Eur. J. Epidemiol. 0392-2990
March 1991, p. 147-153

EUROPEAN JOURNAL OF EPIDEMIOLOGY

Vol. 7, No. 2

# ETHICAL PROBLEMS RAISED BY ANTI-HIV VACCINATION

P. ENEL*[1], J. CHARREL*, M.P. LARHER*, D. REVIRON**, C. MANUEL* and J.L. SAN MARCO*

*Public Health Department - Faculté de Medecine, 27, Bd Jean Moulin - 13385 Marseille Cédex 5 FRANCE.

**Blood Transfusion Center, CTS, Bd Baille, 13005 - Marseille - FRANCE.

**Key words:** AIDS - HIV - Vaccination - Ethical problems

At present questions are being asked world-wide about the risk of the AIDS epidemic. The discovery of an anti-HIV vaccine has become an urgent priority, but it also raises a number of sensitive questions. Ethical problems in this field are particularly delicate, since the perspectives of individual health and public health do not seem to coincide. Our research team conducted a review of more than 400 articles on the ethical problems raised by AIDS. We concentrated particularly on the ethical and legal issues raised by research on anti-HIV vaccine. These problems fall into three main categories:

- therapeutic assays, which must be controlled by a strict agreement defined by international norms;
- manufacture of the future vaccine, raising legal difficulties which must be faced and solved now;
- distribution of the vaccine to the population, which should be conducted on a general basis, i.e. it should be offered to all individuals and not only to risk groups.

## INTRODUCTION

Vaccination is now widely used as a simple and efficient means of preventing viral infections. The success of vaccines against smallpox and poliomyelits is unanimously acknowledged. Because of the magnitude of the threat represented by the AIDS epidemic, the discovery of an anti-HIV vaccine has become an urgent priority. But the issue of vaccination raises a number of sensitive problems, which were discussed at the Sixth International Cônference on AIDS in San Francisco in 1990.

In particular, there seems to exist a conflict between the health of the patient as an individual and the perspective of public health. While vaccination is supposed to protect society, it must not be forgotten that certain vaccines represent a danger for the individual, and that the primordial therapeutic aim is to help the patient. This raises important ethical problems in the case of AIDS, since this illness does not affect all social groups equally, as do illnesses which spread in a less selective manner and for which there already exist vaccines that can be used for everyone in case of an epidemic. Moreover, the acceleration of research programs (precocious assays on voluntary subjects), the rapid broadcast of results by the media (raising false hopes and illusions), as well as political, social and financial pressures (problems of distribution of research-funds and research-priorities) are the source of mistakes and conflicts found both in specialised medical literature and in literature addressed to the general public.

## MATERIAL

Since 1988 our research team, which is made up of public health doctors, has conducted bibliographical

[1] Corresponding author.

research on AIDS and ethical issues. We searched four data banks (Medline, Pascal, Bioethics, AIDS) for literature published since 1983 with the following main key-words: AIDS, of course, associated with Ethics, Legislation, Jurisprudence and Human Rights. We also examined lay publications and participated in general ethical commissions. We collected abstracts of more than 200 articles. Our methodology has been fully described in a previous article (44). We then concentrated on the ethical and legal problems because of the interest demonstrated in the scientific papers on these topics. There problems fall into three main categories, which are, in chronological order in research:

- therapeutic assays;
- manufacture of the vaccine;
- distribution of the vaccine.

We express all the opinions found in the medical publications even if these positions have no rational or ethical arguments.

## THERAPEUTIC ASSAYS

Medical research on human beings constitutes a bottomless pit of ethical, legal and logistical problems, in addition to those related to the strictly scientific aspects (16, 36, 60). There has always been a conflict between *the scientific rigor of therapeutic assays and the human rights of the individuals involved in research protocol* (37, 53, 64). This conflict is exacerbated in the case of a fatal illness like AIDS.

In the first part of this study we will cover the ethical problems raised by therapeutic assays in general. We will then present problems specifically raised by anti-HIV vaccine.

### Ethical aspects of clinical assays

Accidents in the 1960's, with "thalidomide babies" and cases of medical research conducted without patients' consent (H. Bercher listed 22 cases in 1966), shocked both the general public and scientific researchers. The fear of scandal, which governs both political and social change, led to new drug laws aimed at protecting both the individual and society. Medical research is now conducted under the eye of the public, which has become suspicious, interested and very well informed on health issues (25, 26, 53).

