In this issue:

2 Letter from the editor
Magnus Gisslén

4 How to use Etravirine in clinical practice?
Christine Katlama

7 Report from CROI 2012 in Seattle
Per Lundblad

15 Rilpivirine – how should this new NNRTI be used in the clinic?
Magnus Gisslén

17 Integrating HAART: The advent of QUAD
José Arribas

20 HIV and Inflammation
Graeme J. Moyle

25 Some facts and thoughts on Progressive Multifocal Leukoencephalopathy (PML)
Paola Cinque

28 Topical Conferences in 2012

The 2012 Conference on Retroviruses and Opportunistic Infections (CROI) took place in Seattle. In total, 4,253 participants had come to the city on the north end of the west coast of USA. Page 7
Dear Readers,

First, I would like to thank for all positive response and encouragement that HIV & Virology News has received. It has been overwhelming and we are very grateful for this recognition. I also want to thank the advertisers who make it possible to provide this magazine to over 15,000 Infectious Disease physicians across 13 European countries. We hope that we can continue to offer interesting articles and opinion pieces.

This fourth issue will cover the annual retrovirus conference, CROI 2012, that recently took place in Seattle, Washington, USA with a report from our medical writer Per Lundblad. As usual a lot of very interesting studies were presented covering a variety of areas. Compared to previous conferences, less focus was placed on new antiretroviral drugs although this area also was included. Among the hot topics on this year’s conference were neurological and cognitive complications of HIV as well as latency and “the search for a cure”. Another area that attracted a lot of attention was treatment of hepatitis C, in co-infected but also, in at least one study, in mono-infected, emphasizing the fast development currently taking place in hepatitis C treatment.

This issue will also include opinions on three HIV drugs, two already licensed NNRTIs, etravirine (Christine Katlama) and rilpivirine (Magnus Gisslén) as well as the new integrase inhibitor elvitegravir as part of the combination pill QUAD (José Arribas). Elvitegravir will probably be available within one year or so if nothing goes wrong. The arsenal of treatment alternatives is still increasing, of good for the patients.

In HIV, like in many other infections and immunological diseases, inflammation is a main pathogenic driver. Graeme Moyle reviews the role of chronic immune activation in HIV, both in the untreated and treated setting. Finally, the second article in the series “Clinical update on opportunistic complications in HIV” could be found in this issue of the magazine. This time Paola Cinque who is a well-recognized expert in the field give her thoughts about PML and its significance in the cART-era.

Enjoy your reading!

MAGNUS GISSLÉN
Editor
Advertisement
How to use Etravirine in clinical practice?

Antiretroviral therapy has definitely entered a new era where therapy represents not only the means to avoid progression of immune deficit towards HIV disease but also the means to prevent all deleterious inflammatory manifestations of HIV replication and to prevent transmission to patients’ sexual partners [1]. Until a sterilizing or a functional cure is found, life long treatment has to be maintained over decades. Thus we need to use all the advantages of available drugs paying particular attention to viral potency, virologic robustness and long-term tolerability. This is why the class of NNRTI is a key in our arsenal for HIV therapy.

Etravirine: Strengths and weaknesses
Etravirine is a second generation NNRTI, a di-arylpyrimidine that blocks both HIV RNA- and DNA-dependent polymerase activities and prevents the synthesis of viral DNA [2].

How to use etravirine in patients with virological failure?
The pivotal DUET studies [3] – have clearly shown that etravirine in combination with darunavir and optimized background therapy – to which all patients enrolled were naïve had a greater success rate of 60% compared to 40% in absence of etravirine. In the TRIO trial [4] the combination of 3 potent drugs such as raltegravir, darunavir and etravirine had resulted in over a 90% success rate. However, this data concerned patients with resistance to NRTI, PI and to NNRTI with a minimum of 5,000 copies HIV RNA at baseline. In a large US Phase III cohort study that had evaluated ETV on 2,969 patients who had failed multiple success antiretroviral regimens, the virological rate in the 2,578 patients from the ITT population, with a background of TDF/FTC in 65%, darunavir/r (62%) or raltegravir (57%) was good with 62.3% of patients having maximal viral suppression [5].

The context of virological failure has progressively moved over time in clinical practice with an earlier management of failure and therefore less resistance and more potent drugs. Therefore in case of NNRTI failure, etravirine can be combined with many other drugs as soon as the key rule of a minimum of 2 active drugs, based on a genotype resistance, is respected.

How to use etravirine in naïve patients?
The efficacy of etravirine in a large set of viral strains, the good tolerance of etravirine, its potential for QD dosing combined with the potential robustness of the drug makes in theory etravirine an appealing compound for initial therapy. Indeed etravirine is highly effective as a third agent in naïve patients as shown in the SENSE trial, designed essentially to evaluate whether etravirine could be better tolerated in comparison to efavirenz with success rates in intent to treat analysis of 76% in the ETV arm and 74% in the EFV arm [6]. Although the numbers are too small to draw more definite conclusions, it should be noted that the 4 patients who failed on etravirine did not de-

Strengths
- Active in vitro against a large range of HIV-1 groups and subtypes with median EC50 ranging from 0.29 to 1.65 nmol/L.
- Active against NNRTI resistant HIV1 viruses: in vitro active against virus harboring the common NNRTI resistance mutations (single or double mutant) and active against > 90% of clinical viral strains harbouring NNRTI associated mutations.
- Genetic barrier to resistance ++: in vitro higher than first generation NNRTI with mutations less easily selected and more mutations required to confer resistance.
- Pharmacology ++: long terminal half life with a potential for a QD dosing; high intracellular concentration in BID and QD regimen.
- Tolerability profile ++: excellent with lipid friendly profile. no CNS disorders; limited rash; no metabolic toxicity reported up to now.

Weaknesses
- The main weakness of etravirine is the relatively high number of pills with 4 pills given as 2 pills (100 g x 2) twice daily or 4 pills (400 mg QD). The pills are easily soluble.
- Metabolization through Cytochrome P450 with subsequent expected drug interactions.
velop any resistance mutations neither on NNRTI nor on NRTI with therefore a protective effect on the NRTI class, whereas 4 of the 7 patients who virologically failed with the EFV containing regimen developed resistance mutations. A larger ongoing study should be able to assess firmly whether or not there is a genetic barrier to resistance of etravirine and thus whether etravirine has an advantage, in naïve patients, over rilpivirine which soon will be licensed as a combination with tenofovir/emtricitabine.

How to use etravirine in patients with suppressed viremia?

In daily management of HIV infected patients, several clinical situations may require you to think about switching ART: either to replace PI/r because of metabolic complications, cerebral ischemia or lipodystrophy or to replace NRTI because of a decrease in renal function, lipodystrophy or bone disorders. Drugs like etravirine with limited toxicity and no metabolic toxicity have become very attractive. Yet there has been no large switch study with limited toxicity and no metabolic disorder. However, there is a need for a more compact formulation and need for investigation of an etravirine containing regimen other than the classic ones.

