RANDOMISED PLACEBO-CONTROLLED TRIALS AND HIV-INFECTED PREGNANT WOMEN IN DEVELOPING COUNTRIES. ETHICAL IMPERIALISM OR UNETHICAL EXPLOITATION?

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ABSTRACT

The maternal-fetal HIV transmission trials, conducted in developing countries in the 1990s, undoubtedly generated one of the most intense, high profile controversies in international research ethics. They sparked off a prolonged acrimonious and public debate and deeply divided the scientific community. They also provided an impetus for the revision of the Declaration of Helsinki – the most widely known guideline for international research. In this paper, I provide a brief summary of the context, outline the arguments for and against the controversial use of placebo controls, and focus on particular areas that I believe merit further discussion or clarification. On balance, I argue that the researchers failed in their duties to protect the best interests of their research subjects, and to promote distributive justice. I discuss the difficulties of obtaining valid consent in this research context, and argue that it is unethical to inform women of their HIV status without at least offering them prophylactic treatment for their unborn children. A global view of justice, which endorses international equity, cannot be squared with international research guidelines that allow ‘local conditions’ to define the scope of duty to the control group. Finally, I suggest that the heated debate reflects a tension, if not an outright war, between two conflicting meta-ethical systems, or incommensurable paradigms, that underpin scientific research involving human subjects.
INTRODUCTION

UNAIDS reported 34.3 million people living with HIV/AIDS at the end of 1999, with 5.4 million newly infected in that year alone.\(^1\) The total number of deaths since the beginning of the epidemic until this time totals 18.8 million, with 3.8 million children under 15. Those living in Sub-Saharan Africa account for around two thirds of those infected with the virus. The majority of these infections are acquired from heterosexual or mother-to-child (vertical) transmission. Around 1600 babies, infected via vertical transmission, are born daily. An estimated 2.4 million HIV-infected women, 80% residing in Africa, give birth annually. UNAIDS estimated that 1.3 million children are infected with the virus (90% in Africa). The AIDS epidemic has created around 13.2 million orphans (defined as children who have lost their mother or both parents to AIDS when they were under 15). These grim facts spell out an urgent need to contain the spread of this devastating disease. The tragic irony is that the countries with the highest prevalence are those with the fewest resources to combat the disease.

The gross inequity in resources, particularly in health care provision, that exists today between the affluent and the poor countries is brought into sharp focus by the contrasting fates of women infected with HIV. Women living in resource-rich countries, with access to appropriate medical care and to triple combination anti-retroviral therapy (HAART), can expect to live for several years with a reasonable quality of life. In pregnancy, they can be confident that their offspring will evade infection (see below).\(^2\) This destiny contrasts with that of the majority of HIV-infected women residing in resource-poor countries: they cannot benefit from modern treatments and interventions, and are faced with the prospect of a fatal progressive disease. Their chances of infecting their offspring are one in three to four, and the prognosis for their infected children is bleak.

In 1994, the Paediatric AIDS Clinical Trial Group (PACTG) performed a large randomised trial involving non-breastfeeding women from developed countries (France and the USA). This showed unequivocally that a regime – the 076 regime – of the anti-retroviral drug zidovudine (AZT) reduced the vertical

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transmission of HIV from 25% to 8% — i.e. by two thirds. Following this, the majority of developed countries adopted the regime for HIV-infected pregnant women. Further refinements to anti-retroviral therapy, and planned caesarian section in selected cases, have produced even better outcomes, such that vertical transmission can be reduced to even less than 2%. In other words, vertically acquired HIV infection is a near-preventable disease. The 076 regime is, however, costly and cumbersome to use. It comprises a three part prophylactic protocol that involves giving oral AZT to HIV-infected pregnant women several weeks before birth, intravenous AZT during labour and delivery, and AZT syrup daily to the infants for six weeks after birth. This is clearly impractical to administer in a setting where women may not present for antenatal care until late in pregnancy, or even in labour — if at all. In developing countries, birth may not take place in a medical setting, or be in the presence of trained medical staff. Even if this takes place, the technology required for intravenous infusion is often absent. In other words, the delivery of this regime requires an infrastructure within which high quality antenatal care can be provided. This prerequisite does not exist in many areas with the highest prevalence. In addition, giving the treatment selectively to HIV-positive women entails a resource-intensive HIV testing programme. And finally, the 076 trial was performed in a non-breastfeeding population. In most countries with a high prevalence, breast-feeding is almost universal, and there is a correspondingly higher rate of transmission than in non-

breastfeeding populations (23–35% versus 15–25%). It was shown in 1992 that avoidance of breast-feeding decreased transmission by around 14%.10 Further studies have shown even higher transmission of the virus through breast milk (16%), the major part occurring during the first three months.11

There is therefore clearly a strong case for finding a shorter, simpler, cheaper and safe regimen suitable for breast-feeding women in resource-poor countries. In addition, non-drug treatments could be of benefit to all women, and would not require voluntary named testing – for example vitamin supplementation.

