Risk of HIV dementia and opportunistic brain disease in AIDS and zidovudine therapy

Torsten Baldeweg, José Catalan, Brian G Gazzard

Abstract
Objective—To determine the incidence of HIV dementia and opportunistic brain disease in AIDS relative to the use of licensed antiretroviral medication (zidovudine, zalcitabine, didanosine, and stavudine).

Method—Medical records were evaluated retrospectively in a longitudinal cohort of 1109 patients with AIDS during the period 1991–4. Treatment groups were defined by start and duration of zidovudine treatment, the drugs used most often during this period were: (a) no zidovudine, (b) zidovudine before AIDS, (c) zidovudine before and after AIDS, and (d) zidovudine used in AIDS. Main outcome measures were cumulative incidence and survival from AIDS to onset of HIV dementia, progressive multifocal leukoencephalopathy (PML), cerebral toxoplasmosis, and primary CNS lymphoma.

Results—Risk of brain disease including HIV dementia and opportunistic brain disease was reduced in patients who started zidovudine before AIDS and continued in AIDS (relative risk (RR) 0.55, 95% confidence interval (95% CI) 0.36–0.84) as well as zidovudine initiated in AIDS (RR 0.27, 95% CI 0.17–0.45) compared with untreated subjects. Treatment effects were not constant over time, decreasing by 14%–32% for each six months of follow up. This was supported by unadjusted incidences across groups stratified by duration of zidovudine use, indicating reduced risk with treatment for up to 18 months but not with longer duration of use of zidovudine. Other antiretroviral drugs had no significant effect, although these were used by only 14% of patients in this cohort.

Conclusion—The time limited but effective neuroprotection offered by zidovudine monotherapy for <18 months suggests that non-specific mechanisms of cerebral immunological defence may benefit from antiretroviral treatment. Due to the limitations of a retrospective study these findings require confirmation and further investigation in the context of current combination drug treatments.

Keywords: dementia; AIDS; zidovudine; progressive multifocal leukoencephalopathy; cerebral toxoplasmosis; CNS lymphoma

Neurological diseases affecting the brain during the late stages of HIV infection cause considerable morbidity and are associated with a poor prognosis. These late complications can be due to diffuse HIV related pathology such as in HIV dementia (also called AIDS dementia complex, HIV-1 associated cognitive/motor complex) or due to focal lesions caused by opportunistic pathogens. The group of opportunistic brain diseases consists mainly of progressive multifocal leukoencephalopathy, cerebral toxoplasmosis, and primary CNS lymphoma. Recent comprehensive reviews on diagnosis and treatment of neurological complications in HIV-1 infection have been reported. Research into possible neuroprophylactic effects of antiretroviral treatment has focused on direct pathology related to HIV, in particular, HIV dementia. An earlier report suggested an association between the introduction of zidovudine treatment and a decline in the incidence of HIV dementia. However, the analysis of short term effects of antiretroviral medication in a prospective cohort did not support a neuroprotective role of zidovudine in either HIV dementia or opportunistic brain disease. The possibility of long term effects was not considered in this analysis. Although this issue has remained controversial, recent research focused on the development of adjuvant treatments for HIV dementia. However, these are still under development and the CNS efficacy of new antiretroviral drugs has not yet been tested for the brain. We therefore attempted to establish whether the use of currently licensed antiretroviral drugs such as zidovudine (AZT), zalcitabine (ddC), didanosine (ddI), and stavudine (d4T) have had an impact on the incidence of brain disease in a large cohort of patients with AIDS.

Due to uncertainty about the optimal time for initiation of drug therapy, patterns of antiretroviral treatment varied between patients, including preparation, dosage, time of initiation, and duration of treatment. Although many patients opted not to use antiretroviral medication, others received treatment of variable duration at different stages of infection. A retrospective analysis during the period 1991–4 was therefore conducted to establish whether any of these treatment patterns was effective in reducing the burden of HIV dementia and opportunistic brain disease in patients with AIDS.

