

Ethical and practical challenges in implementing informed consent in HIV/AIDS clinical trials in developing or resource-limited countries

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Abstract

Background/rationale: Ethical issues regarding HIV/AIDS human research in the developing world remain under continuous evaluation; a critical area of concern includes informed consent. This paper reviews several of the most important ethical and practical aspects of informed consent in HIV research in developing countries. Enhancement of overall understanding of such key issues might promote higher ethical standards of future research.

Objectives: The major objective was to address informed consent in human research in non-Western societies, and specifically in HIV clinical trials of affected adults. Secondary end-points included the consent complexities in HIV research involving vulnerable patient populations in resource-limited nations, such as children, adolescents and women.

Methods: A systematic review of the published literature using MEDLINE and EMBASE from 1998 until December 2008 was performed, using the search terms 'HIV/AIDS', 'informed consent', 'clinical trials', 'developing world'.

Results: Ethical complexities such as participants' diminished autonomy, coercion or monetary inducement, language difficulties, illiteracy or lack of true understanding of the entire study, cultural barriers mainly due to communitarianism and social diversities were identified in the 44 studies reviewed. Informed consent of vulnerable patient populations must be tailored to their sex and developmental age, while counselling is fundamental. Children and adolescents' assent must be ensured. Local language is to be used, while trusted community leaders and local cultural representatives may convey information.

Discussion: Despite the heterogeneity of studies, similarities were identified. Providing adequate and comprehensive information and assessing the true understanding of the research represent fundamental prerequisites. Potential solutions to the critical areas of concern include peer counselling and meetings with local community leaders or local cultural representatives.

Conclusions: International investigators of HIV human research should bear in mind these ethical issues and their potential solutions, when trying to ensure ethical research conduct, based on a truly informed and culturally relevant consent.

Keywords: HIV/AIDS, clinical trials, developing world, informed consent.

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Résumé

Les problèmes éthiques concernant la recherche humaine dans le monde en voie de développement font l'objet d'une évaluation soutenue; un secteur de préoccupation important concerne le consentement éclairé. Ce document passe en revue plusieurs des aspects moraux et pratiques les plus saillants de ce consentement éclairé dans le cadre de la recherche sur le VIH dans les pays en voie de développement. L'amélioration de la compréhension globale de cette problématique pourrait promouvoir un niveau de valeur morale élevé pour le futur de la recherche.

Le but principal était d'adresser le consentement éclairé dans le contexte de la recherche humaine dans les sociétés non-occidentales, et particulièrement dans le cas des essais cliniques sur le VIH chez les adultes affectés. Les résultats secondaires incluaient les complexités dans la recherche sur le VIH quant aux populations de patients vulnérables dans les nations à ressources limitées, comme les enfants, les adolescents et les femmes.

Une critique systématique de la littérature publiée entre 1998 et décembre 2008, utilisant MEDLINE et EMBASE, a été conduite, en utilisant les termes de recherche 'HIV/AIDS', 'informed consent', 'clinical trials', 'developing world'. Les complexités morales, comme l'autonomie réduite des participants, la coercition ou la motivation économique, les difficultés de langage, l'illettrisme ou le manque de compréhension de l'étude dans sa totalité, ainsi que les obstacles culturels dus principalement à l'importance de la vie communautaire et des diversités sociales ont été identifiées dans les 44 études qui ont été passés en revue.

Dans le cas de populations de patients vulnérables, le consentement éclairé doit être taillé à leur genre et à leur stade de développement et concurrentement, l'assistance psychosociale est fondamentale. Le consentement des enfants et des adolescents doit être assuré. La langue locale doit être utilisée et les chefs de communautés de confiance et des représentants culturels devraient transmettre l'information. En dépit de la nature diverse de ces études, des similarités ont été identifiées. Les pré-conditions/pré-requis fondamentaux de cette étude sont la provision adéquate et compréhensive d'informations et l'évaluation de la juste compréhension de la recherche.

Des solutions potentielles aux secteurs de préoccupations cruciales sont entre autres l'assistance psychologique par les pairs du groupe lui-même et des réunions avec les chefs des communautés locales ou les représentants culturels. Les chercheurs internationaux dans le domaine de la recherche humaine sur le VIH devraient tenir compte de ces problèmes moraux et de leurs solutions potentielles, quand ils tentent d'assurer le comportement éthique dans la recherche, sur la base d'un consentement véritablement informé et culturellement pertinent.

Mots clés: VIH/SIDA, tests cliniques, monde en voie de développement; consentement éclairé.

Introduction

Ethical dilemmas and policy issues regarding the framework of biomedical research on human subjects still remain under continuous evaluation (Bhutta, 2004). Western societies articulate policy issues regarding the ethical conduct of human research, with particular emphasis on international, collaborative clinical trials in the developing world. One of the most challenging areas of policy development involves the informed consent process in poor-resource countries, especially when conducting clinical trials in the developing world (Dawson & Kass, 2005; Hyder & Wali, 2006). Obtaining a truly informed and culturally relevant consent is fundamental to ethical research conduct and of particular importance in populations of non-Western societies, where illiteracy and unawareness of medical rights prevail.

The AIDS epidemic has infected more than 50 million and claimed the lives of more than 20 million people worldwide; its devastating effect is particularly seen in the Third World. Such a chronic, infectious disease offers tremendous opportunities for

research given the need for discovering new drugs and vaccines and developing new strategies for treatment and prevention. In those countries' HIV research, it is questionable if informed consent is properly implemented and if the prospective subjects understand the concept, its process of administration and its implications. Specific issues need to be addressed in therapeutic trials, in preventive vaccine trials and in research involving adolescents, pregnant women and/or perinatal intervention (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2004; Lindegger & Richter, 2000; Muthuswamy, 2005).

