Reducing viral load to undetectable levels in patients with HIV infection has been achieved using a number of drug combinations, according to the results of studies presented at the 11th International Conference on AIDS [Vancouver, Canada; July 1996]. In one study, plasma levels were still below the level of detection after 1 year of treatment with zidovudine, zalcitabine and nevirapine. Such studies herald a new era of hope for patients with HIV infection. As recently as last year, viewing HIV infection as a manageable chronic disease was considered unrealistic, but now it appears to be a real possibility. Future research must now concentrate on determining whether viral suppression can be maintained in the long term, and on the effects of combination treatments on clinical outcome.

There are at least 11 ongoing clinical studies of triple anti-HIV therapy that have zidovudine + lamivudine as the 2-drug foundation to which a third drug is added.¹ There is a considerable amount of data in support of the zidovudine + lamivudine base combination, including the results of a trial that was terminated early due to the clear clinical benefits of adding lamivudine to zidovudine or zidovudine combinations, compared with adding placebo [see boxed text].

One of the triple-therapy regimens based on zidovudine + lamivudine involves the addition of the protease inhibitor indinavir ['Crixivan'; Merck] to the combination. To date, treatment with the standard regimen of zidovudine + lamivudine* plus indinavir 800mg 3-times daily has been initiated in 33 patients. Plasma levels of HIV were found to be undetectable in 6/7 patients who have completed 48 weeks of therapy. Furthermore, a median increase in CD4+ count of 218 cells/mm³ from baseline has been documented in these patients. Trials to determine the clinical outcome associated with these effects on surrogate markers of HIV disease are now underway.

'We should not think of monotherapy and we should not delay therapy'.
Dr David Ho, Aaron Diamond Research Center, New York, US

In another investigation, a combination of zidovudine, lamivudine and the protease inhibitor ritonavir ['Norvir'; Abbott] has led to dramatic reductions in viral load in 12 patients who received therapy during the primary phase of HIV infection. Three of the patients discontinued treatment due to noncompliance or drug intolerance.

However, viral load was reduced to undetectable levels in the 9 remaining patients. Treatment consisted of the standard regimen of zidovudine + lamivudine plus ritonavir 600mg twice daily. Assessments of viral load using culture and plasma HIV RNA measurements were made between 13 and 43 weeks after treatment initiation.

The researchers plan to continue treatment for a minimum of 1 year, at which time lymph node tissue will be obtained to assess the level of active HIV replication.

Similar results were obtained in an open-label study which evaluated the effects of zidovudine, lamivudine and the protease inhibitor nelfinavir ['Viracept', Agouron] in 12 patients with HIV infection. Treatment involved the standard regimen of zidovudine + lamivudine plus nelfinavir 750mg 3-times daily for 4 months.

'While this is encouraging news, it's important to note that these results cannot yet be called a cure. We don't yet know if the virus will rebound if patients were to cease the regimen'.
Dr Martin Markowitz, Aaron Diamond Research Center, New York, US

CAESAR study results
Adding lamivudine to zidovudine-based antiretroviral therapy leads to a significant delay in disease progression and to prolongation of survival, compared with the addition of placebo, according to the results of the CAESAR** study.¹

In the trial, 1427 patients with HIV infection were randomised to receive either lamivudine, lamivudine + the NNRTI loviride [Janssen; phase II], or placebo, in addition to their existing zidovudine-based anti-HIV therapy (or in combination with zidovudine in those patients who had not received antiretroviral treatment prior to study entry). Discontinuation of the study nearly 8 months early was recommended by an independent Data Safety and Monitoring Board in view of the results of an interim analysis that showed the clear benefits of lamivudine over placebo. The median duration of treatment at the time of study discontinuation was 12 months.

According to the interim data, disease progression or death occurred in 9 and 17% of patients receiving lamivudine (with or without loviride) and placebo, respectively. This represented a 54% difference in this endpoint between the 2 groups in favour of lamivudine. The addition of loviride was not seen to provide any additional benefit to that of adding lamivudine alone.

All 3 treatment regimens were generally well tolerated. Treatment discontinuation due to adverse events occurred in 5, 3 and 2% of patients receiving placebo, lamivudine + loviride, or lamivudine alone in addition to zidovudine-based therapy.

In other clinical trials, the most commonly reported adverse events associated with the combination of zidovudine and lamivudine have been headache, nausea, malaise/fatigue, nasol conjestion, diarrhoea, anaemia and low white blood cell counts. In addition, pancreatitis has been observed in 15% of paediatric patients with HIV infection who have received this combination.

* The standard regimen of zidovudine + lamivudine is zidovudine 200mg 3-times daily + lamivudine 150mg twice daily.
** CAESAR is an acronym based on the countries involved in the study (Canada, Australia, Europe and South Africa)

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New era of combination therapy for HIV infection – continued

In 11/12 patients, plasma levels of HIV were undetectable after this treatment period. Furthermore, CD4+ counts were increased by an average of 100 cells/mm³ over baseline levels.