Subjects and methods
A longitudinal survey was conducted in a cohort of patients with AIDS who were cared for at the St Stephen’s Centre, Chelsea and Westminster Hospital, London, from 1 January 1991 to 31 December 1994.
IDENTIFICATION OF CASES
A total of 1517 patients with an AIDS defining illness between 1 January 1990 and 31 December 1994 were identified from a central database. Firstly, presumptive cases of HIV dementia were identified in three ways: (a) by interrogating the central database, (b) by approaching the medical and nursing team involved in the care of each AIDS patient to establish whether cognitive impairment was diagnosed or suspected, and (c) from the medical records of the Mental Health Centre to identify patients referred to the clinical service. Medical notes of all presumptive cases were then examined in more detail to establish whether or not they met the World Health Organisation (WHO) criteria for HIV dementia.7 Evidence for decline in memory and intellectual abilities had to be present for at least one month, and other aetiological factors were excluded. All cases were classified in one of three categories: (a) no brain impairment, (b) HIV dementia, and (c) other neurological or psychiatric disorders. Because information about neurological disorders affecting meninges, peripheral nervous system, and muscle were not systematically reported in the database only cases of progressive multifocal leukoencephalopathy, cerebral toxoplasmosis, and primary CNS lymphoma were considered for analysis. Neurological diagnosis and treatment were carried out by specialised physicians and neurologists.

For 395 cases, case notes were re-examined by three investigators blinded to the original classification. This included all cases with suspected HIV dementia, for which the diagnoses were confirmed in 87% of cases. When discrepancies were found, a consensus was sought between all clinicians involved.

EXCLUSION CRITERIA
Patients who had less than two visits to the local clinic were excluded from all subsequent analyses. Furthermore, information was sought from the local and central Medical Research Council clinical trials offices for all patients who had participated in a clinical study with antiretroviral drugs. Because complete un-blinded treatment information was impossible to obtain in many such cases all trial participants were also excluded from the analysis. Thus the total number of cases used in the analysis was reduced from 1517 to 1109.

Due to the clinical practice to start zidovudine in patients with progressing cognitive decline a considerable overlap between start of treatment and diagnosis of HIV dementia was expected. We therefore established the dates of diagnosis or onset of symptoms for patients with brain disease. Thus only patients for whom dates of diagnosis could be reliably established from the medical notes (162 out of 195) were included in the analysis as described below. Furthermore, patients who started their first zidovudine treatment only after diagnosis of brain disease were regarded as having no previous zidovudine use in the analysis.

DEFINITION OF DIAGNOSTIC AND TREATMENT GROUPS
The following research diagnostic groups were defined: (a) no brain impairment, (b) HIV dementia, (c) opportunistic brain disease including progressive multifocal leukoencephalopathy, toxoplasmosis, and primary CNS lymphoma.

Table 1 Cumulative incidence of brain disease during the period of observation from 1991 to 1994

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No brain impairment</td>
<td>914</td>
<td>82.4</td>
</tr>
<tr>
<td>HIV dementia</td>
<td>88</td>
<td>7.9</td>
</tr>
<tr>
<td>Opportunistic brain disease</td>
<td>107</td>
<td>9.7</td>
</tr>
</tbody>
</table>

Table 2 Demographic and immunological characteristics of the diagnostic groups. Laboratory markers are shown at diagnosis of AIDS and at onset of brain disease

