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Volume 12, 1 – Spring 2003

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T-20, A NEVER ENDING STORY

LIMITED ACCESS AND HIGH
PRICE FOR A DIFFICULT TO TAKE
BUT NEEDED DRUG

THE I-CAB

NATIONAL COMMUNITY ADVISORY
BOARDS SPREAD IN EUROPE

CROI 2003

A COMMUNITY APPROACH

Getting to **know each other**

EATG Groups start presenting their work

Have we been properly introduced?

If you are a usual reader of the magazine, you might have been quite surprised not to have had any information about it for the last two months. Also, you might have thought that it was another one of the HIV publications which had not survived or that we had forgotten to send it to you contrarily to what we usually do.

Neither of the two are true. We had simply decided to give the magazine a short break. Undoubtedly, all the work done so far had earned that but in reality we had reached a point that if we really wanted to grow up, if we really wished to make our voice heard more clearly and to make our opinions more influencing, we needed to assess deeply and honestly the impact of our words, their fitness to the current situation, the interest of the issues selected, the focuses of our data, in other words how our readers perceive and evaluate us.

This is why we decided to send a questionnaire to our subscribers whose answers would be analysed in order to improve our awareness of who we had established contact with. That is what we are currently doing and we can assure you that your opinions and your preferences will be taken into account.

However we would like to go further and make this contact a two-way process moving towards a true dialogue. For this purpose, we decided to include in this special issue a series of presentations on EATG work group activities, the pan-European organisation that publishes this bulletin.

For this occasion, the groups which are presenting their work are those which focus on issues such as treatment access in developing countries, women, HIV and treatments, as well as the very young but very enthusiastic group on vaccines, and the group which regulates the development and internal participation of the EATG members.

We hope that this reciprocal description of our profiles, of our organisation and of you as readers, will allow us to know each other better, to develop a sense of trust and confirm our relationship.

Evidently, as we usually do and have always done, we will not forget to mention another issue that is very worrying to us which is the price of anti-HIV drugs.

We, European activists, have been questioning Roche, as we have always been and as we will always be questioning other companies, trying to understand why. Why it took so much time to make T-20 (Fuzeon) available? The drug is available now, although with some limits. Why is its price so high? The Swiss multinational announced that the annual price would be approximately 19,000 Euros, giving as a pretext the complexity of the production process and the need to finance research costs. Given that neither of these two reasons has been proven to us, we can only doubt that neither of them is true.

Companies believe that National Healthcare systems will be ready to support anything and it seems that the race for whom is going to get the most money in the least time, has started. This situation cannot continue. If every new anti-HIV drug, above all when it is vital for a large number of people, is commercialised with a price much higher than that of the previous drugs, budgets will be overwhelmed and restrictive drug access policies will have to be faced. Immigrants will be the first to be affected, as is the case already in some countries. Then the next victim would be the freedom of treatment options: "Keep on with the same combination although its side effects bother you, because we will not pay for another option."

We call to the good sense of these big companies and to the European authorities so that they will wield their authority against them. A number of community actions are taking place now to denounce the price of Fuzeon and others are under way. You want to know the reason why? Because everything has its limits.



Volume 12, 1 – Spring 2003

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Printing:

Service-Druck Kleinherne, Neuss

ISSN:

1026-1648

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Statement of purpose

European AIDS Treatment News is published by the European AIDS Treatment Group (EATG). The EATG is a growing group of advocates and activists from Europe who participate in treatment activism and advocacy, community-based research advice and treatment training programmes. EATN helps in the dialog between the HIV+ person and their care-giver(s), helping them make treatment decisions from a knowledge-sharing position. The EATN reflects the growing complexity and diversity of information and information needs. EATN invites you to copy all or part of it and distribute it. If you use and/or copy any part, we hope you cite us as the source.

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T-20 in combination with an optimised background regimen: an efficient but compelling option

After experiencing treatment failure, when drugs were no longer efficient, Billy was able to participate in the T-20 trial.

Billy is 50 years old. He has known that he is HIV+ since 1988. In 2001, he was in treatment failure: “nothing worked anymore”. His viral load was high and his CD4 count was dropping. In July his doctor suggested that he should participate in the T-20 International trial. A few weeks after signing an

approval letter, he was informed that his participation in the trial was accepted. He was then randomised to the group of those who would not receive T-20. At study entry, his doctor changed and intensified his background anti-HIV treatment. After eight weeks, no real significant results were



observed. As was planned in the trial, Billy's doctor asked that he should receive T-20.

The first injection

Billy received the first T-20 injection at the hospital in November 2001. Billy was nervous and scared. When the nurse injected the substance beneath his skin, Billy thought it was rather painful. She showed him how to do it and the hospital offered to send a nurse to his house during the first week. But from that night, Billy decided to self-inject the substance. The use of T-20 did not seem really difficult to him since he had had a subcutaneous treatment before.

What is T-20?

T-20 (enfuvirtide, Fuzeon) is the first of a new class of anti-HIV drugs known as entry inhibitors, so-called because they stop HIV from entering CD4 cells (see Remaides #39, p 4).

T-20 is active on HIV strains resistant to all the other anti-HIV drugs. It is therefore interesting for patients who, like Billy, are failing every other existing treatments. Other different entry inhibitors are currently under development. Some of them, such as T-1249, will be administered by subcutaneous injection but others could be taken orally (capsule or pill) (see Remaides #44, pp 4 and 26, 27).

Getting everything ready

After washing his hands, Billy gets everything ready for the injection: the ampoule with freeze-dried powder, the ampoule with sterile water, pads for disinfecting and two syringes.

The exact amount

The drug has to be reconstituted with exactly 1.1 ml of sterile water. The rest of the water has to be thrown away.

T-20 daily

Billy benefits from T-20, a new anti-HIV drug. He has to self-administer the substance twice daily by subcutaneous injection. We decided to meet him.



The only adverse effect is pain during injections

For the last few months, Billy has prepared and self-injected T-20 twice daily, around 9:30 a.m. and around 9:30 p.m. He has noticed that pain is not decreasing with time. When a friend drops in, he asks him/her to do the injection and when he goes to the hospital, he gets the nurses to do it for him. Apart from the pain during injections, Billy did not report any other adverse effects, "except from that strange sensation which lasts half an hour and makes you feel like the substance has just been injected".

A tiring but efficient option

His background HIV treatment is composed of Invirase, Kaletra, Ziagen, Epivir and Viread and is "very hard to bear: I suffer from flatulence, intestinal gas and muscle pains. Above all, I am very tired".

From the very first month of using T-20, Billy's viral load became undetectable and his CD4 count slightly increased. Billy feels better even though the treatment is not easy to take. He would like to find a part-time work but he is too tired.

Emmanuel Trénado

Source: Remaides #46, December 2002

Europe

Access to T-20 in Europe

According to an EATN survey about the accessibility of the Roche HIV fusion inhibitor T-20 (Fuzeon®) in Europe, about 50% of the slots available in the ongoing studies have been assigned by the end of February. Italy is the best with about 100% of the slots filled and Portugal the worst with only 25% of the slots filled. See text boxes on the Portuguese and the French situations. So far, the studies have only been done in EU countries, the eastern countries being left with only news from the western countries. UK expanded access programme has filled about half its slots and is enrolling steadily, but there has not been a huge immediate demand, according to Simon Collins, London, UK. In Spain, also only about 50% of the slots (157) have been assigned, despite the fact some surveys say up to 500 people were appropriate candidates to benefit from T-20, according to Joan Tallada, Barcelona, Spain. He stated that Roche in Spain recognizes that they were too cautious, fearing that a open call would have created an over-

whelming demand they wanted to avoid by all means. Another factor that may have been an influence is that the National Health System created a centralized commission to assign the drug. The commission meets once a week in Madrid, and some doctors and patients may have seen this as an extra bureaucratic barrier to surmount. According to Maite Suarez, Barcelona, Spain, the upcoming arrival of Tipranavir's Phase III trials may have influenced the decisions of some doctors in terms of recommending to their patients to start (or not to start) with T-20. Talking to a Spanish doctor from a leading Madrid hospital during last CROI, she took note of his own words: "when I explain to them how T-20 works and how it has to be used, and then I tell them about the near-future availability of Tipranavir, it turns out that there are not that many patients that cannot afford to wait for a couple of months (for the trial RESIST-2 to start), and that's what most of them prefer to do: wait". According to him, many could construct a viable regimen with Tipranavir plus an optimized background regimen, and tolerability/efficacy of this PI, based on this doctor's own experience, is very good. Another issue, Maite recalls, is that RESIST-2 won't have the room to take all the deep-salvage patients from Spain. Also, according to this Spanish doctor, immediately after the Barcelona Conference, there was a big increase of questions about T-20 (many

Reconstitution and waiting

Billy injects the sterile water in the T-20 ampoule. Then he rocks it from side to side, very carefully so that the mixture should not foam. It takes 20 minutes for the powder to dissolve, sometimes more, so do not be in a rush! To save time, you can prepare two doses and keep one in the freezer for a maximum of 24 hours.



The Injection

You can choose to inject the liquid beneath the skin of the abdomen, the arm or the thigh. The injection is easy to do but like many people using the drug, Billy says that it can cause some discomfort and even pain.



The follow-up book

People using T-20 receive information on how to use the drug and a follow-up book where all the events concerning their health condition will be reported.



patients thought it was the miracle drug, and also that it could be taken in monotherapy, something that we thought could be attributed to the vicious marketing campaign of Roche plus the biased coverage by some media, in Maite's words), but that in a couple of months such interest had gone down to almost none. Finally, the problem of pricing should be strongly raised. As Mauro Guarinieri, Bologna, Italy, points out, although probably impossible the US activists have considered asking the FDA to force Roche to pre-declare the price which is likely to be much over \$10/12.000 / year. This means T-20 may be the first anti-HIV drug which availability may be at risk for reasons of budget.

Portugal

Access to T-20 in Portugal

In Portugal, the difficult access to T-20 is an example of the barriers set up against the access to (ARV and other) drugs without marketing authorization but with preliminary established clinical results. These barriers may result in the death of people in ARV treatment failure.

The portuguese drug commission (INFARMED) unreasonably refuses compassionate access programs and creates extra bureaucratic barriers for the use of drugs without marketing authorization. Also, uninterest from clinicians occurs and slow work is done by the local hospital or drug commissions in approving the studies.

The portuguese treatment activists succeeded to get from Roche 20 slots assigned for Portugal in the study 305. Partly due to admission restrictions in the study, only 11 slots were filled. The study is now over and INFARMED keeps denying compassionate use, so the only way to allow access to T-20 for the portuguese patients in need of salvage therapy was to include them in the roll-over study. A portuguese activists' move allowed the assignment of 43 slots in this phase. The enrollment will be over by the end of March and up to now only 2 of these new slots have been filled. Together with

the 11 slots covered before, this makes a total of thirteen patients who are benefiting from T-20 in Portugal now. Seven other patients are still waiting – until when? – for the approval from their hospital ethical commission. Meanwhile, 10 out of the 43 slots have been transferred to countries with faster response (which does not mean greater need).

ARE THE PORTUGUESE AUTHORITIES PLAYING WITH THE LIVES OF THE PEOPLE LIVING WITH HIV/AIDS? SHOULD NOT THESE ATTITUDES BE CALLED CRIMINAL?

*Pedro Silvério Marques – Lisbon, Portugal
Article in Abraço Newsletter March/April 2003*

France

A restricted access in France

Access to T-20 is far too restricted. This shortage is due to the Roche Laboratories strategies which, for economical reasons, have postponed mass production of T-20. However, AIDS associations brought the issue to Roche's attention as soon as they knew of the potential interest of T-20. For more than two years, there have been an

EATG's Press release on price

Düsseldorf, February 24 – Roche's announcement today that its new fusion inhibitor T-20 will cost over twice as much as the most expensive drug on the market [Norvir Abbott Labs \$9,387.22] in European Countries that elect to undertake a special license sales (SLS) program before regulatory approval is granted has raised great concerns among European's treatment activists setting up a wrenching debate over who will receive it and who will pay for it.

Roche said it will price the drug, called Fuzeon, in Europe at €18,980 (\$20,424) for a year's supply fuelling controversy about access to T-20 even in relatively rich countries. "Being the SLS program price announced today indicative of eventual global commercial prices this confirms the fear that a number of us had been feeling for the last few weeks – that the price would be even worse than we had dared imagine" said Mauro Guarinieri – Vice Chair of the European AIDS Treatment Group and chair of the EATG Access Working Group. "Many of us were very hopeful about what this drug can do considering Fuzeon the

biggest advance in AIDS treatment since the advent of so-called protease inhibitors in the mid-1990s because of its ability to beat down the hardest forms of the virus. After having known the price we don't know whether our health systems will have the money to pay for it or not" he added.

The already-steep cost of AIDS treatment has stirred controversy because of the limits it puts on access to these drugs in Africa and other developing regions. Now, the spiralling price of new medicine threatens to further restrict access to new AIDS treatments even in relatively wealthy countries. EATG has been already involved in tough price negotiation with Roche when urging the pharmaceutical company to reduce its price for nelfinavir, a crucial second-line AIDS drug that was priced out of reach of most patients in developing countries.

Roche's announcement today will probably fuel further debate and may eventually lead patients' group to campaign against the Swiss company. "We don't want to face another situation in which patients who

increasing number of protest moves, such as petitions published in Remaides, public protests by Act-Up, meetings with the Ministry of Health, repeated discussions with Roche, AIDES posters denouncing the laboratories practices... To no avail: T-20 shortage will last for several months and will also continue after marketing approval which is scheduled in Europe for the middle of 2003.

Nevertheless, repeated petitions from the associative group TRT-5(*) have conducted Roche to increase the number of treatments available and 121 more people have been taking T-20 since October 2002. In France, 250 to 300 people are currently using the substance. A number much below what would be necessary.

Currently, T-20 is available through trial, only to patients with a CD4 count below 100, a viral load above 10,000 and who are experienced with all the existing classes of anti-HIV drugs. The list of hospitals participating in the trial is available on the Web (www.aides.org) or by contacting Emmanuel Trénado of AIDES (tel: (+33) (0)1 41 83 46 13). As from March 2003, access to T-20 should become slightly less restrictive thanks to a temporary use authorisation.