Conclusion

Etravirine is the only second generation NNRTI which offers a unique opportunity to maintain the use of this class of drug, which up to now, has no metabolic disorders, which is something precious to aging populations. However, there is a need for a more compact formulation and need for investigation of an etravirine containing regimen other than the classic ones.

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.

References:
CROI 2012 in Seattle

The 2012 Conference on Retroviruses and Opportunistic Infections (CROI) took place in Seattle. In total, 4,253 participants had come to the city on the north end of the west coast of USA. They came from 81 countries – and 47% of the delegates came from outside USA.

CROI is a scientifically focused meeting of the world’s leading researchers working to understand, prevent, and treat HIV/AIDS and its complications. The goal of CROI is to provide a forum for translating laboratory and clinical research into progress against the AIDS epidemic.

A total of 1,076 abstracts had been accepted for CROI 2012. 89% of these were presented as posters, and 11% were orally presented in Seattle.

Proof of efficacy

In the last decade there’s been a remarkable increase in the scale of antiretroviral therapy around the world. By the end of 2002 it was estimated there were less than 500,000 individuals in low and middle-income countries that were receiving access to these life-saving medications.

– Remarkably – and almost miraculously – by the end of 2010 the number had reached more than six and a half million individuals, said Wafaa El-Sadr in her lecture at the first Plenary Session of CROI in Seattle 2012.

It was titled ART for Prevention: The Science and the Art.

The first evidence of the effectiveness of ART for prevention came from the programs for prevention for mother to child transmission, said Dr El-Sadr. She presented data from the WITS study 1990–2004. A graph illustrated that going from monotherapy first, then in later years Multi-ART and finally HAART proves a remarkably decrease in mother to child transmission (MTCT).

– This is a proof of concept of the efficacy of ART for prevention, Dr El-Sadr stated.

Home based testing

What are the implications that we must have in place in order to achieve the promise of ART for prevention – i.e. the Art?

It requires a continuum – a HIV Care/Prevention continuum, Dr El-Sadr said and described it as follows:

– It requires testing for HIV in order to find those who are positive, linkage of those who are positive to Pre-ART care or HIV care, determine ART eligibility, then initiation of ART in those who are eligible and lastly, of course, ensure adherence and viral suppression. This continuum is absolutely critical, whether we’re looking at treatment or prevention!

Dr El-Sadr then dissected this continuum step by step, and started with HIV testing. 🌟
She presented data on HIV testing from the preceding year in sub-Saharan Africa. Only a small minority of individuals had been tested in the prior 12 months. In general it was more likely that women were tested, compared with men.

One of the attempts to reach more people for testing was home based testing. She presented a study that found this much more effective and reaching more members in the household – and identified more infected individuals.

A vibrant research agenda is required
According to Dr El-Sadr, the evidence in support of efficacy of ART has galvanized the HIV prevention agenda.
– I also believe it has galvanized the HIV treatment agenda. More than ever, we now have evidence that must drive us to reach those who need treatment today – both for their own good, as well for the prevention benefit.

There are studies planned to evaluate the impact of ART for prevention at a population level, and an ongoing study to evaluate the risk/benefit of early ART for HIV-infected individuals – to convince us that we are preserving the good for the individual, as well as the good for society.
– A phased and accelerated approach that takes into account the science – what we know – the art, the health system realities and the principals of ethics and equity, is required as we extend ART for prevention.
– And lastly I believe that optimisation of the complex components that are critical for the success of ART for prevention – or for treatment for that matter – will require a vibrant research agenda, creative implementation efforts and meaningful partnerships in order to achieve our mutual goals, Dr El-Sadr summarised her talk.

Should ART for children be interrupted?
One Session in Seattle was devoted to critical treatment issues in women and children.

Dalton Wamalwa presented results on treatment interruption after early ART in Kenyan infants. There is a unique potential benefit of interruption in children.
– The survival benefit of early ART in infants is clear – it’s been shown in the landmark study CHER from South Africa. In addition to improving survival, early ART is likely to preserve or even salvage thymic function in infancy, Dr Wamalwa said.

The question that remains is if this is sufficient to modify the natural history of paediatric HIV, and to allow these children an interruption after CD4 restoration.

Adult studies on treatment interruption (TI) may not fully inform on paediatric TI.
– There are some key differences: Infants can be identified early and be treated during acute infection. In addition infants have an immune system under development, he pointed out.

High rate of early restart
Hence the study Dr Wamalwa presented – a non-blinded RCT to compare growth and morbidity among infants randomised to continued, versus interrupted, ART.

One of the key findings in this study was the high rate of restart that was experienced in the interrupted arm. 16 of 21 (76%) met the CD4 criteria for restart.
– I’d like to point out that no child was restarted due to poor growth or opportunistic infections, Dr Wamalwa said.

In summary they found a high proportion of infants with early restart following interruption, growth and severe adverse events were similar and a lower CD4 percentage predicted early restart.
– It’s envisioned that there may be infants that are asymptomatic, or with higher CD4 at TI, may be a better group for TI, was his conclusion.

Early ART standard
Mark Cotton presented data on the same subject. It was the final results from the 6-year randomised CHER trial in South Africa.
– We all know that HIV infected infants have a high risk of death and disease progression early on. On the other hand we know that early initiation of ART commits to lifelong therapy and several risks.

Therefore Dr Cotton and his group had developed a hypothesis: Early, limited ART initiated from 12 weeks of age (or

Wafaa El-Sadr
Dalton Wamalwa
Mark Cotton
Jintanat Ananworanich
less) followed by interruption is feasible and safe – resulting in long-term benefit of delaying immunological and clinical HIV progression, compared to deferred ART.

Early on in the study – the first year – an interim analysis showed that early ART was superior to deferred ART and associated with less mortality. It then became standard of care.

**Interuption seems safe**

Now the six years results could be summarised.

– Early ART until the first or second birthday, followed by interruption and compared to deferred ART appears safe in children having regular clinical and CD4 monitoring. It halves mortality and reduces disease progression, said Dr Cotton.

Early treatment for two years compared to one-year results in similar ART exposure, longer subsequent interruption and a trend towards fewer clinical events, he added.

His conclusion was that treatment during early infancy protects against HIV-related high mortality and morbidity. Also that ART interruption after infancy appears safe.

– But the following are still needed: Further analyses of virologic suppression and resistance – and the immunological response to restarting ART after interruption, Dr Cotton finished his talk.

### HIV-positive children more likely to develop neurological problems

Jintanat Ananworanich talked about the PREDICT study. In this 299 HIV-infected Thai and Cambodian children, aged between 1 and 12 years and CD4 15–24% were randomised into immediate ART and deferred ART until CD4 were less than 15%.

In this cohort they had performed a neurodevelopmental sub study, in order to determine the neurodevelopmental outcomes at week 144 of immediate versus deferred ART in children. Week 144 outcomes were measured, and they included testing of IQ, processing speed, visual-motor integration, memory scores and behaviour problems.

– In all of these, we could not see any difference between the two randomised arms of the study, said Dr Ananworanich.

But in all areas measured, scores were lower in HIV-positive children compared to HIV-negative controls, she added.