<table>
<thead>
<tr>
<th></th>
<th>No brain impairment</th>
<th>HIV dementia</th>
<th>Opportunistic brain disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=914</td>
<td>n=88</td>
<td>n=107</td>
</tr>
<tr>
<td>Sex (female (n (%))</td>
<td>32 (3.5)</td>
<td>4 (4.5)</td>
<td>5 (4.7)</td>
</tr>
<tr>
<td>IV drug user (n (%))</td>
<td>53 (5.8)</td>
<td>5 (5.7)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Heterosexual (n (%))</td>
<td>61 (6.7)</td>
<td>6 (6.8)</td>
<td>10 (9.3)</td>
</tr>
<tr>
<td>Age, mean in years (mean (95% CI))</td>
<td>36.5 (35.9–37.0)</td>
<td>39.6 (37.7–41.5)</td>
<td>37.1 (35.5–38.7)</td>
</tr>
<tr>
<td>CD4 count /10⁹ l (mean (95% CI))</td>
<td>121 (111–132)</td>
<td>84 (64–104)</td>
<td>69 (52–86)</td>
</tr>
<tr>
<td>CD8 count /10⁹ l (mean (95% CI))</td>
<td>67 (37–96)</td>
<td>60 (42–77)</td>
<td>0.001</td>
</tr>
<tr>
<td>AIDS (n=951)</td>
<td>858 (817–899)</td>
<td>858 (712–1003)</td>
<td>707 (606–809)</td>
</tr>
<tr>
<td>Onset brain disease (n=144)</td>
<td>—</td>
<td>629 (475–782)</td>
<td>611 (506–717)</td>
</tr>
<tr>
<td>Haemoglobin, mg/dl (mean (95% CI))</td>
<td>12.2 (12.1–12.4)</td>
<td>11.9 (11.5–12.3)</td>
<td>12.0 (11.5–12.4)</td>
</tr>
<tr>
<td>AIDS (n=791)</td>
<td>68.5 (67.4–69.5)</td>
<td>68.1 (64.8–71.4)</td>
<td>68.9 (65.1–72.6)</td>
</tr>
<tr>
<td>Onset brain disease (n=48)</td>
<td>—</td>
<td>69.5 (63.2–75.8)</td>
<td>67.1 (63.9–70.4)</td>
</tr>
</tbody>
</table>
Themostcommonlyprescribedantiretroviral
drugduringtheperiod1991–4waszidovudine,
used by 706/1109 (64%) of the cohort. In 153
(14%) patientsother drugswere used: zalcitab-
ine in 125, didanosine in 10, and stavudine in
11. Only 38 of those patients had not used zido-
vudine. The main analysis of effects of treat-
ments will therefore be confined to the follow-
ing zidovudine treatment groups defined by start
and end of treatment relative to AIDS diagnosis.

**Group 1**
No zidovudine use or discontinued after one
week (no zidovudine).

**Group 2**
Zidovudine used only before AIDS (zidovu-
dine before AIDS).

**Group 3**
Zidovudine used before and after first AIDS
diagnosis (zidovudine before and after AIDS).

**Group 4**
Zidovudine used only in AIDS (zidovudine in
AIDS).

The use of other antiretroviral drugs (dida-
osine, zalcitabine, stavudine) was included in
the analysis as reported later. The mean times
for start and end of zidovudine treatment
across treatment groups were (weeks (95%
confidence interval (95% CI))), for group 2:
start 105 (96–115) and end 42 (35–49) weeks
before AIDS; for group 3: start 74 (67–81)
weeks before AIDS and end 50 (45–55) weeks
after AIDS; and for group 4: start 39 (33–43)
weeks and end 106 (97–116) weeks after
AIDS. The zidovudine treatment groups also
differed in CD4 counts at the time of AIDS
diagnosis, with those patients treated before
AIDS showing lower counts (mean in cells/10^9
(95% CI): 66 (52–80), 95 (81–109), for groups
2 and 3, respectively) than untreated patients
(118 (100–136), 147 (128–166), for groups 1
and 4, respectively).

Also zidovudine treatment strata were de-
defined according to duration of treatment and
were derived from quartiles of total times from
initiation until permanent discontinuation of
zidovudine treatment: (a) no zidovudine, (b)
Zidovudine <6 months, (c) zidovudine 6–18
months, (d) zidovudine >18–30 months, (e)
zidovudine >30 months. Although the duration
treatment cannot be separated from survival
time, long term treatment was in fact more
closely associated with early initiation of treat-
ment rather than very long AIDS survival time.
Most short to medium term treatment (<6
months, 6–18 months) was initiated in AIDS
(65% and 52%, respectively), whereas long
term treatment (18–30 months and >30
months) was predominantly initiated before
AIDS (68% and 69% respectively).

