HIV & VIROLOGY NEWS

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FRANCE

HIV DRUG THERAPY CONGRESS GLASGOW 2014 · WHERE NOW FOR PROTEASE INHIBITORS?
PROTEA: THE END OF THE ROAD OF PROTEASE INHIBITOR MONOTHERAPY? · HIV NEWS FROM GLASGOW 2014
HIV NORDIC CONFERENCE STOCKHOLM 2014 · SATELLITE SYMPOSIUMS AT THE HIV NORDIC CONFERENCE
AASLD 2014: THE ERA OF IFN-FREE HEPATITIS C TREATMENT IS ENTERING CLINICAL PRACTICE!
HIV & VIROLOGY NEWS

HIV & Virology News is a quarterly publication with four issues per year. The magazine is distributed free of charge to all those specialists in the field of infectious diseases in 13 European countries including the UK, the Netherlands, Belgium, Germany, France, Spain, Italy, Sweden, Norway, Denmark, Finland, Austria and Switzerland.

The magazine is in English with all content being HIV and virology related. It also include summaries of research results from the above mentioned countries as well as consensus relating from the fields of HIV and virology. Also featured are educational programmes and excerpts from seminars and conferences.

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In this issue:

2 Letter from the Editor
Magnus Gisslén

3 HIV Drug Therapy Congress Glasgow 2014
Per Lundblad

11 Where now for Protease inhibitors?
Graeme Moyle

15 PROTEA: the end of the road of protease inhibitor monotherapy?
José R Arribas

19 HIV News from Glasgow 2014
Christine Katlama

27 HIV Nordic Conference Stockholm 2014
Per Lundblad

38 Satellite Symposiums at the HIV Nordic Conference
Per Lundblad

40 AASLD 2014: the era of IFN-free hepatitis C treatment is entering clinical practice!
Heiner Wedemeyer

45 Notes 2014
Leo Flamholc

48 Topical Conferences

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This marks the concluding issue of HIV & Virology News for 2014. As the year draws to a close, I would like to thank my co-editors and all the other contributors for their continued efforts to make this journal successful. Several interesting and important aspects of HIV and hepatitis have been covered during 2014, and we greatly appreciate all the positive responses and encouragement we have received. If you have suggestions for topics or themes that you would like to see in these pages in 2015, please do not hesitate to contact the editorial office and share your thoughts.

I also want to thank the advertisers who have made it possible to distribute each issue of the magazine to over 15,000 physicians in the field of infectious diseases in 13 European countries. We look forward to returning in 2015 and continuing to follow and comment on relevant topics in the sphere of HIV and hepatitis.

We will also present more reports about the Ebola epidemic in West Africa. What is happening with the epidemic seems somewhat unpredictable at the moment. While it is clearly decreasing in Monrovia, the capital of Liberia, it is still out of control in Sierra Leone and some rural parts of Liberia and Guinea. Initially, organizations such as Médecins Sans Frontières (MSF) and the International Red Cross were the main—or only—ones operating treatment and care centers of any magnitude in the affected region. Now, finally, the international community has responded and has launched large-scale assistance programs. Some clinical treatment studies have already commenced or are about to begin, and it will be of great interest to see the results of those studies. An effective protective vaccine will probably be in place within 6 to 12 months; the reports of initial results have been encouraging. However, when the worst of the crisis has subsided, the enormous task of rebuilding the normal healthcare systems of the affected countries remains. Ebola has had devastating effects on the general provision of healthcare, including HIV treatment projects.

Of the approximately 1.2 million Americans with HIV, only 30% achieved viral suppression, according to November’s Vital Signs Report in MMWR. The results are definitely much better in many European countries, although several still have a long way to go to reach the UNAIDS 90-90-90 goals that

• By 2020, 90% of all people living with HIV will know their HIV status.
• By 2020, 90% of all people diagnosed with an HIV infection will receive sustained antiretroviral therapy.
• By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression.

The first goal is probably the hardest to achieve. Too many patients are still detected late and with low CD4 cell counts. Better and broader testing programs are needed, and the awareness of HIV among healthcare providers also has to be improved. An unacceptable number of those infected with HIV who have indicator diagnoses are still being missed. The two last goals are easier and have already been achieved in some nations, including the Nordic countries. In Sweden, 93.6% of all diagnosed HIV-infected patients are on antiretroviral treatment. According to a snapshot analysis, 95.4% of these have a plasma viral load < 50 copies/mL (InfCare HIV, December 2014).

The development of antiretroviral drugs has been an exceptional success, transforming HIV from a disease that inevitably led to death into a chronic disease without significant impact on life expectancy. Moreover, the contagiousness of HIV has also been reduced to extremely low levels. Will it ever be possible to achieve an AIDS-free world? Is universal antiretroviral treatment a viable option for achieving such a goal, or is the elusive, long sought protective HIV vaccine the only solution? Many strategies will probably be needed to close the book on the AIDS epidemic, but as UNAIDS points out, one thing is certain: “It will be impossible to end the epidemic without bringing HIV treatment to all who need it.”
The first HIV Drug Therapy Congress was held in Glasgow in 1992. The biannual Glasgow Congress is today a strong brand name – it is the most popular Meeting in Europe for exchanging scientific information on HIV. In 2014 the Congress was held 2 – 6 of November, and more than 2,500 delegates from 86 countries came to attend.

All of this was pointed out by Prof Ian Weller, who was co-Chair of the Scientific Committee, in his welcoming address.

This Session had a lecture dedicated to Joep Lange and Jacqueline van Tongeren, in recognition of their commitment and passion to rid the world of HIV/AIDS.

They both tragically lost their life when the airplane they were travelling on crashed in Ukraine earlier in 2014. Prof Peter Reiss, who on a personal note introduced the lecture, described them as two close friends.

The lecture itself was given by Prof Kevin Fenton and the title was Curbing the HIV epidemic on both sides of the Atlantic – a public health perspective. He began this by describing the situation in the US.

**Trends in US and UK**
- An estimated 1.1 million people in USA is living with HIV. Annually approx. 50,000 Americans are infected and there are 18,000 deaths, Prof Fenton stated.
- The HIV prevalence increased by 8% from 2006 to 2009. But there are also some good news:
  - HIV transmission rate has declined 9% during these years.
- In UK 2012, an estimated 98,400 people are living with HIV/AIDS. There were 6,000 people newly diagnosed in 2013. Overall there is a declining trend since the peak in 2005, Prof Fenton continued.
- A key factor in the UK is the new diagnoses among men who have sex with men (MSM). They were 3,250 in 2013, which is a figure that is up 22% since 2005. And 1 in 6 newly diagnosed is over 50 years of age – compared with 1 in 14 in 2004.

Over the last decade in UK there has been a steady increase in the number of new HIV diagnoses in MSM. They accounted for 51% of new diagnoses in 2012, the he highest number ever reported.
- The rise in diagnoses in MSM may be explained by both an increase in HIV testing and on-going high rates of transmission, he said.

**Public health implications**
- In US MSM account for 2% of the population but for 64% of new HIV infections. In 2009 there were 11,200 new HIV infections among US women. The rate among black women was 15 times higher than that of white women.
- In both UK and US HIV is an urban disease, and in both countries epidemics continue to evolve and have become more concentrated over time. There has been some success in reducing incidence and diagnoses in intravenous drug users (IDU) and heterosexuals, and we need to cele-
brate those successes. But MSM remain at increased risk, Prof Fenton pointed out. Hyperendemic diseases within urban areas are driven by numerous factors including migration, risk behaviours and social determinants.

– I would argue that these data confirm the need for continued and re-energised focus on addressing the epidemic – by identification and prioritisation of key populations, targeting and tailored approaches to prevention and strengthening placed-based and social determinants approaches.

Prof Fenton added that linkage to care and retention in care is excellent in UK.

– In stark contrast to the US...

Relies on political will

Prof Fenton presented the US national HIV/AIDS strategy (NHAS) from 2010 and the English sexual health strategy from 2013, and discussed the differences between them.

– The English is broader, because it is addressing general sexual health.

He stressed that national HIV strategies remain a critical component of an effective national response to the epidemic.

– The impact of the US NHAS – the first of its kind – has been instrumental in delivering greater coordination, profile, accountability and community engagement.

The integrated sexual health strategy in England is innovative, but must keep visibility and focus on HIV.

But both strategies rely on political will, commitment and visibility.

– A willingness to challenge convention – not business as usual! We cannot fight the rapidly evolving epidemic, changing behavioural and social norms in a fragile economic context using the same tools and approaches that helped us get here.

Prof Fenton therefore ended his lecture with a call for research for new prevention, diagnostic and treatment modalities and a focus on implementation science.

– This research must drive towards a greater health impact, reduced costs – and a greater acceptance of people’s rights, lives and diversity, he ended his lecture.

Implants and retroviral therapy

Progestosterone containing subdermal implants is a highly effective contraceptive option, for which the contraceptive failure rate is less than 1%. It’s a discrete, female-controlled, long-acting contraception. When removed, the woman rapidly returns to fertility.

One commonly used subdermal implant contains levonorgestrel as the active progestosterone.

Kimberly Scarsi presented a study on characterizing the pharmacokinetics of levonorgestrel in HIV-infected women receiving efavirenz (EFV) based or nevirapine (NVP) based ART. It was a non-randomized, open-label, parallel group, pharmacokinetic study among HIV-infected Ugandan women.

– We found that women on NVP-based ART had consistently higher levonorgestrel concentrations through week 24 of combined use. Conversely levonorgestrel concentrations were reduced by 40 – 54% over 24 weeks in women receiving EFV-based ART, she said.

She added that these data add to the growing concern of reduced contraceptive efficacy with this implant and EFV-based ART.

Darunavir throughout pregnancy and postpartum

ART is recommended during pregnancy for prevention of mother-to-child transmission (MTCT) of HIV. Physiological changes during pregnancy are known to affect the pharmacokinetics of protease inhibitors (PI), leading to lower exposures in pregnant women.

– Darunavir (DRV) is a second generation PI indicated for use in a treatment experienced as well as treatment naive populations. It is effective in vitro against both wild type and PI-resistant HIV. However, pharmacokinetic data on DRV throughout pregnancy is limited to a few studies, said John Lambert.

He presented a study on darunavir/ritonavir (DRV/r) 800/100 mg daily in 23 women over the course of pregnancy and post-partum.

The study had enrolled 23 women, and 11 of these initiated treatment during pregnancy. All but 2 were virally suppressed at time of delivery. There were 23 live births and no cases of MTCT.

– In most cases examined, the regimen was effective at achieving adequate therapeutic drug levels during pregnancy. However, reduced DRV in the second and third trimester highlights the need for therapeutic drug monitoring in this population – and warrants further study of pregnancy-associated changes in DRV pharmacokinetics, Dr Lambert reported.

The transplacental transfer of DRV found in the study was low, and this result is consistent with previous reports, he continued.

– Most importantly – no woman delivered an infant infected with HIV!

Does pregnancy increase the risk of hepatotoxicity in HIV-infected women?

Dr Susie Huntington presented a study that aimed to assess whether pregnancy is associated with an increased risk of li-
ver enzyme elevation in ART.

– This study differs from previous studies – which found no association – in that it has a long follow-up and in that women were included both when they were pregnant and when they were not – thereby acting as their own controls, Dr Huntington explained.

The study included pregnancies conceived on ART and pregnancies during which ART was started.

She concluded that their study had found further evidence that pregnancy poses an increased risk for liver enzyme elevation. This highlights the importance of close monitoring of liver biomarkers and clinical symptoms of toxicity during antenatal care.

– Clinicians should also be mindful that in pregnancy, due to the effect of portal vein embolization, a lower alanine transaminase threshold is used to indicate toxicity, Dr Huntington pointed out.

A tale of two viruses
The Ebola epidemic ongoing in West Africa set its mark on the Glasgow Congress. The traditional Lock lecture should have been delivered by Prof Wafaa El-Sadr, but due to the Ebola crisis she was unable to come to Glasgow. Instead this was presented by Prof Kevin De Cock.

– Prof El-Sadr thought that Ebola has to be addressed in HIV. Therefore I have chosen to give this lecture, entitled Ebola and HIV: A tale of two viruses, Prof De Cock initially explained.

After presenting data on earlier outbreaks, he talked about Ebola virus pathogenesis: Direct infection of tissues, immune dysregulation, hypovolemia and vascular collapse.

– The incubation period is 2 – 21 days, and the patient is infectious only when symptomatic. Early symptoms include fever, fatigue, headache, sore throat, muscle and joint pains – the diagnosis is difficult. Later symptoms are vomiting, diarrhoea, hemorrhage and multiorgan failure, Prof De Cock said.

Death comes from hypovolemic shock, hemorrhage and multiorgan failure. The fatality rate is 41 – 90 %.

There are at present no approved Ebola treatments or vaccines.

– It is an assumption that you only get infected once, and – if surviving – then have immunity.

Health workers have paid a high price
There are many challenges in field work to fight Ebola.

– It is carried out in resource-poor areas, with limited disease surveillance and limited laboratory support. It also includes negotiating with communities that can be hostile, Prof De Cock stated.

The outbreak also has several secondary – but largely unmeasured – consequences: It has an economic impact, schools are closed and mass gatherings are halted. It has led to family disruption, orphanhood and a collapse of the health care system.

– Health workers have paid a high price – they account for 15 % of deaths in Liberia. For patients with HIV and/or AIDS, we must take into account the interruption of their treatment. This is also much unmeasured, Prof De Cock continued.

There are many similarities between HIV and Ebola, but also differences.

– The stigma surrounded to people that has been in Ebola countries, is very similar to those patients with HIV experienced in early days.

Lessons learned from the HIV response in Africa are relevant. They concern workforce innovations, laboratory systems, outreach activities, community mobilisation, civil society involvement and human rights, Prof De Cock stated.

– Ebola epidemic has enormous economic, political and security consequences. Our experience from HIV has taught us
that a science-based response must prevail. The recovery from Ebola in West Africa will be long and difficult – it is a collective responsibility and it is achievable, he summarised.

What to consider when starting ART
EACS President Prof Manuel Battegay talked about the choice of initial therapy.

- Different recommended initial ART regimens for adult HIV-positive persons demonstrate excellent potency and low – but existing – risk for adverse events, he said.

Prof Battegay presented an overview of the regimens recommended by EACS. He continued by talking about resistance as one of the first considerations.

- In Europe, the prevalence of transmitted HIV drug resistance is 11.1 % in MSM, 6.6 % in heterosexuals and 5.1 % in people who inject drugs.

Genotypic resistance test is recommended at HIV diagnosis prior to ART, otherwise before initiation of ART.

- If ART needs to be initiated before the results are available – include a ritonavir-boosted protease inhibitor (PI) in the first-line regimen, Prof Battegay said.

He also talked about adherence.

- A meta-analysis showed that adherence was better for one-pill regimens.

