HEPATITIS TREATMENT AT THE ILC IN LONDON
HHS GUIDELINES UPDATE: WHAT YOU SHOULDN´T MISS
TUBULAR ALARM BELLS
NEWS FROM CROI & EASL ON TREATMENT OF HEPATITIS C IN PATIENTS WITH HIV
EASL 2014: THE “100 %” MELTING!
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INTEGRASE INHIBITORS IN CLINICAL PRACTICE: TODAY AND TOMORROW
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With the European Commission’s approval of sofosbuvir in January 2014, a new era in hepatitis C treatment has begun. Sofosbuvir is a very potent drug and several new, upcoming hepatitis C drugs also look very promising. The possibility of curing hepatitis C in virtually all infected individuals with a short course of oral combination treatment (without interferon) has actually become a reality. This is a tremendous achievement!

On the other hand, the extremely high prices of these new hepatitis C drugs at present dim the hope of making them available universally, restricting treatment for now to those with the greatest need, i.e., patients with advanced fibrosis. However, even such patients run a considerable risk of future complications (such as hepatocellular cancer) also after curing their hepatitis C, making it far more desirable to treat patients earlier, namely, before they develop severe fibrosis. Although this approach would likely be more cost-effective already, there is no realistic possibility of treating a larger number of hepatitis C patients with such extremely high priced drugs at the moment. To achieve the goal of treating all, we will have to wait for drug prices to come down, something that will most probably occur due to competition within a couple of years as new drugs enter the market.

So far price competition has not taken hold in the anti-HIV drug market either. However, the introduction of generics may change this. Generic efavirenz is now available and more will come soon. Efavirenz has its deficiencies but is a very potent drug that is widely used and recommended as a first line option in all treatment guidelines. At my clinic, we have begun changing the regimen of patients on Atripla to generic efavirenz (or the parallel imported Stocrin, depending on whichever is cheapest) plus either Truvada or, if the patient is HLA-B*5701-negative and hepatitis B-negative, Kivexa. Truvada plus the lowest priced efavirenz available is more than 2,000 Euros cheaper than Atripla per patient per year; and by using Kivexa instead of Truvada, another 2,000 Euro can be saved. Considering the large number of patients being treated with Atripla, a great deal of money could be directed to other important medical need, such as the treatment of hepatitis C. Similarly, switching from one pill Atripla to its containing substances (two or three pills) has previously been done in Denmark, to my knowledge without significant problems. Thus far, the vast majority of patients I have informed about this situation have understood and accepted the reason for changing from one to two pills once a day.

The introduction of generic HIV drugs will probably bring about a change in what we prescribe. Unless there is specific reason for doing so, it will become questionable to initiate treatment with a drug combination that is considerably more expensive than a generic combination (for example, efavirenz + abacavir + lamivudine, all soon to be available as generics), even if other combinations may be slightly better in some respects. The effect of all the combinations that we use is highly effective as long as there is no drug resistance and patients take their pills. Differences between the combinations are mainly in their side-effects and convenience (one versus two pills). Adverse events are normally mild and patients who develop side-effects can be changed to another regimen. The argument one often hears that treatment adherence will be jeopardized by taking two instead of one pill is, in my opinion, very seldom valid.

Magnus Gisslén
Editor
Hepatitis treatment at the ILC in London

The International Liver Congress (ILC) had its 49th annual Meeting in early April at the Excel Centre in London. The Congress is arranged by European Association for the study of the Liver (EASL). In 2014, the Congress attracted a record-breaking number of attendees – 10,810 clinicians and scientists came to the British capital. New treatments for hepatitis C (HCV) were one of the core topics on the agenda.

At the Opening of the Congress, Georgina Vergani, who together with Markus Peck-Radosavljevic held the Chair, greeted all delegates welcome to London.

– I think this is going to be the best Liver Meeting ever! It seems we have come to an end of HCV – and therefore this Congress will be remembered, she said.

Ten times higher mortality compared to HIV
Mortality from viral hepatitis is significantly higher than from HIV/AIDS across EU countries, according to results from The Global Burden of Disease Study 2010 (GBD 2010), which were announced for the first time at the Congress.

GBD 2010 is the most recent version of a large epidemiological study, funded by the Bill and Melinda Gates Foundation and coordinated by the Institute of Health Metrics and Evaluation at the University of Washington.

In the EU, HCV and hepatitis B (HBV) are estimated to have caused nearly 90,000 deaths that year. HCV caused nearly 57,000 deaths and HBV nearly 31,000 deaths – while there were just over 8,000 deaths from HIV/AIDS.

It was EASL:s Vice-Secretary Dr Laubrent Castera that presented these thought-provoking figures.

– Although HIV/AIDS undeniably remains a key global health priority, the higher mortality from viral hepatitis in the EU means that hepatitis B and C should clearly now be counted among the top global and local priorities for health, Dr Castera said.

He added that additional resources are needed to prevent, detect and treat HBV and HCV – in order to address these imbalances in major preventable causes of human death.

Globally, mortality is rising
GBD 2010 is the largest ever systematic effort to describe the global distribution and causes of a wide array of major diseases, injuries and health risk factors. GBD 2010 has collected estimates of 291 diseases and injuries and 1,160 sequelae to identify the causes of human death worldwide.

Using country-level and regional causes of death, mortality attributed to HBV, HCV and HIV/AIDS between 1990 and 2010 has been compared across Europe – by region and for specific countries. These findings have then been compared to global trends.