**ESTIMATION OF ONSET OF BRAIN DISEASE**
As well as survival time from AIDS until onset
of brain disease a second estimate was derived
from the point when consecutive CD4 counts
for the first time dropped below the threshold
of 200 cells/µl (CD4<200). This point was
taken as the baseline for the second outcome
measure “time from CD4<200 to onset of
brain disease”. This measure could be deter-
mined for 785 patients out of 914 with
available CD4 counts at AIDS.

**STATISTICAL ANALYSIS**
For comparison of demographic and labora-
tory data χ² statistics and analysis of variance
(ANOVA) were used with diagnostic and treat-
ment group as between subjects factors. All p
values are two sided with 95% CIs. To adjust
for differences in immunological status at
baseline and to control for multiple demo-
graphic and clinical factors Cox’s regression
analysis was applied to the survival times until
the onset of brain disease. Time dependent
covariates for treatment effects were used
because development of viral resistance may

![Figure 1](http://jnnp.bmj.com/)

Kaplan-Meier plot of survival from first AIDS diagnosis until the onset of brain disease.

| Table 3 Factors influencing survival from AIDS to onset of brain disease |
|-----------------------------|-----------------------------|-----------------------------|
| Covariate                  | Total brain disease | HIV dementia | Opportunistic brain disease |
|                           | Relative risk | 95% CI | p Value | Relative risk | 95% CI | p Value | Relative risk | 95% CI | p Value |
| Older age                  | 1.028 | 1.009–1.048 | 0.006 | 1.052 | 1.021–1.084 | 0.001 | 1.013 | 0.987–1.039 | 0.335 |
| Increased CD4 at AIDS      | 0.995 | 0.993–0.997 | 0.001 | 0.996 | 0.996–0.999 | 0.015 | 0.994 | 0.992–0.997 | 0.001 |
| No ZDV treatment ✱         | 1     |      |      |      |      |      |      |      |      |
| ZDV before AIDS            | 0.805 | 0.489–1.326 | 0.395 | 0.605 | 0.244–1.503 | 0.279 | 0.897 | 0.493–1.633 | 0.722 |
| ZDV before and after AIDS  | 0.551 | 0.360–0.843 | 0.006 | 0.524 | 0.258–1.063 | 0.073 | 0.548 | 0.322–0.931 | 0.026 |
| ZDV in AIDS‡               | 0.272 | 0.165–0.449 | 0.001 | 0.361 | 0.171–0.763 | 0.007 | 0.209 | 0.105–0.415 | 0.001 |

*Analysis based on 914 cases with available CD4 count.
†Time by treatment interaction (relative risk = 1.213, p= 0.017) in analysis of total brain disease.
‡Time by treatment interaction (relative risk = 1.318, p= 0.036) in analysis of total brain disease.
ZDV=zidovudine.
limit the drug effects over time. This time dependent variable was computed in six month intervals. For patients without brain impairment (censored cases) the time until death or last observation was entered into the calculation. Survival times until onset of brain disease were computed in two different ways; firstly, survival from AIDS, and secondly, survival from CD4<200. The following independent variables were included in the model: age, zidovudine treatment group (no zidovudine, zidovudine before AIDS, zidovudine before and after AIDS, zidovudine after AIDS) and use of other antiretroviral drugs (either didanosine, zalcitabine, or stavudine). Separate analyses were computed including CD4 counts at AIDS diagnosis as a covariate. Relative risk (RR) was computed with reference to the no zidovudine group or stratum. Separate analyses were computed for HIV dementia, opportunistic brain disease, and for both groups combined (total brain disease). Also unadjusted incidences and corresponding RRs were computed. Survival plots were obtained by Kaplan-Meier analysis and compared by log-rank test.

