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Communication, recruitment and enrolment in the preventative and therapeutic phase I clinical trial against HIV/AIDS based on the recombinant HIV-1 Tat protein

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Communication, recruitment and enrolment in the preventative and therapeutic phase I clinical trial against HIV/AIDS based on the recombinant HIV-1 Tat protein

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The role of volunteer recruitment in HIV vaccine trials has recently been considered particularly with respect to critical issues, such as motivation, psychological assessment and social impact. The preventative and therapeutic phase I trials based on the recombinant biologically active Tat vaccine candidate, sponsored in Italy by the Istituto Superiore di Sanità, included a specific centralised procedure (SCP) developed to support both the sponsor and the volunteers during trial enrolment and conduction. This process, which is an integrated, multidisciplinary, biomedical and psycho-socio-behavioural network, represented a novel and important aspect for the conduction and success of the clinical study. A specific flow of information from the sponsor to the population was developed through the SCP which started from the national announcement of the trials (through a press conference and a press release) to the enrolment of the volunteers. To this aim a telephone counselling intervention was performed to supply the scientific information translated in personalised message, allowing to select potential participants prior to the first contact with the clinical sites. Furthermore, the multi-step procedure contributed in reinforcing the motivation to participation and trial retention, providing important hints for the design of standardised enrolment procedures to be used in clinical studies. Indeed, this methodological approach, which foresees the joined participation of researchers and expert of communication, could be followed in future vaccine trials in order to improve the effectiveness of enrolment procedures.

Keywords: HIV; Tat; enrolment procedures; telephone HIV-AIDS counselling/AIDS Help Line; clinical trials

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Introduction

HIV therapeutic and preventative vaccine trials recruitment has received in recent years substantial attention, particularly regarding motivation, psychological assessment and social impact, but also concerning the administration of informed consent (Haidich & Ioannidis, 2001; Mills et al., 2006). Although these issues are usually raised in the context of Phase III efficacy trials, they are also relevant for safety (Phase I) and immunogenicity (Phase II) studies (Buchbinder et al., 2004; Starace et al., 2006; Thapinta et al., 2002), where no evaluation of efficacy is anticipated and also healthy volunteers with relatively low HIV exposure risk need to be enrolled (Baigis, Francis, & Hoffman, 2003; Colfax et al., 2005; Sheon et al., 1998).

A crucial issue in the recruitment process for Phase I clinical trials and, in particular, for the development of a vaccine against HIV/AIDS, is represented by the information released by the sponsor, both in terms of content of knowledge, which must be transferred to the potential volunteers, and in terms of communication tools used by governmental and academic institutes according to legal requirements for the dissemination of the relevant information, in order to achieve a correct and comprehensive communication (Bellotti & Bellani, 1997; de Mei, Luzi, & Gallo, 1998; Haidich & Ioannidis, 2001; Silverman & Altman, 1996). The challenge is to translate complex scientific concepts into easy information, well understandable by the community, with care on both the risks and the benefits for potential participants (Halpern, Metzger, Berlin, & Ubel, 2001). In addition, although the primary endpoint of a Phase I and Phase II clinical trials are the evaluation of safety and immunogenicity and no evaluation of efficacy is anticipated, the access to the trial should be guaranteed to all socio-economic groups of the population.

A specific centralised recruitment procedure (SCP) has been developed for the conduction of parallel Phase I preventative and therapeutic clinical trials of the Tat vaccine (Ensoli et al., 2006) sponsored in Italy by the Istituto Superiore di Sanità (ISS) (ClinicalTrials.gov identifiers: NCT00529698, NCT00505401). The main objective of SCP was to

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support the volunteers in the early phase of the studies by the development of a specific flow of information required for recruitment and for the more appropriate information to the population. Therefore, the content and flow of information to the volunteers allowed access to the entire population (with no discriminations with respect to the socio-economical status) as well as a good understanding of the nature of the trial and of the risks and benefits for the potential participants, through the involvement of a National AIDS Help Line service.