Globally, deaths from both viral hepatitis and HIV increased from 1990 to 2010, with HIV/AIDS ranking 6th with 1.47 million deaths, and HBV and HCV combined ranking 9th with 1.29 million deaths in

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2010. Whereas HIV-related deaths in the EU fell by more than half following the late 1990s, in Eastern Europe HIV mortality has risen sharply.

– This goes some way to explaining why mortality from viral hepatitis does not appear to be higher than that of HIV/AIDS in other areas of Europe outside the EU, Dr Castera concluded.

Very effective regimen in treatment-experienced HCV patients

At the Opening Session, Prof Stefan Zeuzem, Germany, presented data from the SAPHIRE-II trial. It is the first large, phase 3, international, randomised, placebo-controlled trial to examine the safety and efficacy of an interferon-free regimen in treatment-experienced HCV genotype 1 (GT1) infected patients.

– Current interferon (IFN) based therapies for HCV GT1 infection is associated with treatment-limiting toxicity. Many patients are contraindicated for IFN-based therapies due to co-existing medical conditions – and many patients decline IFN-based therapies, Prof Zeuzem initially explained.

Efficacy in retreatment of HCV-infected patients is associated with type of response – relapsers, partial responders and null responders – to prior treatment, he continued.

ABT-450 is a potent NS3/4A protease inhibitor, identified by AbbVie and Enanta. Ombitasvir is a potent NS5A inhibitor, and dasabuvir is a non-nucleoside NS5B polymerase inhibitor. These formed the three direct-acting antivirals (DAAs), plus ribavirin (RBV), used in SAPHIRE-II. The results that Prof Zeuzem reported were remarkable.

– The intention to treat (ITT) sustained virological response rate at 12 weeks (SVR12) for treatment-experienced patients was 96.3 %. The SVR12 rates were high, regardless of HCV subtype: 96.0 % in GT1a and 96.7 % in GT1b. There were also high SVR12 rates across all prior pegIFN/RBV response groups – 95.3 % in prior relapers, 100 % in prior partial responders and 95.2 % in prior null responders.

– The regimen was generally well-tolerated, with a low rate (1 %) of study drug discontinuation due to adverse events, Prof Zeuzem concluded.

Data from SAPHIRE-I were presented later at the Congress.

Adding PEG-INF in treatment of HBV

Three new studies on hepatitis B (HBV) were also presented at the Congress. In one of these – also presented at the Opening Session – Dr Willem Pieter Brouwer, Holland, presented the week 96 results from the ARES study.

The aim of it was to study whether pegylated-interferon (PEG-IFN) add-on treatment increases response to entecavir (ETV) in hepatitis B e antigen (HBeAG)-positive chronic HBV patients.

– Entecavir is a potent nucleoside analogue; however it does not seem to induce off-treatment disease remission. PEG-IFN is an immune modifying agent which results in more decline and clearance of HBeAg and HBsAg (the surface antigen of HBV) compared to ETV, Dr Brouwer stated.

Therefore adding-on PEG-IFN to ETV therapy may increase serological response rates.

– ARES is an investigator initiated trial in 14 countries. A very important finding of the study is that PEG-IFN add-ons results in more sustained off-treatment response, Dr Brouwer continued.

The combination was safe and well tolerated.

– PEG-IFN add-on appeared to prevent relapse and may therefore facilitate the discontinuation of nucleoside analogue therapy, was his conclusion.

Combination therapy for HDV – or not?

Hepatitis Delta, or hepatitis D (HDV), is the most severe form of chronic viral hepatitis. PEG-IFN alpha for 1 - 1.5 years is effective in 25 – 30 % of patients.

Prof Heiner Wedemeyer, Germany, presented the investigator-initiated HIDIT-2 study, in which the two following questions were addressed: Can prolonged treatment improve response rates and prevent post-treatment relapse – and is there a role for combination with tenofovir?

– We found that 96 weeks of PEG-IFNa-2a and tenofovir is possible, but associated with frequent severe adverse events. Liver cirrhosis is associated with higher response rates, Prof Wedemeyer said.

Combination treatment showed numerically higher rates of on-treatment HDV RNA suppression but similar effects on hepatitis B surface antigen (HBsAG) reduction as compared to PEG-IFNa-2a alone. In his summary Prof Wedemeyer also pointed out that hepatitis B surface antigen HBsAG levels are predictive of HDV
RNA response, and that more than one third of patients experience a post-treatment HDV RNA relapse, despite prolonged therapy.

- Patients with HDV and compensated liver cirrhosis should be treated with PEG-IFNa. Combination therapy with tenofovir does not provide obvious benefits in HDV patients with low baseline HBV-DNA levels, he stated.
- HBsAg levels may be used to individualise treatment duration. And alternative treatment options are urgently needed for HDV-infected patients, Prof Wedemeyer concluded his talk.

**Many more people are likely to seek treatment**

Results from three Phase III trials – ION-1, ION-2 and ION-3 – evaluating the investigational once-daily fixed-dose combination of the nucleotide analogue polymerase inhibitor sofosbuvir (SOF) and the NS5A inhibitor ledipasvir (LDV) with and without ribavirin for the treatment HDV-infected patients, Prof Wedemeyer concluded his talk.

**Fewer adverse events**

Of the 1,952 patients randomised in the three ION studies, 1,886 (96,6 %) achieved the primary endpoint of SVR12.

