

For women, the results of the stigmatization due to TB have been particularly severe—divorce, loss of work, and separation from their children



The Garden – Aimeé García
Oil/canvas and fabric flowers
(150 x 90 cm)

‘Nothing has changed
The body is susceptible to pain,
It must eat and sleep,
it has thin skin and blood right underneath
and adequate stock of teeth and nails...’

Tortures (Poem) – Wislawa Szymborska

Aimeé García
Matanzas, Cuba

Aimeé García studied at the Vocational School of Art (Matanzas), the Professional School of Fine Arts (Camagüey), and the Higher Institute of Art (Havana). Since 1992, she has held solo exhibitions and group exhibitions in Austria, Costa Rica, Cuba, the Dominican Republic, Israel, Mexico, Norway, South Korea, Spain, United States, and Venezuela. Her works are in the collections of the Arizona State University Art Museum (Arizona); Museo del Barrio (New York); Museo Nacional de Bellas Artes (Havana); Oficina del Historiador de la Ciudad (Havana); and in the University of Virginia Art Museum (Virginia).

CHAPTER 27

Conducting Tuberculosis Vaccine Trials in Vulnerable Communities

Michèle Tameris

South African Tuberculosis Vaccine Initiative (SATVI) has been conducting Phase I and II clinical trials of TB vaccines in the Worcester region of the Western Cape since September 2005. Four of the leading vaccine candidates have been tested in safety and immunogenicity trials in healthy adults, adolescents, children, and infants and in TB and/or HIV-infected adults. In this chapter I hope to share some of our experiences and lessons learnt.

In July 2009, the first infant was enrolled and vaccinated at our research site in a Phase IIb, proof of concept trial of a TB vaccine, the first in almost a hundred years since Koch tested BCG in 1921. The candidate TB vaccines currently in the research pipeline all look very promising and large Phase IIb and Phase III clinical trials, enrolling thousands of volunteers—presumably mostly infants—will take place in the next five years. Unlike a hundred years ago there are now strict regulations and codes of practice for clinical research, with increasing attention being paid to the role of vulnerable communities and groups. The first known regulations governing clinical research were in fact introduced in 1931—the German *‘Richtlinien’*—in response to the Lübeck disaster where, following the large-scale vaccination with the newly introduced BCG vaccine of 250 newborns, 208 developed TB and 77 died (1). The next chapter in the development of research ethical guidelines is the better known Nuremberg Doctors Trials and subsequent Nuremberg Code of 1947 which emphasizes voluntary informed consent by a person, with the legal capacity to do so and in the absence of coercion, to research which is of benefit to society (2). This was followed in 1964 by the World Medical Association’s Declaration of Helsinki, legally binding for all signatories, which

again emphasized the importance of informed consent and also discussed the role of surrogate consent for and assent by persons not legally capable of consent. Subsequent amendments have dealt with the issue of placebos and with post-trial access to identified beneficial procedures and care (3). The Declaration of Helsinki is the first to specifically refer to vulnerable populations which need special protection, specifically mentioning the economically and medically disadvantaged.

The Belmont Report followed in 1979 in response to the Tuskegee syphilis study and introduced the three concepts which have now become the cornerstone of research ethics, namely, (i) *autonomy* of the individual and that those with diminished autonomy, that is, the vulnerable must be protected from exploitation; (ii) *beneficence*, meaning maximal benefit and minimum harm done; and (iii) *justice*, or the selection of participants so that those who bear the risk of the research also stand to benefit from it (4). This last principle implies that women and children, and other minorities, who stand to benefit from the results of a trial and were previously excluded, should be allowed to participate. Their participation also ensures that the scientific findings of a trial are more generalizable.

Section E6 of the International Conference on Harmonization Guidelines to Good Clinical Practice (ICH-GCP) of 1990 provides a unified ethical and scientific standard for the conduct of clinical research to ensure the participant's rights are protected and includes mention of vulnerable communities (5). Section E11 is entirely devoted to research in paediatric participants (6).

The CIOMS published ethical guidelines in 1982, revised in 1993 and 2002, which dealt with research in resource-poor countries by researchers from resource-rich countries and the vulnerability of individuals, groups, and communities, in particular women (7).

