In 1996, there were 4944 AIDS-related deaths in New York, US. This is a 30% reduction from the 7046 AIDS-related deaths that occurred in New York in 1995. This is the first time that a drop in the number of AIDS deaths has been seen since 1983, i.e. the year in which the reporting of AIDS mortality rates first began.

Many researchers have linked the reduction of mortality rates to the efficacy of new triple-therapy regimens and to improved patient access to these drugs.

**Sustained effects with early treatment**

A recent study has shown that treatment with zidovudine, lamivudine + indinavir can lead to undetectable levels of HIV for more than 68 weeks in patients who begin to receive treatment early in the course of their infection. To date, this is the longest sustained effect of treatment to be reported. The long-term effect was seen in 18/21 patients included in the study.

Another study also looked at the effects of treating HIV soon after infection. The results of this study were reported by Dr Martin Markowitz from the Aaron Diamond AIDS Center, New York. In Dr Markowitz' study, 24 patients were treated with various triple-therapy regimens within 90 days of infection. Undetectable levels of HIV were achieved in 18 of these patients, and were sustained in some patients for up to 64 weeks.

Of particular importance is the finding that the levels of HIV were even reduced in the lymph tissue of 2 patients. Lymph tissue is thought to act as a reservoir for HIV – a place where the virus can 'hide' while waiting to re-emerge should treatment be stopped. The small amount of virus that was found in the lymph tissue was inactive, i.e. it appeared to be trapped inside cells.

It is thought that these virus-holding cells may die off after 2–3 years of continued triple therapy, said Dr David Ho, director of the Aaron Diamond AIDS Center. Patients will only be given the option of terminating antiretroviral therapy if researchers can confirm that this has occurred.

**Late treatment can be effective**

Patients with HIV infection who do not start triple therapy early in the course of their disease may still benefit from late treatment, according to study results presented by Dr Martin Hirsch from Harvard Medical School, US.

This study involved 320 patients with long-term HIV infection who had CD4+ cell counts of < 50/mm³. The patients received triple therapy with zidovudine, lamivudine and indinavir, dual therapy with zidovudine + lamivudine, or monotherapy with indinavir. Importantly, there was no apparent prior resistance to zidovudine or lamivudine in any of the patients.

At 6 months' follow up, 65% of patients receiving triple therapy had undetectable levels of HIV. In comparison, this was achieved in only 2% of patients receiving indinavir alone, and in no patients receiving dual therapy.

**Understanding immune recovery**

Although treatment with antiretroviral drugs is now able to reduce the amount of HIV to undetectable levels in many patients, the immune systems of these patients do not appear to fully recover.

It is important to have an understanding of the new, partially recovered immune system in order to know how patients will respond to new challenges of infection, said Dr Michael Lederman from the Case Western Reserve University Hospitals of Cleveland, US.

Accordingly, Dr Lederman and colleagues initiated the AIDS Clinical Trials Group (ACTG)-315 trial. This ongoing study has been designed to investigate the immunological consequences of 1 year's treatment with zidovudine, lamivudine and ritonavir.
AIDS: latest conference news – continued

in patients with HIV infection (CD4+ cell counts of 100–300/mm³).

Preliminary 12-week data from 33 patients has indicated that treatment leads to an increase in the levels of naive CD4+ and CD8+ cells, and memory CD4+ cells. Memory cells are cells of the immune system that have experienced prior exposure to HIV, while naive cells are those that have not previously encountered HIV or any other antigen. No increases in activated CD4+ or CD8+ cells were observed.

Researchers reported a partial restoration of functional immune responses, as measured by delayed-type hypersensitivity and lymphocyte proliferation assays.

Support for these findings came from another study presented by Dr HC Lane from the US National Institutes of Allergy and Infectious Diseases (NIAID). Regarding the initial changes following antiretroviral treatment, Dr Lane found that increases in immune cells were due to an expansion of the existing cell populations, such as memory and naive cells, rather than due to an influx of new cells from a thymic environment.