Of the 66 patients (3,4 %) who failed to achieve SVR12, 38 (1,9%) experienced virological failure – 36 due to relapse and two patients due to on-treatment breakthrough (with documented non-compliance). 28 patients (1,4 %) were lost to follow-up.

Fewer adverse events were observed in the RBV-free, fixed-dose combination arms compared to the RBV-containing arms in all the ION studies.

- Adverse events observed in those taking LDV/SOF were generally mild and included fatigue and headache. Anaemia – which is a common side effect associated with RBV – was reported in 0,5 % in the LDV/SOF arm versus 9,2 % of patients in the RBV-containing arms. Less than 1 % of patients in the studies discontinued treatment due to treatment-emergent adverse events, continued Prof Peck-Radošavljević.

GT1 is the most common – but the hardest to treat – strain of the hepatitis C virus. Sofosbuvir belongs to a class of DAA drugs known as nucleotide analogue polymerase inhibitors, which are designed to block an enzyme the virus needs to copy itself.

- Ledipasvir belongs to a promising new class of DAA drugs that work by blocking the NS5A protein, which the virus also needs to replicate, he explained.

**Positive results for genotype 4 for simeprevir**

Prof Peck-Radošavljević also presented results from RESTORE – a Phase III, multicentre, single-arm, open-label study on the efficacy of simeprevir- and sofosbuvir-based regimens in HCV genotype 4-infected patients. Although HCV GT4 is mainly found in the Middle East, Egypt and Central Africa, it has recently spread in several Western countries – particularly in Europe – with rates of 10 % to 24 %.

In his study conducted in France and Belgium, 107 patients with chronic HCV GT4 received simeprevir once daily with PEG-IFN and RBV for 12 weeks.

Simeprevir is an NS3/4A protease inhibitor jointly developed by Janssen R&D Ireland and Medivir AB. Taken as one capsule, once-daily, simeprevir works by blocking the protease enzyme that enables HCV to replicate in host cells.

Overall 65,4 % of patients achieved SVR12 – 82,9 % of treatment-naive, 86,4 % of prior-relapser, 60 % of prior partial-responder and 40 % of prior null responder patients.

- HCV GT4 is a strain of virus which currently only has limited treatment options. We therefore welcome these positive results for the simeprevir-based regimen, Prof Peck-Radošavljević said.

**Positive results for genotype 4 for sofosbuvir**

In a second study, involving patients of Egyptian ancestry – both treatment-naive and treatment-experienced – with chronic HCV GT4 infection, sofosbuvir plus ribavirin was shown to provide a simple,
effective and well-tolerated IFN-free regimen. SVR12 rates were 79% in treatment-naive and 59% in treatment-experienced patients.

- Extending treatment duration to 24 weeks resulted in higher SVR12 rates – 100% in treatment-naive and 87% in treatment-experienced patients, Prof Peck-Radosavljevic continued.

Most adverse events were mild or moderate in severity and consistent with the known side effects of ribavirin.

- What makes the results from this study with sofosbuvir so important is that it included those patients who were interferon-eligible, or intolerant, and failures – where a significant unmet medical need exists, Prof Peck-Radosavljevic summarised.

Chinese herbal medicine has significant potential

SBEL1 is a compound extracted from a herb found in certain regions of Taiwan and Southern China. In Chinese medicine it is used to treat sore throats and inflammation. The function of SBEL1 within the plant is unknown, and its role and origins is currently being investigated.

Data from a late-breaking abstract presented at the Congress showed that SBEL1 has the ability to inhibit HCV activity at several points of the virus’ lifecycle. Scientists pre-treated human liver cells in vitro with SBEL1 prior to HCV infection and found that SBEL1 pre-treated cells contained 23% less HCV protein than the control, suggesting that SBEL1 blocks virus entry. Data also suggests that SBEL1 as well inhibits IRES-mediated translation, a critical process for viral protein production.

In addition, the HCV ribonucleic acid levels were significantly reduced by 78% in HCV infected cells treated with SBEL1, compared to the control group. This demonstrates that SBEL1 may also affect the viral RNA replication process.

- Recent advances mean that we can now virtually cure HCV without unpleasant side effects. However, the different virus genotypes, coupled with the complexity of the disease means there is still a major unmet need to improve options for all populations, said Prof Peck-Radosavljevic.

The fact that SBEL1 has demonstrated significant inhibition of HCV at multiple stages of the virus lifecycle is an exciting discovery, he continued.

- Ultimately this adds to our library of knowledge that may bring us closer to improving future treatment outcomes.

An exciting time for HCV investigators

The impact and importance – and the challenges – of the new therapies for HCV were discussed at several satellite Symposia.

- I do believe we are at the beginning of the end of HCV, said Prof Graham R. Forster, UK, who was the Chair for a Symposium entitled Transforming HCV Management, sponsored by Gilead Sciences.

Prof Patrick Marcellin, France, presented a historical overview and told the audience that the virus first was identified in 1989.

- Liver cancer is now the second most common cause of cancer deaths worldwide, with an estimated 746,000 deaths in 2012, he underlined.

The problem today is that we only treat the top of the iceberg, according to Prof Marcellin.

Prof Ira Jacobson, USA, thought it was an exciting time to be an investigator in HCV trials.

- There’s been a rapid development of new DAAs of different drug classes – with high efficacy and short treatment duration. Sofosbuvir is the first once-daily oral NS5B polymerase inhibitor to be approved in Europe.