Following the PACTG 076 trial, the World Health Organisation and UNAIDS took up the challenge, and coordinated an international research effort for developing cheaper interventions. The majority of these were placebo-controlled randomised controlled trials (PCTs) in developing countries.12, 13

The ethical aspects of these trials led to an explosion of articles and correspondence in the scientific and bioethical literature, and even the lay press.

In 1997, Lurie and Wolf identified 15 placebo-controlled trials in developing countries, nine of which were sponsored by the US government (via the CDC and NIH).14 They claimed that these seriously disturbed equipoise and deprived many infants of life-saving prophylaxis. They also claimed that the trials contravened existing international guidelines for research, notably those of the Declaration of Helsinki,15 and the Council for International Organisations of Medical Sciences (CIOMS).16 They argued that the scientific rationale for the use of a placebo arm was flawed, and that equivalency trials, using the

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best-known regime compared against another, would provide even more useful results than the placebo-controlled trials, and, more importantly, would avoid unnecessary infant deaths. Marcia Angell, editor of the *New England Journal of Medicine*, was even more vehement in her criticism, and compared some of the trials to the infamous Tuskegee syphilis study of poor African Americans in the USA.\(^\text{17}\)

**ARGUMENTS IN FAVOUR OF PLACEBO-CONTROLLED RCT’S**

*Methodology*

The frequentist principles underpinning research methodology form the vanguard of arguments supporting the use of PCT’s. The widespread consensus in the scientific and clinical community is that the prospective randomised controlled trial (RCT) provides the most reliable method for making valid causal inferences about the effects of treatments.\(^\text{18}\) The RCT is therefore viewed as the ‘gold standard’ for research into the safety and efficacy of a treatment. The use of a placebo is not a necessary or specific feature of the RCT, but it is required for answering the research question ‘Is this treatment better than nothing?’ An alternative question might be ‘Is this treatment as good as, or nearly as good as, the accepted effective treatment?’ The latter question would call for an equivalency trial (preferably as a double blind trial to eliminate bias), as recommended by Lurie and Wolfe.

The proponents of the PCT’s argue that since the 076 regime cannot be implemented in developing countries, the relevant research question is whether another regime, appropriate to the needs and resources of the host country, is better than nothing. Only a placebo-controlled trial can properly answer this question. They maintain that equivalency trials (as suggested by Lurie and Wolf) are less reliable. For example, Varmus and Satcher are of the view that randomised controlled trials (RCT’s) provide the only method for achieving sufficient scientific rigour, and that only placebo-controlled studies can provide ‘definitive answers to questions about the safety and value of an intervention’ in a


resource-poor setting. Resnik emphasises the fact that the PACTG trial was with a very different population. Women in developing countries are often malnourished, anaemic, and harbouring other infections aside from HIV.

PCT's are also viewed as the most efficient in terms of time and resources. This leads to the utilitarian argument that if an effective, affordable and practical treatment is found, it can be made available to pregnant women in poor countries more quickly, and with fewer lives lost.

Local context

The 'local context argument' pervades all the others, including, as we have seen, the choice of methodology. There are a number of other pragmatic, or utilitarian, justifications for the PCT's that refer to 'local context'. PCT proponents argue that research subjects, in this case pregnant women in poor countries, are not being deprived of any benefit, as they would not receive any anti-retroviral treatment in their country. Even though the women in the control group cannot benefit from the trials, the future benefit to those living in their country outweighs this deprivation of benefit. In addition, the women in the treated group receive treatment that they wouldn’t otherwise.