In addition to these international codes aiming to ensure the safety and well-being of all trial participants but particularly those considered vulnerable, there are also country specific guidelines and regulations. In the USA, all human subjects are protected by federal law (45 CFR (Code of Federal Regulations) 46 or the Common Rule) (8) with the role of children in clinical research separately addressed in the FDA's 21 CFR 50 subpart D (9) and in the Pediatric Research Equity Act of 2003 (10) which obliges pharmaceutical companies to test medicines intended for children on children. The European Medicines Agency representing the EU members has a similar Paediatric Regulation of 2006 (11) which aims to improve the health of children in Europe by, inter alia, only submitting them to high quality and ethical research. India (12), the Philippines (13), and South Africa (14) have guidelines specifically dealing with research in HIV-positive individuals.

South Africa has developed its own guidelines to GCP (1998, revised 2006) (15) with particular emphasis on special classes of participants such as children and adolescents, pregnant women, prisoners, people with mental disabilities, people for whom English is not a first language, or people from vulnerable communities. It goes on to define vulnerable communities as those of limited economic development, inadequate experience with understanding scientific research, limited available health care and treatment options, and limited ability to provide informed consent, with a section covering HIV-related research including HIV vaccines. Research ethics committees are tasked with ensuring that the rights of these vulnerable peoples and communities are safeguarded, especially with regard to informed consent. It suggests that for 'research to be carried out at community level (e.g. vaccine trials) sponsors are encouraged to establish community advisory groups', ensure good communication of information between the researcher and the community and 'that communities are educated on the aspects of research before recruitment begins. The benefits of research are to be made available to the research population and the local communities from which they were drawn'.

It remains the principal investigator's responsibility to ensure that a clinical trial is conducted according to the protocol, international and national ethical guidelines, and other relevant legislation.

HIV-Positive Participants

The current resurgence in the TB epidemic is attributed to the growing HIV epidemic worldwide as well as to the increase in MDR and XDR forms of the disease. Whereas only 10 per cent of all people infected with TB develop disease, HIV/TB coinfection results in a 30-fold increased risk of active TB, a leading cause of death in HIV-infected persons. For this reason we need a new TB vaccine which is safe and effective in all including those who are HIV-positive.

As previously mentioned, South Africa's GCP (2006) is unique in its inclusion of a section relating to clinical and epidemiological research in HIV-positive individuals, in response to the challenges and failures experienced previously in this field throughout the world. It states [that] 'the many tensions, dilemmas and ethical considerations surrounding HIV/AIDS related research necessitates a wide consultative process. PWAs (People living with HIV/AIDS) are critical to this process and should form part of the consultation from the very early stages of the research process.'

The first major challenge in enrolling HIV-positive individuals in a clinical trial is that of identifying them. Bound by confidentiality, the public health clinic

staff who are performing the HIV tests and providing the antiretroviral (ARV) therapy may not share the identity of those testing positive with researchers. We at SATVI developed a system whereby the HIV counsellor or clinic nurse would ask known HIV-positive clients if they would be interested in participating in a TB vaccine trial and if so, if their names and contact details could be passed on to us. The client would complete a form with his or her contact details, whether we could visit them at home, could phone them, or should wait for a phone call from them in cases where they had not divulged their status at home and were anxious that our visit or call would bring questions they did not wish to answer. The form included an acknowledgement that by providing their details they were disclosing their status to SATVI staff. We could always reassure volunteers that nobody at our trials clinic would need to know their status as there were a number of ongoing trials with adult participants both HIV-positive and -negative with no distinguishers on the files as to HIV status. Confidentiality is a big issue in a small community where the trial nurse or counsellor could be your neighbour or family friend and we take all possible measures to preserve this and make our participants feel 'safe'. This is often difficult when HIV-positive people are still stigmatized. If our SATVI-branded vehicles are seen parked outside the home of someone known to be positive, it is assumed by the community that if our car is outside your home you are also positive. This initially had a negative impact on our enrolment of HIV-negative controls in one study but seemed to improve with time as the HIV epidemic spread, infecting and affecting more people but resulting in an increased understanding and acceptance. An early, non-vaccine trial amongst HIV-positive mothers reimbursed its participants with grocery parcels, supposedly a welcome relief for the largely unemployed group involved. Unfortunately, to be seen leaving the clinic or entering your home with a large parcel of canned goods and other staples immediately got you labelled as being positive and further ostracized the participant so we had to change our practice. According to the South African regulatory body, we are obliged to reimburse all clinical trial participants by a set amount per visit, in cash, an amount which is more than twice the daily minimum wage. In a trial population which is largely unemployed and live in poorly serviced informal settlements the question of undue inducement often arises. Many argue that the screening medical examination alone is an inducement to participation as is the understanding that if clinically significant abnormalities are found during screening the volunteer is referred to the appropriate specialist clinic in the public health system, thus fast-tracking their passage through the system. In the informed consent process, great care is taken to explain the investigational nature of the vaccine, the possible risks of participating, and the volunteer's right not to participate. By this means we hope to prevent participation only for the financial reward.