– In HIV-positive children who survived beyond one year of age without ART, there were similar neurodevelopmental outcomes with ART initiation at CD4 15–24% and at CD4 less than 15%.

Access to therapy is unfortunately often missed in the majority of infected infants in resource-limited settings, raising the question of how best to care for these older children.

– We all recognize the challenges the children and families face in adhering to daily therapy, Dr Ananworanich pointed out.

The poorer performance on neurodevelopmental testing among HIV-positive children may be related to the early HIV insult to the brain, and suggests that the optimal window of opportunity for ART initiation remains early in infancy, she concluded.

### HIV infected individuals living in malaria endemic areas

Malaria and HIV cause significant morbidity and mortality worldwide, but particularly in Sub-Saharan Africa.

– Despite existing control interventions, HIV infected individuals living in malaria endemic areas continue to suffer high rates of malaria, said Jane Achan.

It therefore looks like in these populations, additional protective interventions may be warranted – especially for those living in high malaria transmissions settings, she continued.

Dr Achan presented a study on the hypothesis that the incidence of malaria among HIV-infected children receiving Lopinavir/ritonavir-based ART will be significantly lower than among children receiving NNRTI-based ART.

HIV-infected children aged from 2 months to 5 years in Tororo, Uganda (an area of high malaria transmission) were randomised into Lopinavir/ritonavir-based ART + 2 NRTIs or Nevirapine or Efavirenz + 2 NRTIs.
Advertisement
Prolonged prophylactic effect
- In this study, HIV-infected children treated with LPV/r based ART regimens had a significantly lower risk of malaria, compared to those treated with an NNRTI-based regimen. We think there are a number of explanations for this observation. The main being the pharmacokinetic effect on LPV/r on lumefantrine levels, leading to a prolonged “post-treatment” prophylactic effect following treatment, Dr Achan said.

To a lesser extent, both the antimalarial effect of LPV/r and the antiparasitic synergy between LPV/r and lumefantrine, also played a role, she continued.
- We also think that this study highlights the possible role of “pharmacoenhancement” as a tool for reducing the burden of malaria in highly endemic settings, Dr Achan concluded.

Key advance in MTCT
The elimination of mother to child transmission (MTCT) of HIV was the topic for a Plenary Session. In this, Dorothy Mbori-Ngacha spoke on elimination of new HIV infections in children and keeping mothers alive.
- In June last year, world leaders launched the global plan to reduce new infections in children to less than 5% by 2015, and reduce the number of new infections among children by 90%. Also to reduce the number of AIDS-related maternal deaths by 50%, she said.

These are ambitious targets, which have generated a debate of whether they are attainable.
- We know that without prevention HIV can be transmitted from mother to child at three time points: During the antenatal period, during labour and delivery and during breastfeeding, Dr Mbori-Ngacha continued.

Breastfeeding poses a public health dilemma, as it pits the risk of transmission against the risk of death from malnutrition. Therefore focus has been on reducing this risk, and Dr Mbori-Ngacha presented data that showed that the lowest rate of transmission was achieved when mothers received triple ARV drugs, starting early in the second trimester.
- In general, all the triple drug regimens show rates below 5–8%. I consider that these results are a key advance in MTCT, and a reason for optimism that the target of less than 5% in resource constraint settings is indeed feasible, she stated.

We can rewrite history
So will we be able to meet the elimination target?
- All I can say is that there has been major progress in the prevention of MTCT in the last five years, with new interventions to prevent postnatal transmission now identified in clinical trials, said Dr Mbori-Ngacha.

We have a need to scale up these interventions to ensure universal coverage and equitable access to the interventions. We also need to strengthen our health systems to be responsive to that, she concluded and finished her talk with a quote from Robert F Kennedy:

“Few will have the greatness to bend history itself, but each of us can work to change a small portion of events. It is from countless acts of courage and belief that human history is shaped”.  
- None of us are going to get the Nobel Prize for eliminating the MTCT, but together we can rewrite history by each of us contributing, she said.

When does ART really start worldwide?
An epidemiological study on the CD4 count at the start of ART in five continents was presented by Matthias Egger.

Initiation of ART at higher CD 4 T-cell counts prevents clinical progression in the individual and reduces transmission of HIV-1 at the population level.
- The CD4 count at the start of ART is therefore of great interest for public health, Dr Egger said.

The study had analysed data from 48 countries and 309,585 patients. They found that the median CD4 count at the start of ART increased in most countries, but remained under 200 in lower income countries and 350 in high-income countries.
- High ART coverage – i.e. more than 80% – was associated with higher counts. A high burden of patients waiting for ART is an important barrier to start ART early.
- People go to treatment later than they should. Substantial effort and resources are needed to achieve earlier implementation of ART globally, was his conclusion.

The results were from 2010, and Dr Egger said that they are planning an update later this year.
Risk for cardiovascular disease

Rates of metabolic syndrome, cardiovascular disease and diabetes are elevated in HIV-infection. Coronary artery calcification (CAC) is an indicator of overall atherosclerotic burden.

– Among non HIV-infected patients, CAC score is a strong predictor of cardiovascular events. CAC is significantly higher among HIV-infected individuals with metabolic syndrome, Kathleen Fitch said.

She presented a study, which hypothesised that lifestyle modification, and Metformin (an oral antidiabetic drug in the biguanide class) would improve cardiovascular indices in these patients.

– Modifications of risk factors for cardiovascular disease are important in the management of HIV-infection, including strategies for insulin resistance, Dr Fitch said.

At present the mechanisms of Metformin to prevent CAC progression are not known. Potential mechanisms include effects on insulin resistance, anti-inflammatory effects and activation of AMP-activated protein kinase.

The study found that treatment with Metformin over one year prevents plaque progression in this population.

– Metformin may be a useful drug to modify cardiovascular risk, but further studies are clearly needed to understand the mechanisms. Larger longer-term studies using Metformin in HIV patients, with metabolic syndrome and insulin resistance, will be useful to determine whether this strategy will prevent cardiovascular events, Dr Fitch said.

Sterilising or functional cure

The pathways for a cure of HIV infection was the topic for one Symposium.

Sharon Lewin gave a talk on the subject, and started by defining what it is that we one day hope to achieve – cure or remission.

– I like to think of cure as in the classic infectious disease model – i.e. where we could eliminate all HIV-infected cells and HIV RNA would be persistently undetectable to less than one copy per ml. This is now commonly referred to as sterilising cure.

The other – perhaps more achievable – goal would be to one day put HIV in remission: Long term health in absence of combination antiretroviral therapy (cART), low levels of virus less than 50 copies per ml. This is commonly referred to as functional cure, she continued.

So what are the barriers for a cure?

– Virus persists in all patients on cART, Dr Lewin underlined.

It is generally thought that there are three major sources of virus. These include latently infected T-cells, residual viral replication and anatomical reservoirs.

Additional challenge

There are already some current clinical trials aimed at cure.

– The strategies being pursued include eliminating latently infected cells, eliminating residual virus replication, enhancing HIV-specific immunity and making cells “resistant” to HIV.

Dr Lewin continued by going through some of these trials.