The 076 regime (accepted treatment), even in a research context, may be exceedingly difficult to implement in some areas, as discussed earlier. In addition, the cost of $800 per person (the cost of the AZT 076 regime), in a country that may spend less than $10 per capita per year (as do the majority of Sub-Saharan Africa countries), is prohibitive. If the alternative, simplified regime were shown to be less effective, however, proponents of the PCT’s argue that governments would find it politically difficult to implement an inferior regime. They also argue that pharmaceutical companies may not sponsor non-placebo controlled trials. And if the simpler regime is not implemented, resources have been wasted, and research subjects put through unnecessary procedures and inconvenience. Likewise, if the 076 treatment, owing to cost and complexity, will not be used in the country where the study is being conducted, is it ethical to use it at all? The proponents of the PCT’s argue that to use as a control a regime that can never be

19 H. Varmus and D. Satcher, op. cit. note 12.
implemented in the host country is tantamount to ‘ethical imperialism’.\textsuperscript{22} It also contravenes an ethical principle of distributive justice whereby the research participants can benefit post-trial if an intervention proves effective.\textsuperscript{23, 24}

Another variant of the local context argument relies on the uncontroversial fact that the infrastructure required to deliver AZT, even with the Bangkok regime (see below), is beyond the reach of resource-poor developing countries. As discussed above, the implementation strategy requires an HIV testing and counselling programme, and considerably higher standards of antenatal care than is generally available in these countries.

Some authors argue that countries in the greatest need will be deprived of the benefit arising from the research findings – affordable and feasible prophylaxis – if research criteria are too stringent. Wilkinson, Karim and Coovadia take the view that abandonment of placebo controls may prohibit studies into the use of non-drug therapies for the prevention of vertical transmission of HIV. They argue that these would be cheap and easy to implement widely, and of therapeutic value even if they only had a ‘modest effect’ on transmission. ‘Widespread application of an intervention with a relatively low risk reduction is of greater public health benefit than the limited application of a highly effective intervention’.\textsuperscript{25}

A widely cited placebo-controlled trial in Thailand, known as the Bangkok trial, used a shortened, simplified regime of oral AZT, and still reduced vertical transmission by 50\% – at a cost of $50 per mother and child treated.\textsuperscript{26} An extension of the local context argument is the observation that both the PACTG 076 trial and the widely cited Bangkok trial involved populations of non-breastfeeding women. These regimes may be of little value in countries where breastfeeding is the norm, and alternatives to breast milk are costly, may entail stigma, and a greatly increased

\textsuperscript{24} T.A. Brennan. Proposed revisions to the Declaration of Helsinki: will they weaken the ethical principles underlying human research? \textit{Bulletin of Medical Ethics} 1999; 150: 24–28.
\textsuperscript{25} D. Wilkinson, S.S.A. Karim and H.M. Coovadia. op. cit. note 22.
risk of infant infections, aside from HIV. This problem presents a serious stumbling block to the critics of the PCT’s, particularly of those studies carried out with breast-feeding women.

COUNTERARGUMENTS TO THE USE OF PCT’S

Methodology

With regard to the scientific methodology, the arguments are complex, and will not be discussed in great detail. Lurie and Wolfe refute the notion that significantly greater numbers are needed for an equivalency trial, or that the information gained is of lesser value. Information can also be obtained about background transmission without a placebo-arm. An observational study using anonymised sampling methods and ‘untreated’ controls is possible, although not as methodologically rigorous. Regarding population idiosyncrasies, there is good evidence that improving the nutritional status of pregnant women, in particular vitamin A levels, improves the adverse pregnancy outcomes associated with HIV infection in resource-poor countries. It could be arranged that all women partaking in trials for the prevention of HIV transmission be given vitamin and nutritional supplements in order to maximise their chances of a good pregnancy outcome, and concomitantly to lower the theoretical risk of an enhanced sensitivity to AZT toxicity. This would, however, increase the complexity of implementation for the trials, and reduce their generalisability.

Other methodological variations are possible in order to reduce harm, such as using a smaller number of subjects in the placebo arm.

The 076 trial provided us with solid evidence of risk reduction for vertical transmission. If the 076 regime in its original format cannot be readily provided, a simpler, and equally effective,
variant should be found and used as a control for comparison to an even simpler regime (see Lallemant’s work below). If the latter is not as effective, but is nevertheless useful, then a compromise might well be accepted, particularly if the regime is attuned to the idiosyncrasies of the population in question.

