Ethical reflections on pharmacogenetics and DNA banking in a cohort of HIV-infected patients

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Abstract

The aim of this study was to analyze ethical questions concerning the storage of human biological samples to be used in genetic analyses and pharmacogenetic research based on a French experience of DNA banking in a cohort of HIV-infected patients receiving protease inhibitor treatment (APROCO). We describe the ethical issues raised during the establishment of a DNA bank, including questions dealing with autonomy, benefit to the patient, information sharing and confidentiality as well as guarantees concerning the storage and use of DNA. We describe the practical applications of themes illustrated theoretically in the literature. Most of the points raised are not specific to HIV, but some of them may be more accurate due to the characteristics of the HIV population. The questions raised are not exhaustive and we conclude with specific points that remain to be defined. Our results are summarized in the memorandum and consent form presented in the appendices. This work should allow other researchers and members of evaluation committees to enrich their considerations and should stimulate discussion on this subject.

Introduction

The recent discovery of factors associated with response and susceptibility to HIV treatment has opened up new possibilities for genetic testing, which should make it possible to tailor treatment to individual patients. This prospect raises a number of questions and stimulates ethical reflections. The demonstration that chemokine receptor genes are associated with treatment response lead to further studies on other genes [1,2]. In the pathways by which protease inhibitors (PI) are metabolized, cytochrome P 450 polymorphisms affect drug metabolism and might be involved in drug toxicity [3-6]. The ethical debate is currently most relevant to researchers, but will soon extend to consultants, nurses and other care givers and, given the major implications unique to this disease, patients, in the form of patient associations. It will also concern public research institutions and industrial partners.

In France, a strict procedure must be followed for all genetic tests. This procedure was defined in bioethics laws in 1994 and obliges the physician to obtain consent from the patient, after providing complete information about the test to be carried out. In addition, any new medical technology that is to be used on humans in France must, according to the Huriet-Sérusclat law concerning biomedical research, be evaluated by a research committee, the Consultative Committee Protecting Persons in Biomedical Research (CCPPRB). Two types of research are covered by this law: those with and without direct individual benefits for the participant. Moreover, if medical data are to be analyzed by computers in a research context, they must first be declared to the CNIL (the French national data protection agency, responsible for monitoring citizen's rights with respect to data concerning them held on computers).

In this study, we consider the ethical questions relating to pharmacogenetics for a French cohort of HIV-infected patients, who had already started treatment with protease inhibitors (APROCO) [7-11]. The cohort is briefly described in Annex 1. A DNA bank was set up for this cohort, for use in studies of the genetic factors associated with response to treatment or poor tolerance of the antiretroviral drugs. The ethical questions considered are those raised by clinical research in general, by predictive medicine and genetic factors involved in multi-factorial determinism of the onset or prognosis of a disease, and by DNA banking [12-13]. The specificity of these questions relates to their association with the beneficial and possibly harmful effects of a drug on the human body, this drug being prescribed by a physician, and taken by a patient. This situation raises questions about the shared responsibility of the contract between physician and patient [14-15]. Our aim was to

analyze ethical aspects as a whole in relation to the constitution of a DNA bank in this context.

Ethical issues related to DNA banking

Respecting patient's choices and commitment

Patients are ensured that their decision to participate in this type of research is respected. They are guaranteed that they have the fundamental right to refuse to suffer the slightest damage to his/her corporal integrity and for the duty to respect the privacy of the individual [16]. It must be recognized that although some of the possible consequences of this research are clear from the beginning of the study, others are unknown or uncertain, and may only be outlined during the study. The knowledge of a genetic predisposition, is, like all knowledge, a factor that increases the individual's freedom and responsibility with respect to his or her future. However, it may also restrict freedom, by limiting the individual's future prospects and by altering his or her quality of life as a result of anxiety.