Results
CHARACTERISTICS OF THE RESEARCH DIAGNOSTIC GROUPS
Table 1 shows the cumulative incidence of brain disease during 1991–4. No differences in risk group, intravenous drug use, and sex was found between groups (table 2). Patients with HIV dementia were significantly older than patients in the other two groups. Both brain disease groups had lower CD4 counts at AIDS (table 2). Median survival with AIDS was shorter in both brain disease groups (for HIV dementia: 78 weeks (95% CI 62–94), log-rank 11.4, p<0.001, for opportunistic brain disease: 93 weeks (95% CI 75–111), log-rank 10.9, p<0.001) than in the unimpaired group (118 weeks (95% CI 109–127)). The onset of brain disease after AIDS was not different between HIV dementia (61 weeks (95% CI 37–86)) and opportunistic brain disease (55 weeks (95% CI 42–67)). Haemoglobin values at the onset of brain disease were significantly lower in the demented patients than in cases of opportunistic brain disease.

ANTIRETROVIRAL TREATMENT ACROSS DIAGNOSTIC GROUPS
Zidovudine was used by 56.4% of patients with HIV dementia and 46.2% of patients with opportunistic brain disease compared with 64.8% of subjects without brain disease. Treatment was started after the onset of brain disease in another 13% of patients with HIV dementia and 6.6% of patients with opportunistic brain disease. Diagnostic groups did not differ in the dose of zidovudine used (median 500 mg, range 100–1250 mg) both at the beginning and the end of treatment. No difference in the use of zalcitabine, didanosine, or stavudine was found between the diagnostic groups: 14% in the unimpaired group, 8% in HIV dementia, and 14% in opportunistic brain disease groups.

ZIDOVUDINE TREATMENT AND RISK OF BRAIN DISEASE
Independent risk factors for brain disease in the cohort were determined by Cox's regression analysis of survival from AIDS to onset of brain disease (fig 1). For the analysis of total brain disease, combining HIV dementia and opportunistic brain disease, younger age, and zidovudine use in AIDS (group 4) was associated with reduced risk (0.14, 95% CI 0.07–0.28). This effect was time dependent (p=0.017), indicating a 21% loss of effect with every six months of follow up (table 3). Use of other antiretroviral drugs had no significant effect (RR 1.004, 95% CI 0.63–1.60, p=0.9870) in this or any of the subsequent analyses and was omitted from tables 3 and 4.

Table 4 Factors influencing survival from first CD4 count below 200 cells/µl (CD4<200) to onset of brain disease

<table>
<thead>
<tr>
<th>Covariate*</th>
<th>Total brain disease</th>
<th>HIV dementia</th>
<th>Opportunistic brain disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative risk</td>
<td>95% CI</td>
<td>p Value</td>
</tr>
<tr>
<td>Older age</td>
<td>1.013</td>
<td>0.993–1.033</td>
<td>0.196</td>
</tr>
<tr>
<td>Increased CD4 at AIDS</td>
<td>0.998</td>
<td>0.996–1.000</td>
<td>0.048</td>
</tr>
<tr>
<td>No ZDV treatment</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ZDV before AIDS</td>
<td>0.222</td>
<td>0.091–0.540</td>
<td>0.001</td>
</tr>
<tr>
<td>ZDV before and after AIDS</td>
<td>0.290</td>
<td>0.146–0.584</td>
<td>0.001</td>
</tr>
<tr>
<td>ZDV in AIDS</td>
<td>0.153</td>
<td>0.065–0.359</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Analysis based on 785 cases.
†Time by treatment interaction (relative risk = 1.237, p= 0.039) in analysis of total brain disease.
‡Time by treatment interaction (relative risk = 1.142, p= 0.152) in analysis of total brain disease.
§Time by treatment interaction (relative risk = 1.286, p= 0.012) in analysis of total brain disease.
ZDV=zidovudine.
Table 5 Unadjusted incidences and relative risk of brain disease across zidovudine strata defined by duration of treatment