- It is a highly effective short-term therapy, in combination with RBV and with, or without, PEG-IFN. And more drug approvals are on the way, Prof Jacobson pointed out.

An option for every patient

Prof Heiner Wedemeyer talked about the importance of understanding the relevance of genotype.

- GT3 is associated with rapid fibrosis progression and poor survival, he said.

Sofosbuvir has activity against all HCV genotypes. Nearly all patients become HCV RNA negative early during therapy, and retain this at end of trial, he continued.

- But relapses may occur after stopping therapy. This differs between therapies!

For patients with GT1, 4, 5 or 6 with chronic hepatitis C SOF + RBV + PEG-IFN with duration for 12 weeks is recommended. For patients ineligible or intolerant to PEG-IFN, a combination of SOF + RBV with duration of 24 weeks is the recommended option.

- Patients with GT2, go for SOF + RBV for 12 weeks.

For patients with GT3, either SOF + RBV + PEG-IFN for 12 weeks, or SOF + RBV for 24 weeks are the options. Patients with chronic HCV awaiting liver transplantation should receive SOF + RBV until transplantation.

- HCV genotype is still relevant. The clear message today is that we have an option for every patient, Prof Wedemeyer stated.

Challenge for tomorrow

Prof Forster underlined that the HCV population is ageing.

- This means that serious liver disease associated with HCV will have a greater healthcare system impact as the infected population ages. The costs are climbing due to patients progressing to more advanced liver disease.

More oral therapies are anticipated in the future. Simpler equals better – because then we can reach the currently unreachable patients.

- The ultimate aim is eradication, Prof Forster said.

So how can we approve access to treatment?

- Now we are treating only a small number of patients. Many – i.e. the rest of the iceberg – have to be diagnosed and treated. This is the challenge for tomorrow, said Prof Marcellin.

Need for a treatment strategy

Another satellite Symposium, supported...
by Janssen Pharmaceutica, aimed to improve the understanding of DAAs as the standard of care by providing practical guidance on treatment initiation and special patient populations based on case discussions.

Dr John Dillon, UK, started by defining the HCV problem.

- Risk factors for HCV infection have changed over time in European countries. What began as a problem for the older patient population, infected with blood products or transfusion, has changed to a younger patient population infected through i.v. drug use, Dr Dillon said.

The new powerful treatments are highly effective and easily tolerated. No one should die from HCV, and no one should develop the complications of cirrhosis.

- If they do – who is accountable? With great power, comes great responsibility.

That is our problem. This demands a strategic response – but how should we drive the provision of one, he continued by asking.

- In your country, region or locality – how many are infected with HCV? How many are you treating – and how many do you need to treat?

The audience was asked to vote electronically to answer the question on “what proportion of HCV patients under your care are you actively treating”. The most common (31 %) answer was “less than 10 %”.

Understanding the epidemiology is vital

Dr Dillon showed data on the estimated uptake of HCV antiviral therapy by country.

- In my home country Scotland, the estimated number of people living with HCV is 38,000. Of those, the annual treatment uptake is 2.8%. The by far best figure comes from France – where the uptake is 6.7 %, he said.

He ended his talk by concluding that hepatitis C is an important global problem.

- Understanding the epidemiology of HCV in your country or locality is vital. Treatment must be delivered as a strategic action in order to maximise benefit – not only in the clinic but in the population.

- And remember that treatment can be used as a prevention strategy, he finished his talk.

Considerations besides clinical need

Prof Michael Manns, who was the Chair of the Symposium, talked about the development of new regimens for treating HCV. There are many factors – genotype, co-infections, fibrosis or cirrhosis stage among many others – that are determining the treatment choice.

- The question that remains is if we will have a use for ribavirin in the future. The good news is that there now is a treatment for GT4, and that we can treat patients that have failed earlier therapy.

However, there are considerations besides clinical need. One of these is the availability of new compounds – there is a delay from approval to availability in many countries.

- Another question is what will happen in cost-sensitive markets.

The new DAAs demonstrate superior efficacy, shortened treatment durations and improved safety profiles in comparison with existing treatment options. They also show promise for the treatment of difficult-to-treat patients with prior null response or failure on PR and PI-containing regimens.

- This is encouraging! There remains however an unmet need for the treatment of other difficult patient populations, including those with decompensated cirrhosis.

After his talk some patient cases were presented and discussed interactively, with the audience participating by voting for different alternatives.

New recommendations available online

EASL’s new recommendations on the management of hepatitis C were presented at the International Liver Congress in London. They reflect the approval of three direct-acting antivirals during 2014 by the European Medicines Agency.

Sofosbuvir was approved in January 2014, simeprevir will be approved in May 2014 and daclatasvir is likely to be approved in August or September 2014.

- Since EASL published the HCV Clinical Practice Guidelines in 2013, the treatment paradigm for HCV has changed with three additional direct-acting antivirals for use in patients infected with HCV GT1, said Prof Jean-Michel Pawlowski, coordinator of the recommendations and Director of the French National Reference Centre for Viral Hepatitis.

The recommendations are available online, and can be found on the EASL website at www.easl.eu.

- These new EASL on-line recommendations on the management of HCV reflect how the treatment landscape has evolved for this disease, and will further help physicians and other healthcare providers optimise management of patients with acute and chronic HCV, said EASL Governing Board member and recommendation panel member Dr Alessio Aghemo, Italy.