(*) TRT-5 (Treatments and drug research): Act-Up Paris, Actions Traitements, AIDES, Arcat, Dessine-moi un mouton, Nova Dona, Sida Info Service, Sol en Si. www.trt-5.org



have failed to respond to other medications may have to fight again to access new antiretrovirals as it was in the past for protease inhibitors" said Guarinieri, urging for a public debate over fair pricing on essential drugs.

The EATG

The European AIDS Treatment Group (EATG) is a pan-European charitable NGO advocating for the treatment-related interests of people living with HIV and AIDS at the European level. The EATG was founded in 1991 as a co-operative structure of people from 10 different nationalities and communities affected by HIV and AIDS in Europe. Today the EATG has members in 27 European countries. National networks support these efforts. EATG provides information about treatments and trials, gives guidance to public and private organisations and organises community input into trial design. EATG receives funding from a variety of private and public funders to secure its impartiality.

Contacts: office@eatg.org

The Access Working Group

The EATG views access to health as a basic human right and access to medicines as a global issue affecting the HIV+ community throughout the world to varying

degrees. The Access Working Group has been established with the aim of improving and enlarging the scope of the EATG in the field of access-to-treatment in Eastern Europe and developing countries. The primary aim of the AWG is to increase the awareness on access' issues, to network with other groups already involved in the field, to establish relationship with local communities trying to work together in building up their capacities, to work on, define and develop strategies to put and maintain pressure on pharmaceutical companies, local government agencies, international bodies and health organizations to make treatments and drugs available wherever there is a need.

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Please send contact details to office@eatg.org

DEVELOPMENT and MEMBERSHIP WORKING GROUP – DMWG

Introduction

In contrast to all other EATG Working Groups the DMWG is the only one that doesn't focus on life in the real world, trying to achieve the EATG goals and aims concerning HIV treatment as much and as soon as possible.

The DMWG concentrates on the inner structures and organisation of EATG and its membership.

The DMWG merged from two separate Working Groups, the Development Working Group (DWG) and the Membership Working Group (MWG). Both groups were initiated at the General Assembly 1997 (Rotterdam/ the Netherlands), shortly after the change of EATG headquarters from Berlin to Düsseldorf (Germany).

By that time it had become clear that the rather simple EATG Constitution from 1992 needed re-writing to adapt it to the changing needs of a growing pan-European HIV Organisation, which should be easy to understand for its members, who have so many different cultural and national backgrounds. This work was to be done by the DWG.

It also was obvious that the entire membership administration needed re-organisation, clearing a whole lot of so-called dormant, inactive members, who were in fact blocking the admission of new members, since EATG cannot afford to grow too big too soon. This job was to be done by the MWG.

DMG

This group started working on an entirely new EATG Constitution that would respect all the legal and tax regulations for a charitable NGO in Germany, where EATG is registered, and also would give a stable and easy-to-understand framework for EATG's members and especially for its

elected governors, the Board of Directors. Because of the Association's registration in Germany, the original text had to be written in German. A lot of time however was spent on a very precise English translation. The result was presented and accepted by the General Assembly in Raunheim (Germany) in June 1998 (minor changes were made during the General Assembly in Athens Greece in May 2000).

Of course the EATG Constitution doesn't cover in detail day-to-day business and routines: a set of clear household rules, or protocols, was needed. After investigation of EATG's inner structure and organisation Peter Scott (London, UK) presented at the General Assembly in Lisbon, Portugal, in October 1998 a first draft for a set of protocols, entitled "Membership Handbook". A revised version, drafted by the new Development and Membership Working Group (DMWG) was accepted by the General Assembly in May 2001 in Brussels, Belgium.

MWG

At the Rotterdam General Assembly 1997 it was decided not to accept any new members until the MWG had reviewed the membership administration and made the necessary recommendation to the Board of Directors on the termination of dormant, inactive, resting memberships. This turned out to be a difficult job, since there was no proper membership administration at all (although this is required by German law), but in October 1998 the group was able to present first results to the General Assembly. The MWG developed guidelines for the acceptance of new members and worked on ideas to improve members' input by suggesting several Working Groups. The important role of the MWG, especially

considering the acceptance of new members, was stressed in the new EATG Constitution: The MWG is the only EATG Working Group that is explicitly mentioned in the EATG Constitution, including its relation to the Board of Directors.

After several request from the General Assembly the MWG paid special attention to the area of possible conflicts of interest of members. To address this difficult issue the group's follow-up DMWG introduced a self-reporting assessment, called "Declaration of Interest".

DMWG

At the General Assembly 2000 in Athens it was decided to merge the DMG and the MWG into the Development and Membership Working Group, as it had become clear that the work of these groups was so much interrelated. The close connection between the two groups had become clear during the work on the protocols for the "Membership Handbook".

Once merged the DMWG was ready to take another huge step: the development of an EATG Membership Database. This Database should not only include efficient tools for the EATG Office for the membership administration, but also extensive information on other members' properties like profession, organisational background, language skills, knowledge of a whole range of different aspects of HIV treatment, multiple other skills, talents and experiences and members' needs for training, schooling and education. To collect all these data an extensive questionnaire went out to all members in 2001. The response was extremely well: Over 95% of the questionnaires were returned. Data input was completed by the end of 2002. The system is already in operation for office (administrative) use. The statistical results and interpretation of the members' properties is scheduled for the General Assembly in 2003 in Budapest (Hungary).

DMWG and its own protocol

According to the current DMWG protocol in the Membership Handbook the group's main tasks are:

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- To develop transparent, fair and effective membership involvement and development systems
- To assess the adequacy and effectiveness of the working structures, systems and protocols of the EATG and make recommendations for their development.
- To monitor the correct running of the EATG according to the Constitution and the protocols adopted by the General Assembly
- To intervene in conflictual matters, when it deems that the smooth running of the Organisation is under threat.

To achieve all this the DMWG works in close relations with the EATG Board of Directors, all other Working Groups, the Internal Auditor(s) and the Ombudsperson(s). Depending on the issues on the agenda of the group it can be considered as an advisory or supervisory board, but its powers are limited to recommendations.

DMWG routines

The DMWG consist currently of 5 members and a liaison person from the Board of Directors and meets approx. 4 times per year. In the short period in advance of a General Assembly the work accumulates, when the Board of Directors, Working Groups and individual members ask for the group's assistance. During the General Assembly the members of the DMWG feel a special responsibility, that the EATG

Constitution and all protocols are respected. The ongoing work of the group includes:

- To consider applications for membership and make recommendations to the Board of Directors and the General Assembly;
- To evaluate members' participation and make recommendations to the Board of Directors and the General Assembly for maximising members' effective involvement in the work of the EATG.
- To review members' Declaration of Interest and deliver an opinion on possible conflicts of interest;
- To assist the Ombudsperson in framing recommendations to the Board of Directors and General Assembly for conflict avoidance and resolution measures;
- To assist the Board of Directors in drafting and presenting new protocols where they are needed;
- To continue the process of developing membership protocols and procedures, including grievance and disciplinary protocols; to assist new working groups in formulating protocols;
- To identify other organisational systems or Working Groups, which are needed and make proposals to the Board of Directors and General Assemblies;

- To develop protocols for an organisational audit of skills and training needs;
- To oversee the development and maintenance of the EATG Handbook: the compilation of all existing EATG protocols and rules;
- To monitor that the Constitution is being upheld;
- To make recommendations to the General Assembly for continued improvement and clarification of the Constitution;
- To establish and keep updated a membership database;
- To evaluate members' participation in EATG in general and in Working Group in particular.

In many aspects the work of the DMWG may seem rather dull for the majority of the EATG members. They joined the organisation because they wanted to participate in treatment activism. Little of that seems obvious with the DMWG. This Working Group however is facilitating the smooth running of this growing organisation EATG, with all its members from so many different countries, a variety of cultural backgrounds and many languages. It is providing clear and understandable structures, hoping it will respect and bridge the diversity.

Eric J. Welling, Germany



The Access Working Group

The EATG Access Working Group (AWG) was established in May 2001 by the EATG General Assembly with the goal of improving and enlarging the scope of the EATG in the field of access-to-treatment. The primary goal of the AWG is to increase the awareness on access' issues within the EATG, to network with other groups already involved in the field, to establish contacts with local communities, to work on, define and develop strategies to put and maintain pressure on pharmaceutical companies, local government agencies, international bodies and health organizations to make treatments and drugs available wherever there is a need.

The AWG sees the HIV/AIDS epidemic as a global public health emergency, access to health as a basic human right and access to medicines as a global right. Although the affordability of medicines is not the only reason for the gap in access for obtaining drugs that are needed, it is probably the single most important one. Thus it believes that the production and marketing of generics, that should be subject to strict quality control, is not only justifiable but also necessary, as well as price reductions by pharmaceutical companies, and that the issue

of patenting should not be a barrier to access and that health rights should always outweigh the protection of intellectual property rights.

Activities

- Constitutional meeting: July 14th 2001
- First Meeting: November 23rd 2001
- Access Position paper developed in cooperation with PWG and finalized on a consensus based process.
- Position paper on ethics of conducting clinical trials in developing countries developed in cooperation with ECAB
- AWG officially presented at last ECCATH (Athens 2001)
- AWG invited by MSF, CPT, OXFAM and HAI to attend a meeting on "Implementation of the Doha Declaration" (Geneva, April 2002)
- AWG/MSF met Roche in Basel (April 18th 2002) to pressure to company in order to reduce nelfinavir price in developing countries
- AWG invited to attend the WTO Public Symposium on "THE DOHA DEVELOPMENT AGENDA AND BEYOND" (Geneva, May 2002)
- HIV&TREATMENT: one-day seminar on the 23rd of May 2002.

- Presentation at CHAIN Meeting (BCN 2002)
- Bratislava, Slovakia: Training on Access to treatment in cooperation with TWG (2002). Partially funded by the Open Society Foundation
- Several articles on patents and access to treatment issued on the EATN
- Involved in the steering committee of the last Migrants' Meeting (Brussels 2002)
- Involved in the Treatment Preparedness Initiative (Capetown, 2003)
- Invited to join ITAC (International HIV Treatment Access Coalition)
- Press release on T-20 price (see page 6)

Members of the Access Working Group are

- Albert Adalainstenson, Iceland
- William Babumba, UK
- Svilen Conov, Bulgaria
- Mauro Guarinieri, IT (Chair)
- Smiljka Malesevic, Russia/YUG
- Stefan Stojanovik, Macedonia
- Marija Rakovik, YUG
- Alain Volny-Anne, FR (BOD Liaison)

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Why should we go global on access?

Access to treatment has raised global attention having some commonalities with other global movements, as it was the civil rights movement in the past, and as it is either the anti-globalization and the movement against war now. First, and most fundamentally, all actions carried out by Treatment Access Activists were about providing treatment for the millions of people in developing countries suffering from AIDS. Second, the participants of these actions subscribe to an analysis of the challenges of the AIDS pandemic that is profoundly consonant with that of the larger anti-globalization movement, in which Treatment Access Activists have also played as an active contingent. Like the larger anti-globalization movement, AIDS activists see the interna-

tional institutions of the World Bank, IMF and WTO, multinational corporations (particularly those making up the international pharmaceutical industry) and government captive to the interest of these corporations as primary causes of the problem we seek to solve. A third commonality is that the movement has been international in nature, with participants and protest sites from countries in both the Global North and the Global South.

The global framework

The problem of global access is, superficially, quite simple. Although medications exist that extend both the duration and quality of life exist for most people who take them, they are not available to over 90% of the

world's HIV positive population. Activists' first goal is to make these medications available globally. However, though the general problem is simply stated, its causes and therefore the steps that must be taken to remedy the situation are not. Being exposing disparities the primary goal of global treatment access movement, Global AIDS activism has a number of characteristics that make it an ideal test to recommit activists from the Global North to justice and equity, touching on problems of drug pricing, global intellectual property agreement, lack of resources and the crippling debt of developing countries.

Why the Global Treatment Access Movement is different from other global campaigns?

The global treatment access movement is substantially a bit different from other global campaigns in an important way. Unlike Chiapas, debt relief campaign, anti-sweatshop labor, and any number of campaigns

targeting change in the Global South, AIDS activism tends to involve a built-in personal element. Although HIV/AIDS is clearly experienced very differently in the Global North and South, AIDS is one of the few issues severely affecting the Global South for which activists in the Global North have frames of reference. Many activists have first hand knowledge of the stigma, medical manifestations, and loss engendered by an AIDS diagnosis. Thus, it is possible that some of the social characteristics of AIDS activism come from a relatively rare occurrence of shared experience across the North-South divide. This shared experience may well foster stronger and more easily developed personal bonds among activists than is the experience with other causes. It may be possible for the global treatment access movement both to make strengthening new alliances with other social movement much easier and to disseminate to others the constitutive principle of built-in personal elements, abilities and inclination as key to social participation, possible. It is precisely this combination that has made AIDS activism unique. How many times we discussed how to transmit to others our experience? What a better chance to make it real than this?

Our role as EATG

What can we add as EATG to this? First, we want to join the front lines in this struggle. Second, we want to keep raising the problem of Eastern Europe, NIS and former-Yugoslavia to international forums as one of the fields where the struggle has to be actually struggled. Third, we want the EATG to start working more on fair pricing, intellectual property rights, the North/South divide, thus regaining some of the key principles of AIDS activism might have been blurred out by rocket-science. Fourth, we want to share our experience with others, not only teaching but learning as well. That's why we decided to launch, besides other activities planned for 2003, a Treatment and Advocacy Preparedness Seminar.

The Treatment and Advocacy Preparedness Seminar

The Treatment and Advocacy Preparedness Seminar will be the first initiative which will involve activists from the Global South, divided into two phases: a face-to-face skills building training seminar and, since educational events are transitory

and disappear once the sessions are over, further online distance learning sessions which will hopefully capture the information and deliver it once again to many more learners. The Treatment and Advocacy Preparedness Seminar has been designed as a collaborative project between EATG, Ensemble Contre le Sida (ECS), Community Health And Information Network (CHAIN), European Project AIDS & Mobility, and AIDES. The selection process will get involved 5 African advocates representing Eastern, Western, Central and South Africa.