– Multiple barriers to eradication, means that a combination approach will almost certainly be likely. Multiple strategies are already being tested in early proof of concept studies, including activation strategies, gene therapy, vaccination and intensification.

Early trials designed to demonstrate activity in vivo may be negative while we identify the best assays, dosing, testing strategies and therefore need to be focused on the long term goal.

– And I think, finally, we need to always keep in mind that we have a significant additional challenge: If we ever find a strategy that does do anything to latent reservoir, it needs ultimately to be cheap, scalable and widely available, she concluded.

Latency can be targeted

Resting CD4+ cell infection is extremely stable despite ART and is a primary reservoir of persistent HIV infection. Histone Deacetylases (HDACs) are shown to contribute to the restriction of latency of HIV integrated into the genome of CD4+ T-cells.

Vorinostat – or suberolanilide hydroxamic acid – is a potent oral HDAC inhibitor that is licensed for treatment of cancer.

David Margolis presented a study in which it was shown that Vorinostat disrupts HIV-1 latency in patients on ART.

– A single dose of Vorinostat is shown to induce expression of full-length HIV RNA within latently infected resting CD4 T cells. This is the first direct measurement of disruption of latent HIV infection in vivo, Dr Margolis said.

The optimal dosing schedule of Vorinostat, and its ability to deplete latent infection remains to be established.

– It will be the next immediate goal for my work, Dr Margolis told the audience.

The finding is a proof of concept, demonstrating that latency could be targeted, and therefore a significant step towards eradication of HIV infection, he added.

– The efforts to fully understand such approaches to influence both the natural history and clinical management of HIV infection, deserve urgent and accelerated investigation, he concluded.

The future of treatment for TB

One day of the Congress is also the “TB-day”. This day was introduced by Eric Nuermberger at the last Plenary Session on Thursday morning. The title of his talk was Developing TB Regimens for the next 40 Years.

– New TB drugs in clinical trials have sterilising activity, suggesting they could very well improve current therapy of tuberculosis, he said.

These drugs should be evaluated and deployed carefully in optimised doses –
in combinations and in settings that enhance their efficacy and protect them against resistance.

- New, rapid and robust surrogate markers for sterilizing activity are greatly needed and would greatly accelerate preclinical and clinical drug development towards their goals, Dr Nuernberger continued.

Over the next 40 years it will be critical for continued investment to ensure a drug pipeline exists. Sponsors and stakeholders must collaborate to inform the optimal use new drugs, both before and after approval – so we can make optimal use as soon as possible. Every Phase 2b/3 trial is an opportunity to learn about the pharmacokinetic and pharmacodynamic (PK/PD) of these drugs, and potential surrogate markers.

- Ultimately iterative studies relating PK/PD of these drugs, and persister markers in various models and lesion types, may finally define “sterilizing activity” as a quantifiable measure – and permit ever more confident use and interpretation of pre-clinical models and early clinical trials, Dr Nuernberger said.

**Systematisation of descriptive epidemiology**

This Plenary Session ended with Christopher Murray talking on AIDS and the Global Burden of Disease (GBD). He started by defining what GBD is.

- It’s a systematic scientific effort to quantify the comparative magnitude of health loss due to diseases, injuries and risk factors by age, sex, geographies for specific points in time, Dr Murray explained.

In other words it is a very ambitious effort to systematize descriptive epidemiology. The purpose is to help scientists, policy-makers and decision-makers around the world understand the broad picture around what is killing and harming people in terms of disease, incidence and prevalence, he added.

Dr Murray gave an in-depth and thorough background to how GBD is calculated – it includes many diseases – and then focused on the burden of HIV.

**Incredible progress**

Among the many interesting things Dr Murray pointed out was a global map of the percent decline in HIV mortality from the peak of the epidemic in each country to present.

- Incredible progress has been made! The decline could be due to the epidemic curve itself – the natural curve goes up and down. It could also be due to the prevention programs in some places, and dominantly it’s due to the scale-up of antiretrovirals.

The map showed that in Western Europe and high-income countries from the peak to present there has been a 60-70% decline in HIV mortality. But also in many other countries – including low-resource settings – there have been 30-50% declines in mortalities because of the scale-up of investments by the global health community, and its effectiveness.

- There is an important variation though: Some parts of central Africa have seen little decline since peak mortality – but still there is an incredible progress in many key places, particularly in the parts of the world with the largest epidemics, Dr Murray continued.

**Huge expansion of resources**

Another way to think of burden of HIV is to look at countries where HIV is among the top ten causes of the burden of disease. This includes many parts of Latin America, almost all of Africa except for Ethiopia and Somalia, parts of Eastern Europe with for example Ukraine and the Russian federation and important parts of South-East Asia.

- So HIV may not be the number one cause in many countries, but it’s certainly among the top causes in a large number – even though we’ve seen this incredible progress in the last 5-10 years.

Where does this progress come from? A key part is the scale-up of the resources for global health, Dr Murray said.

- In real dollars, corrected for inflation, the money flowing in to global health programs from high-income countries has gone from just under six billion in 1990 to 27 billion in 2011. It’s a huge expansion, and of course it has been a part of the engine leading to this progress we’ve seen for HIV in a number of countries.

**Double burden**

There was a period of slow growth in a period from 1990 to 2000. Then there’s been explosive growth from 2002 to 2008, and then – since the global financial crisis – we’ve entered a period of quite lower growth.

- There are reasons to expect that that slower growth may be a challenge for going forward, said Dr Murray.

Substantial reductions in HIV related mortality are directly related to investments in ART, prevention for MTCT, and prevention programs in some settings like India, he underlined.

- Continued progress on what we have seen depends on continued increased funding. Or much more efficient ways of delivering ART, or therapeutic breakthroughs on the prevention or treatment side that could transform the way we manage the epidemic.

Despite all the progress Dr Murray had pointed out, HIV remains the number one cause of burden in 12 countries – and in the top five in more than 30.

- Some of the countries with the largest HIV epidemics, like South Africa, are also facing new challenges: Non-communicable diseases and the associated risks like obesity and tobacco!

He ended his highly appreciated talk by revealing that some time during the summer all interested researchers and members of the public will be able to access the full GBD report via the Internet.
Advertisement
The half life of rilpivirine is long (45–50 hours) which is comparable to efavirenz and making it possible to dose once a day. Selection of the 25 mg dose was based on the fact that no dose-response relationship was demonstrated in Phase 2 studies comparing 25 mg, 75 mg and 150 mg of rilpivirine, while a significant positive correlation was observed between increase in QTc-interval and exposure (rilpivirine AUC).

However, initially, before data on risk of QT prolongation were available, the 75 mg q.d. dose was suggested for further development of rilpivirine since the proportion of virologic failures in the rilpivirine 25 mg q.d. group was higher compared to higher dosages (not significant). There was also a trend towards lower efficacy of the 25 mg q.d group among those with a high baseline viral load.