One must, however, be aware of the problem of ‘professional participants’ who use different IDs to take part in many, often conflicting, trials. For this reason, some research sites use fingerprint identification of all participants.

Although our trial site is in an urban setting, many of the inhabitants have settled here from rural areas in an attempt to access the better social services such as health care and education available; of these, many are illiterate or semi-literate, necessitating an impartial witness to the informed consent process. As the HIV pretest counselling forms part of this process, we ask the witness to attest that we are performing pretest counselling but to be absent from the actual interview as much confidential information about lifestyle choices and personal risk factors are discussed at this point. Similarly, the posttest counselling is done without a witness. Informed consent is only taken in the volunteer’s home language or one nominated by him/her from the three major languages of our area and, wherever possible, the language used is as simple and easily understood as possible. This can be difficult where an individual has limited health literacy, little research insight, and his language of choice does not have scientific vocabulary to adequately explain it.

In our experience, the volunteers for our trial in HIV-infected people were often extremely ill but still not attending the clinic or yet receiving ARVs. Although our cut-off CD4 value is 300, we were screening people with values in the 20s. Previous TB disease or use of ARVs are exclusion criteria to participation which results in many screening failures as HIV is often first diagnosed at the TB clinic or at the first antenatal clinic visit. If a woman is diagnosed at an antenatal visit, she is then started on the Prevention of Mother to Child Transmission (PMTCT) programme’s ARV treatment. Only occasionally do we get to know, after enrolment and vaccination, that a participant has been on ARVs for months or was previously treated for TB. We are not certain whether this is a deliberate withholding of information in order to be included in the trial and gain access to all its benefits or due to a lack of understanding of our questions and terms used, but we are aware of the problem and are developing new ways to pose our questions, explain the trial, and verify the history.

Although we have not yet performed vaccine trials in HIV-exposed and/ or HIV-positive infants, we have done other research in this challenging group. Due to a well-functioning two-drug PMTCT programme in our area, the picture of vertical transmission has skewed and those infants who are born HIV-positive were probably infected early in pregnancy, are often underweight at birth, and sickly from an early age resulting in frequent hospitalizations and a high mortality rate in the first year of life. We were forced to rewrite our protocol many times, reducing the volume of blood drawn at any visit, the number of visits, and even to change our statistical analysis plan from a longitudinal design to a cross-sectional one in order

to ensure sufficient numbers. The effective PMTCT programme also made achieving our recruitment targets difficult.

One big concern when discussing research in HIV-positive persons is the fear that they are being over-researched; in any ARV clinic in the big centres, nursing staff compete with researchers from a variety of disciplines such as social work, clinical psychology, pharmacology, as well as therapeutic and preventative clinical trials, for their client's time and attention. One oft quoted measure of diagnosing 'over-researched' is when you start struggling to get volunteers for your study and trial. It is hoped that through active engagement with the community we will be sensitive to such issues and not become a nuisance factor in the public's eye.

Adolescent Participants

As any parent will tell you, adolescents are a breed of their own and have to be approached in a completely different way from younger children or young adults. In vaccine trials enrolling adolescents, we have to be as sensitive to their physical, mental, and hormonal in-between status as does their parent. As adolescents are considered to have enough insight into clinical research while still being legal minors, their assent has to be obtained as well as the parent or legal guardian's consent. We found this one of the first hurdles as many of the adolescents volunteering were AIDS orphans being raised by a family member who had taken in their deceased relative's children with no desire for material gain and had thus not formalized the guardianship in the courts and were therefore not able to sign consent. Similarly, it is customary in South Africa for children to be sent from the rural areas to a family member in the bigger towns for the better schooling opportunities available there, resulting in the parental signature being difficult or impossible to obtain.

We were initially concerned about the mandatory cash reimbursement for trial participation as our area has a large alcohol and drug abuse problem, especially from *tik* or methamphetamine, amongst the youth. We consulted our community advisory board on this issue with the conclusion that it did not matter what form the reimbursement took, the addict would find a way to convert it to drugs. We have been pleasantly surprised by our young participants who along with new hairstyles and brand-name shoes also tell of school uniforms and school textbooks bought with the money received.

As these adolescents are still attending school, we have to be creative in our clinic appointment times, often seeing them before school or in the school principal's office quickly between lessons. Exam rosters can play havoc with the protocol's permissible window for a study visit as can the long summer

break when these adolescents are sent to family in other towns or districts so that the mother can continue working without worrying about day care.