The seminar is meant to empower participants:

- To be able to train others on treatment issues.
- To be able to produce and disseminate information on treatment.
- To establish links with migrants communities in Europe.

The Skills Building Training Seminar will take place the 3rd-9th of November 2003 in Leiden, Holland. The seminar is meant for a group of sub-Saharan African advocates and migrant activists. The objectives are those to improve treatment literacy and advocacy knowledge and skills of the participants and to support them in strengthening their capacity to engage effectively in access negotiations at local, national and international levels. The EATG will develop an "Activists' Training Centre" which will be training resource for HIV/AIDS activists. The "Training Centre" will be open to advocates/activists from all parts of the world where access to treatment and treatment information is lacking, whether it is Africa, Central and Eastern Europe or the NIS. One important component of the whole project will be the Activists' Training Centre or ATC, which will be training resource for HIV/AIDS activists. ATC has been designed as a pilot project to benefit the whole EATG in:

- Reaching more activists with EATG's training programmes,
- Increasing the interactivity of training efforts,
- Extending learning beyond one-time educational events,

- Improving ongoing networking among participants of EATG training events,
- Utilising training funds more efficiently.

The final product resulting from this pilot phase will be a fully stand-alone web-based course that includes lecture-type static information combined with problem-based, collaborative tutorial sessions that allow the learner to apply knowledge and skills gained from the lecture material.

The ATC will consist of the following components:

- Downloadable files (also available on CD-ROM) with a training manual and transcripts of lectures, including PowerPoint presentations
- Learner-centred, problem-based, online tutorials, designed to use the information presented in the lectures to solve relevant, real-life treatment and/or advocacy problems. The goal of these tutorials is twofold: solve problems and create networks. Each tutorial will present a simulation of a potential event for which activism/advocacy would be required. The group would go online at regular intervals to interact with each other and the moderator to solve this problem. In doing so, the learners will build relationships that will extend beyond the training sessions.
- Web support: a homepage will be established as the focus point for students and moderators. On it will be copies of the "lecture" materials and the tutorial case studies. Students will login from here to access the ongoing discussions to solve the cases. Further resources, such as links to other educational institutions and potential network partners will be presented on this homepage. The homepage will also contain the course manual for students and tutorial moderators.

An integrated approach to training will be taken to capitalise on the various training methods.

Didactic presentations at the Skills Building Training Seminar for African Advocates will be captured and transcribed for use on a

CD-ROM and for posting on the internet site. The “lectures” will provide basic background information and act as a resource for participants.

Online tutorial sessions will provide participants with the possibility to solve relevant, real-life problems using information from the lectures and external sources in a group setting. Online discussion groups will be moderated to ensure full participation from learners and to facilitate the process. Problem-based, collaborative learning is an

effective way in which to integrate new knowledge and skills into practice. Tutorial problems will be solved and defended using evidence available from course materials, external sources and the experience of the participants.

Each tutorial will consist of two phases, each two weeks long. The first phase will give the participants an opportunity to discuss the problem and to do an inventory of learning needs. Using a discussion board over a two-week period, each participant

will identify what they already know and what they need to find out and then tasks will be distributed among the group members to find out this relevant information. The second session will review all of the evidence gathered on the discussion board and a number of possible solutions to the case will be proposed, along with their advantages and disadvantages. At the end of the two weeks allotted to the second phase, the group will need to decide on one course of action to solve the problem posed in the tutorial.

THE VWG: Vaccine Working Group

The VWG was set up by the EATG-GA in 2002, meeting in Bologna (Italy). It operates independently from the European Community Advisory Board (ECAB) – which is EATG’s traditional forum for community input to scientific trials. That said, these two groups do work together! Other potential interactions of the VWG are with the AWG (Access Working Group), the PWG (Policy working Group), and XX-StG (Women’s Study Group), TWG (Training Working Group). Networking is considered, in the VWG, to be a priority in order that vaccine issues are integrated in other work by EATG.

Why a VWG in the EATG?

- 7,000 people die from AIDS and another 15,000 become infected with HIV every day. Prevention programmes and treatment opportunities have slowed the spread of HIV but have failed to stop it at a global level. If a successful vaccine can be added to the means of controlling the epidemic, it could help turn this situation around.
- Treatment research has yielded important new AIDS therapies, but there is a long way to go before they can be made available to everyone who needs them. Most people with HIV still have no access at all to antiretroviral treatment. In industrialised nations, where drugs are more readily available, side effects and increased rates of viral resistance have raised concerns about their long-term use. If vaccines can reduce the need for other treatment by preventing infection, delaying illness or otherwise reducing the need for treatment, they could be of great value for public health and people’s quality of life.

- Preventive and therapeutic vaccines are presently undergoing intensified development and people with HIV and HIV-negative people are being recruited into vaccine trials. It is therefore clearly within the aims and goals of EATG to look at vaccine development.

Objectives of VWG

- To educate target audiences (e.g. EATG members, HIV communities) about vaccines development and related ethical, scientific and regulatory issues;
- To generate, validate and disseminate information about vaccine issues;
- To support policy development regarding HIV/AIDS vaccines through advocacy and lobbying;
- To contribute to and support the ethical discourse in the interest of (prospective) trial participants;
- To monitor and comment on research for and development of vaccines;
- To work towards assuring access to vaccines once they are proven to be safe and effective;
- To identify partners and develop strategic collaborations.

Activities of VWG

- To integrate a vaccine agenda into the overall activities of EATG;
- To identify sources in vaccine research in Europe;
- To gather information from these sources aiming for strategic partnerships;
- To provide an overview of research activities both in preventive and therapeutic vaccine development;
- To investigate the informational needs

and to provide appropriate information to the EATG membership and its target audiences;

- To organise educational programmes for the European HIV community;
- To link up with established groups working on vaccines (e.g. EUROVAC, IAVI, the ANRS);
- To meet with pharmaceutical companies that have a vaccine development programme;
- To develop relationships with international bodies and institutions with established vaccine programmes (e.g. UNAIDS, WHO, ICASO) to raise ethical/community issues and to participate in the development of guidelines concerning vaccine programmes (e.g. around recruitment, informed consent).
- To attract funding for VWG activities and to establish transparent and responsible use of these funds;
- To actively participate in conferences and meetings.

Meetings and Projects of the VWG

The inaugural meeting was held in Brussels, April 12th/13th 2002. The group defined its goals, with a working protocol that contains the EATG general guidelines on the issue of HIV/AIDS vaccines. The need for work in the therapeutic field emerges clearly from EATG’s traditional focus on treatments. A specific need for work on preventive vaccines arises in Eastern Europe, where the need for better means of prevention is both urgent and likely to continue for many years. It was agreed – to produce an overview of current vaccine trials in Europe. This should take the form of a database to allow better

orientation towards the field and identification of opportunities for upholding patients' rights in those trials.

In the second meeting (held in August 2002) we identified some priority working areas:

- European Therapeutic Vaccine Trials Data Base;
- Within the group, we developed a framework for community involvement in therapeutic vaccine trials, identifying issues that need to be discussed between researchers and community representatives;
- A background paper on "Success and Failure" in Vaccine Research was commissioned (free of charge) to give information on responses to the forthcoming announcement of the results of the first Phase III preventive vaccine trial by the US company VaxGen
- Organization of a special V-ECAB on Vaccines (June 2003).

The Trials Data Base has within six months been able to identify eleven ongoing therapeutic vaccine trials in five European countries. Ten countries have been surveyed and more planned trials have been identified. The aim is to present an easy overview of trials and to enhance community participation in these trials.

There has been much discussion of ethical considerations in relation to preventive vaccines, but far less in relation to therapeutic vaccines. The VWG has therefore begun to develop a strategy and material to strengthen informed consent and the capacity of community groups to review therapeutic vaccine trial plans and results.

Many people concerned with HIV and AIDS are rightly anxious about the risks to established prevention efforts of misunderstandings about vaccine efficacy and availability, which could arise from poorly reported vaccine trials. The outcome of the first Phase III (efficacy) trial for a preventive vaccine (AIDSVAX), from VaxGen, was expected to be one of the biggest AIDS news stories of 2003.

The AIDSVAX vaccines are composed of genetically engineered proteins designed to be similar to gp120, the protein on the surface of HIV. Researchers have found that most people receiving the AIDSVAX vaccine

do produce antibodies against HIV. The question was whether these antibodies are truly protective against HIV infection, and if so, what level of protection they provide, to whom, and for how long.

The Vaccines Working Group views the completion by VaxGen of the first Phase III trial of a preventive HIV vaccine, AIDSVAX B/B, as an historic achievement. The outcome of this trial is disappointing in that it has not conclusively shown less HIV infection in the vaccinated group compared to placebo recipients. However, we believe and hope it is a step towards better vaccine preparations in the future. Now we know that efficacy trials are possible and strong support from the communities of people affected by HIV/AIDS secured reliable results and compliance. Overall infection rates as low as 2.7% are a major achievement for us. We are deeply grateful to trial participants and physicians, and to everyone who supported this effort. Thus both prevention and treatment continue to be vital in response to AIDS in Europe and worldwide, for all communities affected by the pandemic. There is a clear need for more resources and sustained political commitment to take additional products forwards into full-scale (Phase III) clinical trials. There are more than 20 other products in development and this research must continue with many companies, trials, and institutions working towards vaccines. Future products may work on entirely different principles and need trials designed in different ways to AIDSVAX.

Success and failure in vaccine research is a background paper developed for the VWG by Julian Meldrum of NAM (UK) that should help on this issue.

Key points that are discussed here include:

- There is no magic bullet;
- Preventive and therapeutic uses of a vaccine must be considered separately
- Success and failure for a preventive vaccine must be considered in relation to what it is supposed to achieve, which could be: to prevent HIV infection; to prevent or delay disease; to prevent onward transmission
- Success and failure for a therapeutic vaccine needs to be defined in terms of the burden of disease and of its treatment, as it translates into quality of life
- Success and failure of a clinical trial is distinct from the success or failure of a product.

The VWG is also very involved in the organization of a special ECAB on Vaccines expected to be held in June 2003 (20/22). We are calling this a **V-ECAB** meeting. It will include a training session on basic immunology related to vaccines, a survey of the HIV/AIDS vaccine pipeline, a discussion of clinical trial designs with gender implications of HIV vaccine development. Four of pharmaceutical companies involved in vaccine research have agreed to update us about their potential products in preclinical and clinical trials. There will be also exam case studies, from two national NGOs, of treatment activism in the vaccine field. The final session will be centred on different perspectives on HIV/AIDS vaccine trials (both therapeutic and preventive) with the participation of ANRS, IAVI, AVAC and the EMEA.

Thanks to Emanuel Trenado (member of the VWG), the group had the opportunity to meet VaxGen in Paris in December 2002 with the TRT-5 French coalition. The meeting gave us the opportunity of presenting ourselves officially to a company for the first time.

AIDS vaccine advocacy today is very important. We all think that, in the coming months, lots of questions, doubts and related implications will be raised in the HIV-international world scene (especially in the community) concerning the introduction of partial effective vaccine. The VWG feels that it is important to be ready to give possible answers to this implications. This will also be a central point in the V-ECAB meeting of June.

The main efforts of the **VWG third meeting (22/23 Feb 2003)** are mainly directed in trying to finalize projects described above, trying to develop opportunities to operate and be actively present in the HIV-international community scene, with the important strategy of "being in network" through the connection with other WGs (projects to develop together) and a connection with international bodies or other NGOs.

Members of the VWG are

- Emmanuel Trénado (F)
- Matthias Wienold (D)
- Keith Alcorn (UK)
- Simone Marcotullio (I)
- Filippo von Schlöesser (I)
- Vlastimil Mayer (SK)
- Julian Meldrum (UK)
- Joan Tallada (Spain)

I'd like to thank all my comrades in all the efforts they do in trying to be active and present on the HIV-scenario, going to conferences that are considered strategic in the vaccine field and trying to involve, when possible, the VWG in all kinds of related activities. All people of the EATG that are interested in working on this specific matter,

that is the field of vaccines, are welcome to work with us although, in my very modest opinion, eight people for this new WG are enough. Nonetheless, we remain open to anyone who would like to join us, contributing actively to the work of the VWG, and recognise – among other deficiencies – that the group would be stronger if we

could recruit one or more women members. In the meantime, we hope to be able to work with other groups (for instance XX-StG, which is concerned with women's needs in relation to HIV) that is willing to work with us on very specific issues.

The XX-Study Group

Sure you got it, but just in case let's clarify that the "XX" that baptizes our Study-Group refers to the chromosomal characterization of females (what in males are the XY chromosomes). In the vast majority of cases, that rich mixture of bio-physiological and socio-cultural factors that one tends to bluntly qualify as being "a man" or "a woman" gets engineered upon one of those two chromosomal combinations.

Origins of the XX-Study Group

The European AIDS Treatment Group, EATG, was formally constituted in February 1992. Back then, the EATG had 20 founding members, of whom 2 were women (another woman was present as an observer). Today, 27 of the current 92 members of the EATG are women, and quite a few of them also work actively in the European Community Advisory Board (ECAB) and other Working Groups of the EATG. Interestingly enough, just a 22% of the total female members of the EATG live with HIV, whereas that's the case for a 64% of the male members of the group.

Figuring out the multiple reasons underpinning the chronic misrepresentation of women, and more even so of HIV+ women, in HIV activism at large, and in HIV-treatment activism in particular, could be a fascinating exercise of socio-epidemiological thinking, but clearly exceeds the boundaries of this article (*). Let's just elliptically note that by January 2000, a group of female members of the EATG, and notably of the ECAB, had managed to get sufficient leadership and momentum as to decide to push forward the creation of a women only group. The group was called "XX" as a catchy metaphor of women's difference and for purposes of simplicity was constituted as a "Study Group" as opposed to the formal "Working Group" status – which requires a formal

chairing and has to present yearly plans and budgets for review and approval to the General Assembly of the EATG.

