International Journal of STD & AIDS 2001; 12: 94–99

ORIGINAL ARTICLE

Participants in HIV clinical trials in Europe

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Summary: In recent years an increasing number of antiretrovirals have become available. In order to define the optimal treatment regimens an increasing number of clinical trials are needed.

Our objective was to study the profile of participants in HIV clinical trials in Europe and learn from their experience and views. Between August 1996 and September 1997, self-administered anonymous questionnaires were distributed to people with HIV infection at inpatient and outpatient clinics in 11 European countries. One thousand three hundred and sixty-six people completed the questionnaire (50% response rate). Four hundred and twenty (31%) of the respondents reported that they had previously participated in at least one HIV clinical trial. The percentage of people who had taken part in a clinical trial varied widely between the different centres, from 12% in Athens to 61% in Antwerp and Brussels. A significantly higher participation rate was observed in the northern and central part of Europe compared with the south (respectively 40% *vs* 18%) and also among people with a higher income. Most people (92%) stated that they were 'well' or 'very well' informed prior to enrolment in the trial. However, 4% reported that they had not given written approval and 22% felt that they were pushed into participating. Only 21% stated that they were informed about the outcome of the study on its completion. The most important reason for non-participation (37% of the non-participants) was because a clinical trial had never been proposed. In conclusion, a majority of people with HIV infection in European HIV treatment reference centres were willing to participate in clinical trials. HIV clinical trials in Europe should adhere more strictly to universal ethical standards.

Keywords: HIV infection, clinical trials, Europe

INTRODUCTION

There is probably no field of medicine where clinical research has progressed so rapidly as in AIDS. The number of HIV clinical trials has increased exponentially over recent years and it is expected that this increase will continue. Continuous design of antiretroviral drugs requires more and more clinical trials. New drugs also need to be studied in combination with other drugs. Obviously, this further increases the need for larger numbers of trial participants. The motivation of people with HIV infection to participate in clinical trials may be decreasing: it is usually no longer necessary to enrol in a trial to obtain a life-saving drug, since several antiviral drugs are now registered.

Clinical trials provide vital information about drug safety and effectiveness[1]. An important ethical prerequisite in clinical trials is that participants sign an informed consent before enrolment in the study. In order to give an informed consent, the volunteer must be well informed about the study and the possible implications. Due to the high pressure to obtain trial results as fast as possible, there is a possibility that these ethical standards are not always adhered to.

In this paper we report the results of a large survey among people with HIV infection in Europe. This study examined the characteristics of people who participated in clinical trials, to

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assess whether different sub-populations are equally represented. We also investigated whether study participants signed an informed consent form, whether people felt free to participate or not and what their main reasons were for participating in a clinical trial.

METHOD

In 1995, an initiative was launched by the Institute of Tropical Medicine (ITM), Antwerp, to assess the quality of support for people with HIV infection in Europe. This project was sponsored by the European Community (DG V). Within this project, a questionnaire survey was organized in 11 participating countries: Belgium (Antwerp and Brussels), Denmark (Copenhagen), France (a patient organization with 13 different locations), Germany (München), Greece (Athens), Italy (Rome and Milan), Luxembourg (Luxembourg), Portugal (Lisbon), Spain (Madrid and La Coruña), The Netherlands (Utrecht) and the United Kingdom (London and Manchester). For practical reasons we will refer to countries rather than specific centres in this article. The participating centres are not necessarily representative for each country.

Questionnaires were completed anonymously by people with HIV infection. Outpatients, diagnosed with HIV infection for at least one year, who were able to complete the questionnaire on their own, were eligible to participate. People who did not speak one of the main languages of the participating country were excluded for practical reasons. The questionnaire contained 108 questions and took an estimated 40 min to complete. Respondents were not compensated financially or by other means. The topics addressed in the questionnaire included: access to treatment and clinical trials, psycho-social support, perceived way of transmission, perceived stage of illness, experience with outpatient care, hospital and home care, cost of various care/support items, and degree of satisfaction with healthcare services. A clinical trial was defined as 'a study of a new medication that was not otherwise commercially available'. Questionnaires were distributed in HIV reference centres and HIV support organizations (Table 1).

The questionnaire was pre-tested with patients to check for clarity of the questions. These questionnaires were excluded from analysis. No further attempt to validate the questionnaire was undertaken.

