 (Jan 2001)
Viral load 240 (Jan 2001)
Deterioration

- Gradual decline from -/06/01
- Decreased cognition
- Parkinsonian symptoms
- Agitated wandering
- Increasing incontinence
- Increased difficulty in maintaining adherence
- HAART stopped -/09/01
- Died 12/11/01
CD4 & viral load

**July 2001**

- CD4: 164
- VL: 52 copies/ml

**October 2001**

- CD4: 776
- VL: >50 copies/ml
Case study 2

- 40 year old Zimbabwean woman
- Presented 6 week history of confusion and decreasing mobility
- Stigmata of HIV disease
- PUO
- Diagnosed HIV+
Further investigations

- CD4 36   VL 150000
- CXR – Right sided pneumonia
- MRI – in keeping with HIV encephalopathy
- Poor swallow
Treatment

- NBM
- IV antibiotics for chest
- PEG insertion
- Started AZT/3TC/Lopinavir/r
Rehabilitation

- Gradual improvement
- “Absences”
- Started sodium valproate
- 3 months later discharged to independent living
Questions?