There is a significantly increased risk of myocardial infarction with cumulative exposure of abacavir, lopinavir/r – but not of efavirenz or atazanavir/r.

- Abacavir should be used with caution in persons with a high risk for cardiovascular disease.

Individualisation of therapy
Drug-drug interactions are important, but Prof Battegay said he would not speak so much on the subject.

- Very good information is available on the Internet – at www.hiv-druginteractions.org and in EACS guidelines.

The choice of initial ART should take into consideration many individually presented factors such as resistance, co-morbidities, drug-drug interactions, adherence, convenience and others.

- Individualisation of therapy should actively be discussed, also taking the view of the patient into consideration, Prof Battegay underlined.

He presented a survey on the patient’s perspective in which 88 % agreed or strongly agreed in the statement “I was involved in the choice of ART”. 33 % agreed or strongly agreed to “I had a preference for a certain ART regimen”.

- Newer drugs and drug regimens, as well as alternative regimens, add to the possibilities of initial choice of therapy, he summarised.

Dolutegravir once daily
Prof Jean-Michel Molina presented the 96 week results from the FLAMINGO study.

In this multicentre, open-label, randomised study HIV infected patients were randomly assigned to receive dolutegravir (DTG) 50 mg once daily, plus 2 NRTIs, or darunavir (DRV) 800 mg plus ritonavir 100 mg once daily, plus 2 NRTIs.

The study is ongoing, with patients after 96 weeks entering the extension phase on DTG + ART, to provide more long-term data in subjects receiving DTG.

- We found that DTG 50 mg once daily was superior to DRV /r 800mg/100 mg once daily through 96 weeks, Prof Molina said.

This result was driven by lower virological failure rates, and fewer withdrawals due to adverse events. There were no virological failures in the DTG arm after week 24. No emergent integrase inhibitor, protease inhibitor or nucleoside reverse transcriptase inhibitors mutations were found in any arm.

- Consistent with data from week 48, DTG 50 mg once daily was well tolerated with a good safety profile trough week 96. DTG 50 mg once daily with either ABC/3TC or TDF/FTC provides an attractive option for treatment-naïve patients, was Prof Molina’s conclusion.

Where does the patient fit in?
At a satellite symposium sponsored by ViiV Healthcare, the difference between patients in clinical trials and in clinical practice was discussed.

- We have got several antiretrovirals in 2014 – but we also got a lot of patients that differ from each other, Dr Mark Nelson pointed out.

He continued by stating that we often talk of “the average patient”. But what is that?

- It is a male, white, ART-naïve MSM that is 36 years old – and by that I mean the patient that enter studies and that we see in clinical trials, Dr Nelson answered his own question.

In real life there is a gap between patients in trials and those we see in our practice, he said.

- Therefore we need to think where our patients fit in when we read guidelines.

Dr Nelson drew attention to the fact that patients and doctors do not think ali-
ke when it comes to ARV therapy.

- Patients say: You decide! You’re the doctor. They want something that works, and Single Tablet Regimen (STR) is not high up on their wishing list.

90-90-90 by 2020

Robert Fieldhouse then talked about the patient’s perspective.

- I stand here as a lucky man with access to care – but it is not so for everyone, he started by saying.

He presented WHO’s list on unmet needs in key EU populations. It included MSM, people in prison, people with intravenous drug use (PWID), sex workers and transgender people.

- Simple, tolerable and effective treatment options are current unmet needs for many of these populations. The time between EU approval of HIV medicines and clinic availability is another. Prevention of stock-outs and access to medicines across the EU is a third, he said.

UNAIDS recently set new targets for testing and treatment to end AIDS by 2030 by achieving “90-90-90” by 2020.

- It means that 90% of all people living with HIV should know their status, that 90% of all those who are diagnosed HIV-positive to be on sustained ART and 90% of those on ART should have an undetectable viral load, Mr Fieldhouse explained.

Making resources for healthcare count

In general terms, HIV prevention strategies are highly cost-effective due to the high cost of HIV treatment, Andrew Briggs, Prof in Health Economics, said.

He was talking in a Session on the optimal way of managing HIV.

- HAART treatment is made more cost-effective by considering the lower transmission risk, he continued.

Health care costs are rising across all jurisdictions, and Prof Briggs thought that technology will save us is probably a myth.

- Health care systems have been in “crisis” for the last 20 years, and it is unlikely that technology will end cost pressures.

The role of economic evaluation/cost-effectiveness analysis is increasing globally. Modelling and extrapolation remain important, but validation against real world data is required.

- The success of innovation in the HIV arena continues to pose challenges, with an increasing use of multiple treatments and sequential lines of therapy. The question is if “an ounce of prevention still is worth a pound of cure”, he asked.

Task shifting

Prof Nathan Clumeck talked about the WHO recommendations on task shifting approaches – i.e. reorganisation and decentralisation of health services. He presented experiences in this from Thyolo district in Malawi, Africa.

- It shows that universal access to ART can be achieved and sustained in resource-limited rural settings, he said.

When adequate training and supervision of staff is performed, task shifting is a proven strategy to support increased access to ART care in these settings. The decentralisation of care from hospital to health centre level can be achieved in a manner that reinforces primary health care services.

- Innovative programme adoptions must continue to support the further expansion of ART coverage, while maximising long-term benefit for those already receiving treatment, Prof Clumeck summarised.

Clinical Nurse Specialist Linda Panton talked about the nurse’s role in task shifting.

- The nurse is the point of contact for new patients – not only for the patient but also for all other specialists.

She explained that the nurse is enhancing and sustaining established pathways between primary care, specialist care, psychological services, social care and third sector support services.

- The nurse also has a gatekeeper role.

Skills that make a specialist nurse special – Nurse Panton presented include offering compassion to the patient and teaching empathy as a life skill – not as a lesson plan.

- Also to be an effective listener – listen to what the patient has to say, she ended her talk.

The major cause of death in HCV

In a session on hepatitis C, Dr Karine Lacombe talked about HCV in resource limited settings. She described the situation in Africa.

- The main routes of infection are health settings-acquired – hospitals and primary care centers – community-acquired (traditional scarifications) and drug use which is an emerging concern in big cities, she said.

There are also great concerns over screening and diagnosis, due to lack of national policies for systematic screening, unreliable screening methods and unavailability of HCV-RNA and genotype testing.

- Liver-related deaths are the first cause of death in HCV-positive individuals. There are higher mortality rates in HIV/HCV co-infected patients, compared to HIV- or HCV-infected alone. The liver-related co-morbidities also affect the kidney, the brain and the cardiovascular
system, Dr Lacombe continued.

She presented the updated EACS guidelines that underline fibrosis evaluation in chronic HCV. If the evaluation gives F0 or F1, treatment can be deferred in general. For F2/3, HCV treatment should be considered and for F4 interferon (IFN)-free treatment is recommended.

– It is important to screen the patients every sixth month – even if they have reached sustained virological response (SVR), she reminded the audience.

Three direct-acting-antiviral regimen
Dr Roger Trinh presented interim results from TURQUOISE-I, the first study of an IFN-free regimen in patients with HCV genotype 1 and HIV-1 co-infection to include HCV treatment-experienced patients, including those with Child-Pugh A cirrhosis.

– IFN-free regimens have shown promise with higher SVR rates and an improved safety profile – although rates are lower in patients with genotype 1b and patients with cirrhosis, and data are limited in treatment-experienced patients, he explained.

The multi-targeted three direct-acting-antiviral (3D) regimen included om bitasvir (a potent NS5A inhibitor), ABT-450 (a potent NS3/4A protease inhibitor, co-dosed with low-dose ritonavir) and dasabuvir (a non-nucleoside NS5B polymerase inhibitor).

Dr Trinh reported that high rates of SVR12 were achieved with 12 or 24 weeks of 3D + RBV therapy in patients receiving concomitant atazanavir or raltegravir ART.

– Two patients in the 24-week group had evidence of HCV re-infection post-treatment emphasizing the importance of patient counselling on behaviours associated with HCV re-infection, he said.

3D + RBV co-administered with ART was well tolerated – this was evidenced by no treatment-emergent serious adverse events, and no patient discontinuations owing to adverse events.

– The high SVR rates were consistent with rates achieved in phase III studies of HCV patients receiving the 3D + RBV regimen. A cohort of patients on stable darunavir-inclusive ART regimen receiving treatment with the 3D + RBV regimen for 12 weeks is being evaluated at present, Dr Trinh concluded.

TB in Eastern Europe
Dr Ole Kirk talked about factors associated with TB increase in Eastern Europe.

– There is economic and social destabilisation, and a decline in public health infrastructure has led to deterioration of TB control service. The incidence of TB in Russia has increased after the break-up of the Soviet Union, he said.

HIV-positive persons infected with TB are more likely to develop active TB disease.

– The HIV epidemic, combined with poor institutional infection control, can lead to TB and multi-drug resistant TB epidemics as seen in New York City in the early 1990s, he continued.

Dr Kirk presented a chart with alarmingly high one-year mortality among HIV-positive patients with a TB diagnosis. In Eastern Europe this was 33 %, to be compared with 8 – 14 % in Argentina, Southern, Central and Northern Europe.

– There is a need for multi-disciplinary actions, including effective infection control to stop spreads of TB and multi-drug resistant TB. There is also a need for improved collaboration between TB, HIV and other services.

Dr Kirk also underlined the need for adequate empiric TB-treatment and subsequent TB-treatment guided by results of drug susceptibility testing – and for treatment of co-morbidities, and supportive treatment for intravenous drug users.

– And most important of all: Political awareness and commitment is needed, he summarised.

On third had multi-drug resistant TB
TB is the most common co-infection among HIV-positive patients, and the most common cause of death. In Eastern Europe there is a rapidly increasing incidence of HIV, and overlapping risk groups for HIV and TB – and the world’s highest proportions of multi-drug resistant TB.

Dr Anne Marie Efsen presented a study that aimed to compare clinical characte-
istics of TB/HIV co-infected patients in three European regions and Latin America at the time of TB diagnosis. Also the study wanted to identify factors associated with having multi-drug resistant TB. It was a collaboration of in total 62 TB and HIV clinics.

- The situation in Eastern Europe was characterised by a lower proportion of definite TB diagnosis and drug susceptibility testing. Approximately one third of people living with HIV who were diagnosed with TB had multi-drug resistant TB. And we found a pronounced variation between countries within Eastern Europe in levels of multi-drug resistant TB and in the empiric anti-TB regimens described, Dr Efsen said.

She concluded that there is a clear need for improving and implementing more accurate and rapidly available diagnostics.

- Also to improve empiric anti-TB therapy, particularly in high resistance settings such as Eastern Europe.

Dr Efsen added that the long-term clinical consequences will be further analysed as follow-up data accumulates.

**ART significantly reduced the rate of hepatic decompensation**

In a Satellite symposium sponsored by Gilead, Prof Jürgen Rockstroh talked about HCV. He quoted the updated EACS guidelines that states that for HIV patients co-infected with HCV, treatment should start if the CD4-count is below 500.

- But beware of drug-drug interactions, he underlined.

EASL has also published new online guidelines. They state that indications for HCV treatment in HIV/HCV-co-infected patients are identical to those in HCV mono infection. Same treatment regimens can be used in HIV/HCV patients as in patients without HIV infection, as the virological results of therapy are identical.

Prof Rockstroh presented a study that had evaluated 10,090 HIV/HCV co-infected males from the Veterans Aging Cohort, who had not initiated ART at entry, for incident hepatic decompensation between 1996 and 2010.

- The study found that initiation of ART significantly reduced the rate of hepatic decompensation by 28 – 41 % on average.

HCV disease progression remains faster in co-infected patients, despite effective ART, Prof Rockstroh underlined.

**Debate**

In another Satellite symposium, this sponsored by Abbvie, Prof David Cooper said that liver disease associated with HCV has become a leading cause of mortality among subjects co-infected with HIV and HCV.

- Sustained virological response in subjects with HIV/HCV slows fibrosis progression and reduces morbidity and mortality – even in subjects with mild liver disease, he continued.

Dr Ashley Brown said with the new IFN-free regimens, treatment is going to be simple for all patients.

- Virologic cure – yes, I use the C-word – is associated with reduced all-cause mortality – CVD, renal disease etc.

In the debate between the two speakers that followed, Prof Cooper underlined that there are special populations, normally not included in trials.

- Perinatal transmission, children and drug users for example. Then there is the question on if simple curative therapies encourage high risk behaviour, he said.

Dr Brown did not agree.

- There will be no perinatal transmission, because we will treat the mothers before delivery! Today we treat children for HIV – and they are good at taking their pills. And we are already treating intravenous drug users today!

Prof Cooper said that Dr Brown might be right.

- But I’d like to see this implemented before I finally believe in it, he said.
The synthesis of peptidomimetic protease inhibitors (PIs), firstly at Roche (saquinavir) and subsequently at Merck (indinavir) heralded the start of an era of improved HIV therapy. These drugs, together with ritonavir were approved in 1996/1997 and became the dominant choice of ‘third agent’ for a number of years.

These agents all had limitations due to poor pharmacology, challenging administrative schedules and adverse effects. Nelfinavir, a similar product but with some improved pharmacokinetics enabling twice daily dosing superseded this first generation of products in the late 1990s. Subsequently, an era of ritonavir boosting began with the establishment of a fixed dose formulation on lopinavir/ritonavir (LPV/r) for twice daily dosing and the more effective and better tolerated once daily regimens of atazanavir/ritonavir and darunavir/ritonavir. The CASTLE [1] and ARTEMIS [2] studies in treatment naïve subjects established the advantages of these regimens over LPV/r in terms of tolerability and efficacy. The two once daily PIs have both been preferred by a range of national and international guideline committees for greater than 5 years and have been huge commercial successes for their manufacturers.

However, use of PIs in initial therapy regimens is in decline. Their popularity has been impacted by a range of factors including the rise of single tablet regimens which are either NNRTI- (Atripla, Evipera/Complera) or integrase inhibitor- (Striibild, Triumeq) based, cost pressures (notably the aggressive pricing of ritonavir in some markets and the arrival of generic efavirenz as well as the global financial crisis placing pressure of healthcare budgets), the extent of drug interactions and the perception of poorer tolerability relative to at least some alternatives, most notably the integrase inhibitors.

However, there remain several attractions of PIs that are likely to keep them at the forefront of treatment choice:

- A strong evidence base with extensive use in high viral load and low CD4 count subjects
- A low risk of loss of treatment options at failure, with both low rates of PI and NRTI resistance.
- Activity against common resistant viruses strains seen in transmitted resistance and after failure.
- An expansion of formulations in fixed doses to reduce pill burdens
- Established safety and efficacy in women and notably in pregnancy (Atazanavir/r only, US label)
- Predictable and manageable safety profiles including in women and older subjects
- Well studied drug interaction profiles which make dosing adjustments readily evidence based and manageable
- Established minimal effective concentrations which have enabled the generation of data indicating flexibility in dose timing accuracy and for therapeutic drug monitoring

Evidence base

Shifts in the choice of PI has been driven by improvements in efficacy and tolerability. The evidence base is especially strong for atazanavir/r which has been equivalent to efavirenz (ACTG5202 [3], ALTAIR [4]), Raltegravir (ACTG 5257 [5], virologic efficacy endpoint) and Striibild (Gilead 103)[6] and has been used with both ABC/3TC and TDF/FTC backbones [3]. Atazanavir was at least as good as LPV/r over 96 weeks in the CASTLE study, with 95% confidence intervals suggesting superiority [1]. Across these studies atazanavir/r showed consistent efficacy regardless of baseline characteristics.