The facts, the aims

The "XX Study-Group" was born with a general objective: **to embark on a programme of targeted learning and strategic intervention from within the EATG/ECAB about HIV treatment issues affecting women.**

The need for specific gender and sex-related activism on HIV treatment issues for and from HIV+ women was first and foremost rooted in a global situation that by the end of the nineties was already dramatically clear: the increasing "feminization" of the HIV pandemic and the progressive exacerbation of gender-related inequalities in the context of HIV disease.

We already knew that women in most countries of the world are disadvantaged in terms of human rights, reproductive health, poverty and burdens of family care. By now, we also know that women account for more than half of HIV cases world-wide, that they get infected earlier but diagnosed later than men, or that overall they have less and later access to therapy.

Further, years into the epidemic and in spite of the relative progresses made in some settings, it's still the case that women are underrepresented in HIV clinical trials and studies and that HIV treatment is mostly assessed for efficacy, safety and toxicity in men's bodies. **Most clinical trials show male bias and even if their results are transferred to women's bodies they are often not applicable.**

In addition, some gender differences in the history of HIV disease – both natural and on

treatment – have been postulated over the years. Adequate knowledge of such differences and of their potential impact on HIV care and treatment outcomes in HIV+ women is still gruesomely insufficient:

- Women have consistently lower viral loads than men at similar stages of infection
- Women appear to have an increased risk of progression to AIDS compared with men with the same viral load
- For any given CD4 cell count, women may be at a higher risk of HIV progression
- Female hormones appear to have immunoregulatory effects through production of cytokines
- Several antiretroviral agents are known to interfere with the metabolism of oral contraceptives
- Women have increased risk of adverse drug reactions compared to men (25% of men vs. 37% of women)
- Women experience different body habitus changes (with a higher tendency of fat accumulation) and serum lipid abnormalities while receiving Highly Active Antiretroviral Treatment (HAART)

The XX-Study Group philosophy is to fight for female education and prevention programs, for healthcare at the doorstep and equal access to experimental and approved therapies, for comprehensive reproductive health services, for good clinical trials with women, on women and for women. The XX-Group stresses the following specific objectives for the group:

- To develop, inform and support the empowerment of women infected and affected by HIV
- To focus on:
 - communities most affected by HIV
 - clinical and scientific developments related to HIV+ women and their treatments

Working with women and for women within the ECAB

Community Advisory Boards (CAB's) can be very efficacious instruments for HIV activism on treatment issues at large and for women and treatment activism in particular. The following points merit to be stressed in the context of the ongoing work of the XX-Group:

- The role of the ECAB is to promote relevant research, care and treatment for people living with HIV infection. By working with researchers, clinicians and industry, the ECAB plays a significant role in the shaping and implementation of research, treatment and care strategies for HIV communities across Europe.
- By building knowledge and solidarity, and by getting actively involved in ECAB work, such a structure could facilitate the process of women becoming strong advocates for themselves and for other women infected with, and affected by, HIV. Women, and women's advocates, work within the ECAB could contribute to both research and clinical practice meeting the overlooked needs of HIV+ women.
- ECAB meetings offer critical opportunities for ECAB and/or XX-Group members to raise questions pertinent to women and to offer advice on trials' design and conduction that facilitate women's involvement in HIV research. The XX-Group specifically aims to increase awareness about sex and gender-specific aspects of HIV disease and its treatments during discussions with companies, clinicians and researchers and to increase the number of female patients in studies
- The members of the XX-group can contribute with their expertise to enhance the knowledge of the ECAB on special issues, and the (i.e. HIV and hormones). Conversely, XX-members can benefit from specific education and training sessions organized within the ECAB around sex and gender issues in HIV.
- Members of the XX-group network with a number of other groups and individuals involved on HIV and women issues on national, European and international levels. The ECAB offers a relatively flexible setting for some of those individual and or group networks to be started, shared, and enriched.

- social and cultural milieu in which women live their daily lives
- advocating for due attention to be given to HIV treatment issues affecting women by
 1. generating and disseminating women-specific information
 2. organising monographic meetings for HIV women and treatments' related training, advocacy and policy purposes
 3. collaborating with other networks in the field for mutual learning and support

Achievements of the XX-Group

First monographic ECAB on HIV and Women Issues: April 2000

The first ECAB meeting exclusively focused on women and HIV issues organized by the

XX-Group took place in April 2000. During a 2-days gathering in Offenbach (Germany), ECAB members together with HIV+ women and women working on HIV and treatment issues across Europe, industry representatives, HIV clinicians and researchers, focused their talks and discussions on sex and gender issues concerning HIV' epidemiology, pathogenesis, clinical trials, migrant populations, clinical care and support, long-term adverse effects of HAART (i.e. metabolic and body changes), neurological manifestations of HIV disease, side effects, adherence, pharmacology and studies looking at gender differences.

This first ECAB meeting on HIV and women issues provided an invaluable forum for women-specific treatment issues to be raised at a European level, as well as a great

opportunity to increase the profile of the XX-Group within and beyond Europe. A comprehensive report from the meeting was produced and disseminated to relevant organisations. An article published in EATN (the regular newsletter of the EATG) reached a wide network of community activists, health professionals and industry representatives (**).

ECAB on Women and Regulatory Issues: February 2003

Ever since this first monographic ECAB on women's issues and before, it was clear to the XX-Group that the scope of our demands necessarily involved working with the European Regulatory Authorities in charge of overseeing and validating HIV research and HIV approval of new therapies.

Liasing and working together with the European Medicinal Agency (EMA) and with its Committee for Proprietary Medicinal Products (CPMP) was therefore understood as a crucial step in the implementations of our aims. Although a number of reasons made 2001 a relatively dormant year for the XX-Group, by mid-2002 organizing a second XX-ECAB meeting, this time with an extra focus on Women and Regulatory Issues in Europe, became the goal of the XX-Group activities.

Last February, this meeting finally took place in Brussels. For 3 full days, more than 30 Pan-European treatment activists of the ECAB, including the XX-members and their guests, worked together with research experts and representatives of pharmaceutical companies and the European Agency for the Evaluation of Medicinal Products (EMA). The ECAB aimed to identify current gaps in the sex and gender considerations in the clinical evaluation of drugs and to elaborate an agenda of specific suggestions to be included in the Note for Guidance on the Clinical Development of HIV-Medicinal Products issued by the EMA. A total of 5 working groups lead by experts-guests on the relevant topic (Hormones; Safety, Efficacy and Quality of Treatments; Pharmacokinetics, Pharmacodynamics and Pharmacogenetics; Psychosocial Issues and Pregnancy) successfully worked on the above-mentioned document and made their specific requests for wording inclusion, change, or amendment. Conclusions were

later presented to the whole group and submitted to general discussion and approval.

A monographic EATG Report detailing the proceedings of this ECAB meeting on Women and Regulatory Issues' is being planned as this EATN issue goes into printing.

Future objectives

- To become a reference group to other important actors in the field of European HIV and treatment when it comes to women' issues (i.e. pharmaceutical industry, regulatory agencies, independent researchers, policy makers).
- To contribute to EATG's collaboration with the European Agency for the Evaluation of Medicinal Products (EMA) to ensure that the new guidance for the development of anti-HIV medicinal products pertinently highlights the need to include women in every significant stage of HIV clinical research and to draw the necessary conclusions about the use of HIV medicinal products in women's bodies.

- To encourage and facilitate the presence and participation of women from every HIV-community of Europe in the XX-group and in every working level of the EATG
- To facilitate communication and liaison between XX members' and other working groups of the EATG so as to impregnate the work of the organization with a adequate sex and gender perspective (i.e. ECAB, Access Working Group, Vaccines Working Group, Policy Working Group)

Conclusions

The XX-group's e-mail forum includes almost all female members of the EATG from several European countries (in total – male and female – the EATG membership comes from 27 countries). Since its creation in January 2000, the XX-Group has embarked on a programme of targeted learning and strategic intervention from within the EATG/ECAB about HIV treatment issues affecting women. The XX-group has been successful in increasing the awareness about women-

specific aspects of HIV research, treatment and prevention, and in giving women a voice within the EATG and the ECAB. A first monographic ECAB meeting about HIV and women issues has been very recently followed by a second ECAB meeting organized by the XX-Group, this time with an extra focus on HIV+ women and regulatory issues in Europe. A monographic Report about the conclusions of this landmark ECAB meeting on Women and Regulatory Issues' is being planned as this EATN issue goes into printing.

() For further information on this point see: Let's talk about gender.*

Ulrike Sonnenberg-Schwan. EATN, September 2002, Vol. 11, N° 4, p 6-7. www.eatg.org/eatn/11_04/en/indice.html

*(**) Polly Clayden: Women and HIV. Report from the front. EATN, Summer 2000; Vol. 9. N° 4, p 4-11.*

A Note on Declaration on TRIPS at Doha

The Doha meeting of the WTO adopted a "Declaration on the TRIPS Agreement and Public Health". The declaration has been hailed as a landmark in the negotiating history of the World Trade Organisation. In a way it is a landmark because this is the first time, since the signing of the WTO Agreement in 1994, that a portion of that agreement has been interpreted in a manner that is favourable to developing countries. While there is a need to recognise the significance of this, there is also the need to examine the events, which led to the adoption of the declaration. Also, we need to understand how much has really been gained by the adoption of the declaration.

History of the TRIPS Accord

The Trade Related Intellectual Property Rights (TRIPS) agreement, signed as a part of the WTO agreement, was the most bitterly fought during the GATT negotiations. Till 1989 countries like India, Brazil, Argentina, Thailand and others had opposed even the inclusion of the issues in TRIPS in the negotiating agenda. They did so based on the sound argument that Intellectual Property

Rights – which includes Patents over medicines is a non trade issue. India and others had argued that rights provided in domestic laws regarding intellectual property should not be linked with trade. They had further argued that the history of IPRs shows that all countries have evolved their domestic laws in consonance with the stage of economic development and development of S&T capabilities. Laws that provide strong Patent protection limit the ability of developing countries to enhance their S&T capabilities and retard dissemination of knowledge. Japan, for example, was able to enhance its domestic capabilities through the medium of weak patent protection for decades – well into the second half of the twentieth century. Italy changed to a stronger protection regime only in 1978 and Canada as late as in 1992. It was thus natural that many countries like India had domestic laws that did not favour strong protection to Patents before the WTO agreement was signed. It was illogical to thrust a single patent structure on all countries of the globe, irrespective of their stage of development. These arguments were however system-

atically subverted during the GATT negotiations, leading to the signing of the TRIPS agreement. The TRIPS agreement required countries like India to change over to a strong patent protection regime. A regime that would no longer allow countries to continue with domestic laws that enabled domestic companies to manufacture new drugs invented elsewhere, at prices that were anything between one twentieth and one hundredth of global prices. It may be recalled that it was the 1970 Patent Act which, by encouraging Indian companies to develop new processes for patented drugs, also facilitated the development of world class manufacturing facilities in a developing country like India.

Today the campaign on access to drugs draws strength from Indian companies like Cipla who are offering anti-AIDS drugs at one tenth to one fortieth of the prices being charged by large pharmaceutical countries. It also draws strength from the ability of Brazil to indigenously manufacture 8 out of the 12 anti-AIDS drugs and also to distribute them to all those who require these drugs.

Let us not forget that this could not have happened if the TRIPS accord had been signed in 1975 and not in 1995! It is this that we stand to lose as we move towards "harmonised" standards of strong patent protection.

Importance of the TRIPS Accord

Implications of a product patent regime are not limited only to the area of technological self-reliance. Technological dependence on MNCs is the proverbial "thin edge" which will be used by the MNCs to establish their suzerainty over the Indian Drug market once again (a position they had lost after the mid seventies). They will then again start charging exorbitant prices for drugs in the Indian market. Since the early eighties, the categories of drugs, which show the maximum rise in sales are categories which include overwhelming majority of drugs still under Product Patent or whose Product patents have expired recently. In other words if we had a product patent regime today, the drugs showing fastest growth would have been priced way beyond the capacity of the average consumer.

It must be understood that, notwithstanding the rhetoric, the TRIPS accord was not pushed through just to access markets of developing countries. These markets represent just a fraction of the global market: India, for example, accounts for 0.8% of the market, in contrast to 33%, 24% and 20% for the US, Europe and Japan respectively. Rather the TRIPS agreement became a necessity to protect the markets of large pharmaceutical companies in the developing world against competition from cheaper generic drugs manufactured in countries like India and Brazil. TRIPS in other words is not about "free" trade, but has to do with protection of markets in developed countries. In order to safeguard this market giant pharmaceutical companies railroaded all opposition and forced the signing of the TRIPS accord. The draft which formed the bases of the accord was prepared by industry representatives from the US, Europe and Japan.

There were other compelling reasons why developed Capitalist countries, led by the US, exerted such enormous pressure during the GATT negotiations to ensure that the TRIPS agreement was pushed through. In the mid-80's the United States was faced with waning industrial competitiveness, which hurt

U.S. companies and U.S. trade internationally. As a consequence it began searching for new areas of commerce which would maintain U.S. dominance in the world market. Around this time several intellectual property dependent industries, namely information technology, entertainment (records, films, and books) and pharmaceutical who were becoming extremely important contributors to the U.S. economy. All these sectors were heavily IPR dependant as they dealt in products where the development costs were high but the replication costs were small. These were sectors where, in order to maintain high levels of returns, monopoly "rent" incomes had to be protected through the mechanism of strong Intellectual Property Protection.

The importance of the knowledge-based sectors to the US (and global) economy can be gauged from the performance of large companies today. Among the top fifteen companies with the highest returns (profits) on Revenues (turnover), six are pharmaceutical companies: Microsoft, Cable and Wireless, E.I. du Pont de Nemours, Eli Lilly, Glaxo Wellcome, Roche Group, Bristol-Myers Squibb, Novartis and Pfizer. Five are from the information technology sector Microsoft, Cable and Wireless, Telefonos de Mexico, Intel and Textron. Yet, none of these figure anywhere among the top 100 in terms of turnover. Microsoft is 216th in the list in terms of turnover, but has the highest return on revenues (39.4%). Clearly rent incomes, today, are one of the major driving forces of the economies of the developed countries.