Respecting an individual's autonomy requires that the information given to the patient concerning the known and unknown consequences of the commitment is phrased carefully and appropriately [17]. This is a psychological challenge, calling into question the patient's pugnacity towards the disease, his or her compliance with preventive measures, and plans to procreate. Not only must the information be truthful, clear, appropriate, complete, and up to date, but the physician must be confident that the patient has as complete an understanding as possible of the consequences of his or her decisions [18,19]. Some studies have shown a marked discrepancy between the information given by the physician and the patient's understanding of that information. In pharmacogenetics, the complexity of the information provided makes it particularly difficult to ensure that the patient has correctly understood [20]. Asking the patient to reformulate the information is one way of making sure that they understand. Studies can be set up to analyze patients' understanding and other associated factors. Education policies on these genetic questions aimed at the general population are beginning to be developed. The French Genome Train Exhibition, in October 2001, is one such example.

Another important aspect of respect for the patients' wishes is the length the commitment they are asked to make. It appears to be desirable to limit the period of commitment, given the changing and uncertain nature of the consequences of patients' choices. However, it would be regrettable to destroy material as precious as DNA, which could be useful in the light of new discoveries in the future. Thus, in accordance with the

CNIL's recommendations, it has been decided that DNA samples should be stored for ten years after the closure of the cohort. Should the physician wish to prolong the storage period, we reserve the right to contact the patient to request a renewal of the commitment while asking for the CNIL to prolong the authorization. The patient's consent is required for the extension of the storage period. If the patient refuses or if no other research project is decided, the samples and any related information will be destroyed or anonymized. The length of the storage time has received little attention in research, but we think that it should be seen as a means of respecting the patient's wishes in the long term. Two problems are associated with renewing consent: first, the possibility of a number of the participants in the cohort dying and second, the difficulty keeping in contact with all the patients in the long term**.** Actively searching for patients lost to follow-up, includes making enquiries at the town councils of patients' birthplaces, as stipulated in the general APROCO study, in accordance with the CNIL.

Benefits to the patients

The question of the benefit of genetic testing to the patient has been the subject of a long debate. At first sight, the study of genes associated with the response to and tolerance of antiretroviral drugs may seem to be a cognitive research project without any direct individual benefits (according to the French Huriet-Sérusclat Law), useful mostly to the patient community as a whole. However, work on predictive elements could be beneficial to individual patients. By studying genetic factors predictive of disease progression and drug side effects, it should be possible to adapt the treatment to each patient, thereby minimizing possible undesirable effects and maximizing the response. Above all, the genetic factors studied will be genes for which functions have already been established in preliminary work. The significance of these genes, within the context of other, multiple determinants of the effect of the drug, will be analyzed here. This is different from a "blind" investigation, in which the aim is to search for unknown genes affecting the response to and tolerance of treatment. The French research committee (CCPPRB) accepted that this project has direct individual benefits. This debate illustrates the difficulty involved in distinguishing between the two types of classification, recently highlighted in the new version of the Helsinki Declaration [21], and which will probably be debated during the next revision of French bioethics laws. It may even form part of the revision of the 1988 Huriet-Sérusclat law [22], proposed by Mr Huriet this year. In the context of this work, we accept this choice of benefit for the patient as the research undertaken could have an impact on the treatment of the

participants considering that HIV treatments may generate drug side effects. Preliminary results from a questionnaire addressed to the APROCO patients showed that they retained the notion of direct individual benefit as the possibility to gain a treatment adapted to their own (data not published). However, as mentioned by the American NBAC [23], several conditions have to be fulfilled before returning the results from genetic research: first, the results should be scientifically validated and reproducible, second, the results should have a significant implication for the individual's health and third, means to improve, to prevent or to cure should exist. Returning results requires appropriate genetic counseling and fresh samples should also be retested by a diagnostic laboratory. The participants who expressed their wish to know about the research results should imperatively be informed about the general results and should be proposed, when possible, a test after its validation to know his/her personal genetic status. There is some uncertainty as to the delay before results can be returned and this question also has financial aspects, which have not received much attention to date. A specific budget could be estimated at the beginning of a research project with all the difficulty that this represents. The report of Clarke et al proposed that health authorities in concert with research ethic committees could estimate the relevance of result return by allowing the necessary budget and the setting up of new clinical services [24].