Three studies on an investigational regimen

The new interferon-free, all-oral, DAA treatment regimen in development by AbbVie has achieved very high rates of virological response in patients infected with HCV GT1, according to results presented at the Congress by Dr Aghemo.

The DAA regimen consists of HCV NS3/4A protease inhibitor ABT-450 dosed with ritonavir, the NS5A inhibitor ABT-267 and the NSSB RNA polymerase inhibitor ABT-333.

Dr Aghemo presented the study SAPP-HIRE-I, in which treatment-naive patients with chronic HCV GT1 infection and no evidence of liver cirrhosis were given 12 weeks of treatment with the DAA regimen, plus ribavirin.

After 12 weeks the overall intention-to-treat SVR12 rate was 96.2 %. Even in the more difficult-to-treat subtype GT1a – which made up the majority of patients in this study – the SVR12 rate was 95.3 %, compared to 98 % in GT1b patients.

Dr Aghemo also presented the results from TURQUOISE-II, which demonstra-
active IFN-free regimens – protease inhibitors in treatment naive adults with chronic GT1b and no evidence of liver cirrhosis, were randomised to receive the regimen with or without ribavirin. Following 12 weeks of treatment, 99 % of those receiving the regimen without ribavirin, and 99.5 % of those receiving, achieved SVR12.

- This collection of studies show encouraging data and further support our understanding of the efficacy and safety of this DAA regimen in a variant of patient types, Dr Aghemo summarised.

- Such research continues to highlight the advances being made in treating complex diseases of this type!

“Newscast”
All of these reports presented at the Congress were reflected upon in a satellite Symposium funded by Bristol-Myers Squibb.

Probably due to the amount of information the delegates until then had digested in London, it was presented in a slightly different format: News at six - hepatitis C special. Prof Mark Thursz, UK, was the “news anchorman” – i.e. the Chair.

Prof Jean-Michel Pawlotsky began this by summarising as follows:

- There are four classes of HCV DAA s that could be combined to achieve highly active IFN-free regimens – protease inhibitors, nucleoside/nucleotide analogue inhibitors of RNA-dependent RNA polymerase (RdRp), non-nucleoside inhibitors of RdRp and non-structural protein 5A (NS5A) inhibitors.

Three options for combinations are available (or are already available in some cases): Nucleotide-based therapies, nucleotide-free triple combinations and nucleotide-free double combinations.

- Finally, I’d like to remind you that resistance will need to be carefully monitored in those few patients who may fail on these therapies, Prof Pawlotsky said.

For and against IFN- and RBV-free regimens
After this there was a debate: Has the time come for all-oral interferon/ribavirin-free regimens?

Prof Heiner Wedemeyer thought so.

- Interferon and ribavirin are no longer needed to increase cure rates. Interferon may cause irreversible side effects and death. And I’m convinced that we won’t use ribavirin in the future.

On the fact of the costs, he pointed out that there are other costs than just for drugs to consider. These include among others days lost from work, patient’s quality of life, and the costs of intensive monitoring and management of side effects. Prof Wedemeyer underlined that we have to treat more patients in order to avoid big problems with liver diseases – and the cost of those – in the future.

- But in order to do that, we must have treatments without severe side effects, he stated.

Dr Ashley Brown, UK, did not agree.

- I will not throw away interferon – because I want to cure my patients, he said. Dr Brown showed data that demonstrated that if interferon was added to DAA s in hard-to-treat patients, the SVR was better.

- I’m not going to give my patients interferon for two years – but for 12 weeks. And if you give interferon to cirrhotic patients, of course you will get trouble, Dr Brown continued.

Interferon offers a multipronged, pan-genotypic approach and may be particularly useful in resource-constrained settings.

- Addition of interferon and/or ribavirin may maximise the potential of DAA regimens, and will shorten treatment duration in specific patient groups, was Dr Brown’s statement.

Patient and specialist views
The Symposium ended with some experts’ angle on HCV management challenges.

Charles Gore, UK, President of the World Hepatitis Challenge, was the first speaker.

- In Europe we’re treating around 3 % of people with HCV – and this is totally unacceptable. People are going to die! There are several reasons for this: We’ve been poor at diagnosing, and people’s fear of interferon is higher than their actual experience of the drug motivates. And there are prejudices on who we shouldn’t treat – inmates at prison, drug users etc.

He stated that we must enter an era when a person who wants treatment also has access to it.

Dr Alessandra Mangia, Italy, pointed out that current therapies provide low SVR rates in patients with advanced liver disease.

- Pegylated interferon treatments against HCV GT1 do not work in 25 - 33 % of patients in clinical trials, and in 39 - 42 % of patients in a “real world” setting. Current management of those patients that has failed is challenging. But there are promising options for these patient populations, including daclatasvir, sofosbuvir and ledipasvir, she summarised.

Dr Graham R. Foster talked (via video link from his hospital in London) about the problem in patients with GT3 and cirrhosis.

- Many of them are so advanced that they can’t tolerate interferon-based regimens. So, I’m facing a very large number of patients for whom I have very limited treatment options, he said.

Finally, Prof Rafael Esteban, Spain, presented his views.

- Tolerability is also an issue, with high withdrawal rates. Drug-drug interactions with transplant medications are a concern too. But new DAA regimens are effective, well tolerated and lower risk of drug-drug interactions, he said.