Data were computerized in Access and Excel format. Baseline parameters considered as potential predictors of trial participation were: age, gender, CD4+ cell count, education, income, HIV transmission category, stage of HIV disease and region. Income was divided into 2 categories, more than 40,000 Belgian francs per month (992 Euros) or less than 40,000 Belgian francs which was considered as low income. There were 2 regional divisions: North-Central and South. North-Central included Denmark, Germany, The Netherlands, Belgium, France, United Kingdom and Luxembourg; South included Italy, Spain, Portugal and Greece. Univariate logistic regression was done to explore these potential covariates. Variables with P values less than 0.05 in the univariate model were entered in a multivariate logistic regression model, using a backward procedure. Analyses were performed using SPSS, version 7.5.

RESULTS

One thousand three hundred and sixty-six people completed the questionnaire (50% response rate).

Table 1. Distribution of the questionnaires in 11 European countries

Country	City	No. dis.	No. rec.	Response rate	Collection period	Way of distribution*
B	Antwerp	146	119	82%	Sept 96–Aug 97	1 & 2
B	Brussels	51	43	84%	Feb 97–Jun 97	1
DK	Copenhagen	150	96	64%	Nov 96–June 97	2
D	München	175	108	62%	Aug 96–Aug 97	1
F	13 localities	112	100	89%	May 97–Sept 97	2
G	Athens	±230	158	69%	Feb 97–Sept 97	2
I	Milan	300	165	55%	Feb 97–May 97	1
I	Rome	100	25	25%	May 97–Oct 97	1
L	Luxembourg	125	44	35%	Apr 97–Aug 97	1 & 2
NL	Utrecht	±155	65	42%	Nov 96–Jun 97	2
P	Lisbon	±250	93	37%	Jun 96–Jun 97	1 & 2
ES	Barcelona	±300	110	37%	Feb 97–Jun 97	1 & 2
ES	La Coruña	107	50	47%	May 97–Sept 97	1 & 2
UK	London	250	96	38%	Feb 97–Jul 97	1 & 2
UK	Manchester	±300	98	33%	Aug 96–Sept 97	1 & 2
European Union		±2751	1366	50%	Aug 96–Sept 97	1 & 2

*Questionnaires were distributed: (1) to outpatients by staff at an HIV/AIDS reference centre or (2) by self-support group volunteers (during workshops, and/or at hospitals to in/out patients)
No. dis.=Number of questionnaires distributed; No. rec.=Number of questionnaires received

Table 2. Characteristics of the Eurosupport II study participants

Country	Males (%)	Mean age (years)	Reported mode of transmission: Homosexual contact (%)	IVDU (%)	Heterosexual contact (%)	Mean duration seropositivity (years)	CD4 count $<200/mm^3$ (%)	Secondary and higher education (%)
Denmark (*n*=96)	88	42	74	2	16	8	37	31
The Netherlands (*n*=65)	79	40	65	6	19	7	43	28
United Kingdom (*n*=194)	93	38	81	4	8	6	54	50
Belgium (*n*=163)	87	40	64	4	23	6	46	38
France (*n*=100)	84	37	68	9	14	7	29	27
Germany (*n*=108)	87	42	71	5	11	6	46	27
Luxembourg (*n*=44)	77	38	55	9	36	6	35	16
North-Central (*n*=770)	87	40	71	5	16	7	44	35
Greece (*n*=158)	82	38	44	0	31	4	21	36
Italy (*n*=190)	70	36	31	34	28	7	46	18
Portugal (*n*=93)	76	33	45	24	23	4	33	28
Spain (*n*=155)	68	34	23	49	23	7	34	16
South (*n*=596)	73	36	35	27	27	6	34	24
Total (*n*=1366)	81	38	55	15	20	6	40	30

IVDU=intravenous drug users

Table 3. Participants in HIV trials

	No. of respondents (*n*)	Proportion ever participated in a trial (%)
Total	1366	31
CD4 cell count ($/mm^3$)		
<200	527	44
200–500	500	25
>500	209	19
Education		
Primary school	282	24
Higher education	1065	33
Income		
<992 Euros (<40000BEF)	554	27
>992 Euros (>40000BEF)	574	37
Region		
North-Central	770	40
South	596	18
Sex		
Male	1104	33
Female	258	22
Clinical stage		
Asymptomatic	585	23
Symptomatic, no AIDS	439	36
AIDS	254	45
Risk group		
Homosexual	773	35
Heterosexual	273	23
IVDU	192	20
Other	130	28

BEF=Belgian francs; IVDU=intravenous drug user

The characteristics of the respondents are shown in Table 2. No information was available about non-respondents. In some countries people HIV positive for less than one year (2%) or persons from ethnic minorities (4%) were enrolled in the study. Their results have been included in our analysis. The data collection period varied from 5 months in Belgium, France, Italy, Luxembourg and Spain to 13 months in Germany, Portugal, and the United Kingdom.