Confidentiality and the risk to the patient

The protection of human genetic material, and of the data generated by research raises questions concerning the quality of organization and filing [25-26]. One essential question concerns confidentiality. At no point should it be possible to establish a link between a genotype and a person ("firewall"), unless the result is passed on directly by the physician to the patient [27]. This security measure is already in place for all biological data from the APROCO cohort. The procedures are conform to the actual guidelines concerning the processing of computerized medical data as validated by experts from the CNIL organization. The laboratories storing and studying genes only have access to a coded identifier, making it possible to reconstruct the genetic data and clinical/biological data. Only the physician responsible for the patient has the key to make the connection between a result and a patient. To maximize respect for the privacy of the individual, we should consider whether genetic data should be introduced into the database in "resident" form for a therapeutic test, or whether it would be better to group the data together provisionally for analysis, to answer a precise question, the shared data files being deleted once the work is completed. We do not have a definitive answer for this question yet.

As certain genotypes are more frequent in some ethnic communities than in others, it may be necessary to consider ways to prevent stigmatization. The protection of genetic information concerning the effects of a drug on a given patient is also a social issue because of the relationship between health and employment or insurance. The finding that a given individual responds poorly to existing treatments or has a higher susceptibility to the HIV virus might increase the risk of discrimination. Ideally, we consider that the French law should clearly indicate that stigmatization of persons due to genetic characteristics must be forbidden and that employers and insurance companies cannot base their decisions on this type of result, even though insurance companies have contributed to the development of risk theories [28].

The sharing of information

Respect for patient confidentiality also raises the problem of sharing this type of information with families recently considered in a paper of Knoppers [29]. This problem is common to the identification of any predictive genetic factor. In the HIV context, the patient may wish to keep all of the medical data associated with their HIV status a secret. Also, if such results are not obtained as part of the general treatment program, patients may feel guilty and may not wish to share this information. However, it may have consequences for other members of the family taking the same drugs, or other drugs prescribed for a completely different disease, but acting on the same metabolic pathways. We believe that the decision to share information should be left to the patient after he/she has been correctly informed by the physician about the interest of sharing a particular piece of information.

Guarantees concerning DNA storage and uses:

A very sensible security measure to safeguard genetic material is to store each sample at two different sites. This practice of double storage remains poorly organized and controlled in France, and its improvement requires a clear commitment from the community. This commitment would make it possible to create storage sites solely for duplicates. The use of shared technical resources, managed according to defined procedures, would resolve the problem faced by a large number of laboratories that do not have the means to ensure the long-term storage of samples in conditions of optimum security. The transfer of genetic material to a laboratory outside the storage site, for a specific study, raises the problem of the potential use of the genetic material for purposes other than those initially planned, for which

the patient has not given consent. The possibility of transferring only the genome fragment (amplicon) required for the study is the way of preventing such misuse we adopted.

Important issues concerning the patients' interest are the choice, hierarchy and methods used in studies carried out using the DNA bank. Once stored, the DNA may be of interest to many investigators, for many purposes. The establishment of rules provides patients with a guarantee that the use of this material will be well thought out in their interests [13,20]. Indeed, it would be potentially dangerous for a single principal investigator, or even a scientific committee managing therapeutic research, to attempt to consider all the various challenges and make the most suitable choices, given the limited amount of DNA extracted and the possibly discordant interests of the patients and the community. One of the rules of the APROCO study was to establish a specific DNA bank Monitoring Committee, consisting of the principal investigators, backed by colleagues working more specifically in ethics, lawyers, a representative of the study promoter, and a representative of patient associations. The members of this committee are sometimes required to take part in delicate interdisciplinary choices, but this structure guarantees objectivity and neutrality. Its main aim is to evaluate the genes to be studied and to decide which ones are most relevant to the APROCO study. For each gene, a research protocol including scientific references and a bibliography of the team are evaluated, to estimate their scientific competence in the field. The committee must respond to the questions raised by studies of genes associated with the response to or toxicity of antiretroviral drugs and ensure that the information given to the patients is relevant to these questions. Indeed, it should be noted that the patients from the APROCO cohort are followed up in the medical center attached to the research at a four month regular interval and that they receive oral information through their physician.

