

Provision of HIV treatment in HIV preventive vaccine trials: a developing country perspective[☆]

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Abstract

HIV treatment for participants who become infected during HIV vaccine trials has been the focus of ethical controversy. The obligations of sponsors to ensure that participants have access to antiretrovirals have been a particular focus of this debate.

This paper presents three arguments that have been made in this regard, and some of their limitations, in anticipation of HIV vaccine trials in South Africa.

The first argument is that HIV risk behaviour increases in such trials, and HIV infection can be viewed as a research-related injury, justifying sponsor provision of treatment on grounds of compensation for harm. We conclude that risk-behaviour studies to date do not show general increases in risk behaviour that could constitute the basis for a general obligation. Participation may well adversely impact on risk behaviour for some individuals, and conceivably this could be demonstrated. This argument may, therefore, have merit at the individual level; however, it seems a weak platform from which to argue that sponsors should treat all HIV infections acquired during trials.

The second argument is that treatment should be provided based on distributive justice. We conclude that traditional concepts of “distributive justice” in research appear limited in justifying obligations of sponsors to ensure access to antiretrovirals. Further, using research initiatives to reduce global health care inequities is controversial, and even proponents may disagree about the fairest use of finite resources.

The third argument is that sponsors should ensure antiretroviral access on grounds of beneficence; namely, the maxim that if one can do something beneficial without sacrificing anything of comparable significance, it ought to be done. Thus, sponsors should provide more interventions than those minimally required to conduct the research. However, beneficence may demand levels of altruism that exceeds what is reasonable.

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While the latter arguments may provide stronger justifications than the first, it is difficult to use these arguments to establish that sponsor provision of antiretrovirals to infected individuals is obligatory.

Keywords: HIV vaccines; Consent; Justice; Research ethics; Standard of care; South Africa

Introduction

The HIV/AIDS epidemic remains an unprecedented challenge. A number of initiatives are underway worldwide to develop and test candidate HIV preventive vaccines.

HIV vaccine trials involve several phases, from phase I (involving small numbers of healthy, HIV-uninfected, persons) to test safety, vaccination schedule and route and immune responses; to phase II trials to test safety and immunogenicity in larger numbers (Abdool Karim, 2002); to phase III trials (involving thousands of healthy volunteers, at high risk of HIV infection) to test vaccine efficacy in preventing HIV infection or disease amelioration.

HIV vaccine trials are ethically complex. Amongst other factors they involve partnerships between sponsors (institutions that finance the trial or own the candidate vaccine) often drawn from resource-rich nations, and communities and participants drawn from “host” nations that may be resource-constrained. Investigators, responsible for designing and implementing trials, may be drawn from both host and sponsor nations. In some cases, clinical trials are implemented in both sponsor and host countries.

Despite risk reduction interventions, some participants will become infected with HIV during trials. Controversy surrounds the obligations of sponsors towards participants who become HIV infected and have no access to treatment, and the mechanisms via which such treatment could be made available to participants. Current guidelines recommend that relevant host stakeholders develop acceptable treatment packages (cf. UNAIDS, 2000). The ethical complexity of conducting such trials in countries where public sector HIV treatment is limited may be heightened by the urgent need for interventions and the simultaneously more severe consequences should trial participants have a false sense of security about risk behaviour.

HIV treatment and care will comprise multiple components (that could be provided at varying levels of quality), such as voluntary testing and counselling, sexually transmitted disease management, antiretrovirals (ARVs), and treatment of opportunistic infections. However, access to Antiretroviral Treatment (ART) has been most controversial (Bayer, 2000). ART is a holistic treatment of HIV making use of antiretrovirals. ARVs are currently the most effective treatment for HIV. It is

recommended that in resource-limited settings, ART should be given when patients have symptomatic disease (AIDS) or when the CD4 count is low (below 200/mm³) (World Health Organisation (WHO), 2003).

The debate about HIV treatment for HIV vaccine trial participants has been referred to as the “standard of care” debate (Bayer, 2000). This term originated in the medico-legal context (National Bioethics Advisory Commission (NBAC), 2001) and has been applied to the controversy about the most appropriate comparator against which to test new interventions in resource poor settings (Benatar & Singer, 2000). It has recently been explicitly defined as the interventions to be provided to participants *in research* (Nuffield Council on Bioethics, 2002, p. 87). The controversy about HIV treatment for phase I and II participants, however, rests on the understanding that treatment may only be required long *after* trial completion. HIV treatment for phase III participants may well be provided as part of the research because assessment of disease progression will benefit from provision of standardised ARV regimens (Fitzgerald, Pape, Wasserheit, Counts, & Corey, 2003).