The rationale of our review was to describe and critically examine several of the most important ethical issues and practical complexities arising during the informed consent process in HIV clinical trials in the developing world. Potential solutions to those ambiguities, as well as reported suggestions to improve the informed consent procedure are also analysed. By addressing those most important problems, we aimed to enhance the understanding of key issues regarding the informed

consent in HIV research in the developing world. Implementing the most appropriate and effective consent can ensure that research is conducted with the highest ethical standards.

Objectives

The major objective of our study was to review the informed consent process in clinical trials in the developing or resource-limited nations in general, and specifically for AIDS human research. Thus, we focused on the informed consent of HIV-positive adults in the developing world and their potential participation in therapeutic clinical trials. Secondary endpoints of our study included the analysis of the most important challenges when obtaining an informed consent from affected vulnerable patient populations in the developing world willing to participate in clinical research. As a result, we focused on informed consent and assent of children and adolescents participating in therapeutic clinical research and preventive vaccine trials, respectively, on informed consent of affected women and young girls willing to participate in research, as well as of pregnant women willing to prevent vertical disease transmission.

Data and methods

The electronic bibliographic databases of MEDLINE and EMBASE were searched from 1998 to December 2008 using the search terms 'HIV/AIDS', 'clinical trials', 'informed consent', 'developing world'. Original articles, descriptive or interventional, as well as previous review articles concerning informed consent in HIV human research in the developing countries were included. No age, sex or types of clinical trials restrictions were needed. As a result, almost all available studies on adults, children, adolescents and pregnant women were retrieved, derived from the extensive literature review. Informed consent when HIV-testing, as well as in therapeutic clinical research, preventive vaccine trials and trials preventing vertical disease transmission were included.

The articles reviewed, based on our professional experience, were divided into three major categories: informed consent of HIV-affected adults participating in clinical trials, of children and adolescents recruited to participate in therapeutic research or preventive vaccine trials, as well as of HIV-positive women presenting as potential research participants and/or of pregnant women willing to prevent vertical disease transmission.

Data from the reviewed articles were collected and analysed on the basis of one or more of the four essential components of the informed consent as described by the Council for International Organizations of Medical Sciences (CIOMS, 2002): disclosure of all relevant information about the research; comprehension

of this information by the prospective participant in order to make an informed decision; freedom of the prospective participant from any coercion, undue influence, inducement or intimidation; explicit and formal consent by the participant, usually in written form (CIOMS, 2002; Macrae, 2007).

Results of desk review

Based on the aforementioned systematic criteria, a total of 44 studies were reviewed. Ten articles involved the informed consent in the developing world in general, while 15 analysed the consent process in therapeutic clinical research of HIV-positive adults. Nine articles addressed the informed consent of children and adolescents recruited to participate in therapeutic research or preventive vaccine trials respectively (from those only 2 papers involved studies on HIV-positive infants and children). Ten studies focused on women participating in clinical trials and/or HIV-positive pregnant women willing to prevent vertical disease transmission.

A. Informed consent in the developing world and in HIV/AIDS research of affected adults in resource-limited nations

I. Cultural barriers

Informed consent is considered the cornerstone of biomedical research. Current guidelines for research ethics must be modified to include the operational flexibility of applying the informed consent process in resource-limited countries (Crigger *et al.*, 2001; del Rio, 1998; Faden & Kass, 1998; Shaibu, 2007). The application of standards for consent can be daunting for researchers when they face the pragmatic constraints of the field and the reality of cultural beliefs about consent in the developing nations (Crigger *et al.*, 2001; del Rio, 1998; Faden & Kass, 1998; Shaibu, 2007). The implementation of consent in Botswana, for instance, was influenced by several factors: family-centered decision-making, cultural dynamics pertaining to sex, relationship to older persons, and the caregiving arrangement (Shaibu, 2007). Furthermore, certain principles of individual informed consent may not be in keeping with the cultural norms and practices of non-Western societies (Crigger *et al.*, 2001; Hyder & Wali, 2006; Macklin, 1999; Shaibu, 2007; Zion, 2005(a)). Investigators quickly discover that there is a need to reconstruct the standards of informed consent in the developing world, with full recognition of cultural diversities, cultural preservation and plurality of standards (Crigger *et al.*, 2001; Macklin, 1999; Shaibu, 2007; Zion, 2005 (a)).

A detailed overview of the informed consent process in HIV vaccine trials of South Africa (Moodley, 2002) revealed the extent to which informed consent concepts are interpreted

