MRC policy on antiretroviral therapy (ART) for people infected with HIV and involved in research in developing countries -
General guidance notes for consideration

(developed in the light of a meeting at MRC Head Office, 17 July 2002)

Contents

1. Background

The increasing use of ART in the developing world has led to special ethical challenges for researchers. The MRC identified the need to consider what advice should be given to Council-supported researchers on issues relating to the use of ART for AIDS in research in developing countries, taking into account evolving views on standards of care and ethical values. This advice was relevant both to research on AIDS and to the management of patients in developing countries involved in research on other topics, who developed AIDS during the course of the research. Discussion had been catalysed by Government agendas; MRC researchers had been approached by and had worked closely with the Governments in both The Gambia and Uganda.

A meeting was therefore held in July 2002 to develop some preliminary views – these are set out below and are being circulated for wider consultation. Membership of the group is listed in the table below. Participants were unaware of any policy specifically addressing this issue that had as yet been adopted by other research organisations or donor agencies.

Participants - including members of MRC's ad-hoc panel on ethics of research in developing countries	
Mr Nick Winterton (Chairman)	MRC Head Office
Ms Gillian Dada, Dr David Lalloo	Liverpool School of Tropical Medicine
Dr John Porter	London School of Hygiene and Tropical Diseases
Dr Alastair Robb	Department for International Development
Mrs Shahwar Sadeque, Dr Tumani Corrah	MRC - The Gambia
Dr Di Gibb	MRC Clinical Trials Unit
Dr Charlie Gilks	Imperial College
Dr Phil Nieburg, Dr Marguerite Pappaioanou	Centre for Disease Control, Atlanta, USA
Dr Anatoli Kamali Dr Jimmy Whitworth	MRC - Uganda
Dr Maarten Schim	MRC Tropical Epidemiology Group, LSH

2. Issues requiring consideration

a. General

- It was essential for researchers to establish partnerships with the political and social stakeholders in the country where they were working. Any activities should be set within the local framework; a link to health promotion and education policy would be valuable. It was necessary to recognise the risk of research organisations inappropriately forcing a government agenda, eg introducing ART in research studies could lead to governments diverting resources from other equally important programmes.

- There was little consistency in how the ART issue was being handled between research groups currently working in developing countries, or between governments, and it would be valuable to have an ongoing dialogue between researchers in different locations as well as between researchers and local governments.

- There should be clear, ethical decision-making processes. The decision making-process, rather than the decision, was key. Standardised guidelines would not be very useful, so emphasis should be placed on agreeing the process eg taking account of community views and ensuring all potential partners were consulted and their views taken into account.

- Each situation was unique and needed to be recognised as such. The global context was changing rapidly and any policy should be flexible enough to allow for developments.

- The level of obligation to provide care in a research context needed to be carefully considered. For example, provision of ART to HIV-positive people participating in existing cohort studies might be appropriate, but whether this should be extended to new HIV cases identified while recruiting to preventive studies (vaccines, microbicides), or incident cases discovered in the context of other trials (eg malaria) needed to be established before starting. If ART were to be provided, the importance of sustainability would have to be considered, and an acceptable way of handling this would need to be negotiated with all relevant parties. Many trials (not directly researching ART) would not have the capacity to deliver clinical care for AIDS (eg prevention trials - vaccines, behavioural interventions, microbicides).

- It was thought appropriate at present to continue to undertake non-interventional studies provided they were relevant to the evolving health systems within a particular country.

- There was a need to look broadly at the social and public health picture in a given country. In particular, it was important to recognise that the "social contract" between researchers and the individuals and communities who participated in the research would grow over time when there was a prolonged commitment to a disease or population in a treatment area.

- It was important to be aware of the dangers of making an exceptional case for ART when other healthcare investments might benefit individuals and communities more. However, the reality was that, currently, it might be more practical to initiate changes in HIV treatment policy than in other areas. It also needed to be borne in mind that there are major cost differences between the provision of ART and many other public health initiatives.

- Capacity building in research and treatment issues, as well as ethical review, was essential to assist sustainability. NGOs could usefully be involved in discussing proposals with local people as they were trusted and had "grass roots knowledge".

- The introduction of ART in developing countries would open up new research areas, including for example the unique opportunity to study the effectiveness of ART in HIV-2 disease in The Gambia.

b. Particular considerations

i) Trials

- Where trials of ART were being planned, a national HIV prevention policy should be in place before trials started. Co-ordination of ART trials/studies/programmes was highly desirable. There had been no large trials of ART in resource-poor environments. A knowledge base was needed, especially to provide the basis for guidance on monitoring, delivery and appropriate regimens, including structured interruptions to therapy.

- Access to trial recruitment needed to be equitable and clearly defined in advance of the trial beginning. There were questions about breadth of responsibility, for example to immediate and extended family (recognising the risk of pill-sharing if other members of the family are sick).

- Care needed to be taken over perception of inducement. Enrolment and termination criteria need to be clearly stated and approved before a trial started. (In the early days of ART becoming available in the USA, access was only available through entering trials).

- In some cases it would not be possible to resolve end of trial supply at the beginning of ART studies. If so, this lack of resolution would need to be recognised by all stakeholders before a study began. Fully informed consent would be especially important here: those entering the trial should be aware that they might not continue to receive ART once the trial ended.

- Engagement of the Global Fund at an early stage might prove valuable. For example, if the Fund were able to commit to provide funds to purchase effective treatment (should it prove effective) at an early stage, the end of trial problem would be resolved.