Most of the study participants were male (81%), varying from 68% in Spain, to 93% in the United Kingdom. Mean age of the study population was 38 years (range 18–75, SD 9.4 years). Approximately half of the respondents reported male homosexual contact as HIV transmission mode, but this varied widely between the participating countries: from 23% in Spain, to 81% in the United Kingdom. Spain had the highest percentage of study participants infected by intravenous drug use (IVDU) (49%), followed by Italy (34%) and Portugal (24%).

Forty per cent of the participants reported having a CD4 lymphocyte count less than $200/mm^3$ (85% of the CD4 lymphocyte counts were obtained in the previous 3 months). The number of respondents reporting having symptomatic disease or AIDS varied from 37% in Greece to 71% in the United Kingdom. The duration of seropositivity varied from <1 year to 18 years (mean 6.1, SD 3.8 years).

Four hundred and twenty (31%) respondents reported previous participation in at least one clinical trial (Table 3). The participation rate varied widely among the 11 participating countries, from 12% in Greece to 61% in Belgium. Sex and transmission mode were not found to be significant predictors in multivariate analysis (Table 4), while monthly income, region, CD4 cell count and stage of the disease were significant predictors for participation in clinical trials. Participants with a monthly income lower than 992 Euros were less

frequently enrolled in a trial than those earning more than this (27% *vs* 37%; odds ratio [OR]=1.426; confidence interval [CI]=1.066–1.909). Approximately 40% of the respondents in the North-Central region had participated in at least one trial, compared with 18% in the South (OR=0.438; CI=0.318–0.603). Patients with a CD4 lymphocyte count less than 200/mm^3 had been recruited more often in a trial than those with a CD4 lymphocyte count higher than 200/mm^3 and people who reported having AIDS were more often enrolled in a trial than asymptomatic persons.

Ninety-two per cent of people enrolled in clinical trials described themselves as 'well' or 'very well' informed prior to their enrolment in the trial. Four per cent reported that they had not given their written approval. Twenty-two per cent felt that they were pushed into participating. Only 21% stated that they were informed about the outcome of the study, on completion of the trial.

Motivation to participate in a trial varied among the respondents. 'To help science' was given as the most important reason for 73% of the participants. Other important reasons were: 'because it is the only way to obtain that particular medication' (50%) and 'to receive better medical care' (45%).

Three hundred and forty-two (37% of the non-participants) stated that the main reason for not participating was because a trial had never been proposed.

DISCUSSION

In this survey among a large number of people with HIV infection, important differences in participation rates in HIV clinical trials were found between HIV treatment centres in Europe. Participation rates were lower in Southern Europe, as was previously reported by the EuroSIDA study group[2]. Other studies have shown that people with a higher level of education and/or homosexual men were more likely to have participated in a HIV clinical trial, than people with lower levels of education and/or IVDU[3,4]. This study did not find education level and transmission mode to be significant predictors for participation in a trial. Representation of different sub-populations during the clinical experimental stage of a drug enhances general applicability of the study results. Excluding segments of the population may result in crucial variations in drug effects and side effects going undetected[5]. In this study, only 25% of the women questioned had participated in a trial, compared with 36% of the men. Female participation in clinical trials is important so that sex-related differences regarding efficiency and toxicity can

Table 4. Participants in HIV trials: bivariate and multivariate analyses

	Bivariate analysis		Multivariate analysis	
	OR	95% CI	OR	95% CI
Age	1.032	1.019–1.045	–	
CD4 cell count (/mm^3)				
<200	1		1	
200–500	0.401	0.305–0.527	0.512	0.366–0.718
>500	0.271	0.184–0.401	0.404	0.251–0.651
Education				
Primary school	1		–	
Higher education	1.256	0.901–1.752		
Income				
<992 Euros (<40000BEF)	1		1	
>992 Euros (>40000BEF)	1.490	1.153–1.927	1.426	1.066–1.909
Region				
North-Central	1		1	
South	0.363	0.280–0.469	0.438	0.318–0.603
Sex				
Male	1		–	
Female	0.605	0.436–0.838		
Clinical stage				
Asymptomatic	1		1	
Symptomatic, no AIDS	1.929	1.459–0.838	1.388	0.978–1.970
AIDS	2.948	2.132–4.078	1.921	1.250–2.952
Risk group				
Homosexual	1		–	
Heterosexual	0.557	0.403–0.771		
IVDU	0.468	0.316–0.695		
Other	0.668	0.439–1.017		

BEF=Belgian francs; IVDU=intravenous drug user

be documented[3,6]. Multivariate analyses showed that in our study population, sex was not a significant predictor for participation in clinical trials. The low participation rate of women can be explained by the lower rate of HIV infection among women in Northern countries, where more clinical trials are conducted.

