EATG Position paper on clinical research and drug users

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Executive summary

The number of injecting drug users are estimated at 13.2 million worldwide. At least 41 countries have IDU populations with HIV prevalence above 5%. In 25 countries, the prevalence is higher than 20%, in 15 countries even above 50%. In much of Europe, Asia, the Middle East, Latin America and the United States, sharing of injecting equipment is the primary mode of HIV transmission.

Despite high HIV prevalence, drug users have largely been excluded from clinical trials. In order to address questions relevant to the clinical care of active drug users, they must be properly represented in clinical research.

To date, antiretroviral agents are marketed without adequate information on potentially life-threatening interactions with commonly used illicit drugs; users and their clinicians are often forced to rely on data from studies that did not include drug users or investigate drug-drug interactions. The EATG therefore strongly advocates for the inclusion of drug users in clinical research.

Scientific research must be clinically relevant, and relevant to the populations in whom the drugs and/or interventions will be used. It is not acceptable to have clinical research exclude real life situations, because of the fear that they might influence the outcome of clinical trials.

Science should serve to improve peoples' lives, not discriminate between legal and illegal substances.

Drug users are often excluded from trials because of concerns about adherence and loss to follow-up. Since research has shown that this is not necessarily true, the blanket exclusion of drug users in trials is not acceptable. If drug users are not included, the result of such trials may not be relevant for them. A sufficient number of drug users should be incorporated into clinical trials to enable stratification by substance abuse status. Dissemination plans must include venues where drug users receive services. Clinicians must receive training on working with active drug users.

The rationale for excluding drug users from clinical trials has changed over the past decades. In the past, a history of substance abuse was enough to keep an HIV-infected person out of clinical trials. That proscription later changed to "active substance abuse", of course judged by the investigator. Lack of research is driving refusal to prescribe ARVs and to enroll active drug users in clinical research.

The bulk of information about interactions between prescribed drugs is in sharp contrast to the paucity of reliable evidence about possible interactions with illegal drugs. In some cases, interactions are researched prior to approval, but often they are extrapolated from in vitro pharmacokinetic experiments, case reports, or animal model studies, based on theoretical knowledge regarding the drug's metabolic pathway of street drugs, and information often relies on informed guesswork or anecdotal reports. Conceivably it is extremely difficult to apply such data to clinical practice settings.

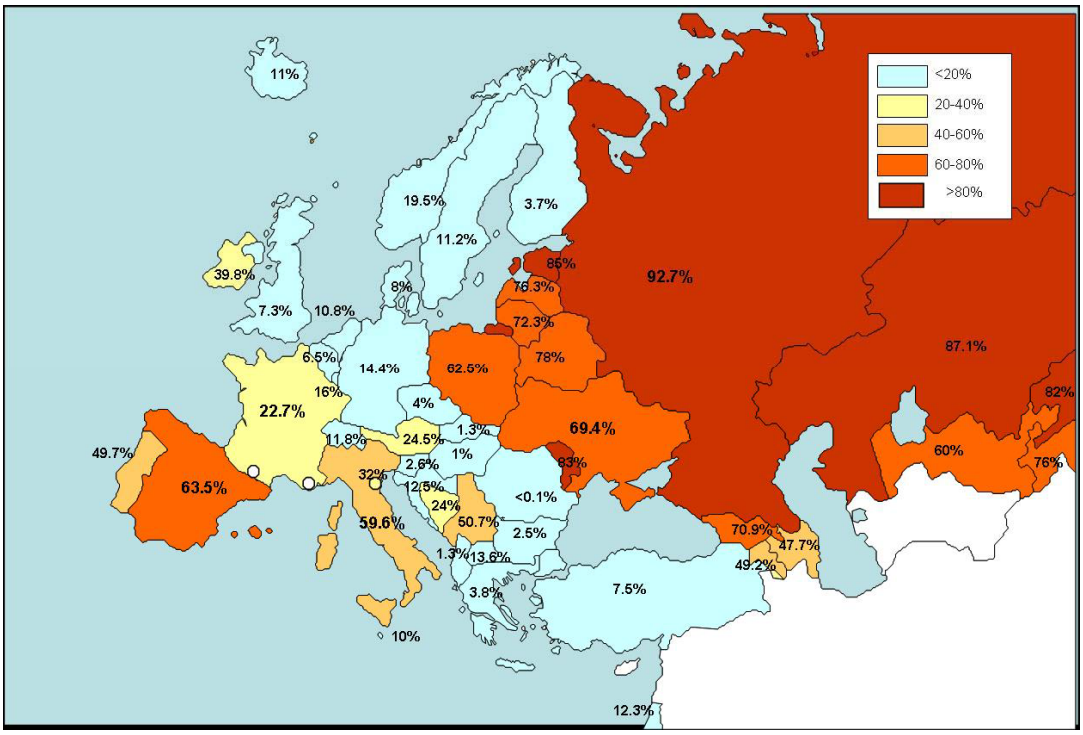
The EATG demands all governments to remove legal barriers for conducting clinical research on interaction between ARV and illicit drugs. Refusing to study potentially life-threatening interactions is unethical. Drug users not using pure drugs shouldn't be an obstacle for conducting research.

