Clinical trials of antiretroviral drugs: the role of the MRC AIDS Therapeutic Trials Committee (ATTC) and the MRC Clinical Trials Unit (CTU)

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Since the development of the first MRC trial in 1987, the MRC AIDS Therapeutic Trials Committee (ATTC) and MRC Clinical Trials Unit (CTU) have made an important contribution to the clinical trials that have led to the development of effective antiretroviral therapy (ART) regimens, which are widely used in the developed world today. ART has led to major reductions in mortality and morbidity but at considerable cost, both financial and in terms of the adverse effects and impact on quality of life which the complex life-long therapy regimens impose. The first trial of zidovudine (AZT, ZDV) demonstrated a significant reduction in mortality and morbidity in people with acquired immunodeficiency syndrome (AIDS) and advanced AIDS-related complex (ARC), and this increased the pressure on the ATTC to respond to an epidemic of a highly fatal, and until then untreatable, disease affecting young people, for which drugs were becoming available and urgent action was needed if they were to be properly investigated [1]. The increasing number of drugs that have become available have dramatically improved the prognosis of human immunodeficiency virus (HIV) infection in developed countries but without achieving eradication of the virus and cure. However, the challenges to the evaluation of new therapies have increased in parallel, and the need to identify therapeutic regimens that can be used in resource-poor countries has become more urgent, as the prices of drugs have been considerably reduced due to international pressure and ways of funding therapy are being actively pursued through initiatives such as the Global Health Fund.

Developments in antiretroviral therapy

The first class of drugs to be shown to have activity against HIV were the nucleoside analogue reverse transcriptase inhibitors (NRTIs), with the first trial of zidovudine (AZT) showing an improvement in both mortality and morbidity over an average follow-up of

only 16 weeks [1]. This led to great optimism that AZT given earlier in the course of HIV infection would lead to even greater benefits, and a number of trials in the US and Europe were conducted [2–6]. Concorde [6] was a double-blind placebo-controlled trial of immediate *versus* deferred AZT in asymptomatic HIV infection. It was the first trial funded by the MRC and the beginning of a long collaboration with the Agence Nationale de Recherches sur le SIDA in France and the Wellcome Foundation, both of whom have continued to be major players in the therapy of HIV infection.

The key question in Concorde was whether AZT early in asymptomatic HIV infection delayed the onset of AIDS and prolonged life. It was an eventful trial and crucial to its success was the involvement of the HIV community groups in the UK. When a similar trial was stopped early because of a, not unexpected, short-term benefit, Concorde continued but not without some difficult discussions [3]. The final results were important but disappointing to participants, HIV-infected individuals, doctors, the trial team and the Wellcome Foundation as there was no evidence of benefit from the early use of AZT in terms of survival or disease progression over a longer period of follow-up [7]. A systematic overview based on individual patient data of all the trials of AZT, conducted by the HIV Trialists Collaborative Group and co-ordinated by the MRC CTU, confirmed the results of Concorde showing no benefit from early AZT in terms of survival or disease progression [8]. However, there was clear evidence of a short-term delay in the development of AIDS in the first year, consistent with the first, short-term, trial. The loss of benefit over time was explained by the emergence of viral resistance to AZT, not surprisingly to those familiar with the story of tuberculosis treatment [9].

Subsequently, two other NRTIs, didanosine (ddI) and zalcitabine (ddC), became available, although it rapidly became clear that both were associated with the development of peripheral neuropathy and ddI was associated with pancreatitis. The second MRC trial, Alpha, extended the collaboration with the French to include several other European countries and Australia, and demonstrated that lower doses of ddI were no less effective than higher doses but were associated with less toxicity

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[10]. The next step was to explore combination therapies and the collaboration was in place to set up a large trial, Delta, which was a double-blind randomized trial of AZT monotherapy *versus* combination NRTI therapy of AZT plus ddI or ddC in both AZT-naïve and AZT-experienced individuals [11]. There were concerns during the trial that it would be difficult to demonstrate differences between the regimens because many participants stopped trial treatment either because of toxicity or to go on to combination therapy. However the final results clearly demonstrated that the combination regimens prolonged life and delayed disease progression, with a suggestion that ddI was more effective than ddC. These findings were confirmed in the second systematic overview of all combination trials to which Delta was the largest contributor, and which showed a survival benefit for AZT + ddI over AZT + ddC [8].

