SOUTHERN AFRICAN HIV CLINICIANS SOCIETY **AIDS REVIEW**

ANTIRETROVIRAL THERAPY IN CHILDREN — INCREASED BENEFIT FROM INCREASED COMPLEXITY

Antiretroviral therapy (ART) started as monotherapy with significant short-term gains. With the advent of newer drugs management has become more complex, but with significant gains in quality and quantity of life.

The evolution of ART in children lags behind that of adults for many reasons. These include an unwillingness to use new medications in children before efficacy has been established and also difficulty in developing suitable formulations for children. ART has progressed from monotherapy to dual, triple and even quadruple therapy, stimulated by insights into the rapidity of viral replication, development of resistance, and availability of new agents.

The most pressing concern with ART is its lack of accessibility to the majority of patients that need it. Other important issues are how and when to use it in ways that promote durability of response but avoid unnecessary use. Most information is derived from studies with relatively short periods of follow-up. The long-term durability of therapy is not known, but with development of new agents should be sustained.

HISTORY

The acquired immunodeficiency syndrome (AIDS) was first recognised in 1981 after a cluster of 5 adult males presented with *Pneumocystis carinii* pneumonia (PCP) in California, USA.[1] One year later, the first report of unexplained immunodeficency in infants appeared. All infants were born to mothers considered to be at high risk for AIDS and the possibility of a transmissible agent passing from mother to child was first postulated.[2] The first indication that AIDS was caused by a retrovirus was the discovery of a virus containing reverse transcriptase by Barre-Sinoussi and colleagues from lymphoid tissue from a man with the persistent lymphadenopathy syndrome.[3] The retrovirus initially termed 'lymphadenopathy-associated virus' was subsequently renamed the 'human immunodeficiency virus' (HIV-1) and has been conclusively shown to be the cause of AIDS.[4]

INDICATIONS FOR INITIATING THERAPY

Indications for initiating therapy have been formulated by expert committees, primarily in North America.[5] In children, the recommendations for treatment are broadly based and are updated as soon as new drugs or information become available (http://www.hivatis.org). Recently the International AIDS Society published guidelines for ART in Africa. Triple therapy was recommended, with dual therapy regarded as a less effective but cheaper alternative. Children in whom ART was indicated included all those who were symptomatic, especially where the diagnosis was confirmed early in life, and asymptomatic children with a CD4 percentage below 25%. Clinical studies were recommended to identify new patient groups for therapy.[6]

EFFECT OF ANTIRETROVIRAL THERAPY ON PROGNOSIS

Many factors influence the prognosis of HIV-1 infection. These include socio-economic circumstances, since even before ART became available, outcome varied geographically. For example, before the use of PCP prophylaxis and ART, Scott and colleagues showed a median survival period of 38 months from time of diagnosis in a cohort of perinatally infected children in Florida.[7] Eighty per cent presented under the age of 2 years. In contrast, Bobat *et al.* showed that in Durban 83% of deaths occurred in infants below 10 months of age, also in the absence of ART.[8]

ART has had an enormous beneficial impact on the outcome of HIV-1 infection in adults with AIDS. Since the introduction of highly active antiretroviral therapy (HAART) in 1995, mortality trends have reversed, declining from 30 to 10 per 100 person-years.[9] The impact of HAART on children has been equally dramatic. De Martino and colleagues recently reported their observations in 1 142 HIV-1-infected children born between 1980 and 1997. Survival was similar in birth cohorts from 1980 to 1989 and 1990 through 1995. Thereafter the risk of death declined by 30% in children receiving two antiretroviral (ARV) agents and 70% in those receiving triple therapy.[10]

MONITORING THE EFFICACY OF ANTIRETROVIRAL AGENTS

Measuring of CD4+ T-cell counts and percentages and, more recently, plasma HIV-1 RNA are essential for monitoring the success of therapy. In paediatric care, attention should also be given to the maintenance of continued growth and development. From the outset, ART studies in children have included evaluation of these parameters.[11-13]

MONOTHERAPY VERSUS DUAL THERAPY

The elucidation of the life cycle of HIV and the characterisation of proteins involved in entry and key enzymatic steps have assisted the development of ARV agents. Zidovudine (ZDV), a nucleoside reverse transcriptase inhibitor (NRTI), was initially synthesised as an anti-cancer drug. It has been used clinically since the successful conclusion of a 6-month placebo-controlled trial in which it was associated with a dramatic difference in mortality in adults (1 of 143 v. 19 of 137).[14] This study was terminated early. Regrettably, the benefits were not durable and a clinical trial lasting 3 years showed no survival or morbidity benefits.[15]

