


Antiviral chemotherapy against HTLV-III/LAV infections

The identification of a retrovirus (HTLV-III/LAV) as the primary cause of the acquired immunodeficiency syndrome (AIDS) (Barré-Sinoussi et al., 1983; Gallo et al., 1984) offers a target for antiviral chemotherapy. This is not an easy target, however, owing to the presence of the viral genome as a provirus and the latent state of the infection. Several important questions require answers. It must be established which infected cells release HTLV-III/LAV, how long these infected cells survive in vivo, whether these cells can be eliminated and whether further spread of virus to new cells can be prevented.

Originally, it was thought that only the T4 helper-inducer subset of T cells was infected by HTLV-III/LAV but now it is clear that other cells, such as mononuclear cells, macrophages, glial cells and EBV-infected B cells can also be infected. However, the infection of T4+ cells with HTLV-III/LAV is a crucial event in the development of AIDS. The presence of other infections such as cytomegalovirus may contribute to the development of the disease by reactivation of HTLV-III/LAV through T4+ stimulation. It has also been found that HTLV-III/LAV-infected persons cannot respond to HTLV-III/LAV antigen by T4+ activation, a unique property of HTLV-III/LAV infection (Wahren et al., 1985).

The half-lives of infected cells able to release virus are not known but it seems likely that dividing T4+ cells can be destroyed by a lytic multiplication of HTLV-III/LAV. Thus a mitogenic stimulation of T4+ cells should increase the elimination rate of infected cells but, unfortunately, at the same time provide more virus for infection of new cells. However, if the HTLV-III/LAV reverse transcriptase activity was blocked by a selective inhibitor, the infection of new cells might be prevented. The expression of the viral genome, already presented as a DNA provirus, is mediated by cellular RNA polymerase II and is therefore not susceptible to inhibitors of viral reverse transcriptase.

Table I lists some inhibitors of HTLV-III/LAV reverse transcriptase and viral replication in cell culture, with their effects on cellular DNA polymerase α and on the multiplication of uninfected cells. It should be emphasized that, since the assay conditions differ, the information is still incomplete and in-vitro data might not relate to in-vivo efficacy. 3'Azidothymidine is phosphorylated by cellular enzymes...
Table I. Activity of inhibitors of HTLV-III/LAV reverse transcriptase and viral replication in cell culture

<table>
<thead>
<tr>
<th>Drug</th>
<th>HTLV-III/LAV reverse transcriptase</th>
<th>50% inhibitory concentration (mg/l)</th>
<th>Cellular DNA polymerase α</th>
<th>HTLV-III/LAV replication in lymphocytes</th>
<th>Cell growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>3'-Azidothymidine</td>
<td>0.02 (TP)</td>
<td>30</td>
<td>0.0014-0.13</td>
<td>?</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>0.03-0.06</td>
<td>15</td>
<td>10</td>
<td>300</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>HPA-23</td>
<td>11-30</td>
<td>0-3</td>
<td>-</td>
<td>?</td>
<td>&lt;1000</td>
</tr>
<tr>
<td>Interferon α</td>
<td>-</td>
<td>-</td>
<td>4-64 (u)</td>
<td>&gt;1024(u)</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>&gt;500 (TP)</td>
<td>-</td>
<td>30-50</td>
<td>10</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Suramin</td>
<td>80</td>
<td>0.15</td>
<td>10-50</td>
<td>100</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

TP, Triphosphate. References are given in the text.

to the triphosphate form, which competes with TTP and inhibits the action of reverse transcriptase as a chain terminator, thus blocking viral replication and provirus formation (St Clair et al., 1985; Furman et al., 1985; Mitsuya et al., 1985; L. Vrang, personal communication). Foscarnet is a selective, non-competitive inhibitor of HTLV-III/LAV reverse transcriptase (Sandström et al., 1985; Sarin et al., 1985; Vrang & Öberg, 1986). The mechanism of inhibition seems to be analogous to that reported for viral DNA polymerases (Öberg, 1983). The very short half-life of HPA-23 and its observed action against murine retrovirus in vivo indicate that effects other than a competitive inhibition of reverse transcriptase may be of importance (Ono et al., 1984; Dormont et al., 1985; Rozenbaum et al., 1985); this is also suggested by the more efficient inhibition of DNA polymerase α than of reverse transcriptase (Ono et al., 1984; Dormont et al., 1985). High cellular toxicity has been observed (unpublished observation). Interferon prevents viral replication at concentrations which are not inhibitory to cell growth (Ho et al., 1985). Ribavirin does not appear to inhibit HTLV-III/LAV selectively in cell culture but a reversible cellular toxicity might permit its use as an inhibitor of HTLV-III/LAV replication (Larsson, Stenberg & Öberg, 1978; McCormick et al., 1984). Ribavirin triphosphate does not inhibit reverse transcriptase (L. Vrang, personal communication). Finally, the activity of suramin in cell culture (Mitsuya et al., 1984) is unlikely to be directed against the HTLV-III/LAV reverse transcriptase. Very little, if any, selectivity at the enzyme level was found for suramin when cellular DNA polymerase and reverse transcriptases were compared, and the effect was dependent on the amount of protein present
problem in the clinical trials will be the lack of fast quantitative methods to determine the effects of antiviral drugs directed against HTLV-III/LAV.

As mentioned it might be necessary to increase the destruction rate of infected cells, for example by inducing cell division and lytic virus multiplication in already infected cells. A mitotic activation of T4+ cells in vivo could possibly be achieved by treatment with agents such as interleukin-2, isoprinosine or γ-interferon. This may result in eradication of infected T4+ cells and restore normality to the immune system. However, since other cells are infected, especially in the CNS, the implications of mitotic activation remain to be studied as do alternative methods of eliminating infected cells such as the use of monoclonal antibodies.

A rapid development of new antiviral agents directed against HTLV-III/LAV is likely to take place in the next years. In addition to reverse transcriptase, other targets such as the trans activator gene and its product will probably be studied. The pathogenesis of the HTLV-III/LAV infection needs to be determined in more detail in order to find more targets for therapy. Important lessons could probably be learnt from the pathogenesis of vira virus infection, especially about immunopathologic effects in the CNS (Nathanson et al., 1976).

It is probable that therapy of HTLV-III/LAV infections will require combination therapies affecting both virus replication and the immune system. Therapy might have to be lifelong and the evaluation of various treatment regimens will take a considerable time. Prolonged treatment will probably present major problems from the point of view of toxicity and is also likely to increase the risk of the emergence of resistance. In such a situation combination therapy with antivirals with different modes of action will be especially important.

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References