Two randomized placebo controlled phase 3 trials of rilpivirine 25 mg q.d. versus efavirenz 600 mg q.d. have been performed on antiretroviral naïve HIV-1 infected subjects. A fixed NRTI-backbone with TDF/FTC was given in the ECHO-study [1] while a background regimen containing 2 investigator initiated NRTIs (either abacavir (ABC)/lamivudine (3TC), zidovudine (ZDV)/3TC or TDF/FTC) were given in the THRIVE-study [2]. Choice of NRTI backbone did not impact on outcome and as the two trials had almost identical design a preplanned pooled analysis of week 48 data have been performed to allow for greater statistical power [3].

It should however be mentioned that ABC/3TC was only prescribed to 10% of subjects in the THRIVE-study, in total 35 patients in the rilpivirine arm and that rilpivirine thus mainly has been evaluated together with TDF/FTC. At week 48, rilpivirine and efavirenz had comparable response rates (84 and 82%, respectively, in ITT-TLOVR analysis with HIV-RNA < 50 copies/mL as cut of) and the primary endpoint of non-inferiority at the 12% margin was met for rilpivirine 25 mg compared to efavirenz 600 mg, (figure 1).

The proportions of patients with treatment failure were similar between rilpivirine and efavirenz (13% vs 9%), but the reasons were different; for rilpivirine this predominantly was virological failure and for EFV adverse events. This difference was driven by subjects with high baseline viral load and as a consequence, rilpivirine has been licensed for treatment of antiretroviral naïve patients with viral load < 100 000 copies/mL, (figure 2).

In a clinical point of view it is a large difference to be forced to change treatment regimen because of virological failure compared to side effects. As a consequence of weaker virological response when baseline viral load is high, the number of patients ending up with resistance was much higher for the rilpivirine-treated patients compared to patients on efavirenz. Among subjects with baseline viral load > 100 000 copies/mL, NNRTI-mutations were detected in 10% of rilpivirine-treated compared to 3% of efavirenz-treated, most of those had also NRTI-mutations (10% vs 2%).

The emerging NNRTI mutations in patients failing with rilpivirine were associated with cross-resistance to all other NNRTIs, while in contrast, those failing efavirenz therapy would generally still be able to use etravirine. There were no difference in emergence of NNRTI resistant mutations between arms in patients with low baseline viral load, but it could be noted that NRTI-mutations was detected in 7/368 on rilpivirine compared to 2/330 on efavirenz with baseline viral load < 100 000 copies/mL.

Post-hoc analyses showed that suboptimal adherence increased the risk of virological failure and resistance development and with rilpivirine, very high adherence is probably of outmost importance for a successful outcome. Another factor that may have contributed to the results is that rilpivirine needs to be taken together with food. Intake in fasting state...
or together with only a small meal will have considerable negative effect on drug concentration, (figure 3), and increase the risk of failure and resistance development. Also, interactions with some other medications may have impact. One important interaction is with acid lowering agents and proton pump inhibitors are contraindicated as they have large effect on absorption of rilpivirine.

On the good side is that rilpivirine generally is very well tolerated and has few side effects. It doesn’t seem to impact on blood lipids at all and compared to efavirenz, it has much less CNS side effects and lower frequency of rash.

Switch-studies are ongoing, one concern has been that efavirenz lower rilpivirine exposure because of enzyme induction leading to initially low drug concentrations the first weeks after switching from efavirenz to rilpivirine [4]. However, efavirenz concentration decrease slowly corresponding to increase in rilpivirine concentration and switch is probably safe in patients with suppressed viral load. This is supported by data on 49 vireologically suppressed subjects switching from fixed-dose TDF/FTC/efavirenz to TDF/FTC/rilpivirine who all maintained viral suppression (HIV-RNA <50 copies/mL) 12 weeks after switch [5]. However, longer-term follow-up is required to provide further reassurance and more data will soon be presented.

Another important caveat is that no data are available on switch before viral suppression has been achieved. In the relatively common situation where patients need to switch therapy because of tolerability problems during the first weeks after start on an efavirenz-based regimen, HIV-RNA has commonly not reached undetectable levels. I would in such situation be reluctant to and not recommend a switch to rilpivirine until data are available showing that such switch is safe. Until then, a switch to for example a boosted PI is more appealing during those circumstances. Studies on switch from boosted PIs to rilpivirine is ongoing and is most probable safe as long as the patient has no history of treatment failure or resistance.

In conclusion, rilpivirine is a very good new treatment alternative due to its great tolerability but it has to be given to the right patient. It requires very high adherence and to always be taken together with a meal. The main disadvantage with rilpivirine is that 25 mg dose has somewhat lower virologic efficacy compared to other first-line alternatives. I will personally not use rilpivirine generally to antiretroviral naïve subjects, even if they have a viral load below 100 000 copies/mL, as we have several other very good options. But, a lot of patients suffer from side-effects and my experience, as well as many others, is that for example more patients on efavirenz than previously thought have low-grade CNS side-effects that often not are recognized until efavirenz treatment is discontinued. Side-effects are also quite common in subjects on boosted PIs. Switch to rilpivirine is an attractive alternative for adherent patients with side-effects.

Conflict of Interests
Magnus Gisslén has received research grants from Abbott, Baxter, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Pfizer, Roche and Tibotec/Janssen. He has received honoraria as speaker and/or advisor from Abbott, Bionvent, Boehringer-Ingelheim, Bristol-Myers Squibb, Glaxo Sciences, GlaxoSmithKline, Merck, Pfizer, Roche, Tibotec/Janssen and Viiv.

References:
Elvitegravir is big news after the 19th Conference on Retrovirus and Opportunistic Infections. In Seattle we saw for the first time the data of two large double blind randomized clinical trials comparing Elvitegravir versus two drugs that are standards of therapy in antiretroviral naïve patients: Efavirenz and Atazanavir/ritonavir.

In these two registrational trials Elvitegravir was given as a single tablet regimen that also included Tenofovir, Emtricitabine and Cobicistat (COBI). Together these four drugs are denominated “QUAD”. In QUAD, COBI is used as a pharmacokinetic enhancer in the same way low dose ritonavir is used to potentiate protease inhibitors.

Compared to ritonavir, COBI is a more specific inhibitor of CYP3A without antiretroviral activity. COBI is a weak inhibitor of CYP2D6, does no inhibit other CYP isoforms and probably is less susceptible to induction. In vitro data also suggest that COBI produces less perturbation of normal adipocyte functions such as lipid accumulation and/or response to insulin. Consequently COBI theoretically had the potential for fewer adverse biochemical effects relative to ritonavir. The full spectrum of COBI interactions is still not known.

COBI is an inhibitor of a renal tubular transporter called toxin extrusion protein 1 (MATE1). Other drugs such as ritonavir, trimethoprim, and cimetidine inhibit the same transporter. Because MATE1 mediates the tubular efflux of creatinine, COBI can increase serum creatinine and decrease estimated glomerular filtration rate by inhibiting this tubular efflux of creatinine without directly affecting actual glomerular filtration rates. Interestingly Dolutegravir, another integrase transfer inhibitor, inhibits a different proximal tubule transporter, OCT2 (organic cation transport) with a similar impact on calculated glomerular filtration rates (Figure 1).