differently, in different parts of the world. The clash between the communitarian cultures of the developing societies and the autonomy orientation of the informed consent requirements of the Western world has to be addressed. In traditional, rural, African communities, patients are considered as members of the society rather than autonomous individuals. In such civilisations, 'research is an altruistic endeavour for the benefit of communities and societies' (Marshall & Rotimi, 2001). Western ethical concepts, which emphasise the individual over the community – the private over the public sphere – would be mostly difficult to transpose to such cultures (Lau *et al.*, 2008). Culture in the developing world is dynamic and, although constantly changing, family-centred is more common than individual decision-making. In such non-industrialised societies, decision-making is the prerogative of a group that might be the extended family or even community leaders (Shaibu, 2007). Furthermore, communities of the Third World have operated under the consent 'the doctor knows it all and has my interests at heart' (Makgoba, 2002). The lack of public understanding of doctors' and/or of scientific methods' fallibility or limitations (including those of clinical trials') seem to be some of the unresolved cultural issues in AIDS trials; a clash of the scientific culture with the non-expert, traditional culture. Because of cultural barriers, research participants in the developing world might give consent that is uninformed by Western standards (Crigger *et al.*, 2001). Furthermore, patients of the developing world might be intimidated by the authority of the physician and might be afraid to ask questions, or state their unwillingness to participate in the research trial (Karim *et al.*, 1998). In most settings in Africa due to cultural barriers, truly voluntary, valid informed consent may be problematic and difficult, and it may even preclude ethical research conduct (Annas & Grodin, 1998). In such cases counsellors might be more effective in communicating and providing information regarding the research (Fitzgerald, Marotte, Verdier, Johnson & Pape, 2002; Muthuswamy, 2005; Woodsong & Karim, 2005).

Cultural barriers during human research in the developing world include the symbolic power of blood and other bodily fluids or tissues in non-Western countries; they may have an impact on the understanding and signing of the informed consent form in HIV human studies (Taylor, 1991). As widely reported, the use of contraceptive methods – principally condoms – which is recommended throughout an HIV/AIDS clinical trial, represents another cultural issue to be solved; in most countries of the developing world they are not used, since they are perceived as instruments to promote unfaithfulness and extra-marital relationships (De Bruyn & Paxton, 2005).

Recent publications suggest that the informed consent comprehension is enhanced, when study participants are provided with information prior to consent and when study communities are engaged in discussion about research – through counselling, meetings with local leaders or public forums (Crigger *et al.*, 2001; Dickert & Sugarman, 2005; Muthuswamy, 2005). Respecting the community and its values is essential: the research protocol should start and end with the community (Crigger *et al.*, 2001). Woodsong and Karim (2005), based on their experience with the HIV Prevention Trials Network, outlined a full model designed to enhance the informed consent process. The model focused on both individual and community concerns and included three stages: pre-enrolment, enrolment and post-enrolment. Understanding of the information discussed during the consent process is reported as enhanced through counselling and consultation with cultural experts and/or local cultural representatives (Fitzgerald *et al.*, 2002; MacQueen *et al.*, 2004; Marshall & Rotimi, 2001; Strauss *et al.*, 2001; Woodsong & Karim, 2005). Joining the community is recommended: the researcher's most effective method is an open dialogue allowed between himself or herself, the community representatives and the research participant (Crigger *et al.*, 2001). Researchers should partner with the community in all phases of formulating, planning and assimilating the informed consent process, instead of presenting as a powerful stranger (Crigger *et al.*, 2001, Hyder & Wali, 2006). It is important for non-Western research participants not to disengage from their cultures; Western procedures might have limitations and local cultures might dictate the norms (Crigger *et al.*, 2001; Shaibu, 2007). There is also a need to reconstruct the standards of informed consent with reference to social and cultural conventions that might influence decision-making. Informed consent in non-Western countries should not be modelled only on Western standards; the choice of culturally acceptable strategies of decision-making in informed consent is central to people's definition of themselves in relation to their natural and social environment (Crigger *et al.*, 2001; Shaibu, 2007). More flexibility in informed consent regulations and the need of Western Institutional Review Board (IRB) members to be more familiar with the local context of the research are some of the recommendations to improve informed consent procedure in clinical trials in the developing countries (Dawson & Kass, 2005; Klitzman, 2008; Shaibu, 2007).

II. Stigma and discrimination, privacy and confidentiality

The HIV epidemic has pushed the affected individuals of the developing world to the margins of their societies. Stigma and discrimination can hamper all AIDS patients. While screening

the population for the disease, researchers should always take into consideration an individual's right to refuse HIV testing (Muthuswamy, 2005).

Maintaining confidentiality and anonymity during research conducted in the developing world represents another major issue (Muthuswamy, 2005; Shaibu, 2007). Participants enrolled in research do not hesitate to share their private information with neighbours or other family members who happen to drop in during interviews. Arrangement of homes also does not induce privacy; study interviews might be conducted in very small, poor rooms or under the shade of a tree, thus enabling others to intrude (Shaibu, 2007).

III. Participants' autonomy

Ethical conduct of human research in settings of the developing world, where rights are not protected, is crucially important (Abdool Karim, 2000; Karim *et al.*, 1998; Kass & Hyder 2001; Pace *et al.*, 2005; Shapiro & Meslin, 2001; Upvall & Hashwani, 2001).

Diminished study participant's autonomy is a common phenomenon in poor-resource countries (Bhutta, 2004; Dawson & Kass, 2005). In such non-industrialised communities with excessively high levels of poverty, concerns are raised that payment provided to study volunteers may unduly induce participants to enrol in the HIV/AIDS clinical trial. Payment, even if small, is potentially seen as coercion, when those recruited are very poor or if the benefits are substantial (Crigger *et al.*, 2001; Zion, 2005(b)). Furthermore, when no other treatment options are available, voluntary choice to participate in the research is questionable. Since highly active antiretroviral treatment is not available, or if available, not affordable to affected populations of non-Western societies, patients might agree to participate in HIV clinical research in order to receive some form of medical care (Muthuswamy, 2005). In the absence of health care, virtually any offer of medical assistance (even in the guise of research) will be accepted as better than nothing and research will almost inevitably be confused with treatment, making informed consent even more difficult (Annas & Grodin, 1998). Although African countries have established comprehensive programmes for HIV/AIDS, a gap still remains between the number of people who need treatment and those who benefit from the available support. In this context, HIV patients of resource-limited countries may regard participation in therapeutic clinical trials as a necessary alternative (Abdool Karim, 2000; Muthuswamy, 2005).