PER LUNDBLAD
The guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents developed by the US Health and Human Services are probably the most influential guide for the use of antiretroviral therapy (ART) in the developed world. On May 1st, 2014 HHS guidelines published its last major update [1]. In this commentary I have highlighted what I consider the most important changes.

From “preferred” to “recommended”
As many HIV clinicians, when an update is published I go directly to the table of preferred and alternative regimens looking for the “ups and downs” (Table 1). First surprise in this update: there are no longer “preferred” regimens. Since this update, HHS has opted for the wording “recommended regimens” instead of “preferred regimens”. In the Merriam-Webster dictionary “to prefer” is “to like (someone or something) better than someone or something else”, while “to recommend” is “to say that (someone or something) is good and deserves to be chosen”. Therefore –if I got it right. I’m not a native English speaker- the panel no longer states that a particular regimen is better than the other, it just say that a particular regimen is good and deserves to be chosen.

The rational behind this change is that currently there are numerous regimens for treatment naïve individuals and options for therapy have expanded.

## Two different scenarios in naïve: high and low viral loads
The other big news in the table of recommended regimens is the separation between regimens that are recommended regardless of viral load and regimens that are recommended only if patients are below 200 cells/mm³. Fosamprenavir with TDF/FTC or ABC/3TC no longer appears in this table. Finally, the other change is that there is no longer a table with “other” ART regimens that previously included drugs such as Maraviroc or Nevirapine.

### Goodbye to CD4 monitoring when above 500 cells/mm³?
During the past year several studies have highlighted that if an HIV infected patient has experienced good immune reconstitution after starting ART, repeated measurements of CD4 cell count has very little implication in the management of those patients [4-6]. Only if patients are below 200 cells/mm³, CD4 monitoring is important to guide the need for opportunistic infection prophylaxis. The guidelines emphasize the importance of continuous monitoring of vi-
the big debates in HIV therapeutics in the incoming year.

**Simplification is just one of the reasons to switch ART**

The section previously entitled “Regimen Simplification” now is called “Regimen Switching in the Setting of Viral Suppression”. Apart for this change in terminolo-


<table>
<thead>
<tr>
<th>Table 2 Alternative initial ART regimen options</th>
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<tbody>
<tr>
<td><strong>For all patients, regardless of pre-ART viral load or CD4 cell count</strong></td>
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<tr>
<td><strong>Pi-Based Regimen</strong></td>
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<tr>
<td>• DRV/r plus ABC/3TC (BII) – only for patients who are HLA-B5701 negative</td>
</tr>
<tr>
<td>• LPV/r (once or twice daily) plus ABC/3TC (BI) – only for patients who are HLA-B5701 negative</td>
</tr>
<tr>
<td>• LPV/r (once or twice daily) plus TDF/FTC (BI)</td>
</tr>
<tr>
<td><strong>INSTI-Based Regimen</strong></td>
</tr>
<tr>
<td>• RAL plus ABC/3TC (BII) – only for patients who are HLA-B5701 negative</td>
</tr>
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</table>

Several highlights of this new table:

- **Switch from TDF to ABC in patients with “bone density effects”. Guidelines recognize that the clinical significance of this change is uncertain.**
- **Switch away from EFV in patients with CNS/Neuropsychiatric Side Effects. Multiple options: RPV, Etravirine, Nevirapine, Protease inhibitor or Integrase Inhibitors**
- **Dyslipidemia in patients receiving Ritonavir, Cobicistat or EFV. Multiple options:Raltegravir, Dolutegravir (interesting, because there are no trials exploring Dolutegravir in this setting), RPV, Nevirapine or unboostered ATV**
- **Gastrointestinal effects (nausea, diarrhea) of LPV/r. Multiple options: ATV/r, DRV/r, RAL, DTG, EVG/cobi/TDF/FTC**
- **Renal Effects including proximal renal tubulopathy and elevated creatinine in patients receiving TDF: switch to ABC.**
- **The panel righteously emphasize that in patients switching treatments, the key principle is to maintain viral suppression without compromising future options. This is particularly important when switching from a high genetic barrier regimen including a boosted protease inhibitor to a regimen including non-nucleoside reverse transcriptase inhibitors, RAL, EVG/cobi/TDF/FTC or unboosted ATV.**

**Rescue therapy. New data informing guidelines**

The HHS guidelines discussed recent evidence of how to manage patients failing 2 NRTI + 1 NNRTI regimen. Two important trials (see HIV news 3) SECOND-LINE [9] and EARNEST [10] have demonstrated that in this setting there are two good strategies: a fully active protease inhibitor plus either “recycled” N(t)RTIs or an integrase inhibitor. In patients needing deep salvage the guidelines stress the importance of the number of active agents and not necessarily the drug class included. In this setting the OPTIONS trial [11] demonstrated that virologic outcomes were equal, whether or not the regimen was supplemented with NRTIs provided that patients took at least 2 fully active drugs. Unsolved issues: there are two relatively common problems in HIV therapeutics for which we are still far from optimal guidance

**What to do with treated patients who have low-level viral loads?**

Little advance in this scenario. The panel still sticks with the 200 HIV-RNA copies/mL to define virologic failure. What to do with patients who have viral rebound below 200 copies/mL? Guidelines recognized that the published literature is conflicting with studies showing an increased risk of subsequent failure [12] not confirmed by other studies [13]

**Suboptimal immunological response**

Although we lack a clear definition, we all have patients who despite prolonged suppression have not achieved a substantial immunological response. There are no data to support a change of ART regimen in this situation. A recent study [14] has shown that virally suppressed HIV-positive individuals on cART who do not achieve a CD4 count >200 cells/mm³ have substantially increased long-term mortality. It is clear that more research is needed in this situation.
In summary, the 2014 update of the HHS guidelines provides interesting changes in the way regimens are recommended and put in the forefront the importance of cost-effectiveness of ART in the near future.

