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More than 2,600 delegates from 79 countries had come to Serbia’s capital Belgrade to participate in the 13th European Aids Conference. Page 5

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28 Topical Conferences in 2012
In the recently released “World AIDS day report 2011”, UNAIDS reported that both new estimated HIV infections and AIDS-related deaths have decreased with approximately 20% since the peak of the AIDS epidemic, see figure. The HIV incidence has fallen in 33 countries, 22 of them in sub-Saharan Africa, the region most affected by the HIV epidemic.

There are large differences in various countries and regions and an exception to the positive trend could be found in Eastern Europe and Central Asia where the number of people living with HIV have increased with 250% from 2001 to 2010. Unlike most other regions, AIDS-related deaths continue to rise in this region, reflecting that only a minority of eligible HIV-infected individuals receive antiretroviral treatment. This is in contrast to the situation in several African countries, and for example Botswana, Namibia and Rwanda have now universal access to treatment, defined as 80%, or greater coverage. In low- and middle-income countries 47% of the 14.2 million eligible people living with HIV were on antiretroviral therapy at the end of 2010, compared to 39% at the end of 2009. There is of course still a long way to go until we reach global universal access, but for me this is impressive and treatment coverage is continuing to increase. In low- and middle-income countries globally, treatment has averted 2.5 million AIDS deaths since 1995, the majority in the past few years, an amazing success. You can find the full report at www.unaids.org.

In this third issue of HIV and Virology News, we report from the recently completed 13th European AIDS Conference in Belgrade, Serbia. You will also find an interview with Peter Reiss, president of European AIDS Clinical Society (EACS), the organizers of this conference. What I don’t think everybody knows is that EACS offers a number of high-quality educational programs and information about those could be found on page 8. Regular information from EACS will be provided in forthcoming issues of the magazine. EACS has also just published new treatment guidelines and José Arribas comments on those in this issue. One new aspect in the new guidelines is that the integrase inhibitor raltegravir now is recommended as part of a first line regimen to antiretroviral naive patients starting treatment, which is in consistency with US DHHS and IAS guidelines.

While raltegravir is effective and well-tolerated, it has a low genetic barrier and high-level cross-resistance with elvitegravir, the second integrase inhibitor in development. Christine Katlama reviews current data on dolutegravir, a new integrase inhibitor in development by GSK/ViiV. Data on dolutegravir looks very good so far with effect also on virus with integrase inhibitor resistance, at least at a low-medium level.

Best wishes
MAGNUS GİSSLİN
Editor
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A step towards education and awareness

Peter Reiss is Professor of Medicine and is working at the Division of Infectious Diseases and the Department of Global Health at the Academic Medical Centre in Amsterdam. Since 2008 he is also President of the European AIDS Clinical Society – EACS.

The European Aids Conference has always been a very clinically orientated conference, most delegates are working in health care, Prof Reiss says to HIV & Virology News.

– Of course there are also basic scientists, but their symposia have a clinically orientated content, he continues.

Problems with testing

We ask Prof Reiss how the HIV epidemic at present is developing in Europe.

– There is not a single answer to that question. The epidemic looks different in different parts of Europe, he answers.

In Western European countries, there are a lot of late presenters – i.e. diagnosed and presenting to care late.

– It puts them in a worse situation. You can conclude there are many individuals in society that are unaware of being infected. So we have to work on testing.

In South-Eastern Europe to which Serbia belongs, the epidemic is particularly driven by men who have sex with men, and fear of stigma is an important barrier to get tested.

– If you live in an environment where sexual orientation – like men who have sex with men – is connected with stigma, it also leads to avoiding testing.

Educational challenge

What can EACS do for this problem?

– EACS is not a huge organisation and remains limited in what it can accomplish. One of the most important things we do is organising this Conference. By bringing it to a different city in Europe every two years, it can help draw attention to particular local and regional problems.

The care for people living with HIV faces a number of challenges. The first of these is having treatment available everywhere.

– Where care is available, we face a lifelong treatment – people need to be treated for life. We only partially know what that really means over the longterm.

People get older, and they get other diseases.

– How does the treatment of those diseases influence the treatment for HIV? What about drug-drug interactions? Certain drugs for controlling blood lipids levels for example can’t be taken with some of the medications for HIV. This is an educational issue, and one of the challenges that we face.

Tough goal

One of the key scientific challenges ahead is to look for a cure. According to Prof Reiss an important reason for the recent initiative to try and mobilise a large coordinated scientific effort to search for a cure is the need for life-long treatment patients and health-care systems face.

– When thinking of the number of patients in need of treatment globally it is hard to imagine that this will be sustainable. Therefore we have to find out much more about the virus – importantly what mechanisms exactly are involved to make it hide within a cell?

– If we could solve that, it would be progress, Prof Reiss says.

But he admits that the goal of finding a cure is a tough one.

– I cannot give a prediction of when this could happen.

Younger population with the problems of the elderly

The growing population of elderly HIV-patients poses some problems of its own.

– We don’t yet know if it’s true that they are likely to develop other diseases associated with older age – like cardiovascular diseases, osteoporosis etc – at an earlier stage than people without HIV. If it is true, than we have a new situation: A younger population with the problems of the elderly. In that case – how do you manage that?

Prof Reiss exemplifies with the following: What will happen when these patients need a nursing home?

– The staff there doesn’t have the competence and awareness to deal with these patients.

This represents yet another need to advocate for further education and awareness.

– This Conference is a small step on the way of doing just that, Prof Reiss finishes.
In the Opening Ceremony, EACS’ President Peter Reiss, greeted everyone welcome.
– One of the important goals of the EACS in organising this biannual European conference is to promote an interest in HIV clinical research amongst young researchers and clinicians from across Europe at an early stage in their career, he said.

Nathan Clumeck, EACS’ Treasurer, reminded the audience that prevention – not only treatment – also is one of the main issues for the conference.

Successes and failures
One of the Keynote lectures given at the Opening Ceremony was AIDS in Europe – epidemiology and prediction, presented by Roy Anderson, UK.

Dr Anderson began his talk by looking at some successes and failures to this date.
– Successes include diagnostics – both immunological and virological, the biological details of pathogenesis – although there are still surprises evolving in this field. But the big success is the effective anti-retroviral combination therapy. And we’ve learned – painfully – over the last ten years the importance of patient’s adherence to the evolution of drug resistance, Dr Anderson said.

He then turned to the failures. The most important of these was the failure to develop a vaccine, and the failure to get public health messages across to all at risk.
– And also the failure – particularly in some regions of the world – to get treatment to all in need for it. As a consequence of that we still have a growing epidemic in some regions of the world.

A new task ahead of us
Dr Anderson pointed out that Eastern Europe and Central Asia are the only regions where HIV prevalence clearly continues to increase, with an estimated 130,000 new infections in 2009 alone.

In the same year, 1.4 million adults were already living with HIV in Eastern Europe and Central Asia. Eastern Europe is also the only region where the annual number of HIV-related deaths continues to rise – increasing fourfold from 18,000 in 2001 to 76,000 in 2009.

– East and central Europe have a problem, but I don’t believe that we in Western Europe can pat ourselves on the back and say that our problems are solved. Many of our infected are unaware of their infection, he continued.

He said that in all of Europe we therefore need to reassert a very strong educational campaign, not just for clinicians and physicians – but also to the public.
– We need to recruit the media for publicity and informational campaigns about the risk of HIV to the young again! There are many severe consequences of being unaware that you’re infected.