Another issue is the creation of commercial products as a result of the study of these samples, without the patient being financially rewarded. While we think it is important to protect the bank of samples and data from commercial enterprises in general, we also think that it is important to establish conditions such that collaborations with manufacturers are possible. Again, this can be achieved by using amplicons corresponding to the regions of interest. The results obtained could be used to develop new treatments beneficial to the patient, and to other patients with similar characteristics.

Information and consent:

Information and consent are matters of concern [19,30]. All of the previous considerations have been formalized and made available to the patients, to help them to

commit to the research project, in which they are a special partner, in full possession of all the relevant facts (appendices 1 and 2). The four-page memorandum is as exhaustive as possible, including all the information that can be given to the patients. The first part deals with the context of the study, the reason behind it and its objectives. The second part concerns the development of the study, discussing how the sample will be collected and treated, and the nature, purpose and duration of storage. The third part deals with the patient's rights and duties (confidentiality procedures, declaration to CNIL [French national data protection agency] and conformity with the data protection act, the contact details of the promoter, of physicians and of the information processing site, approval of the project by a CCPPRB [site and date], the procedures for the return of information and the commercial aspects of the bank). We think it is important to make patients responsible for their role in treatment. Many patients are lost to follow-up, due to moving house or changing physician, for example. In the memorandum and consent form, we have repeatedly stressed the necessity for patients to pass on their new details or those of the physician treating them. The aim is to ensure that it is possible to request consent from patients a second time, for a new study, and to transmit results to them.

Another important point that must be respected is the patient's right not to receive the results. It may be desirable in some cases not to pass on information that it is psychologically difficult for the patient. Therefore, the consent form and memorandum asked patients to express their wishes on this point and made it clear that these wishes can be revised during the study. It might be interesting to determine whether the patient is really capable of making this choice with reasons considering the general aspect of the research project. Some authors [24] recommend that individual result return should not be proposed in pharmacogenomic research, given the speculative aspect of the results. However, the same authors also agree that if a research using coded samples generates results that may be of clinical relevance, there is an ethical obligation to return the findings to the participants. It appears that a main difficulty is currently to evaluate the potential clinical application of pharmacogenomics. Our choice was to consider the existence of such general research results and to give the participants the option as to whether received them or not.

Conclusion

The attractive prospects opened up by characterizing the pharmacogenetic profile of an individual and the hope of reducing iatrogenic complications, should be counterbalanced by the major demands for maintaining the autonomy and free will of individuals taking part in

research. We need to increase and to maintain the level of knowledge of the general population in line with complex scientific progress in this area, to prevent a growing discrepancy between the instigators of research and the individuals participating in research, as this would threaten the most vulnerable people [31]. To evaluate the results of our work, we are currently investigating how the information concerning the pharmacogenetic research protocol was perceived by the members of the APROCO cohort. The evaluation of the practical organization as well as the analysis of the application of theoretical reflections in the field of biological sampling and storage for genetic analysis are essential to animate the debate that must accompany the setting up of such practices and DNA banks.