The 236-103 trial randomized 708 subjects with a mean CD4 cell count of approximately 370 cells/µL, 39% with viral loads ≥ 100,000 copies/mL, all with creatinine clearance above 70 mL/min to receive QUAD or TDF/FTC + ATV/r. After 48 weeks of follow-up QUAD was non inferior to TDF/FTC + ATV/r with 90% and 87% respectively having HIV-RNA of < 50 copies/mL. In the 236-013 trial the type of analysis performed to evaluate efficacy is different from the usual TLOVR. The analysis used is the FDA snapshot algorithm. While the TLOVR used data from every visit to consider the pattern of HIV-1 RNA results (e.g., confirmed suppression/rebound), the new snapshot method uses only the HIV-1 RNA data at the visit of interest (see figure 1 for explanation).

None of the 8 patients with virologic failure analyzed for resistance in the ATV/r arm had isolates with resistant mutations while all the 5 patients analyzed for resistance in the QUAD arm had isolates with nucleoside or integrase resistance.
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
There was no difference between arms in CD4 cell recovery.

In patients with high viral loads at baseline response rates were similar (QUAD 85%, TDF/FTC + ATV/r 82%). Discontinuations rates for adverse events were similar (QUAD 4%, TDF/FTC + ATV/r 5%). Median creatinine clearance decreased significantly more from baseline in the QUAD group: -12.7 mL/min in QUAD and -9.5 mL/min in TDF/FTC + ATV/r. Triglycerides increases were significantly higher in the ATV/r group. There were no differences in bone mineral density changes from baseline up to week 48.

The 236-102 trial randomized 700 patients with a mean CD4 cell count of approximately 386 cells/µL, 33% with viral loads ≥ 100,000 copies/mL, all with creatinine clearance above 70 mL/min, to receive QUAD or coformulated TDF/FTC/EFV. After 48 weeks of follow-up QUAD met the non-inferiority criteria with 88% and 84% of QUAD and TDF/FTC/EFV recipients achieving viral suppression respectively by the snapshot algorithm. In patients with high viral loads at baseline response rates were similar (QUAD 84%, TDF/FTC/EFV 82%). CD4 cell recovery was significantly higher with QUAD (239 vs 206 cells/µL). All the 8 patients with virologic failure analyzed for resistance in the QUAD arm had isolates with nucleoside resistance (seven of them also with integrase mutations). In the Efavirenz arm 8 patients were analyzed for resistance due to virologic failure. All of them had mutations conferring resistance to non-nucleosides while only 2 had nucleoside mutations.

Discontinuations rates for adverse events were similar (QUAD 3%, TDF/FTC/EFV 5%). While nausea was more common at baseline in patients randomized to QUAD, not surprisingly abnormal dreams, dizziness, insomnia and rash were more frequent in the TDF/FTC/EFV treated patients. As it happened in the 103 trial median creatinine clearance decreased significantly more from baseline in the QUAD group: -14.3 mL/min in QUAD and -3 mL/min in TDF/FTC/EFV. Total cholesterol and LDL increases were significantly lower for QUAD.

The results of the 102 and 103 trials clearly demonstrate that QUAD can be used in antiretroviral naïve patients. The efficacy of QUAD is almost identical to the efficacy of coformulated TDF/FTC/EFV or TDF/FTC plus ATV/r. Given these results it is quite likely that QUAD is going to be approved and supported by guidelines to be used in naïve patients.

It should be highlighted that QUAD in the two pivotal trials has been used in patients with creatinine clearance above 70 mL/min. In both trials COBI produced small increases in serum creatinine that are probably not clinically significant but clinicians should be aware of the need for monitoring renal function in patients receiving QUAD. Deciding if creatinine increases are due to TDF or COBI is not going to be simple although in the oral presentation at CROI it was suggested that only elevations of creatinine above 0.4 mg/dL were associated with markers of tubular dysfunction such as proteinuria more likely to be caused by TDF.

The 102 and 103 trials included patients with very high CD4 cell count (close to 400). This is in contrast with a baseline CD4 cell count of around 218 cells/µL in the STARTMBR trial (reported in 2008), which explored Raltegravir in antiretroviral naïve patients. This difference among trials in baseline CD4 probably reflects the current clinical practice of earlier treatment of HIV infected patients. However it should be noted that since patients with very low CD4 were underrepresented in the 102 and 103 trials caution is needed before using QUAD in a patient with very advanced disease.

In summary QUAD is first single tablet regimen that matches the antiviral eficacy of TDF/FTC/EFV and TDF/FTC plus ATV/r. Given that QUAD lacks the CNS adverse events that are the signature toxicity of EFV and that is simpler to administer than ATV/r or Raltegravir, I consider it as an important addition to our antiretroviral armamentarium.

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:
1. DeJesus E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 627.
Diseases such as rheumatoid arthritis and inflammatory bowel disease as well as HIV infection that are associated with chronic immune activation and increased inflammatory cytokine production lead to premature onset and increased incidence of common prevalent diseases of aging including cardiovascular disease (CVD), diabetes mellitus, chronic kidney disease, osteoporosis and malignancies.

These diseases account for the majority of morbidity and mortality events in persons with HIV receiving virologically suppressive antiretroviral therapy (ART). Untreated HIV triggers a state of immune activation that is normally part of the immune responses that facilitate clearance of a pathogen. Indeed in HIV infection, immune activation initially leads to decrease in HIV replication, but subsequently the establishment of chronic immune activation leads to reduced CD4 recovery on treatment, lymphoid tissue fibrosis, increased T cell turnover, exhaustion and immune senescence. This state of immune activation and resulting chronic inflammation is only partially reduced by virologically suppressive, successful ART. Why chronic activation and inflammation persists despite viral suppression is incompletely understood but represents a key unmet need for HIV care.

**What drives chronic immune activation in HIV-infection?**
A range of different events have been hypothesised that may cause chronic immune activation to persist despite HIV suppression:

These include
- Residual viral replication below the limits of standard assay detection.
- Co-infection such as with cytomegalovirus, other herpes viruses, HCV, TB.
- Leakage of gut endotoxin/lipopolysaccharide (LPS)/microbial translocation due to reduced gut mucosal barrier and loss of gastrointestinal associated lymphoid tissue (GALT).
- Hyperglycemia and other metabolic disorders triggering activation of NF-kappaB pathways.

With immunosenesce being contributed to by
- Reduced thymic output.
- Telomere shortening possibly as a result of NRTI inhibition of telomerase.
- Immune dysregulation.
- Lymphoid fibrosis and loss of follicular dendritic networks.

The hypotheses have been investigated both directly and via intervention studies. Often there is a difficulty with the available data in separating out whether the observations represent a cause of immune activation or a consequence.

**It remains unclear** if low level viremia detected in modified ultrasensitive assays with detection limits of <3 copies/ml represents on-going cycles of replication potentially amenable to therapy intensification or simply release of virus from long-lived cells such as monocytes and macrophages that were infected prior to initiation of ART.