<table>
<thead>
<tr>
<th>Zidovudine strata</th>
<th>n</th>
<th>HIV dementia</th>
<th>Opportunistic brain disease</th>
<th>Total</th>
<th>95% CI</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No zidovudine</td>
<td>400</td>
<td>24 (6.0)</td>
<td>57 (14.3)</td>
<td>81 (20.3)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Zidovudine &lt;6 months</td>
<td>30</td>
<td>10 (6.4)</td>
<td>6 (3.9)</td>
<td>16 (9.9)</td>
<td>0.91</td>
<td>0.42–1.95</td>
</tr>
<tr>
<td>Zidovudine 6-18 months</td>
<td>160</td>
<td>3 (1.9)</td>
<td>8 (4.8)</td>
<td>11 (6.5)</td>
<td>0.25</td>
<td>0.07–0.84</td>
</tr>
<tr>
<td>Zidovudine &gt;18-30 months</td>
<td>164</td>
<td>8 (5.4)</td>
<td>17 (10.9)</td>
<td>25 (15.2)</td>
<td>0.76</td>
<td>0.33–1.74</td>
</tr>
<tr>
<td>Zidovudine &gt;30 months</td>
<td>167</td>
<td>10 (6.7)</td>
<td>18 (11.5)</td>
<td>28 (16.8)</td>
<td>0.95</td>
<td>0.44–2.05</td>
</tr>
</tbody>
</table>

When CD4 count at AIDS diagnosis was included in the model reduced risk was found with zidovudine use initiated before AIDS and continued in AIDS (RR 0.55, 95%CI 0.36–0.84) as well as zidovudine initiated in AIDS (RR 0.27, 95% CI 0.17–0.45). Also lower CD4 count at AIDS and older age were independent predictors. The same treatment variables were significant when separate analyses were computed for HIV dementia and opportunistic brain disease (table 3), however older age was only predictive of HIV dementia.

These findings are supported by a separate analysis based on survival from drop in consecutive CD4 counts below the 200 mark (CD4<200) to onset of brain disease (fig 2). Zidovudine use in all three treatment groups was associated with prolonged survival free of brain disease (table 4). As treatment seemed to have an effect that was not constant over time of follow up unadjusted incidences and RRs were computed across groups stratified for duration of zidovudine use (table 5). For HIV dementia zidovudine use for a duration of six to 18 months was associated with reduced risk, whereas treatment duration shorter than six months and longer than 18 months had no significant effect. For the combined group of opportunistic brain diseases zidovudine treatment for up to 18 months showed a similar time limited effect. Because duration of treatment may be determined by survival time a further Cox’s regression analysis was computed for onset of total brain disease, which used CD4 count, zidovudine treatment strata, and AIDS survival as covariates. The following RR values were obtained for each treatment stratum compared with untreated patients: for <6 months 0.55 (95% CI 0.32–0.96, p=0.038); for 6–18 months 0.29 (95% CI 0.15–0.56, p<0.001); for 18–30 months: 0.80 (95% CI 0.49–1.28, p=0.346); and for >30 months: 0.90 (95% CI 0.55–1.45, p=0.654).

The effect of time limited treatment is therefore independent of duration of AIDS survival.

Seventy per cent of patients with progressive multifocal leukoencephalopathy, 53% of cases with toxoplasmosis, and 50% patients with lymphoma had not used zidovudine, compared with 35% in the unimpaired group. The corresponding RRs in zidovudine treated (combined groups 2–4) compared with untreated patients (group 1) amounted to 0.23 (95% CI 0.06–0.90) for progressive multifocal leukoencephalopathy, 0.49 (95% CI 0.30–0.78) for toxoplasmosis, and 0.54 (95% CI 0.22–1.32) for lymphoma. The estimated RRs associated with zidovudine use for <18 months and >18 months respectively, were as follows: for progressive multifocal leukoencephalopathy 0.14 (95% CI 0.02–1.14), and 0.36 (95% CI 0.07–1.72); for toxoplasmosis 0.41 (95% CI 0.23–0.75) and 0.59 (95% CI 0.33–1.05); and for lymphoma 0.29 (95% CI 0.08–1.07) and 0.87 (95% CI 0.33–2.32).