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Annexe 1:

The French APROCO cohort included 1181 HIV-infected patients who began taking a PI-containing antiretroviral therapy in one of 47 centers between 1997 and 1999. The aim of the study was to describe the effects, efficacy and tolerance, of theses new therapies in the context of routine clinical practice. After a median follow-up of two years, the rate of progression to AIDS was 2% and the death rate was 2 per 100 patient-years. The rate of viral rebound was 20 per 100 patient-years and median CD4 count had increased approximately from 300 to 400/mm^3. The rate of serious adverse events attributable to antiretrovirals was 11 per 100 patient-years.

Appendix 1: Memorandum to patients

Basic host genetic effects on the response to and tolerance of treatment in HIV-infected patients treated with protease inhibitors.

Creation of the APROCO cohort DNA bank – ANRS EP11

Promoter: Agence Nationale de Recherche sur le Sida (ANRS) [National AIDS Research Agency]

Dear Sir or Madam,

We would like to thank you for your participation in the APROCO Cohort. Protease inhibitors, in association with other antiretroviral drugs designed to improve immune status, are an efficient treatment against HIV infection. You probably know that these drugs are not devoid of side effects, which can make their use problematic. The aim of the APROCO Cohort is to describe the effect of the drugs in terms of clinical progression, virological and immunological responses (increase in CD4 lymphocyte counts), but also the possible disadvantages. Once these effects have been described, the next vital step, in our opinion, is to study the factors predicting the efficiency of treatment and the onset of complications under treatment.

What is this study for?

Some of these predictive factors are unique to each individual, and concern the genes within the cells. It has been established that some genes are associated with a slower progression of HIV infection and a better response to treatment. In other diseases, it has been shown that certain genes are associated with a higher risk of side effects of the drugs used for treatment, particularly for drugs metabolized in the liver. Thus, studying factors, including genetic factors, predictive of disease progression and drug side effects should make it possible to adapt the treatment appropriately to the patient, thereby minimizing possible undesirable effects and maximizing the response.

What are the study's aims?

This study aims to analyze a large number of genes (about 100) involved in the control of virus multiplication and metabolism of antiretroviral drugs. The objectives justifying the storage and use of DNA are part of the cohort's general objectives: **to determine the effect of**

genetic factors, and of other factors: virological (viral load), immunological (CD4 counts), pharmacological (drug dose), and compliance (regular taking of treatment), on

- **The response to treatment**
- **The complications linked to the treatment (toxicity).**

For this reason, this project was submitted to the **CCPPRB (Advisory Board for the Protection of Human Subjects in Biomedical Research) as a study with Direct Individual Benefits.**

The list of genes to be studied is incomplete but currently contains those encoding the chemokine receptors (CCR5 and CX3CR1), which clearly play a role in disease progression.

How will the study develop?

All the patients in the APROCO Cohort will be asked for an additional 30 ml blood sample during a planned blood test in a scheduled follow up appointment. DNA will be extracted from the blood cells in this sample and the remaining cells will be preserved in the form of a dry pellet. The DNA and dry pellet will be stored for subsequent use in studies of various genotypes. The collection will be regularly maintained at a single site, which will be responsible for DNA extraction and maintenance of the collection. Samples will be stored at two sites for security reasons: The Immunopathology Laboratory at Pitié-Salpétrière Hospital and Généthon, Evry. The choice of the genes to be studied and the order of priority of the genes studied will be defined by the Monitoring Committee. The decision to use the stored DNA is the responsibility of the principal investigators of the Cohort, following the discussion by the Study Monitoring Committee. The person responsible for managing the collection at each site is not permitted to use or to pass on any DNA sample unless consent is obtained from the principal investigators. The samples will be stored and used for up to 10 years after the cohort's closure. If it becomes necessary to prolong this period, your consent will be expressly requested. Depending on the type of study, the stored genetic material will be transferred to most appropriate public or private laboratory, and the material transmitted will be used only for the objective defined for the study. After completion of the study, any remaining material will be destroyed or returned to the central collection to prevent any trace of the genetic material being archived at any site other than those established for this purpose.

What are your rights?