Ethical considerations

This paper will review three arguments for sponsor provision of treatment to infected participants, and their limitations and complexities. These are that sponsors should provide treatment: firstly, on grounds of compensation for research-related injury; secondly to ensure a just distribution of risks and benefits or to reduce inequalities in health care between collaborating countries; and thirdly, because of the principle of “beneficence”.

Treatment for HIV infection as compensation for research-related injury

It is generally agreed that if participants suffer injury as a result of the research, then those who stand to benefit from the research, such as sponsor organisations, are obliged to compensate them (Levine, 1988). It has been argued that participants in HIV vaccine trials are likely to falsely believe that the experimental HIV vaccine will protect them from HIV infection, which will lead participants to engage in increased high-risk

behaviour (Schüklenk & Ashcroft, 2000). This in turn would put them at increased risk of HIV infection. These concerns resonate with a more general concern that participants may suffer from the “therapeutic misconception”; that is, a belief that the purpose of a trial is to benefit them rather than to gather data or that the experimental product will treat their condition or be good for them (Appelbaum et al., 1982 in NBAC, 2001). It has been expressly argued that in HIV vaccine trials, the therapeutic misconception “will inevitably result” in a number of newly infected participants (Schüklenk & Ashcroft, 2000, p. 168). Accordingly, HIV infection should be viewed as a harm that is related to trial participation. In order to compensate participants for the harm arising from increased risk of infection, sponsors should provide high quality treatment for HIV infections acquired during trials.

The therapeutic misconception and changes in risk behaviour over the course of HIV preventive vaccine trials

Several empirical studies have been conducted to assess whether key concepts of trial participation are understood, including that candidate HIV vaccines may not afford protection from HIV infection. A literature search was conducted making use of the EbscoHost Research Databases. Studies identified through this review are reported in Table 1.

It appears that few published studies assess the comprehension of participants in actual HIV vaccine trials. Furthermore, the majority of studies appear to rely on forced-choice checklists that may obscure the distinction between what a participant recalls, a personal appreciation of the information (Lindegger & Richter, 2000) and acceptance that the information is true. That is, the validity of these “tests” of understanding could be questioned. These complexities notwithstanding, it appears that several studies reported that participants can be assisted to have realistic expectations of vaccine efficacy (Fureman et al., 1997; MacQueen et al., 1999). However others caution that deficits in understanding regarding vaccine efficacy may indeed occur and persist (Coletti et al., 2003).

Several empirical studies have assessed changes in trial participants’ risk behaviour over the course of trials. To collect this data, literature searches were conducted making use of the EbscoHost Research Databases. In addition, an attempt was made to contact site Principal Investigators via email. There was a 15% response rate. Studies identified through this review are reported in Table 2.

It is very challenging to obtain reliable estimates of risk behaviour, as reported changes can be actual or artefactual. There is also a lack of data from HIV vaccine trials in African settings. However, our review indicates that data from phase I and II trials is mixed

(although no decreases were reported for phase I trials) while data from two related phase III trials of similar Vaxgen vaccines in Northern America and Thailand indicated that participant risk behaviour decreased overall from baseline, despite some individual and group variations during the trial (Bartholow et al., 2004). This review does not provide unequivocal support for the hypothesis that participants’ risk behaviour generally increases over trials. It is difficult to argue that as a general rule HIV infections in trials should be treated as though they are research-related, and compensated by sponsor provision of high quality treatment. Of course, the current lack of evidence does not mean that future general risk-behaviour increases will not occur. This possibility should be carefully monitored, in more settings and with longer follow-up periods.

Research-related injury in individual cases

It is possible that for certain individuals, participation may lead to false beliefs about vaccine efficacy, which could impact negatively on risk behaviour. Studies may report aggregate results that obscure possible increases in risk behaviour by certain individual participants. Certain studies explicitly report that despite overall decreases in risk behaviour, certain individuals evidenced increased risk behaviour at least for a period in the trial (Bartholow et al., 2004). It must therefore be acknowledged that certain individuals may evidence increased risk behaviour over trials, and it is possible that this is caused by trial participation.