CD4 count at onset of brain disease

To determine whether the apparent neuroprotective effect of zidovudine was mediated through its effect on systemic immunity CD4 counts at the onset of brain disease were compared between diagnostic groups and zidovudine treatment strata with ANOVA. The CD4 counts at the onset of brain impairment were lower in patients treated with zidovudine for <18 months (28 cells/µl, 95% CI 16–40) compared with untreated patients (68 cells/µl, 95% CI 42–94) and those treated for 18 months or longer (58 cells/µl, 95% CI 42–75; F(2,144)=3.26, p=0.041). This effect was not different between the HIV dementia and opportunistic brain disease groups (F(1,144)=0.32, NS).

Discussion

LIMITATIONS OF THE STUDY

This retrospective, observational study is clearly limited in generalisation of the finding of reduced incidence of HIV related brain disease relative to zidovudine treatment to other populations. No information on compliance and continuity of antiretroviral treatment and no data on use of antibacterial prophylaxis were available. Furthermore, the estimated cumulative incidence of brain disease of 17.6% in this cohort clearly underestimates the true incidence because other brain disorders such as vacuolar myelopathy, cryptococcal meningitis, and cytomegalovirus (CMV) encephalitis were not considered. The large unselected study population, however, included most patients with AIDS attending a specialised centre of HIV medicine over a period 1991–4 with exclusion only of participants in clinical trials with antiretroviral drugs. Detailed information on use of licensed antiretroviral drugs, laboratory markers, and clinical history were carefully reviewed.

ZIDOVUDINE TREATMENT AND BRAIN DISEASE

The effect of zidovudine on incidence of HIV dementia confirms previous reports. To find an even larger effect on incidence of opportunistic brain disease, however, was unexpected and will be discussed in more detail later.
Brain disease in AIDS and use of zidovudine

HIV dementia
The increased risk of HIV dementia with older age and the finding of lower haemoglobin values at the onset of symptoms confirm data from the multicentre AIDS cohort study. By contrast with that study, however, zidovudine use for a period of six to 18 months was associated with a reduced risk of HIV dementia, whereas treatment for longer than for 18 months was not beneficial. This finding is in agreement with a recent multicentre study in Europe which also reported a lower incidence of HIV dementia with treatment for less than 18 months but no effect with longer duration of zidovudine use. The lack of prophylactic effects with less than six months of treatment is compatible with an earlier finding that deficits in neuropsychological performance in patients with AIDS were only improved when zidovudine use was continued for a prolonged period. Several neuropathological surveys reported a lower incidence of HIV multinucleated giant cell encephalitis in patients treated with zidovudine with the lowest incidence found after six to 12 months treatment. The present study is also in agreement with previous evidence for neuroprotective properties of zidovudine from placebo controlled and observational cohort studies. Its use for treatment of HIV dementia has been supported by clinical findings and by a placebo controlled study.

Opportunistic brain disease
It cannot be ruled out that the lower risk in patients treated with zidovudine in this study is due to other therapeutic interventions. Although this is possible for cerebral toxoplasmosis, no prophylaxis is currently known for primary CNS lymphoma and progressive multifocal leukoencephalopathy.

Cerebral toxoplasmosis
Cerebral toxoplasmosis is the most frequent neurological opportunistic infection, thought to be due to reactivation of a previously acquired infection. It responds well to pyrimethamine/sulphadiazine combination treatment, which also confirms the diagnosis. Clyndamycin and pyrimethamine may also be beneficial. Low dose trimethoprim-sulphamethoxazole seems to be an effective prophylactic. Another controlled study suggested dapsone combined with pyrimethamine for primary prophylaxis. Apart from an earlier report, which stressed the efficacy of zidovudine in treating cerebral toxoplasmosis, two recent studies noted improved survival with toxoplasmosis after zidovudine treatment.