The *theory of therapeutic assays* has thus been greatly developed over the last few years. It applies to all fields, imposing randoms, double-blind tests versus placebo, or reference-drug when it exists. Besides this technical aspect, a number of organisations have established rules of conduct concerning the human aspects of the question (30, 34, 47, 55, 58).

The Nüremberg Code established in 1949 the basic principle of obtaining the subject's voluntary consent to biomedical research, and made it compulsory to give complete information to the subject. In 1979, the North American Committee specified the *ethical principles applicable to research on human subjects* (Belmont Report of the National Commission for the Protection of Human Subjects of Biomedical and Behaviour Research): principles of respect and justice for all, balance between risk and benefit. Medical research on human beings was also the subject of a world-wide declaration in 1983 (Helsinki declaration) concerning both scientific and social aspects (70). In 1985, the Institutional Review Boards Services (IRB) elaborated precise research protocols, whose principal aim is to protect the rights of individuals (32). France was lagging behind in this field, but caught up in 1988 with the establishment of "*Good Clinical Practice*" concerning therapeutic assays in general (11, 42).

However, now that laws have been established governing general procedure in therapeutic assays, the debate has been reopened in the case of very serious or fatal diseases. Indeed, does not the very application of this kind of test in such cases go against certain ethical principles of medical practice, as many authors insist? They declare that it is immoral and criminal to give placebos, and not to try any new therapy, even if the treatment gives only a feeble hope of prolonging life, with no hope of a cure. Do condemned patients not have the right to try anything (the right to fight against one's own death) (14, 18, 43)? Their judgement agrees with one of the basic principles of the Helsinki declaration: the interest of the subject should always take priority over and above those of science and society (24, 48, 59).

Other authors believe that random double-blind tests should always be applied, since they are the best means of distinguishing between the genuine effectiveness of a drug and momentary effects based on chance (14, 43). They emphasize the serious mistakes, sometimes irremediable, brought about by assays conducted too quickly without proper respect for strict scientific protocol: future patients must have the benefit of rigorous scientific methods which are the most likely to bring them real help (40, 65, 66). AIDS, being at present the most serious of all diseases, is a good example: 70% of assays conducted at present are not random, do not involve a reference group, and do not involve the use of a placebo. They can be criticised on those grounds. Such unscientific methods brought about the hasty distribution of AZT after publication and broadcast by the media of the first results (17, 23, 39, 56). This necessitated new assays to really prove the efficacy of the new antiviral therapy, which is now distributed to particular HIV-infected populations.

The whole question of assay protocol is, thus, once more the subject of debate within the context of AIDS: whereas norms governing clinical assays seemed to be generally accepted, crucial questions still remain controversial. This brings us to the particular problems raised by the testing of anti-HIV vaccine (27, 61, 68).

### The testing of anti-HIV vaccine

Research on anti-HIV vaccines applicable to man are making rapid progress, but we will have to wait

some 8 to 20 years before we can consider distributing this kind of vaccine to a whole population. In May 1987, the National Institute of Health (NIH) in the U.S.A. established standardised procedures for clinical assays on man specifically defined for anti-HIV vaccine, following the first assays conducted by the researcher D. Zagury and other volunteers in Zaïre. The aim of the NIH was less to discover whether a vaccine is effective, than to control the epidemic and to protect human beings by preventing *in vitro* research and animal-research from being extended too rapidly and without precautions for human subjects (7, 19, 49, 62).

At the end of 1986 the *World Health Organisation* held and informal meeting in Geneva to examine problems involved in the study of anti-AIDS vaccine in man. For the testing of any vaccine, the WHO recommends that a *standardised procedure* be observed, *which will take into account scientific, ethical, legal and socio-political considerations.* The WHO also recommends that widespread exchange of information be organised, so that prior planning and international collaboration in phase III of clinical assays may be established. Assay-planning must take into account the following points (1, 38, 72):

- The conception of clinical assays (phase III) must be based on the use of placebos and on measures encouraging volunteers to take part in these studies. A *very strict protocol* must be defined beforehand. Phase III must be preceded by *in vitro* tests and animal tests, and must be supervised by a medical ethics committee;