There has been much debate and discussion in the scientific community about ensuring justice for trial participants. It is

necessary that potential volunteers are adequately informed of both the long- and short-term consequences of initiating prolonged regimes of multiple antiretroviral drugs. Ethically it is necessary to ensure that these participants have sustainability of care and access to drugs even after the trial ends. Different groups have come up with innovative approaches to ensure that research participants continue to be provided with care through co-payments, pharmaceutical donations and drug funds (Salvi & Damania, 2006). However, the very concept of providing sustained care has, paradoxically, led to another ethical dilemma: Would the decision to participate in the trial or not be influenced by the prospect of receiving care and effective drugs? Although funds from international health agencies have made standard antiretroviral treatment available in many African settings, limited infrastructure and facilities may oblige HIV-positive patients to enrol in research in order to receive antiretroviral therapy. In addition, although problematic, the use of cash incentives might be necessary to cover transportation costs.

Furthermore, individuals of the non-Western societies may defer decisions to family members or to community leaders (Dawson & Kass, 2005; Kass & Hyder, 2001; Macklin, 1999; Shaibu, 2007; Shapiro & Meslin, 2001; Zion, 2005(a)). Permission for inclusion in research trials in the developing world is reported to be sought from a family member (Kass & Hyder, 2001; Macklin, 1999; Shaibu, 2007; Shapiro & Meslin, 2001; Zion 2005(a)). In some cases decisions may lie with a male member of the family even if he is not necessarily the head of the family (Shaibu, 2007). Community leader or family-centered decision-making might be more common than individual decision-making. As a result, truly voluntary individuals' participation in HIV research of the developing world remains under question.

Voluntary participation depends on accurate understanding not only of the purpose and design of the study, but also of the possibility to withdraw from it at any time. Most of the black population participating in a study of parental HIV transmission in South Africa, reported they felt compelled to participate in the study and believed that the hospital would not allow them to withdraw, because they thought refusing would compromise their care (Karim *et al.*, 1998). To address concerns about coercion, eligible subjects must always be told they are free not to participate in the study if they are unwilling to do so, and that they are capable of withdrawing from the research whenever they wish.

In HIV human research, participants' truly voluntary consent is essential. Any screening or testing for the disease demands right to self-autonomy, with the provision of best possible services of pre- and post-test counselling (Muthuswamy,

2005). Muthuswamy (2005) suggests that counselling, prior to informed consent should be performed in a conducive and enabling environment, preparing patients with accurate information to cope physically and mentally with the disease burden, as well as to evaluate the availability of all therapeutic facilities. The recognition of all possible risks and benefits from the research and decisions on treatment options free from any undue influence, inducement or intimidation should be considered. The right to refuse HIV testing or to participate in human research trials should also be respected and no undue pressure or coercion should be exercised on each individual potential study participant.

IV. Illiteracy, language difficulties or inadequate information?

Language barriers, as well, raise significant concerns with regard to candidates' full comprehension of the technical, product and methodological information of the research (Bhutta, 2004; Dawson & Kass, 2005). In Africa and most developing countries, people speak and live for most of their lives in a different language from the language of the researchers and practitioners, and with an educational level far below standard. However, interpretation of study purposes includes not only the translation of language, but cultural factors as well (Kaufert *et al.*, 1998). Potential participants may lack education or exposure to Western scientific concepts in health research and their language might lack terminology for these concepts (Dawson & Kass, 2005). The need to translate scientific terms, particularly when there are no equivalent expressions for certain words, raises difficulties in the comprehension of the informed consent. International investigators argue that in many African languages there is no word for research or science and that in some of them, these are the same words as medicine (Kass & Hyder, 2001). Research participants might be unable to assimilate the study information owing to educational limitations, since illiteracy prevails, and might give an informed consent that is uninformed by Western standards (Crigger *et al.*, 2001).

An article by Achrekar and Gupta (1998), raised the major issue of how 'actually informed' the informed consent is. The authors studied the design of a placebo-controlled trial conducted in Thailand to evaluate the safety and efficacy of zidovudine to reduce perinatal transmission of HIV. A comparison of the two versions of the informed consent form – Thai and English version – revealed a number of inconsistencies concerning the description of the study-related procedures. One of the inconsistencies reported by the authors was that the word 'placebo' or a synonym one did not appear anywhere in the

Thai version, but was referred to in three different points of the English version, under the phrases 'placebo', 'inactive substance' and 'sugar pill'. In lieu of 'placebo', the Thai informed consent form included the following phrase: 'comparison drug that does not contain zidovudine' (Achrekar & Gupta, 1998). In such situations, however, where the information disclosed may be inaccurate, incomplete, or even misleading, consent cannot be genuine. Additionally, most researchers argue that the concepts 'randomisation' and 'placebo' used in clinical trials can be especially hard to explain, particularly when international researchers are working with communities and individuals who may be illiterate (Muthuswamy, 2005). Suggestions about how to combat therapeutic misconception and subjects' failure to understand the unfamiliar terminology of 'randomisation', 'placebo' or 'double blind' in trials of the Western societies, should be adapted to the context of the developing world as well, where certainly the notions of 'chance', of 'inactive medical substance' and of 'someone purposely choosing not to know something' can be explained in local languages. Furthermore, although placebo-controlled trials produce must faster results and are favoured by the scientific community, in a situation such as HIV/AIDS where accepted modes of intervention are available, it is unethical to conduct placebo-controlled trials (Resnik, 1998). Experimental designs should compare different therapies instead of using a placebo-group (Resnik, 1998).

