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OPINION ETHICS OF RESEARCH AND CARE EN

2002 APRIL 9TH

REAPPRAISED STATEMENT ON THE PARTICIPATION OF WOMEN OF CHILD BEARING AGE IN PREVACCINE TRIALS SUPPORTED BY THE NATIONAL AIDS RESEARCH AGENCY (ANRS) WITH HIV NEGATIVE VOLUNTEERS

Research on vaccine preparations designed to prevent HIV infection has generated important efforts on the part of many national and international scientific organizations. Developing an anti-HIV vaccine could be one of the solutions to eradicate the world wide pandemic, which is particularly dramatic in parts of the world where access to treatment is very poor. After an initial report followed by a statement and recommendations approved on May 23rd 1996, the National AIDS Council decided to reappraise its recommendations on the participation of women of child bearing age in the trials supported by the National AIDS Research Agency (ANRS) on healthy HIV negative volunteers.

THE 1996 STATEMENT : A SHORT REVIEW

In 1996, the National AIDS Council considered three types of potential risks related to participation in vaccine trials, whatever the participants : recruitment modalities for volunteer network candidates were to take into account possible biological risks, social risks, as well as psychological and behavioural risks owing especially to the persistence of immunological traces long after the immunization trial.

Having delineated these various items, the Council clearly stated that beyond the limits set by the legal requirements, there was on principle no impediment to the recruitment of women of child bearing age for pre-vaccine immunization trials. Considering the " impossibility of eliminating all somatic and psychological risks for any volunteer (man or woman) or for the unborn baby ", the Council completed its general standpoint with the following recommendations :

- as much information as possible should be collected on the local immunity induced by the preparations tested on animal models;
- results obtained on women already participating in pre-vaccine trials should be studied further ;
- women for whom " pregnancy is an unlikely occurrence " should be recruited topmost in future trials ;
- effective participation of women recruited among ANRS volunteers should be limited to trials specifically investigating the female genital system.

These recommendations led to the recruitment, within the ANRS volunteer network, of women exclusively aged between 40 and 55.

HIV VACCINE RESEARCH IN FRANCE

To date, some ten ANRS-sponsored pre-vaccine trials with non HIV-infected volunteers have been conducted. Five are scheduled within the framework of the next campaign. These trials are designed to assess tolerance to vaccine preparations and their ability to stimulate the body's immune responses. The trials therefore correspond to phases I and II of development of medications for human use, subject to the usual pharmaceutical research frameworks.

The preparations test a candidate vaccine that consists of a recombinant vector virus with a canarypox virus and various lipopeptides. These products do not contain any natural HIV elements and their administration does not cause any risk whatsoever of viral infection to the trial participants.

Should a vaccine be developed at the outcome of these trials, it would be designed to induce strong cellular immunity and to stimulate natural local immunity of the mucosa (and particularly vaginal mucosa), which is a route for the virus into the body during unprotected sexual intercourse.

Heterosexual intercourse and mother-to-child transmission are nowadays the most frequent transmission routes throughout the world ; moreover, women represent the majority of new infections in many countries with high HIV prevalence. Consequently women of child bearing age are a privileged target for French vaccine research ; large scale phase III trials, prior to vaccination campaigns, will have to include as many women as possible.

Now, the teams conducting research with or within the ANRS have gradually come up against a two-fold recruitment problem.

At quantitative level, the number of new volunteers gradually decreased between 1992 and 2001 ; also the women not enrolled owing to their age (under 40) are a relatively important loss of potential participants. Recruitment rules applicable to them have therefore been less strict since 2001.

It is important that young women be able to participate in pre-vaccine trials. Indeed, at qualitative level, humoral immunity of the vaginal mucosa can lessen with age and trials conducted up to now have not involved participants likely to be closest to the actual targets of a potential vaccine.

WHAT THE NATIONAL AIDS COUNCIL SUGGESTS

• The Council considers that enrolling women of child bearing age for ANRS pre-vaccine phase I and II trials is advisable from a scientific point of view. Investigating the humoral immunity of mucosa and particularly the local immunity of the vaginal mucosa, implies the inclusion of such women in the trials ; administrating a possible vaccine by vaginal route may moreover be contemplated and would require specific research ; also, it can be hoped that the tested preparations will prove efficient on cellular immunity, which may vary according to participants' age and gender.

• The National AIDS Council notes that the risk of thrombocytopenia, mentioned in the 1996 Statement, is now dismissed. It was never documented during the past trials. The risk was originally due to a defectively synthesized HIV envelope glycoprotein used at the time in the vaccine preparations which has since been corrected.

• Persistent immunological traces resulting from participants' immunization during the trials is in no way analogous to an HIV infection. The presence of antibodies passively transferred to the child is temporary and there is no biological risk whatsoever for the child within the current trials' framework.

• But the National AIDS Council does consider that the presence of antibodies generated by vaccination –pseudo-seropositivity- can cause various psychological and social problems for the participants, whatever their gender.

Such risks result from a gap between information received, knowledge acquired and individual rationalities. Information common to all participants in vaccine trials must therefore be clear and must differentiate proven risks from risks based on scientifically unjustified interpretation. Once this medical information is provided, recruitment teams must make sure it is correctly understood by the candidates, particularly as regards somatic risks. Efforts made during volunteers' enrollment must be sustained throughout, regardless of trial participation.

Having observed that the occurrence of such psychological and social problems is poorly documented despite experience acquired, the National AIDS Council suggests that the National AIDS Research Agency and its partners evaluate specific difficulties met by volunteers during their participation in immunization trials. The Council acknowledges the efforts made by the ANRS on information and also the precautions taken as regards consent and support of trial candidates. In this respect, the Council recommends follow up of the psychological and social consequences of trial participation during and after the process.

• The more or less predictable character of certain events did not only lead to the exclusion of women aged 18 to 40 from vaccine trial participation. Thus, whatever their gender, students and unemployed people, whose ability to comply with trial requirements might falter due to an ulterior job, were also turned down. However, actually having a job at the time of enrollment in the network does not appear to be a systematically relevant indicator of candidates' future availability.

According to the same principle of operation, ANRS' enrollment of women exclusively aged over 40, has up to now been based on the "improbable" character of pregnancy during participation in the volunteer network. It would seem that the "probability" is difficult to establish once the need to recruit younger women has been acknowledged.

The National AIDS Council considers that if throughout the various recruitment stages, specific and regularly repeated information on the trials' requirements is provided, a woman can make her own choice. Any planned pregnancy must necessarily take into account possible participation in a trial ; conversely, it seems justified that candidates for the volunteer network make their decision with clear knowledge of the constraints implied by their participation in the trials. As enrollment requires using contraception, it also means temporarily giving up motherhood ; voluntary commitment can come to an end, as a volunteer can withdraw at any time.

This position is justified by a general ethical principle held by the National AIDS Council, which grants any person, man or woman, the responsibility of deciding to participate in biomedical research, if and when risks incurred and expected benefits are not disproportionate, trials meet legal and administrative requirements and the person is in a position to make an informed choice.

CONCLUSION

The National AIDS Council revises its previous statement and no longer recommends excluding women of child bearing age from participation in ANRS phase I and II pre-vaccine trials.

The Council advises long term follow up of trial participants, particularly at psychological and social level.