was not an efficacy study, but rather a pharmacokinetics and safety study of zidovudine (AZT) and lamivudine (3TC) for 14 days in 20 mothers in late pregnancy, and in their neonates for a week. The lower rate of mother-to-infant transmission in a study of 20 women in comparison with the vertical transmission rate in a retrospective cohort study cannot be used as argument for the routine use of antiretroviral therapy in HIV-positive pregnant women.

The World Health Organisation and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have recognised that the ACTG 076 regimen is not applicable in those parts of the world where most mother-to-infant transmissions occur, and have called for placebo-controlled trials as the best option for obtaining rapid and scientifically valid results. These trials should include antiretroviral agents given for short durations in late pregnancy, in labour, and to neonates for 1 or 2 days; oral therapy in labour only; and combinations of different antiretroviral drugs. An ongoing trial, PETRA (perinatal transmission), supported by UNAIDS but designed in conjunction with African scientists, is currently in progress in a number of African centres, including Durban and Johannesburg. The aim of this placebo-controlled trial is to evaluate whether shorter regimens, which can realistically be implemented in test countries, are better than no treatment at all. Subanalysis of the ACTG 076 study has shown that less than 12-week regimens are as effective as those of more than 12 weeks. This, however, does not give any indication of the efficacy of a 2 - 3-week regimen.

Another debatable issue not included in the article by Matchaba and Chapanduka but that needs to be mentioned is the ethical considerations of placebo-controlled trials in developing countries.[4] Critics maintain that nearly all such trials violate accepted international ethical standards because participating control groups are only offered placebos, as opposed to being given antiretroviral therapy that is known to be effective.

The debate has led to comparisons with the Tuskegee study, in which effective treatment was withheld from some 400 African Americans without their knowledge in order to establish the natural history of syphilis. This study has been described as a 'metaphor for racism in medicine.' Comparison with vertical transmission HIV studies in pregnancy, however, is unfair. Trials in Africa are frequently conducted by African scientists who have contributed significantly to the design of the studies and who are concerned for the welfare of their particular communities. In addition, local government authorities are informed of all such studies and ethical permission, usually from university ethical committees, will have been obtained. Subjects are informed of the existence of a placebo arm and give written consent. They are not intentionally deceived or deprived of treatments that are affordable, readily available and known to be effective, as was the case in the Tuskegee experiment. Placebo-controlled antiretroviral trials in developing countries will continue until a short applicable regimen is found to be effective in reducing mother-to-infant transmission.

The level of information provided to participant women and consent procedures are two further criticisms of these studies. Certainly in the trials conducted in South Africa, women were fully informed regarding the benefits and disadvantages involved, including the placebo component.

Criticism of HIV trials in developing countries has raised the question of whether these studies could be undertaken in the First World. The question of double standards, however, lies not in the way the trials are being conducted, but in unequal access to medicines in different countries.

It is our conclusion that before demands are made for the immediate use of antiretrovirals in pregnancy, an interaction is urgently needed between researchers, health authorities, pharmaceutical companies and global institutional programmes such as UNAIDS. This interaction would help prepare the infrastructure for the application of a short and cost-effective antiretroviral regimen when proven effective in developing countries.

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Preventing perinatal HIV transmission — now is the time to act!

We thank Moodley *et al.* for their response to our paper.[1] We are pleased to note that they concur that the major intervention in the prevention of perinatal HIV transmission is AZT use. In our paper we stated the need for the development of local protocols, outlined the reasons for this and certainly did not recommend that protocol ACTG 076[2] be used here. We believe that all the 'realities of the situation in respect of health care in developing countries' referred to by Moodley *et al.* in their response were sufficiently addressed in our original paper. The breast-feeding issue was also addressed at length.

They seem, however, to have missed two important issues raised by ourselves. Instead they focused on the issue of placebo-controlled trials, which we elected not to raise in our editorial[1] because of the volatile nature of the topic. We did not want to distract from the main thrust of our editorial, namely that 'now is the right time to act' in dealing with perinatal HIV transmission using zidovudine (AZT) as part of the national maternal and child health care (MCHC) programme. We will, however, address the issue of placebo trials in perinatal HIV transmission later in this article.