Darunavir has fared somewhat less well in large scale comparator studies. While it was as effective as once or twice daily LPV/r in Artemis [2] (Note: LPV/r once daily is not approved in the EU) and in some (but not the FDA snapshot) analyses better than LPV/r it has struggled against integrase inhibitors, mostly due to lower efficacy in high viral load subjects.

In the open label ACTG 5257, it met protocol defined equivalence to raltegravir (the upper limit of the 95% CI was 9.9%, the equivalence delta 10%) but the lower bound of the 95% CI at 1.3% suggesting raltegravir was also superior, albeit that the ACTG statisticians did not test for superiority [5]. In this study, the number of subjects defined as virologic failures was 85 for raltegravir, 94 for atazanavir/r and 115 for darunavir/r. The 21 fewer virologic failures with atazanavir resulted in 2.1% numerical advantage to atazanavir over darunavir which gave confidence intervals within the 10% equivalence delta and crossing 0. Tolerability endpoints in the study, however, favoured raltegravir over both PIs and darunavir over atazanavir.

In Flamingo, an open label comparison of darunavir/r and dolutegravir with investigator selected NRTIs, dolutegravir was superior to darunavir/r over 48 weeks.
weeks (90% vs 83%) largely due to the poor performance of darunavir in subjects with baseline VL >100,000 copies/ml with just 70% achieving success, while for the lower viral load subjects 85% achieved treatment success. For dolutegravir, 90% of subjects achieved success regardless of baseline viral load [7].

Of note, the favourable results of PI/r with 2 NRTIs have not been reproduced when combined in large scale studies with other classes including DRV/r with raltegravir (ACTG5256, NEAT1) [8] or DRV/r with maraviroc (Modern) [9].

Lack of resistance at failure
This has been the hallmark of boosted PI studies and remains a key issue in choosing a regimen in a subject with higher risk of failure (such as an active substance user) where a balance must be struck between consequences of failure and single tablet dosing. Consistently, large scale studies involving 100s of subjects have not found primary PI mutations at failure of a PI/r regimen, unlike the individual resistance ‘signatures’ characteristic of unboosted PI use. In ACTG5257 no PI/r subject (over 1200) developed PI resistance whereas approximately 3% of subjects randomised raltegravir had integrase inhibitor resistance at failure [5]. Similar experience was seen with Stribild versus truvada+ATV/r in GS103 [6] and LPV/r versus efavirenz in ACTG5142 [10].

Furthermore, these studies also find that fewer subjects have mutations, and if mutations are seen they are less in type and number, in the NRTI region relative to comparator arms where the third agent is an integrase inhibitor or NNRTI (Note: it is difficult to comment on data from dolutegravir studies where GSK/Shionogi/ViiV used different testing protocols than typically used by other companies or independent investigators. This may have led to low reported rates of resistance in all study arms). The ‘genetic barrier’ (the number of specific ‘resistance associated mutations’ (RAMs) required for clinically relevant shifts in susceptibility) with boosted PIs may be higher (probably greater than 2 but less than 5 from specific and rather differing lists of RAMs for each of LPV/r, ATV/r and DRV/r) provides an explanation for lack of resistance to the PI it does not explain the apparent ‘protection’ against NRTI mutations. Of note, PI/r do not protect against resistance to NNRTIs (e.g. LPV/r+EFV in ACTG5142) [10] or integrase inhibitors (e.g. DRV/r=raltegravir in NEAT1) [8] suggesting the observations with NNRTIs are not explained by adherence or pharmacokinetics decay tails.

Evidence that this lack of apparent resistance does not relate to ‘missed’ resistance, for example mutations arising outside the sequenced regions such as a cleavage site mutation, comes from the observation that the majority of PI/r ‘failures’ in ACTG studies could achieve viral (re-)suppression simply by recommencing their NR-TI+PI/r regimen [11].

Activity against commonly transmitted strains
Resistance transmission in Europe appears stable and relatively uncommon (<10% of new infections, more common in MSM that heterosexuals) [12]. The most common mutations observed NNRTI mutations such as K103N and thymidine analogue mutations (TAMs) which have remained remarkable prevalent despite the sharp declines in thymidine NRTI use. While integrase inhibitor resistance transmission has been reported, it appears rare at present but is likely to increase as use (and failure) on these drugs expands.

Transmitted PI mutations are vanishingly rare and as single mutations typically do not impact ATV/r or DRV/r these agents remain fully active. Most guidelines and some NNRTI and integrase inhibitor EU labels warn against using these lower genetic barrier regimens in subjects with transmitted resistance, noting that resistance tests have the potential to underestimate the extent of resistance (especially if there are multiple founder species or superinfection has occurred).

Transmitted resistance missed on standard ‘bulk’ sequencing has been shown to increase the risk of failure of NNRTI based regimens. This subset of patients where transmitted resistance is known or suspected remains a key group where PIs will be preferred.

New Fixed Formulations
While Abbott (now Abbvie) would not cooperate with other PI manufacturers to create alternative fixed dose formulations to LPV/r, Gilead have made their pharmacoenhancer cobicistat available. Abbvie’s lack of collaboration was in large part due to the monopoly ritonavir gave it over boosting (hence their decision to exploit this through predatory pricing of ritonavir in the US) and the monopoly LPV/r gave it over fixed dose PI formulation (which was exploited through not making ritonavir available in some markets, leaving LPV/r the only way to prescribe a boosted PI). Fixed dose formulations of atazanavir and darunavir with cobicistat are under regulatory consideration at present and further combinations including NRTIs may be possible.

These combinations promise the potential to reduce PI dosing to two and perhaps a single tablet in the future, in part addressing the not-very-complex ‘complexity’ of current PI regimens. However, a range of drug interactions will need to be solved (such as atazanavir/cobicistat and the oral contraceptive pill) and the regimens will still involve a panopoly of drug interactions and the creatinine secretion/renal safety monitoring issues with cobicistat. Both fixed dose formulations are expected to be available in the EU in 2015.

Women and Pregnancy
While limited data exist with integrase inhibitors and many physicians remain

Protease inhibitors

HIV & VIROLOGY NEWS 4 · 2014
cautious about use of efavirenz in pregnancy. PIs, usually lopinavir/r and atazanavir/r, remain widely recommended in both women planning pregnancy. Atazanavir has a US label for use in pregnancy, an FDA category B (based on lack of mutagenicity in the in vitro Ames test and saf- ety and lack of teratogenicity in pregnant rodents, both rabbits and rats studied at human-equivalent exposures) with sup- portive pharmacokinetic and safety data. In the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester ex- posure to atazanavir in humans have been monitored to be able to detect at least a 2-fold increase in risk of overall birth de- fects. No such increase in birth defects has been observed with atazanavir. The pre- valence of birth defects with first-trimester atazanavir exposure was 2.1% (16 of 746 births; 95% confidence interval [CI], 1.2%–3.5%) compared with a 2.7% total prevalence in the US population, based on Centers for Disease Control and Pre- vention (CDC) surveillance [12]. Uncon- jugated hyperbilirubinemia induced by atazanavir is not considered a risk for ker- niciterus and should not necessitate pho- totherapy. Data on darunavir are more li- mited and it is classified as Food and Drug Administration Pregnancy Category C. As darunavir clearance appears increased in pregnancy leading to lower trough con- centrations, 600mg bd is generally consi- dered preferred if DRV/r is necessary in pregnancy.

Safety in specific populations
Atazanavir has been subject to extensive investigation in first line use including the CASTLE, ALFAIR, ACTG5202, ACTG 5257 and Gilead 103 and 114 studies. Se- veral of these studies incorporated 25% or more female subjects (a similar pro- portion to the percent of females in the EU HIV population) and a representative proportion of older (>40 or >50 years old) subjects. Efficacy and safety of atazana- vir/r was similar in women and men in CASTLE [1] but was less good in female subjects in ACTG5202 relative to Efa- virenz [13] due to more discontinuations. Specifically, atazanavir/r can be coadmin- istered with the oral contraceptive pill (OCP) as long as a minimum 30µg oestro- gen pill is used. Progestogens are increa- sed by 85% by atazanavir/r, with no dose adjustment needed [14]. While there are fewer initial therapy studies with Daruna- vir, both the ARTEMIS [2] and ACTG5257 [5] studies have included around 25% wo- men, with no efficacy or safety issues re- ported. Darunavir/r cannot be used with the OCP [14].

For all ART there is a paucity of data in older individuals, especially those over 60. The DAD study has specifically re- ported no association between Atazanavir use and myocardial infarction risk [15]. Darunavir has not been assessed thus far in DAD. The ACTG5257 study reported significantly less carotid intimal thickness progression with Atazanavir/r relative to Darunavir/r [16]. However, DAD and other cohort studies have reported Ata- zanavir/r (again Darunavir data have not been reported) is associated with increa- sed risk of tenofovir DF-related declines in renal function [17] and Atazanavir/r has been associated with nephrolithiasis and rarely interstitial nephritis. Darunavir in urinary crystals has also been reported [18]. Atazanavir, but not darunavir, is acid dependent for absorption, so must be se- perated from H2 antagonists and proton pump inhibitors at standard doses.

PK profiles
Protease inhibitors have a correlation with efficacy and Cmin plasma concen- trations. Exposures of approximately 10 fold above the in vitro IC50 have been identified as minimum effective concen- trations required for optimal efficacy with lopinavir and atazanavir and estimated for darunavir. Atazanavir in vitro is the most potent PI with an IC50 of approximately 10ng, darunavir has an IC50 around 55ng and lopinavir 100ng. Atazanavir expo- sures correlate with plasma bilirubin lev- els and there is an exposure dependent competitive inhibition of UGT1A1 leading to unconjugated bilirubin elevation. In- dividuals who experienced bilirubin eleva- tions on the CASTLE study have been shown to have enjoyed better efficacy [19], the bilirubin acting as a marker of exposu- re and medication adherence, thus a form of ‘free’ therapeutic drug monitoring.

However, excessive bilirubin elevation may lead to occurrence of scleral icterus, the most common cause of atazanavir discontinuation. Analysis of ACTG 5202 suggested grade 3 and 4 bilirubin eleva- tion were considerably more common in people with Gilbert’s syndrome, a variant of UGT1A1 [20]. This may therefor pro- vide a simple screening tool for choice of subjects potentially less suitable for ata- zanavir, in a similar way to the US label warning about sulpha drug allergy and a possible increased risk of rash on daru- navir. Other means of managing hyper- bilirubin with atazanavir include co-ad- ministration of zinc [21], which chelates bilirubin in the gut, and consideration of using unboosted atazanavir, an approach which has been successfully evaluated in 2 induction-maintenance studies.

While lopinavir has a short plasma half-life, making its unsuitable for once daily dosing, forgiveness studies with atazanavir and darunavir suggest all (ata- zanavir) and most (darunavir) still have therapeutic exposures of drug if a dose is delayed by 6 hours and about half of sub- jects have therapeutic exposures if dosing is delayed 12 hours [22]. This provides practical information for patients who therefore do not need to dose strictly at the same time every day but have some dose timing flexibility when travelling or changing routine.

Summary
Protease inhibitors have a number of key characteristics that will mean they remain common choices in initial therapy and the mainstay of regimens in treatment expe- rienced subjects. New co-formulated and fixed dose formulations have the potential to address one obstacle to wider use. Pre- dictions of the imminent demise of pro- tease inhibitors are evidently misguided.

References


PROTEA: the end of the road of protease inhibitor monotherapy?

The first trial of lopinavir/ritonavir monotherapy as a switch strategy in patients who have already achieved virological suppression while receiving triple drug therapy was published in 2005 [1].

During the following decade, multiple studies have been performed to explore the efficacy and safety of protease inhibitor monotherapy as a maintenance strategy. Monotherapy with boosted protease inhibitors has always been a controversial therapeutic option. International expert guidelines did not reach consensus. HHS and IAS never recommended this strategy outside from clinical trials. EACS guidelines and GESIDA guidelines have endorsed protease inhibitor monotherapy in selected patients.

Knowledge after ten years of experience
What have we learned about protease inhibitor monotherapy after 10 years of experience? This is a short list of the most important findings

1. Protease inhibitor monotherapy as a switch strategy is slightly less efficacious than continuation with triple therapy. Non-inferiority criteria have not been convincingly met when the “switch equals failure” analysis has been used.

2. Protease inhibitor monotherapy as switch strategy repeatedly met the non-inferiority criteria when the “switch included analysis” has been used. This analysis ignores patients who rebound while receiving monotherapy and are successfully re-induced adding two nucleoside reverse transcriptase inhibitors. This strategy is possible because in trials of protease inhibitor monotherapy in the developed world, resistance development has not occurred in patients exposed to monotherapy. In the PIVOT trial patients exposed to monotherapy did not have a higher risk of losing therapeutic options [2].

3. Darunavir/ritonavir once daily and Lopinavir/ritonavir twice daily had better results than Atazanavir/ritonavir when used as monotherapy.

4. Clinical trials have not shown advantages of monotherapy in safety endpoints. Lipid levels in general worsened after discontinuation of tenofovir. Renal function and bone endpoints have not been better in patients receiving monotherapy. The only clear advantage is pharmacoeconomic.

5. The PIVOT trial [2] and one cohort study [3] have not shown differences in neurocognitive endpoints between patients treated with monotherapy and triple therapy.

In the International Congress of Drug Therapy in HIV Infection held on 2–6 November 2014 in Glasgow several studies have focused in protease inhibitor monotherapy, adding some new information to what was already known. The most important of these studies is the PROTEA clinical trial [4]

A clinical trial
PROTEA is a randomized clinical trial comparing darunavir/ritonavir with or without nucleoside analogues for maintenance of virological suppression. PROTEA included 273 patients who were still receiving his first-line antiretroviral therapy regimen. Randomization was stratified by HCV antibody results (anti HCV negative or positive). The reason for this stratification is that in a prior trial –MO-NET- patients with a positive HCV serology had a higher risk of viral rebound than patients with a negative serology [5].

As in other simplification trials patients had to have at least six months of suppressed plasma viral load. Key exclusion criteria were nadir CD4 count ≤ 100 cells/µL and ≤ 200 cells/µL at screening. Subsequent to screening, patients entered a 4-week run-in period in which all patients received darunavir/ritonavir 800/100 mg once daily with their current two nucleoside reverse transcriptase inhibitors.