Local context

With regard to the pragmatic and contextual issues, the proponents of placebo-controlled trials make several assumptions. These have all been proved unreliable. The first is that effective treatment would be unavailable to the research participants during the trial. The Bangkok trial provides an example of how women in the placebo group were deprived of treatment that was available to them in their country during the trial. Phanuphak highlights the fact that the Thai Red Cross Donation Programme and the Ministry of Public Health had provided funding for perinatal AZT treatment to a substantial number of women by 1997, before the Bangkok trial had terminated. He argues: ‘The availability of resources is usually relative. It depends on the judgment and commitment of policy makers, who can always reshuffle budget priorities', and that ‘scientists may have to reconsider or change their approaches as circumstances change’.33

The second assumption is that the cheaper, simpler treatment, if effective, will be made available in the host country. Unfortunately, this has not always proven to be the case. Schüklken has pointed out that local governments may not even implement the cheaper regime.34 South Africa and Thailand provide contrasting examples. The Ministry of Public Health of Thailand started a large pilot programme in July 1998 to reduce mother-to-infant HIV transmission with short-course AZT, shortly after the Bangkok trial was reported. The government now supports a nationwide implementation of a perinatal HIV prevention programme.35

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32 N Shaffer et al. op. cit. note 26.

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dose nevirapine with a short course of AZT, and showed that nevirapine lowered the risk of transmission in the first 14–16 weeks of life by nearly 50%, in a breast-feeding population.\textsuperscript{36} The wholesale cost of this regime is quoted as being $4 per mother/child. In South Africa, where approximately 20% of pregnant women are infected, the government has resisted implementing a programme for reduction in HIV vertical transmission.\textsuperscript{37} Indeed, there is still a lack of clarity as to whether the president accepts that HIV causes AIDS.\textsuperscript{38, 39} This governmental inertia exists despite the offer of drugs at reduced costs by the pharmaceutical companies, and cost-effectiveness studies suggesting that the HIVNET regime may be cost-effective in the high seroprevalence settings of Sub-Saharan Africa and South Africa.\textsuperscript{40}

The third assumption is that the AZT treatment has to be given as in the original 076 study. Lallemant et al. have shown that the 076 regime can be both simplified and successfully implemented in a less well developed country, without causing a significant alteration in dosage and efficacy – thus disproving this assumption.\textsuperscript{41}

It must be pointed out, however, that Thailand is a country with a superior infrastructure and economy compared to many Sub-Saharan countries.

Fourthly, doubts were cast on the value of equivalency studies, but equivalency trials, such as the HIVNET trial, \textit{have} provided us with valuable information that can be implemented in developing countries.

One can understand why some of these assumptions were made, and it seems unfair to criticise researchers for attempting to develop a cheaper, simpler regime, when they intended to benefit the population of which the research participants formed

a part. But these false assumptions do highlight the inherent weakness in making ethical decisions heavily dependent on predicted outcomes and/or perceived extrinsic circumstances, rather than relying more on intrinsic duties or virtues. If we use circumstances and potential outcomes to justify our moral actions, we can then end up with violated human rights, and little or no gain in utility if the former proves false. Phanuphak’s point is also important: researchers must be responsive to changes in circumstances.

The researcher’s duties and standards of care

The main thrust of the counter-arguments to the placebo-controlled trials is based on the deontological principle that the duty of care is fundamental to the practice of medicine. This duty entails respecting the autonomy of the individual patient (as reflected in the process of consent) along with protecting his or her best interests (beneficence). The two duties are normally inextricably linked. To quote Pellegrino and Thomasma: ‘Respecting wishes of patients is an essential feature of acting in their best interests’. Arguably, these duties apply to the clinician-researcher and the subject-patient. An editorial in *The Lancet* argues that the women in the placebo group were harmed by not receiving effective treatment to prevent the transmission of HIV to their children. This omission is described as an abrogation of a fundamental principle of medical practice (non-maleficence).

The duty of care is not at variance with the duty to perform rigorous scientific research. Clearly, poorly designed, slipshod scientific research that cannot yield reliable, relevant results is unethical, as both the research participants and future persons cannot benefit. The moot point is whether the research question

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itself is ethical. Should one be asking whether X is better than nothing, when one knows that Y exists that is very much better than nothing? The quest for scientific rigour must be balanced by ethical rigour.

Defenders of the PCT’s appear to view the duty of care to individual research subjects to be of lesser importance than other, competing duties. For example, in the consensus statement of the Perinatal HIV Intervention Research in Developing Countries Workshop, the participants – the vast majority from the USA – make no direct reference to the duty of care except to absolve researchers from providing the participants with ‘the highest standard of care attainable elsewhere in the world’. Those authors that do refer to the duty of care view it as conflicting with, and of lesser importance than, the duty to perform scientifically rigorous research. For example, Resnik argues that provision of AZT, unavailable to the general population of the host country, is a ‘supererogatory’ requirement. He concludes that researchers’ ethical obligations are dependent on socio-economic context. Crouch and Arras also consider the researcher’s special fiduciary relationship to the research subject, but take the view that there is no special obligation for the researcher to provide treatment that is unavailable in the host country, and to which ‘its citizens have no independent right of access’. They argue that there is a stronger duty to successfully complete ‘desperately needed clinical trials’.