Strictly, in order to qualify for compensation, an individual’s HIV infection should meet criteria for research-related injury. That is, it must be demonstrated that the injury, on the “balance of probabilities”, was the result of a trial product or procedure (Department of Health (DOH), 2000). While certain vaccine approaches (e.g., live attenuated) carry some risk of direct infection, HIV vaccines currently in development do not rest on such approaches. The theoretical risk that a participant who is vaccinated and subsequently exposed to HIV may have increased susceptibility to infection or disease is not supported by evidence from clinical studies to date (Popovic, 2003). It is theoretically possible that HIV infection could be linked, demonstrably, to trial procedures such as inadequate consent or poor risk-reduction. It would, however, be difficult to establish that a participant’s HIV infection was not the result of other influences (e.g., peer pressure) and would not have occurred but for trial participation. If it could be established, however, that on balance, an individual’s HIV infection was more likely to be related to trial participation than other factors, then this could constitute legitimate grounds for compensation.

‘Compensation for injury’ reasoning could, therefore, conceivably be used to make a case that certain

Table 1
Studies investigating understanding of trial participation concepts, including expectations about vaccine efficacy

Author	Sample	N	Measure	Results
Harrison, Vlahov, Jones, Charron, and Clements (1995)	High risk population (suitable for HIV vaccine trial)	214	True-false checklist	Less than 1% responded that the HIV vaccine would confer protective immunity 96% stated they would use condoms with a new partner after enrolment
Queroz da Fonseca, and Lie (1995)	Gay and bisexual (in vaccine preparedness study)	161	Forced choice attitude questionnaire (Likert scale)	75% did not think they would be completely protected against infection if vaccinated 95% said they would still need safe sex behaviour after vaccination
MacQueen et al. (1999)	Intravenous drug users (IDUs) (in HIV vaccine trial feasibility study)	20	Fixed choice questionnaire, some open ended questions	Baseline: 98.4% agreed that participants should continue to practice safe behaviours. Follow up: increased to 100%
McGrath et al. (2001)	Military men (in HIV vaccine trial feasibility study)	193	True-false questionnaire	At each visit most (not specified) reported they would not be protected if participating in a trial
Fureman, Meyers, McLellan, Metzger, and Woody (1997)	High risk population (in HIV vaccine trial feasibility study)	1182 (base-line)	Semi-structured interviews	Six months: only 0.3% indicated that they would increase their sexual partners if in a trial
Coletti et al. (2003)	High risk persons (in a vaccine preparedness study)	544 (24 months)	Agree-disagree questionnaire	Subsequent visits: most (not specified) agreed that participants should not stop using condoms
Queroz da Fonseca, and Lie (1999)	Gay men (in HIV incidence study)	186	Self-administered questionnaire	Over 90% understood that the vaccine would not be 100% effective
Bartholow et al. (2004)	Men who have sex with men (MSM) and women in the Vaxgen Phase III HIV vaccine trial	4176 (18 months)	Fixed choice questionnaire, some open ended questions	19 months: most common and persistent knowledge deficit was related to unknown safety and unproven efficacy of candidate vaccines (stated by 42–45%) 6% said they would be less careful once vaccinated, regardless of the efficacy of the vaccine
		66	Fixed choice questionnaire, some open ended questions	53% of men and 50% of women stated they did not know vaccine efficacy. Women were more optimistic than men, with 21% versus 13% indicating that they thought the vaccine was 76–100% effective