Patients included in PROTEA had been taking antiretroviral therapy for an average of slightly more than five years and had a median CD4 cell count of 593 cells/µL in the monotherapy arm and 623 in the triple therapy arm. There were more patients with a nadir CD4+ cell count lower than 200 cells/µL in the monotherapy arm compared with the triple therapy arm (30% vs 22%). Importantly, randomization was not stratified by nadir CD4 cell count.

After 48 weeks of follow-up, 86.1% and 94.9% of patients randomized to monotherapy or to triple therapy respectively remained with HIV RNA < 50 copies/mL by the FDA snapshot switch = failure analysis. As shown in Figure 1 the 95%
confidence interval around this difference does not meet the non-inferiority criteria (non inferiority margin was 12%). In the switch included analysis non-inferiority was clearly demonstrated. Interestingly, in a post-hoc analysis the main determinant of efficacy results was nadir CD4 (Fig 2). For patients with a CD4 cell nadir above 200 cells/μL there were almost no difference in efficacy between arms. Differences clearly concentrated in those patients with a CD4 cell nadir below 200 cells/μL.

Neuropsychological evolution
PROTEA explored neuropsychological evolution by means of the NPZ5 [6]. Global Z scores were calculated for five cognitive domains. A “Z score” is the number of standard deviations an observation is separated from the mean. A score of 0 represents the reference population mean. Higher Z scores represents better neuropsychological function. The neuropsychological tests performed were: Colour Trail Test, Hopkins Verbal Learning Test and Grooved Pegboard Test. After one year of follow up there were no differences in the Global NPZ5 Score between groups.

One patient in the darunavir/ritonavir monotherapy arm was hospitalized with HIV encephalomyelitis at Week 24. This patient had a very low CD4 nadir of 15 cells/μL, which was below the inclusion limit of 100 cells/μL. At Week 24, the HIV-1 RNA level in the CSF was 2500 copies/mL, with a plasma level of 125 copies/mL at the same visit. The patient was intensified with ZDV/3TC, and the symptoms resolved.

In the neuropsychological substudy of PROTEA, CSF samples were taken by lumbar puncture for evaluation of HIV RNA levels in 19 patients per arm. In this substudy one patient on the monotherapy arm -with CD4 nadir of 166 cells/μL- developed viral rebound in both CSF and plasma. Overall 26.4% and 10.5% of patients randomized to monotherapy or triple therapy respectively had HIV-RNA detection in the CSF. This detection was concomitant with viral rebound in plasma.

New information provided by PROTEA
What is the most important new information provided by PROTEA? In my opinion most of the findings were already known.

1. The efficacy of monotherapy was in the range of prior trials of darunavir/ritonavir monotherapy. In MONET [5] the efficacy of darunavir/ritonavir monotherapy by intention to treat was 84.3% while in PROTEA was 86.1%. It is in the triple therapy arm where the differences of efficacy between MONET and PROTEA are more pronounced: 94.9% vs. 85.3% respectively. In PROTEA the control arm has performed better than in MONET, almost a 10% difference. At any rate, a prior meta-analysis has already shown that monotherapy was less efficacious than triple therapy [7]. However when the analysis is performed with the switch included approach -ignoring treatment changes such as reinduction with nucleosides- the monotherapy arm
was non-inferior. The non-inferiority of the strategy of using monotherapy AND reinduction with nucleosides as needed has been repeatedly shown in prior monotherapy trials. In fact, in the Glasgow meeting a new meta-analysis showed similar results [8].

2. In prior trials, a low nadir CD4 cell count had been identified as risk factor for loss of virological control while on monotherapy with lopinavir/ritonavir [9,10]. In contrast a low CD4 nadir was not associated with virological failure in patients receiving darunavir/ritonavir monotherapy. MONET is the first trial of darunavir/ritonavir monotherapy in which nadir CD4 count was found to be predictive of treatment response in a post-hoc analysis. It should be emphasized than in PROTEA just by chance more patients in the monotherapy arm had CD4 cells nadir < 200 cells/µL than in the triple therapy arm.

3. There was one patient who developed encephalomyelitis while receiving monotherapy. Encephalomyelitis was not a result of viral escape in the CSF because patient had already a plasma level of 125 copies/mL. Importantly this patient had a very low CD4 nadir of 15 cells/µL. There have been prior reports of patients developing mild neurological transient symptoms while receiving monotherapy in the MONOI clinical trial [11]. Interestingly a low CD4 nadir has been identified as an important risk factor for neurocognitive impairment in patients receiving antiretroviral therapy [12].

4. Neurocognitive function endpoints were similar in both arms. Several trials and cohorts have repeatedly shown that patients exposed to monotherapy do not appear to be at a higher risk of developing neurocognitive impairment than patients receiving triple drug ART [2,3].

Results of PROTEA would be used both by critics and defenders of protease inhibitor monotherapy. Critics would say that it is less efficacious than triple therapy and that there is a higher risk of HIV encephalitis. Defenders would claim that most of the data were already known, that the strategy of using nucleosides only as needed still shows non-inferiority and that neurocognitive evolution does not appear to be affected by monotherapy.

In my opinion this discussion might be meta-analysis. PLoS ONE 2011; 6:e22003.


13. Arribas JR, SALT & OLE. “If you can beat them, join them” (but just one of them). HIV & VIROLOGY NEWS 3 : 2014

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13. Arribas JR, SALT & OLE. “If you can beat them, join them” (but just one of them). HIV & VIROLOGY NEWS 3 : 2014

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Every two years the HIV Drug Therapy Conference that takes place in Glasgow in November is something special among our HIV conferences: it is early autumn, falling leaves start to cover the lawns, a mist is on the river, and the low sky is dull at four in the afternoon. The cold humidity envelopes you as you step into a Glasgow city cab at the airport. It is a vintage taxi whose driver chats with you about the recent Scottish vote in a rough but warm accent. You say “Yessss”, not sure that you caught everything.

This year the weather was especially warm, a kind of late summer with minimal rain and unusual light outdoors and indoors as well. Could this have anything to do with global warming? We are grateful to Professor Ian Weller, the past chair, and Professor Andrew Philips, his successor, for hosting us in Glasgow.

Dolutegravir confirms its high efficacy over 96 weeks

- Flamingo is a Phase 3 open-label study aiming to compare the efficacy of dolutegravir (DTG) 50 mg once daily to darunavir (DRV) 800/100 mg with a tenofovir (TDF)/FTC or abacavir (ABC)/3TC backbone (as per investigator choice) in ART-naïve patients with viral load (VL) ≥ 1000 c/mL and no baseline PI or RT resistance.
- The proportion of patients with HIV-1 RNA < 50 c/mL at Week 48, using a snapshot analysis with a −12% non-inferiority (NI) margin, constituted the primary endpoints. Secondary endpoints were antiviral activity, safety, tolerability, health outcomes, and virological resistance (1).
- The Week 96 results were presented at the Glasgow Conference by Professor J.M. Molina from Paris (2).

There was a total of 484 patients (242 in each arm), mostly male (85%), with a median age of 34 years and a relatively good immune status. Their moderate VL corresponded to current naïve patients with a baseline median VL of 4.49 log cp/mL, 25% of whom were above 100 000 cp/mL with a median CD4 cells of 395 cells/mm³, and only 10% with less than 200/mm³.

Two-thirds of the patients received TDF/FTC as a moderate NRTI backbone.

Efficacy

At 48 weeks, the proportion of patients with less than 50c/mL was 83% in the DRV arm and 90% in the DTG arm—a difference between the two arms of 7.1% (confidence interval [CI] 0.9%–13.2%). This allowed the investigators to assess the non-inferiority of the DTG arm in comparison with the DRV arm (Figure 1 (1)).

The extended follow-up to 96 weeks showed that among the 208 patients remaining in the DTG group (86% of the initial number enrolled), and in the 179 patients remaining in the DRV group (79% of the initial enrollees), the two therapies performed very well. There was a 68% rate of efficacy with defined viral suppression less than 50c/mL in the PI arm and 80% in the INI arm.

- The difference between the DRV and the DTG-based regimens is now 12.4%, with a CI of 4.7%–20.2%. The graph clearly shows that throughout the study there was constantly a higher proportion of patients with full viral suppression in the DTG arm, as compared to the DRV arm. This becomes significantly different at Week 96 (p < 0.002).

![Proportion (95% CI) of Individuals With HIV-1 RNA <50 c/mL Over Time – Snapshot](image_url)
In order to better understand why DRV, the PI “star”, seems slightly weaker than DTG, we need to examine the performance of each drug in those patients with the highest VL. It has been well known since the early years of ART that the higher the VL, the longer it may take to reach full viral suppression, now defined as less than 50 cp/mL.

Among those patients with a VL > 100,000 cp/mL at Week 96 (Figure 2), the proportion with VL < 50 cp/mL was 82% in the DTG arm, compared to 52% in the DRV arm; whereas in patients with VL < 100,000 cp/mL, the proportions were 80% and 73%, respectively. There was no difference according to the NRTI backbone: ABC/3TC performs as well as TDF/FTC.

• If one considers these reassuring numbers and the higher proportion of patients fully suppressed by DTG, we see that those patients who were failing on DRV had VL between 50 and 200 cp/mL, that is, they were more on the “low level viremia” side, rather than on the complete virological treatment failure one.

• However, since full viral suppression should be the ultimate goal of ART, there is an advantage to using DTG in patients with high VL. Whether these minimal differences will have consequences remains to be seen.

• In terms of tolerability, the results at Week 96 are very similar to those at Week 48: both drugs have an excellent profile. Digestive disorders such as diarrhea or nausea were similar in the two groups, namely, slightly less than 40% in the first year, dropping to less than 20% the second year for both DRV and DTG. Thus, there were no excess events in the PI arm. Discontinuation for adverse effects was rare and only occurred in the case of four patients in the DTG arm and eight in the DRV arm.

As expected from an INI drug, DTG has a better lipid profile than DRV, with a smaller increase in cholesterol and triglycerides. There was a higher number of grade 2 or higher fasting LDL abnormalities by Week 96 in the DRV/r arm (22%) versus the DTG arm (7%) (p < 0.001).

Conclusion
DTG has confirmed its outstanding efficacy as having one of—if not the—greatest antiviral potencies available today. The speed of viral reduction with this robust drug appears to be particularly important in patients with the highest VL. As in the case of DRV, the absence of mutations induced in these naive patients suggests that PI may no longer be the only drug with a very high genetic barrier to resistance. This quality DTG gives us the opportunity to investigate innovative strategies.

Doravirine (DOR): a new NNRTI on the scene?
• The need for ART to be administrated over a lifetime has made the use of associated comorbidities such as those for NRTI or PI very attractive. However, NNRTI commonly have other negative consequences or disadvantages in their efficacy and safety profiles, such as frequent CNS adverse events (AE) or lipid elevation accompanied by efavirenz (EFV) hypersensitivity to nevirapine (NVP), a major reason to have discontinued its use. Most NNRTI have a low genetic barrier to resistance. In addition, rilpivirine (RVP) has to be taken with a substantial meal to maximize its absorption. Among treatment-naïve patients in both the US and EU its use has been limited to those with RNA ≤ 100,000 c/mL. Etravirine (ETR), a second generation nNRTI, has a high efficacy rate, even on viruses harboring resistance-associated NNRTI mutations. However, ETR has only been licensed for use as a twice daily drug.

DOR is a novel NNRTI developed by Merck
• high in vitro potency versus a broad panel of isolates, including common NNRTI-resistant variants (3)
• primarily metabolized by CYP3A4, rather than being an inducer or inhibitor
• dosed once daily without regard to food

Study 007, presented first at CROI (4) and then at the HIV Drug Therapy Conference in Glasgow by José Gatell, is a randomized, double-blind, two part, 96 week dose finding study (5).

The first part is a five-arm dose ranging study that enrolled 210 ART-naïve patients randomized in one of five groups: DOR 25 mg (n = 41), DOR 50 mg (n = 43), DOR 100 mg (n = 42), DOR 200 mg (n = 41), or EFV (n = 43) combined with both TDF/FTC. The second part included 132 patients equally-divided in two arms: DOR 100 mg (n = 66) and EFV 600 mg (n = 66). Results for the primary endpoint of virological suppression of less than 40 cp/mL at Week 24 were 80%, 76%, 71%, and 78% for the increasing DOR doses versus 64% for the EFV arm, respectively. Using a cut-off of < 200 cp/mL, the results were 85%, 85%, 92%, and 90% versus 81%, respectively. CD4 increases were +137 for the combined DOR groups versus +121 for the EFV arm. DOR exhibited a good safety profile at all doses. Based on Week 24 data, a dose of DOR 100 mg was chosen for further development based on its high
CNS AE with DRV 100 mg compared to EFV

When efficacy was analyzed at Week 48 in patients from Part 1, the proportion of those with pVL < 40 cp/mL was 76.2% in the DOR 100 mg group and 71.4% in the EFV group, while viral suppression was < 200 cp/mL 85.7% and 78.6%, respectively (Figure 4).

The virological response in patients with VL > 100 000 cp/mL does not indicate any difference between DOR and EFV, although the number of patients evaluated was very limited. The increase in CD4 cells was similar in the two groups at about 150 cells/mm3 (Figure 5).

The frequency of resistance development was low in both the DOR and EFV arms. Although genotype resistance testing was only performed in patients with VL > 500 cp, such testing in 6 patients from the DOR arm and 1 from the EFV arm showed no mutation, with the exception of one patient in the DOR arm (K101K/E) (Figure 6).

With regard to safety profile, including transaminases, glucose, LDL, and total cholesterol, there was no signal of toxicity in any DOR arms, compared to EFV.

Conclusion

In HIV naïve patients:
- DOR 100 mg QD for 8 weeks demonstrates a significantly lower rate of treatment-emergent CNS AE than EFV.
- DOR 25 to 200 mg QD for 48 weeks also shows:
  - antiretroviral activity and immunological effect similar to EFV.
  - low frequency of resistance development.
  - good safety and tolerability profile.
Phase 3 DOR 100 mg once daily studies are in progress.

**Attachment inhibitor BMS 663068**

Not only are new drugs needed in old categories; new drug categories are also needed. Considering mandatory life-long therapy, optimal survival, its correlates of aging and the comorbidities that overlap in long-term ART toxicity, as well as the development of viral-resistant escape mutants—all despite the potent drugs currently available, we see that there is still a need for a new class of drugs for use in experienced patients with cumulative resistance and toxicity.

- BMS-663068 is the first-in-class attachment inhibitor that binds to gp120, preventing initial virus attachment and entry in the host CD4 cell. As a prodrug that metabolizes to the active compound BMS-626529, it is active in vitro against HIV-1 viruses, with the exception of subtypes AE and O. By binding directly to the virus, this drug is not affected by tropism and can be used in all patients.

- BMS-626529 has a unique resistance profile with no in-vitro cross resistance to other antiretrovirals (6-7) (Figure 7).