There are many moral, ethical and political questions related to clinical research. We urge the key stakeholders to include drug users with HIV/AIDS and their communities to solve these questions. Clinical research should serve the people who suffer the most. Policies on drug users often confuse treatment with punishment.

The EATG will continue to address these issues at meetings and conferences with all stake holders of clinical research, with governments, public health authorities, drug users and their representatives.

Preamble

UNAIDS estimates that at least 13.2 million people, worldwide, are injecting drug users. Up to 80% live in developing and transitional countries, reflecting the global distribution of HIV. At least 41 countries have IDU populations in which HIV prevalence is above 5%. Figures above 20% have been recorded at sites in 25 of these countries, and above 50% in 15 of them. In much of Europe, Asia, the Middle East, the Southern cone of Latin America, and many parts of the United States, the sharing of injecting equipment is the primary mode of HIV transmission. The proportion is set to grow even further as infection rates continue to rise in countries where poverty, poor health care systems and limited resources for prevention and care fuel the spread of the virus.



Proportion of Injecting Drug Users Among Reported HIV Cases in the European Region

(Source: European Commission; EuroHIV; Council of Europe)

Despite high HIV prevalence, drug users have largely been excluded from clinical trials. The following table, presented by Dr. Friedland at the 3rd International Workshop on Clinical Pharmacology of HIV Therapy, Washington, DC, April 13, 2002, demonstrates clearly that drug users have not been proportionally enrolled in a few North American and European trials, as well as in studies conducted by two US research groups, the AIDS Clinical Trials Group (ACTG) and the Community Programs for Clinical Research on AIDS (CPCRA):

Network or trial	**Percentage of IDUs enrolled**
ACTG	13.2
CPCRA	23.3
Delta (Europe)	12 (n = 3207)
Caesar (Canada, Australia, Europe, South Africa)	13 (n = 1840)
DuPont 006 (US, Canada, Germany, Puerto Rico)	12 (n = 1266)

The prevalence of illicit drug use among PLWHA is probably much higher than officially reported. In order to address questions relevant to the clinical care of active drug users, they should be properly represented in clinical research. Clinical research should include active IDUs as well as users under substitution treatments, under antagonist treatment, recreational or non-problematic drug users and patients using illicit drugs to relief symptoms and side effects.

To date antiretroviral agents are marketed without adequate information on potentially life-threatening interactions with commonly used illicit drugs; drug users and their clinicians are often forced to rely on data from studies that did not include drug users or investigate drug-drug interactions. But the problem we address here is not only a function of under-representation: adequate representation is not a substitute for rigorous and thorough investigation of drug-drug interactions, side effect, toxicities and other research questions

relevant to the clinical care of IDUs. That such studies are rarely conducted clearly represents an unacceptable situation.

The European AIDS Treatment Group strongly opposes the exclusion of drug users from clinical research, based on the following rationale

1. Scientific research must be clinically relevant, and relevant to the populations in whom the drugs and/or interventions will be used. HIV doesn't discriminate; neither should scientific research.
2. Age specific mortality rates among drug users are 10 to 20 times higher than those of non-users. Many drug users have multiple medical and psychiatric co-morbidities, including trauma, neurological disorders, hepatic, renal and pulmonary diseases, psychiatric problems and the like (Friedland et al). It is not acceptable to have clinical research exclude real life situations, because of the fear that they might influence the outcome of clinical trials. Science should serve to improve peoples' lives: this is more important than adverse results for researchers' careers or companies' financial results.
3. Drug users are often excluded from trials because of concerns about adherence and loss to follow-up. Since research has shown that this is not necessarily true, the blanket exclusion of drug users in clinical trials is not acceptable. More research about treatment adherence of drug users is needed in order to replace assumptions with facts.
4. If drug users are not included in clinical trials, the result of such trials may not be relevant for them (i.e. some antiretroviral drugs, particularly protease inhibitors, were shown to have clinical effects in real life opposite to those predicted in the test tube). This includes studies of pharmacokinetic and drug-drug interactions with ARV treatment, for complications of antiretroviral therapy and HIV disease itself, as well as prophylaxis of opportunistic infections, and interaction with methadone, buprenorphine, and the above.
5. A sufficient number of drug users should be incorporated into clinical trials to enable stratification by substance abuse status.