Surrogate markers

Concorde and Delta not only produced key results on how to use ART but also provided data that demonstrated the difficulties of using emerging highly prognostic laboratory markers as surrogate endpoints in HIV trials. There was considerable optimism that CD4 cell counts and viral load, as measured by plasma HIV RNA, which were both excellent predictors of prognosis, could be used to reduce the duration of follow-up and/or the numbers of participants in clinical trials, and hence speed up the drug development process. To be a valid surrogate, a marker must be a good predictor of clinical outcome, the association between the marker and outcome should not vary between treatments and the treatment should not have an effect on the outcome not captured by the marker [12]. CD4 count and viral load, as measured by HIV RNA, have been shown to be independent predictors of death and disease progression in many cohort studies and trials. In Concorde, there was a clear and persistent difference between the groups in CD4 count but this did not translate into a difference in clinical outcome [6]. In Delta there were again differences in CD4 count but this time they were consistent with the clinical outcome [11]. The hopes that HIV RNA would be a much better surrogate than CD4 were dispelled by the elegant demonstration from the Delta data that short-term viral load changes were not adequate surrogates [13]. However, the increasing difficulties in undertaking clinical trials with clinical endpoints, because of the time scale and the option of changing to a new ART regimen in the event of virological and immunological deterioration before clinical disease progression, have led to the use of viral and immunological endpoints but with a better understanding of the problems of their interpretation. Delta also demonstrated that the clinical outcome

of AIDS was itself a poor surrogate for survival as the wide variety of diagnoses including opportunistic infections and tumours have very different prognosis. The difficulties in undertaking trials with clinical outcomes have led to suggestions that information on the clinical benefits of ART regimens can best be obtained from observational studies. While these can undoubtedly provide useful information on major issues, such as the marked improvement in survival from the introduction of triple combination regimens, Delta clearly demonstrated the risks of attempting to make comparisons of different regimens using observational data. The results of a randomized comparison between AZT + ddI and AZT + ddC in patients who had already had AZT were compared with the results of a similar comparison in participants who, having been randomized to AZT monotherapy, had switched, on an open non-randomized basis, to one of the two combinations [14]. Whereas in the randomized comparison, AZT + ddI was more effective, in the non-randomized comparison AZT + ddC appeared better, and the difference remained even after adjusting for potential differences between the two groups at baseline.

Further developments in ART

The development of two new classes of drugs, namely protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) led to major improvements in the outcome of therapy based on combinations of three and four drugs. The next key question was how to use the increasing number of drugs from the three classes most effectively, as it rapidly became apparent that the benefits were time-limited in some, if not all, patients.

The next major international trial, INITIO, which the MRC team played a leading role in developing through an EU Concerted Action, was set up to explore the implications of initial therapy for long-term outcome, namely, whether it is better to start with a combination of three drugs consisting of two NRTIs plus a PI, or two NRTIs plus an NNRTI, or of four drugs from all three classes [15]. The complexity of the trial was increased by its extension to several more countries and five pharmaceutical companies, and the difficulties of finalizing plans for and funding such a complex trial led to major delays in its initiation. The trial is now fully recruited and follow-up of the 913 participants is ongoing.

In parallel with INITIO, a small exploratory trial, PROCOM, was developed in the UK to investigate an induction/maintenance phase approach, following the tuberculosis model. The initial design compared a regimen with a four-drug induction phase and two-drug maintenance phase with a regimen of four drugs throughout. Delays in securing the funding meant that

other groups rapidly demonstrated that a two-drug maintenance phase was probably not adequate and the design was amended to compare a four-drug induction/three-drug maintenance phase regimen with the, by then, standard three-drug regimen in the FORTE trial. Recruitment is now complete and follow-up ongoing. One of the potential advantages of the revised design is that the PI is only given in the induction phase of 6 months, which may reduce the risk of lipodystrophy and metabolic toxicity (associated particularly with prolonged PI therapy).

Treatment failure

The limited long-term success of current ART regimens raises a number of issues around treatment failure. The ATTC developed a series of studies to rationalize the management of therapeutic failure by assessing the role of viral resistance assays and therapeutic drug monitoring, and by exploring different therapeutic strategies. The ERA trial (Evaluation of Resistance Assays), which is exploring the role of assays of viral resistance, has completed recruitment into the part of the trial that is comparing different types of assays. Unfortunately recruitment was insufficient into the part of the trial that compared management with and without assays, but the data from this part of the trial will be combined with a similar trial in children conducted through the Paediatric European Network for the Treatment of AIDS (PENTA) which is close to completing recruitment. Funding was not secured for a trial to assess the role of therapeutic drug monitoring (OPIUM), developed by the Department of Pharmacology in Liverpool with the CTU and strongly supported by the ATTC. This highlights the difficulties the ATTC has had in recent years in securing funding in a timely way for the novel trials it has developed.