Providing adequate and comprehensible information remains the principal prerequisite of the informed consent process. In this context, all study-related procedures should be presented in the local language and addressed to varying levels of age, sex and education, both orally and in writing, thus enabling participants to fully comprehend the design, risks and potential benefits of the clinical study (Mills *et al.*, 2006). Flexibility in the documentation and securing of such consent, both on the individual and community level, is demanded (Hyder & Wali, 2006). Language may be a barrier to understanding and this can be resolved by ensuring that native language speakers translate either the script or the spoken word (Crigger *et al.*, 2001). Elementary language should be used in communication with participants and not the technical or high-level language used in the informed consent forms of the Western societies. Dialects can also be used, sensitive enough for the concepts discussed. Words must be clear and have the correct meaning. The training of translators in research methods may help to eliminate or reduce the introduction of personal interpretations and attitudes (Crigger *et al.*, 2001). Furthermore, a case control study on HIV-1 transmission in Haiti assessed research volunteers' comprehension of the informed consent (Fitzgerald *et al.*, 2002). The authors concluded that participants can comprehend a complex consent form, if sufficient care is

taken to inform them. They noted that the comprehension of the consent process increased substantially when preceded by several meetings between volunteers and investigators, in which information about the study was provided; the standard consent process of a single meeting between investigator and volunteer was found insufficient. They recommended the presence of a counsellor; counsellors had more experience in communication methods and information disclosure, when compared to physician investigators (Fitzgerald *et al.*, 2002).

V. Signing the written informed consent

Obtaining written informed consent from HIV/AIDS study participants is considered a fundamental requirement. Still, drawing the distinction between the signed informed consent form and the truly understood informed consent is of particular importance.

Signing a paper for participation in a clinical study may seem inconceivable in some countries, either because of the level of illiteracy, or because the procedure might carry substantial risks; in oppressive regimes for instance, where force of any kind can be applied to potential study participants (Shapiro & Meslin, 2001). Furthermore, most of the HIV-positive patients in the developing world are of low socio-economic and educational status, with limited awareness of their disease burden, not capable of understanding and signing an informed consent. On the other hand in many cultural settings, agreements based upon trust do not require a signature. For example, in comparing the negotiation of informed consent in Pakistan and Swaziland (Upvall & Hashwani, 2001) participants were uncomfortable signing the form to participate in the study if they were illiterate or did not understand its content. Signing a consent form was particularly threatening to those patients, since signatures were only used for documenting major events such as marriage. Western guidelines for research can be problematic, especially when dealing with older people, who become suspicious when researchers insist on written consent (Shaibu, 2007).

In any case, obtaining a signed informed consent is no guarantee that the participant has truly understood the proposed research (Pace *et al.*, 2005; Shapiro & Meslin, 2001; Upvall & Hashwani, 2001). Research conducted on populations in developing nations often challenges the ability of participants to understand sufficiently the research and its implications (Crigger *et al.*, 2001). Pace *et al.* (2005) noted that although most responders, in a study on comprehension of consent from a randomised drug trial among HIV-positive patients in Thailand, said they were well informed only one-third of them reported that half of the participants would receive the experimental drug.

B. Informed consent in HIV/AIDS complex research of vulnerable patient populations in the developing world

I. Enrolling adolescents and children

Adolescents of the developing world are severely affected by the HIV epidemic. In sub-Saharan Africa for instance, about 10 million young people – aged between 15 and 24 – are living with AIDS. Disease prevention with vaccine trials in this vulnerable subgroup of patients is of particular importance (Pettifor *et al.*, 2005; Shisana & Simbayi, 2002).

Preventive vaccine trials require participants' informed consent at a multi-step process (UNAIDS, 2004). Primarily, informed consent must be obtained prior to the initiation of any screening procedure; such a screening is performed solely for the purpose of determining eligibility for participation in the study. Once judged eligible for enrolment, the individual should be fully informed about the nature, risks and potential benefits of the study, so as to give free consent to participate. Subsequent efforts should be made by the investigators throughout the trial to ensure that participation continues to be the result of a voluntary, well-informed and un-coerced choice (UNAIDS, 2004).

Various ethical complexities arise when trying to obtain an informed consent from adolescents of HIV vaccine trials. In South Africa, for adolescent trials to be lawful, consent must be given by a participant with legal capacity to consent, or if not competent, by a person with the authority to consent on the participant's behalf. As already pointed out, it is one thing to endorse the enrolment of adolescents in AIDS vaccine clinical trials and another to actually enrol them (UNAIDS, 2004). One of the most intriguing challenges for the researcher is to obtain informed consent from the parents or legal guardians, while protecting the privacy rights of the adolescent. Although it is legally acceptable for an eighteen year old male living at home to make his own decisions, it is customary for the son to obtain the consent of his father before entering into any obligation or contract, including participation in research (Loue & Okello, 2000). The social stigma and discrimination attached to AIDS, especially in the developing countries, severely hampers this demanding effort. Moreover, the consent process may force young people to admit their sexual activity, which could potentially result in a series of severe adverse consequences for the adolescent. Privacy rights for sexual risk information and HIV status will have to be delineated and both parents and adolescents will have to understand what information parents will/will not have access to.