The first point they overlooked was the length of time it is taking to get protocols or interim results from the local studies being done. During this time perinatal transmission of HIV continues unabated.

The ACTG 076 study commenced in 1993 in the USA and France, where the first scheduled interim analysis was carried out on 364 mother/child pairs. On 17 February 1994, on the basis of an interim analysis, the independent Data and Safety Monitoring Board overseeing ACTG 076 determined that there was significant efficacy (67.5% relative reduction in transmission), and recommended that enrolment into the study be terminated and all women under study be offered AZT. The speed with which the study was performed in countries with an HIV-positive antenatal seroprevalence rate of only 0.1% is to be commended. Accordingly, in 1997 there was a reduction in paediatric AIDS cases in the USA for the first time. The reverse appears to be the case in Third-World communities where the rate of HIV seropositivity at antenatal clinics is bordering on 30%. We wonder how many readers are aware of the PETRA trial sponsored by the Joint United Nations Programme on HIV/AIDS (UNAIDS), the protocols used, etc., and that this trial was commissioned in 1995.

Three years later we are still waiting for the results of the first interim analysis to be published. The idealism of waiting for the scientifically perfect paper when interim results could possibly confirm a significant clinical breakthrough cannot be condoned in the face of an issue of such public importance.

The second issue Moodley *et al.* appear to have missed is our point that offering no treatment as an alternative, for whatever reason, is 'penny wise and pound foolish'. In the long run more money is spent dealing with paediatric AIDS. The assertion that there are other priorities in developing countries which have led to continued shrinkage of health care budgets further supports our belief that these countries are pursuing self-defeatist policies by not preventing HIV perinatal transmission. In South Africa we have witnessed the effects of a shrinking health budget. Sadly this is largely due to central government maintaining a tight monetary and fiscal policy, as dictated by the policy of growth, employment and reconstruction (GEAR). The idea underlying the implementation of GEAR was that bodies such as the International Monetary Fund, the World Bank and other private foreign investors would invest in South Africa, creating jobs and economic growth. This is not the forum to debate the merits or demerits of GEAR, but we warn that similar programmes implemented elsewhere in developing countries have resulted in a shameful deterioration of health care. If a foreign army were to invade this country, possibly incapacitating 30% of its economically active population, would the government not respond with all the military and economic might at its disposal? The fact that this invasion is being accomplished by a virus is overlooked when it comes to health budget allocations. Cost, as we stated previously, is a relative concept.

We will now address the issue that Moodley *et al.* spent considerable time on, namely placebo-controlled trials in developing countries, including South Africa. Our position is clear: they are both scientifically and morally unjustifiable.

When one considers the results of ACTG 076, it does not make scientific sense to substitute the currently accepted 'gold standard' (ACTG 076) with a no-treatment placebo arm. We appreciate the use of trials with shorter AZT/lamivudine (3TC) dosage schedules. These make sense in terms of cost, the fact that the major transmission of HIV is peripartum, and because there is less chance of inducing viral resistance this way. However, at research level the control must be ACTG 076. In the end each country must decide what percentage decrease in vertical transmission they are willing to settle for in terms both of cost and perinatal mortality rate. To suggest that a no-treatment/placebo arm at research level is still justifiable on the grounds that most of the patients concerned would not be on treatment anyway, is to miss the point that we are at pains to make, namely that the no-treatment option will cost more later. This is besides the moral implications. The fact that these trials are being conducted by 'African scientists' does not give them the moral or scientific high ground. These 'African scientists' have, through no fault of their own, failed to influence their governments' expenditure on health and research. If truth be told, Africans and Asians could have done more to prevent the spread of HIV, which has been met with denial, procrastination and bungling. From a public health point of view this has been a disaster. Will we again miss the chance to act decisively when it comes to perinatal transmission? For African scientists to try to politicise criticism of placebo trials as intervention from the West is wrong. Rather, they must convince their governments to spend more money on combating HIV, and less on defence.

At a recent conference on 'Global strategies for the prevention of HIV transmission from mothers to infants' (3 - 6 September 1997, Washington, DC, USA), Dr Gayle from the Centers for Disease Control commented on the issue of placebo trials: 'Acceptance of this tragedy as a reality that cannot be changed is not acceptable morally, not realistic practically and not defensible intellectually.'

We concur.

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