Even if the researcher’s duty of care is acknowledged, we find that the scope of this duty is narrowed down, such that local scarcity sets the boundaries. After 1994, the 076 regime represents the standard treatment for comparison in an RCT. Those against the PCT’s would hold that the researcher had the duty to provide this known, effective treatment. As previously mentioned, however, the practicalities of providing this regime in countries with a poorly developed infrastructure for antenatal and child care are daunting. The CIOMS guidelines state that the researchers have ‘an ethical responsibility to provide treatment that conforms to the standard of care in the sponsoring country, when possible’. Article II 3 of the Declaration of Helsinki (1996

46 D.B. Resnik. op. cit. note 20.
version) states: ‘In any medical study every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method’. Clearly these guidelines create difficulties if they are interpreted to mean the provision of the best care available worldwide.

Those who wished to justify the use of placebos responded by creating a new standard: ‘the highest standard of care practically attainable in the country in which the research is being carried out’ (emphasis added).48 The Nuffield Council of Bioethics, in their discussion paper, *The ethics of clinical research in developing countries*, propose an interpretation of this article to mean the best locally available diagnostic and therapeutic method. This suggestion is reflected in the proposed revision of the Declaration of Helsinki considered by the World Medical Association (WMA) in 1999 (and eventually rejected in October 2000): ‘In any biomedical research protocol every patient-subject including those from the control group, if any, should be assured that he or she will not be denied access to the best proven diagnostic, prophylactic or therapeutic method that would otherwise be available to him or her.’ (emphasis added). If no treatment is available in the host country, then the use of placebos does not contravene any guidelines, and the ‘problem’ disappears. This proposed revision did not represent a mere tinkering at the edges, but a fundamental shift. It would have opened the door to the exploitation of residents of poor countries by researchers funded by rich countries or powerful multinational pharmaceutical companies.49, 50, 51

The PCT’s provide an example of the blurred boundaries between therapeutic and non-therapeutic research. Levine and Gillon have highlighted the difficulties in differentiating between the two.52 As Raanan Gillon points out, “... clinical research ... always has two components: a component of pure research intended to produce generalisable medical knowledge and a component of therapy, where the intention is to benefit the particular patient/subject’s own health”.

48 Perinatal HIV Intervention Research in Developing Countries Workshop Participants. Consensus statement. op. cit. note 45.
He goes on to say:

The less a trial shares in that Hippocratic commitment, i.e. the less it is intended and likely to benefit the individual patient subject, the more it should be treated as non-therapeutic research aimed at benefiting others and not the participant subjects, and therefore the more such a trial should incorporate the safeguards appropriate to non-therapeutic research, including the need for extensively informed consent.53

The matter is further complicated by the fact that even the women who receive prophylactic treatment do not benefit directly – only their future offspring do. Most of the women would vicariously benefit, as they would want their child to be protected from this lethal and stigmatising disease. Those in the placebo group, however, are analogous to subjects undergoing non-therapeutic research, and should have a greater claim to have their interests, or rather those of their future offspring, protected. They are also entitled to ‘extensively informed consent’.

In summary, the abrogation of the duty of care, particularly towards vulnerable individuals and their future offspring, may set dangerous precedents and erode the barriers to exploitation. On the other hand, if the intention is to benefit future populations who can avail themselves of treatment, this does mitigate the harm committed. But if the PCT’s do not lead to the widespread implementation of a cheaper, simpler prophylactic treatment (as in Africa), I would argue that those women who received the placebo have been doubly harmed.

PROBLEMS WITH CONSENT

Can pregnant women in developing countries give valid consent to a placebo? If so, is it ethical for researchers to ask them to waive the interests of their future children? The conscientiousness with which consent is sought reflects the respect for the individual, and his or her right to self-determination. For consent to be ethically and legally valid, in Western countries, it must be competent, informed and voluntary. Individual consent is defined as an ethical imperative in guideline 8 of the CIOMS guidelines. Arguably, individual autonomy may well represent a

Western concept, and the process of giving individual consent may be alien to certain cultures. For example, a woman may have to consult her partner, her family and even community elders before consenting to HIV testing or treatment.\textsuperscript{54, 55}