The problem is likely to grow in the short to medium term. The coming decades will see a linear rise in the proportion of the population requiring healthcare and treatment. ☼
HIV surveillance and AIDS case reporting is good in a number of countries – and it’s exceedingly poor in others.

– Back calculation and model projections for the next 10 years may help to convince policy makers in the East of the seriousness of the problem. And I think a serious attempt to do this is required.

He ended by stating that in his own country – and in many other Western countries, including the US – infection continues, and we therefore have a new task ahead of us.

**Stigma causes human rights violation**
The relation between HIV/AIDS and human rights was recognized in the early beginning of the HIV epidemic. The epidemic causes human rights violation – and is also driven by human rights violations. The promotion and protection of human rights must therefore be at the centre of all aspects of an effective response to the epidemic.

These were facts established by Nenad Petkovic, Serbia, at the beginning of his talk on HIV and Human Rights, another Keynote Lecture at the Opening Ceremony.

– One of the major causes of human rights violation in the field of HIV/AIDS is stigma. Homophobia fuels the HIV epidemic, by keeping people hidden and away from health and HIV services. Men who have sex with men (MSM) are confronted with widespread violence and discrimination, Dr Petkovic continued.

He illustrated this with some violent pictures taken at the attempt to arrange a gay pride festival in Belgrade in 2009. He also added that we have seen similar pictures from other countries.

People with HIV are released from their jobs; children are isolated and are not allowed to go to school and some people do not receive needed care because of the fear of infection.

**Responsibility of governments**
If we want to reduce these violations of man’s dignity, we need to have a human rights based approach, Dr Petkovic stated.

– It focuses on empowering people – especially the most vulnerable and marginalized – with knowledge and the resources to understand and assert their rights. It also simultaneously focuses on capacity building of duty-holders – i.e. the government – to be able to protect human rights!

He described the background and sources of these rights, and also the treaties, decisions and obligations that are associated with them in more detail.

So where are we today in this matter? Dr Petkovic illustrated the present situation with a glass that is half-empty, or – depending on how you choose to look at it – half-full.

He finished his talk with what is needed in Serbia in order to improve these rights in the HIV/AIDS field.

– First it is the treatment issues. We have adopted the EACS guidelines, but we don’t have the conditions to meet them. Most of the new drugs are not available, nor is basic diagnostic tests in most of the health services. So there is a clear responsibility for the government to provide, and secure, the conditions for people living with HIV –and to those who treat them, he ended his talk.

**Questions on PrEP**

In the first Plenary Lecture, Kenneth Mayer, USA, talked about Pre-Exposure Prophylaxis (PrEP).

– When we think of HIV prevention, as infectious disease specialists we tend to think in three boxes: To decrease infectiousness, to decrease host susceptibility and to alter behaviour. But with HIV we have to take a more holistic approach that focuses on promoting sexual health, Dr Mayer stated.

There are many questions linked to treating for prevention. Is it best supplied before, or after, and is it best supplied orally or topically?

Many couples – even if they are discordant – may not disclose their HIV status to each other. And some HIV-infected, or at risk people, may not discuss their status with new casual partners because of stigma.

– We also have to pay attention to the fact that in one study, a quarter of the new infections were not linked to the partner. When the uninfected partner got infected, it was from another partner.

**Adherence counselling**
Dr Mayer reminded the audience that we have to keep in mind that there are several reasons to why people engage in
EACS TREATMENT GUIDELINES
The European Guidelines for treatment of HIV-infected adults in Europe are produced by EACS and are regularly updated by our teams of specialists. The importance and success of the EACS guidelines are demonstrated by their widespread dissemination. Over 6,000 copies of the updated version (Version 6) have been distributed at the 13th European AIDS Conference in Belgrade, 12-15 October 2011. They are available on the EACS website in 13 different languages.

EACS EDUCATIONAL PROGRAMMES
The European AIDS Clinical Society offers a number of educational programmes:

❖ ECReCO (European Clinical Research Course)
A 3-days course to train physicians in the basics of clinical research and to write clinical research programmes, protocols and abstracts. The first course was held in Zagreb from June 15-17, 2011, it was attended by 33 medical doctors from 15 different countries and moderated by a team of statisticians and clinicians.

❖ Medical Exchange Programme & One-Year Fellowship Programme
Enable doctors from Europe and developing countries to take part in a four-month or one-year exchange programme in one of 14 currently participating clinical centres in 8 European countries.

❖ Advanced HIV Course
An intensive 3-day course in Antiretroviral Therapy and Comprehensive Care for people living with HIV/AIDS focused on the clinical management of HIV and aimed at experienced practitioners. The course is attended by an average of 60 candidates from 30 different countries every year.

Webcasts of the 13th European AIDS Conference available at
www.europeanaidsclinicalsociety.org

The 13th European AIDS Conference is over!
Save the date for the 14th European AIDS Conference

The 14th European AIDS Conference
October 16–19, 2013
Brussels, Belgium
risk. These include substance use, mental health treatment, housing and food security.

– These are major drivers for risk taking behaviour.

He concluded by establishing that it’s all down to combination antiretroviral prevention. This includes interventions to increase testing.

If the test is positive, enrol the patient to care and treatment. If negative, make a risk assessment. Some of these people will benefit from an oral or topical PrEP.

– Those individuals will need adherence counselling. For the positive, also address concomitant concerns like depression, substance use and adherence. If we can do all these things together, we can have an impact with combination antiretroviral prevention, Dr Mayer summarised his talk.

Choice of PrEP by gender?

At a press conference after his talk, Dr Mayer together with Nikos Dedes, Greece, expanded on the subject.

– We know that PrEP works, but there are still many questions. They represent a challenging set of issues, but it’s good to have the possibility of PrEP.

They both underlined that social sciences are very important for this work.

– Do people want to take a tablet, or use a gel before they go to a club etc, Dr Mayer exemplified.

– We have limited resources, and therefore also a responsibility to utilise these in the best possible way, Dr Dedes said.

Dr Mayer pointed out that the worst-case scenario would be an individual that takes PrEP only now and then.

– Therefore this individual would – wrongly – be convinced that he or she couldn’t get HIV and therefore not testing for it. This person then gets the virus and spreads it. But so far we have not seen this behaviour in trials.

Oral PrEP could be best for MSM, because it goes to the rectum.

– But not so much to the vagina. Therefore it is possible that a gel could be a better choice for women, they said.

Even so, they underlined that they had no data yet to support that orally administered chemoprevention is not effective for women.

Challenges for concurrent HIV and TB therapy

Anton Pozniak, UK, talked on Advances in managing TB in those with HIV. He began this by showing WHO’s recommendations on the matter:

Adults and adolescents who are living with HIV and have positive, tuberculosis skin test status and are unlikely to have active TB should receive isoniazid preventive therapy (IPT) for at least six months – if in settings with higher TB transmission for 36 months.

– That’s a tall order if you consider India or Africa, he commented.

In the same recommendation it is also stated that IPT should be given to individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and to pregnant women.

There are many challenges to concurrent HIV and TB therapy.

– These include pill burden, overlapping drug toxicities, pharmacokinetic drug – drug interactions and an increased risk of immune restoration inflammatory syndrome (IRIS). All these things go through concerned people’s mind, Dr Pozniak said.

When should you start ART?