References

11. Tashima K, Smeaton L, Andrade A. Omitting NRTI from ARV regimens is not inferior to adding NRTI in treatmentexperienced HIV+ subjects failing a protease inhibitor regimen: The ACTG OPTIONS Study. Abstract 153LB. 20th Conference on Retroviruses and Opportunistic Infections; 2013; Atlanta GA.
Tubular alarm bells

Abnormal kidney function is common in the general population and, therefore, is unsurprisingly routinely seen in persons with HIV infection. Aside from HIV-associated nephropathy, which is largely seen in late presenters of African origin, much of the renal disease seen in persons with HIV is similar to that seen in the general population.

Nephrologists generally focus on glomerular diseases, either the glomerular nephritides or glomerular disease secondary to hypertension, diabetes mellitus and that which accompanies aging. Declines in glomerular filtration rate (GFR) with aging are well documented (typically 1-2 units in estimated glomerular filtration rate (GFR) with aging are well documented (typically 1-2 units in estimated GFR per annum) and may be accelerated by a range of risk factors including female sex, black race, smoking, dyslipidemia, obesity, significant family history and Hepatitis C infection. Of note many risk factors for declining eGFR, especially modifiable ones, are similar those for cardiovascular disease. Thus, declining eGFR is a signal to actively manage CV risk. Most people with kidney disease die of cardiovascular events or congestive cardiac failure, not end stage renal disease. People with HIV often carry a higher burden of these risk factors hence are perceived to be at higher risk of renal disease. Of note, diabetes mellitus is 3 times more common in persons with HIV than in matched controls, and smoking is generally considerably more prevalent in HIV cohorts. It is less clear if hypertension is more common with HIV.

The true glomerular filtration rate (GFR) can be determined from the renal clearance of a marker that achieves stable plasma concentration, is inert, and is freely filtered by the glomeruli but not reabsorbed, secreted, or metabolized. Agents typically used for this are administered inulin and iothalamate. Unfortunately, an ideal endogenous marker does not exist. Thus, use of serum creatinine has long been used by clinicians as a marker of convenience of renal function. About 15% of creatinine is actively secreted in the renal tubules. Estimates of creatinine clearance by the Cockcroft-Gault equation is weight plus creatinine based and was originally validated in healthy individuals. The Modified Diet in Renal Disease (MDRD) and CK-Epi equations were established in the setting of renal disease and do not require weight assessments and produce an estimated glomerular filtration rate (eGFR). Changes in body mass (with wasting, body building, amputation), faddish diets (vegetarian, high meat intake) and supplements (notably creatine, a ‘training’ supplement often used by body builders) may impact these equations by raising or lowering plasma creatinine or influencing creatinine loss from muscles. Drugs, including some over the counter products (such as ascorbic acid) are a key factor in altering GFR estimates, sometimes due to renal effects, sometimes due to affecting the interactions with laboratory reagents used in the Jaffe reaction to quantitate creatinine. A list of drugs that effect calculated GFR are listed below. (Table 1)

It is important to emphasize that often the isolated use of serum creatinine concentration may not reflect the actual degree of kidney dysfunction of a particular subject and rises in serum creatinine may be a late marker of declines in true glomerular function. This underlines that declines in eGFR are worth acting on clinically. The categories of renal disease (when considered in conjunction with abnormal kidney function for >3 months and evidence of abnormal renal pathology or a surrogate marker (albuminuria, proteinuria, abnormal urinalysis or abnormal renal sonogram) are tabulated below. (Table 2)

As noted above, some widely used drugs, including trimethoprim and potassium sparing diuretics, may reduce transport of creatinine, leading to an apparent decline in eGFR after these drugs are initiated. Glomerular disease is also characterised by leakage of large proteins, the dominant one of which is albumin. Diabetics and hypertensive patients are routinely followed with measurements of albumin/creatinine ratios (ACR). As low molecular weight tubular proteins are also of interest to HIV physicians a protein/creatinine ratio (PCR) has become widely recommended for monitoring within guidelines. This, however, at best remains a blunt tool for identifying tubular problems as the dominant protein in the urine continues to be albumin.

Impact of antiretrovirals

Antiretroviral drugs may impact eGFR calculations in a range of ways and several drugs may impact kidney function causing renal injury. This article will address these issues.

Of note, Atazanavir and indinavir both cause rises in unconjugated bilirubin. Most laboratories use a modified version of the Jaffe reaction, which uses alkaline picrate and leads to a colour reaction, as the cornerstone of routine methods of creatinine measurement. While adjustments and modifications exist, underestimation of creatinine occurs with hyperbilirubinemia in a way that is dependent not only on the bilirubin concentration, but also on the creatinine concentration itself. The greatest impact seems to be with high or very high bilirubin concentrations (>100mmol/l) more typically as-

<table>
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<th>Table 1</th>
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<tr>
<td>Cimetidine, trimethoprim, probenecid, potassium-sparing diuretics</td>
</tr>
<tr>
<td>Ketoacids, ascorbic acid, glucose, some cephalosporins</td>
</tr>
<tr>
<td>Bilirubin, haemoglobin</td>
</tr>
<tr>
<td>Fluocytosine, haemoglobin</td>
</tr>
<tr>
<td>Metamizole, methylpred, ethamsylate</td>
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Firstly, the impact of tenofovir DF (TDF) on the renal tubule and secondly the importance of isolated markers of tubular dysfunction, which potentially interplay. More recently, interest in has been in two subclinical markers of tubular dysfunction, measurement and clinical significance of exposure longer. However, the practical subject choice may be less selective, and in cohort studies where PRTD appears uncommon, typically <1%.