Recent data from the FRAM study found that in 1116 subjects stratified by viremia (not detected at <1 copy/ml, 1-19,
in CD4-cell activation between arms was statistically significant (P = 0.028). While the percentage of activated T cells in rectal tissue did not change significantly with placebo, percentages of activated CD4 and CD8 cells in rectal tissue nearly doubled in the maraviroc group while LPS levels declined [5]. Thus, declines in LPS did not associate with declines in peripheral CD4 or CD8 activation.

Furthermore, studies with an oral therapy based on bovine colostrum containing high affinity anti-LPS antibodies also showed no effects on T cell activation or recovery in HIV positive patients on successful ART [6]. These data suggests that rather than causative of immune activation raised LPS may be a consequence of the damage to GALT by acute and chronic immune activation, leading to incompetence of the mucosal barrier and LPS leakage into the systemic circulation.

**Leakage or translocation** of microbial products such as endotoxin and LPS from the gut into systemic circulation was identified as an important component of HIV pathogenesis in untreated patients and proposed a cause of persistent chronic inflammation during successful ART. Early destruction and poor structural reconstitution of GALT are likely key contributors to the weakening of the mucosal barrier.

In a study of 42 individuals with suppressed HIV for least 1 year but a CD4 count still below 350 randomised to maraviroc or placebo for 24 weeks, viral load measured by a single-copy assay dropped significantly in both treatment arms and CD4 count rose, with no difference between arms. In a subset of 15 people who underwent serial rectal biopsies, maraviroc tended to reduce CD8 activation in rectal tissue (-7%, P = 0.07) while CD8 activation in peripheral blood rose in those taking maraviroc (+18%, P = 0.07) while falling through 24 weeks in the placebo group (-11%, P = 0.039). CD4-cell activation in peripheral blood dropped significantly in the placebo group through 24 weeks (-25%, P = 0.001) but not in the maraviroc group. The 24-week difference

**Inflammatory states are known** to accompany various metabolic disorders, including visceral obesity and insulin resistance. Thymidine NRTI injury of peripheral fat is known to establish a chronic inflammatory tissue infiltrate in association with lipoatrophy [12]. Diabetes mellitus is 3–4 fold more prevalent in HIV infected populations relative to age and sex matched HIV negative subjects [13]. Elevated glucose levels lead to NF-κB activation and Toll-like receptor expression [14]. Similarly, dyslipidemia may also activate this pathway as seen is subjects with familial dyslipidemia leading to higher inflammatory markers such as IL-6 and hsCRP [15]. This in turn progressively increases insulin resistance, creating a vicious cycle of immune activation and metabolic disorder. It is not known if a similar effect is seen when dyslipidemia is triggered by antiretroviral agents. While NF-κB plays a key role in regulating the immune response to infection, dysregulation of NF-κB has been linked via a chronic immune activation states to cancer, inflammatory and autoimmune diseases.

**What can be done?**

Attempts to reduce immune activation and inflammatory markers in HIV infected subjects with suppressed HIV RNA have been disappointing. As noted above addition of raltegravir and maraviroc have not shown consistent benefits. Immune modulators such as IL-2, while increasing CD4 numbers and decreasing T cell activation in HIV patients, failed in clinical endpoint studies [16]. Hydroxychloroquine also has shown potential in reducing immune activation particularly in immune poor responders [17] but did not demonstrate effects on immune activation or slow CD4 decline in untreated individuals [18].

While valganciclovir has been successful in short term studies its cost and toxicities do not make sustained administration practical. The benefits of chronic acyclovir use are less well established regarding immune activation and in individuals with suppressed HIV RNA.
Convincing data have been reported with HMG-coxreductase inhibitors (statins). In a 24 patient, randomised, double-blind, placebo-controlled crossover trial of 8 weeks of 80 mg atorvastatin in persons with untreated HIV infection, while HIV RNA level was unaffected by the intervention (-0.13 log(10) copies/mL; p = .85), atorvastatin use resulted in reductions in circulating proportions of CD4(+) HLA-DR(+) (-2.5%; P = .02), CD8(+) HLA-DR(+) (-5%; P = .006), and CD8(+) HLA-DR(+)/CD38(+) T cells (-3%; P = .03). Reductions in immune activation did not correlate with declines in serum levels of low-density lipoprotein cholesterol [19]. In suppressed patients, a case-control study over 48 weeks (133 cases on atorvastatin – 266 controls not on a statin) CD38 activation was significantly lower in cases vs. controls, with no difference in high-sensitivity C-reactive protein (hsCRP) and CD4 [20].

Recently, the John Hopkins cohort has reported an analysis of 1538 HIV-infected patients with HIV RNA suppression for >180 days, of whom 238 (15.5%) received a statin while taking ART. There were 85 deaths (7 in statin users, 78 in non-users) during follow-up. By multivariate Cox regression, statin use was associated with a relative hazard of 0.33 (95% CI: 0.14, 0.76; P = 0.009) after adjusting for CD4, HIV-1 RNA, hemoglobin and cholesterol levels at the start of HAART, age, race, HIV risk group, prior use of ART, year of HAART start, NNRTI vs. PI-based ART, prior AIDS-defining illness, and viral hepatits coinfection. Malignancy, non-AIDS-defining infection and liver failure were particularly prominent causes of death. While it is unclear if these outcomes related to reduced immune activation, the data underline the importance of early initiation of statins in people with HIV [21].

Finally, earlier initiation of ART may limit the duration and magnitude of exposure to the viral antigenic drive towards chronic inflammation. A recent study compared residual levels of T-cell activation in patients who initiated ART within 6 months and those initiating 2 or more years after primary HIV infection. After a median duration of treatment of over 2 years, both CD4+ and CD8+ activation marker levels were significantly lower in early initiators. However, CD8+ activation levels remained significantly higher and CD4+ activation levels relatively higher than HIV-negative controls suggesting a partial benefit of early ART initiation [22].

**Conflict of Interests**

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

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

---

**References:**


Advertisement
Talking about PML in 2012
While starting writing this article, we just dismissed our last patient with PML. He is a 48-years old man, who was admitted one month ago with a four-weeks history of progressive visual, speech and cognitive problems and brain lesions at magnetic resonance imaging (MRI), for which he had been treated with intravenous dexamethazone. He was unaware to be HIV-seropositive and HIV infection and PML were diagnosed simultaneously upon admission. His CD4 cell count was of 323/µL, with a viral load of 5810 c/mL. The diagnosis of PML was not difficult, with MRI showing characteristic T2-hyperintense and T1-hypointense signal alterations (Figure 1a), and JC virus (JCV)-DNA detected in the cerebrospinal fluid (CSF) at 7000 c/mL. Combination antiretroviral therapy (cART) was started immediately, but it was followed by important clinical and radiological worsening (Figure 1b). Immune reconstitution inflammatory syndrome (IRIS) was diagnosed and our patient received a first course of intravenous methylprednisolone 1 g/day for 5 days, and, after one week, intravenous dexamethazone 8 mg tid for 10 days followed by oral taper, eventually leading to clinical and MRI improvement (Figure 1c). After 6 weeks of cART and steroid treatment, VL is undetectable, but CD4 have dropped to 88/µL and our patient just presented with fever and 4800 c/mL of plasma cytomegalovirus DNA. Repeat CSF examination for JCV-DNA measurement is planned.