The WHO recommendations are to start ART in all HIV-infected individuals with active TB, irrespective of the CD4 cell count. Start TB treatment first, followed by ART as soon as possible afterwards – within the first eight weeks.

But Dr Pozniak also presented a study on CD4 threshold that indicated that you should only start ART when the HIV/TB patient has a CD4 cell count that is less than 50.

The guidelines also have a strong recommendation to use efavirenz as the preferred Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) in patients starting ART while on TB treatment.

– But the jury is out on what dose of efavirenz. Pharmacokinetic data favours 800 mg if patient is over 60 kg. But most patients with TB weigh less than 60 kg – so clinical data has seen no difference.

Bernard Hirschel awarded

In between these two lectures, two awards were presented.

They were the EACS Award for Excellence in HIV Medicine in 2011. The first was given to Professor Bernard Hirschel, Switzerland. He was presented by Manuel Battegay, EACS’ Vice-president.

– In 1980 Prof Hirschel returned to Geneva after a few years working with studies in USA. In Geneva he later became Chief of the HIV/AIDS Division. Confronted with HIV/AIDS already in 1982, he is a real pioneer in the field. Since then he has fought the disease and its social consequences, included stigma encountered by patients. He has published more than 400 papers, many of them being landmark studies.

– Not only is he an excellent clinician and clinical researcher, he also contributed tremendously to the success of the Swiss HIV cohort study. For the 12th World Aids Conference held in Geneva 1988, Bernard held the Chair, Dr Battegay said and welcomed Dr Hirschel up to accept the award.

Brian Gazzard awarded

Anton Pozniak then introduced the second person to receive the award.
– It goes to Professor Brian Gazzard, UK. There are very few of us in the HIV world that don’t know about Brian, and we have enjoyed his presentations over the years, he said.

After starting out as a Consultant in Gastroenterology, in the early eighties when confronted with HIV patients coming in to his GI-unit, Prof Gazzard decided to looking after and managing them.

– His research interest went all the way through the eighties; he was a pioneer in describing many of the clinical manifestations of HIV, produced many landmark papers and had a special interest in immunology. He also founded the British HIV association and was President for that for many years.

Earlier in 2011 Dr Gazzard was given the award Commander of the British Empire by the Queen, for his work on HIV and AIDS.

– It’s one of the highest awards you can get as a civilian in Britain! So it’s fantastic that he today will receive another award for all the work he has done – not only in Europe, but also worldwide for HIV and AIDS, Dr Pozniak said.

– It’s the only advantage of getting old – you will receive awards. Remember that, all of you young researchers, Dr Gazzard said when accepting it.

– The most important award I’ve got now enables me to go down and command on the Falkland Islands – which is all that is left of the British Empire, he said.

### Search for a cure

The search for a cure for HIV infection is back on the researchers’ agenda.

This became evident in Belgrade, when an EACS – International AIDS Society (IAS) Joint Session on the topic was held. Nikos Dedes pointed out to the audience that significant morbidity persists on HAART. These include, among others, cardiovascular disease, metabolic disorders and neurocognitive disorders. Long-term HAART for everyone is a major challenge.

– For every 2 people starting HAART, there are 5 new infections. There is an urgent need to increase coverage in low-and middle-income countries from current levels of 40% – and as little as only 21% in Eastern Europe.

There are also the costs of treatment to consider.

– AIDS treatment alone will account for half the US foreign aid budget by 2016.

### Latently infected T-cells

Therefore a new search for a cure started in 2008.

Its objectives include to accelerate research towards a potential HIV cure, to re-engage the broader HIV community in basic science, strategize to accelerate the translation of findings into clinical practice and to provide a networking opportunity for HIV scientists to share ideas and debate with peers, Dr Dedes said.

Sharon Lewin, Australia, talked on barriers for a cure. Among these are latently infected T-cells, residual viral replication and anatomical reservoirs.

– The last year we’ve learned that many cells can be latently infected, she said. These cells can form latent reservoirs in the body.

– Anatomical reservoirs can form in the urinary tract, in CNS and in the GI-tract – the latter is a significant viral reservoir for patients on cART.

### Several clinical and implementation challenges

What are the potential strategies to achieve a cure, Dr Lewin continued by asking.

She first defined the difference between cure and remission. A patient in remission has a long term of health in absence of HAART. In a cure, we should see the elimination of all HIV-infected cells.

– Several studies have all shown that eliminating residual viral replication treatment doesn’t work. The cell-to-cell infection is not blocked by cART.
A proposed strategy is to eliminate latently infected T-cells. This is one of the hardest challenges, according to Dr Lewin.

- We need to wake up the latent virus – contrary to what we normally do – so it can be eradicated.

Several drugs that activate latently infected cells are in development. Of these histone deacetylase inhibitors Vorinostat and Romidepsin are licensed.

 Combination therapy enhances potency of activation, so Dr Lewin thought it is likely that we will have to adopt the therapy for cancer, in which combo therapy is used. We also need better in vitro and animal models in order to evaluate new strategies – both alone and in combination.

- So the clinical and implementation challenges are several: Universal access to cART must remain a top priority. People living with HIV/AIDS are doing well, so any intervention must have limited – or no – toxicity. The clinical endpoints for successful eradication are unclear – when will a treatment interruption be OK? There are also multiple unknowns with gene therapy, she summarized.

**Measuring latently infected cells is a challenge**

At the time for testing new approaches to treat HIV infection focusing on HIV latency, we need to discuss the means that could be used to evaluate impact of drugs aiming at reducing reservoirs, said Christine Rouzioux, France.

- The reservoir is a very complex mix of different cells, she added.

Dr Rouzioux continued her talk with markers – both for exploring basic science and pathophysiological aspects of HIV latency, and markers to follow HIV reservoirs in infected patients within clinical trials.

- Integrated HIV-DNA is a good marker for latency, and has the advantage that one can use frozen samples. Total HIV-DNA (measures un-integrated, integrated, linear DNA and 2LTR circles in blood and tissues) is predictive of disease progression, independently of HIV-RNA and CD4+ T-cell count. It gives important information to the patient!

There are several different strategies to tackle HIV reservoirs: Increase the drug distribution in tissues, increase specific immune responses, very early treatment with potent HAART, HAART intensification, immunomodulators – or to deregulate the mechanisms of latency.

- The lack of standardized approaches to measure infrequent latently infected cells is currently a major challenge in implementing multi-site clinical trials. Moreover, we need to define appropriate end-points for clinical trials, aimed at reducing and/or eradicating HIV latently infected cells – not only in blood, but also in tissues, compartments and sanctuaries, Dr Rouzioux concluded.

**One drug will not cure HIV**

- The word cure is no longer taboo, Alan Lefeuillade, France, explained.

At present there are eleven ongoing clinical trials on HIV cure, and at least two more are planned, he continued.

Dr Lefeuillade chairs the subgroup on clinical trials in IAS international working group on global scientific strategy for a cure for HIV.

The issue of ART potency is not closed. There are new drugs, in better combinations, regarding the reservoir. Also there are new delivery systems, like nanotechnologies, Dr Lefeuillade pointed out.

- The main question is when is the ideal moment to test total eradication? When is the window of opportunity?

These questions remain to be answered.

- But it has to be a step-by-step approach – one drug will not cure HIV.

After his talk there was a round table discussion with the speakers and some more experts. The panel had to answer many questions from the audience, and the debate was lively.

