8th European Conference on the Clinical Aspects and Treatment of HIV Infection

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Report by Kirsty Machon
HIV Health Policy Analyst, National Association of People Living with HIV/AIDS

First things ... 

First: a whinge. Might as well get it over and done with. This conference came hard on the heels of the 3rd Lipodystrophy Workshop, and was a three-and-a-half day intense affair, including several Satellite Symposia, sponsored by the pharmaceutical companies, each book-ending the days with breakfast and early evening sessions. Problematically, these symposia offered (from my point of view) very little information above and beyond what was presented in the oral presentations in the conference proper. In addition, there was ample possibility for companies to turn these events into essentially PR exercises in rescuing or furthering the reputation of their own stable of drugs, or taking the chance to have a blatant swipe at the enemy. True, one could be overly cynical, and suggest that there was literally nothing to be gained from these sessions. And drug companies are perhaps not so disingenuous as to exercise no restraint at all. Nonetheless, it is my view that by curtailing the ‘rights’ of the companies to these often over-articulated sessions – primarily by ensuring sessions and speakers were not repetitively programmed into the general conference — you could have shaved at least a day from the conference and lost nothing.

At the very least, it would have spared those of us who’ve been around too long to be susceptible to or even amused by such things the indignity of having to cringe our way through sessions which attempted to explore HIV biology through Greek mythology (Roche), or the predictable metaphor of the Olympics (BMS-Pharma).

With that aside out of the way, we can proceed.

Big pictures

What was very interesting for me, as an Australian, was to be at a conference in which so many of the stellar names in their fields were presenting. Lest you should think I am engaging in the unbecoming equivalent of HIV groupiedom, I should say that the reason is precisely because a number of these people were terrific presenters, and capable of seamlessly drawing together certain aspects of the bigger picture in a way I have seen few presenters (Australia’s Sharon Lewin comes to mind) do with such clarity and
utility. In particular, Graeme Moyle’s adept summing up of the lipodystrophy workshop, and Veronica Miller’s very helpful survey of current thinking about the use of resistance assays were exemplary, as was Brigitte Autran’s survey of immune interventions in HIV.

For all of this admirably solid distillation of current thinking, though, there was very little which emerged at the European conference which was particularly new or groundbreaking. This, I think, is a feature of many conferences now, and given that there are so many in the year, might give our organisations pause when we consider the use of sending delegates to the many conferences on offer. Breakthrough news of the calibre of the protease moment hardly happens frequently, and while “more bricks in the wall” is certainly useful and helpful, it is hardly terribly romantic. When ‘breakthroughs’ do occur, it’s just as often (as with Kees Brinkman’s theory of mitochondrial toxicity, presented at the First Lipodystrophy Workshop) that we are unsure for some time of their significance or import.

For this reason, I’d like to first comment on some broad background issues of culture and epidemiology in Europe which I think may add to our accumulated understanding.

**HIV in Europe**

Epidemiologically, Europe appears to have at least three discernible epidemics: that of the West, Central Europe, and of course, Eastern Europe, which rapidly threatens to become the new Central Africa, and is in every way as alarming.

**Western Europe**

One of the truly eye-opening things for me was the high rate of hepatitis C co-infection across Western Europe, and an epidemiological update from Peter Ghys of UNAIDS Geneva underscored also the extent to which injecting drug use has been a primary force driving that epidemic (with the UK, with its primarily MSM epidemic, being an exception). Injecting drug use has been the primary mode of transmission in AIDS cases across all of Europe, with increasingly heterosexual and MSM patterns emerging. The UK also is reporting a rise in incidence among pregnant women – possibly reflecting the high proportion of women from African countries living in the UK – especially in inner London.

Collectively, Western Europe reports a cumulative total of 540,000 HIV infections, with about 30,000 new infections reported per annum, from a population of 396 million. Interestingly – which I did not know – a number of European countries including Spain, Italy, Portugal and France, do not report or collect their HIV figures at a national level.
Central Europe
It is reported that Central Europe, with its population of 88 million, has a much smaller epidemic than Western Europe, primarily driven by IDU and MSM.