Table 2
Studies assessing change in risk behaviour of participants

Author/Principal Investigator	Trial location	Sample	N	Results
<i>Phase I</i>				
Salmon (personal communication, 29 November 2002)	Six ANRS trials, France	Low risk volunteers	Not specified	No risk behaviour changes
Slobod (personal communication, 20 November 2002)	St Jude Children's Hospital, USA	Low risk volunteers	Not specified	No data on risk behaviour changes
Kovacs (personal communication, 2 December 2002)	Two NIAID trials, USA	Not specified	Not specified	No data on risk behaviour changes
<i>Phases I and II</i>				
Thapinta et al. (1999)	Two sites, Thailand	Low risk volunteers	52	No increase in risk behaviour
Kohler et al. (1994) in Thapinta et al. (1999)	Thai Red Cross Vaccine Trial	Low risk volunteers	Not specified	No increase in risk behaviour
Chesney, Chambers, and Kahn (1997)	USA	High risk volunteers	48	Risk behaviour increased over the course of the trials. Baseline to 6 months: insertive unprotected anal intercourse (UAI) increased (9–13%), 12 months: UAI increased (13–20%). High-risk histories associated with belief in vaccine efficacy
<i>Phase II</i>				
McElrath et al. (1996) in Thapinta et al. (1999)	USA	High risk volunteers	Not specified	No evidence of increased risk behaviour
Belshe et al. (2001)	14 sites, USA	Men who have sex with men (MSM), IDUs and heterosexual populations	435	Baseline to 12 months: overall decrease in risk behaviour. Within each risk group some reported increased risk taking
<i>Phase III: Vaxgen, Thailand</i>				
Pitisuttithum (2000)	Thailand	IDUs	2500	Baseline to 6 months: IDU decreased (96–83%), regular drug use decreased (30–20%), sharing needles decreased (30–14%), methadone maintenance increased (45–78%), and 100% condom use increased (55–69%)
Vanichseni et al. (2002)	Thailand	As above	2545	Baseline to 12 months: overall risk behaviour decreased IDU decreased (93.8–66.6%) and needle sharing decreased (33–17.5%)
Van Griensven et al. (2003)	Thailand	As above	2545	Baseline to 36 months: IDU decreased (93.8–56%), needle sharing decreased (33–16.3%)
<i>Phase III: Vaxgen</i>				
Jermano (2000)	USA, Canada and the Netherlands	94% MSM	5415	Baseline to 6 months: risk behaviour for MSM decreased. Proportion of MSM with more than

Table 2 (continued)

Author/Principal Investigator	Trial location	Sample	N	Results
Bartholow et al. (2002)	As above, 61 sites	As above	5109 MSM, 309 women	five sex partners declined (54–44%) and unprotected sex with HIV + male partners appeared to decrease Baseline to 6 months: as above 6–24 months: risk behaviour increased for MSM (49–52%), Risk behaviour increased among women (44–52%), 24 months: risk behaviour (UAI) remained below baseline. Risk behaviour (UVI) returned to baseline
Bartholow et al. (2004)	As above	Same group	5095 MSM, 308 women	Baseline to 36 months: overall, UAI and UVI decreased. Baseline to 6 months: UAI in HIV uninfected men decreased (58–49%), 6–30 months: UAI increased (49–52%), 36 months: UAI returned to 50% (below baseline). Baseline to 12 months: UVI decreased (55–41%), 12–36 months: UVI increased (41–50%, below baseline)
Buchbinder et al. (2003)	5 sites	MSM	732 vaccine trial participants (VTP), 688 non trial participants (NTP)	Baseline to 18 months: risk behaviour decreased overall, but the decline was greater for NTP (64–54%) than VTP (57–54%)

individuals be provided with treatment for HIV infection by trial sponsors. It provides insufficient grounds, however, to establish a general obligation. In order to use this line of reasoning to establish a general obligation, a proponent would have to argue that it is not possible to identify those individuals who subscribe to false beliefs, or whose risk behaviour has been adversely affected by participation. Compensation for harm reasoning may be strengthened if levelled at trials that make no attempt to assess comprehension or risk behaviour.

Compensation for harm reasoning infers that trial procedures are the most likely determinant of risk behaviour, ignoring the possibility that participants may knowingly engage in inadvisable high-risk behaviour. When participants understand the trial product, procedures and consequences of their actions and nevertheless autonomously engage in high-risk behaviour, then the obligation for sponsors to treat, based on the reasoning that participants have been harmed, is diminished.

Treatment for HIV infection as an expression of justice

It could be argued that sponsors and investigators are obligated to ensure access to HIV treatment based on justice considerations. Conceptions of justice are complex and controversial, leading to some controversy regarding the services owed to research participants on justice grounds (cf. Emanuel, Wendler, Killen, & Grady, 2004).