- Elementary precautions must be taken in *the choice of a site for such assays:* sanitary infrastructure research governed by official authorities, before a country may be considered a suitable site for such assays. Indeed, there is a strong temptation to go to poor countries, where the incidence of AIDS is high, in order to find more subjects. However, the epidemiological nature of the illness is different in such countries. There is no strict control of research. And enormous risks are involved in the study of the effects of a live vaccine (at present the only kind considered) on a population with reduced immune defences (examples in Africa) (12);

- *Selection and protection* of subjects are an absolute necessity. Ethical considerations are primordial (provision of information for the subjects, confidentiality of results). Moreover, thought must be given in advance to the problem of discrimination against subjects who become seropositive as a result of the assay (3, 5, 21, 67).

- An *ethical and legal check on experimental protocol* is indispensable. Representation of high-risk groups should be ensured within the committees presiding over the assays. Problems of legal liability should be considered in advance, in order to reduce the unfortunate conflicts which will inevitably arise between manufacturers of the vaccine, research organisations and government officials (15).

There various recommendations are intended to cover most problems:

- What *kind of vaccine* should be tested? The spread of the illness may be stopped in various ways: blocking infection by the virus in the first place, protection against secondary illnesses, or preventing transmission to another person. The present choice is a live vaccine, with all the risks involved for an individual with a reduced immune defence system, and for the whole population if the incidence of AIDS-infection increases;

- Should proof first be given of effective *protection of animals*, before the efficiency and safety of a vaccine are tested on man? Chimpanzees and, more recently, rhesus monkeys are the only animals known to have been infected by the HIV virus, but they do not constitute a perfect model of immune defences in man. Moreover, these chimpanzees are exposed to very high doses of the virus, and not to normal doses (31, 54, 57).

- Who are the first *subjects to be tested*, how many and for how long? For assays in phase I we should have 20 volunteers who are not members of risk-goups, in order to study the effects of a vaccine which is not dangerous and which provokes an immune reaction. In phase II between 40 and 200 people, from high and low risk groups, are required in order to define doses and frequency. In phase III of evaluation of efficiency, we need many people in contact with the disease, i.e. belonging to risk-groups, and the assays will be long and costly.

- What examinations will allow us to test the *immune response*? We must be able to distinguish between immunisation and infection. This problem has not yet been completely solved. Moreover, these serological changes make it necessary to protect subjects who become seropositive as a result of the assay against any discrimination (declaration to employers and insurance companies that the anti-HIV anti-bodies are due to the clinical assay, in case future legislation gives them access to this information) (33, 69).

However, there is one essential point which is specific to AIDS. The mode of transmission of the infection, by blood or by sexual contact, raises the problem of *the choice of subjects to be submitted to the assay* and this problem has not yet been completely cleared up. In a very low-risk population, immune response and possible side effects can be measured, but no conclusion can be drawn as to the protective value of the vaccine. With subjects belonging to risk-groups, the difficulties are even greater. The delay between contagion and seroconversion makes it absolutely necessary to be certain that the subject to be vaccinated is not already infected. This is necessary, firstly, to avoid attributing to the vaccine an AIDS-infection contracted previously, and secondly because of the danger represented by a live vaccine for an organism with reduced immune defences. But there are no simple, efficient and morally acceptable means of distinguishing between a non-infected risk-

subject and an infected risk-subject before seroconversion.

The very introduction of the patient into a scientific protocol tends to modify his behaviour. When the risk is as great as that represented by HIV, this modification can only be encouraged, as long as we have no obviously effective weapon against the disease. This inevitable awareness of volunteers as to the risks involved and the means of protection at their disposal, can falsify results of the assay: it may engender false hopes as to the effectiveness of a drug, or, on the contrary, make any conclusion impossible. The protective value of the vaccine will appear all the more clearly if the subjects have taken no steps to reduce the risk of contamination.

However, the moral problem remains: to try to obtain the subject's consent to submit to a new vaccine; to decide whether or not he or she is a suitable subject who has not already incurred infection; not to try to convince him her to take all known measures to reduce the risk of contamination: such a procedure is *ethically unacceptable.*

An "ideal" duo can be imagined:

- a non-infected risk-subject;
- a researcher who tries sincerely, but in vain, to convince the subject to take steps for his own protection;
- the subject refuses to change his behaviour, and the researcher proposes the vaccine (4, 6, 22, 35, 50).