The study presented to you is in no way obligatory; you can withdraw from it at any time without being in any way liable.

All information concerning you will be strictly confidential and will be protected by strict medical confidentiality rules, including rules governing the site of DNA storage. The data collected will be coded before processing. In accordance with the Data Protection Act of January 6, 1978, the processing of individual data requires approval from CNIL (the French national data protection agency). The data collected will be processed by INSERM Unit 330 (Université Victor Ségalen Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux cedex). Article 40 of the Data Protection Act makes provision for your right of access, opposition, and rectification of the data processed at any time, through the intermediary of your physician. The study has been approved by the Cochin CCPPRB (Advisory Board for the Protection of Human Subjects in Biomedical Research), following examination at the session held on June 26, 2001 (amendment no. 1 October 23 2001).

The study promoter, the Agence Nationale de Recherche sur le Sida (National AIDS Research Agency), 101 rue of Tolbiac – 75013 PARIS, has taken out insurance in accordance with the Huriet Law (art. L 209-7 of the Public Health Code from January 20 1988 and art.5 from July 25 1994).

The DNA bank and data will not be exploited commercially. However, their analysis may be used in collaboration with manufacturers and may contribute to the creation of commercial products, from which you are not entitled to receive any financial reward.

It is possible for you to request the destruction of the DNA stored from your cells, or for it not to be used for a certain type of study. The use of the sample will be the responsibility of the Cohort's principal investigators, following discussion by the Study Monitoring Committee. You will be informed of this by your physician and the results concerning the use of DNA extracted from your cells will be passed on to you by the physician treating you. As these studies may last several years, in the event of your changing physician, we recommend that you send the details of your new physician and, if you wish, your own contact details, to the person in charge of the cohort, so that the results can be passed on. The results of some studies might not have an immediate application, but may have long-term applications. Results of this type will be made available to you upon request, but it is also possible that you may not wish to be informed of these results. You can indicate this on the consent form.

The stored DNA that has been extracted from your cells will only be used in studies that meet the objectives indicated above, for which you have given your consent. Any other use, which may be considered desirable in several years time due to progress in science and technology, cannot be undertaken unless you are contacted directly and give specific consent.

Name of physician who delivered the memorandum: ……..

Address: …….

Telephone no: ……..

Appendix 2: **CONSENT for participation in the study:**

Basic host genetic effects on the response to and tolerance of treatment in HIV-infected patients treated with protease inhibitors

Creation of the APROCO cohort DNA bank – ANRS EP11

I, the undersigned ..... agree to give a blood sample for genetic analysis. The aim of the study is to determine the effect of genetic factors, along with other virological (viral load), immunological (CD4 counts), pharmacological (drug dose) and compliance (regular taking of treatment) factors, on the progression of HIV infection, response to treatment and complications linked to antiretroviral drugs (toxicity). The sample will be used strictly for the purpose of the study. I declare that I have been fully informed of the nature of the studies that will be carried out and that I have understood that this is a study with some direct individual benefits. The use of the DNA extracted from my blood will be the responsibility of the APROCO cohort's principal investigators, following discussion by the Study Monitoring Committee. The analysis of my sample may be used for the creation of commercial products from which I am entitled to no financial reward.

It has been made clear to me that this genetic study may last several years and that the blood sample may be stored in a DNA bank for 10 years after the closure of the cohort.

I have understood that the study proposed is in no way obligatory and that I can withdraw from it at any time without being in any way liable. I can also ask for the blood sample or extracted DNA to be destroyed at any time.

The studies of certain genes may produce results with long-term rather than immediate consequences for my treatment. I wish **or** do not wish **(delete as appropriate)** to be informed of such results**.** To ensure that it is possible for you to inform me of these results, I will inform you of any change of address or telephone number, or I will indicate below the coordinates of the physician who will pass the results on to me:

……

……

Date ....

Physician's signature: Signature:

Address(optional)

Telephone (optional)