**A vicious circle**

A well-attended symposium, sponsored by Gilead, addressed the problems of stigma and how to overcome them.

- Welcome to one of the most important symposiums of this conference, said Jane Anderson who was the Chair.

Dr Anderson called stigma “the third epidemic”. She presented a photo – and the name – of a woman that was murdered by her partner when he found out that she had HIV.

- The issues of stigma are difficult to grasp – there are so many: Spoiled identity, social inequality and exclusion, rejection – the blame of individuals and groups, and also the experience and expectation of judgement, Dr Anderson said.

The stigma feeds from all other stigmas in the world – like sex, gender, race and class. People with HIV are seen as marginalized groups – that in turn are seen as responsible for the HIV epidemic. It’s a vicious circle.

- Employers, schools, partners, housing agencies – and even health care workers are among those who discriminate. The critical issues are among others testing, disclosure adherence and access to treatment. Stigma is obstructing all of these issues, she said.

**Need for a physician that listens and supports**

Silvia Petretti, UK, told the audience about an incident that had taken place in Manchester a few weeks before the conference. Eggs had been thrown on a house there, and the word AIDS had been sprayed on the door.

- We cannot consider stigma just on its own! The Gay Pride Parade here in Belgrade was cancelled three weeks ago – due to the fact that the authorities here were not able to guarantee the security of...
the gay people participating! These are the stories I’m hearing in Europe – today, she said.

Dr Petretti continued explaining that people living with HIV want equality, involvement and human rights. In order to ensure this, she described a “partnership ring” needed to surround them.

This ring should – in order to address these issues – consist of research, peer support, networks of people living with HIV, stigma index/participatory research and a partnership with healthcare providers.

– And for the latter, there is a special need for a physician that listens and supports them, she summarized.

Train to overcome stigma
WHO cites fear of stigma and discrimination as key factors as to why people are reluctant to be tested, to disclose their HIV status or to take ART, said Jose Munoz-Moreno, Spain.

He spoke of the psychological impact of stigma in people living with HIV.

– Stigma is strongly related to mental health, and associated with depression, anxiety and other psychological disorders, he stated.

Training, employment and integration are among the things that can be done to overcome stigma.

– We can deal with this from a psychological viewpoint. We have to work with health-care staff when it comes to education, respect and acceptance. But I think one of the best things we can do is training the patient to overcome stigma, Dr Munoz-Moreno said.

Better adherence with one pill per day
The word stigma is originally Greek. In its origins it referred to a kind of tattoo mark that was cut, or burned, into the skin of criminals, slaves or traitors – in order to visibly identify them as blemished or morally polluted persons.

This lesson in etymology was given by José Arribas, Spain. He spoke on Evolution of HIV medicine in the stigma context.

Dr Arribas presented a list of 16 reasons why patients do not take their drugs. It came from a structured questionnaire on reasons given for missing antiretroviral doses.

One of the reasons was that they didn’t want other to notice.

For six of the reasons given, including the one just mentioned, a possible intervention would be to simplify the dosing schedule. Dr Arribas presented a study that showed that patients adhere better with a one-pill regimen, compared to a two-pill regimen. Another study showed a consistently lower hospitalization risk for those on single tablet per day regimen, versus other regimens.

– With current therapies, control of HIV replication is possible in the majority of patients. In this context quality of life issues become ponderant. Issues of simplicity, convenience and low toxicity – in order to make our HIV-patients life easier, he said.

Stigma index on the web
– I think most of you sitting in this room have experienced stigma from colleagues, just for the fact that you are working with HIV patients, said Nikos Dedes, Greece.

He presented The People Living With HIV Stigma Index, a tool that will measure and detect changing trends in relation to stigma and discrimination experienced by people living with HIV. It can be accessed online on www.stigmaindex.org.

It aims to address stigma relating to HIV while also advocating on the key barriers and issues perpetuating stigma – a key obstacle to HIV treatment, prevention, care and support.

– We decided to develop an instrument to measure stigma, he explained.

Dr Dedes presented a list on things needed to be done. It included working with advocacy groups, and to translate the impact of the science of HIV to the media, the general public and the community.

– Legal protection can be a very efficient way to go. Awareness and education – start in primary and secondary schools. In medical schools, HIV lessons are still not mandatory today! Also remember the issue of visibility – today it is critical that we normalise HIV-infection, he said.

After the talks, a panel discussion was held with many comments and questions from the audience.

CNS HIV infection
There is a renewed interest of research in CNS complications of HIV infection, Richard Price, USA, said. He talked on epidemiology and pathogenesis of HAND (HIV-associated neurocognitive disorders).

– The reason for this is that it appears to be continued disease and infection in treated patients. There is the pharmacological issue of access of ART to CNS, which may be limited by barriers to the passage of drugs. There is also the poten-
tial of an additive or synergistic effect that may accelerate the brain ageing process, said Dr Price.

CNS HIV infection is a nearly universal aspect of systemic infection: It occurs early during primarily infection, it’s linked over time to systemic viremia because there is an exchange of virus between the systemic and the CNS compartments.

– It continues through the course of untreated infection. If one looks in the spinal fluid on patients, one can detect virus very early in the infection – without treatment it continues to the terminals stages of infection.

In treated patients virus in the spinal fluid is most often well suppressed. But there are also uncommon cases, where one can see CNS escape.

Tools for definition are needed

When we detect virus in the spinal fluid it doesn’t always mean there is a disease. Dr Price presented a report from Gothenburg reviewing 69 patients where 10% had low detectable CSF viral load.

– The clinical significance for these wasn’t certain. They did have elevated immune activation, but they were entirely asymptomatic. We need to follow up on these cases.

The good news is that severe disease has been largely eliminated in well treated populations. Dementia is unusual.

– What has emerged is that less severe disease has been noted both in people that have been treated and untreated. This is the focus of attention now, he continued.

These patients require treatment, whether they require special treatment, or a standard ART regimen is a controversial issue, according to Dr Price.

– One of the real problems we have is that we need tools to define what is active disease and what is a legacy from the past.

He finished with the following three suggestions for steps in approach to HIV-related neurological disease:

– Suspect clinically, diagnose biologically and treat virologically!

Mental health issues call for psychiatrists

Even long lasting aviremic patients can suffer from HAND.

– A patient complaining of cognitive disorders should be tested for the presence of HAND, said Gabriele Arendt, Germany.

The diagnostic approaches are neuropsychological testing, neuro-imaging and CFS analysis. The differential diagnoses include cerebral opportunistic infections, vascular dementia, Alzheimers dementia, endocrinological disease and metabolic disorder.

– cART remains the best and most needed treatment for HAND, but it may not always be sufficient, she continued.

In addition to cART, neuroprotective drugs are also needed, but so far trials have been disappointing.

– Mental health issues are frequent in HIV+ patients, and they should be treated by specially trained psychiatrists, Dr Arendt stated.

Treating HAND is important

Eventually, virtually all ARV regimens that work systematically will also work in CNS. And there are more potent drugs available than in the past.

This was pointed out by Paola Cinque, Italy.

– But these drugs may not achieve therapeutic level and efficacy in infected CNS cells, and drug resistance HIV strains may selectively develop within CNS, she added.

Recognizing and treating HAND is an important step forwards for optimal management of HIV infection. Challenges ahead include understanding the biology of HAND. Also to learn more on the efficacy of old and new ARV drugs and treatment approaches on CNS HIV infection.