Eastern Europe
I have rarely seen an epidemiological infection rate chart where, at a single point, the graph literally turns upward at a right angle, but that is the rate at which HIV infections are taking off in the former Soviet Union and Eastern Bloc. Some horrific figures:

- In St Petersburg, in 2000, it was estimated that 20 percent of IDU were HIV positive
- In Kaliningrad, in the Russian Republic, 65 percent of that city’s sex workers who also injected drugs were HIV positive.

It has long been talked about that Eastern Europe could be the next site of a genuine AIDS apocalypse, with figures possibly set to rival Africa. And the story appears bleak indeed. However, it is important to recognise the complicated convergence of cultural and economic factors feeding into this situation, including:

- Massive increase in injecting, especially among young people, and availability of drugs combined with a virtual lack of effective treatment or care
- Increased rates of sex work due to economic and cultural circumstances
- Epidemics of sexually transmissible infections
- Cultural shifts, including a shift in the sexual culture
- Corruption, chaos, and the reign of the black market
- Geographical proximity to parts of Central Asia and into the Middle East.

The HIV positive culture in Europe
A Finnish representative of the European AIDS Treatment Group, Jorma Kosinken, was the chosen HIV positive delegate to address the opening plenary.

Kosinken offered a clearly analytical framework for discussing the positive experience, and identified some important issues about clinical research, in which he rightly excoriated elements of the research community for designing “trials which do not make sense.” Such trials could be characterised by poor questions and irrelevant outcomes, largely because they completely fail to reflect the real circumstances of positive peoples lives, he said.

“Often, trials filter out the elements that reflect the actual circumstances in which drugs will be taken. This is fantasy. We need real life to be put into trial design. We are condemned to be lifelong consumers of these products, and so feel we have every right in the world to expect pharmacovigilance.”
However, he went on to identify some problems which I feel mark out the European experience as different from that in Australia. He commented, for example, that it was his view that trial investigators should “never be the person’s treating physician”, on the basis that it could irrevocably damage the relationship of trust. (There goes half of the Australian research response, I was thinking). In general, I got the feeling that there exists in Europe a much more profound mistrust of ‘clinical science’ than might be the case here.

The European AIDS Treatment Group is a community-based lobbying and advocacy body, which operates across Europe, and incorporates positive activists and their supporters. They work with a range of groups and provide patient group and community representation and input at EU level, in parliaments, for pharmaceutical companies (to advise on clinical trials), steering groups of clinical studies, and local government, on the bodies of conference organizing committees etc.

Theory, practice ...

Resistance in clinical practice: Veronica Miller

Even over the last year, there have been massive advances in the application of resistance assays in clinical practice, and they are broadly accepted as a standard tool in clinical practice.

Guidelines for the use of resistance testing in Europe have been developed and administered by a pan-European group of doctors, the Euroguidelines Trust. They recommend resistance assays in a couple of contexts where the new ASHM proposed guidelines do not, but nonetheless the European experience will be helpful in the ongoing push for Medicare funded resistance tests in Australia.

The guidelines themselves are available at [http://www.euroguidelines.com](http://www.euroguidelines.com) and as such, probably need no further comment. However, Miller did make the following points about relating resistance assays to a clinical response.

There are a number of challenges to defining clinically relevant resistance:

- Large data sets are needed to understand this better.
- Individual drugs are also part of a combination and may behave differently (interactions, PK)
- There is a heterogeneity among pos people of prescribing history, pre-treatment history, and definitions of ‘response’
- Phenotypic testing is less reliably standardised, with question marks over technical cut off points (the lowest drug concentration which would still be pharmacologically active), the range of apt levels in individuals, and the extent of an association between in vitro PT resistance and clinical outcome is very dependent on the drug
The various algorithms used to determine GT resistance ranged from 30-80 percent in effectiveness and reliability.