A fair balance of research-related risks and benefits

Applied to research, justice emphasises the need to ensure a fair distribution of research-related risks and benefits amongst all collaborating partners, that is, “distributive justice” (cf. Emanuel, Wendler, & Grady, 2000). It is a difficult task to define precisely what constitutes a fair distribution (Macklin, 1998). Research-related benefits traditionally include the knowledge generated by research, capacity building, medical benefits, and/ or (in later studies) a proven safe and effective product (Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO), 2002). Participants may benefit from health care provided in research; i.e., those tests and interventions that are related to the research objectives and required for the conduct of the research. Typically, these medical benefits (along with other benefits, such as those to society in terms of knowledge gained) are weighed against the risks that participants may assume, to establish if the risk-benefit ratio is fair (CIOMS, 2002). In early trials of candidate HIV vaccines, like other clinical trials, health care interventions required for the conduct of research

that may benefit participants include close monitoring and supervision by a research team.

It is, however, somewhat more controversial whether, and to what degree, sponsors and investigators are obligated to provide medical care beyond what is necessary to implement a research design safely and validly (Richardson & Belsky, 2004), that is, to provide benefits that are “non-experimental” health care (Powers, 1998). Our review indicates that an assumed causal relationship between HIV infection and trial participation can be challenged. Early HIV vaccine trials aim to establish safety and immunogenicity of vaccines. Therefore, treatment for HIV infection acquired during the conduct of early trials can reasonably be viewed as unrelated to trial objectives, and therefore amounts to “adjunctive” service provision. It has been argued that the latter should not be weighed against risks in risk-benefit evaluations, otherwise simply adding more unrelated services could make the benefits outweigh even the riskiest research (Emanuel et al., 2000).

According to this view, the provision of treatment for HIV infection falls outside the scope of what should be judged in fairness assessments for HIV vaccine trials. Furthermore, research ethics committees, responsible for ensuring that a fair balance of risks and benefits is achieved, could determine that alternative research components adequately fulfil distributive justice requirements. These include that the research investigates a health problem of direct relevance to the host community or country; results will be translated into accessible care (Benatar & Singer, 2000); existing health care services will not be undermined (Policy Forum, 2002); or provision is made for access to a proven safe and effective intervention.

Reducing inequities in health care

The argument that access to non-experimental health care is outside the scope of fairness assessments that should be the concern of justice in health research can be challenged. It could be argued that inequalities in the distribution of goods between nations should be combated, and that international research initiatives are legitimate vehicles through which inequalities in access to such goods (including health care) can be reduced. Bearing in mind the social determinants of health (Daniels, Kennedy & Kawachi, 2000), access to health care and research participation could be construed as a basic liberty in a classic model of justice. Based on such a model, it could be argued that fair social and economic arrangements should seek to maximise the welfare of the least advantaged, or worst off, group and attempt to ensure a fair distribution of goods so that, at a minimum, the least advantaged are as well off as possible (Rawls, 1989). In some cases, HIV vaccine trials will be funded by sponsors from countries with

greater wealth and health care than host countries where effective treatment for HIV infection is not readily available. Some HIV vaccine trials will involve trial arms in both sponsor and host countries. Participants in resource-poor host countries will generally have lower levels of treatment for HIV infection than participants in sponsor countries (e.g., the United States) who will generally have access to treatment for HIV infection either through the public health sector, private health insurance or per arrangement with investigators. It could be argued that host country participants, as a group, compared to their US counterparts, are thus disadvantaged and that these differences are inequitable, as they are avoidable, and unnecessary (Whitehead & Dahlgren, 1991, in Daniels et al., 2000). Reductions in drug prices, and the availability of generics, make the provision of antiretrovirals ever more feasible (Fitzgerald et al., 2003). Therefore, in order to rectify inequities in health care and to attain a fair arrangement, sponsors from resource rich nations should ensure that participants in poor host countries who become infected with HIV during the conduct of a trial are provided with antiretrovirals. This argument could also be applied to participants within sponsor nations with no access to antiretrovirals.

What are the limitations and complexities of this argument? There is much debate about which inequalities should be the focus of justice, and the implications of the Rawlsian approach to biomedical ethics remains unclear (Kahn, Mastroianni, & Sugarman, 1998). Furthermore, the use of international research initiatives to reduce health care inequities has been questioned, including on the grounds that it strains the role and powers of sponsor and research institutions (Ashcroft, 2002), and may create barriers to research. In response, if health research is a social good (which it plausibly is), then it is a legitimate vehicle for the reasonable reduction of inequities. Presumably sponsors could make an argument that the financial and logistical demands of antiretroviral provision could not practically be borne and that demands in this regard threaten the future of trials; however, substantial advances in availability of drugs and access mechanisms in developing countries lessen the likelihood of this (cf. Fitzgerald et al., 2003).