– There is still a lot of work to be done, Dr Cinque said.

A constant conflict

In the panel discussion with the audience afterwards, there were those that argued against the definition of CNS active drugs in the new EACS Guidelines, presented in Belgrade.

– The matter is too complex, and we do not have much data available. Therefore these recommendations have not much clinical significance, one debater in the audience stated.

The question of a relevant clinical marker was also raised.

– We don’t have one now, but we are working in that direction, was the answer from the panel.

Gabriele Arendt summarized the whole issue with the following statement:

– There is a constant conflict between preventing brain damage and preventing toxicity, she said.
The past decade has seen a dramatic drop in the price of certain medications to treat HIV in developing countries, leading to wider access to care and the saving of countless lives.

Around 5.25 million people in low- and middle-income countries now receive antiretrovirals (http://www.who.int/hiv/pub/2010progressreport/report/en/index.html) something that would not have been possible without cheaper antiretrovirals. Political will and leadership, most notably from the Clinton Foundation and more recently the Bill and Melinda Gates Foundation, activist pressure, competition between generic manufacturers, and direct negotiation with pharmaceutical companies have all contributed to these price declines. Most specifically, a number of large pharmaceutical companies whose financial commitment and scientific innovation led to developed of new antiretrovirals chose not to defend their patents in some developing countries or sell their medications at cost price in others.

Rising numbers of people receiving antiretroviral treatment in Europe coupled with an urgent need for governments experiencing debt crises to save money has created a new focus on HIV drug budgets in national health services. At a cost of approximately 8,000–15,000 Euros per person per year [1], and close to 1 million people in central and western Europe living with HIV (http://www.unaids.org/documents/20101123_GlobalReport_Chp2_em.pdf) the cost of antiretroviral drugs both annually and cumulatively over an individual’s lifetime is both substantial and potentially unsustainable. Prices of generic regimens in countries using the Clinton Health Access Initiative (CHAI) are more than a logarithm lower. For example co-formulated tenofovir DF, 3TC and efavirenz is $169 per annum and a co-packaged tenofovir DF, 3TC ATV/r sells at $395 per annum (http://clintonhealthaccess.org/files/chai_arv_ceiling-PriceList_201105_english.pdf).

A generic drug is an identical or bioequivalent copy of a branded, proprietary drug. Generics are the same as their branded drugs in terms of dosage, efficacy, safety, route of administration, manufacturing standards, performance characteristics and use. Their manufacturers, however, for the most part do not invest in the research that leads to drug discovery and new therapies. Patent protection, typically lasting 20 years from when a drug is identified (so typically 10 or so years from approval after the drug development process) enables research companies to recoup expenses and earn returns that they plough back into inventing (hopefully) better drugs.

While AZT, d4T and ddI had substantially declined in use by the time their
The big losers in this process are those patients who are still in urgent need of new agents, new mechanisms of action and activity against resistant virus.

patents expired, over the next 2 years we will see the expiry of patents for 3TC and efavirenz, agents that are at the core of many antiretroviral regimens and, at least for efavirenz still growing brands. While tenofovir DF’s patent has many years to run (US 2017, EU 2018) making generic tenofovir DF unavailable for some time, the patent expiry for abacavir (CHAI price $210 per annum), the main alternative, is also imminent (although co-formulated abacavir-3TC remains on patent for several more years). Thus, the potential for wholly generic regimens at vastly lower costs will soon exist and may become the preferred regimen of payers for HIV care. Replacing a drug with a less expensive generic equivalent is a generally accepted practice in all areas of medicine when patent rights runs out.

However, as many antiretrovirals agents are predominately used in fixed dose formulations (FDC) and many more co-formulations including several further single tablet regimens are planned, patients and providers will be faced with the potential dilemma of increasing pill burden and regimen complexity, factors which are known to unfavourably impact adherence, to achieve cost savings from generics.

If increased treatment failure ensues from such an approach any savings on initial therapies will likely be lost on more expensive second-line regimens as well as extra laboratory testing. Lower pill burdens and less frequent dosing is clearly preferred by patients, both at a hypothetical level [2] and in clinical studies. Trials where subjects have switched to co-formulations which reduce pill burden and dosing frequency consistently report patient related outcomes, such as increased regimen satisfaction and reduced regimen intrusiveness, that favour simplified dosing [3-5].

However, improved clinical or virological outcomes, the benchmarks used to assess cost utility by payers, have not been observed. Open-label studies comparing the efficacy of separate pill dosing to co-formulated dosing as initial therapy have not been performed but are clearly needed, and should incorporate pharmacoeconomic outcomes.

Furthermore, treatment switching that increases pill burden and dosing frequency has also been reported to lead to improved satisfaction with treatment [6] and recently a twice daily regimen reported intent-to-treat efficacy advantages over a once daily regimen, albeit that the drug administration in the study was blinded and all subjects dosed twice daily [7]. These data suggest patient preference counts little in predicting short to medium term treatment outcomes, especially if differences in tolerability exist.

Furthermore, it supports the payers view that co-formulations that seek to charge more than the individual components may not be worth paying for as they do not reliably add value. The manufacturers of co-formulations need to support independent research that tests the value in these preparations, whether they reduce dosing errors, accidental dual or monotherapy leading to more treatment failure and resistance [8] and ultimately better clinical outcomes.

The advent of generic therapy and lower costs is a clear disincentive for new drug development. With a typical lag time of 5 years from entry-in-to-man to drug approval for an HIV agent, as well as cost of $500 million in today’s money to bring a drug to market, research led companies are clearly taking a financial risk in hoping to develop a new chemical entity for HIV that will reach the market when the majority of NRTI, NNRTI and PI we use today will be generic. I believe this concern, that the companies will not get their money back, let alone a return on investment, is being reflected in the slower developmental pipelines and reduced research activity we now see. The big losers in this process are those patients who are still in urgent need of new agents, new mechanisms of action and activity against resistant virus.

Conflict of Interests
Dr Moyle has received research grants from Abbott, Ardea Biosciences, Bionor, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies and Tibotec.

He has received honoraria as speaker and/or advisor from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies, Tibotec and ViV Healthcare.

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SEASONING FOR A CURE
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Introduction
Hepatitis C virus (HCV) is the foremost cause of parenterally transmitted non-A, non-B hepatitis [1, 2], and chronic infection is associated with liver fibrosis, cirrhosis, and hepatocellular carcinoma [3, 4]. Due to the improved and highly effective antiretroviral therapy for HIV, complications from hepatitis C virus (HCV) co-infection have also emerged as a significant cause of morbidity and mortality in HIV infected patients [5]. Treatment with pegylated interferon-a and ribavirin yields sustained viral response (SVR) rates of 50–80% [6-8] among HCV mono-infected patients, with higher SVR rates seen in patients infected with HCV of genotypes 2 and 3. With the recent licensing of two inhibitors of the HCV NS3/4A protease (boceprevir from Merck, New Jersey and telaprevir from Vertex Pharmaceutical, Massachusetts), SVR rates among HCV genotype 1 infected patients have improved to 70–75% among treatment naïve patients [9-11] and 30–90% among treatment experienced patients [12, 13], with treatment duration halved in many patients. At the AASLD Liver Meeting held in San Francisco, California, November 3–8, 2011, promising preliminary data were presented from several ongoing trials with other Directly-Acing-Antivirals (DAAs) targeting various aspects of the HCV life cycle (Figure 1) that are currently in the pipeline. These pivotal trials are proof of principle that SVR is achievable in a substantial proportion of infected patients without the addition of interferon-a. Thus an exciting era in the management of hepatitis C is dawning with potentially fewer side effects and treatment duration possibly as short as 12 weeks for all genotypes.