She called for better research to understand phenotypic cut off points, and better genotypic algorithms.

**Kaletra in the clinic**

Julio Montaner reported on Kaletra in practice. Of note:

- Rates of diarrhoea, at about 17 percent, are similar to NFV
- 10 percent rate of dyslipdemia, with 11 percent elevated trigs, and the rises in cholesterol appear to occur earlier, rather than later, in treatment
- All of this means a need for monitoring and dietary counseling.

The risks for lipid elevations included:

- Elevated baseline levels
- Prior PI use (for cholesterol)
- Age over 35 (for cholesterol)
- Diagnosis greater than a year
- For
- Prior PI/ current NNRTI (for trigs)

Anthony Japour also reported that in PI-naïve patients, there were no cases of phenotypic or genotypic resistance to Kaletra in one group studied.

Other PI boosting regimes are now being studied, including SQV/ RTV, and APV/ RTV (where RTV is a boost-only dose).

**Filling the gaps**

**New-Fill Study Results**

No news of polylactic acid at the lipo workshop, but an update from EACCT on an open-label French study, now 18 months out.

This was a group of people with severe lipoatrophy, and a history of therapy more than 3 years. Endpoints were: cutaneous thickness, tolerance of product, and evolution of patient wellbeing. There were 49 men and 1 woman on study, each of whom received four injections of PLA.

The results were impressive. Cutaneous thickness improved from an average baseline of 2.1 mm to 9mm after 5 injections (p. < 0.001). Some severe atrophies completely resolved after four injections.

Significantly, scores of general wellbeing (self-reported) significantly increased by the end of the injection cycle. No adverse events were
experienced, though nearly all patients had transient redness and swelling following injection, which resolved within a couple of days.

The researchers will perform a final evaluation and analysis at 24 months, and stressed the main issue would be longevity of the effect.

**Interleukin-2**

Jan Gertsoft updated people on the predictors for a good CD4 response to IL-2 on the ESPRIT study. ESPRIT is a multinational study, aiming to recruit about 4,000 patients, with 2,100 currently enrolled. These patients have a median CD4 count on entering study of 538.

IL-2 can produce varying severity of side effect and tolerability, and this was reflected in that 10 percent of patients needed a dose reduction after starting. To date, 63 percent of people have completed their third cycle on treatment.

By month 8, people had experienced a median CD4 increase of 352, however, the point of the study is to understand what effect these CD4 rises will have on clinical outcome.

The researchers have examined a number of things to determine what might predict a good CD4 response.

- A lower CD4 nadir is associated with a decreased response
- Older patients had generally less response
- For every increase in CD4 nadir of 100 cells, there was a 50 cell rise in response following treatment
- There is no statistical relationship between CD4 response and baseline viral load

So:

- Nadir CD4 appears the only significant predictor of a good CD4 response
- Age, gender and body weight could be of borderline significance
- There may be a dose-related effect

However, even in people who had had a CD4 nadir of less than 100 cells, significant responses were observed.

**Mitochondrial depletion with NRTI treatment**

Simon Mallal of Perth, probably one of the best-respected experts on the subject of lipodystrophy and the mitochondrial effects of treatment, reported on an exploration of the causes of mitochondrial DNA toxicity and depletion. They did this by quantifying MtDNA in fat tissues.

This was a non-randomised study, comparing people taking AZT, people taking 3TC, HIV negative and positive ART-naive controls. They found that
d4T was strongly associated with mitochondrial DNA depletion, with reductions of up to 90 percent in the d4T group.

The study concluded:
- d4T depletes mitochondria to a greater extent than AZT;
- both groups differed from controls, with the average depletion in anyone receiving nucleoside therapy at 79 percent;
- they called for longitudinal studies to assess the relationships between mitochondrial DNA loss, fat wasting, and cellular toxicity
- the effect appears to be rapid, not cumulative.