This brief report summarizes not only the diagnostic work-up leading quickly to cART initiation, but also illustrates some not so typical aspects in PML presentation and management: onset with relatively high CD4 cell count, development of IRIS, treatment with steroids with its consequences.

Unlike most opportunistic infections, PML does occur also in patients with CD4>200/µL, like in our patient, in patients starting cART, and, although more rarely, in long-term treated patients with full viral suppression. PML occurrence in such atypical contexts, together with its relatively high mortality, make PML a truly scaring disease. Indeed, PML is currently the second cause of AIDS-related deaths, after non-Hodgkin lymphoma [1], with a mortality that is ten-times higher than the combined mortality of all AIDS-related diseases [2].

A disease with many secrets
It is not clear why PML presents in these unusual scenarios and, more in general, many aspects of PML pathogenesis remain undefined.

PML is well-known to be caused by the ubiquitous polyomavirus JC, which, following primary infection, establishes a persistent infection in the urinary tract and possibly in the brain or other peripheral tissues [3]. In patients with immune disorders or on immunosuppressive or immunomodulant therapies, JCV may cause the lytic infection of oligodendrocytes leading to brain demyelination and tissue distruction, which will determine the progressively fatal disease course [4].

This natural course can be modified by reversion of the underlying immune deficit, e.g., starting cART in HIV-associated...
Advertisement
PML, or removing immunosuppressive or immunomodulant drugs. Thus, considering that PML presents in persons with an immune deficit and that it may remit following reversion of the immune deficit, it is clear that the host immunity plays a key role in both PML onset and outcome. In fact, T-lymphocytes from patients with PML seem to respond poorly to JCV proteins in vitro and, on the other hand, higher and earlier T-cell responses following diagnosis of PML have been associated with higher rates of disease remission [5, 6].

Virus factors are also involved in the pathogenesis of PML. ‘Rearranged’ sequences of NCCR (the ‘Non Coding Control Region’, which contains binding sites for cell proteins and sequences necessary to virus replication) are constantly observed in viruses obtained from brain or CSF, but not from urine, of PML patients [7]. Similarly, the CSF, but not the urines, of PML patients, contains JCV sequences carrying specific ‘PML-associated mutations’ in the VPI region (VPI stands for the Viral Protein-I, which forms the virus capsid and is essential for both binding to cell receptors and immune responses) [8].

Overall, these observations suggest a general model by which intra-patient selection of ‘PML-genic’ virus, i.e., carrying NCCR rearrangements and VP1 mutations, together with the loss of immune control, would concur to PML development. However, many questions remain unanswered, including when this virus is selected (just before PML or pre-existent?), where (in brain or in peripheral tissues?) and how (as a consequence of loss of immune control?).

**Easier to recognize, hard to manage**

Despite the many shadows in understanding the mechanisms behind PML, tools and experience have developed over the last 25–30 years that may enable a prompt diagnosis in most of the cases. The diagnosis of PML relies on clinical history, neurological and MRI findings and, usually, JCV-DNA detection in CSF (Table 1), and it is not difficult in typical cases, especially now that other central nervous system (CNS)-OIs are infrequent. In some cases, however, evidence of inflammation at MRI, such as contrast enhancement, edema or mass effect, may make the diagnosis more problematic.

**Table 1. Diagnostic criteria of PML**

<table>
<thead>
<tr>
<th><strong>Definite diagnosis</strong></th>
<th><strong>Presumptive diagnosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. CSF-confirmed: clinical and MRI findings consistent with PML and JCV-DNA detected in CSF</td>
<td>a. Typical clinical and MRI findings, with tissue examination and lumbar puncture either not performed or JCV DNA not detected in CSF</td>
</tr>
<tr>
<td>b. Tissue-confirmed: neuropathology (biopsy or autopsy) consistent with PML and JCV DNA or protein detected by in situ techniques</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Treatment of PML by cART**

<table>
<thead>
<tr>
<th>Presumptive diagnosis</th>
<th>Definite diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Off cART (naive or cART interruption): initiate cART</td>
<td>a. Off cART (naive or cART interruption): initiate cART</td>
</tr>
<tr>
<td>b. Recently started cART (&lt;6 months): Continue cART</td>
<td>b. Recently started cART (&lt;6 months): Continue cART</td>
</tr>
<tr>
<td>c. Chronic cART, HIV-1 suppressed: Continue cART, consider cART intensification</td>
<td>c. Chronic cART, HIV-1 suppressed: Continue cART, consider cART intensification</td>
</tr>
<tr>
<td>d. Chronic cART, HIV-1 non suppressed: Optimize cART</td>
<td>d. Chronic cART, HIV-1 non suppressed: Optimize cART</td>
</tr>
</tbody>
</table>

**Easier to recognize, hard to manage**

Despite the many shadows in understanding the mechanisms behind PML, tools and experience have developed over the last 25–30 years that may enable a prompt diagnosis in most of the cases. The diagnosis of PML relies on clinical history, neurological and MRI findings and, usually, JCV-DNA detection in CSF (Table 1), and it is not difficult in typical cases, especially now that other central nervous system (CNS)-OIs are infrequent. In some cases, however, evidence of inflammation at MRI, such as contrast enhancement, edema or mass effect, may make the diagnosis more problematic.

cART is the only effective treatment of PML but, unfortunately, it is not always successful, with a one year survival of only between 40% and 75% [3, 9]. Once PML is diagnosed, cART has to be initiated immediately, or continued, if patient is on treatment (Table 2). Subsequent disease evolution is unpredictable, and it can be monitored by clinical examination, MRI and CSF examination for JCV DNA, which will show clearance of the virus in remitting cases [10].

Several cART strategies have been suggested, such as using more than three drugs or drugs with high CNS penetration [9], however these have not been confirmed to be more useful than standard approaches. Although there is no clear evidence that PML survival has improved with time, it is possible that the newer cART combinations, including more potent and better tolerated drugs, could accelerate the immune recovery and thus increase the chances to halt PML progression. There are, on the other hand, no JCV-specific drugs that have been shown to be effective in PML, despite several studies have been done using cytarabine, cidoviro, mitazapine, mefloquine or other drugs [summarized in ref 3].

**An uncertain future**

What can we reasonably expect in a near future to reduce the burden of mortality and morbidity of PML? The development of effective antiviral drugs would probably represent the best option for cure but, unfortunately, this solution is not behind the corner. Nevertheless, a better understanding of the interactions between virus and immune response would hopefully translate into development of immune-based treatments, aiming to both prevent PML development in patients at risk and...
to limit the damage once it is initiated. In the meanwhile, expedite PML diagnosis, cART and careful control of IRIS remain our first-line weapons for PML management – to be used at the best of their potential.

Conflict of interests
Paola Cinque has received research grants from Biogen Idec, Mundipharma and honoraria as speaker and/or advisor consultar from Abbott, Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Elan, Gilead Sciences, GlaxoSmithKline, Janssen, Johnson & Johnson, Merck, Mundipharma, Viiv.

References: