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OPINION

ETHICS OF RESEARCH AND CARE

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OPINION ON THE MONITORING OF HIV-NEGATIVE CHILDREN EXPOSED TO ZIDOVUDINE DURING THE PERINATAL PERIOD

Asked for its views by *Agence du Médicament* / the French Drug Agency, the National AIDS Council addressed the issue of the monitoring of HIV-negative children exposed to Zidovudine during the perinatal period, which is of relevance to over 90 % of children born in these conditions.

After hearing evidence from Professor Stéphane Blanche (Enfants-Malades Children's Hospital), Professor Jean-François Delfraissy (Bicêtre Hospital), Doctor Laurent Mandelbrot (Port-Royal Maternity Clinic), and Professor Georges David (member of the Academy of Medicine, founder of the Centres d'étude et de conservation de l'œuf et du sperme humains (CECOS) / Human Egg and Sperm Conservation Study Centres) and after requesting the opinion of Doctor Marie-Jeanne Mayaux (INSERM Unit U292), the NAC defined the following grounds for the present Opinion.

Following the publication of the results of the Franco-American ACTG 076 / ANRS 024 medical trial in February 1994, indicating that HIV transmission from mother to child can be reduced from 24 % to 8 % by administering Zidovudine to HIV-positive pregnant women and newborns under specific conditions, most industrialized countries have recommended such treatment for women matching the profile of those who took part in the trial. In France, 90 % of HIV-positive women, wishing to take their pregnancy to term, are said to be treated according to the procedure proposed in the trial.

If administered at the end of pregnancy, Zidovudine can have no impact on the development of the embryo. Surveys studying this topic confirm the absence of neonatal malformation (ACTG 076 trial ; Wellcome register ; Abstract 380, Washington Congress, January 30, 1995).

Conversely, it is not possible in principle to rule out all risk of the emergence of a range of medical conditions, possibly serious, decades after perinatal treatment with Zidovudine.

Zidovudine is a nucleoside analogue that acts on the viral genome. It may have as yet unknown long-term effects, particularly on systems not completely differentiated at birth, such as the nervous, muscular and immune systems.

Consequently, while there can be no question of restricting access to treatment of proven immediate benefit, two steps are required :

- the putting in place of an early-warning system for the detection of possible incidents and to curb any groundless worries on this score ;
- the monitoring of all children exposed to Zidovudine during the perinatal period.

Children born to HIV-positive mothers are usually monitored in paediatric departments until the age of 18 months, after which only those in whom infection is diagnosed are specifically followed up. The monitoring procedure for children born during the ACTG 076 / ANRS 024 trial, of whom 92 % are HIV-negative, is still to be determined.

The main difficulty resides in the maintenance of long-term monitoring which, as in the case of other pre- and perinatal medical assistance procedures, jeopardizes parent/child confidentiality. Two categories of issue arise here : the technical feasibility of such monitoring and its ethical justification.

In all probability, children not infected by HIV (effective diagnosis now being possible less than two months after birth) will not be monitored by paediatric services near their place of birth, especially since their respective family units are likely to change over time.

The records currently maintained by hospital pharmacies and medical data management systems do not guarantee reliable collection of usable data over periods measured in decades. Furthermore, the size of a representative sample is unknown, since we cannot predict the percentage of subjects that will be "lost" from the sample, or the frequency of medical conditions that may occur

after 10, 20 or 30 years. Monitoring based on sampling allows medical problems to be detected if they are sufficiently frequent, but it will not allow a physician working alone who detects an isolated anomaly 20 years after the birth to link this up with perinatal treatment.

The ethical problems relate to parent/child confidentiality, professional confidentiality regarding the mother's medical condition, and the constraints thus imposed upon individuals over their lifetimes due to developments in medical techniques and methods for the preservation of data.

Given the above, the National AIDS Council now issues the following Opinion :

The National AIDS Council considers that monitoring is imperative and cannot be restricted to children whose mothers agreed to take part in a prospective medical trial in 1992 and 1993. There is no possibility of success on satisfactory scientific and ethical terms for the exhaustive monitoring of all HIV-negative children born to a HIV-positive mother and receiving perinatal treatment with Zidovudine.

Consequently, the National AIDS Council recommends :

- Firstly, a prospective lifetime study must be organized on the basis of a cohort composed of the largest possible number of children born in the conditions described above, irrespective of family and social context, parental nationality and health. This cohort must be built up in accordance with scientific rules and must include informed agreement given in writing by the mother, family relatives or possibly the guardian, as well as the subsequent informed consent of the child when he or she reaches 18 years of age. The coordination of the information collected in this context falls within the drug control remit of the Agence du Médicament / French Drug Agency, which must receive the resources needed to carry out the monitoring.
- Secondly, hospital records of all Zidovudine prescriptions in paediatric form should be kept throughout the entire monitoring period, under the responsibility of the DDASS, the French Social Welfare Department, with consultation of the data being possible only with the permission of the Ministry of Health.

The need to obtain the mother's agreement before beginning treatment to reduce the risk of infecting her child makes it essential that a dialogue be established with her from the beginning of the pregnancy. Here again, the possibility of medical action justifies the necessity of proposing a prenatal test on terms providing safeguards in terms of ethics and prevention.

The National AIDS Council emphasizes the importance of raising still further the level of knowledge of healthcare personnel, in order to enhance the quality of HIV treatment during pregnancy.

Notes :

The Opinion issued by the National AIDS Council was the subject of a press release issued by the Minister of Health and a joint circular of the French Hospitals Directorate and the General Health Directorate.