Protease Inhibitors (PI)
Upon translation into a single polyprotein, HCV is cleaved by both host and viral proteases, including the virally encoded NS3/4A complex, which functions as the major molecular scissors without which functional viral enzymes are not produced. Several phase II–III trials are ongoing with newer generation protease inhibitors, including among many others TMC435 from Medivir/Tibotec Pharmaceuticals, MK-5172 from Merck, B1201335 from Boehringer Ingelheim Pharma, Danoprevir from Roche, Asunaprevir from Bristol-Myers Squibb, and new results from a few of these studies are highlighted below:

TMC435 from Medivir/Tibotec Pharmaceuticals (Pillar Study)
Fried et al. reported the final results of the phase II Pillar Study (n=386) with 5 arms investigating 75 vs. 150 mg dosing as well as 12 vs. 24 weeks duration of the first generation protease inhibitor TMC435 treatment in combination with interferon and ribavirin as compared to interferon and ribavirin therapy without the addition of TMC435. Patients achieving RVR (defined as HCV RNA <25 IU/mL at week 4) or not were treated in total for 24 or 48 weeks respectively. The experimental arms had SVR 75–86% as compared to 65% for the control group (Figure 2). This newer generation protease inhibitor, which reportedly has few adverse events aside from transient mild elevation of bilirubin generally not considered clinically significant, is dosed once daily orally, and reportedly has now entered phase III.

B1201335 from Boehringer Ingelheim Pharma (SILEN-C1 and -C3 Studies)
Sulkowski et al. and Dieterich et al. presented the results from the SILEN-C1 and -C3 studies respectively. In the SILEN-C1 trial (n=420) the first generation protease inhibitor B1201335 120 mg once daily was compared to 240 mg as well as placebo in combination with interferon and ribavirin, and in the SILEN-C3 study (n=159) 12 vs. 24 weeks of 120 mg once daily dosing of B1201335 in combination with interferon and ribavirin was investigated with or without an initial 3-day lead-in. In the SILEN-C1 study the SVR rate was 82% in the 240 mg QD arm vs. 56% in the
interferon and ribavirin control arm, with all 22 patients with IL28B CC genotype treated with 240 mg QD achieving SVR. And in the SILEN-C3 study SVR rates were 65% and 73% in the 12 and 24-week arms respectively. In the SILEN-C1 study nausea, diarrhea, pruritus, mild to moderate jaundice and rash were more common among patients treated receiving BI201335. Phase III trials have reportedly been initiated.

Danoprevir from Roche (RG7227; Atlas Study, Terrault et al.)

Treatment naïve, non-cirrhotic HCV genotype 1 infected patients were randomized to 300 mg Q8h, 600 mg Q12h, 900 mg Q12h or placebo in combination with interferon and ribavirin for 12 weeks, after which an additional 12 or 36 weeks of interferon and ribavirin was given based on whether eRVR (i.e. undetectable HCV RNA weeks 4–20) was achieved or not. The 900 mg Q12h arm was prematurely terminated because of 3 cases of reversible grade 4 elevation of alanine aminotransferase (ALT) to >10 times the upper limit of normal. Similarly one patient receiving 600 mg Q12h also reported grade 4 ALT elevations. SVR was 68% and 85% in the 300 mg and 600 mg arms respectively as compared to 43% in the control group receiving interferon and ribavirin. In upcoming trials co-administration of ritonavir is reportedly planned.

MK-5172 from Merck

Donald Graham et al. and Luderer et al. reported that this novel pan-genotypic second generation protease inhibitor has activity against HCV genotype 1–6 as well as several resistance associated variants (RAVs) that commonly emerge following unsuccessful therapy with first generation protease inhibitors such as boceprevir and telaprevir. Although MK-5172 lacks much of the cross-resistance reported for other HCV protease inhibitors, RAVs at position A156 (T/V) were the least sensitive to MK-5172 with IC50 values ranging from 200 to 781 nM. Among HCV genotypes, MK-5172 showed the least activity against genotype 3a proteases with IC50 values ranging from 90 to 260 nM.

Polymerase inhibitors

By mimicking the building blocks of RNA, the incorporation of nucleoside/nucleotide analogs by the HCV RNA-dependent RNA N55B polymerase, which lacks proofreading capacity, leads to premature chain termination and thus disrupts the viral life cycle. These DAAs are receiving increasing attention due to their pan-genotypic activity and their high barrier to resistance.

Mericitabine (RG7128) from Roche

Margeridon et al. reported that RAVs bearing the Mericitabine resistant variant S282T has not been detected in any samples from DAA treatment-naïve HCV infected patients, and Guedj et al. observed that kinetics of HCV RNA reduction when treating with Mericitabine does not fit the classical first and second phase decline observed with interferon and ribavirin therapy, and also that the initial decline was slower than with interferon- or protease inhibitors.

PSI-7977 (ELECTRON and PROTON Studies) from Pharmasset

PSI-7977 is a potent uridine nucleotide analog, which upon entry into hepatocytes is, rapidly converted to an active triphosphate that effectively inhibits the N55B polymerase of all HCV genotypes. It is administered once daily, with or without food, is safe and well tolerated, has a high barrier to resistance, and leads to a rapid decline in HCV RNA. Gane et al. reported that among genotype 2/3 infected patients (n=40) treated with PSI-
viral, the barrier to resistance is high as life cycle, and since it is not directly anti-host protein that is crucial for the HCV
follow-up.

Although the precise function of NS5A
ama
tion of interferon was reported by Chay-
and Asunaprevir (NS3/4A Protease In-
clatasvir (NS5A inhibitor BMS-790052)
Dual oral combination therapy with Da-
bristol-Myers squibb

Conclusion
Although much work remains to be done especially among difficult-to-cure patients, interferon-free therapy for HCV, which was once a utopic dream, is rapidly becoming an achievable goal. Preliminary data reported from the recently concluded AASLD meeting are very encouraging, and if ongoing as well as planned Phase III trials bare fruit, discussions regarding the selection of appropriate candidates for HCV therapy may become obsolete and be replaced by more radical eradica-
tion programs much as was the case after the introduction of penicillin for syphilis in the not too distant past.

Conflict of interest
The author has no association that might pose a conflict of interest.

References:

Other Targets:

Daclatasvir and Asunaprevir from Bristol-Myers Squibb
Dual oral combination therapy with Da-

Aliporivir (DEB025) from Novartis
This cyclophilin A inhibitor targets a host protein that is crucial for the HCV life cycle, and since it is not directly antiviral, the barrier to resistance is high as reported by Li et al. and its effect pan-genotypic as exemplified by half of HCV genotype 2/3 infected patients treated with Aliporivir (n=334) without interferon achieved undetectable HCV RNA by week 6 (Pawlotsky et al.).
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EACS Guidelines: Ready for the point of care

During the 13th EACS (European AIDS Clinical Society) Conference celebrated in Belgrade last October, the sixth update of the EACS guidelines was presented [1].