Resnik recognises that informed consent is a requirement for ethical research, particularly with the use of placebos, but he argues that Western interpretations of informed consent should not be imposed on non-Western individuals. Weijer and Emanuel describe a checklist for identifying the ‘morally relevant criteria’ of a community, and a model for seeking ‘community consent’.\textsuperscript{56} They advocate a combination of community consent and individual consent to provide ‘added protection’. Resnik also endorses the employment of ‘trusted community leaders’ to inform local populations.\textsuperscript{57} The question here is how coercive is this leadership? If a male leader advises research participation, in the context of a male-dominated culture, would this not make a pregnant woman in the community feel obliged to agree to being a participant (or vice versa)? Weijer and Emanuel acknowledge the problem, but do not provide clear solutions. Carel Ijsselmuiden and Ruth Faden highlight the dangers of assuming that tribal leaders or government officials genuinely represent the best interests of the study participants. They also challenge the real value of obtaining community consent in addition to individual consent.\textsuperscript{58}

I submit that if you cannot obtain consent that fulfils ‘Western’ criteria, there is a stronger case for absolute stringency in fulfilling article 1.10 of the Helsinki Declaration (1996 version) which states: “The researcher should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress”.\textsuperscript{59} The Nuffield Council of Bioethics highlighted the danger of duress in allowing community elders or


\textsuperscript{57} D.B. Resnik. op. cit. note 20.


\textsuperscript{59} World Medical Association Declaration of Helsinki. \textit{Ethical principles for medical research involving human subjects.} Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964. Fourth amendment. 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996.
family members to consent on behalf of participants. Moreover, if autonomy is limited by cultural factors, the researcher’s moral circumspection in avoiding harm should be increased.

Competence depends on sufficient understanding by the decision-maker, such that the relevant information given makes sense and can be acted upon. Understanding may be problematic in some settings – for example the word, and hence the concept of ‘randomisation’, may not exist in some languages. Indeed randomisation to treatment is a difficult concept to grasp, even in Western populations. There is an implicit assumption that health care professionals will always protect patients’ best interests, and provide effective treatment. It is hard for some patients to accept or understand that this may not always be the case. Some of this lack of understanding may also stem from a reluctance to accept the uncertainties inherent in medicine. I would argue that if individuals’ competence is vitiated by a lack of understanding, they should be afforded greater protection, not less.

Voluntariness implies freedom from coercion. There is a real risk that pregnant women may experience coercion in resource-poor settings. Schülenk has pointed out that women may well view participation in a trial as being their only opportunity to obtain treatment for themselves and their future offspring. There is evidence to suggest that women being recruited for trials may believe that they will be deprived of antenatal care or receive sub-standard care if they refuse HIV testing.

Even if we believe that informed consent is possible in this context, and I have produced some evidence to doubt this, it may not suffice. Angell believes that even informed consent does not give sufficient protection from exploitation ‘because of the asymmetry of knowledge and authority between researchers and their subjects’.

60 Nuffield Council on Bioethics. op. cit. note 54.
63 U. Schülenk. op. cit. note 34.
Finally, the defenders of the PCT’s sidestep the issue that we are not only dealing with women, but also with ‘third parties’ (fetuses) who cannot consent or protect their own interests. Most women would want to protect their unborn children from harm and seek the best care possible. Can it be ethical to ask women to deny their child-to-be the opportunity to avoid a grisly and fatal disease by taking a placebo?

THE BURDENS OF HIV TESTING

The harm done to the research subject who tests positive, but does not receive treatment for herself, or prophylactic treatment for her child in-utero, is often overlooked. Broadly speaking, screening for a major condition can only be ethical if a therapeutic intervention is available for the individual testing positive. There may be exceptions: individuals with a genetic predisposition to a disease may wish to modify their lifestyle (for example smokers with a greater predilection to cancer), or take prophylactic medicine (for example, daily aspirin, if there is a strong family history of heart disease), or be more closely medically monitored (as with women carrying the BRCA1 gene which increases the risk of breast cancer), or make reproductive choices (carriers of an inheritable deficiency disease such as cystic fibrosis).