- Monitoring and revisiting ethical aspects of studies would be needed on a regular basis, along with a continuing dialogue with participants.

- Participants should be given the option to receive the results of their tests. (It would not be ethical to insist that they receive them.) Voluntary counselling and testing should always be offered. Participants should be informed (as part of the process) that if they would like to know their HIV status in the future (for example if treatment became readily available) they could be re-tested at any time.

ii) Pregnancy/children

- As a minimum, Nevirapine should be offered to HIV-positive pregnant women to reduce the risk of mother-to-child transmission (MTCT) However, the case for continuing treatment of mothers was being debated; some had raised doubts about the practice of treating mothers for 1-2 weeks only with the intention to prevent infection in the child.
- Consideration needed to be given to whether fathers, siblings and extended families should be offered treatment also.
- The risks to the child associated with exposure to triple therapy via breastmilk were not known.

3. Principles to be taken into account

Sustainability
Every effort should be made to ensure that if therapy were provided as part of a research project or clinical trial, it was done in a sustainable way, for example using the national health care system so that there would be opportunities for capacity-building and training. Long-term responsibility for care should be agreed with Government.

Appropriateness
Any research on ART supported by MRC should be developed with all stakeholders, including ethics committees, and should be agreed to be appropriate to the population.

Partnership
A full, open and ongoing dialogue with all stakeholders was essential. All partners should agree about their relative contributions and responsibilities.

Flexibility
It was impossible to have a "one size fits all" approach – situations varied considerably between countries and between individual studies in one country. As the global environment is evolving rapidly, flexibility of approach and regular review of approaches are extremely important.

4. Conclusions and guidance

1. The Nuffield Council on Bioethics report "*The ethics of research related to healthcare in developing countries*" provides a good basis for advice.

2. An MRC framework should address the following particularly important issues:

- All stakeholders (governments, NGOs, community, donors) should be fully involved in developing any new research programme/trial and the expectations and responsibilities of all partners should be agreed at that time. This should include end of trial issues and continuity of treatment.

- Attention to process and transparency of reaching decisions in each case was key.

- Existing research programmes should be re-examined on a regular basis from an ethical point of view; in so doing, it was important to be aware of emerging findings from trials, new guidelines, and the changing global situation. Flexibility to respond to rapid changes was essential.

- The nature of the research and the nature of the social contract between researchers and the local community should be taken into account in determining the appropriate level of commitment for the research funder. Thus participants in a cohort study on HIV/AIDS, extending over many years, might reasonably expect greater priority to be given to treatment of AIDS identified in the course of the research than participants in a short study on some completely different topic.

- When treating patients within a research programme (where treatment was not directly research-related) the starting point should be that the best locally available treatment should be used, as discussed and agreed by all stakeholders before recruitment began. Thus, the management of patients with HIV/AIDS identified in the course of research on other conditions would not automatically involve ART if that were not part of the best standard of care available locally. However, if ART were not to be given, the basis for this decision would need to be made clear, and regular monitoring in the light of changes in the national and global situation would be particularly important.

- If individuals chose not to receive test results (whatever the reason) ongoing testing and counselling service might minimise the problems – both to the individual and potentially to sexual partners; encouraging people to be retested should be done if the situation changed (eg if ART became more readily available).

- Capacity building – both in research and ethical review - would be expected to be an integral part of the programmes (and, as a stakeholder, Council should be contributing to this). Wherever possible, treatment should be delivered within the local context, building on it as required.

- Good co-ordination between funders, researchers, and national programmes was essential and should be fostered.

- Local situations varied considerably – between and within countries. The particular needs of the community in question, as well as the best standard of care available locally, should be considered and taken into account.

Annex: Current policy and practice in Uganda and The Gambia

Uganda

- the Government's National Health Policy of 1999 had not included the use of ART.
- the 2001/2002 Health Policy Statement recommended expansion of access to ART to all regional referral hospitals; provision of Nevirapine to HIV positive women was Government policy.
- although the cost of anti-retroviral drugs had been reduced considerably, funding of ART through the health sector remained a major constraint - less that 1% of those who met WHO criteria to begin ART were receiving it.
- there was increasing pressure from the Ugandan population for government and non-governmental service providers to make ART available and affordable, but substantial support for drugs and delivery (and associated services) was still required
- MRC programme on AIDS in Uganda was in a unique position to assist the Government in understanding the complex issues related to the provision of ART in rural areas - those who belonged to MRC cohorts had access to treatment for opportunistic infections

The Gambia and neighbouring countries

- Neither the MRC Unit in The Gambia nor the Gambian government routinely provided anti-retrovirals to treat AIDS at present; the view locally was that it would be increasingly difficult for institutions like MRC to study HIV in Africa without offering some form of ART.
- UNAIDS had assessed Gambia recently and agreed that The Gambia was ready to ntroduce ART, gradually. The Gambian government had recently announced its intention to introduce ART by the end of 2002, using part of a US$18 million loan from the HIV/AIDS rapid response programme from the World Bank. An application for additional funds had been made to the Global Fund.
- The Government had approached MRC-Gambia to ask for technical and policy advice about the use of ART and to assist the Royal Victoria Hospital in building up an AIDS treatment centre. Current practice (MRC) for HIV positive cohorts was the offer of treatment of opportunistic infections and Nevirapine (or AZT) to HIV positive pregnant women. There were research opportunities that would arise with starting ART in Gambia
- In Senegal, there was limited access to ART (576 patients; drug costs were met by research groups, NGOs and the Government). In Cote d'Ivoire, the Government had also begun introducing ART (funded by research groups and UNAIDS)

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