Even if it is accepted that sponsor resources should be used to reduce health care inequities, it could be argued that provision of antiretrovirals for a small number of individuals does not represent the fairest use of finite resources; that is, it is not the best mechanism for remedying global health care injustices. It could be argued the latter is best served by improving basic health care infrastructure and capacity in service centres in trial-linked host communities (cf. Benatar & Singer, 2000). Furthermore, such an arrangement could be argued to more faithfully benefit the “least advantaged”,

by trying to ensure that those persons resident in resource-poor communities who are not healthy enough to qualify for trial participation (such as those already HIV infected) benefit from the arrangement.

A further complexity is that the provision of antiretrovirals to infected participants may introduce research-linked inequalities between participants and community members, and also between participants in various host-country HIV prevention studies. It could be argued that inequalities in access to treatment within a community are as unjust as inequities “across the waters” or between collaborating nations, or at least that it is logically inconsistent to use justice-based arguments to introduce further local inequalities. In the short term this may be a fair objection, but the long-term goal of justice is to treat equals equally, and the implementation of these long-term goals must realistically be regarded as a process (Benatar, 2002).

A final counter-argument is that there are likely to be many components of treatment and care for HIV infection along which sponsor and host nations will differ, that a focus on antiretrovirals is narrow and arbitrary and that other components may be deserving of efforts to “close the gap” in health care. This position might suggest that even if a host country implements a public health ARV program, efforts should be made to strengthen other host health care components.

It is also reasonable to maintain that participants should have their capacity for autonomous decision-making promoted, and that inducements that will impair decision-making should be avoided. Some might possibly assert that providing participants with antiretrovirals will act as an undue inducement that will cause participants to ignore or devalue concerns about risks, and to expose themselves to risks which they would otherwise have viewed as unacceptable and refused (cf. NBAC, 2001). Indeed, it has been argued that to avoid undue inducements, antiretrovirals should not be offered to participants in resource poor contexts (Kilmarx, Ramjee, Kitayaporn, & Kunasol, 2001). It is, however, plausible that acceptance of such treatment may be based on self-interest (a potential benefit to the participant), or enlightened self-interest (benefit to the participant, as well as a contribution to the social good: NBAC, 2001). That is, it could be based on reasonable choice and not necessarily because the offer has compromised decision-making.

While such an offer should not, in principle, be seen as undue influence, it must be conceded that for certain participants this may distort their evaluation of research-related risks. This may be somewhat offset by sound consent procedures. Concerns about participants exposing themselves to unacceptable levels of risk *per se* should be minimised by rigorous independent review. Even if the chance of undue inducement for some participants cannot be eliminated, this principle must be

balanced with other ethical principles, such as the need to treat participants fairly. That is, ethical reasoning about this complex issue will require adjudication between competing principles, and some resistance of the tendency to allow respect for autonomy to override all other considerations (Beauchamp & Childress, 2001).

Because of the complexity of this issue, it is recommended that informed and transparent discussion between relevant stakeholders take place well in advance of protocols being submitted for ethical review, and stakeholders should have their capacity developed in order to participate meaningfully in these complex debates.

Treatment as an expression of beneficence

It could be argued that sponsors should ensure access to antiretrovirals on grounds of beneficence. While there is some debate as to its meaning, this principle generally establishes that one should prevent and remove harms, and actively provide benefit (Beauchamp & Childress, 2001). A Utilitarian construction of beneficence asserts that an act should be done if it can be done, and if doing so will prevent foreseeable suffering and death and not sacrifice anything of comparable moral significance (Singer, 1999).

It can only be determined that one party (*X*) has an obligation of beneficence to another specified party (*Y*) when the following conditions are met:

- (1) *Y* is at risk of significant loss of, or damage to, life or health or some other major interest;
- (2) *X*'s action is needed (singly or in concert with others) to prevent this loss or damage;
- (3) *X*'s action (singly or in concert with others) has a high probability of preventing it;
- (4) *X*'s action would not present significant risks, costs or burdens to *X*;
- (5) The benefit that *Y* can be expected to gain outweighs any harms, costs or burdens that *X* is likely to incur (Beauchamp & Childress, 2001).