Women who test positive for HIV can be given strategies to help cope with the disease, prepare for the future, reduce risk behaviour (horizontal transmission), and make reproductive choices. But ‘reproductive choice’ may be empty rhetoric for many African women. In some cultures and countries, high fecundity is prized, male partners shun barrier methods, and HIV positivity carries the threat, not only of stigma and social isolation, but also of abandonment and violence from partners and/or family members. This may explain why several researchers found that many women participating in trials in

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Africa do not actively request their results.\textsuperscript{69, 70, 71, 72} In other words, in countries where effective anti-retroviral treatment is unavailable, knowledge of HIV status may be particularly burdensome. As one researcher expressed it, “There is not much that we can offer African women once we have told them the bad news.”\textsuperscript{73} This is in sharp contrast to women living in resource-rich countries – although they too may be unable to avail themselves of treatment unless they are financially privileged.\textsuperscript{74}

\section*{OTHER ETHICAL PROBLEMS}

There remain other ethical problems associated with the treatment to prevent vertical transmission: Sub-optimal doses of monotherapy in pregnancy may potentially put women at risk of subsequent resistance to anti-retrovirals. To date this has not been a significant problem.\textsuperscript{75} Distributive justice would normally require the women themselves to receive treatment for their disease. In developed countries, the gold standard of care for adults is triple combination therapy at an early stage of infection. This represents a much higher cost than prophylactic therapy for the newborn, and is not even considered in resource-poor countries. Children of mothers infected with HIV have a higher mortality rate. One study in Kenya, for example, found that infant mortality was around 20\% for both formula and breast-fed

\textsuperscript{69} F. Dabis et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d’Ivoire and Burkina Faso: a double blind placebo-controlled multicentre trial. \textit{The Lancet} 1999; 353: 786–792.


\textsuperscript{73} M. Temmerman et al. op. cit. note 67.

\textsuperscript{74} R. Bayer. 1994. Ethical challenges posed by zidovudine treatment to reduce vertical transmission of HIV. \textit{N\textbf{E}JM} 1994; 331: 1223–1225.

infants.\textsuperscript{76} Orphaned children also have limited survival prospects. There is the anxiety that perinatal treatment is a recipe for ‘planned orphanhood’. Another disturbing possibility is that anti-retrovirals may harm babies who would otherwise escape the disease. The evidence so far is reassuring\textsuperscript{77}, but a group in France found mitochondrial dysfunction in eight uninfected infants.\textsuperscript{78} Nevertheless, at present the benefits of substantially reducing transmission outweigh the risks of drug-induced damage.

**THE REVISION OF THE DECLARATION OF HELSINKI**

As discussed earlier, the backlash to the criticisms of the placebo-controlled trials appeared to involve a powerful bid to change the international guidelines for research, such that the standard of care could be modified in the light of local availability.

The WMA released the fifth revision of the Declaration of Helsinki in October 2000. These guidelines have reinforced the duties of the researchers to their research subjects, and prohibited the use of placebos in situations of local scarcity if ‘the best current method’ exists elsewhere. They have strengthened the requirements for informed consent, and maximised distributive justice, such that every patient participant has access to ‘the best prophylactic, diagnostic or therapeutic methods identified by the study’ at the end of the study.\textsuperscript{79}

The WMA specifically addressed the potential for abuse of people living in poor countries. The revised version of the Helsinki Declaration reinforces the deontological or ‘clinical care’ ethic, as opposed to the utilitarian ethic. Some might argue that the revised guidelines will create serious obstacles to carrying out research that could benefit poorer nations. Others would argue that this is the price that has to be paid if the moral


\textsuperscript{79} World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. At www.wma.net/e/policy.
responsibilities of researchers to individual participants are maintained.

TOWARDS A GLOBAL CONCEPT OF JUSTICE

Following the 076 study, anti-retroviral prophylaxis to reduce maternal-fetal transmission has been whittled down, or changed, such that cheaper, simpler and reasonably effective regimes, suitable for breast feeding populations, have been found. For example, the regime yielded from the HIVNET 012 study. Lallemant’s work has provided further insights into maximising efficacy by fine-tuning the duration of AZT monotherapy in pregnant women and their infants.80

Yet these regimes are not being implemented in those countries that need them most. A number of factors contribute to this, the most relevant being the lack of resources and political will. Trials have been undertaken, and are planned, to test simple interventions to reduce HIV transmission. To date they have shown little of the efficacy of anti-retroviral treatment.81, 82

Arguably at this stage little significant progress can be made in further efforts to find a cheaper, simpler prophylactic regime without over-compromising efficacy. In addition, it is easy to forget that the most effective way of reducing paediatric AIDS is by primary prevention in women of reproductive age. Senegal and Uganda provide shining examples of countries that have significantly reduced or contained their HIV burden with vigorous and widespread education campaigns informing and encouraging people to limit horizontal transmission.83

Inevitably, a major health issue requires a political response. Benatar and Singer highlight the exploitation of resource poor countries by the resource-rich countries. They suggest that ‘Research ethics must be deeply rooted in the context of global health’, and that ‘... it must ultimately be concerned with

reducing inequalities in global health and achieving justice in health research and health care.\textsuperscript{84} They also provide a comprehensive framework for conducting research in developing countries. Globalisation, underpinned by a market ethic, does not necessarily benefit the worst off – often the reverse is true. But a global ethics, underpinned by an ethic of distributive justice, and framed in terms of human rights, has the potential to redress the balance and promote greater equity.