The same conclusion can be drawn for transmission mode: only 23% of the people infected by IVDU had participated in a trial, compared with 35% of participants infected by other modes of transmission. This effect was also eliminated by multivariate analyses, suggesting that the lower participation in clinical trial for IVDU was related to other factors, such as region and low income[7,8]. The importance of including drug users with HIV is two-fold: HIV-positive drug users may present a different clinical spectrum than a non-drug using population[9–14]. Secondly, there may be interactions between the trial medication, the recreational drugs or the medication used in the treatment of the addiction. It may be that the form of the product and the treatment schedule also needs to be modified for this population. For example, multiple daily doses or long-term frequent administrations, may be less appropriate.

In this study, ethnic minorities were not included, for linguistic reasons: only people from ethnic minorities who could read and understand the local language would have been able to fill in the questionnaire. Ethnic minorities also belong to the traditionally under-represented populations in clinical trials. Cultural differences, language barriers, financial inequities, and a distrust of the traditional medical community may impede participation[3,15].

Informed consent is an important ethical issue in clinical trials. Each time a person fulfils participation requirements and is interested in participating in the trial, he must be fully informed about the study, preferably both orally and in writing. Thorough understanding of the trial enables a participant to give his informed consent for participation. In our study, 4% of the trial participants reported that they had not given a written consent for the trial. Informed consent is a basic principle within the context of a medication trial and a 4% contravention rate is unacceptable. Furthermore, 22% of the people who enrolled in a trial felt pushed into participating, which contravenes to the principle of informed consent. This study also shows that once the trial data had been analysed, only 21% of the trial participants were informed about the study results. Since the study participants are the ones actually taking the study drugs, they are the first people who should hear about the study results[16].

The results of this study should be interpreted with caution. Participating centres were contacted through a network of HIV professionals. One or two centres per country participated. These centres are not necessarily representative for their country. The situation in other centres might have been quite different. The method of distributing the questionnaires was not the same in every centre (Table 1). No information about non-respondents is available.

Collecting data about how HIV-infected people experience participation in drug trials, gives important information about how these trials are conducted. The high number of trial participants who did not sign a written consent or felt pushed into participating despite having signed an informed consent form, indicates the necessity of a better control in the organization of clinical trials.

Another important conclusion of this study is that a majority of the respondents were willing to participate in clinical trials. Many of the respondents had not yet participated in a clinical trial because they had never been asked to do so. Considering the increasing number of available antiretroviral drugs, it is imperative that clinical trials are organized to identify the best treatment regimens. There are still many unanswered questions about how to best treat patients. Without clinical trials there is a risk that patients will be exposed to sub-optimal or potentially harmful treatment regimens. Given the large number of trial participants needed, Europe still has some important potential. It is therefore important to facilitate the participation of Europeans in clinical trials. A second important reason for including more Europeans in clinical studies is that earlier access to new medications, through drug trials and compassionate use, can be very important for those failing to respond to all registered medications. Collaborating in clinical trials will also enhance the understanding of, and contribution to, evidence-based medicine by European healthcare professionals.

Acknowledgements: Fleerackers Y, Andraghetti R (Institute of Tropical Medicine, Antwerp), Dewit S (Hôpital St Pierre, Belgium), Degraeve D (UFSIA, Belgium), Kvinesdal B, Schmidt K (Hvidovre Hospital, Denmark), Bourez J (Centre Hospitalier de Tourcoing, France), Bouchoucha S (AIDES Fédération Nationale, France), Vyras P (ELPIDA, Greece), Gargalianos P, Lelekis M, Stefanou J, Papadopoulos N (General Hospital of Athens), Finazzi R (Instituto Scientifico Ospedale S Raffaele, Milano, Italy), Vaccaro C, Zucconi C, Liotta G (Università degli Studi di Roma, Italy), Stadelman C (AIDSberodung de la Croix Rouge, Luxembourg), Hemmer R (Centre Hospitalier de Luxembourg, Luxembourg), Caldeira L, Antunes F (Hospital de Santa Maria, Lisbon, Portugal), Ferro N (Liga Portuguesa contra a SIDA, Portugal), Garcia F (Servicio de Enfermedades Infecciosas, Barcelona, Spain), Cobena Guardia J (Associacio Anti-SIDA de Catalunya), Castro A (Servicio de Medicina Interna, La Coruña, Spain), Borleffs J (Academisch Ziekenhuis Utrecht, The Netherlands), Dijkgraaf M (National Institute of Public

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This study was supported by funding from the European Commission.

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(Accepted 11 August 2000)