- AI438011 is an ongoing Phase 2b study that is blinded to the BMS 663068 dose-ranging study. It has five arms: four with BMS-663068 400 mg BID, 600 mg BID, 600 mg QD, and 1200 mg QD, and a control arm with atazanavir (ATV)/r 300/100 mg each, combined with a backbone of raltegravir (RAL) and TDF.

Patients enrolled had to be treatment experienced; have an HIV RNA > 1000 cp/mL; a virus sensitive to TDF, ATV, RAL; and a CD4 count > 50/mm³. The primary endpoint was defined as the rate of viral suppression at Week 24. A follow-up is planned to Week 48 and Week 96.

**Results**

A total of 251 patients (approximately 50 in each arm) were enrolled. They had a median CD4 cell count of about 220 cells/mm³, plasma HIV RNA of 4.85 log10 cp/mL, and 45% had a VL > 100 000 cp/mL. Approximately 50% had at least one major PI mutation in addition to NRTI or NNRTI-associated mutations (M184V 31%, K103N 29%, TAM 13%, PI 2%).

Over 7 days of monotherapy, the reduction in HIV RNA ranged from −0.7 to −1.5 log10. A snapshot analysis at Week 24 presented at CROI 2014 showed a 75% rate of full viral suppression in the four TDF/
RAL/BMS-663068 arms, as well as in the TDF/RAL/ATV arm (8) (Figure 8).

The profile presented at Glasgow shows that the drug is generally well-tolerated. Serious AE occurred in 13/200 subjects (6.5%) in all groups across the BMS-663068 treatment arms and 5/51 subjects (9.8%) in the ATV/r group. None of these were related to either drug. The most common AE reported was headache, which was 14% across the BMS-663068 arms compared to 9.8% in the ATV/r group.

There were no noticeable AE of laboratory grades 3–4: neutropenia was detected in 5/196 patients, and liver enzymes elevation in 2/196. In the ATV/r arm 25/51 patients had total bilirubine elevation. No change was observed in serum creatinine or lipid profile. Phase 3 trials in heavily-experienced patients are expected to start in early 2015.

**Conclusion**

Although the recruitment of an experienced study population with prior viral resistance is a challenge, it is necessary in order to pursue a new class of drugs that could overcome comorbidities and resistance. While the median time our patients are on ART is currently about 10 to 15 years, we can anticipate that it will be much greater in the coming decades.

**References**


Superior to PI-based regimens in maintaining virologic suppression at week 48 in a study recently published in the Lancet⁸

- **Good tolerability** – the tolerability profile you have come to expect from the integrase inhibitor class⁹, as demonstrated by the low discontinuation rate <6% across both pivotal studies⁶,⁷
- **Very convenient** – one dose daily to assist adherence⁹

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**Powerful performance in HIV¹⁻⁷**

- **Highly effective** – robust virologic response in both naïve and switch studies³⁻⁸
  - Naïve: data from two pivotal studies shows high sustained efficacy with Striobil over 144 weeks⁶,⁷
  - Switch: Striobil was superior to PI-based regimens in maintaining virologic suppression at week 48⁸

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The first Nordic HIV conference was held in Stockholm in October 2-3, 2014. During this, 11 Plenary lectures were given, three Satellite Symposia were held and three oral abstract presentations were given – and 28 Posters were presented. More than 200 delegates had come to the Swedish capital to attend.

On the behalf of the Organising Committee, Prof Magnus Gisslén greeted them all welcome to Stockholm.

– I’m very pleased of the high number of attendees, he said.

He also thanked the sponsors – Bristol-Myers Squibb, Gilead, ViV Healthcare, Janssen and MSD – and the Organising Committee.

– They consist of 11 international experts from different countries, Prof Gisslén pointed out.

Co-factors important for life expectancy

At the Opening Plenary Session, Prof Niels Obel talked about the Danish HIV Cohort study.

– It all started with 29 patients in 1999, and I could then never have guessed that I would present a lecture on it in the first Nordic Conference, Prof Obel stated.

Today the nationwide, population based cohort study encompasses more than 6,000 patients – 25 % being women. The study is linked to several Danish registries.

– You can’t imagine what we know about our population in Denmark, Prof Obel continued.

There are approximately 250 new HIV infections in Denmark per year, and this number is stable. The mortality for HIV is declining, and life expectancy for HIV patients is around 65 years, he said.

– Co-factors are very important for life expectancy. But these seem to be the same for HIV patients, as they are for the background population. Smoking is however a big problem in the HIV population.

By using data generated from the other registries, Prof Obel could point out that social group has a lot to do with life expectancy – as it also does for the background population.

Cardiovascular disease (CVD) and hepatitis as causes of death are on the rise among HIV patients. Smoking is important as a risk factor.

– We must talk to our patients about risk.

Siblings mortality is higher

HIV patients have a higher risk for lung cancer – but also the mothers and the fathers to these patients are at a higher risk. Prof Obel showed that high or low education level impacts on the risk for cancer.

– And we found that the mortality in siblings of patients co-infected with HIV and Hepatitis C virus (HCV) is significantly higher than in siblings of population controls.

On the topic of ageing, he said they had found that HIV patients have more cataract operations associated with age and more fractures than background population.

– They do not more often get diabetes, though. And they have less prostate hypertrophy. So there are data indicating that ageing does not relate to HIV.

Prof Obel ended his lecture by presenting a question mark that represents that there are unknown risk factors that influences mortality and more rapid ageing in HIV patients.

– My guess is that it represents smoking, drug abuse and social factors, he said.

HIV vaccine research still at a discovery stage

Prof Robin A Weiss had a talk on HIV vaccine and immunotherapy research. He started this by stating that “prevention is better than cure”, and mentioned several successful vaccines against viral diseases such as smallpox, polio myelites and hepatitis B among others.

– All vaccines demands multidisciplinary research. HIV/AIDS, TB, Malaria, Hepatitis C, Dengue and Ebola are still awaiting a safe and efficacious vaccine. The three first mentioned are major killers in the world, Prof Weiss continued.

He added that he was going to be very gloomy on the prospects of a HIV/AIDS vaccine.
One reason for this is the variations and subtypes of HIV, this diversification affects antigenic drift and drug resistance.

Prof Weiss presented six HIV vaccines that have been in clinical trials, but none of them had shown strong protection against HIV infection. He was also pessimistic in his view on the current HIV vaccine pipeline.

- I hope I’m wrong, but I don’t think any of them will work.

The HIV vaccine field is still in the discovery stage: The best immunogens are not identified, suitable immunisations and adjuvant methods are not determined – yet there is immense pressure from funding agencies to go into human efficacy trials. Prof Weiss said.

**Work with llamas**

He described the “conundrum of antigenicity and immunogenicity”.

- Naturally infected individuals have weakly neutralising antibodies with little breadth. But a few HIV-positive individuals make good titre broadly neutralising antibodies, which have their antigen-binding properties confined to a single fragment, the VHH, and a preference for cleftrcognition. In Prof Weiss own unit, at University College London, they are presently working with llama VHH as immune tools.

- We are getting good results, but we do not have a vaccine yet, he underlined.

Prof Weiss ended his lecture with a quote from Samuel Beckett: “Ever tried. Ever failed. No matter. Try again. Fail better!”

One day we might even succeed – HIV-researchers are long-term non responders!

**Strong support for early ART**

Prof Margaret Johnson talked about five important studies in 2013 – 2014, and started with HIV Prevention Trials Network (HPTN) 052. It is a Phase III, two-arm, multi-site, randomized trial to determine the effectiveness of two treatment strategies in preventing the sexual transmission of HIV in HIV-serodiscordant couples.

In the early arm, ART was started when CD4 count was between 350 and 550. In the delayed arm, treatment was started when CD4 was 250 or below.

- The study was stopped early, on recommendation from the data safety monitoring board. It was recommended that all participants in the delayed control group should receive ART. The results provide strong support for early initiation of antiretroviral treatment, Prof Johnson said.

The PARTNER study aimed to evaluate the risk of within-couple HIV transmission during periods where condoms are not used consistently, and the partner is on suppressive ART. The results showed no transmissions – despite high levels of STI in HIV-positive men who have sex with men (MSM).

- It has been calculated that if the HIV-positive not had been on ART, at this two year interim analysis 86 transmissions would have been suspected!

**Much higher virological rebound for PI mono**

The third study Prof Johnson presented concerned long-term ART in early or acute HIV infection.

- It was known that this may reduce the reservoir of latently infected cells which has been observed in elite controllers and post treatment controllers, she continued.

In the study they also looked for T cell subsets. The finding was that early treatment patients reduced total HIV DNA in effector memory and terminally differentiated memory CD4 cells – but not in the less mature longer lived central memory stem T cells.

- Early treatment, even if continued for more than 10 years, is unlikely to lead to cure. But low viral reservoirs and durable HIV-1 T cell responses make the patients good candidates for future studies.

PIVOT is a study on PI monotherapy versus triple ART. The primary endpoint was loss of future drug option by 36 months, and the results were 0,7 % for triple ART and 2,1 % for PI mono.

- The virological rebound for triple ART was 3,2 % versus 35 % for PI mono. The difference was 31,8 %.

Prof Johnson said she thought that PI monotherapy will not save any money.

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Margaret Johnson  
Robin A Weiss
– The difference is that the cost comes later.

**Time to abandon efavirenz as first line?**

She then presented a study on efavirenz and the risk for suicide – it was an analysis of trial data. The objective was to compare time to suicidality with efavirenz-containing regimen versus efavirenz-free regimens for initial treatment of HIV.

The results showed that there were 47 events in the efavirenz group – 8.08 per 1000 patient years – and 15 events – 3.66 per 1000 patient years – in the efavirenz-free group.

– I want to highlight that 32% of the participants had psychiatric history or were on psychoactive medication – perhaps not those we consider for this regimen today, Prof Johnson pointed out.

The findings have nevertheless led to a discussion on if the time has come to abandon Efavirenz for first-line antiretroviral therapy.

– It will be interesting to see in future guidelines.

The last study was comparing two combinations: DTG + ABC/3TC QD versus EFV/TDF/FTC QD.

– Week 144 treatment-emergent resistance data shows better resistance for DTG + ABC/3TC QD. This means we will not have to monitor our patients as often, Prof Johnson said.

**Establishment of the reservoir**

The top five papers in basic HIV research in 2013-14 were presented by Prof Francesca Chiodi. The first two of these concern establishment of the reservoir.

– A paper published in *Nature* in 2014 describes a new type of reservoir for HIV in CD4+ T cells with stem cell-like properties. The authors show that during suppressive ART, CD4+ T memory stem cells (TSCM cells) harbour high per-cell levels of HIV-1 DNA and make increasing contributions to the total viral CD4+ T cell reservoir over time, Prof Chiodi said.

Moreover, the authors conducted phylogenetic studies that suggested long-term persistence of viral quasispecies in CD4 TSCM cells. Thus, HIV-1 may exploit the stem cell characteristics of cellular immune memory to promote long-term viral persistence.

– In ART treated patients, per cell levels of HIV-1 DNA were highest in CD4+ TSCM.

They are functionally capable of resuming active viral gene expression.

The second paper, published in *Science* 2014, evaluated the contribution of infected-cell proliferation and sites of proviral integration to HIV persistence. They found that integrations were overrepresented in genes associated with cancer – and favoured in 12 genes across multiple participants.

– Over time on ART, a greater proportion of persisting proviruses were in proliferating cells. HIV integration into specific genes may promote proliferation of HIV-infected cells, slowing viral decay during ART, Prof Chiodi continued.

HIV integration could disrupt the regulation of these genes, as is known to occur during tumor induction by non-acute oncogenic retroviruses.

HIV integration into genes associated with cancer or cell cycle regulation appears to confer a survival advantage for reservoir cells allowing them to persist and divide during suppressive ART.

– Accordingly, cell proliferation appears to serve as an important mechanism of HIV persistence.

**Broadly neutralizing antibodies**

The next three papers were on novel therapy strategies to cure HIV. *NEJM* published in 2014 *Gene editing of CCR5 in autologous CD 4 T cells of persons infected with HIV.***

CCR5 is the major co-receptor for HIV. The aim of the study was to investigate whether site-specific modification of the gene (“gene editing”) – in this case, the infusion of autologous CD4 T cells in which the CCR5 gene was rendered permanently dysfunctional by a zinc-finger nuclease (ZFN) – is safe.

During treatment interruption and the resultant viremia, the decline in circulating CCR5-modified cells (-1.81 cells per day) was significantly less than the decli-
ne in unmodified cells (7.25 cells per day).
- CCR5-modified autologous CD4 T-cell infusions are safe within the limits of this study. It supports the feasibility of targeted genome editing to introduce a disease-resistance allele.

The second study on new therapy Prof Chiodi presented was on broadly neutralizing antibodies (bNAbs). It was published in Cell in 2014.
- The study established the principle that HIV reservoir can be altered in vivo by combination therapy with 3 antibodies and 3 inducers of viral replication.

The combination of 3 antibodies with 1 inducer had no effect in preventing viral rebound. It is a very interesting and promising result, Prof Chiodi stated.

The last paper had a completely different principle: Cell death by pyroptosis drives CD4 T cell depletion in HIV-1 infection. (Published in Nature 2014).

Abortive infection of non-permissive T cells leads to death by pyroptosis (an inflammatory form of programmed cell death) mediated by caspase-1. The production of inflammatory signals during pyroptosis attracts more cells to become abortively infected and die by pyroptosis.
- An existing small molecule, VX-765, is an efficient inhibitor of caspase-1 and could constitute a new therapy to maintain numbers of CD4 T cells. I think this is also a very interesting and very concrete result, Prof Chiodi said and summarized her lecture with the following general conclusion:
- The field of HIV basic research remains very exciting – and sparking with a lot of promises for translational interventions!

Significant association with blips and high baseline HIV-1 RNA
Erik Sörstedt presented an oral abstract on HIV viral blips in ART.
- Viral blips were first mentioned 15 years ago. Several studies have since been made, but the problem is that they each had different blip definitions, said Dr Sörstedt.

The American definition on virological blip is that after virological suppression, an isolated detectable HIV RNA level rise that is followed by a return to virologic suppression.
- No one knows what the origin of blip is, but there are theories. It could be low-level ongoing viral replication, or a temporarily increased HIV replication due to a co-infection of another bacteria or virus. Blips could stem from laboratory techniques and errors – or from low drug concentrations in blood. The latter could of course be due to low adherence, which is difficult to study, Dr Sörstedt explained.

In the study he presented they had defined a blip as a viral load between 50 and 500 copies – both preceded and followed by a viral load of less than 50 copies/ml.

Two values within six weeks in this range were interpreted as one blip.

They had followed 751 patients in three centers in Sweden for six and a half years.
- In our study 2 % of all samples were blips. We found a significant association with blips and high baseline HIV-1 RNA levels. We also found it was more common with blips in PI-based CART. There was no significant correlation between blips and viral failure, Dr Sörstedt summarised.