## THE MANUFACTURE OF ANTI-HIV VACCINE

The scientific, technical and ethical obstacles to testing a vaccine are considerable. While the scientist's task remains fairly clear, usually defined by research programmes and controlled by professional norms, the legal and ethical problems raised by future manufacture of a vaccin are still unclear. Indeed, not only must the manufacturers of the vaccine be encouraged, but vaccinated subjects must also protected against short and long term side effects:

- The public must have confidence in the vaccine. It is possible that the public will reject the vaccine, and the possibility of this reaction may dissuade a manufacturer from developing and distributing the product (45).
- In poor countries, such as Africa, where there is a very high incidence of AIDS, the vaccine must be distributed free of charge, but chemical industries develop their programmes according to the financial profits to be expected. This constitutes a serious financial obstacle to the participation of private industry in the development of a vaccine. On the other hand, the massive free distribution of vaccine may also constitute a capital advance for private industry which will subsequently be profitable if the vaccine is a success (example of the vaccine against cerebral-spinal meningitis);
- While we speak of the beneficial action of a future anti-HIV vaccine, the question must be raised of which laboratories will be foolhardy enough to develop such a vaccine commercially, given the astronomical damages they will have to pay to compensate side-effects, since this vaccine is considered to be "inevitably dangerous". Manufacturers are often fully liable for any prejudice caused by their drugs regarded as commercial products (strict liability and negligence), as is the case in the U.S.A. (8). But, if a vaccine is discovered, it is inconceivable that it should not be produced for economic reasons or for fear of court proceedings.

In this perspective, in order to prepare the ground for the future vaccine, there exist in the U.S.A. plans for collaboration between public health services, universities and private industry: these partners are now dealing with legal problems which have rarely been considered elsewhere. For example, a substantial draft law has now reached the stage of amendment in California, which aims *at limiting the liability of manufacturers in case of accident:*

- Individuals will still have the right to take the company to court for damages (negligence), but strict liability will be eliminated; liability will be assumed and covered by the State (financial compensation, free medical treatment);
- Financial aid of 6 million dollars will be given to clinical research; unsold vaccines will be bought back under strictly defined conditions (69, 71).

Already, at this stage, manufacturers can feel that they are understood, supported and encouraged: they will thus be less reticent to take part in research (1, 63).

## DISTRIBUTION OF THE VACCINE

In this field ethical problems also remain predominant, and among them is the following: *who is to be vaccinated*? Here, again, the question is raised of the apparent conflict between protection of individual liberties and protection of society: compulsory vaccination of the whole population or of the population not yet infected, or again compulsory and discriminatory vaccination of risk-groups, or again vaccination on a voluntary basis.

The vaccines presently being studied are live vaccines. Persons with reduced immune defences are strongly advised not to use them. It is, therefore, absolutely necessary to ascertain that the subject to be vaccinated is not already infected. Hence, the great danger, which we have already emphasised, of conducting the first assays in a population where incidence of infection is high, as in Africa. The only "reasonable" solution is to prepare a vaccine which would protect *the healthy population* against the virus (2, 13). The protection of the population not yet infected requires *a preliminary HIV serological test.* Once again, we encounter *the ethical problems of mass screening* (28, 41, 52).

### Vaccination on a general basis

The principle behind *compulsory vaccination for*

*all* is to protect people against the consequences of their own behaviour and against the negligence of others. But this principle runs into numerous medico-legal problems: what risk(s) justify compulsory vaccination? It is easy to reply that the safety of the population always takes priority over the right of the individual to liberty and free choice. This is the principle that usually applies in cases of court proceedings: such was the often quoted judgement in the case "Jacobson versus the State of Massachusetts", concerning compulsory vaccination against small pox during an epidemic. Another reply given is that protecting the individual amounts to protecting all citizens, even if coercive measures are enforced (29, 51, 63). Moreover, this is the argument invoked to justify any compulsory vaccination imposed by the Ministry of Health.