Most South African research ethics committees have relied on the recommendations made in ethical guidelines which broadly require parental or guardianship consent for research plus the assent of the adolescent (Slack *et al.*, 2007). There is an implied legal obligation to obtain assent; as 'assent' is the means by which to get the adolescent's perspective to establish their 'best interest' for every matter with which they are concerned. Assent has been variously defined as: 'the agreement to participate in research based upon less than full understanding', 'the initial and ongoing willingness of the participants themselves to participate' and 'a subject's affirmative agreement to participate in research' (Slaughter *et al.*, 2007).

Slack *et al.* (2007) concluded that investigators responsible for preventive vaccine trials should plan all complex consent processes required, including assessment of adolescents' understanding. They suggested that the consent protocol should focus on broader ethical requirements to promote the adolescents' welfare, as well as on what information should be disclosed to parents. They recommended that consent before the inclusion of an adolescent in an HIV/AIDS vaccine trial should also be obtained from the parent/legal guardian. Moreover, adolescents and their parents/legal guardians must fully understand the research to be able to provide assent and/or consent to participation. Adolescents should agree to participate in the vaccine trial if they are capable of assenting (Jaspan *et al.*, 2008; Mc Clure *et al.*, 2008; Slack *et al.*, 2007). The adolescent's right to autonomy should be respected, while post-consent testing should provide verification of adolescents' understanding of concrete elements of the research (Slack *et al.*, 2007). Adolescents who agree to enrol in the research trial should receive comprehensive prevention counselling, tailored to their developmental age (Mc Clure *et al.*, 2008). The information sheets for informed consent for adolescents and their parents/legal guardians should address age-specific concerns to ensure truly informed consent (Bekker *et al.*, 2005). Parental permission is reported as necessary to protect the minor's interests. Thus, parental concerns to post-study vaccine-induced seropositivity, as well as to the stigma and fear of such an HIV-positive diagnosis should be addressed (Mc Clure *et al.*, 2008). Agreement to participate to Phase I/II trials of safety and immunogenicity should be given by potential study participants and their parents only after thorough evaluation of information available from previous trials among adults and only if the research does not place them at greater than minimal risk (Jaspan *et al.*, 2008; Mc Clure *et al.*, 2008). Reasonable safety data should be available after trial completion in an adult cohort (Bekker *et al.*, 2005; Jaspan *et al.*, 2008; Mc Clure *et al.*, 2008; Slack, *et al.*, 2007). Protocols should be designed in close consultation with local community leaders and community

attitudes, adolescent consultants and experts (Mc Clure *et al.*, 2008), as well as with regulatory authorities (Jaspan *et al.*, 2008). Recruitment materials and clinic sites that are friendly, attractive and accessible to adolescents should be used (Mc Clure *et al.*, 2008). In setting an appropriate youth-friendly environment to attract adolescents, the trial sites must also consider the parent/legal guardian who will need to be assured of professionalism and expertise (Bekker *et al.*, 2005). Youth language and peer education should be available, along with the establishment of mechanisms for protection of study volunteers (Mc Clure *et al.*, 2008). Since most of these trials are of minimal individual benefit, appropriate community education, peer support, adequate counselling, community preparedness and clinical services before and after the trial should be available (Bekker *et al.*, 2005).

Limited data are available as far as children are concerned. Children's participation in research trials requires the fully informed consent of the parent or legal guardian, to whom most of the information is commonly directed. For non-therapeutic trials 'assent' must be obtained from children at appropriate developmental ages. The age of assent for all HIV-paediatric clinical studies, including those in resource-limited nations (Little *et al.*, 2008) is seven years.

Research subjects should not be drawn from such a vulnerable population in the developing countries unless the population is the only group in which the research can be conducted and the group itself will derive benefits from the research (Annas & Grodin, 1998). The development of medicines for children lags years behind those of adults and a global standard register for HIV therapeutic clinical trials for children is only recently finalised (Keeton, 2007). Despite increased availability of antiretroviral therapy in the developing world, children remain a neglected population. Initial results from the Children-with-HIV-Early-Antiretroviral-Therapy (CHER) study have found a significant increase in survival among infants who received immediate antiretroviral therapy, when tested HIV-positive within their first six weeks of life. All the mothers recruited in the trial took part in group screening sessions and individual sessions to help them understand what joining the trial would mean and give a truly informed consent. Mothers were given a summary of the treatment to take home and study and after doing so, they had an individual session with their treating physician. Diagrams and questions were used to assess their understanding of the research and importance of early treatment of their affected children. A long informed consent form was given to them and had to be signed prior to treatment initiation; the form was available in seven different languages (Keeton, 2007).

II. Enrolling affected women, young girls and/or pregnant women

Enrolling women in HIV/AIDS clinical trials represents another, equally daunting, challenge that needs to be addressed (De Bruyn & Paxton, 2005; Homsey *et al.*, 2007; Karamagi *et al.*, 2006; Mills *et al.*, 2006; Pettifor *et al.*, 2005; Salvi & Damania, 2006). Mills *et al.* (2006) when examining patients' recruitment and enrollment in HIV vaccine trials reported that women in poorer countries often lacked formal education and could not fully understand the uncertainty that existed within clinical trials; known as the 'therapeutic fallacy' in the medical ethics literature. Furthermore, women's decision-making was often subject to parental or husband control, religious coercion or social hierarchy, conditions under which free informed consent was unfeasible to obtain (De Bruyn & Paxton, 2005; Homsey *et al.*, 2007; Karamagi *et al.*, 2006; Salvi & Damania, 2006; Shaibu, 2007; UNAIDS, 2004). Most of the women who tested HIV positive experienced significantly more discrimination from their partners, families and community members (Homsey *et al.*, 2007; Karamagi *et al.*, 2006).