Consequences of limited immune recovery

The important ‘take-home’ message from recent studies of immune system recovery is that it is inappropriate to prematurely withdraw drugs that protect patients from opportunistic infections. At present, this is true for all patients, even those with undetectable levels of virus, said Dr Lederman.

Evidence for this comes from 5 case reports presented at the conference by Dr Mark Jacobson from the UC-Medical Center, US. Dr Jacobson described 5 cases of cytomegalovirus (CMV) retinitis in patients who, theoretically at least, appeared to be recovering well.

CMV retinitis is usually only seen in patients with CD4+ cell counts of < 50/mm³. However, in the cases described by Dr Jacobson, the patients all had cell counts of > 200/mm³.

Update on chemokine receptors

The notion that chemokine receptors may be the long-sought co-factors that enable HIV to enter and infect human immune cells caused great excitement among the AIDS research community last year. At the conference, Dr Edward Berger from the NIAID reported on the latest findings in this important area of research. According to Dr Berger:

- strains of HIV that tend to infect macrophages early in the course of disease appear to use CCR-5, CCR-3 or CCR-2b chemokine receptors
- strains of HIV that act later in the course of disease, usually infecting CD4+ cells, appear to use fusin receptors
- binding between HIV and CCR-5 occurs via an interaction between the receptor and the HIV gp-120 protein
- HIV/CCR-5 binding is greatly enhanced by the presence of CD4+ cells

- a defect in the gene that encodes the CCR-5 receptor may account for the ability of some individuals to resist HIV infection despite being exposed to the virus in a high-risk setting on numerous occasions.

Will nevirapine reduce vertical transmission?

The ACTG-250 study, which has shown that nevirapine is well tolerated in both mothers and neonates when given during labour, has paved the way for an efficacy study in this setting.

In the ACTG-250 trial, a single dose of nevirapine was administered during labour to each of 7 women with HIV infection, and a further single dose was given to neonates between 48 and 72 hours after birth. The mothers had also been receiving zidovudine.

A pharmacokinetic analysis showed that the above regimen was associated with therapeutic levels of nevirapine throughout the neonates' first week of life. The drug was well tolerated in both mothers and neonates.

These findings have encouraged researchers to conduct an efficacy trial to investigate whether the addition of nevirapine further reduces the risk of HIV transmission from mother to neonate, compared with zidovudine alone. In the ACTG-076 trial, zidovudine reduced the rate of HIV transmission in this setting from 25 to 8%, compared with placebo.* The hope of researchers is that this rate can be reduced even further by using nevirapine to increase the strength of the antiviral therapy.

Triple therapy effective in infants

In another study, treatment with triple therapy led to reductions in HIV RNA of 0.5–3 log₁₀ compared with baseline levels, in 7/8 infants (aged between 2.5 and 16 months). Two of the infants had undetectable levels of viraemia after 6 months of treatment. The triple-therapy combination comprised zidovudine, nevirapine and didanosine.

The findings of this trial support the results of an earlier study involving the use of a similar triple-therapy regimen in adults with HIV infection, said Dr Katherine Luzuriaga from the University of Massachusetts Medical Center, US.

Nevirapine has already received approval in a number of countries for use in triple-therapy combinations in adults. An application for approval for its use in infants will be submitted to the US FDA later this year. At present, it is available for use in children through an expanded use programme in the US.

New combination has potential

A combination of Glaxo Wellcome’s reverse transcriptase inhibitor 1592U89 and its protease inhibitor VX-478 has shown preliminary efficacy in a phase I/II trial.

In the ongoing trial, levels of viraemia were undetectable after 4 weeks of treatment in 5/7 patients with HIV infection. The average increase in CD4+ cells

* See Inpharma 1066: 13, 7 Dec 1996; 800458277 and Inpharma 951: 3, 20 Aug 1994; 800287098