### Vaccination on a selective basis

Another proposition is to immunise, not the whole population, but only *risk groups*. Such a procedure would be severely discriminatory, and all the more so since it would necessarily suppose target screening of known risk-factors for the disease, which would inevitably put heavy pressure on anonymity and confidentiality. Such target screening is rejected by (almost) everybody. In the U.S.A. compulsory vaccination is being considered for homosexuals, drug-addicts and Haïtians (in this last case, vaccination would be combined with a law on pre-immigration and quarantine). Vaccination would be voluntary for haemophiliacs. Such a procedure would miss non-risk subjects who become infected by AIDS. Indeed, the AIDS epidemic has already extended beyond known risk-groups: "AIDS is a risk for everyone". This argument is used to support vaccination on a general basis (20, 35, 51).

### Voluntary vaccination

In countries where vaccination has always been carried out on a voluntary basis, as in Great Britain and the U.S.A., there can be no question of compulsory vaccination. In France, as in other countries, compulsory vaccination exists for serious, contagious diseases, which represent social scourges, such as tuberculosis and poliomyelitis. However, this does not apply to diseases transmitted in a selective manner, by sexual contact or by blood, unless it be at the height of an epidemic. AIDS does not correspond to these criteria, and if discussion is raised about anti-HIV vaccination, it is because of the specific mode of AIDS transmission. It can be assimilated to anti-B-hepatitis vaccination, voluntary and freely offered to people exposed to risk, such as medical and paramedical staff in laboratories, and in services of surgery, dialysis, etc. Since vaccination is not without danger, can it be made compulsory for people whose behaviour does not *a priori* expose them to infection?

Satisfactory protection by vaccination can be obtained on a voluntary basis, as shown by results in the U.S.A.. However, in the case of AIDS, it is to be feared that many people whose behaviour exposes them to risk of infection and who, therefore, need vaccination will not wish to identify themselve as such by going to a vaccination centre (social ostracism linked to the disease) (9, 10). The risk does, therefore, exist of a drift towards surreptitous and uncontrolled vaccination.

## CONCLUSION

We will conclude this reflection by emphasising the role of the media, which is particularly important in the AIDS context. The media are always on the look-out for shattering news of "miracle" drugs. If no solution is found, then the future is terrifying, and each therapeutic discovery will bring with it a terrible burden of hope and responsability. In this context, the testing of a vaccine is an unprecedented wager.

But the media have other roles to play in the context of this disease. They can warn political and sanitary authorities and the general public, but they can also modify individual behaviour. As long as no cureing treatment exists, the individual can in any case learn to protect himself. And perhaps that is what really matters, as we saw it at the meeting in Annecy "AIDS 2001" in April 1989.

## REFERENCES


1. *Acquired immunodeficiency syndrome (AIDS)* (1987): Vaccine development - Weekly Epidemiological Record, *62:* 93-95.
2. *American College of Physicians* (1986): Acquired immunodeficiency syndrome (position paper) - Ann. Intern. Med. *104:* 575-581.
3. *American Psychological Association* (1986): Statement on Ethical Issues in Psychological Research on AIDS. - IRB: A Review of Human Subjects Research *8:* 8-10.
4. *American Psychological Association* (1986): Ethical Issues in Psychological Research on AIDS. Committee for Protection of Human Participants in Research in cooperation with the Committee on Gay Concerns - J. Homosex *13:* 109-116.
5. *Anonymous* (1986): The constitutional rights of AIDS carriers - Harvard Law Review *99:* 1274-1292.
6. *Avin A.L.* and *Lo B.* (1989): To tell or not to tell: the ethical dilemmas of HIV test notification in epidemiologic research - Am. J. Public Health *79:* 1544-1548.
7. *Barinaga M.* (1988): Placebos prompt new protocols for AIDS drug tests news - Nature *335:* 485.
8. *Barnes S. D.M.* (1986): Will an AIDS vaccine

bankrupt the company that makes it? - Science *233:* 1035.