Setback to Pharmaceutical Companies

In 1995 the pharmaceutical MNCs seemed to be sitting on top of the world. Unanticipated by them a major development in the field of health care set in motion a chain of events. The AIDS epidemic was fast gripping the imagination of the global community. In the nineties almost the whole continent of Africa was under the grip of this epidemic. In some countries an estimated third of the adult population were infected by AIDS! The tragedy was compounded when drugs to contain AIDS started being developed. These drugs allowed AIDS patients the opportunity to live normal lives even if they were infected. But there was a catch. Because of Patent protection these drugs were priced beyond the reach of patients in

developing countries. The ridiculous effect of Patent protection was evident when one found that the cost of treating AIDS patients in some African countries was many times their total GNP! Even more ridiculous, and tragic, when we know that these drugs can be produced at one fortieth of prices being charged by MNCs.

AIDS became a rallying point for activists from all parts of the world and developing country governments alike. In a few years one saw the forging of an unparalleled global coalition. Countries like Brazil and Thailand defied the TRIPS agreement and allowed domestic companies to produce cheap anti-AIDS drugs. South Africa changed its laws to allow imports of cheap anti-AIDS drugs. The MNCs and the developed countries struck back. 39 pharmaceutical companies challenged the South African law in the country's court of law. Brazil was dragged by the US to the WTO appellate body for infringement of TRIPS. But the tide was clearly turning. In the face of mounting criticism and hostile reactions towards the pharmaceutical industry, the industry and its sponsors were forced to step back. The companies were forced to withdraw their case in South Africa and the US did not proceed with its dispute with Brazil in the WTO.

The coalition that was built around the AIDS issue then pressed for clarifications from the WTO that the TRIPS accord did not prevent country governments from legislating in favour of protection of public health. In this they were supported by almost the entire community of developing nations. The industry fought to the last to prevent this. In the draft declaration circulated in September the US and other developed countries tried to limit any clarification to just measures related to AIDS. But the momentum of the global movement was able to increase the scope of the declaration to include public health crises not limited only to AIDS.

What has Been Achieved

Let us now turn to what has been achieved by the declaration. Contrary to popular perception, the declaration in no way changes the TRIPS accord. It does not even say that the accord needs to be renegotiated. In that sense it is really in the nature of a clarification, stating what can be done by countries to safeguard public health while not at the

same time infringing the TRIPS accord. Thus the declaration says: "Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all". Clearly the intent is still to maintain that the TRIPS accord is inviolable and at the same time say that the accord allows certain measures to safeguard public health. Specifically, the declaration clarifies that countries can issue compulsory licenses when faced with a health crisis or emergency. It further states that: "Each Member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted". It must be understood that such clarifications do constitute an advance because, in the past, the US has tried to prevent countries like Brazil and Thailand from doing exactly what the clarifications now say are perfectly compatible with TRIPS.

In concrete terms it means that countries can provide a license to produce life saving drugs to domestic companies, even if patents for these drugs are held by foreign patent holders. But this is still far short of what the 1970 Patents Act of India allowed. Our Patents Act did not allow patents to be held for any product, irrespective of whether they were required to address any health crisis or not. It is this provision that allowed the development of a domestic drug industry and also the development of an R&D base in the pharmaceutical sector. It needs to be realised that what may be construed to be drugs "that are required to address emergencies" will always constitute a small fraction of the total number of drugs manufactured. Hence MNCs will be able to control the production and distribution of a majority of drugs. This would mean that

Indian companies will not have the unhindered freedom that the 1970 Patents Act provided. In the long run this will have an impact on the balance in the pharmaceutical sector, allowing the MNCs to once again assume a dominant position. Moreover R&D and manufacturing capabilities are built over a period, and cannot be suddenly switched on when "emergencies" arise. Restricting the space in which domestic companies can operate to produce newer drugs will have an adverse impact on their manufacturing and R&D capabilities as well as R&D capabilities built up in the public sector.

The declaration falls short of requirements in another key area. It says that: "We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002". Most developing countries, unlike India, have no manufacturing capability. So the declaration does not enable them to access cheaper drugs because they cannot get these drugs produced cheaply in their country. The declaration does not explicitly allow them to import cheaper drugs from countries like India.

A Long Road to Travel

In other words, there is a long road to travel before it can be claimed that the TRIPS accord has been successfully undermined. What we see today is a small retreat in the face of hostile global reaction. The issue of access to AIDS drugs is, arguably, the weakest link in the TRIPS accord and the emerging global patenting system. The tremendous evocative appeal of the "Access Campaign to AIDS Drugs" lends it the potential to delegitimise the TRIPS agreement.

However, to effectively strike at the "weakest link" the campaign for access to cheap medicines has to look beyond AIDS or even beyond "health emergencies" and beyond the TRIPS framework. The "access campaign" must eventually extend itself to cover access to all essential medication and draw in interest groups from across the globe. The campaign needs also to look beyond the TRIPS framework. While arguing for a more "liberal" interpretation of the TRIPS language to ensure better access, it is also necessary to understand that the TRIPS agreement was arrived at on the basis of submissions of the pharmaceutical industry. It is an agreement designed to promote monopolies and hinder competition. The campaign needs to look beyond TRIPS, and use the present momentum to force that the TRIPS agreement be interpreted in a manner that promotes competition and technology dissemination. The minimum that such an interpretation must recognise is the automatic invocation of provisions that promote competition in all markets, and curb the monopoly over knowledge that the present TRIPS regime is interpreted to allow.

Finally, we need to note that India is a late entrant in this recent fight against TRIPS. After abandoning the ship in 1989 we seem to have just got on board again. In the last few years India's voice was not heard clearly with those of Brazil, Thailand and the large group of African countries. This was evident even in Seattle in 1999. The Access Campaign will be hoping that the Indian negotiating team's perseverance in Doha was not merely an attempt to play to the gallery.

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A National CAB experience: the Italian Community Advisory Board (I-CAB)

An interview with the I-CAB coordinator Alessandra Cerioli

The Italian community advisory board was born in November 1999, founded by Italian members of European Aids Treatment Group (EATG). The team's aim is to promote the involvement of PLWHA in the design and evaluation of clinical trials by forming alliances with research institutes, private and individual researchers in order to improve collaboration between the scientific community and patient associations.

I-CAB wants to be also a meeting point for associations whose clear aim is to work together and to confer on common topics around clinical and scientific progress, safeguarding the PLWHA "global" right to improve life quality.

I-CAB, in spreading information from clinical studies and meetings with pharmaceutical companies, always advises :

1. Not to self-medicate or alter a therapeutic regime on the basis of I-CAB information where this is part of a study not yet concluded, which implies they are not sufficiently tested.
2. That I-CAB does not necessarily endorse studies or objectives they mention in the news.
3. That I-CAB's mission is to support PLWHA and activists who work on treatments.
4. That I-CAB's aim is also to be a support mechanism to single associations, favoring information sharing.
5. That all of I-CAB activities are exclusively for the benefit of the community. All information is to be used freely, not for the sake of gain or profit.

Therefore I-CAB proposes itself as a place to negotiate for the scientific community and the private field about the development of research protocols, the definition of wide access programs and revision of informed consent forms. One of the main activities is spreading collected information and publishing this to the community of people living with HIV/AIDS. Furthermore the group attempts to establish contacts with any other figure or organization considered important to the achievement of their aims.

At present, these following associations are

part of I-CAB: Archè, Associazione beta2/ Forum AIDS, ASA- Associazione Solidarietà AIDS, Lega Italiana per la Lotta contro l'AIDS (LILA), Nadir ONLUS.

We recently had the chance to ask some direct questions of the I-CAB coordinator Alessandra Cerioli (LILA) , who took office in May 2002.

Hi Alessandra. Starting from the introduction I have made for our readers, could you tell us something about I-CAB's history, showing us the main points for European activists?

I-CAB's history is of a few associations, already mentioned by you, which decided to form a coalition to undertake all advisory and direct intervention work about HIV/AIDS treatments and correlated pathologies (e.g. HBV, HCV etc.). These associations chose to carry out in synergy a common, not separate, political action. Thanks to I-CAB, even those association which, for various reasons, didn't have specific interest in treatment activism, gained a scientific competence and a bigger weight in activism as well. Therefore I-CAB plays the role of the "propeller" for these associations, building up at the same time alliances and "synergies" as regards associations that have been historically concerned with treatment activism.

In your opinion which aims has I-CAB actually achieved and which ones will I-CAB work on?

I-CAB has certainly obtained legitimacy as regards the scientific community: after three years of activity we can actually define ourselves as a coalition of associations of patients, acknowledged by scientific interlocutors and by the private sector. We're filling a serious gap in the North-American scenery, in which treatment activism has historical and well determined roots, but eventually we are on the right way. We must work on our institutional recognition, which in Italy still remains problematic: I'm talking about institutions devoted to HIV/AIDS, like the National AIDS Commission, and the ministry of Health itself. One of the



Alessandra Cerioli, Italy

coalition's aims is to become a reference point for all the associations and, in general, for PLWHA, for all that concerns information and treatment activism. Spreading information, which is one of the most important activities of the group, often isn't enough. We must try for a "networking" strategy, more incisive at local level, that means trying to involve all the little associations, which for different reasons, need information on treatments.

Could you summarize last year I-CAB's work (meetings, actions...)?

In the last year we worked particularly hard. We intervened directly on the expanded access program of Atazanavir, Tipranavir, T-20 and on Tenofovir commercialization problems. I-CAB took the role of political action on protocols, intervening on informed consents, and maintaining monitoring of problems raised by the group.

Which are the main problems I-CAB has to deal with particularly regarding the Italian situation in treatments access?

The main problem in treatment access concerns bureaucracy: in June 2002 a new law was enacted that forces all medicines, even life-saving ones (such as antiretrovirals), to be approved three times by three different institutions. This procedure slows down drastically the entry of new drugs into the market. This rule infringes an European Union law: all members of UE must guarantee the national commercialization of every medicine within six months from the European Commission approval.

What about your relationship with pharmaceutical companies?

Our relationship with pharmaceutical companies is quite good. They understood our quality work and our competence. Also, they understood I-CAB's work is synergic and complementary with scientific community activity. I-CAB gained a personal role with them. We work in order to protect patients enrolled in clinical controlled trials: a role that sometimes can produce antagonistic interactions with partners that have, as their final aim, a profit motive.

What kind of direct relations does I-CAB have with Italian scientific-world exponents?

I-CAB is actively present in some important national studies: above all, ICONA, where an I-CAB member is present on equal terms with the other researchers, having participated substantially in the study design and being currently involved in designing a "nested" study proposed by the community. I-CAB also has a lot of "external supporters". They are young researchers, but also affirmed researchers that are supportive of I-CAB projects. I-CAB also contributed to the concept of a study on quality of life for PLWHA.

In what ways does I-CAB interact with Italian institutions?

We collaborate with "Istituto Superiore di Sanità", the national research institute, and we are directly involved in designing clinic research protocols. For example, there is a research protocol on quality of life and a specific study on women's issues, on mother to child transmission in Italy. I-CAB participates in the trials about the ISS anti-tat preventive and therapeutic vaccine, in which I-CAB firmly required, and obtained, that patients associations were directly involved in such an important project. As to Political Institutions there is a lot of work to do. In Italy PLWHA aren't easily accepted as partners (also as associations); furthermore the actual political situation characterized by activities of the neo-liberalist ultra-Right government headed by Silvio Berlusconi, isn't favorable to the development of social projects, or of involving civil society. I-CAB recently asked the Ministry of Health to include a person living with HIV on the National AIDS commission, a commission directly designed and nominated by the Ministry. Even though we don't expect anything by this government, we dutifully raised the question.

Could you show us a concrete example of a real intervention made by I-CAB as regards a specific problem?

An important example is the action, a little while ago, on improved access to ABT-378 (Lopinavir). The program was, at the beginning, absolutely insufficient for the real needs. Despite the drug being eagerly anticipated Abbott, at first, offered a number of treatments which was objectively ridiculous. Through specific pressure on the pharmaceutical company, our intervention led to the opening of the expanded access program and to the abolition of any access barriers. Not only Italian patients, even other European Nations benefited by our action.

In your opinion, what must be added to I-CAB's program for the future?

We must gain a bigger influence in addressing scientific research's aims, in order to genuinely support PLWHA. We must try to promote and influence public research. Finally we must try to be present in institutions and influence the political debate.

Tell us about the relationships between the various associations in I-CAB?

Sometimes they are good, other times they are more conflictual. It depends also on the variety of I-CAB associations. We always try to find a point in common related to our mission: the fight against any possible discrimination against PLWHA, the defense of people participating in clinical trials, information spreading and a continuing pressure on the scientific community and the private sector to make research more relevant for PLWHA.

How do you see the relationship between ECAB and I-CAB?

In my opinion I-CAB and ECAB are tied by an umbilical cord: I-CAB was initially created by Italian members of EATG, people who got their experience in ECAB and believed it necessary to found an Italian CAB. There must be a natural synergy, it must improve the flow of information from ECAB to I-CAB and vice versa. Personally I consider ECAB as an ideal junction between all national CABs, which in this way could support exchanging ideas, opinions and observations. It's obvious that ECAB intervenes at earlier phases of clinical studies: therefore ECAB's work becomes a precursor to national CABs, who often work with phase III studies. A recent example of this synergy is the

phase III study RESIST-II on Tipranavir: thanks to ECAB's strong influence on this excellent international study we could focus our energies on specific aspects, related to the Italian situation.

Considering the variety of Italian associations (in the specific field of HIV/AIDS) and the communities historically most hit by the infection, is I-CAB representative?

In I-CAB there is the presence of all the categories called "specific or at risk" like former-drug users or the gay community. There is also a strong female presence inside the group. From this situation arises the development of specific politics and the attempt to prevent all kinds of discrimination. We have also an association dealing specifically with children living with HIV/AIDS.

Does I-CAB express political views or is it neutral as regards general aspects not concerning research?