6. Representation also comprises inclusion of drug users beyond participation in clinical trials: drug users must have the opportunity to participate in advisory boards (community or other), and Institutional Review Boards.
7. Dissemination plans must include venues where drug users receive services. Clinicians must receive training on working with active drug users, including incorporation of the philosophy of harm reduction and concrete service delivery, such as demonstration of safe injection techniques and adherence support.

Active drug users can be adherent as anybody else

Drug users are often denied access to anti-HIV therapies on the grounds of poor adherence, but data supports that 1) physicians are notoriously poor at predicting adherence, 2) when their needs are properly addressed drug users are capable of adherence comparable to that of non-users, and 3) when active drug users are successfully retained in treatment the full benefits of highly-active antiretroviral therapy are not compromised. Numerous studies from different countries around the world have indeed shown that active drug users can effectively adhere and respond to demanding HAART regimens, and in particular:

1. The EuroSIDA study, which included over 6000 European HIV-positive patients from over 50 medical centres, revealed no differences in CD4 or viral load responses to therapy between IDUs, homosexuals, and heterosexual non-IDUs, who started therapy. “Intravenous drug users were significantly less likely to start HAART, but among those who did, response to therapy was similar to that of other exposure groups (Mocroft et al).
2. A sub-analysis of the same study in those patients who had baseline and follow-up viral load or CD4 counts, revealed no difference in response to therapy between IDUs and other exposure groups. History of drug use was not an independent predictor of treatment failure. “Despite our study including a relatively large percentage of intravenous drug users, who are believed to adhere worse when they are outside of drug substitution programs, no differences were found in virologic response depending on transmission category (Paredes et al).
3. In Switzerland, a study of 100 patients starting any form of antiretroviral therapy at a regional health clinic revealed that psychiatric history and history of drug use did not predict poor compliance (Ostrop et al).
4. In Spain, a prospective study of 133 patients, 71% of whom were IDUs, revealed that 58% of patients achieved undetectable viral load. Compliance rates were lower for IDUs, but only statistically significantly so at 6 months. In general, compliance rates in IDUs were only slightly lower and they enjoyed similar clinical outcomes (Roca et al).

5. A second Swiss study of patients who were eligible to begin AZT therapy between 1989 and 1992 revealed equivalent compliance in IDUs and non-IDUs (81.3% vs. 83.2%)(Broers et al).
6. In the United States, a study of 83 patients seen at the HIV clinic of a large public hospital showed that on average, IDUs achieved 83% compliance with AZT therapy. A history of recent drug use did not predict poor compliance (Samet et al).
7. A prospective US study of 273 HIV-positive patients, many of whom were injection drug users, showed that injection drug use was associated with treatment failure when a bi-variate analysis was applied. However, the use of a multivariate analysis revealed that high rates of missed clinic appointments were the only predictor of treatment failure. Thus, while drug use may contribute to higher rates of missing clinic appointments, drug users who are able to keep their appointments enjoy equal outcomes to other patients (Lucas et al).
8. The widespread myths of drug users non adherence might have more to do with feelings of uneasiness of physicians and scientists and little with their abilities. In a study conducted in the US in 1990, over 50% of physicians surveyed reported negative attitudes toward treating IDUs, while only 28% reported feeling comfortable in caring for them (Gerbert et al).

Since active drug users can adhere to a therapeutic regime if it is appropriately designed, and considering that numerous studies from different countries around the world indicate that active drug users do adhere and respond to demanding HAART regimens it is important to work closely with *all* patients eligible for therapy. No physician should therefore refuse effective therapy to active drug users who want it.