Other nucleoside analogue foundations

At the AIDS conference, data were also presented on the use of other nucleoside analogues as foundations for combination therapy [see table]. These included studies of stavudine in combination with nelfinavir, and studies of zidovudine + zalcitabine in combination with ritonavir or nevirapine. The trial of stavudine and nelfinavir was conducted at the Montrose Clinic, Houston, Texas, US. It involved 33 patients with HIV infection who received standard doses of stavudine alone or in combination with nelfinavir 500, 750 or 1000mg 3-times daily. After 60 days of treatment, patients receiving combination therapy had mean viral load reductions of 1.7–2.4 log₁₀ compared with 0.8 log₁₀ in stavudine monotherapy recipients. The reductions seen in combination therapy recipients were maintained at a 5-month assessment. Previous open-label studies have shown that diarrhoea is the most commonly reported adverse effect associated with nelfinavir treatment. Currently, more than 700 patients are receiving nelfinavir in phase II/III trials in the US.

Latest data on ritonavir combination

Sixty-week data on combination therapy with zidovudine, zalcitabine and ritonavir were presented at the conference. The combination was investigated in an open-label study involving 17 patients with advanced HIV infection (CD4+ counts of < 250 cells/mm³). The patients had not received any previous antiretroviral treatment. In the study, patients received daily total doses of zidovudine 600mg, zalcitabine 2.25mg and ritonavir 1200mg. After 60 weeks, a mean increase in CD4+ count of 180 cells/mm³ from baseline was seen. Also, viral load was reduced from baseline by an average of nearly 2.0 log₁₀. The most common adverse events were nausea, diarrhoea, paraesthesia, excessive menstrual bleeding and weakness.

1-year viral load reduction with nevirapine

Plasma levels of HIV were kept below the limits of detection by a combination of zidovudine, zalcitabine and nevirapine administered for 12 months, according to Dr Julio Montaner from the Canadian HIV Trial Network.

"This study has shown that we do not have to use protease inhibitors to attain long-term suppression of the virus", said Dr Montaner. Nevirapine, which is the first non-nucleoside reverse transcriptase inhibitor (NNRTI) to be approved as a treatment for HIV infection in the US, has a different mechanism of action and tolerability profile to other approved anti-HIV drugs.

The effects of the combination of nevirapine with the 2 nucleoside analogues were demonstrated in a randomised, double-blind, placebo-controlled trial involving 151 patients with previously untreated HIV infection (CD4+ counts of 200-600 cells/mm³). Patients received open-label zidovudine 600 mg/day + zalcitabine 400 mg/day plus blinded treatment with nevirapine 400 mg/day or placebo.

After 1 year of treatment, viral load was below the limit of detection in > 50% of patients receiving triple therapy. This was a significantly greater number

| Selected combination therapy studies presented at the 11th International Conference on AIDS |
| --- | --- | --- | --- |
| Components of combination therapy | Length of study | Number of patients | Results |
| Nucleoside analogues | Other anti-HIV drugs | | |
| Zidovudine + lamivudine | Indinavir | 48 weeks | 33 (results for 7 patients to date) | Undetectable plasma levels of virus in 67% patients; median increase in CD4+ count of 218 cells/mm³ from baseline |
| Zidovudine + lamivudine | Ritonavir | 13–43 weeks (to be continued for 1 year) | 12 | Undetectable plasma levels of virus in 9/12 patients (remaining 3 patients discontinued treatment) |
| Zidovudine + lamivudine | Nelfinavir | 4 months | 12 | Undetectable plasma levels of virus in 11/12 patients; average increase in CD4+ count of 100 cells/mm³ from baseline |
| Stavudine | Nelfinavir | 60 days | 33 | Significantly greater viral load reduction in combination therapy recipients compared with that in patients receiving stavudine alone; effect maintained at 5 months |
| Zidovudine + zalcitabine | Ritonavir | 60 weeks | 17 | Viral load reduction from baseline of approximately 2.0 log₁₀ mean increase in CD4+ count of 180 cells/mm³ from baseline |

The great divide

The cost of triple therapy is prohibitive to many patients with HIV infection. For patients living in developing countries, such treatment is out of the question. This is of particular concern, considering that some 90% of the world's 22 million patients with HIV infection live in developing countries, according to United Nations estimates.¹

In these areas, emphasis is currently placed on educating people about preventive behaviour. Beyond this, clinicians can only hope that drug prices are brought into line with the spending power of developing countries, or that an anti-HIV vaccine becomes a reality. Until then, there is likely to be considerable heated debate regarding anti-HIV drug availability in the developing world. If prices remain at current levels, the majority of patients with HIV infection will not benefit from recent scientific advances.