9. *Birchfield J.L.* (1987): AIDS: the legal aspects of a disease - Med. Law, *6:* 407-426.
10. *Booth W.* (1988): An underground drug for AIDS - Science *241:* 1279-1281.
11. *Caulin C.* (1989): L'essai thérapeutique et les Bonnes Pratiques Cliniques -Monographies Choay, N° 22, Paris.
12. *Christakis N.A.* (1988): The ethical design of an AIDS vaccine trial in Africa - Hasting Center Report *18:* 31-37.
13. *Confronting AIDS* (1989): Update 1988. Institute of Medecine - National Academy Press, Washington DC 69-80.
14. *Cooper E.C.* (1989): Controlled clinical trials of AIDS drugs: the best hope - JAMA *261:* 2445.
15. *Corvol P.* and *Poyart C.* (1989): Regards sur la recherche clinique. 3ème colloque d'animation de la recherche - Paris 1988, INSERM, 99.
16. *Curran W.J.* (1987): The impact of legal issues on the practice of infectious disease: National Survey of AIDS Legislation - Bull. NY Acad. Med. *63:* 569-581.
17. *Davey P.G.* (1990): New antiviral and antifungal drugs - BMJ *300:* 793-798.
18. *Delaney M.* (1989): The case for patient access to experimental therapy - J. Infect. Dis. *159:* 416-419.
19. *Dossier SIDA*: Le Nouvel Observateur, Dec. 1988, 38-43.
20. *Druhot D.M.* (1986): Immigration laws excluding aliens on the basis of health. A reassessment after AIDS - J. Leg. Med. *7:* 85-112.
21. *Dubler N.N.* and *Sidel V.W.* (1989): On research on HIV infection and AIDS in correctional institutions - Milbank Q *67:* 171-207.
22. *Edelman R.* (1984): From the National Institutes of Health. Summary of the National Institutes of Health Research Workshop on the Epidemiology of the Acquired Immunodeficiency Syndrome (AIDS) - J. Infect. Dis. *150:* 295-303.
23. *Nightingale S.L.* (1990): Expanded indication for zidovudine approved - J. Am. Med. Assoc. *2421:* 263-268.
24. *Ezzell C.* (1989): Drugs testing. Parallel trial controversy - Nature *340:* 331.
25. *Fanci A.S.* (1989): AIDS: challenges to basic and clinical biomedical research - Acad. Med. *64:* 115-119.
26. *Forsdyke D.R.* (1988): An ethical dilemna - Nature *332:* 200.
27. *Freedman B.* (1989): Non validated therapies and HIV disease - Hastings Center Report *19:* 14-20.
28. *Gillon R.* (1987): Testing for HIV without permission - Br. Med. J. Clin. Res. *294:* 821-823.
29. *Gostin L.O.* (1989): Public Health strategies for confronting AIDS - JAMA *261:* 1621-1630.
30. *Grodin M.A., Kaminow P.V.* and *Sassower R.* (1986): Ethical issues in AIDS research - Q. R. B. *12:* 347-352.
31. *Holland B.* (1988): Two chimps, too few letter - Nature *334:* 478.
32. *I. R. B.* (1985): The use of placebo in randomized clinical trial - A Review of Human Subject Research 7 (1).
33. *Jager H.* (1986): Ethical issues in AIDS - AIDS-Forschung *1:* 513-514.
34. *Jessiman I.M.* (1987): AIDS: a faltering step - B.M.J. *295:* 267-268.
35. *Judson F.N.* (1989): What do we really know about AIDS control? - Am. J. Public Health *79:* 878-882.
36. *Kelly K.* (1987): AIDS and ethics. An overview - Gen. Hosp. Psychiatry *9:* 331-340.
37. *Kirby M.D.* (1986): AIDS legislation-turning up the heat - J. Med. Ethics *12:* 187-194.
38. *Koff W.C.* and *Hoth D.F.* (1988): Development and testing of AIDS vaccines - Science *241:* 426-432.
39. *Kouzan S.* and *Nabout S.* (1989): Zidovudine. Etat actuel de son évaluation - Therapie *44:* 393-394.
40. *Laplanche A., Com Nougue C.* and *Flamant R.* (1987): Méthodes statistiques appliquées à la recherche clinique - Médecine et Sciences , Flammarion.
41. *Lo B., Steinbrook R.L., Cooke M.* et al. (1989): Voluntary screening for HIV infection. Weighing the benefits and harms - Ann. Intern. Med. *110:* 727-733.
42. Loi n° 88-1138 du 20 Dec. 1988 relative à la protection des personnes qui se prêtent à des recherches médicales - Journal Officiel de la République Française, 22 Dec. 1988.
43. *Macklin R.* and *Friedland G.* (1986): AIDS research: the ethics of clinical trials - Law, Medicine and Health Care *14:* 273-280.
44. *Manuel C., Enel P., Charrel J., Reviron D., Larher M.P., Thirion X.* and *San Marco J.L.* (1990): The ethical approach to AIDS. A bibliographical review - J. Med. Ethics *16:* 14-17.
45. *Mariner W.K.* and *Gallo R.C.* (1987): Getting to market: the scientific and legal climate for developing an AIDS vaccine - Law, Medicine and Health Care *15:* 17-26.
46. *Mariner W.K.* (1989): Why clinical trials of AIDS

vaccines are premature - American Journal of Public Health *79:* 86-91.