Every time a "private" matter (such as disease) enters the "public field" we're dealing with a political fact. In the last year we denounced a series of problems traditionally belonging to the private field transforming them into political problems to discuss. It's important to emphasize that all our work is public, everyone has access to information, all activities of the group are visible. Our information can be used by anyone: we opened a website (<http://icab.bravepages.com>) where it's possible to download all our stuff, material, ask questions or report particular situations that could need our intervention. The website is the historical memory of the group.

Would you like to add something more for our readers?

As EATN is a European-wide newsletter, I hope this interview will be useful for all countries which still don't have a CAB. I also hope that from this interview could be born improved and closer relationships with other national CABs. ECAB should work to build up an European network in which all national CABs could join together.

Simone Marcotullio

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Getting high and safe

Although in different percentages, IV drug users represent a relevant part of HIV infected individuals around the world. Drug users are a population that has been widely disenfranchised and marginalized. Often they do not have access to the best standard of care, they are excluded from clinical trials and they are badly informed about the best way to manage anti-HIV treatments and “street drugs”. If we consider all HIV+ individuals who use various legal or illegal psychoactive drugs (from poppers, to psychotropic drugs, to Ecstasy) their number surely increased while one of the main problems still is the lack of information on potential pharmacological interactions between anti-HIV medications and recreational drugs. While numerous interactions of varying clinical significance between antiretrovirals and many approved medication have been well described, less is known about the potential for drug interactions with recreational drugs. In October 1996, for the first time, activists harshly advised Abbott laboratories about a potential life threatening interaction between its protease inhibitor ritonavir and certain recreational drugs. This came as a consequence of the death of a British PWA after taking 3,4-methylenedioxymethamphetamine, which is what clubbers commonly call ecstasy, XTC, Adam, and Essence, while taking ritonavir. According to the coroner’s report, death was caused by an MDMA overdose, with a blood level “nearly ten times the one which

Abbott declared:

“Illegal/recreational drugs are never safe to use, therefore, Abbott will not condone their use under any circumstances.”

is expected to cause serious toxic effects” (as the coroner officially reported) – roughly the level that would be expected after taking 22 MDMA tablets. In a letter dated January 27, 1997, Dr. P. Kon of Abbott’s British branch wrote “Abbott has not conducted, and does not plan on conducting any drug-drug interaction studies between ritonavir and any illegal substances, including ecstasy”, but he noted that the company’s scientists had evaluated the theoretical interaction between the two drugs. MDMA’s metabolism is mediated by the P450 2D6 isoform, an enzyme that processes many other substances (both legal and illegal) in the liver. This enzyme is partially

inhibited by ritonavir. Therefore, the use of these two drugs together could result in “a 2 to 3 fold increase” in MDMA levels. At the end of the letter, Abbott declared “Illegal/recreational drugs are never safe to use, therefore, Abbott will not condone their use under any circumstances”. Notwithstanding the above mentioned letter from Abbott laboratories, thanks to the intervention of activists groups all over the world, the company has compiled theoretical models of possible interactions between ritonavir and common recreational drugs. This data was provided to European investigators, and was summarised in the British newsletter AIDS Treatment Update and in the American Aids Treatment News. According to Abbott, ritonavir should cause a decrease (about 50%) in blood levels of heroin. Mixing ritonavir and methadone should result in a large increase (about 3 fold) of methadone levels, and, always according to the company, a reduction in methadone doses of at least 50% is necessary. Norvir may also increase levels of amphetamines by 2 to 3 fold. No serious interaction with cocaine is predicted. In 1998 Abbott finally decided to conduct a small, but important study (11 people – seven men and four women) on the effects of methadone when taken with their protease inhibitor. Prior to beginning the study, their theoretical models were predicting that ritonavir would increase methadone levels by as much as 300%. What they found was the opposite: methadone was decreased by 36%. Considering that in the entire methadone-taking population there is a 40% HIV seroprevalence, how many of these people suffered from withdrawal symptoms because of ritonavir? Fortunately, with time, other companies along with Abbott themselves, expressed their interest in conducting clinical trials. Currently, the companies systematically conduct studies on the effects of new compounds when taken with methadone, which is a legal, controlled substance manufactured in a pure form and with a predictable amount in each dose. Some of these studies have documented methadone’s interactions with rifampin (which decreases methadone concentration by 33%-93%), with fluconazole/diflucan (which increases methadone concentration by 30%) and nevirapine (which decreases methadone concentration by 52%). Other studies showed that methadone increases AZT plasma levels by 50%, ddI

levels by 52%, and d4T levels by 13%. As a consequence researchers issued the following recommendations for people taking methadone and anti-retroviral drugs:

- Patients using methadone should be counselled about the possibility of methadone withdrawal symptoms before they are prescribed certain medications
- Once patients have started a treatment with one of these compounds, they should be closely monitored for symptoms of methadone withdrawal
- Should symptoms of methadone withdrawal occur, the dose of methadone should be “promptly increased” to avoid the discomfort of withdrawal and to prevent discontinuation of anti-retroviral therapy
- Once patients stop using those compounds, liver enzymes that process methadone will return to normal function within two weeks. Thus, patients need to be monitored for signs of methadone overdoses

In the last years activists have argued that drug companies should also study interactions between their products and common recreational drugs, not only using mathematical models. However, company representatives continuously affirm that such studies would probably be impossible, and would almost certainly be unhelpful. Activists spoke to several drug companies about these issues and, while none were willing to speak on the record, all expressed similar concerns. Realistically, it is unlikely that pharmacokinetic interactions between drugs used in HIV pharmacotherapy and most recreational agents will be formally studied, due to legal and ethical constraints. However, it is often possible to predict potential interactions using in vitro and in vivo metabolism data. The purpose of this article is to summarise data on drug interactions between recreational drugs and antiretrovirals. Based on anecdotal reports and what we know about the metabolism of these drugs, we believe that harmful drug interactions may occur, especially with the group of antiretrovirals known as protease inhibitors. Some possible interactions of recreational drugs with protease inhibitors are known. Some people who are taking protease inhibitors make the decision to use recreational drugs even while knowing the risks involved. Before making the decision, individuals should be informed of the potential for increased drug potency and the possible increased toxicity of the recreational drugs.

Ecstasy (MDMA)

MDMA is a commonly used substance at all-night dance parties known as raves and is also increasingly being used recreationally. MDMA is an amphetamine-like compound metabolised by CYP2D6. Concomitant administration with CYP2D6 inhibitors could lead to a significant increase of MDMA exposure with potentially dangerous and even fatal consequences. There has already been one death in England when ecstasy was taken with Norvir. Norvir is known to slow down the liver enzyme that breaks down MDMA, so it makes the dose 5 to 10 times stronger. If you're taking any protease inhibitors or non-nucleoside reverse transcriptase inhibitors, MDMA can be extremely dangerous. Of these, Norvir (ritonavir) and Rescriptor (delavirdine) seem the most dangerous, while Viramune (nevirapine) and Sustiva (efavirenz) may be less. If you take MDMA with a protease inhibitor, wait as long as possible after taking the protease inhibitor to take MDMA, and be sure to have someone with you who knows what you have done in case you have problems. These overdoses are often not reversible, so it's really better not to mix these drugs. The danger associated with this interaction may be magnified due to the large variability in the actual amount of MDMA between tablets and the presence of other chemicals (e.g. amphetamines, ephedrine). Other amphetamines, particularly methamphetamines (crystal meth, speed), may be used at raves. These drugs are also mainly metabolised by CYP2D6. Thus potentially dangerous interactions with ritonavir may occur, and the combination should be avoided if possible. Norvir is predicted to increase amphetamine levels in blood by 2 to 3 fold. The other protease inhibitors should have a minor impact, but unpredictable paradoxical results are possible.

Alcohol

Videx can increase the risk of pancreatitis. So, if you are using alcohol regularly, do not use Videx. Occasional and light use of alcohol is not known to interact with any of the anti-HIV drugs; however, chronic heavy use can be destructive to the liver. This can be dangerous because the hepatic pathway through which these drugs are metabolised can be impaired by long-term alcohol toxicity. As a result higher concentrations of the drugs will remain in your body for longer periods, which is likely to cause overdoses and worse side effects. Appropriately conducted studies on

pharmacokinetics are necessary to confirm the existence of an interaction between antiretrovirals and chronic alcohol use and to clarify appropriate management strategies. Alcohol can cause dehydration; so be sure to drink a lot of water to help your body deal with the alcohol you drink.

Marijuana

Protease inhibitors may increase THC levels (the active ingredient in marijuana). So, smaller doses may make you more stoned. This is also true of the synthetic version (Marinol) used in the treatment of weight loss. Since THC overdose is impossible, this interaction is not dangerous. Considering the widespread use of smoked and oral THC derivatives for appetite stimulation and control of nausea and vomiting, and the lack of reports documenting deleterious side effects to the combination of THC and PIs, a clinically significant drug interaction may not exist when THC is used in moderate amounts.

Cocaine

The significant role played by cocaine in the transmission of HIV cannot be underestimated. While injecting cocaine or heroin puts users at risk of acquiring HIV through direct contact with infected blood, smoking "crack" cocaine may independently be associated with acquisition of HIV through its association with high-risk sexual practices. Interactions between cocaine and antiretrovirals have not been described but in test tubes, cocaine doubles the speed at which the virus reproduces, meaning it may speed up how sick you get.

Heroin

Ritonavir seems to reduce heroin levels by 35-50% making overdoses less likely to happen. At the same time people using heroin may experience possible withdrawal symptoms and loss of analgesia. However, ritonavir and other protease inhibitors have sometimes been known to have opposite effects (they reduce methadone levels in real life, while test tube experiments predicted they would increase them), so caution is in order. Some synthetics sold as heroin (fentanyl, alpha-methyl-fentanyl) are potent in very reduced doses and could become lethal if mixed with another drug.

GHB

GHB, also known as liquid ecstasy, or G, is commonly used at raves for its euphoric

effects. Since the precise metabolic pathway of GHB is unknown, people who use this substance should be warned about the potential dangers of a drug interaction with PIs (especially ritonavir) and the NNRTI delavirdine and, possibly, efavirenz.

LSD

LSD is known popularly as acid or blotters. Although CYP450 system may be involved in the metabolism of LSD, the exact contribution of this system in overall LSD clearance and the isoenzymes involved have not been detailed. People using LSD and who receive an antiretroviral treatment should be cautioned about the possibility of an interaction. They should also be familiar with signs of LSD toxicity, and perhaps consider using a smaller amount than normal.

Ketamine

When combined with Norvir, Ketamine, or "Special K", can lead to "chemical hepatitis", an unpleasant liver inflammation resulting in jaundice. Some HIV specialists have come over a few cases of it. Both resolved within several weeks, but anything that damages the liver can be a serious problem for people living with HIV.

PCP

PCP, known on the street as angel dust, rocket fuel, or killer weed, may be used at raves for its hallucinogenic or dissociating properties. It is expected that concurrent use of PCP and PIs, delavirdine, and possibly efavirenz may result in elevated PCP concentrations and resultant toxicity. People using PCP should be cautioned to use less than what they normally use given the potential for drug interaction.

Other interactions, which have not been listed in this article, could be lethal. Street drugs are often not what they are sold as. They are frequently cut with other substances that may interact with the drugs themselves and their potency can vary significantly, even in the same batch. With the lack of research in this area, it is recommended to avoid potential interactions, if possible, even if you're not considering quitting drugs.

Mauro Guarinieri

Reference

Tony Antoniou, Alice Lin-in Tseng, *Ann Pharmacother* 2002; 36: 1598-1631

10th Conference on Retrovirus and Opportunistic Infections (CROI 2003).

Boston, February 10-14.

On women

This conference had a surprisingly strong emphasis on women and additionally the sessions were extremely well attended. This in turn was much commented on – session chair Professor James McIntyre from Soweto chairing the ‘...lone session on women and paediatrics’ remarked that ‘I thought I’d be sitting here alone.’ However still there was limited data reported on women over and beyond their role in mother to child transmission. Chairing the session HIV and Women, Dr Judith Currier emphasised ‘Half of the new infections in the world are in women, yet we spend so little time discussing issues unique to prevention, pathogenesis and treatment as it pertains to their health.’

Women and HIV in India and Africa

Dr Suniti Solomon painted a grim picture of the position of women – and in particular HIV positive women – living in India [1]. She discussed the limitations of prevention strategies in a society where infanticide is not uncommon following the birth of a girl, every 34 minutes a woman is raped, every 93 a woman burnt to death over a dowry and in 1000 child marriages were still reported in one day in the year 2003.

Their vulnerability to HIV can only be enhanced by beliefs such as sex with a virgin can cure sexually transmitted diseases and by a system where monogamy is often unilateral (in one study 95% of HIV positive women were married, 81% housewives and 88% report monogamy). Lack of economic autonomy and job opportunities means that women are frequently forced to remain in a marriage where they are at risk or to support themselves through sex work.

Dr Solomon described their prevention needs, which include:

empowering women, encouraging men to admit that they are vulnerable; gender sensitise the program; engaging men in the process of changing gender norms and initiating structural changes. In other words reconstructing the culture in which as Dr Solomon pointed out at the beginning

of her talk the ‘...social construct of gender has evolved for several hundred years.’ In a society where she estimates that seroprevalence is greater than 5% among women of child bearing age within a population of over a billion, the potential threats and challenges seem insurmountable. ‘How on earth does she get out of bed in the morning to all that?’ remarked my colleague. Leaving her audience completely stunned, Dr Solomon concluded that ‘It is not flattering that it takes a ruthless epidemic to awaken the world to the needs and condition of her women.’

In a session on international strategies Dr Dorothy Mbori-Ngacha from Kenya outlined the situation for women in Africa where ‘As the epidemic has matured the vulnerability of women has come to the fore.’ [2] Current UNAIDS figures indicate that women constitute 58% of all people living with HIV on the continent of Africa and women are more vulnerable to HIV acquisition for a variety of social, cultural, economic and biological reasons.