The risk of precancerous lesions increases with immunosuppression
Dr Christina Carlander presented a study entitled High incidence of cervical cancer among women with HIV in Sweden.

Women with HIV are at high risk of persistent HPV-infections, cervical cancer and precancer.
- Among women with HIV in Sweden the incidence of cervical neoplasia is not known and risk factors for developing cervical neoplasia are not known either, Dr Carlander said.

The typical HIV-infected woman in the study was a migrant (70 %), 30 years old at inclusion, HIV-infected heterosexually and had a CD4 nadir count at 180.

The risk of CIN2+ (precancerous lesions) increases significantly with immunosuppression.

In her conclusion, Dr Carlander pointed out that the risk of CIN2+ is at least five times higher among HIV-infected women compared to HIV-negative women in Sweden.
- The risk is highest among HIV-infected migrants from Sub-Saharan and East Africa. The risk also increases with immunosuppression.

For the future she underlined the importance of early HIV diagnosis.
- Attendance to cervical screening is also very important. I think we can do more on that subject. We also need to have a special focus on migrants, Dr Carlander said.

Study on CSF signs of neuronal damage
HIV enters the CNS shortly after transmission, and establishes a productive infection within the brain. 20 – 30 % of untreated individuals will develop HIV associated dementia (HAD) and this has a major impact on functional capacity and lifespan. With ART, the incidence of HAD has decreased dramatically.

- Milder forms of HIV associated neurocognitive disorders (HAND) remain prevalent, mainly in the forms of asymptomatic neurocognitive impairment and
mild neurocognitive disorder. The prevalence is ranging from 35 to 70 %, said Dr Arvid Edén.

He presented a study that aimed to investigate cerebrospinal fluid (CSF) signs of neuronal damage and intrathecal immune activation in well-characterized subjects on ART with or without neurocognitive impairment.

- We found that CSF biomarkers of immune activation (neopterin) and axonal injury (NFL) were higher in subjects with milder forms of neurocognitive impairment, compared to unimpaired subjects, Dr Edén said.

The correlation seen for NFL and neopterin in impaired subjects indicates an association between intrathecal immune activation, neuronal injury and neurocognitive impairment in subjects on ART with viral suppression, he continued.

- These results indicate that asymptomatic or mild impairment may represent a pathological process in the CNS; Edén also in some virally suppressed individuals. Patients with confirmed neurocognitive impairment may require closer monitoring than currently suggested, were his conclusions.

**Latently infected cells the first target**

Dr David Margolis talked about the current status of HIV cure research.

- Current therapies do not affect latent reservoir, he said and presented the first article on latent reservoir, published in AIDS 1999.

In 2008, the Berlin patient revived the search for a cure for HIV/AIDS. Then came the Mississippi baby in 2013.

- Unfortunately, the baby has now rebound. There must have been at least one latently infected cell that lasted for 27 months, Dr Margolis said.

The latently infected cells are our first target to deal with.

- We need to dare these cells to be exposed, so we can target them!

But there are multiple hurdles to viral escape – from latency cellular state, integration site and chromatin modification to name a few – and Dr Margolis underlined that we systematically need to target these barriers.

What if disrupting latency is not enough?

- When latency is disrupted, mechanisms to kill virus-expressing cells may be needed. We have many tools, but the trick is to find out how to best use – and combine – them.

In his summary, Dr Margolis stated that we are assembling the tools to design, discover and test anti-latitude therapy.

- But there is still a long way to go. Harnessing the immune response, or other cellular pathways, or new technology to assist in the clearance of persistently infected cells is the next step. It’s a rare cell – that probably express antigen for a short time.

Ending AIDS means that we have to find patients earlier and bring treatment to them. It means developing ways to use ART as prevention and to develop vaccines that substantially reduce the risk of transmission.

- We need to build platforms to develop and test curative therapy – perturb latency, block all infection, reach all relevant cells and clear infected cells, Dr Margolis summarised.

**Survivorship bias**

Life expectancy for a HIV-infected 20 year old may, with early ART, start to approach the life expectancy of general population, said Prof Peter Hunt.

He presented data that showed this, and pointed out the difference in life expectancy for those who start ART at a pre-ART CD4 count under 350. This is much lower.

- And the majority of HIV-positive around the world is still starting ART below 350!

But there are caveats in the data – life expectancy may be overestimated.

- It excludes those out of care. And there is a “survivorship bias” for older patients who survived in the 80s and 90s. Many died, and we don’t see them in these statistics, Prof Hunt continued.

Non-AIDS diseases such as non-AIDS malignancy, non-AIDS infection and CVD now account for the majority of deaths in HIV. Many age-associated morbidities – that we ordinarily see in older patients – also increase in treated HIV.

- These chronic diseases of ageing are more common in HIV-positive individuals – even after adjustment for ART use and lifestyle factors.

**A clue from nature**

He presented two monkeys – a Sooty Mangabey and a Rhesus Macaque. If these animals are infected with SIV, the Mangabey will have high levels of viral replication but develop no AIDS and a minimal immune activation. The Macaque will also have high levels of replication, but it will contract AIDS and death – and have a massive immune activation.

- This is a clue from nature: The difference between these two monkeys is not the virus. It’s exactly the same. It is the immune response that differs!

Inflammatory markers remain abnormally high in treated HIV infection. Prof Hunt presented images on increa-
sed arterial inflammation in HIV.

– Inflammation predicts disease in treated HIV infections. Early ART appears to cause greater reduction in residual T cell activation, he underlined.

Earlier initiation of ART may decrease the degree of persistent immune activation, he summarised.

– Statins, ASA, diet and exercise may hold promise. A study presented at CROI this year showed that moderate exercise decreases inflammation in sedentary ART-suppressed HIV-positive patients.

He ended his talk by stating that we need more effective targeted interventions directed at the underlying *causes* of inflammation.

**Pathways of care**

Dr Graeme Moyle talked about balancing adverse effects, efficacy, economy and resistance in ART. He began by describing a “hierarchy of needs”, illustrated as a pyramid in three versions – what *patients* want from treatment, what *physicians* want and what *payers* want from treatment.

– The patients want a minimal impact on life, physicians want long-term virological suppression and the payers want cheaper care, Dr Moyle said.

Therefore the pathways of care are different from these perspectives. The payers want to start with the cheapest.

– Currently Atripla or generic multitablet regimen. Restrict timing of treatment to those at greatest need and ignoring treatment as prevention (TasP).

Only those intolerant of or unsuitable for first line of treatment gets second regimen, even fewer the high cost third line choice etc.

Pathways of care for patients and physicians is different: Start with the easiest and most well tolerated effective therapy, tolerability switches are less likely, acceptability of treatment increases and adherence is supported.

– More treatment success leads to fewer expensive failure events, fewer switches, fewer transmissions and lower morbidity. Length of life, quality of life and life-time costs may be reduced by more individualised treatment choice.

**Innovation and generic options will change the treatment landscape**

People who start treatment early, before they are ill, will have much better tolerability.

– But payers want to wait with treatment until the patient is sick. I think we are going to see this a lot in Hepatitis in the future, Dr Moyle continued.

Recommended ARTs have demonstrated high virological efficacy in RCTs, but in patients with high viral load or CD4 differences in efficacy are apparent.

– The menu of available combinations have differences in safety and tolerability. Some ARVs have known short-term side-effects that are manageable, while others have longer-term safety considerations. We need more drugs to choose from!

While fixed dose regimens can provide the convenience of once-daily dosing, they may not provide the treatment flexibility. Tolerability, lack of food requirements and low potential for drug-drug interventions are key components of convenience.

– And on the matter of costs, innovation and generic options will change the treatment landscape in coming years, Dr Moyle stated.

**Drug-drug interactions an important topic**

Prof Stefan Zeuzem talked about direct acting antivirals (DAAs) for hepatitis C (HCV).

– The real revolution starts now with the interferon-free combinations, he said.

After presenting several studies on these regimens, Prof Zeuzem pointed out that all oral therapies differentiate depending on genotype of HCV and efficacy in standard versus special populations.

– The treatment duration is today the big marketing competition. Resistance does not play much of a role but drug-drug interactions is a main topic.

He summarised some statements and predictions on the future of HCV therapy.

– FDC (from Gilead) and 3D (Abbvie) are supported by large Phase III studies and will follow for more robust treatment
recommendations. Ribavirin will become less important.

Nucleoside inhibitor + 2 DAAs may further shorten therapy and lead to higher sustained virological response (SVR) rates – in particular in patients with cirrhosis. Response to previous, interferon-based, treatment will be less relevant.

- We will see similar SVR rates in mono- and co-infected patients. Cirrhosis (more granular differentiated) is expected to become the key baseline predictor for SVR. Few patients may relapse with any DAA combination and require maintenance therapy, Prof Zeuzem ended his talk.

**NRTI sparing regimen is on the horizon**

Alternative ART regimens for patients ineligible for nucs was the topic of a lecture given by Prof José Gatell.

He began this by addressing the question on when to start ART, and described the evolution of HIV treatment guidelines.

- **All** symptomatic patients should receive ART! Viral load was considered in the 90’s and early 2000, Prof Gatell said.

This was illustrated by presenting the 11th update on IAS-USA antiretroviral guidelines, from which he quoted:

> “ART is recommended for all adults with HIV infection...After confirmed diagnosis of HIV infection, ART should be initiated in all individuals who are willing and ready to start treatment.”

Prof Gatell presented old and current initial paradigms and saw in the future a NRTI sparing or saving regimen on the horizon.

- A relatively small percentage of patients may be ineligible for NRTI’s, except FTC & FTC. That is the main take-home message of my talk, he said.

> “Partially active” NRTI’s have some activity and should be retained unless they can be replaced by fully active drugs. Better NRTI’s may also become available.

- The best results are obtained with PI/r + 3TC. Newer combinations – e.g. DTG + 3TC or RIL – is being explored, Prof Gatell stated.

**Founder virus determines viral load**

The viral load set-point is extremely variable, said Prof Christophe Fraser.

- What drives this extremely variability, he asked.

Host genetic factors account for 13 % of variation in viral load. This means that 87 % is unexplained.

- People with intermediate viral loads are most infectious in the long run. This is due to the fact that people with high viral load do not live as long.

According to Prof Fraser there is a hypothesis that the virus has evolved to maximize its transmission potential. But he thought this to be unlikely.

- Given speedy and error-prone within-host viral replication and relative infrequency of transmission, “long-sighted” evolution to optimise transmission seems implausible!

There is a lot of evidence for that founder virus determines viral load. Prof Fraser described what he called “store & retrieve dynamics”:

- Viruses that transmit through mucosa are more infectious, are preferentially transmitted and stored in viral archives in resting memory CD4+ T cells for years!

He concluded that the role of viral virulence factors in pathogenesis need to be
re-evaluated, as evidence in mechanisms remains largely unknown.

– Mechanistically understanding viral virulence will provide new insights on HIV pathogenesis and evolution, Prof Fraser said.

**Global patterns of viral migration**

Dr Dimitros Paraskevis presented a phylogeographic meta-analysis that aimed to estimate subtype specific HIV-1 global viral migration with special emphasis in Europe.

His conclusion was that for subtype B, America has been influential in driving the Western epidemic through constant mobility to the rest of the world.

– In striking contrast, the role of Europe was secondary and the incoming infections spread mainly among regional populations, he continued.

The highest mobility between any European country and non-European regions was observed for the UK, Switzerland and France.

– UK and France are two of the largest countries in Europe, with significantly social and economic links across the globe. Similarly, Switzerland is an international financial centre — probably there is a lot of person mobility.

Global patterns of viral migration mirror human activities during the last 50 years, Dr Paraskevis pointed out.

The HIV-1 CRF01_AE subtype is a risk factor for fast HIV-1 progression, and Dr Paraskevis reported that their results pinpoint the central role of Thailand in the global CRF01_AE epidemic.

– The key factor in this pattern might be Thailand’s popularity as a tourist destination, the extensive network of commercial sex workers and human mobility.

He underlined that the case of CRF01_AE is unique, regarding factors causing its global dispersal pattern – in contrast to other non-B infections mainly associated with immigration from Africa.

– Currently, South Eastern Asia provides the only exception of a non-African source for the global dissemination of CRF01_AE, was Dr Paraskevis final statement.

At the end of the Conference, Dr Lars Moberg presented the HIV Nordic 2014 Abstract Award — a Research Grant of 2,500 Euro — to Dr Christina Carlberg.

Then the first HIV Nordic Conference was over. It will return in 2015.

**PER LUNDBLAD**
Satellite Symposiums at the HIV Nordic Conference

During the two days in Stockholm, three Satellite Symposiums were held. These were sponsored by the pharmaceutical companies Gilead, ViiV Healthcare and Janssen.

The first Symposium was given prior to the Opening Ceremony. The title was Global access challenges for HIV and HCV drugs and Prof Anna Mia Ekström was the Chair. It was sponsored by Gilead.

Data on ART coverage not correctly calculated
Prof Hans Rosling began by talking on the global burden of HIV and HCV. He stated that in the year 1800, all countries in the world had a life expectancy of below 40 years. By using the internet resource Gapminder (at www.gapminder.org, invented by Prof Rosling) he demonstrated how this has developed into the average life expectancy of 70 years that we have today.

Prof Rosling continued by pointing out that when ART coverage is calculated the number of ARV treated people are divided with the sum of these, plus the number of people eligible for ART.
– This does not give you the true coverage, since the deaths are not counted, he said.

There is also a large treatment need for HCV, but from many countries we do not have data on prevalence and incidence.
– The idea of having the same price for drugs in all countries is stupid. Gilead has introduced a system of prizing the drug differently in the world, and I am very sympathetic to that, Prof Rosling said.

Tiered pricing
– All people should have access to our medicines, regardless of where they live or their economic status, said Clifford M Samuel from Gilead.

Therefore the company has introduced tiered pricing in low, lower-middle and upper-middle income countries – based on a country’s disease burden, development status and healthcare infrastructure. 17 generic partners are licensed to manufacture and sell Gilead therapies – which has reduced the cost of tenofovir by 80 %.

HCV prevalence is higher in Egypt than in any other country in the world. An estimated 72 % of Egyptians are chronically infected with HCV.
– Egypt has been a high priority for Gilead’s HCV treatment expansion efforts. One example is Sovaldi that today costs 900 dollar for three months in Egypt. In USA this costs 84 000 dollar, Mr Samuel said.

He added that Gilead will also partner on medical education to train healthcare providers in hepatitis C diagnosis and care.

Dolutegravir a new treatment option
Tailoring therapy today – talking about dolutegravir, was the title of a Symposium sponsored by ViiV Healthcare. Prof Magnus Gisslén was the Chair, and he began by describing the UNAIDS “90-90-90” campaign.
– This means that by 2020 should 90 % of all people living with HIV know their status, 90 % should be on treatment and 90 % should have durable viral suppression. These are very ambitious goals because they are in an international setting, he explained.