**New and promising treatments**

**Old formulations of new drugs**
There were several studies looking at either new formulations of old drugs (eg. d4T extended release formula, boosting for PIs), or new drugs in practice (eg. tenofovir).

Briefly...

**d4T extended release**
- This is d4T reformulated to allow once-daily dosing
- It appears to be well-tolerated in clinical study, with a similar adverse event profile
- No data is yet available on mitochondrial DNA, but this is being looked at
- This may prove a helpful simplified formulation

**Amprenavir pro-drug**
An amprenavir pro-drug has been developed, which is likely to be used co-dosed with RTV, to improve bioavailability and reduce side effects. It is currently in Phase III study. This will evaluate once-daily dosing using RTV boosting, comparisons with nelfinavir and lopinavir, and lipodystrophy/metabolic parameters.

**Tenofovir**
Several presentations on tenofovir, now licensed in the USA and Europe, confirmed it is well-tolerated, has a favourable resistance profile, and is likely to be a useful addition for both naïve and experienced patients.

**Atazanavir**
A Phase II-III study of the new BMS PI, atazanavir, suggests it is well-tolerated and potent. There was some suggestion that this drug may not affect cholesterol and trigs in the same way as other PIs, though there is as yet no longer-term clinical experience, and this may be taken with a grain of salt.
Other new drugs
Robert Murphy gave a fascinating overview of drugs in progress. Here are some of the new developments.

Nucleosides
- FTC (emtricitabine): this is a compound very like 3TC which is in Phase II studies, and may have some advantages over its sister-drug. May also have a role in hepatitis B?
- DAPD (Triangle Pharmaceuticals): Phase II — appears highly active and with a novel resistance profile. BD dosed.

PIs: Tipranavir
- This drug fell briefly off the rails, but Boehringer is now putting it into Phase II-III studies, and have confirmed Australia is likely to have places.
- There are some dosing issues (the number of pills is high), and it appears to also cause diarrhoea.
- This is a non-peptidic PI, a more advanced formulation which will hopefully improve tolerability.
- Its resistance profile appears generally pretty good.

Tibotec-Virco: high-tech, hard core
Of particular interest are some drugs in very early development with a consortium of Tibotec and Virco, the company which provides the means for virtual phenotyping.

They are working on several drugs, two non-nucleosides (TMC120, TMC125), and a candidate PI (TMC114), with the question of resistance built in at the level of drug design. The idea is, they are trying to make their candidate drugs as structurally ‘resistance-proof’ as possible at the outset, specifically so they have clinical utility in patients failing anti-HIV compounds with the same target. This is really cutting-edge chemistry, and as such, the mechanisms were to say the least, esoteric and the explanation somewhat vague to me. However, in vitro work appears to suggest they have increased the genetic barrier for the infamous 181 mutation, which confers cross-resistance between efavirenz and nevirapine, and makes these drugs so problematic in clinical practice.

Global realities
I want to return, in closing, to the international scene, and an impressive closing plenary from Joep Lange of the Netherlands. Lange is surely one of the clearest thinkers in international work, rejecting the arguments that it is all too hard to get treatments to “the world”, and we must wait for a vaccine.
It is Lange's view that it is the responsibility of resource-rich nations — Western Europe, North America, Australia etc — to ensure that we protect the pricing of drugs in countries where we can afford them, so that they may be reduced for other countries. Once drug companies know their lucrative markets are going to be protected, they may be prepared to budge on the question of price in other parts of the world, he argues. For those who are philosophically opposed to the idea of a two-tiered pricing system, this may sound abhorrent. However, short of a global revolution abolishing capitalism, I for one, feel all options need to be seriously considered, and that, cognisant of the obvious inequities and limitations of such a two-tiered system, nonetheless, it is I think a very practical, perhaps even possible, way forward. Not "the answer", but perhaps better than none.