In USA

Drs Ruth Greenblatt from the WIHS and Kate Squires from the University of Southern California both described the current situation in the US [3,4]. Here HIV is still the greatest cause of death amongst women of colour between 25 and 44 years old, and women living with HIV, and those at high risk, remain a demographically distinctive group. Dr Squires gave an overview of sex and gender differences, and both speakers emphasise how little we actually know and the need for more trials that address these differences and women specific research programmes. Dr Greenblatt was emphatic that ‘...we need to address research related to women much more aggressively.’

And there were a few reports addressing women’s health presented at this meeting...

Osteopenia and fat redistribution

There is no current consensus of the effect of HIV and/or antiretroviral use on the preva-

lence or course of osteopenia in HIV positive women, and particularly older women.

Two oral presentations evaluated bone mineral density in HIV positive women [5,6].

Dr Jacobsen and colleagues from Tufts University, Boston, looked at the association between HAART use and other demographic variables on bone mineral density in a cohort of 141 women over 9-18 months and 21-27 months of follow-up (42 women were followed for 2 years). This cohort is 33% Caucasian, 52% African American, and 22% other with a median age of 39 years.

The median total BMD at first DXA scan was 1.09 gm/cm² (25th% 1.04; 75th% 1.16).

After adjusting for age and weight, neither HAART use nor demographic variables were significantly associated with total BMD.

In this study the median BMD was not found to change over 2 years. The investigators report ‘However, in individuals loss of BMD is associated with loss of lean body mass.’ They also found that ‘Osteopenia is prevalent in HIV-positive Caucasian women.’ and that ‘...smoking and injection drug use may increase the risk of osteopenia’.

Dr Arnsten from the Montefiore Medical Center evaluated the incidence of osteopenia in a cohort of 284 older (above 35 years, median 45 years) peri- and post-menopausal HIV positive (n=144) and negative women (n=140). Using DXA, they analysed BMD of the lumbar spine, hip, and total body older in addition they also analysed the impact of protease-inhibitor (PI) use on BMD. Controlling for race, physical inactivity, smoking, and HIV status. Osteoporosis was more prevalent in post-menopausal (OR = 6.8, p < 0.001), physically inactive (OR = 3.9, p = 0.04), and white (OR = 3.5, p = 0.04) women. HIV infection was not associated with either osteopenia or osteoporosis.

In contrast with previous studies, the investigators also reported that women who had used PIs for more than 1 year were significantly less likely to have osteopenia than women who had used PIs for less than 1 year or not at all (OR = 0.3, p < 0.01). They concluded that ‘PI use among older HIV-infected women

may protect against bone mineral loss by modifying cytokine-mediated disturbances in the synchronized bone-remodeling process.' A poster from Dr Yin and colleagues evaluated the prevalence of osteoporosis and HIV associated risk factors for low bone density (BMD) in 32 postmenopausal HIV+ women [7].

The mean age of this cohort was 56 years, and mean time since onset of menopause 10 years. 88% of women had used HAART for a mean of 5 years. 36% had experienced all three classes of drugs, 36% to nucleosides plus PIs and 7% to nucleosides plus NNRTIs. 72% were Hispanic and 25% African American.

An assessment by DXA was conducted at the lumbar spine and femoral neck. In this small study the investigators found the prevalence of osteoporosis to be considerably higher in African American and Hispanic women with HIV than in comparable HIV negative women. They reported that lower BMD was more strongly associated with generally accepted osteoporosis risk factors (higher weight, time since menopause and use of HRT but not with HIV and treatment related factors. They noted that 'Hispanics and African Americans account for over 80% of HIV+ women over age 50 in New York. As the female HIV population increases and ages, diagnosis and treatment of osteoporosis should play a more prominent role in their long-term management.'

A poster from Dr Howard and colleagues from the Montefiore Medical Centre evaluated fat distribution in a cohort of HIV positive (n=105) and negative (n=120) women and evaluated the impact of antiretroviral use and demographic factors on regional adiposity [8].

Of this group the mean age was 45 years; 45% were African American, 36% Hispanic and 15% white. HIV positive women were younger and more likely to be African American and obesity was greater in HIV negative women. Regional body composition was measured by DXA scan. Among the HIV positive women studied 129 (66%) were using PIs for a median duration of 27 months and 110 (56%) used d4T for a median of 24 months.

The investigators found that in this group of older, predominately obese women after controlling for age, CD4 and PI use in a multivariate analysis, HIV was associated with decreased body mass index (BMI) and percentage of body fat but not with fat redis-

tribution. Amongst the women with HIV, d4T use was associated with an increase in truncal fat and decreased extremity fat, but PI use was not.

Cervical cancer

Likewise there is still no consensus on the effect of HAART use on the course of HPV related cervical pathology in HIV positive women. In response to contrasting reports in the literature Dr Ubert-Foppa and colleagues from Milan assessed the long-term (mean 36.4 months + or - 10.4 months) effect of HAART on persistent HPV infection and histological cervical lesions in 154 HIV positive women (mean age 37.3 years) receiving 2 nucleosides, HAART or no treatment [9]. Women were assessed every 6-12 months using PAP smear and coposcopy (with biopsy if indicated) and high grade cervical lesions were treated with loop electrosurgical incision. Unsurprisingly CD4 levels significantly increased in the HAART receiving women ($p = 0.017$) and in those switching to more potent HAART ($p = 0.0001$), but this was not associated with a decreased persistence of HPV. A significant reduction of positive biopsies though was found only in women on long term HAART ($p = 0.00006$). However the investigators found that in this cohort they could establish no beneficial effect of long term HAART on HPV persistence and related cervical disease and that these conditions persisted in a high proportion of women. They continued explained that HPV-related histological lesions are significantly reduced only in women with stable clinical and virological picture including those untreated or treated with 2 NRTIs or with HAART. HPV pathology persists particularly in those with the longest history of HIV infection, suggesting that, regardless of antiretroviral regimen and its effect on HIV replication, the crucial aspect is the number (and probably the competence) of CD4 cells.' They recommend continuous monitoring and '...strict surveillance of patients is still the best preventive scheme for HPV-related cervical lesions, also in the era of HAART.' A poster from the WIHS describes the magnitude of incidence of cervical cancer in this cohort of HIV positive and at risk women (n = 2,133 women - 463 HIV negative, 1,662 HIV positive, and 8 seroconverters) followed prospectively from October 1994 through September 2001. Women with a history of cervical cancer or hysterectomy were excluded.

Cervical cytology was obtained at 6-month intervals and cervical disease treatment was individualised. They found cases of invasive cervical cancer which were observed in the HIV negative women during 2,380 years of observation - an incidence rate of 0/10,000 woman-years. During 8,260 woman-years of observation, 8 cases of cervical cancer were identified in HIV-positive women but only 2 were confirmed. They found no significant difference in incidence rates between HIV-positive and negative women. The investigators noted that this low incidence cannot be generalised to women who are not under a regular screening and prevention programme or to women not receiving HAART.

Neurological Disease

Finally a poster from Dr Hall and colleagues, in response to previous chart review data suggesting a higher incidence of HIV neurological disease and differences in progression in women and men, reported findings from a longitudinal study evaluating gender differences in nervous system decline [11]. In this prospective longitudinal study of 48 HIV positive, 48 HIV negative women and 52 HIV positive men undergoing standard neurological exams by a neurologist and controlling for factors such as antiretroviral use, the investigators found no evidence that nervous system decline was more likely in one gender than the other.

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References

- [1] Solomon S., Stopping HIV Infection Before It Begins in Women, Abs 114
- [2] Mbori-Ngacha D., Prevention and Care of HIV-infected Women in Sub-Saharan Africa, Abs 47
- [3] R.M. Greenblatt, Natural History of HIV-1 Infection in Women - Findings from the Women's Interagency HIV Study, Abs 115
- [4] Squires K., The impact of Sex/Gender and Antiretroviral Therapy and its Complications, Abs 117
- [5] Jacobson D., Knox T., Shevitz A. et al, Low Bone Mineral Density in HIV-infected Women, Abs 102
- [6] Arntsen JH, Freeman R, Santoro N, et al, HIV Infection and Protease Inhibitor Use are Not Associated with Reduced Bone Mineral Density in Older HIV-infected Women, Abs 103
- [7] Yin MT, Dobkin JF, Brudney KF, et al, Osteoporosis in Postmenopausal HIV+ Women, Abs 766
- [8] Howard A.A., Freeman R., Santoro N., Schoenbaum E.E., Body Composition and Antiretroviral Use in Older HIV-infected Women, Abs 735
- [9] Uberti-Foppa C., Ferrari D., Lodini S., Long-term Effect of Highly Active Antiretroviral Therapy on Histological Cervical Squamous Intra-epithelial Lesions among HIV+ Women, Abs 767
- [10] Massad L.S., Seaberg E., Bitterman P. et al, Incidence of Invasive Cervical Cancer among Women with HIV, Abs 768
- [11] Hall C., Robertson W., Fiscus S. et al, No Gender Differences in Progression of HIV-related Neurological Disease, Abs 703

Nevirapine resistance – the cautionary tales continue

...following labour

Two posters from Susan Eshleman's group reported further analyses of nevirapine resistance from the HIVNET 012 trial in Uganda in which it was famously demonstrated that single dose NVP given as prophylaxis to a mother in labour followed by a single dose to the infant can reduce mother to child transmission. However following analyses of NVP resistance in 111 of the women, 21 (19%) had detectable mutations at 6-8 weeks post dose, most commonly K103N.

In an expanded evaluation of the rate of NVP resistance, paired samples collected at 7 days and 6-8 weeks were compared [1]. NVP mutations were detected in 66 (24%) out of 271 women and a similar number had mutations at both time points, however patterns of mutations were different.

Y181C was detected in 13 (87%) of 15 women with NVP resistance at 7 days, but in only 4 (22%) of 18 women with NVP resistance at 6-8 wks. In contrast, K103N was detected in 6 (40%) of 15 women with NVP resistance at 7 days, but was detected in all 18 women with NVPR at 6-8 weeks. Analysis of paired samples suggests that of the most common mutations associated with NVP resistance Y181C is selected early, but fades from detection in most women by 6-8 weeks, by contrast, K103N is more likely to be detected at 6-8 wks than at 7 days.

The investigators noted that 'The pattern of NVPR mutations detected after single-dose NVP depends on the timing of sample collection.' And they explained that 'The more rapid emergence and fading of Y181C vs K103N may reflect differences in the NVP susceptibility and fitness of HIV-1 with these mutations. Analysis of cloned variants reveals that diverse populations of HIV-1 variants with NVPR mutations are selected as early as 7 days following single dose NVP.'

A second poster from the same group evaluated the samples by subtype using a univariate analysis and their findings suggest that the rate of NVP resistance was higher in women infected with subtype D than with subtype A HIV-1 [2]. Unsurprisingly high baseline viral load and low CD4 were associated with likelihood of acquisition of NVP resistance. The authors speculated that '...the

rate of NVPR following single dose NVP prophylaxis may vary from region to region, depending on which subtypes are prevalent.' In addition, a Thai poster assessed the development of resistance in pregnant HIV-infected women and their infants receiving both short-course zidovudine (ZDV) therapy and single-dose intrapartum/newborn NVP [3]. The authors reported that amongst 133 ARV naive women receiving both prophylaxis strategies, 20 demonstrated NVP and one a ZDV genotypic resistance mutation at 1 month postpartum and of the 3 HIV-infected infants tested, 1 demonstrated NVP resistance.

...and breastfeeding

Breastfeeding may account for as much as a third of mother to child transmission (MTCT) with estimated transmission rates at 0.5%-2% per month. MTCT breastfeeding interventions have included a second dose of NVP to the mother (conferring a threefold increase in incidence of resistance from 19-67% women receiving prophylaxis) [4], and NVP prophylaxis to breastfeeding infants.

In an oral presentation Dr Lee from Stanford University reported findings from a small study conducted in Zimbabwe, comparing the relative concentrations of NVP resistant virus in 33 women enrolled in HPTN 023 who received single dose NVP at the onset of labour [5]. Plasma and breast milk samples were obtained at 2, 8, 16 and 20 weeks post partum. At 8 weeks 23/33 (70%) women had detectable HIV RNA in plasma.

Sequences were available for 33 of the plasma and 20/33 of the breast milk samples. Detection of NVP mutations was significantly higher in the breast milk 3/20 (65%) than the plasma 8/33 (24.2%).

K103N (the mutation most commonly associated with NVP resistance) was the most frequently observed mutation in both breast milk (12/20) and plasma (5/33). Only 4/20 pairs of plasma and breast milk demonstrated the same mutations and all samples were found to be subtype C. The investigators also observed that 'The 20 breast milk and plasma samples from each woman were more closely related to one another than to sequences from other women.' And they

concluded that 'Significantly higher frequency of resistance mutations in breast milk compared to plasma provides evidence for differential selection and expression of NVP resistance in the BM compartment after single dose nevirapine.'

Questions raised following the presentation concerning the limitations of the assays and the possibility that the investigators may be missing minor variants, implications for transmission of resistant virus and the limits these findings may have on the use of NVP prophylaxis for a breastfeeding infant were largely unanswered.

Rapid test

Finally a poster from Susan Eshleman's group reported results from an evaluation of NVP resistance in women in HIVNET 012 using the rapid assay Amp-RT (this assay measures reverse transcriptase enzymic activity and NVP resistance directly in plasma) compared to genotyping using the Applied Biosystems ViroSeq HIV-1 Genotyping System. 29 plasma samples were from 17 women, including pre- and post-NVP samples were tested. They found that 17 samples had no detectable NVP mutations (wild type) and 12 samples had minor variants with NVP resistance mutations.

Results were obtained for 26 (90%) of the 29 samples, including 16 WT samples and 10 samples with minor NVP variants. The other 3 samples had undetectable RT activity. The Amp-RT assay detected NVPR in 6 (60%) of the 10 samples with minor NVPR variants. Thirteen (13; 81%) of the 16 wild type samples were susceptible to NVP in the Amp-RT assay, and 3 had reduced susceptibility. Two (2) of the samples with reduced susceptibility were pre- and post-NVP samples from the same woman who was antiretroviral drug naive prior to NVP administration. The pre-NVP sample had a lower level of NVP resistance than the post-NVP sample. The authors reported that 'In this study, results from the Amp-RT assay were concordant with results from genotyping in the majority of cases' (including detection of minority variants). They speculate that the finding of reduced susceptibility to NVP in the three wild type samples may indicate

Generics

This conference also had a strong emphasis on international and resource limited settings. Production of generic antiretrovirals by generic manufacturers has reduced the cost of HAART to as little as \$1 a day.