In an effort to explore the cultural problems that hindered women's enrolment in HIV clinical trials, De Bruyn and Paxton (2005) concluded that the need for partner consent was the main reason for opting out of routine HIV testing. Furthermore, women in a polygamous marriage refused to participate in preventive vaccine trials because the use of contraceptives was recommended. They feared that using contraceptives would give their husbands an excuse to look for another woman with whom to bear children.

Providing care to adolescent girls may further complicate the informed consent process, mainly because of their additional vulnerabilities; in some cultures, adolescent girls may not be able to exercise true autonomy in the light of gender norms and the influence of their parents or partners (Pettifor *et al.*, 2005; Shisana & Simbayi, 2002).

Enrolling women and girls in HIV clinical trials is of particular importance when trying to reduce the incidence of HIV-positive children born in the developing world. Several countries have initiated pilot projects and national programmes to help infected women give birth to healthy children; trials to prevent such vertical transmission from mother to child engendered fierce debate and resulted in voluminous published literature (Annas & Grodin, 1998; Mayss, 2000; Resnik, 1998). Before obtaining an informed consent from such potential research participants a variety of ethical issues need to be addressed. Many women feel pressured into HIV testing during pregnancy in order to prevent perinatal transmission. As a result, they

do not receive adequate pre-test counselling, do not fulfil the standard criteria for adequate informed consent and do not actually give a truly informed consent (Muthuswamy, 2005). Interviews with women subjects of the placebo-controlled trial in the Ivory Coast supported this conclusion. Pregnant mothers stated that the reason for their entering the study was the offer of free health care to themselves and their babies, along with the hope to shield their babies from a deadly infection. The prospect of help as they brought their babies into the world made taking part in the experiment all but irresistible (Annas & Grodin, 1998). Mothers should be informed on all aspects of the clinical trial; the exercise should not focus only on preventing the disease transmission to their child. The effect of treatment on their body, with its potential risks and harms, should always be taken into consideration, along with the fate of all untreated mothers (Muthuswamy, 2005). It is reported as unfair to test women during pregnancy solely or mainly to prevent perinatal transmission (Taylor, 1991). The criticism that these strategies result in saving children from HIV infection but also lead to a life of an orphan still represents a matter of debate and should always be discussed with the infected mother prior to her consenting to the clinical trial (Muthuswamy, 2005). More recently, emphasis has shifted from voluntary HIV counselling and testing to routine or even mandatory testing of women during pregnancy (Armstrong, 2008). Still, many barriers remain for pregnant women in terms of access to testing, care and treatment in resource-limited nations and mandatory HIV testing during pregnancy cannot be justified (Armstrong, 2008). Perinatal intervention designed to prevent maternal-foetal transmission should always be linked to available HIV care services for the mother (Taylor, 1991). Nevertheless, many pregnant women are more receptive to HIV testing when they understand that vertical transmission can be prevented, once identified.

Furthermore, the role of breast-feeding while receiving treatment should be discussed; the issue remains problematic and mothers should be given infant-feeding counselling and allowed to make informed choices as to whether to formula-feed or breast-feed (Coutsoudis *et al.*, 2008; Doherty *et al.*, 2007). Breast-feeding cannot be avoided for psychosocial reasons or even because breast-milk substitutes are unaffordable or can cause more harm to the child (Muthuswamy, 2005). Providing formula to poor populations with high HIV prevalence cannot be justified by the evidence, by humanitarian considerations, by respect to local traditions or by economic outcomes. Recent studies suggest that greater morbidity and higher mortality for infants in Africa is associated with the switch to powdered formula. Still, exclusive breast-feeding remains problematic and continuing studies need to address how much of a risk breast-feeding poses to those

vulnerable patient populations. Accumulating evidence on the increase in malnutrition, morbidity and mortality associated with the avoidance or early cessation of breast-feeding by HIV-affected mothers and the unanticipated hazards of formula-feeding, demand a deeper assessment of the measures necessary for optimum policies on infant and child nutrition. (Coutsoudis *et al.*, 2008; Doherty *et al.*, 2007)

Discussion

Despite the heterogeneity of studies involved regarding age, sex and type of HIV clinical trial the most important ethical complexities of the informed consent process in the developing countries addressed through our review were similar. Diminished participant autonomy, social coercion and monetary inducement due to high levels of poverty, language difficulties, illiteracy or even lack of true understanding of the entire study purposes, as well as cultural barriers due to communitarianism or social diversities were identified (Annas & Grodin, 1998; del Rio, 1998; Faden & Kass, 1998; Keeton, 2007; Macklin, 1999; Mayss, 2000; Resnik, 1998; Salvi & Damania, 2006; Zion, 2005(a); Zion, 2005(b)).

Providing adequate and comprehensible information remains the principal prerequisite of the informed consent in almost all articles involved. Thus, we suggest that every study-related procedure should be presented in the most simple, local language and addressed to varying levels of age, sex and education, both orally and in writing. Words must be clear and have the correct meaning, while oral documentation of consent might be a necessary alternative. Assessment of understanding of the entire research purposes prior to consenting through specific assessment measures such as self-reports, check-lists, diagrams or question and answer sessions are also fundamental.

Moreover, informed consent in HIV human research should preferably be considered as a continuing process rather than a discrete event or a mere formality. It is therefore important that participants are questioned on their understanding of the trial process not only when they are screened for eligibility, but throughout the entire study. In addition, to address concerns about coercion, eligible subjects must always be told they are free not to be tested for HIV or participate in the study if they are unwilling to do so, and that they are capable of withdrawing from the research whenever they wish.