The first paediatric study began shortly after the conclusion of the adult placebo-controlled study and was published in 1988. Pizzo *et al.* studied continuously administered ZDV in 21 symptomatic children, 13 of whom had encephalopathy. All patients with encephalopathy showed improvement.[12] Two years later, a large multicenter study confirmed the efficacy of oral ZDV in children with advanced HIV disease. The maximal duration of follow-up was 90 weeks.[13]

The next step was to compare specific ARV agents. Englund *et al.* compared ZDV to either didanosine (ddI) or combined therapy in 831 children.[16] At a median follow-up period of 23 months, the ZDV arm was discontinued as it was associated with a significantly increased risk of disease progression compared with combined therapy. By the end of the study (median duration of follow-up 32 months) ddI monotherapy was equivalent to combined therapy both for mortality and disease progression.[16] A second study, however, showed that ddI monotherapy was inferior to dual therapy consisting of ZDV with either ddI or lamivudine.[11] After a median follow-up period of 9 months, there were 38 (16%) failures on ddI versus 15 (6.4%) on ZDV plus lamivudine.

Other dual therapy regimens have also shown efficacy. The combination of ddI and stavudine, in particular, has been associated with a durable but incomplete virological response in children followed up for 48 weeks. It was associated with a 0.5 log (5-fold) reduction in plasma HIV RNA at week 12 that was maintained through week 48.[17] Data presented at the recent AIDS Conference in Durban showed that 7 of 16 children with mild disease (plasma HIV RNA below 50 000 copies per ml) actually achieved maximal suppression of viral replication.

A contentious issue in the South African context is whether monotherapy should be attempted in circumstances where both dual and triple therapy are unaffordable. While a family income might cope with a monthly expenditure of R200, doubling this amount is often beyond reach. We have recently shown that monotherapy can have significant short-term benefits in symptomatic children with a history of frequent or long hospitalisation for intercurrent disease.[18] The limitations of monotherapy should be understood, especially the development of resistance, which might compromise therapeutic options should ART become more accessible.

TRIPLE THERAPY

The addition of either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI) to dual NRTI therapy has had a major positive impact in children. Initial studies suggested that infants and children might have lower response rates than adults receiving triple therapy. Whereas between 43% and 75% of adults might be expected to respond with plasma HIV RNA below the limits of detectability, initial observations suggested that only 25 - 40% of children responded in this way.[19] Supporting this observation is the excessively high plasma HIV RNA levels found in children especially in the first few years of life.[20]

Recent studies, however, have shown that if strict attention is given to compliance and adequate medication is given, therapy may be extremely successful. For example, Van Rossum *et al.* demonstrated in a multi-centred Dutch study that 70% of children had less than 500 RNA copies per ml of plasma and 48% had less than 40 copies per ml after 6 months' follow-up.[21] The PI used was indinavir, which is available only in capsule form and necessitated 8-hourly administration, and was combined with ZDV and lamivudine. The dosage of indinavir needed to be increased in 70% of children following results of pharmacokinetic studies. The difficulty in maintaining adherence cannot be overemphasised. As an illustration of the intensity of supervision, in Van Rossum's study of 28 children, 37 investigators are listed. Even though 15 children had previously been treated with ZDV, an excellent virological response was seen in all those who were compliant.

The use of drugs with long half-lives, permitting once-daily dosing, may contribute towards successful virological suppression. Efavirenz, an NNRTI, together with nelfinavir, a PI and one or more NRTIs was associated with plasma RNA below 400 copies per ml in 76% of children and less than 50 copies per ml in 63% after 48 weeks.[22]

CLINICAL RESPONSE IN THE PRESENCE OF INADEQUATE SUPPRESSION OF VIRAL REPLICATION

Non-adherence is common and is associated with a poor virological response. Adherent patients may have a sustained but incomplete response. Although it is likely that treatment may ultimately fail due to development of resistance, patients may continue to derive benefit from substandard therapy. For example, Watson studied 72 children on HAART of whom 42 were adherent (defined by filling 75% of prescriptions) and 29 non-adherent. Fifty-eight per cent of adherent patients but only 3 of 29 non-adherent patients achieved a plasma HIV-RNA

level below 400 copies per ml. The ages of patients ranged from 3 months to 12 years and the median duration of follow-up was 282 days. There were no deaths in this study, even in the non-adherent patients.[23]