Several sessions included reports of programmes using these affordable drugs in their treatment strategies, including data from Malawi using Triomune [1] and India and Mozambique using NVP-containing generic HAART regimens [2, 3].

were obtained from six international sources and the NVP content of the six products was determined by HPLC. In total, six chromatographic analyses were performed for each individual tablet. The NVP content and demographic data for the individual products are listed in the table.

All products in this study were labeled as containing 200 mg of NVP drug. The average NVP content among the tested preparations was 197.9 mg Average accuracy of nevirapine content in the tested preparations versus labeled amounts was 99.0%.

that mutations other than those defined in subtype B analysis may cause NVP resistance in other subtypes. Using this rapid assay does not require time isolation and culture and therefore can provide results in 1 or 2 days in contrast to conventional phenotype. They also suggest that further studies be undertaken to characterise the full genetic correlates in non-subtype B HIV and to assess the utility of biochemical testing in resource poor settings.

Table 1 Nevirapine Products Analyzed for Drug Content

Product (Company)	Country where product was obtained	Date of manufacture (expiration)	Mean Nevirapine Content (cv [%])
Triomune 30 (Cipla) Nevirapine 200 mg Stavudine 30 mg Lamivudine 150 mg	Kenya	Not provided (1/03)	194.2 mg (3.1)
Viramune (Boehringer) Nevirapine 200 mg	Lithuania	Not provided (Not provided)	201.9 mg (3.0)
Viramune (Boehringer) Nevirapine 200 mg	South Africa	Not provided (12/01)	196.6 mg (2.2)
Triomune 40 (Cipla) Nevirapine 200 mg Lamivudine 150 mg Stavudine 40 mg	Zambia	12/01 (05/03)	191.4 mg (2.1)
Nevimune (Cipla) Nevirapine 200 mg	Zambia	8/01 (07/03)	197.8 mg (3.0)
Nevirex (Aurobindo Pharma Ltd.) Nevirapine 200 mg	Zambia	11/01 (10/03)	205.5 mg (2.1)

However concerns have been raised (with varying agendas) that generic medications may contain little or no active ingredient or not be bioequivalent to originator products. A poster from Dr Penzak and colleagues from the NIH and NAIDS compared the NVP content of several generic and originator formulations as part of a pilot, quality control investigation [4].

The authors explain that 'There are currently no publicly available data describing the integrity (drug content vs. label claim) of these preparations.' These data are essential to enable governments and healthcare providers to make decisions as to which antiretroviral formulations will provide the greatest benefit to the 90% of HIV positive people who currently have no access to these medications.

They obtained tablets containing NVP (alone or in combination with other ARVs)

The investigators concluded that 'The results are encouraging and consistent with stringent manufacturing standards ($\pm 3\%$ of labeled drug amount); these data are particularly reassuring given the widespread use of nevirapine-containing products in the developing world.' Studies are currently in progress to analyse all currently available generic antiretroviral products at the NIH and UAB.

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References

- [1] Hosseinipour M., Namarika D., Magomero K. et al The Malawian Antiretroviral Program: The First Year Experience with Triomune, Abs 172
- [2] Kumarasamy N., Chaguturu S., Mahajan A. et al, Safety, Tolerability, and Effectiveness of Generic HAART Regimens in South India, Abs 174
- [3] Emberti Gialloreti L., De Luca A., Perno C.F. et al, Increase in Survival in HIV-1 Infected Subjects in Matola, Mozambique, after the Introduction of Combination Therapy With Generic-manufactured Antiretrovirals: Preliminary Results from the DREAM Cohort, Abs 175
- [4] Penzak S., Tavel J., Acosta E.P., Quality-Control Analysis of Generic Nevirapine Formulations in the Developing World: An Initial Report, Abs 549a

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References:

- [1] Eshleman S.H., Cunningham S.P., Jones D. et al, Analysis of Nevirapine Resistance Seven Days after Single-dose Nevirapine Prophylaxis: HIVNET 012, Abs 856
- [2] Eshleman S.H., Guay L.A., Mwatha A. et al, Extended Analysis of Nevirapine Resistance in Women with Subtype A vs D HIV-1 6-8 Weeks After Single Dose NVP Prophylaxis: HIVNET 012, Abs 857
- [3] Chaowanachan T., Chotpitayasunondh T., Vanprapar N., Resistance Mutations Following a Single-dose Intrapartum Administration of Nevirapine to HIV-infected Thai Women and Their Infants Receiving Short-course Zidovudine, Abs 855
- [4] Sullivan J., South African Intrapartum Nevirapine Trial: Selection of resistance mutations. XIV International AIDS Conference, Barcelona 2002, Abs LbPpB9024
- [5] Lee E., Kantor R., Johnston E., Breast Milk Shedding of Drug-resistant Subtype C HIV-1 and Among Women Receiving Single-dose Nevirapine, Abs 96
- [6] Eshleman S.H., Cheingsong R., Garcia G., Evaluation of a Rapid Phenotypic Assay for Nevirapine Resistance in Ugandan Women who Received Single-dose NVP Prophylaxis in HIVNET 012, Abs 581

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Half of HIV Cases Spread Heterosexually in Europe

The number of women being diagnosed with HIV in Europe is quickly catching up with men, raising the risk of more babies being born to infected mothers, researchers warned Wednesday. ISIS Research Plc, a health care market research agency, said its analysis of HIV figures showed just how fast this was happening in Europe, even though in the United States homosexual transmission remains the dominant route of infection.

ISIS analyzed 3,000 European patients on HIV therapy from July-October 2002 and found 308 patients had been newly diagnosed with HIV earlier that year. Of these, 51 percent were infected through heterosexual contact and only 36 percent as a result of homosexual contact. Yet, ten years ago, the transmission routes were 28 percent heterosexual and 38 percent homosexual. ISIS examined 3,000 US patients and found that new HIV diagnoses were 51 percent homosexual and 31 percent heterosexual by route of infection.

ISIS analyst Amanda Zeffman said that numerous factors, including different ethnic origins and awareness campaigns, account for the differences in the epidemic between Europe and the United States. The gap is narrowing, however, as more US heterosexuals become infected. The number of European females being diagnosed with HIV is "fast catching up with the number of males," said the report, with the consequent risk of more babies being born to infected mothers. The question arises of "which treatments to use or avoid during pregnancy and at the time of birth to prevent" mother-to-child HIV transmission.

On a positive note, the report said initiatives to supply sterile needles to drug users seemed to be effective, with HIV transmission via intravenous drug use now almost eradicated in France, Germany and the United Kingdom and significantly reduced in Spain and Italy. However, in the United States, where initiatives are less widespread, infection rates have dropped less.

Reuters Health (03.19.03), Richard Woodman

HIV's Ability to Rapidly Evolve Occurs Quicker Than Thought

The virus that causes AIDS evolves more rapidly than previously thought, according to a new finding that underscores challenges to developing an effective vaccine.

The human immunodeficiency virus, or HIV, has long outwitted both scientists and the body's

own defenses with its rapid ability to adapt. The protective envelope of the virus is a particular hotbed of variability, according to a new study by researchers at the University of Calif., San Diego, and ViroLogic Inc., a South San Francisco, Calif., biotechnology company. The virus mutates its protective coating "at an incredibly rapid rate" in order to stay one step ahead of so-called neutralizing antibodies produced by the immune system, said Douglas Richman, lead author of the study, which appears Tuesday in the Proceedings of the National Academy of Sciences.

The study, which uses new methods developed by ViroLogic, provides the closest look yet at how HIV evades the body's powerful efforts to churn out antibodies that can render it ineffective. In recent years, the AIDS virus has been tamed in infected individuals by retroviral and other drugs that disrupt its ability to replicate. Stopping infection in the first place is more difficult. Protecting patients with antibodies has been a major thrust of vaccine developers. So far, however, HIV vaccines haven't worked. In February, VaxGen Inc., Brisbane, Calif., reported that its experimental vaccine didn't protect the people who took it. Dr. Richman said his group's findings and methods may open a path toward more effective vaccine strategies. For instance, vaccines might be developed to target portions of the virus that are unable to undergo rapid change.

Wall Street Journal - March 18, 2003

Antonio Regalado, Staff Reporter of The Wall Street Journal

<http://www2.aegis.org/news/wsj/2003/WJ030305.html>

Experts Launch Guide to Optimising HIV Drug Level Monitoring

Therapeutic drug monitoring (TDM) is a pharmacologic tool used to measure plasma levels and can provide an additional source of information to support physicians and patients in their planning and management of HIV therapy. At a recent scientific workshop dedicated to advances in the field of HIV pharmacology, the utility of TDM was an important issue for debate. The 4th International Workshop on Clinical Pharmacology of HIV Therapy held in Cannes, France, included a special roundtable session with HIV clinicians and pharmacologists where, with the aid of real patient case presentations, delegates discussed the optimal use of TDM. Issues covered in the patient cases included cardio-vascular disease, clinical obesity and first-line treatment on a novel

These news first appeared in the first quarter of 2003 and the state of the art may have changed since. They are meant to support, not replace, your relationship with your health professionals.

regimen of low-dose antiretrovirals. As well as highlighting the real and challenging demands placed upon clinicians, the forum also provided a timely opportunity to discuss clinical scenarios where TDM may be most useful in supporting patient management.

The organisers of the meeting used the occasion to launch a new resource tool entitled Optimising TDM in HIV Clinical Care. The HIVPharmacology.com guide is a pocket-size reference document aimed at clinicians interested in integrating TDM into their patient care. The guide highlights specific indications for TDM including special patient groups and a helpful step-by-step guide to performing TDM. The guide provides recommendations for TDM for managing co-infections or drug-drug interactions may complicate therapy. In special groups such as paediatric patients or pregnant women, TDM may be particularly helpful in helping to identify treatment programmes best suited to individual patient needs.

Dr David Burger, from the University Hospital Nijmegen, the Netherlands, a leading advocate for pharmacologic monitoring of antiretrovirals and responsible for pioneering research in this area, advises physicians: "The level of inter-patient variability that we observe for some drugs can be striking and interactions between medications mean that the potential for patients to receive suboptimal levels cannot be overlooked. We can no longer assume that one dose fits all."

The Guide is not intended to be prescriptive, notes Dr Jonathan Schapiro from Stanford University, USA, "The doctor will need to take into account many other clinical and lifestyle issues. For example, for patients with resistant virus or toxicity management, TDM can be extremely helpful in guiding physicians towards individualising patient care. But any modifications to treatments based upon TDM results should be undertaken with care and involve consultation with an expert clinical pharmacologist and where necessary, an expert clinical virologist."

Optimising TDM in HIV Clinical Care is available onsite at www.HIVPharmacology.com in PDF format or free-of-charge in printed form from Virology Education.

DATES

May

13th Annual Clinical Care Options for HIV Symposium

<http://clinicaloptions.com/hiv/cco2003/info2.htm>

Location: Scottsdale, Arizona United States

Dates: 15-18 May 2003

Sponsor: iMedOptions, LLC.

Northwestern University School of Medicine.

June

XII International HIV Drug Resistance Workshop: Basic Principles and Clinical Implications

<http://informedhorizons.com/resistance2003/welcome.htm>

Location: Los Cabos, Mexico

Dates: 10-14 June 2003

Sponsor: University Hospital Utrecht, The Netherlands. University of Pittsburgh, USA. University of California San Diego/VA Medical Center, USA.

1st Annual Clinical Care Options for Hepatitis Symposium

<http://clinicaloptions.com/hep/ccohep2003/general.asp>

Location: Laguna Niguel, California United States

Dates: 19-22 June 2003

Sponsor: iMedOptions, LLC.

Northwestern University School of Medicine.

July

AIDS Impact 2003: 6th International Conference on Biopsychosocial Aspects of HIV Infection

www.aidsimpact.org

Location: Milan, Italy

Dates: 7-10 July 2003

Sponsor: Università Vita-Salute San Raffaele (UHRS).

5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

http://www.intmedpress.com/lipodystrophy/main_cfm?sect=home

Location: Paris, France

Dates: 8-11 July 2003

Sponsor: International Medical Press

2nd IAS Congress on HIV and Pathogenesis

http://www.ias.se/page_1.asp?pagelid=40

Location: Paris, France

Dates: 13-16 July 2003

Sponsors: International AIDS Society (IAS), ARNS.

September

43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

<http://www.icaac.org/ICAAC.asp>

Location: Chicago, Illinois, United States

Dates: 14-17 September 2003

Sponsor: American Society for Microbiology.

October

9th European Conference on Clinical Aspects and Treatment of HIV Infection

<http://www.eacs-conference2003.com/start.php3>

Location: Warsaw, Poland

Dates: 26-20 October 2003

Sponsor: European AIDS Clinical Society (EACS).

11th International Conference for People Living with HIV/AIDS

<http://www.gnpplus.net>

Location: Kampala, Uganda

Dates: 26-30 October 2003

Sponsor: The Global Network of People Living with HIV/AIDS (GNP+)

December

8th World STI/AIDS Congress

<http://www.micongreso.com/congresos-rohr/stiaids/>

Location: Punta del Este, Uruguay

Dates: 2-5 December 2003

Sponsor: International Union Against Sexually Transmitted Infections (IUSTI).

6th International Conference on Home and Community Based Care for People Living with HIV/AIDS

<http://www.dakarvih2003.sn>

Location: Dakar, Senegal

Dates: 8-11 December 2003

Sponsor: National Council Against AIDS, Senegal. ICASO. ICW. International Federation of Red Cross and Red Crescents Societies.

1st International Workshop on HIV Persistence during Therapy

<http://www.avps.org/2003/hivp.htm>

Location: Saint-Martin, French West Indies

Dates: 10-12 December 2003

Sponsor: Department of Infectious Diseases, Chalucet Hospital.

European AIDS Treatment Group
www.eatg.org