Active discrimination of drug users in clinical research

The rationale for excluding drug users from clinical trials has changed over the past decades. At the beginning a history of substance abuse was enough to keep an HIV-infected person out of clinical trials. Eventually that proscription changed to "active substance abuse," of course judged by the investigator. In these days exclusion from trials rests in the investigator's anticipation of a person's “poor compliance” with the study protocol (Friedland). In the context of clinical research, the following factors play a role in the active discrimination of drug users:

- the misconception that HIV-positive IDUs will be unreliable or difficult research subjects
- the belief that expensive medications should not be “wasted" on drug users
- fears that HIV-positive IDUs have a chaotic lifestyle, which will lead to lack of compliance with treatment regimens and distort research results
- Sexual or reproductive issues (a reasonable proportion of IDUs are women)

Lack of research is driving refusal to prescribe ARVs to and to enrol active drug users in clinical research. Among other reasons, physicians are often hesitant to provide antiretroviral therapy to active drug users because of inadequate data on potential interaction between anti-HIV medication and recreational drugs, while active discrimination of drug users in clinical research reinforces their beliefs.

The need for specific studies on drug drug interactions

In October 1996, activists angrily notified Abbott laboratories about a life threatening interaction between its protease inhibitor ritonavir and MDMA, a recreational drug also known as X, XTC, Adam and Essence. This came after the death of a British PWA caused by an overdose of MDMA. Although it was reported that only one dose caused this, the deceased's blood level was "nearly ten times the one which is expected to cause serious toxic effects" – roughly the level that would be expected after ingesting 22 MDMA tablets (Fatal interaction between ritonavir and MDMA. Lancet 1998; 352: 1751-2).

Up to date, the bulk of information about interactions between prescribed drugs is in sharp contrast to the paucity of reliable evidence about possible interactions with illegal drugs. In some cases, interactions are researched prior to approval, but often they are extrapolated from in vitro pharmacokinetic experiments, case reports, or animal model studies, based on theoretical knowledge regarding the drug's metabolic pathway of street drugs, and information often relies on informed guesswork or anecdotal reports. Conceivably it is extremely difficult to apply such data to clinical practice settings.

Even where reliable information about the interactions between illegal and prescribed drugs does exist, there is disagreement over how it should be used. Some individuals and organizations hold the view that governments are under no obligation to protect the health of individuals who break the law. Others believe this to be a dangerous argument due to the elevated numbers of users of illegal drugs.

Opportunities

In evident contrast to the need of clinically assessing potential interactions between recreational drugs and ARV, there are very few studies on this issue published. Some exceptions include:

1. There are known interactions between opiates and antiretroviral medication. Most of the data come from published studies of HAART in patients treated with methadone in the United States and Europe.
2. There is limited available data about the interaction of marijuana and antiretroviral therapy. Some studies showed statistically significant reductions in the blood concentration of HIV medications in patients who smoke marijuana, but none have shown a clinical impact (Kosel et al).
3. Two studies that randomized patients to dose controlled THC cigarettes, dronabinol (THC) capsules, or placebo found no clinical interactions (Abram et al).

Possible solutions include:

Animal trials: while awaiting a baseline for trials involving human subjects, animal trials on interactions could and should be underway. Primate, especially simian, models would be useful, especially if genetics are analyzed as a factor, as they should be.
Controlled trials: because illegal drugs are involved, it has been argued that randomized trials would not be ethical. However, we do have some good examples of controlled trials involving illegal drugs, like:

- Kosel BW, Aweeka FT, Benowitz NL, Shade SB, Hilton JF, Lizak PS, Abrams DI. (AIDS. 2002 Mar 8;16(4):543-50), a randomized placebo-controlled study designed to evaluate the metabolic effects of smoked marijuana and dronabinol in HIV-infected patients receiving indinavir (IDV) or nelfinavir (NFV); the rationale for this specific study was the use of cannabinoids for appetite stimulation and the management of wasting and antiretroviral side-effects as a common practice in the care of HIV-infected individuals. The

study was conducted by the Department of Clinical Pharmacy, University of California-San Francisco. Study took some 7 years to obtain approval.