The results of our desk review also emphasise the importance of counselling. Counselling prior to consenting is reported as absolutely warranted in all types of clinical trials reviewed. As a result, peer counselling is necessary when screening the population, testing for the disease and/or prior to any

type of experimental treatment initiation in affected adults (Muthuswamy, 2005). Furthermore, adolescents who agree to enrol in preventive vaccine trials should receive comprehensive prevention counselling, tailored to their developmental age (Mc Clure *et al.*, 2008). Pregnant women should undergo counselling sessions prior to participating in research preventing vertical disease transmission (Resnik, 1998) or prior to consenting to treatment initiation of their affected infants (Keeton, 2007). In addition, mothers should be given infant-feeding counselling and allowed to make informed choices as to whether to formula-feed or breast-feed (Coutsoudis *et al.*, 2008; Doherty *et al.*, 2007). Counselling should be performed in a friendly, enabling environment, preparing patients with accurate information to cope with the disease burden, as well as to evaluate the availability of all therapeutic facilities and the entire research purposes (Muthuswamy, 2005). Trained counsellors have been reported as having more experience in communication methods and information disclosure, when compared to physician investigators (Fitzgerald *et al.*, 2002).

Additional, not necessarily different, ethical concerns must be covered when obtaining informed consent for complex HIV research with potentially vulnerable participants in the developing nations. Research subjects should not be drawn unless the population is the only group in which the research can be conducted and the group itself will derive benefits from the research. Adolescents' assent, as well as consent from their parent or legal guardians, should always be obtained (Slack *et al.*, 2007). Our desk review also suggests that future HIV research involving children in the developing world is absolutely warranted; trials preventing vertical disease transmission and treating affected children during their first weeks of life are absolutely mandatory (Keeton, 2007).

Another major concern emphasised throughout our entire study is that due to cultural differences between the developed and the developing societies it is often difficult to obtain adequate consent. In most settings in Africa due to cultural barriers, truly voluntary, valid informed consent may be problematic, and it may even preclude ethical research. We believe that the proper response to these difficulties is to develop an interpretation of the principle of consent that can be applied in the developing nations. The standards of consent need to be constructed with reference to social and cultural conventions that might influence decision-making. Informed consent in non-Western countries should not be modelled only on Western standards, since local conditions play a key role in determining how to apply the ethical principles of research. It is important for non-Western research participants not to disengage from their cultures; Western procedures might have limitations and local cultures might

dictate the norms (Crigger *et al.*, 2001; Shaibu, 2007). Respecting the community and its values is essential: the research protocol should start and end with the community (Crigger *et al.*, 2001). Joining the community is recommended: the researcher's most effective method is an open dialogue allowed between himself, the community representatives and the research participant (Crigger *et al.*, 2001). Based on our findings, we suggest that researchers should use trusted community leaders and/or local cultural representatives to convey information to local people.

Adaptations reported as absolutely necessary to the informed consent in AIDS clinical trials in the developing world include community-level consultation and permission prior to consent, as well as alternative methods of documentation given the high levels of participants' illiteracy and language difficulties. A variety of methods for information disclosure during the informed consent process in developing countries have been described, such as explanation or questions and answers sessions, community meetings and pictorial descriptions (Fitzgerald *et al.*, 2002; Hyder & Wali, 2006; Muthuswamy, 2005; Woodsong & Karim, 2005). At the same time, a variety of methods for consent documentation have been used; mostly visual documentation of oral consent, written consent and approval from village or community leaders. There is a strong call for use of measures to test participants' understanding of information, such as self-reports and check-lists (Fitzgerald *et al.*, 2002; Hyder & Wali, 2006; Woodsong & Karim, 2005). Socio-economic background, caste, gender, age, and education all express and reinforce differences in relative power of individuals during the consent discussion (Kuczewski & Marshall, 2002).

One of the limitations of our study is that it does not represent a comprehensive review. Nevertheless, we tried to present the results of an extensive literature search in a topic we believe is of critical importance. The increasing number of people suffering from the disease and the subsequent clinical trials that are ongoing or about to begin in the developing world make our manuscript of particular importance. The rationale of our study was to analyse specific ethical and practical complexities of the informed consent process in HIV clinical trials in the developing world in order to improve and promote ethical research conduct. The emerging challenge for researchers in international human studies is to recognise the most important ethical complexities of the informed consent process and develop novel strategies, accommodating local cultural norms in decision-making, without diminishing the importance of respect for the individual.

Conclusions

Unquestionably, the HIV/AIDS human research in the resource-limited nations faces numerous challenges, both ethical and practical ones. Identifying the major key issues of consent can help promote the highest ethical standards of future research. Providing adequate and comprehensive information to potential participants and assessing the understanding of the entire research purposes prior to participants' consenting are fundamental. Respecting the local community customs and cultural expectations from where participants are drawn and at the same time respecting individual autonomy facilitates the process. Recruitment strategies, informed consent included, should preferably be organised in consultation with the community local authorities or advisory boards and piloted within the target community and the local cultural norms to ensure age, gender and social sensitivity. Peer counselling by communication experts is warranted prior to any experimental clinical trial.

Informed consent for complex research with potentially vulnerable participants should always be ensured. Counselling, prior to consenting, is fundamental for those patients' subgroups. Adolescent's assent, as well as consent from their parent or legal guardian, should be obtained before participation in the research.

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