The prior version of the EACS guidelines had been presented in 2009. Globally, the DHHS [2], the IAS [3] and the EACS guidelines are the guidelines most followed by clinicians taking care of HIV-infected patients. The DHHS guidelines are presented via a webpage in a very comprehensive and detailed document that was last updated in October 14, 2011. The IAS guidelines are published as a review paper in the Journal of the American Medical Association and were last updated in July, 2010. The EACS guidelines are available at the webpage of the EACS society and also as a small pocket book that can be carried by physicians in their coats. During the conference it was announced that there are plans to develop an app for smartphones. In the EACS webpage translations of the guidelines are available in different languages.

In contrast to the other guidelines, the EACS guidelines can be used as a point of care resource that can offer clinicians rapid answers to the most common management questions raised in HIV clinics. To serve this purpose the EACS guidelines are divided in four important sections:

I) Assessment of HIV-infected patients at initial and subsequent visits.
II) Antiretroviral treatment of HIV-infected patients.
III) Prevention and management of non-infectious comorbidities in HIV.
IV) Clinical management and treatment of chronic hepatitis B and C co-infection in HIV-infected adults.

While in prior updates of the EACS guidelines these four sections were presented as different documents, in the current version they are part of a single document, an improvement that highlights the close interrelatedness of the several aspects of HIV care.

In Part I the reader can find a very practical table that gives detailed guidance about what assessment clinicians have to perform at the time of HIV diagnosis, prior to starting HAART and during subsequent follow-up. This table is quite useful to explain young doctors the overall assessment strategy in HIV clinics. In keeping with recently “discovered” clinical problems the table offers recommendations about how and when to test for bone disease, vitamin D deficiency, neurocognitive impairment and cancer screening.

In Part II (Antiretroviral treatment of HIV-infected patients) starts with a section that is quite unique among guidelines about assessing patients’ readiness to start HAART. HAART initiation is an extremely important therapeutic decision in a disease that currently needs to be treated for decades. Patient readiness to start HAART is a critical factor to maximize the success of ART therapy. The EACS guidelines provide important guidance in how to gauge patient readiness to start HAART.

Probably the two most discussed recommendations in HIV expert guidelines are when to start HAART and what to start with in antiretroviral naïve patients. These two critical questions are dealt with also in Part II of the EACS guidelines. In this update there is a completely new table of “recommendations for initiation of ART in HIV-positive persons without prior ART exposure”. As in the DHHS and IAS guidelines, HAART initiation is recommended in all antiretroviral naïve patients with less than 350 CD4 cells/µL. One important difference is that in asymptomatic patients with CD4 cell counts between 350 and 500 cells/µL HAART is only “considered”. “Considered” means that “some experts would recommend starting ART, whereas others would recommend deferral of ART”. In this subgroup of patients the EACS guidelines are more conservative (Table 1). A very important footnote of the when to start table is that “in serodiscordant couples early initiation of ART as one aspect of the overall strategy to reduce HIV transmission to the seronegative partner should be considered and actively discussed”. This is a very important reminder for clinicians to raise the issue of “treatment for prevention” when discussing the pros and cons of initiating HAART in asymptomatic HIV infected patients with high CD4 cell counts and serodiscordant partners.

Compared to the IAS and DHSS guidelines, the EACS recommendations are more permissive with the HAART regimens recommended in HAART naïve patients. In contrast to the other guidelines, Abacavir, Nevirapine and Lopinavir/r are part of recommended regimens. The main changes in this update are that Raltegravir is also recommended, Saquinavir/ritonavir falls now in the alternative category and Maraviroc appears also in the alternative category. ©
Currently there is agreement among guidelines to recommend four regimens in antiretroviral naïve patients (Table 2). While in the 2009 update there was no reference to generic antiretrovirals, in the current update it is stated that “Generic HIV drugs are becoming more available and can be used as long as they replace the same drug and do not break recommended fixed dose combinations”. There is a lot of debate in the HIV field about the importance of fixed dose combinations. Although it is true that we lack definitive data demonstrating that fixed dose combination improve treatment outcomes, it should be recognized that common sense suggests that fixed dose combinations would help patients facing long-life treatment which is becoming more complicated by the polypharmacy used to treat emerging co-morbidities.

One of the most common therapeutic interventions performed in HIV clinics is antiretroviral drug switches mainly due to toxicity issues in patients who have achieved virological suppression. It is somewhat surprising that until very recently guidelines have not provided detailed recommendations about how to perform these switches. The EACS guidelines provide very sound principles about to use antiretrovirals in this therapeutic scenario.

During the last two years three very important randomized clinical trials dealing with the question of when to start HAART in patients with tuberculosis have been reported [4-6]. The basic take home message is that the lower the CD4 cell count in patients just diagnosed with tuberculosis, the sooner HAART should be started. In keeping with this important finding the EACS guidelines now recommend to start HAART as soon as possible and ideally within 2 weeks in patients diagnosed with tuberculosis with a CD4 cell count of less than 100/µL.

Another very unique aspect of the EACS guidelines is the very detailed and extremely practical section dealing with prevention and management of a wide variety of non-infectious co-morbidities in HIV. In this section the reader can find very succinct guidance about: cancer screening methods, prevention of cardiovascular disease, hypertension, diabetes, dyslipidaemia, depression, bone disease, vitamin D deficiency, kidney disease, increased liver function tests, cirrhosis, lipodystrophy, travel, vaccination, hyperlactatemia, sexual dysfunction and neurocognitive impairment.

The last section of the guidelines deals with the clinical management and treatment of chronic hepatitis B and C coinfection. A very important novelty is a new algorithm to manage acute hepatitis C, a problem whose importance has increased in the recent years. In addition, although very briefly, the guidelines offer recommendations about how to use Telaprevir, a direct acting antiviral.

In summary, the current EACS guidelines update offer clinicians very practical guidance about the most common problems encountered in HIV clinics. I highly recommend that you carry it in your coat pocket and/or in your computer desktop.

Conflict of Interests
Dr Arribas has received advisory fees, speaker fees and grant support from Tibotec, Janssen, Abbott, BMS, Gilead, MSD.

He has received advisory fees and speaker fees from Viiv.

References:
Advertisement
Dolutegravir: a next generation integrase inhibitor

Why do we need new drugs?
Development of new drugs to ensure higher potency and the best long term tolerability, together with a high genetic barrier to resistance, remains a key issue in a chronic viral disease that requires lifelong therapy with a perfect compliance to therapy. Treatment strategies have already moved to earlier initiation of therapy given the fact that today, in addition to an individual benefit, antiretroviral therapy represents a key element in the prevention of the spread of epidemics [1].

What brought the integrase inhibitors class to the HIV treatment scene?
For almost twenty years we have been building antiretroviral therapy with three classes of drugs: NRTI, NNRTI and PI. We know that, in the absence of an HIV cure, long treatment has to be maintained with three requirements: it must be highly effective, simple and as tolerable as possible in order not to interfere too much with a normal life. Without forgetting the fantastic achievement that has represented the advent of triple therapy with the introduction of protease inhibitors, it is time for many patients who have had nearly twenty years of antiretroviral therapy to think about switching ARV combinations at least for a while.

Integrase inhibitors represent the fifth class of antiretroviral drugs developed and a major advance in the armamentarium of ARV with a complete efficacy on resistant viruses and no metabolic effects [2].