- The Effect of Marijuana on Neuropathic Pain in HIV-related Peripheral Neuropathy, Donald Abrams, M.D. (UCSF), is an open-label pilot inpatient study conducted over 9 days, and presented at last CROI in San Francisco. Abrams found that 10 out of 16 subjects reported a greater than 30% reduction in pain after seven days of treatment.
- The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. Kosel BW, Aweeka FT, Benowitz NL, Shade SB, Hilton JF, Lizak PS, Abrams DI. Department of Clinical Pharmacy, University of California-San Francisco, San Francisco, CA 94110, USA.
- In late 2002 Jose Carlos Bouso of the Autonomous University of Madrid earned regulatory approval and begun his own study of MDMA as a treatment for patients with post-traumatic stress disorder. Political pressure led Spanish drug-enforcement officials to halt the trial in May 2002.
- One small study suggests MDMA exhibits non-linear kinetics and that CYP450 2D6 may not be involved with MDMA metabolism (Non-linear pharmacokinetics of MDMA in humans; de la Torre R, Farrè M, Ortuño J, Mas M, Brenneisen R, Roset PN, Segura J, Camí J; Br J Clin Pharmacol, 2000; 49(2):104-9).

All these studies showed that it is possible to get methamphetamines, cannabis, and other illegal substances, for medical research, while the main obstacle remains regulatory approval and political pressure. If these options were offered, users could be asked to participate in an arm of the study but would have to be fully informed of possible side effects.

Pilot or established heroin substitution programs offer an ideal opportunity to investigate interactions between ARVs and heroin. This would be particularly feasible and relevant in regions such as Eastern Europe and the Newly Independent States where 90% of HIV + individuals are active drug users.

Other interactions: It should also be taken into consideration that some antiretroviral drugs may cause false positive reading to common assay used for checking active drug use (i.e. efavirenz can cause a false positive THC reading on the CediaDau Multi-level THC urine test). Further studies on this field may contribute to avoid legal consequences for users.

Legal and operational obstacles

Company representatives continuously affirm that such studies would probably be impossible, and would almost certainly be unhelpful. Among the legal and operational obstacles are the following:

- The conduct of clinical trials using illegal drugs would necessarily require permission from the government, which has been exceedingly reluctant to allow such studies for fear of being perceived as "soft on drugs".

The European AIDS Treatment Group therefore demand all governments to remove legal barriers for conducting clinical research on interaction between ARV and illicit drugs and allow such trials whenever appropriate.

- Pharmaceutical companies have argued that to clarify the dangers associated with interactions with illicit drugs would amount to a reckless signal to the public and the company itself could be perceived as supportive to illegal activity.

The European AIDS treatment Group object that refusing to study potentially life-threatening interactions is far more problematic.

- In some cases it would be difficult to provide clinically significant quantities of pure street drugs. There are no approved versions of drugs such as cocaine. For legal and ethical reasons, drug companies are unwilling to manufacture test versions of such drugs in their own laboratories, even if the government granted permission;

- Illegal drugs are seldom pure, are often contaminated by other substances, and may contain very little or none of the advertised ingredient;
- Illegal drugs rarely have standardized doses: what could be a relatively minor interaction at one dose could be serious at another;
- Manufacturers are concerned about legal liability should they offer advice based on uncertain or potentially incomplete data.

The European AIDS Treatment Group object that since drug users are not using pure drugs this shouldn't be an obstacle for conducting such research and recommend to conduct larger studies so that a range of purity/doses can be accommodated.

- There is little financial incentive for pharmaceutical companies to work on this issue;

The European AIDS Treatment Group believe that ways for providing incentives for conducting clinical research on active drug users should be explored. However, Those who conduct and finance clinical research have to take their responsibility and response to the needs of drug users as they have been discussed here. This is of vital importance, especially in regions where rights of drug users are neglected.

Conclusion and claims

- There are many moral, ethical and political questions related to clinical research. We urge the key holders to include drug users with HIV/Aids and there communities to solve these questions.
- The exclusion of drug users in clinical trials is based on misperceptions and prejudices. Their knowledge and capacities to contribute are not valued. This has to be stopped by the active inclusion of the experiences of drug users in study design, study enrolment and conduction.
- Clinical research should serve the people who suffer the most. Drug users represent a large number of people living with HIV and Aids. There are many open questions related

to drug use and ARV treatment. It is unethical to allow key questions to remain unaddressed.

- Policies on drug users sometimes confuse treatment with punishment. Old Public Health tools (confinement, testing, contact tracing, compulsory treatment etc.) are in place instead of more effective, modern paradigms: harm reduction, education, participation of peers, informed consent etc.). This must be changed! It is the responsibility of key holders of clinical research to take this into close consideration and not to support old public health structures.
- We will continue to address these issues at meetings and conferences with all stake holders of clinical research, with Governments, public health authorities, drug users and their representatives.

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