Applying these conditions, if *X* is a resourced trial sponsor and *Y* an HIV vaccine trial participant with limited access to HIV treatment, then the consequence of taking the principle of beneficence seriously would seem to indicate that sponsors should ensure (singly or in concert with others) antiretroviral access because: (1) HIV infection results in loss and damage to life and health; (2) there may be no guaranteed access to antiretrovirals through a state program (3) antiretrovirals can ameliorate some "damage to life or health" (4) ensuring access to antiretrovirals should not present significant risks, costs or burdens to sponsors (as has been discussed in the justice section); and finally, (5) the

benefits of prolonged life and health cannot, on any humanitarian grounds, weigh less than the fiscal cost of ensuring access. Using the above criteria, it could be argued that sponsors should ensure that participants with limited access to treatment be assured of such access.

One obvious counterpoint is that, despite the limiting conditions, this principle demands levels of compassion, commitment and altruism that simply exceed what is reasonable, therefore in some instances beneficence could be viewed as superogatory rather than obligatory.

The South African situation

In response to the severe HIV epidemic in South Africa, an initiative to develop safe, affordable and effective HIV vaccines was launched in 1999, mandated by the South African government. This initiative (the South African AIDS Vaccine Initiative) has multiple components, including candidate vaccine development and clinical trials.

In South Africa, there is generally limited public sector access to ART. In anticipation of South African vaccine trials, meetings were held in 2001 and 2002 to debate treatment for infected participants. There was reluctance to consign participants to limited public sector treatment. However, there was no consensus on whether sponsors and investigators should provide HIV treatment, ethical justifications, treatment components, and implications for other HIV prevention trials. Certain research ethics committees (RECs) in South Africa judged that trial participants should have access to ART (Altenroxel, 2002). In order to achieve consensus, South Africa's Interim National Health Research Ethics Committee arranged a stakeholder forum, in February 2003, where it was recommended that infected participants have access to antiretrovirals to be financed for a fixed period by sponsor agencies (cf. Tucker & Slack, 2003). It was proposed that a trust fund be established, nationally operated by a managed health-care service provider to enable access to a network of doctors for HIV-related care and antiretrovirals when required, even after trial completion (Tucker & Slack, 2003). Responsibility for the total care of infected participants is to be shared, as public health services are responsible for the treatment of later stages of AIDS, e.g. tuberculosis. In other forums outside South Africa, alternative mechanisms have been proposed to enable access, e.g., that private donors contribute to a trust fund, or sites are capacitated to deliver ART (cf. Fitzgerald et al., 2003) or that sponsors and investigators obtain assurance that participants will be among first recipients of within-country scale-up activities (cf. Bass, 2004).

In November 2003 the South African government committed itself to a national public sector ARV program, asserting that those needing HIV treatment will receive this, “equitably”, by 2008. Multiple factors may affect delivery (GCIS, 2003) and delays in implementation might suggest that investigators may not, at the outset, rely on public sector ART for infected participants. However, this governmental commitment indicates that the proposed mechanism must be reviewed shortly to assess its ongoing relevance.

Implications

What are the implications of the ethical arguments presented in this paper for other trials? The first argument has implications for trials where HIV infection could conceivably be viewed as trial-related, most notably other HIV prevention trials, e.g. Microbicides. In order to assess the degree to which a similar “compensation for harm” argument could be levelled at these studies, investigators and sponsors should review data on risk behaviour and comprehension, and furthermore ensure that assessments of both are routinely implemented in trials using robust measures. The second set of justice-based arguments has implications for clinical trials with international sponsors or multinational trials (where health care is likely to differ between collaborating nations). The complexities of justice-based arguments suggest that sponsors and investigators must consider in advance both the components and recipients of research-linked improvements in health care, in collaboration with relevant stakeholders. The third argument, beneficence, has implications for all research protocols, and suggests that sponsors and investigators should consider how their research will maximise health care, beyond those interventions minimally required to perform the research. These costs must be calculated carefully to ensure that they do not demand the sacrifice of the trial itself. Beneficence implies a shift in the way moral duties are considered in research, ensuring that when the maxim “ought implies can” is being applied, “can” should not be defined too narrowly.

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