47. *Mariner W.K.* (1990): New FDA drug approval policies and HIV vaccination development - Am. J. Public Health *80:* 336-341.
48. *Marshall E.* (1989): Quick release of AIDS drugs - Science *245:* 345-347.
49. *Matthews T.* and *Bolognesi D.* (1988): Les vaccins contre le SIDA - Pour la Science *134:* 106-113.
50. *Novick A., Dubler N.N.* and *Landesman S.H.* (1986): Do research subjects have the right not to know their HIV antibody test results? - I R B: A Review of Human Subjects Research *8:* 6-9.
51. *Organisation Mondiale de la Santé.* Tableau des instruments juridiques relatifs au SIDA et à l'infection à HIV. mai 1990.
52. *PAHO* (1989): Criteria for HIV screening programs - Bull. Pan. Am. Health Organ. *23:* 176-182.
53. *Pan American Health Organisation* (1989): AIDS: social, legal and ethical issues of the "third epidemic" - PAHO Bull. *23:* 95-107.
54. *Prince A.M., Goodall J., Brotman* et al. (1989): Appropriate conditions for maintenance of chimpanzees in studies with blood borne viruses: an epidemiologic and psychosocial perspective - J. Med. Primatol. *18:* 27-42.
55. *Porter J.P., Glass M.J.* and *Koff W.C.* (1989): Ethical considerations in AIDS vaccine testing. - IRB. A Review of Human Subjects Research *11:* 1-4.
56. *Rapport Dormont.* Recommandations du groupe d'experts sur la prise en charge et le traitement précoce de l'infection à VIH - Ministère de la santé, Paris 1990.
57. *Reines B.P.* (1989): Animal experimentation - Science *245:* 583-584.
58. Report of the Presidential Commission on the HIV Epidemia - USA, June 24, 1988.
59. *Richman D.D.* (1989): Public access to experimental drug therapy: AIDS raises yet another conflict between freedom of the individual and welfare of the individual and public - J. Infect. Dis. *159:* 412-415.
60. *Rogers H.L. Jr.* (1987): The implications of AIDS - J. Med. Assoc. Ga, *76:* 620-621.
61. *Rothman D.J.* (1987): Ethical and social issues in the development of new drugs and vaccines - Bull. NY Acad. Med. *63:* 557-568.
62. *Schild G.C.* and *Minor P.D.* (1990): Modern vaccines. Human immuno deficiency virus and AIDS: challenges and progress - Lancet *335:* 1081-1084.
63. *Smith L.G.* and *Brennan R.E.* (1987): Legal ramifications of the development of an AIDS vaccine - N. J. Med. *84:* 702-704.
64. *Somerville M.A.* and *Orkin A.J.* (1989): Human rights, discrimination and AIDS: concept and issues - AIS *3:* 283-287.
65. *Spriet A.* and *Simon P.* (1986): Méthodologie des essais cliniques des médicaments - ed. Laboratoires Hoechst.
66. *Sschwartz D., Flamant R.* and *Lellouch J.* (1984): L'essai thérapeutique chez l'homme - Médecine et Sciences, Flammarion.
67. *Tacket C.O.* and *Edelman R.* (1990): Ethical issues involving volunteers in AIDS vaccine trials - J. Infect. Dis. *161:* 356.
68. *Veatch R.M.* (1989): Drug research in humans: the ethics of non randomized access - Clin. Pharm. *8:* 366-370.
69. *Weisburd S.* (1987): AIDS vaccines: the problems of human testing - Science *131:* 329-332.
70. *WMA* (1983): World Medical Association's Declaration of Helsinki.
71. *Wright K.* (1986): AIDS in California: state aid offered for vaccine - Nature *321:* 105.
72. *Young F.E.* (1988): The FDA's new procedures for the use of investigational drugs in treatment - JAMA *259:* 2267-2270.