The well-developed resource-rich nations now have the uncomfortable choice of either accepting the status-quo: the gross inequity between the rich and the poor nations, and the relentless progress of this devastating and widespread disease, or recognising that this terrible state of affairs creates an ethical imperative for mounting an international strategic response. If we accept a global ethics and a common humanity, then the devastation of Africa by this pandemic is everybody’s problem. This is not to advocate a paternalistic stance, but rather to support countries to find their own solutions, and to work out for themselves their research priorities and how to implement them.\textsuperscript{85,86} Nevertheless, financial concessions and/or targeted aid are essential.

Despite the bleak picture, there are hopeful signs. Pilot programmes for perinatal anti-retroviral therapy are now being designed and implemented with the help of UNICEF, UNAIDS and the International Therapeutic Solidarity Fund in several African countries.\textsuperscript{87} Drug companies have agreed to reduce the costs of some of their drugs for distribution in poorer countries.\textsuperscript{88} The World Bank has pledged its support,\textsuperscript{89} and the USA has designated funds, the bulk of them for Africa, for combating the AIDS epidemic (the LIFE initiative).\textsuperscript{90} The debt burden has been removed from some poorer nations. Political remedies have been suggested, such as the clearance of national debt, the supply of pharmaceuticals at very low cost, the offer of aid contingent on

\textsuperscript{87} F. Dabis and V. Leroy. The AIDS Reader 2000; 10: 241–244.
\textsuperscript{88} Editorial. A positive response to perinatal HIV. The Lancet 1999; 353: 511.
\textsuperscript{90} C. Watts. Thinking big: scaling up HIV-1 interventions in sub-Saharan Africa. The Lancet 1999; 354: 1492.
The facilitation of poorer countries to manufacture drugs should not be unduly constrained by patent law (particularly Trade Related Aspects of Intellectual Property Rights or TRIPS). \(^9\) Sadly, but unsurprisingly, many of these promises have not, as yet, been translated into solid action; the Western governments and powerful pharmaceutical companies still seem to be dominated by the mercenary motto of ‘business as usual’. \(^9\)

CONCLUSION

The research into the prevention of vertical transmission of HIV has engendered an acrimonious debate worldwide and has created a schism in the scientific and medical communities. It has exposed the gross inequity in resources, particularly for health care provision, that exist today between the affluent industrialised nations and the poor, developing countries. It has, for example, revealed the lack of availability of adequate antenatal care, and the high infant mortality rate in many countries. It shows the markedly contrasting fates of HIV-infected pregnant women in affluent nations and those in resource-poor nations. It has highlighted the vulnerability of women in certain cultures, and the lack of choices available to them in terms of contraception, method of delivery, protection from HIV infection, and infant feeding. It has also made more public the risk of social stigmatisation, or worse, that individuals may run in some countries if their HIV status is known.

This high profile controversy may reflect a deeper, philosophical schism. Underlying the arguments, there appears to be tension between the modernist ethic of science, grounded in a mechanistic-reductionist paradigm, and an ethic based on a more humanistic, post-modern paradigm. \(^9\) The RCT strives
to create order and predictability in a world of complexity and uncertainty. It can indeed provide us with ‘hard’ unbiased evidence for the benefit of interventions, but, in order to achieve this, it eschews individual concerns, needs, preferences, and human relationships. “In other words, it eliminates those ‘variables’ that make us act as moral agents to one another. For this reason, we need to have robust ethical safeguards. The postmodern ethic, on the other hand, allows for the individual voice to be heard, and tolerates uncertainty”.

In the field of research ethics, we have witnessed a drive to change the international codes of ethics such that placebo-controlled research is facilitated in countries where the ‘standard treatment’ may be nothing at all. This proposal has been rebutted in the final version of the Declaration of Helsinki. Those advocating the placebo-controlled trials have accused their opponents of ‘ethical imperialism’, but within the new framework of the Helsinki Declaration, the post-1994 placebo-controlled trials would clearly be condemned as unethical imperialism, or exploitation.

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