In Sweden the first target is not yet reached, but the other two have already been reached – 94 % of all diagnosed patients in the country are on treatment and 95 % have a viral load below 50 copies/mL in a snapshot analysis.

Prof Anders Sönnerborg talked about a new treatment option in HIV – dolutegravir (DTG).

In ART-naive patients the SINGLE study showed that DTG + ABC/3TC had statistically superior efficacy versus Atripla, and was better tolerated with fewer discontinuations.

The SPRING study demonstrated that in ART-naive patients DTG was non-inferior to raltegravir, and offered similar tolerability.
– And the FLAMINGO study showed that in ART-naive patients DTG had sta-
statistically superior efficacy versus darunavir/r, and was similarly tolerated, Prof Sönnerborg said.

So far DTG has not showed any resistance in integrase inhibitor treatment naïve patients.

**Integrase inhibitors bind to magnesium**

Prof David Back talked about the key pharmacological attributes of DTG. There is a relationship between DTG dose, plasma concentration and virologic response.

- The PK and PK/PD results from the studies SPRING 1 and 2 and SAILING support the dose selection of DTG 50 mg once daily in the integrase inhibitor treatment naïve population, he said.

Prof Back underlined that integrase inhibitors bind to magnesium.

- So if they are in the gut, they will bind to that. Therefore the recommendations are to take magnesium/aluminium antacids and calcium and iron supplements a minimum of two hours after or 6 hours before DTG.

On the renal effects of DTG, he pointed out that DTG does not affect actual glomerular filtration rate.

- DTG has low probability for drug-drug interactions, Prof Back added.

**Bedaquiline new drug for multiresistant TB**

The third Symposium in Stockholm was sponsored by Janssen. Dr Judith Bruchfeld and Dr Stefan Lindbäck were the Chairs.

- It is important that we now have two new drugs for TB – we’ve been using the same regimen since the 1960s, and multidrug-resistant TB is becoming a big problem, Dr Bruchfeld said.

Dr Koen Andries described the development of the anti-TB drug bedaquiline, the first new medicine to fight TB in 40 years. He called this “a rocky road”, due to many setbacks in the development process.

- In 2006, one more study on bedaquiline in multidrug-resistant TB was decided upon. It showed a good response – although the study was only for safety and PK, Dr Andries said.

Although development looked hopeless at certain times, today not only team members but all Janssen employees feel proud about what they have achieved, he continued and finished with a look into the future.

- Treatment of MDR TB without bedaquiline – i.e. present treatment – means 3250 pills: 5 antibiotics during 24 months, 250 injections, 6 months hospitalisation and severe side effects. Treatment with bedaquiline means 540 pills, 3-4 antibiotics during a period of less than 6 months, no injections, no hospitalisations and reduced side effects!

**The three Ds – factors for success**


He started by presenting data on life expectancy for HIV-infected people under optimal conditions. This shows that it is getting near general population.

- We should therefore plan for the very long term, Prof Stellbrink established.

ART can reduce morbidity, improve life quality, prolong survival and reduce immune activation and transmission. But it can’t cure.

- There is no evidence that we can cure patients, regardless how early we start ART.

Prof Stellbrink also presented two studies that shows better efficacy for a 3-drug regimen, compared to a 2-drug regimen.

- But it is not just about delivering drugs – the next wave of problems comes with virological failure and drug resistance.

He presented factors for success – “the three Ds”: The first is drugs; they need to be well-tolerated highly active drugs for combination therapy. The second is diagnostics – which have to be sensitive, specific and broadly available.

- The third D stands for doctors. They need to be educated, experienced and dedicated physicians, knowledgeable in HIV pathophysiology, diagnosis and treatment of opportunistic diseases and the properties of antiretroviral drugs.

They must also have methods to improve patient adherence and make optimal use of diagnostic methods, Prof Stellbrink summarised.
2014 was a remarkable year in the field of hepatitis C treatment. It is rather unique in modern medicine that the European Medical Agency (EMA) approved four new compounds to treat a specific viral infection within just 10 months and we can expect the next steps already for January 2015.

Even for experts in the field it is not easy to keep track with all developments and data from phase 2 and 3 clinical trials and so called “real-world” registries. On the other hand, some drugs and regimens may have a rather short half life and could even disappear within the next 12-18 months considering the emerging landscape of treatment options.

Currently approved direct-acting antivirals (DAA) are listed in the table including the single-tablet regimen of ledipasvir + sofosbuvir (“Harvoni®”) representing the most recent “kid on the block”. Paritaprevir/r and ombitasvir (“Viekirax®”) in combination with dasabuvir (“Exviera®”) received a positive opinion by EMAs Committee for Medicinal Products for Human Use (CHMP) in November. Thus, by February 2015 the first wave of HCV drug approvals will have been completed in Europe. IFN-free treatment options are now available for basically all patient groups. Additional treatment regimens may then enter the market in Q4 2015 and during 2016.

At AASLD 2014, we saw (i) more data on Gilead’s ledipasvir/sofosbuvir combination and Abbvie’s “3D” combination; (ii) new phase 2 and 3 studies on other drugs; and (iii) first real-world findings on sofosbuvir-based therapies from large US registries.

AASLD 2014: Real-world data for simeprevir & sofosbuvir

Both, simeprevir (SMV) and sofosbuvir (SOF) were approved by the FDA in late 2013 and many US physicians started using this “off-label” combination for the treatment of chronic hepatitis C during the last 12 months - supported by a statement in the AASLD/IDSA HCV treatment recommendations which are available on www.HCVguidelines.org. Before AASLD, the only data supporting this regimen were derived from the phase 2 “Cosmos-study” published as a full paper in the Lancet in November (1). In Boston, varies data from the US TARGET and the TRIO registries were presented supporting the value of this combination therapy. Even though ITT-SVR data were slightly lower than in the Cosmos trial, the biological efficacy of the regimen was confirmed. The TARGET registry included more than 1000 patients treated with SMV/SOF with (n=228) or without (n=784) ribavirin (RBV) (2). It is worthwhile to mention that more than half the patients had already liver cirrhosis, that 18-25% were older than 65 years, and that more than a quarter of patients had failed a previous treatment including an HCV protease inhibitor – even though a theoretical risk of cross-resistance of persisting resistance-associated variants exists. Moreover, several patients with advanced liver cirrhosis (MELD score >10), liver cancer or after liver transplantation were treated with SMV/SOF. Overall, 86-89% of patients achieved a SVR4 after 12 weeks course of therapy. Additional findings were

• SMV/SOF achieved very high SVR rates in genotype 1b patients (>95%) but slightly lower cure rates in genotype 1a. Data for the Q80K variant which is associated with reduced si-meprevir activity in IFNa-treated patients were not available.
• Cirrhotic patients showed numerically slightly lower response rates.
• Previous PI failures had lower response rates but still more than 80% cured HCV (which was not necessarily to be expected!).
• Adverse events were infrequent and in line with findings from previous controlled studies.
• There is no evidence that ribavirin is needed to increase response rates with this specific combination.
• SMV-SOF can also be used in liver transplant recipients with a high chance of success (SVR4 90%) (3)

Data from another US-registry (“TRIO”) were presented by D. Dieterich (4). 322 patients in TRIO received SMV/SOF+/−RBV with 82% achieving a SVR-12. Significant differences between ITT and per protocol analysis’s were observed highlighting the importance of careful patient selection and guidance for these easy to use but highly expensive new treatment regimens.

AASLD 2014: Ledipasvir/sofosbuvir and the “3D” combinations

I discussed the key findings of the pivotal phase 3 studies for the two regimens in the May issue of the Magazine. The ION-studies (Ledipasvir/Sofosbuvir) and...
the Sapphire, Turquoise and Pearl studies (Paritaprevir/Ombitasvir/Dasabuvir) were all published in the New England Journal of Medicine in April and May 2014. At AASLD several additional analyses from these trials were presented focussing on different subgroups such as patients with liver cirrhosis, patients older than 65 years of age or individuals receiving opioid substitution therapy. In general, the impressive antiviral efficacy of both regimens was confirmed across all subgroups. Predictors of response were analysed and revealed statistically significant associations for certain subgroups of patients. E.g., the BMI was associated with SVR in non-cirrhotic HCV genotype 1a patients receiving the Abbvie-3D combination while gender, race and IL28b genotype were correlated with SVR in the ION-3 study investigating 8 vs. 12 weeks of therapy with ledipasvir/sofosbuvir. However, to what extent these findings will be of relevance in clinical practice remains to be determined. Even though “statistically significant”, the absolute differences in SVR rates were very minor in the respective subgroups usually not exceeding 5-9%. It is important to note, that early virological kinetics during therapy were not associated with SVR, neither in the ledipasvir/sofosbuvir trials nor in the paritaprevir/ombitasvir/dasabuvir studies. Thus, it seems unlikely at this stage that we will see a revival of “response-guided” treatment durations also in the setting of IFN-free therapies with the purpose to reduce treatment costs (5).

New trial results were presented for ledipasvir/sofosbuvir by Marc Bouliere (6). An “integrated analysis” of 513 patients with compensated cirrhosis treated in various phase 2 and 3 trials with ledipasvir + sofosbuvir revealed that 12 weeks of LDV/SOF will likely be sufficient in most patients, even in individuals with liver cirrhosis. However, the addition of ribavirin will prevent relapses in up to 6% of patients, in particular in treatment-experienced subjects. To me, 12 weeks of LDV/SOF/RBV vs. 24 weeks of LDV/SOF without ribavirin. If ribavirin is not tolerated well, the dose should be reduced accordingly.

Patients with decompensated liver disease require antiviral therapy most urgently. The analysis by Marc Bouliere and colleagues suggested that low platelet counts (<75,000/μl) may be associated with slightly reduced response rates (6). The most important question, however, is to what extent liver function improves after the initiation of antiviral treatment in patients with decompensated liver cirrhosis. Very importantly, MELD and CPT scores (“model-for-end-stage-liver-disease” & “Child-Pugh”, both indicating severity of liver disease) improved during antiviral therapy with ledipasvir/sofosbuvir in the majority of patients while only few patients experienced a worsening of the respective parameters in the SOLAR-I study presented by Steven Flamm (7) (figure). These findings are very important for clinical practice and strongly suggest antiviral therapy even in patients with very advanced liver disease. However, one has to keep in mind that many patients with decompensated cirrhosis have an impaired renal function and sofosbuvir should not be used in subjects with a creatinine clearance of <30 ml/min.

Table: DAAs to treat HCV infection

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>Dose</th>
<th>How to use?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boceprevir (Victrelis™)</td>
<td>Genotype 1</td>
<td>3x 800 mg</td>
</tr>
<tr>
<td>Telaprevir (Incivo™)</td>
<td>Genotype 1</td>
<td>2 x 1125 mg</td>
</tr>
<tr>
<td>Simeprevir (Olysio™)</td>
<td>Genotypes 1 &amp; 4</td>
<td>1 x 150 mg</td>
</tr>
<tr>
<td>- combination with sofosbuvir (IFN-intolerant + urgent treatment indication)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir (AbbVIE-450)</td>
<td>Genotypes 1 &amp; 4</td>
<td>1 x 150 mg</td>
</tr>
<tr>
<td>Asunaprevir</td>
<td>Genotypes 1 &amp; 4</td>
<td>2 x 200 mg</td>
</tr>
<tr>
<td>Grazoprevir (MK-5172)</td>
<td>Genotypes 1,2,4-6</td>
<td>1 x 100 mg</td>
</tr>
<tr>
<td><strong>HCV-NSSA Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclatasvir (Daklinza™)</td>
<td>Genotypes 1-6</td>
<td>1x 60 mg</td>
</tr>
<tr>
<td>Ledipasvir (part of Harvoni™)</td>
<td>Genotypes 1 (+3 &amp; 4)</td>
<td>1 x 90 mg</td>
</tr>
<tr>
<td>Ombitasvi (part of Viekirax™)</td>
<td>Genotypes 1&amp;4</td>
<td>1 x 25 mg</td>
</tr>
<tr>
<td>Elbasvir (MK-8742)</td>
<td>Genotypes 1-6</td>
<td>1 x 50 mg</td>
</tr>
<tr>
<td>GS-5816</td>
<td>Genotypes 1-6</td>
<td>1 x 100 mg</td>
</tr>
<tr>
<td>Dasabuvir (“Exviera™”)</td>
<td>Genotype 1</td>
<td>2x 250 mg</td>
</tr>
<tr>
<td>Beclabuvir (BMS-791325)</td>
<td>Genotype 1</td>
<td>2x 75 mg</td>
</tr>
<tr>
<td><strong>Nucleos(t)ide polymerase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir (Gonalst)</td>
<td>Genotypes 1-6</td>
<td>1x 400 mg</td>
</tr>
<tr>
<td>- combination with ribavirin for G2 (12 weeks) and G3 (24 weeks) - combination with other DAAs possible: Simeprevir (G1+4), Dasabuvir (G1-6) - combination with ledipasvir (“single-tablet regimen”) (G 1, 3, 4) - combination with GS5861 in Phase 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
als by BMS. The “Trio” combination of asunaprevir, daclatasvir and beclabuvir revealed high SVR rates of >90% in both non-cirrhotic and cirrhotic patients (8). 12 weeks of therapy were studied with or without ribavirin. Similar to the 3D combination of paritaprevir, ombitasvir and dasabuvir, ribavirin seems to be necessary to prevent relapses in particular in HCV genotype 1a patients while the “Trio-combination” without ribavirin could be sufficient in HCV genotype 1b. Daclatasvir in combination with sofosbuvir is currently the preferred treatment option for many HCV genotype 3 infected patients. However, the optimal treatment duration and the requirement of additional ribavirin administration have not been defined yet. The EMA label recommends 24 weeks of combination therapy but 12 weeks would certainly be much more cost-effective. The ALLY-3 study investigated 12 weeks of daclatasvir + sofosbuvir in HCV-genotype 3-infected patients with and without cirrhosis (9). While 93% of non-cirrhotic patients achieved a SVR-12, only 21/30 patients (70%) with liver cirrhosis according to fibro-test score cured their HCV infection. Unfortunately, the study did not include a combination therapy arm with ribavirin. If one would extrapolate experiences from genotype 1 infection with different treatment regimens, one could anticipate that 12 weeks triple therapy with DAC/SOF/RBV would have reached higher response rates in patients with cirrhosis making this regimen the most reasonable treatment option for HCV genotype 3 infection. However, more data are needed to define therapy of HCV genotype 3.

**AASLD 2014: What is the minimal treatment duration required to cure chronic HCV infection?**

A few years ago no expert in the field would have expected that chronic HCV infection could be cured with an IFN-free combination treatment within less than 12 weeks of therapy. Treatment as short as 8 weeks is now already part of an approved label. The NIAID SYNERGY trial showed already that even 6 weeks might be possible for some patients if a triple combination of sofosbuvir with a NS5A inhibitor and a protease inhibitor is used. At AASLD 2014 a trial (“C-SWIFT”) was presented exploring an even shorter therapy with 4 weeks only (sofosbuvir + grazoprevir + elbasvir). Relapse rates were high in this pilot study but still 12/31 patients achieved a sustained virological response (10). To me, this is still a very remarkable finding even though it is unlikely that we will ever have an approved 4-weeks treatment regimen based on this study.