Primary CNS lymphoma
Primary CNS lymphoma is the most common neoplasm of the brain in AIDS, the second most frequent CNS mass lesion in adults, and the most frequent one in children. Its aetiology is thought to be due to Epstein-Barr virus infection. Although the prognosis is generally poor, some patients respond to whole brain radiotherapy. Antiviral drugs have no proved clinical role against Epstein-Barr virus infection except in patients with oral hairy leukoplakia. There are nevertheless in vitro data showing potent inhibition by zidovudine and other anti-HIV nucleoside analogues of Epstein-Barr virus replication and cell transformation induced by the virus.

Progressive multifocal leukoencephalopathy
Progressive multifocal leukoencephalopathy is a demyelinating disease due to JC virus infection, a human papovavirus. Interestingly, there are several case reports that indicate a clinical response to zidovudine treatment, and one that does not. Simpson and Tagliati also recommended high dose zidovudine for treatment of progressive multifocal leukoencephalopathy. It is particularly striking that 70% of progressive multifocal leukoencephalopathy cases in this study had not received any antiretroviral treatment.

In summary, there is tentative evidence that antiretroviral treatment may be of benefit in prophylaxis of opportunistic brain diseases, a possibility that deserves further study. Furthermore, the fact that, similar to HIV dementia, treatment duration longer than 18 months was not effective may indicate a common mechanism. The reason for such a time limited effect may be the development of drug resistance. Although direct assessment of viral load and zidovudine resistance was not available in this study the duration of zidovudine benefit is in agreement with other estimates. Furthermore, if zidovudine would convey a more direct neuroprotective effect a lower CD4 count at the onset of brain disease was predicted. This was the case for patients treated for less than 18 months, but not with longer treatment. In fact the development of zidovudine resistance in HIV-1 isolates from CSF does not seem to be independent from those in the peripheral blood.

Whether non-specific mechanisms of the brain's immunological defence against different viral and bacterial opportunistic agents may benefit from antiretroviral treatment has not yet been considered systematically. The results of this study are indeed compatible with this idea; however, the mechanisms of this apparent neuroprotection are not known. It is likely that several factors have played a part—such as reduction of viral load and modulation of the immunological response in the brain. Positive effects of zidovudine treatment on cerebral perfusion and metabolism have been documented. In fact, recent studies have emphasised the crucial role of HIV infected cerebral endothelium and macrophage/microglia for virus entry and spread into the brain.

Use of other licensed antiretroviral drugs, including zalcitabine, didanosine, and stavudine, was not associated with a detectable reduction in incidence of brain disease, albeit used only by a few patients in this cohort. These drugs have not been evaluated for neurological effects and show generally lower penetration into the CSF than zidovudine. A controlled study in symptomatic patients who were intolerant of zidovudine concluded that
didanosine did not prevent the development of HIV dementia.\(^{11}\) Recently, however, an open label study provided preliminary evidence that atazanavir, a new non-nucleoside reverse transcriptase inhibitor, may be effective in HIV dementia.\(^{12}\) Altogether these data suggest that antiviral drugs which penetrate sufficiently well into the brain are essential for effective neuroprotection.

Unfortunately no effective adjuvant treatments are available so far, which could interfere with the neuropathological process other than viral load. A small unpublished trial (ACTG 162) with nimodipine—a calcium channel blocker—did not show therapeutic efficacy.\(^{13}\) Despite the limitation of this study, data from this large cohort confirm prophylactic effects of zidovudine against HIV dementia, and, for the first time, raise important questions about the possible role of antiretroviral drugs in prevention and treatment of opportunistic brain disease in AIDS. This finding requires confirmation and further study in the context of current combination drug treatment.

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Brain disease in AIDS and use of zidovudine


Risk of HIV dementia and opportunistic brain disease in AIDS and zidovudine therapy

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