Vaccine trials require frequent phlebotomy of fairly large volumes of blood. Invasive procedures are never popular amongst participants and adolescents are no different. One of our very few withdrawals ever was a young boy who cried during the phlebotomy and then got teased at school by a fellow participant. Happily a few weeks later he returned saying proudly that he had grown up and was ready to take part again.

Participants in our vaccine trials keep a daily diary for seven days post vaccination, recording local and systemic reactions, with the aid of a thermometer and small ruler for measuring the local reaction. It appears that school-going adolescents are quite accustomed to an authority figure giving and then collecting homework as these diary cards are mostly well kept.

Infants and Children

As any new TB vaccine will ultimately be for use in infants it is essential that safety, immunogenicity, and efficacy are established in this population. Trials also need to be done in this group to ensure non-interference with the standard Expanded Programme on Immunization (EPI) scheduled vaccines, and for dose finding in this age group.

As many of the mothers of the toddlers and infants included in our vaccine trials are unmarried girls younger than 18 years and thus legal minors, we have to seek the consent for enrolment from the infant's grandparent or the mother's legal guardian. We do explain in the informed consent process that the result of certain blood screening tests, which could have implications about the mother's health, will not be revealed to the consenting adult, for example, if an infant tests positive for HIV the implication is that the mother is positive. Our University's Ethics Committee, which functions as our institutional review board, has determined that the TB vaccine trials involve greater than minimal risk to the child but with the added benefit to the individual of medical care received during study participation which does mean that only one parent need sign consent. However, we have agreed to obtain the consent of both parents, where possible. Mothers are actively encouraged to discuss the study with the child's father before enrolment even if they are not married or cohabiting, and the father has no legal custody; our staff documents her comments on this topic. We are also obliged to inform the parents that as we do visit their homes, for example, to remind them of appointments, if we do see anything which could be interpreted as child abuse we are legally and morally obliged to report it to the appropriate authorities.

For the first time in our years of recruiting participants, we are experiencing refusals by parents not interested in participation—a good reflection of the quality of the informed consent process and of the emotional aspect involved in recruiting infants into a vaccine trial. Frequently it is the father who overrides the mother and refuses to allow his child's participation.

This same emotional aspect comes into play when explaining the need for blood sampling and during the actual phlebotomy. Many mothers elect to leave the room while we are taking blood and it is often they who are most distressed as they cannot see that the baby's cries are in response to being tightly swaddled to prevent movement rather than to pain from the needle. We are restricted by international guidelines in the volume of blood we may withdraw from an infant at any one time and collectively over a period of time. This requires careful recording of the volume permissible for the baby's weight, the volume drawn at that visit, and the cumulative volume over an eight-week period. It also means that if we have to repeat safety blood tests to follow up on an abnormal haematology or biochemistry value, there may be insufficient volume available for immunology samples at that time point.

The standard reference ranges used by our national laboratories for children and infants are western-based. Phase I and IIa trials require absolutely normal haematology and biochemistry values according to the laboratory reference range. We have found that these values are not always appropriate for our population, for example, over 80 per cent of otherwise healthy infants screened show a platelet count above the upper limit of normal according to the standard reference range, suggesting that 'normal' is not the norm. In this case, the sponsor issued a waiver allowing us to enrol these children under certain conditions.

Until non-interference with other vaccines has been demonstrated, we are restricted by protocol to not administering our TB vaccine within a certain number of weeks—usually four weeks for a standard EPI vaccine. We have seen that the third scheduled EPI visit at 14 weeks is often not made promptly, perhaps due to the mother having now returned to work and struggling to get to the clinic, and this often throws out our calculations as to the date eligible for vaccination versus the eligible age according to protocol and the protocol-defined window period for informed consent and screening blood tests.

With any paediatric population one has to cope with a 'background noise' of adverse events—of teething and intercurrent infections, especially respiratory tract infection and gastroenteritis—which may result in hospitalization and cause a severe adverse event reporting. It is hoped that with vaccination for pneumococcal disease and rotavirus gastroenteritis being introduced into the South African EPI schedule, these numbers will drop significantly.

At this stage all the vaccines in clinical trials have been designed as boosters to the priming action of the standard BCG, given at birth or soon thereafter to millions of infants around the world. Recombinant BCGs have now entered into clinical trials and will bring with them unique challenges to the clinical researcher.

We are confident that when the world is introduced to the new TB vaccine in the not too distant future, any part SATVI played in its development was according to all ethical guidelines and regulations and with due respect for the rights of our participants.

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