Raltegravir was the first integrase inhibitor, approved in 2007 [3]. Elvitegravir is a second INI currently in development with once daily administration which needs to be boosted by ritonavir or cobicistat, with an efficacy profile very similar to raltegravir, a complete cross resistance profile to raltegravir, a good tolerability profile [4]. Therefore, development of new integrase inhibitors with different resistance profiles is desirable [5].

Dolutegravir: a second generation integrase inhibitor
• Dolutegravir is a new integrase inhibitor, formerly referred as S/GSK134957 currently in development. It inhibits the integrase catalyzed viral DNA (deoxyribonucleic acid) strand transfer with IC50 values in the nanomolar range (2.7 to 12.6 nM) for HIV1 and HIV2 [6].
• Dolutegravir is active in vitro on INI resistant strains [6]

Of interest, not only is dolutegravir active in vitro on strains with resistance mutations to integrase inhibitors but in vitro, DTG appears to have a higher genetic barrier to resistance with a long duration to generate resistance – passage of strains over 112 days and a median 4.1 fold resistance observed.

• Dolutegravir is a simple drug to take:
Given a long half life, dolutegravir is a once daily drug, primarily metabolized via UGT1A1 with therefore no need for boosting. To date, there are no significant known interactions with other antiretrovirals [7-13].

Dolutegravir is highly effective in naïve patients
– The proof of concept study for dolutegravir consisted of a Phase 2, multicenter, randomized, double-blind, dose ranging, placebo-controlled study to evaluate 3 doses of dolutegravir monotherapy (2 mg - 10 mg - 50 mg) versus placebo in 35 patients antiretroviral naïve therapy and integrase inhibitor-naïve patients off therapy [8] which showed a decrease from -1.51 to -2.46 log10 over 10 days.
– The next step has been the SPRING-1 Phase 1b [14] study which has compared, in a randomized controlled design 3 doses of dolutegravir (10-25-50 mg QD) with efavirenz as a control in approximately 200 ARV naïve patients (50 per arm) with, at baseline, a mean pHIV RNA of 4.46 log10 cp/ml and 324 CD4 cells.

– Overall the proportion at Week 24 of patients with VL< 50 cp/ml was 96%, 90%, 92% with dolutegravir 10, 25, 50 mg respectively compared to 82% with EFV.
– This high efficacy rate was sustained at week 48 with 91%, 88%, 90% at the three doses of dolutegravir and 82% with EFV [15]. No resistance mutations emerged in the patients who failed in the dolutegravir arms. This could be viewed as a positive signal for a higher genetic barrier; however the number of failures is small and the level of viral load at time of failure is also very low.

Dolutegravir is an effective integrase inhibitor in patients with INI resistant strains
Whether dolutegravir would hold up to the promises suggested by the in vitro data has been investigated in the Phase 2b VIKING study. Two cohorts of multi experienced patients with multi resistant viral strains currently failing on a raltegravir regimen (78%) or having failed to Raltegravir (22%) with a viral load of 4.47 log10 and 114 CD4 had been enrolled to receive either dolutegravir 50 mg once daily (Cohort I) or 50 mg twice daily (Cohort II) in addition to their regimen initially for 10 days then with optimization of the regimen whenever possible. Overall in Cohort I the decrease in viral load at Day 11 ranged from -0.72 to -1.82 log10 [14]. At Week 24, 41% and 52% patients achieved < 50 and > 400 cp/ml respectively despite limited options of the OBR. In Cohort II with dolutegravir 50 mg bid and slightly less resistant viruses, the mean change in viral load at Day 11 was -1.76 log10 c/mL [15]. Figure 2.

Which mutations are selected in patients failing dolutegravir?
Too early to say. However in the VIKING study 5/12 patients with a virological failure at W24 had viral strains resistant to dolutegravir at time of failure including 2 with a 143 pathway.
Dolutegravir appears as a safe drug

Like other INI, in these preliminary data, dolutegravir appears well tolerated. The most commonly reported clinical and laboratory events in the Phase 2 clinical development program have been: headache, nausea, mild elevations in serum creatinine (6.4 to 11.9 mmol/l) after one week then stable up to week 20 then back to normal, potential mechanism could be an inhibition of the tubular secretion of creatinine by dolutegravir inhibiting a renal transporter and grade I total bilirubin elevation. Of note there was no CNS disorder, no skin rash and no metabolic abnormalities. [14-15]

If this tolerability profile is encouraging and similar to what has been, so far, reported for the integrase inhibitor class, one should wait for more patients on treatment, more “real life” patients and longer treatment durations to conclude in a more definite manner the tolerability profile of dolutegravir.

In summary

Dolutegravir has moved from a promising drug on in vitro data to an exciting second generation integrase inhibitor which shares with the other compounds of the class a high efficacy rate and a very fast virologic response in naïve patients, a good safety profile. Dolutegravir displays some important advantages relative to first-generation INIs raltegravir and elvitegravir, with a once daily dosing and no need for boosting and as a hallmark for a real second generation drug, a proven activity against isolates resistant to raltegravir or elvitegravir [19-20].

Conflict of Interests

Professor Katlama has received research grants from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, and Tibotec. She has received honoraria as speaker and/or advisor from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Tibotec and ViIV Healthcare.

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References continued on page 28
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2nd International Workshop on HIV & Women
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www.virology-education.com

**January 18–20**
15th Bangkok International Symposium on HIV Medicine
Bangkok, Thailand
www.hivnat.org/symposium/sb15th

**January 20–22**
International Science Symposium on HIV & Infectious Diseases
Chennai, India
http://hivscience.yrgcare.org/

**January 30–31**
5th Paris Hepatitis Conference (PHC)
Paris, France
www.colloquium.eu/site/-Homepage,2334-

**March 5–8**
CROI 2012
Seattle, Washington, USA
http://retroconference.org/

**March 12–16**
International Conference on Adolescent Sexual/Reproductive Health and HIV/AIDS
Enugu, Nigeria

**March 21–26**
HIV Vaccines
Part of the Keystone Symposia Global Health Series
Keystone, Colorado, USA
http://www.keystonesymposia.org/meetings/viewMeetings.cfm?MeetingID=1168

**March 26–31**
Frontiers in HIV Pathogenesis, Therapy and Eradication
Part of the Keystone Symposia Global Health Series
Whistler, British Columbia, USA
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**March 26–27**
International Conference on Viral Hepatitis (ICVH)
New York, United States
www.confmanager.com/main.cfm?cid=2562&nid=15501

**March 28–30**
10th European Meeting on HIV & Hepatitis – Treatment Strategies & Antiviral Drug Resistance
Barcelona, Spain
www.virology-education.com/

**April 17–20**
18th Annual BHIVA Conference
Birmingham, England
www.bhiva.org

**May 3–5**
2nd North European Workshop on HIV-infection in the CNS – HANSIA 2012
Hamburg, Germany

**May 23–25**
ISHEID 2012, International Symposium of HIV & Emerging Infectious Diseases
Marseille, France
www.isheid.com

**May 24–25**
5th International Symposium on HIV Psychiatry
Barcelona, Spain
http://www.psychiatry-hiv.com/

**May 29 – June 2**
11th International Symposium on NeuroVirology and 2012 Conference on HIV in the Nervous System
New York, USA
www.isnv.org

**June 14**
4th Nordic HIV Summer meeting
Gothenburg, Sweden

**July 22–25**
19th Word AIDS Conference
Washington DC, USA
www.aids2012.org