A trial to explore therapeutic strategies in therapeutic failure, OPTIMA, is the first trial to be funded in a trilateral collaboration between the MRC in the UK, the Department of Veterans Affairs in the US and the Canadian Institute of Health Research in Canada. This is exploring two strategic approaches: (i) the use of MEGA ART (with five or more drugs) and (ii) an antiretroviral drug-free period (with the aim of allowing 'wild-type' sensitive strains to re-emerge) in a factorial design in people who have experienced therapeutic failure to all three main classes of antiretroviral drugs. Recruitment is currently ongoing but at a slower rate than anticipated in all three countries.

Developing countries

To date, the ART trials conducted by the MRC CTU under the framework of the ATTC have been per-

formed in the UK in collaboration with other European countries, Australia and North America. The countries most severely affected by the HIV epidemic, particularly those in sub-Saharan Africa, have not had the resources to provide ART although it is now becoming increasingly available to the rich in a far from optimum and often intermittent manner. In 1998 an informed consultation on antiretroviral therapy in Uganda took place in Liverpool hosted by the School of Tropical Medicine with colleagues from Uganda to explore ways of making ART available to resource-poor populations without compromising their effectiveness. The outcome was the DART trial, exploring ways of reducing the amount of drugs required in order to reduce the costs of ART regimens, which eventually, after several major modifications in response to comments and to changing circumstances, was approved by the MRC in 2000, provided the team could obtain supplies of antiretroviral drugs for the trial and make appropriate arrangements for the participants' care at the end of the trial. In 2001 the trial was modified to add an evaluation of different approaches to monitoring ART, in a factorial design, as the costs of regular CD4 and HIV RNA tests are as great a barrier to the extension of ART to resource-poor countries as the cost of the drugs. The Rockefeller Foundation agreed to support the trial in a second centre in Uganda and in Zimbabwe and three pharmaceutical companies agreed to provide drug supplies for first-line therapy (GlaxoSmithKline, Gilead Sciences and Boehringer-Ingelheim) and negotiations are ongoing for supplies of second-line treatment. Funding from the UK Department for International Development and from private individuals has been secured, as well as support from the World Health Organization for the approach. The DART trial, which started in January 2003, highlights the challenges and difficulties in extending ART trials into resource-poor countries. The final design will explore the role of pulsed therapy with the aim of reducing drug costs and toxicity, potentially improving compliance without impairing effectiveness, and, in a factorial design, different approaches to monitoring for both efficacy and toxicity.

Unanswered questions

In spite of the numerous trials throughout the world undertaken by both the industry and academic groups, key questions about the management of HIV infection remain unanswered, although the MRC has a number of ongoing trials that are addressing some of them. We still do not know the optimum time to start therapy, as demonstrated by the changes in international and national guidelines over the years. There have been numerous discussions both within the MRC group and

with international collaborators that have acknowledged the importance of the question but also the difficulty in answering it. A planned trial developed between the CTU and Imperial College will explore the role of therapy at the time of primary HIV infection in Russia, South Africa and the UK, although the results would apply to a limited proportion of the HIV-infected population. INITIO and FORTE are addressing the question of what to start therapy with and a PENTA trial in collaboration with the Paediatric AIDS Clinical Trials Group in the US (PENPACT 1) is exploring different strategies for changing therapy as well. What to change to or how to decide are being addressed by ERA, PERA and OPTIMA. The risks of toxicity with ART vary between classes and between drugs within classes. The long-term nature of ART increases the risks of adverse reactions as does the use of combination therapy with drugs that often have complex interactions. Strategies to reduce toxicity are being explored in DART and a small pilot study in the UK of treatment interruptions (TILT).

The involvement of clinical pharmacologists, virologists and immunologists has been and remains crucial to the MRC's programme of trials in HIV infection. The challenges now are perhaps greater as with effective treatments it becomes even more difficult to assess new therapies, not least because of a reluctance from the HIV infected community to take part in trials when standard therapy is highly effective. The emphasis, as it was in tuberculosis as effective therapies were developed, is likely to shift increasingly to the resourcepoor countries where the burden of the epidemic is greatest.

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