A discordance between virological and CD4+ T-cell response has been observed in children receiving PIs. In a prospective study of 25 children, 22 of whom had prior exposure to NRTIs and NNRTIs, only 5 had sustained suppression of plasma HIV RNA, yet 22 had sustained elevations of CD4+ T cells. All had advanced disease with CD4+ T-cell percentages below 6% at baseline. Median duration of follow-up was 18.8 months.[24]

A reasonable conclusion from these two studies is that it may be worth persisting with 'failing' PI-containing regimens as long as there is a beneficial CD4+ T-cell response. There are few data on the appropriate response to patients in whom NRTI therapy fails. Probably, especially if few options are available, it is better to persist with a failing regimen than discontinue it, but clinical judgement should be exercised. Both ZDV and lamivudine have been associated with resistance mutations that diminish viral replicative capacity.[25,26]

Treatment of primary infection

Progression of HIV disease is associated with ongoing destruction of CD4+ T cells and gradual loss of the immunological repertoire. In a landmark study of the prognostic value of plasma HIV RNA in adults, even a level below 4 500 copies per ml was associated with an 8% risk of developing the acquired immunodeficiency syndrome or death within 5 years.[27] HIV infection may therefore be associated with serious morbidity even in the absence of excessive viral replication.

Because the majority of paediatric infections occur during delivery,[28] it is possible to completely suppress viral replication through early and aggressive therapy as soon as infection is detected and so maintain an intact immunological system. Luzuriaga and colleagues recently reported on 17 HIV-1-infected infants in whom either three or four drugs were initiated between 15 days and 3 months of age. All had sustained suppression of plasma HIV-1 RNA to below 50 copies per ml but continued presence of proviral DNA on follow-up ranged between 16 and 56 months. All had intact immune systems as evidenced by their ability to respond appropriately to various antigenic challenges.[29]

Antiretroviral-experienced children in whom therapy fails

The term 'salvage therapy' has been adopted for heavily treated patients in whom ART has failed. For this group of patients there are a number of options. By changing to three previously unused ARVs, one increases the chances of a favourable response.[30] Genotyping assays have been developed to assist with drug selection by screening for known mutations already associated with drug resistance. Preliminary experience in children supports the use of this assay in ARV-experienced children.[31]

A role for hydroxyurea?

The cytostatic agent hydroxyurea (HU), used previously for chronic myelogenous leukaemia and other lymphoproliferative syndromes, may augment ddI. Long-term use of HU and ddI in adults has recently been reported on. Sustained but incomplete suppression of viral replication occurred in 12 adults after more than 24 months of therapy. Initially the median plasma HIV-RNA was 51 795 copies per ml and CD4+ T-cell count 376 cells/mm^3. By week 122, the plasma HIV-RNA had declined by 2.2 log 10 of virus and the CD4+ T-cell count had increased by an average of 30 cells.[32]

There are only limited data in children. Kline and colleagues performed a phase I study in 16 children who were already receiving either single or dual NRTI therapy (stavudine plus ddI, stavudine alone or stavudine plus lamivudine). A dosage of 30 mg/kg/d of HIV was established. Five children had a decrease of 0.5 log 10 of plasma RNA by week 4.[33]

Avila Figuerroa recently presented an analysis of 21 children between 2 and 8 years of age receiving ddI + D4T and HU (30 mg/kg/d) for 9 months. The mean decline in plasma HIV-RNA was 1.1 log. The incidence of serious infections requiring hospitalisation declined from 3.6 to 1.2 per person-year and furthermore adverse events were negligible.[34] The precise role of HU as a therapeutic option still remains uncertain and in addition there remain concerns regarding side-effects, namely pancreatitis, neoplasms and possible infertility.

Cost-efficacy — the cost of not treating children

Cost-efficacy analyses have mainly concentrated on the overwhelming benefits of introducing an effective programme to reduce mother-to-child transmission. For example, Wilkinson *et al.* have recently calculated that a national programme preventing only 37% of expected paediatric infections will be cost-effective.[35] A recent study from Abidjan showed that the cost of caring for an HIV-infected child for a year was R1 530, 1.7 times more than for an HIV-exposed, uninfected child.[36]

There is a paucity of data on the cost-efficacy of treating HIV-1-infected children with ART. In South African hospitals a large amount is currently spent on palliative care for hospitalised children. The costs to the parents in terms of income loss and transport are unknown, but are likely to be substantial. At Tygerberg Hospital, approximately R1 million

per year has been spent on palliative care for the last 3 years. The average daily cost of medication, food and expendable equipment is approximately R345 (K Muller — personal communication), which is almost sufficient for 1 month of dual NRTI therapy.

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