The present work is aimed at illustrating the integrated biomedical and psycho-socio-behavioural platforms in support of the enrolment for the conduction of the Phase I anti-HIV/AIDS preventive and therapeutic vaccine trials, which represented a novel and important aspect in the conduction and successful completion of the study. All clinical and laboratory activities, as well as psychosocial and behavioural assessments, were harmonised among the clinical centres by establishing standardised and integrated platforms. A psychosocial protocol for the assessment of psychological and socio-behavioural issues was implemented to support volunteers throughout critical steps of the study. The enrolment procedure benefited from the expertise of *Telefono Verde AIDS* (TVA), a free and anonymous National AIDS Help Line established since 1987 by the Italian Ministry of Health at ISS, the leading technical and scientific body of the Italian National Health Service. The TVA mission is to provide general information on HIV/AIDS; specifically, for Tat Phase I vaccine trials, it supplied all the information on participation and enrolment, directing the volunteers at the first visit appointment at the clinical sites and guaranteeing an equal access to the study recruitment.

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Methods

The preventative (ISS P-001) and therapeutic (ISS T-001) phase I clinical trials

The preventative (ISS P-001) and therapeutic (ISS T-001) phase I clinical trials were both randomised, double blind and placebo-controlled and conducted in 20 healthy volunteers (18–55 years of age without identifiable risk of HIV-1 infection) (Bellino et al., 2009; Ensoli et al., 2006) and in 27 asymptomatic HIV-infected individuals, respectively (Ensoli et al., 2006, 2008; Longo et al., 2009).

The study has been conducted in four clinical sites in Italy and it has been implemented with the constitution of a network aimed at integrating and harmonizing the activities of experts in biomedical and psycho-social/behavioural research.

Recruitment and enrolment procedure

In order to promote the Phase I preventative and therapeutic trials of the HIV-1 Tat vaccine, a specific recruitment and enrolment procedure was developed. SCP started from the national announcement of the trials (through a press conference and a press release) to the enrolment of the volunteers.

This procedure mainly consisted of the following five steps.

Step 1: awareness of the study

After a national press release to promote awareness of the study, the AIDS Help-Line Unit (TVA) gave general information on the clinical trial. TVA is a free and anonymous service operating within ISS since 1987 and it is compounded by a team of psychologists specialised in telephone counselling on HIV infection and pathogenesis. Its primary objective is to promote the prevention of HIV infection through the development of a telephone counselling service providing proper and personalised information on the issue.

This intervention is structured in the following phases: (1) phone call early phase, essential to establish an empathetic and trust relationship with the calling person, through active listening. During this step it is important to pay particular attention both to the content and to the emotional aspect of the request; (2) phone call middle phase, characterised by the necessity of focusing the real problem of the caller, of sharing a goal to work on, and of offering personalised information and indications using a simple language. This phase is crucial to suggest and to agree on possible solutions to the problem and to spur personal resources to find consciously and autonomously the most adequate solution; and (3) phone call final phase, necessary to summarise the call contents in order to verify the acquisition of the information provided and to improve a novel awareness for possible behavioural changes and for an adequate conclusion of the counselling intervention (http://www.iss.it/binary/iss3/cont/metodologia.pdf).

Step 2: orientation to the study and identification of the target population

The individuals calling the TVA and expressing their willingness to participate in the trial were identified as the target population. Particularly, detailed information were provided to callers interested in participating to one of the two studies and a brief questionnaire about demographics, transmitted disease history and motivation for joining the trial was administered. According to the enrolment procedure

and to guarantee an equal possibility to be enrolled in the study throughout the country, a personal alphanumeric code, which had to be mandatory reported to the clinical sites, was assigned to subjects wishing to enrol in the study.

Step 3: identification of potential trial participants

Specifically, trained telephone operators (TO) within each clinical site represented the first contact for the volunteers that, upon code verification, were scheduled for an appointment with the clinical investigator. At the end of each working day, TOs communicated to the TVA the list of scheduled appointments corresponding to the assigned codes.

Step 4: identification of eligibility

The individuals attending the visit scheduled by the TOs with the clinical investigator, represented the eligibility fraction. The investigators explained in detail the screening procedures, the study design and the informed consent. In this step the investigators, after a previous check on compliance regarding the major inclusion and exclusion criteria, introduced the volunteers to the psychologist/psychiatrist to define their psychological status and to support them during the screening phase and study conduction.