**Concluding remarks**

From 2015 on, IFN-free treatment options are available for all groups of patients with HCV infection. This is absolutely remarkable and was not necessarily expected just 2-3 years ago. The specific labels for Harvoni and Viekirax/Exviera will be discussed in detail in the next issue of the Magazine. We now must ensure that the exciting new treatment options will become available to all patients who need these drugs and that payers in all countries acknowledge the unique opportunities to reduce and prevent HCV-related morbidity and mortality.

**References**

2. Jensen et al., AASLD 2014; abstract #45 (oral) & Sulkowski et al., Poster #955.
3. Brown et al., AASLD 2014; abstract #LB-4
4. Dieterich et al., AASLD 2014; abstract #46 (oral)
5. Sulkowski et al., AASLD 2014; abstract #1144.
6. Boulware et al., AASLD 2014; abstracts #82 & #LB-6
7. Flamm et al., AASLD 2014; abstract #239
10. Lawitz et al., AASLD 2014; abstract #LB-33.
Tenofovir versus tenofovir/emtricitabine for PrEP

More than 4 000 discordant couples were enrolled in a study of PrEP. Participants were randomized to placebo, tenofovir or tenofovir/emtricitabine. The study was double blind. After an interim review showed that the HIV incidence in the placebo arm was 2 per one hundred person years of follow up versus 0.71 and 0.48 in the two arms receiving active drugs the placebo arm was discontinued and participants from the placebo arm were once again randomized to tenofovir or tenofovir/emtricitabine. Median follow up for those receiving active drugs were 35.9 months and total person years of follow up was 8791 years. During the study 32 and 31 % of the HIV positive partners in the tenofovir and tenofovir/emtricitabine groups started ART. 64 HIV conversions occurred in the 2 active arms, 39 in the tenofovir only arm and 25 in the combined arm. 52 seroconversions remained in the final analysis as it turned out that 12 had been infected already at randomization with positive HIV-RNA in archived plasma. In the final analysis 31 in the tenofovir only arm seroconverted versus 21 in the combination arm. The difference did not reach statistical significance. Having detectable tenofovir was not surprisingly associated with a significant risk reduction compared to not having a detectable drug level. No serious side effects were recorded during the study.


Comment: There was no statistically significant difference between tenofovir only and the combination of tenofovir and emtricitabine as PrEP though both arms were significantly better than placebo. However, the idea of giving ART to the non-infected partner in a discordant couple instead of treating the infected partner is at best a questionable approach both ethically and from a cost effect point of view.

Is SVR 12 good enough?

Sustained viral response after 24 weeks (SVR24) has been the standard primary efficacy end point in clinical trials for hepatitis C treatment. Recently sustained viral response after 12 weeks (SVR12) has been used as a primary efficacy endpoint in clinical trials. To evaluate whether SVR12 is as reliable as SVR 24 five trials of sofosbuvir enrolling a total of 863 patients with different genotypes were retrospectively analyzed. Of the 779 patients with SVR12 777 also achieved SVR24 (99.7 %). Also SVR 4 correlated strongly with SVR12 and SVR24. The positive predictive value of SVR4 for SVR12 was 98 % with 98 % of SVR 4 achieving SVR. Of patients who relapsed post therapy 77.6 % did so within 4 weeks of completing therapy. The authors conclude that SVR12 can be used both in clinical trials and in every day clinical practice.

Yoshida, EM et al.Hepatology 2014; Oct 14 Electronic Publication

Comment: SVR 12 seems to be good enough. It shortens the evaluation of clinical trials and the patients do not have to wait as long to know their treatment results.

Antiviral therapy during third trimester to prevent mother to child transmission of hepatitis B

In a Chinese study 700 pregnant women with e-antigen positive hepatitis B with HBV-DNA levels above 6 log10 and ALT below the upper normal limit were included. Patients were offered antiviral therapy after gestational week 28 with either Lamivudine or Telbivudine but could also choose not to take any antiviral therapy. Standard prophylaxis with hepatitis B immunoglobulin and vaccination was given to all newborns. Antiviral therapy continued until 4 weeks postpartum. 44 subjects were lost to follow up, 374 choose not to have any therapy while 263 were given Telbivudine and 55 Lamivudine. There were 686 infants born to 673 mothers and 661 infants completed 52 weeks of follow up. HBV transmission was significantly reduced in those receiving antiviral therapy. On treatment analysis showed a transmission rate of 0 % in the treatment group compared to 2.84 % in the control group. Non serious flares with ALT elevations were observed both during and after treatment. Grade 1 and 2 adverse side effects were reported but no grade 3-4. Five viral breakthroughs were associated with noncompliance. Genotypic resistance did not show any resistance development.


Comment: Standard prophylaxis with immunoglobulin and vaccination may not be enough to prevent mother to child transmission from mothers with high viral loads. Most guidelines recommend antiviral therapy during the third trimester. It is however still unclear what the optimal viral load cut off level is or which drugs should be used. In this study the cut off level was 6 log10 which may be a reasonable level.

Increased risk of cirrhosis in hepatitis C and new onset diabetes

In the Taiwanese National Health Insurance Research Database the risk of cirrhosis and decompensation in patients with hepatitis C and new onset diabetes were compared to hepatitis C patients without new onset of diabetes. The patients in the study were randomly included from a cohort of 1 million patients. Patients with preexisting cirrhosis or esophageal varices were excluded which was also the case for those with alcohol liver disease or hepatitis B coinfection. In total 424 patients with new onset diabetes and 1708 patients without diabetes were included. It was found that patients with new onset diabetes had a higher incidence of cirrhosis (10.8 vs. 7.1) Also for decompensated cirrhosis there was a difference in the cumulative total incidence (3.3 vs. 1.6 %). The difference remained after controlling for different risk factors like sex, age, obesity etc.

Yi-Wen, H et al. Hepatology 2014;60:807-814

Comment: A possible explanation is that diabetes may cause fatty liver which together with hepatitis can contribute to the development of cirrhosis.
Rapid loss of anti-HBsAg titers after vaccination in HIV infected persons.

A retrospective chart review study for HIV positive individuals who had received three doses of hepatitis B vaccine between 2000 and 2010 was performed in a New York HIV clinic. 309 HIV positive patients who had received 3 doses of vaccine were identified of which 178 had postvaccination hepatitis B surface antigen antibody (HBsAb) tests available. 42 % had HBsAb at the time of testing. CD4 cells less than 350 and AIDS were associated with lack of positive antibody test. The post vaccination testing was performed at variable time points from less than a month to more than a year from last vaccine dose. Likelihood of seroconversion was inversely correlated to time of testing. Testing later than 180 days after the last dose was significantly correlated to less likelihood of positive antibody test. This is interpreted as a rapid loss of anti HBsAb titers after vaccination in primary responders. The authors suggest that titers should be tested 3 months after the last dose instead of 4-6 weeks as is usually recommended and again 6-12 months after last vaccine dose to detect “early secondary vaccine failure”.


Comment: The protective effect of hepatitis B vaccination is usually believed to remain if a titer of ≥10 mIU/mL is achieved even if the titer at a later time is decreasing below that level. Decreasing titers is usually not considered a reason for revaccination. To follow the suggestion of the authors to detect “secondary vaccine failure” would be problematic and may create confusion about optimal management and the long term protective effect of hepatitis B vaccine.

Is diabetes more common in hepatitis C infection?

Many studies have reported an association of hepatitis C with diabetes. The relationship between hepatitis C and diabetes was examined in the U.S. National Health and Nutrition Examination Survey. It is a cross sectional population study representing the U.S. population. Blood samples were analyzed for hepatitis C antibodies. A positive test was confirmed with HCV-RNA. 1.7 % were positive for CHCV antibodies and 1.1 % had detectable HCV-RNA. The comparison group consisted of 14 848 HCV negative individuals. Diabetes status was determined by fasting glucose, HbA1C, insulin levels and evaluation at a mobile examination center. The total sample consisted of more than 15 000 participants with known hepatitis and diabetes status. In summary hepatitis C was not associated with an increased rate of diabetes. However, elevated alanine aminotransferase (ALT) and gamma glutamyltransferases were associated with diabetes. The association between increased rate of diabetes and liver enzyme is explained by the fact that the enzymes are markers of fatty liver which itself is associated with diabetes.

Ruhl, CE et al. Hepatology 2014;60:1139-1149

Comment: In this large well controlled study no association between hepatitis C and diabetes was found which contradicts many earlier reports.

Dolutegravir in cerebrospinal fluid

In a single arm open label multicenter trial treatment with dolutegravir in combination with abacavir/lamivudine was given to naive HIV-infected adults. CSF and plasma levels of dolutegravir were measured week 2 and 16. Thirteen men were included of which 2 withdrew prematurely. One patient withdrew because of pharyngitis and another patient because of insufficient treatment efficacy. At week 2 median dolutegravir CSF concentration was 18 (range 4-23) ng/mL and at week 16 13 (4-18) ng/mL. The in vitro IC50 is 0.2 ng/mL. The CSF/plasma ratio for dolutegravir was 0.52 and 0.41 %. The dolutegravir CSF concentration was similar to the unbound dolutegravir concentration in plasma.


Comment: Dolutegravir based combinations are effective and well tolerated. It is reassuring that sufficient drug levels in CSF are achieved.

Failure of treatment intensification with maraviroc and raltegravir to reduce the viral reservoir

48 HIV positive patients with ongoing first line ART and undetectable viral load were randomized to continue their therapy unchanged or to intensify therapy with the addition of raltegravir and maraviroc. The aim of the study was to explore whether intensification could reduce the viral reservoir. Plasma viremia, cellular proviral DNA (PBMCs), cellular RNA and 2-LTR circles were assayed. In patients who received intensification a gut biopsy was performed at baseline and after 48 weeks in which proviral DNA was measured. All patients had CCR-5 trophic virus. No significant changes in viral reservoirs were achieved. No change in the reservoir size compared to the control group was observed and no change in the gut proviral DNA occurred from baseline to week 48. Plasma RNA levels measured with single copy techniques were unchanged.


Comment: A number of “intensification” trials have been performed. The results have been uniformly negative. This is yet another confirmation that intensification has no effect on low level viremia or viral reservoir. Assuming that low level viremia does not originate from productively infected T cells it is logical to expect that intensification has no effect.

Protective effect of statins against malignancies in patients on ART.

In a retrospective Italian study on the potential protective effect of statin use against the development of AIDS and non-AIDS defining tumors more than 5000 HIV positive patients on ART were included. The total observation time was over 52 000 person years. 14 % of the patients had a history of statin use. The total number of malignancies was 375. The incidence rate was 1.3 /1000 patent years for statin users and 8.4 among non-statin users. The adjusted hazard rate for cancer among ever statin use was 0.45 (0.17-0.71). The most common cancers were Non Hodgkin lymphoma and Hodgkin lymphoma. The use of statins was associated with a 55 % reduction in cancer occurrence in ART treated patients. (2407 – 24/15)
Galli L. et al. AIDS 2014, 28;2407-2415

Comment: The risk of cancer is dramatically reduced with the use of statins in this study of the protective effect of statins against cancer in ART treated individuals. It is hard to exclude confounders but this is not the first study showing a protective effect of statins against tumors and further studies are required to confirm the results.

ALT and development of liver fibrosis

The relationship between ALT values and fibrosis development in hepatitis C positive patients was studied in a cohort of 1200 patients. From the cohort patients who had undergone liver biopsy, had positive HCV-RNA and had available ALT levels at the time of the biopsy and at least one additional ALT value within the following year were included in the study. 243 patients fulfilled the inclusion criteria. Persistently normal ALT (PNALT) was defined as ALT < 30 U/L on at least two different occasions during 12 months. Of the 243 patients 32 were defined as having PNALT. 24/32 (75 %) were women in the PNALT group in contrast to the group with increased ALT where 40 % were women. When ALT values were compared to liver histology there was a strong correlation between normal ALT and cirrhosis while there was no difference in other parameters including mean fibrosis, piecemeal necrosis and other signs of inflammation. In patients with PNALT platelet counts were lower among those with cirrhosis.


Comment: ALT is not a reliable indicator of cirrhosis. In contrast in this study a correlation between normal ALT and cirrhosis is found. However, the cut off value that is used for normal ALT is rather low and does not differentiate between men and women which at least partly may explain the gender imbalance as upper normal ALT values usually are lower for women.
Topical Conferences

**January 22-27**
Host Response in Tuberculosis  
Santa Fe, New Mexico, USA  
[www.keystonesymposia.org/meetings](http://www.keystonesymposia.org/meetings)

**February 21-22**
XXIV International HIV Drug Resistance Workshop  
Seattle, Washington USA  

**February 21-22**
5th International Workshop on HIV & Women, from Adolescence through Menopause  
Seattle, USA  
[www.virology-education.com](http://www.virology-education.com)

**February 23-26**
22nd Conference on Retroviruses and Opportunistic Infections (CROI 2015)  
Seattle, USA  
[www.croi2014.org](http://www.croi2014.org)

**March 22-27**
HIV Vaccines (X5) joint with the meeting on  
The Golden Anniversary of B Cell Discovery (X6)  
Scientific Organizers: Giuseppe Pantaleo, Rafick P. Sekaly and Leonidas Stamatatos  
Fairmont Banff Springs, Banff, Alberta, Canada  
[www.keystonesymposia.org/15X5](http://www.keystonesymposia.org/15X5)

**April 22-26**
EASL 2015. 50th Annual Congress of The European Association for the Study of the Liver - “The International Liver Congress”  
Vienna, Austria  
[www.easl.eu](http://www.easl.eu)

**April 25-28**
ECCMID  
Copenhagen, Denmark  
[www.eccmid.org](http://www.eccmid.org)

**April 26-May 1**
Host Response in Tuberculosis  
Boston Park Plaza, Boston, Massachusetts, USA  
[www.keystonesymposia.org](http://www.keystonesymposia.org)

**April 26-May 1**
Mechanisms of HIV Persistence: Implications for a Cure (E1)  
Scientific Organizers: Olivier Lambotte, Steven G. Deeks and Guido Silvestri  
Boston Park Plaza, Boston, Massachusetts, USA  
[www.keystonesymposia.org/15E1](http://www.keystonesymposia.org/15E1)

**June 28**
The Global Viral Hepatitis Summit – 15th International Symposium on Viral Hepatitis and Liver Disease (ISVHLD)  
Berlin, Germany  
[www.isvhld2015.org](http://www.isvhld2015.org)

**August 5**
Hepatitis C Management: State of the Art  
New York, USA  