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Antiretroviral monotherapies and serum HIV-1 dynamics

In early, frequent sampling of drug-naive patients we demonstrated characteristic responses in serum HIV-1 load with near maximal efficacy (>90%) for zidovudine (ZDV) within 1 to 4 days of onset of treatment. It was self-evident to us and others that HIV-1 turnover must be extremely rapid. Making the assumptions that HIV-1 synthesis and clearance were constant and serum virus was perturbed only by antiretroviral therapy allowed us to estimate the elimination kinetics of HIV-1. Briefly, our "pharmacological constant infusion model" (model A) was based upon cessation (or slowing) of a drug constant infusion at steady state producing an exponential serum drug loss to zero (or to a new constant lower level) according to first order kinetics. By substituting virus load for drug, and onset of antiretroviral therapy for change in infusion flow, we plotted decline in serum HIV-1 against time, superimposed a model computerised curve describing this decline and estimated half-life (T/2) by interpolation from the graphical plot (fig). This approach has been confirmed by using the same analysis upon data from drug infusion experiments (unpublished data).

Parallel, independently developed technology using an elegant computer-based mathematical model developed by Martin Nowak at Oxford described HIV-1 dynamics and its interrelationship with CD4 lymphocyte turnover. We compared model A with the latter (model B) using published data from patient groups receiving single drug therapies with nucleoside reverse transcriptase (RT) inhibitors ZDV, or lamivudine (3TC), and protease inhibitors ABT-538 or L-735,524.

Both models gave T/2 values for RT and protease inhibitors that were statistically indistinguishable (table 1) and a comparison of all values derived from model A and model B in 39 patients produced a linear relationship with a regression coefficient of 0.77 (p < 0.001). Using either approach no mono-therapy examined appeared to be superior in terms of early efficacy estimated by T/2 values.

Either of these models may be used to study serum/plasma HIV-1 dynamics. However, two important caveats must be emphasised in relation to such analyses.

A comparison of the two models (in-house: Model A and Martin Nowak: Model B) for estimating serum/plasma HIV-1 half-life (T/2) in days at the onset of antiretroviral monotherapies

<table>
<thead>
<tr>
<th></th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZDV</td>
<td>1.7 (0-7)</td>
<td>1.9 (1-0)</td>
</tr>
<tr>
<td>3TC</td>
<td>1.6 (1-1)</td>
<td>2.1 (1-5)</td>
</tr>
<tr>
<td>ABT-538</td>
<td>2.0 (0-4)</td>
<td>2.4 (0-5)</td>
</tr>
<tr>
<td>L-735,524</td>
<td>2.1 (0-7)</td>
<td>2.4 (0-6)</td>
</tr>
</tbody>
</table>

sd = standard deviation.

n = patient number per group.

Stat. sig. = statistical significance: paired Student's t test.

NS = Not significant.
Firstly, when T/2 values are as little as 1.5–2.5 days, the time between baseline venesection and first therapy must be recorded accurately as delays of initial dose by only a few hours may produce 10–20% errors in any calculation. Secondly, assumptions made in these models do not allow for sudden biological changes in viral load at or near the time of onset of treatment, and we find such events do occur in up to 10% of patients studied and will totally invalidate the subsequent analysis.

Nevertheless, we believe there is a place for this simple model and have already used it to assist in the early prediction (within 1 month) of the relative efficacies of different antiretroviral therapies in HIV-1 disease. Such "screening" procedures in small patient groups (10–20 patients/group), receiving different combination therapies, using virological endpoints will allow the selection of superior drug combinations that can go forward into longer, more expensive clinical trials.

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Failure of itraconazole to prevent Enterocytozoon bieneusi infection

Microsporidia are obligate intracellular parasites which have been increasingly recognised as a significant cause of morbidity in AIDS patients.1 2 A variety of drugs have been used in attempts to treat the most frequently identified microsporidial agents (Enterocytozoon bieneusi, Encephalitozoon cuniculi, Encephalitozoon hellem, Septata intestinalis). Blinded, placebo-controlled studies, however, are lacking. Preliminary clinical results have shown fumagillin to be promising for treatment of keratoconjunctivitis due to Encephalitozoon hellem,3 and albendazole to have activity against S intestinalis.4 5 Currently, there is no proven effective treatment for Enterocytozoon bieneusi, the most prevalent microsporidian which is capable of causing debilitating diarrhoea and wasting syndrome in AIDS patients. Albendazole may mitigate enterocytozoon-associated diarrhoea but fails to eradicate the parasite.6 Because E bieneusi has not yet been maintained in long-term tissue culture, it has not been possible to evaluate the effects of therapeutic regimens on this microsporidium owing to the lack of an appropriate in vitro testing system. Recent studies, however, have suggested that the polar tubule apparatus contained within the microsporidium spore may be a useful target for chemotherapeutic intervention.7 This structure, characteristic of all microsporidian species, consists of a tightly coiled, hollow, polar tubule which upon appropriate environmental stimulation undergoes extrusion from the spore to attach to a suitable host cell. Subsequently the infectious sporoplasm is passed through the polar tubule into the target cell where a new generation of microsporidial organisms is produced. Recently Leitch et al investigated the capability of different agents to interfere with polar tubule extrusion.8 They used an in vitro assay utilising Enterocytozoon hellem cultured from an AIDS patient. Four agents were found to inhibit polar tubule extrusion: Cytochalasin D, demecolene, nifedipine and itraconazole. One of these agents, itraconazole, has been used to treat microsporidiosis of invertebrates,9 and there has been anecdotal experience that it has activity in the treatment of human ocular microsporidiosis due to encephalitozoon.8 Although it was suggested that itraconazole may have activity against other species of pathogenic microsporidia, its efficacy against E bieneusi has not been investigated. We report the case of an AIDS patient who developed intestinal E bieneusi infection while on high-dose itraconazole for secondary prophylaxis against histoplasmosis.

A 41 year old homosexual patient was diagnosed HIV-positive in 1985. He remained asymptomatic until 1993 when he presented with fever, unproductive cough, dyspnoea and an elevated serum lactic dehydrogenase (LDH). Histoplasma capsulatum was cultured from bone marrow specimens. With amphotericin B therapy the patient recovered. Four weeks later, when LDH and histoplasma polysaccharide antigen titre had normalised, therapy was switched to itraconazole 200 mg bid. Nine months later while still receiving 200 mg bid he started to complain of watery diarrhoea five to 15 times a day accompanied by a weight loss of 1–3 kg. His CD4 cell count at that time was 60 cells/μl. E bieneusi was detected in multiple stool specimens and in a
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