Step 5: identification of the enrolment fraction

Individuals that, according to the preliminary observations of the investigators, were compliant with the inclusion/exclusion criteria and confirmed their willingness to participate in the clinical trial, were asked to sign the informed consent. These subjects (enrolment fraction) were, therefore, initiated to undergo to the pre-screening phase, according to the clinical and psychosocial protocols.

Assessment of informational needs and motivation

The administration of a questionnaire aimed at investigating the motivation to vaccine trial participation was proposed to the potential volunteers at the end of the telephone counselling and contributed to defining the potential volunteer profiles.

To this aim, a preliminary assessment of the informative needs was also performed through the following questions asked by TVA researchers:

(1) Are you willing to participate to the trial to support the biomedical research?
(2) Are you willing to participate to the trial to protect yourself against HIV-1 infection? (For HIV-1 uninfected individuals).
(3) Are you willing to participate to the trial to stop the progression of the disease? (For HIV-1-infected individuals).
(4) Are you willing to participate to the trial to help someone you care about?
(5) Are you willing to participate to the trial to help people?

Results

Characteristics of the population

The SCP, summarised in Figure 1, started in November 2003 with the press release announcing ISS P-001 and ISS T-001 clinical trials initiation. Within the enrolment period (one year), the TVA received a total of 19,808 calls. Of these, 1346 (6.8%) were received from people requesting information on the Phase I clinical trial of the Tat-based vaccine. Most of the TVA users were males (69.5%), with a higher prevalence of individuals with an age ranging between 30 and 40 years and calling from Northern or Central Italy.

Recruitment flow

Out of the 1346 individuals calling the TVA, 470 subjects (34.9%) expressed their willingness to participate to the trial. Of this target population, 70.6% were HIV positive and 29.4% were HIV negative (Table 1). Demographic characteristics were assessed by HIV serostatus and statistically significant differences were detected for *class of age*, *education* and *job*. Specifically, most of HIV-negative individuals were older than 40 years of age, had an high school diploma or university degree and were workers or students, as compared to HIV-positive individuals who were younger, with a lower education and the unemployed category were quite represented.

Three hundred and twenty-five subjects (69.1%) requested the personalised code to proceed to the clinical sites [220 HIV-positive (67.7%) and 105 HIV-negative individuals (32.3%)], and only a fraction of them proceeded through the enrolment process. In particular, a total of 194 individuals (59.7%) called the clinical site (potential participants). These subjects included 138 HIV-positive individuals (71.1%) and 56 HIV-negative individuals (28.9%). Among these, 168 individuals (86.5%) [116 HIV-positive (69.0%) and 52 HIV-negative (31.0%)], requested an appointment with the clinical site operator and attended it (eligibility fraction). They received and discussed with the investigator the

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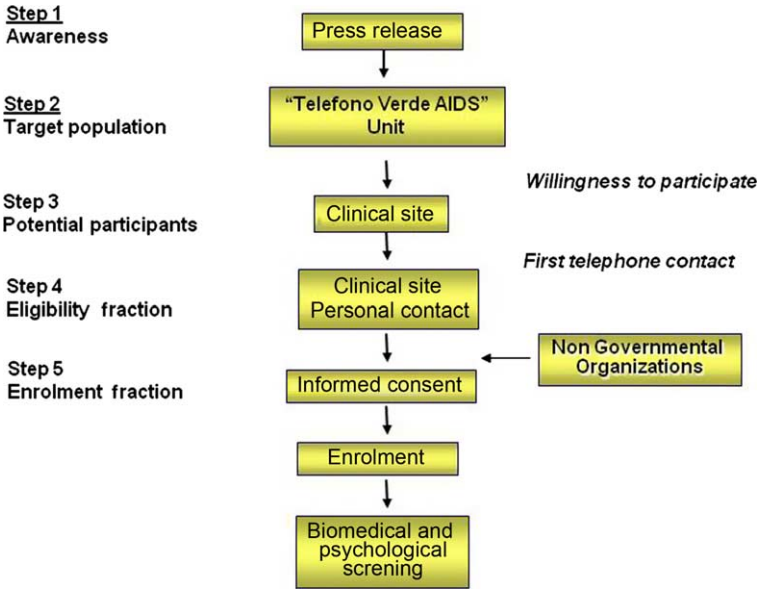

Figure 1. Specific centralised procedure developed in the conduction of parallel Phase I preventative and therapeutic clinical trails of the HIV-1 Tat vaccine candidate.

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informed consent and the patient information sheet. Those who were compliant with the major inclusion and exclusion criteria and signed the informed consent (enrolment fraction), entered the pre-screening phase, according to the clinical and psychosocial protocols. This fraction included a total of 104 subjects (61.9%) [76 HIV-positive (73.1%) and 28 HIV-negative individuals (26.9%)].

The preventative and therapeutic phase I clinical trials were both randomised, double blind and placebo-controlled, conducted in healthy adults volunteers without identifiable risk of HIV-1 infection or in asymptomatic HIV-infected individuals with CD4+ T cell counts $\geq$400/μL, viral load $\leq$50,000 copies/mL and a CD4 nadir $\geq$250, respectively. A preliminary selection of the target population was provided by TVA researchers accordingly with the compliance of the major inclusion/exclusion criteria. In particular, the alpha-numeric code was not given to HIV-negative individuals at high risk of infection and to HIV-positive individuals in advanced stage of disease progression, undergoing antiretroviral therapy. Indeed only about 69% of the target population proceeded to the following step (Figure 2). During the first appointment, the investigator contributed in further selecting the participants, with about 32% of these subjects signing the informed consent, representing the enrolment fraction.

As expected, the peak in the number of alpha-numeric codes requested to the TVA was observed in the first two months following the press release (Figure 3). The attribution of codes was greatly reduced after six months. The peak of signed informed consent and, as a consequence, of individuals entering treatment phase, was observed at four months after the publication of the press release.

Assessment of informational needs and motivation

A preliminary assessment of the informational needs was performed on the 1346 individuals calling the TVA. A total of 4081 questions were reported, mostly related to Phase I clinical trial conduction, and, in particular, to enrolment and inclusion/exclusion criteria. This assessment was repeated on the target population (470 subjects expressing their willingness to participate to the trials) and most of the information required were related to Phase I clinical trials including in particular enrolment (inclusion/exclusion criteria) and clinical sites (Table 2). The motivation to participate in the study was evaluated on the target population (332 HIV-1-infected and 138 uninfected individuals). To this aim, TVA researchers proposed to these subjects a simple questionnaire.

Most subjects indicated altruistic motives, expressing willingness to benefit the research and people in general (Table 3). Among HIV-positive individuals, altruistic motivations (see question number 1 and 4) were comparable to non-altruistic interests, while a more altruistic approach was observed in HIV-negative individuals, as suggested by the different frequency of positive answers to

Table 1. Demographic characteristics.

Target population ($N=470$)	HIV+ ($n=332$) n (%)	HIV– ($n=138$) n (%)	χ^2 test
Gender			
Male	251 (75.6)	97 (70.3)	
Female	81 (24.4)	41 (29.7)	n.s.
Age (years)			
18–30	74 (22.3)	36 (26.1)	
30–40	168 (50.6)	48 (34.8)	
>40	90 (27.1)	54 (39.1)	$p=0.0052$
Nationality			
Italy	324 (97.6)	135 (97.8)	
Other	8 (2.4)	3 (2.2)	n.s.
Geographic distribution			
Italy-North	166 (50.0)	63 (45.6)	
Italy-Middle	130 (39.2)	54 (39.1)	
Italy-South	21 (6.3)	16 (11.6)	
Italy-Islands	15 (4.5)	5 (3.6)	n.s.
Civil status			
Single	211 (63.5)	81 (58.7)	
Married/Living with partner	88 (26.5)	48 (34.8)	
Divorced	27 (8.1)	9 (6.5)	
Not specified	6 (1.8)	0 (0.0)	n.s.
Education			
Lower school	111 (33.4)	20 (14.5)	
High school	161 (48.5)	87 (63.0)	
University degree	54 (16.3)	31 (22.5)	
Not specified	6 (1.8)	0 (0.0)	$p=0.0001$
Job			
Worker	241 (72.6)	108 (78.3)	
Unemployed	37 (11.1)	6 (4.3)	
Student	13 (3.9)	15 (10.9)	
House wife	17 (5.1)	3 (2.2)	
Pensioner	8 (2.4)	4 (2.9)	
Not specified	16 (4.8)	2 (1.4)	$p=0.0027$

Note: n.s., not statistically significant.

question number 2 in the two population groups (stop progression of the disease/protection from HIV-1 infection). Counselling performed by TVA was very important for correct information about a Phase I trial where the primary endpoint was the safety of the Tat vaccine and not the efficacy, which can be evaluated only in following phases. Therefore, TVA researchers explained that in this phase the participation to the trial with the Tat vaccine was not addressed to evaluate protection from HIV infection. Nevertheless, the desire to benefit people was more evident within HIV-positive subjects, as compared to uninfected individuals (26.2% and 12.3% of positive answers to question number 3, respectively).

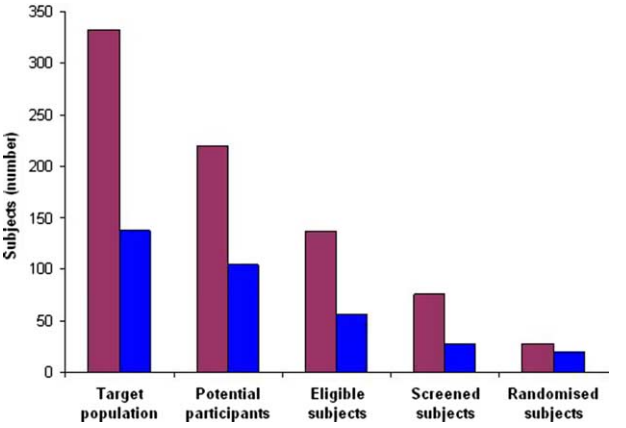

Figure 2. Frequency of subgroups identified during the enrolment procedures, stratified by HIV+ (red bar) and HIV– (blue bar), respectively.

Discussion

UNAIDS/WHO estimates almost 33 million people living today with (HIV) infection in the world. In particular, sub-Saharan Africa and Asia remain the most ravaged regions, characterised by continuously increasing rates of infection (http://www.unaids.org).

The development of antiretroviral drugs has reduced mortality and improved the quality of life of HIV-infected individuals, although the access to therapy and its routine use in developing countries is still limited, especially where infrastructures, medical and economic resources are inadequate or absent. Since drugs cannot eradicate the virus and its spread among individuals, the development of a vaccine against HIV infection represents the only realistic way to control the expansion of the HIV pandemic (Caputo et al., 2009). To this aim, the global scientific community is involved in a challenge for the identification of novel effective vaccine candidates and their testing.

Although recruitment and enrolment are often considered as a single step process, the socio-behavioural research suggests that recruitment for HIV vaccine trials is a complex and dynamic process involving specialists committed to the identification of the most efficacious ways to inform potential participants about trial purpose, procedures, risks and benefits (Gross, Mallory, Heiat, & Krumholz, 2002).

A crucial step in the recruitment process in HIV/AIDS clinical trials is represented by the communication of the related information to the general public. This can be transferred by media, government and academic institutions to potential volunteers in order to achieve a correct and comprehensive communication. Science works in a context of complex hypotheses, empirical evidence and proofs. All these contents

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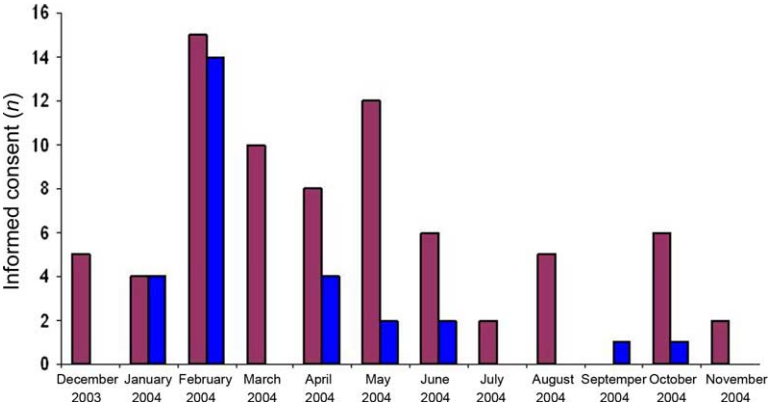

Figure 3. Frequency of subjects who signed the informed consent by month, stratified by HIV+ (red bar) and HIV– (blue bar), respectively.

have to be "translated" according to communication needs in order to be clearly read and understood by the general public. Therefore, the content and flow of information from the investigators/sponsor to the potential volunteers must be accurately evaluated and controlled.

Recruitment of volunteers for HIV vaccine trials is a critical step, particularly for Phase I studies, where only evaluation of safety and immunogenicity (as a secondary endpoint) is performed, no evaluation of efficacy is anticipated and a limited number of volunteers is recruited. For the conduction of the preventative and therapeutic phase I trials of the Tat vaccine the SCP developed a process for: (a) providing the volunteers with an adequate level of information on the trial purpose and procedures by a dedicated telephone counselling; (b) guaranteeing on access to the trial to all the Italian population; (c) supporting clinical sites during the enrolment procedure; and (d) evaluating informative needs and motivation to trial participation.

Table 2. Topics of the questions asked to the target population.

Target population ($N = 470$)	n	%
Topics related to HIV/AIDS		
General	2	0.4
Social issue	1	0.2
Anxiety	9	1.9
Psychological support	5	1.1
Therapies	3	0.6
State-of-the-art on HIV research	1	0.2
Topics related to the Tat vaccine		
Phase I clinical trial	410	87.2
Enrolment criteria	371	78.9
Clinical sites	180	38.3
Inclusion/Exclusion criteria	127	27.0
Following phases of clinical trial	71	15.1
Characteristics of the Tat protein	62	13.2
Tat-related studies	41	8.7
Logistics for trial participation	9	1.9
Privacy	5	1.1
Reimbursement for participation	5	1.1
Insurance	4	0.9
End of enrolment phase	1	0.2

Note: n, number of subjects; %, n/N.

This process, which is an integrated, multidisciplinary, biomedical and psycho-socio-behavioural network, represented a novel and important aspect for the conduction and success of the clinical study.

This process was carried on in an anonymous setting, guaranteeing the privacy of the people calling the TVA and, more importantly, was performed on the basis of specific telephone counselling expertise, at full support of the volunteers' well-being.

The involvement of specific expertise for telephone counselling on HIV infection and communication represented to this regard an essential contribution to the study. The information provided by the TVA allowed the volunteers to weigh risks and benefits of trial participation and to evaluate the level of commitment that such participation involved. This activity not only provided adequate levels of information about the clinical study, but also allowed a preliminary screening of potential study volunteers. On the basis of the expectation for a trial of a novel vaccine against HIV/AIDS, the process of information and communication exerted by the telephone counselling of the TVA researchers greatly contributed to the enrolment procedure by selecting potential participants prior to the first contact with the clinical sites. Furthermore, the multi-step procedure contributed in reinforcing the motivation to participation and trial retention, providing important hints for the design of standardised enrolment procedures to be used in clinical studies.

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Table 3. Questionnaire.

		Yes		No		NK		NA	
	HIV+ individuals	*n*	%	*n*	%	*N*	%	*n*	%
N. 1	Are you willing to participate to the trial to support the biomedical research?	210	63.3	9	2.7	0	0.0	113	34.0
N. 2	Are you willing to participate to the trial to stop the progression of the disease?	199	59.9	19	5.7	1	0.3	113	34.0
N. 3	Are you willing to participate to the trial to help someone you care about?	87	26.2	131	39.5	0	0.0	114	34.3
N. 4	Are you willing to participate to the trial to help people?	201	60.5	17	5.1	0	0.0	114	34.3
	HIV− individuals								
N. 1	Are you willing to participate to the trial to support the biomedical research?	102	73.9	3	2.2	0	0.0	33	23.9
N. 2	Are you willing to participate to the trial to protect yourself against HIV-1 infection?	46	33.3	58	42.0	1	0.7	33	23.9
N. 3	Are you willing to participate to the trial to help someone you care about?	17	12.3	87	63.0	0	0.0	34	24.6
N. 4	Are you willing to prticipate to the trial to help people?	100	72.5	5	3.6	0	0.0	33	23.9

Note: NK, I don't know; NA, no answer.

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Although the lack of comparison with a control group or another vaccine trial could be a limit to the strength of the study, the TVA involvement in the Tat-based vaccine trial represented an innovative approach of recruitment and enrolment of study population. Indeed, this methodological approach, which foresees the joined participation of researchers and expert of communication, could be followed in future vaccine trials in order to improve the effectiveness of enrolment procedures.

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