More recently, interest has been in two renal issues, which potentially interplay. Firstly, the impact of tenofovir DF (TDF) on the renal tubule and secondly the impact of new antiretrovirals on the active tubular transport of creatinine, specifically by the OCT2 and MATE1 transporters, located on the apical (plasma) and basolateral (urine) membranes of the renal tubule, respectively.

With long-term use of TDF-based antiretroviral therapy several degrees of proximal tubular toxicity, from chronic subclinical renal tubular dysfunction to proximal renal tubular dysfunction (PRTD) or Fanconi (-like) syndrome, have been observed in HIV-infected patients. PRTD appears uncommon, typically <1% of subjects in clinical trials albeit perhaps a little higher in cohort studies where subject choice may be less selective, and exposure longer. However, the practical measurement and clinical significance of isolated markers of tubular dysfunction, in the short and long term, remains unclear. In addition, proximal tubular abnormalities, even severe, may be missed until they affect the measurements of glomerular function. Therefore, there is a need for new biomarkers, not only based on serum creatinine and estimated glomerular filtration rates, that might help to identify tubular cell toxicity and predict the clinical outcome in HIV-infected patients.

In the recently published ASSERT study, over 96 weeks of ABC/3TC vs TDF/FTC each with efavirenz, no significant differences in eGFR were observed. However, increased loss of tubular proteins beta-2-microglobulin and retinol-binding protein were significantly more common in TDF/FTC recipients [2]. Thus, no established clinical surrogate correlated with the evidence of tubular injury observed. It remains unclear how TDF causes eGFR declines as it is not a demonstrable glomerular toxin in animal models. It is possible that induction of tubular injury leads to declines in the active efflux of creatinine in the tubule leading to a creatinine rise. Thus, substances that mask changes in active creatinine secretion may potentially mask the extent of tubular distress secondary to TDF increasing the risk of delayed diagnosis and a more severe abnormality at diagnosis.

Tenofovir is an adenosine based nucleotide that is eliminated unchanged in the urine by both passive filtration and about 30% actively transported by proximal renal tubule secretion. The main basolateral transporter is Organic Anion Transporter (OAT) 1 and apical transporters involved include MRP-2 and -4. The mechanism of tubular toxicity is thought to be mitochondrial injury [3] due to excessive Tenofovir diphosphate accumulating in the tubular lumen (i.e. it does not simply passively diffuse back into the plasma).

In animals the effect has been shown to be exposure dependent. The long term consequences of chronic subclinical tubular dysfunction remain unclear but the manifestations of PRTD are well established as this was commonly seen with the related nucleotides cidofovir and adefovir during their development and clinical use. The typical manifestations of PRTD include fractional phosphate loss with hypophosphatemia, and normocytic normochromic anaemia. Loss of phosphate leads to dysregulation of calcium and phosphate and osteomalacia, the loss of bony architecture. Reduced bone mineral density on a DXA scan may represent a late manifestation of osteomalacia as trabecular strength may decline without substantial loss of cortical mass. Subclinical tubular dysfunction is likely to be also associated with a more gradual phosphate loss. Unfortunately, with high rates of diabetes in HIV infected subjects monitoring of glycosuria is not always feasible. Similarly, reliable plasma phosphate levels require prolonged fasting as they are subject to considerable variation due to dietary intake, most notably through cola drinks. Thus, PRTD may be underdiagnosed or experience delays in its diagnosis in the clinic.

Several antiretrovirals inhibit the active transport of creatinine in the kidney. Rilpivirine and to a greater extent dolutegravir inhibit the basolateral OCT2 whereas ritonavir and to a greater degree cobicistat inhibit the apical MATE1 transporters. The greater concern exists with apical transporters as these may lead to accumulation of substances within the tubular cytoplasm. MATE1 is also blocked by trimethoprim and cimetidine. Doses of the abovementioned antiretrovirals used in practice do not seem to result in exposure dependent changes in creatinine, the effect seems similar in all subjects (a 12-15 mmol/l rise with dolutegravir and cobicistat, a 7-8 mmol/l rise with ritonavir, a 3-5mmol/l rise with rilpivirine) regardless of exposure at approved doses.

Regimens that contain ritonavir (lopinavir/r, atazanavir/r) have been associated with greater risk of eGFR decline in large cohorts [4] and this observation associates with tenofovir DF use. A suggested mechanism is that ritonavir increases TDF and tenofovir exposure via a range of mechanisms (increased gut absorption, decreased renal clearance possible through MRP-2 inhibition) leading to increased risk of tenofovir toxicity relative to NNRTI based regimens. While PRTD was not reported in clinical trials of TDF with efavirenz and FTC or 3TC, some cat-

<table>
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<th>Table 2</th>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73m²)</th>
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<tbody>
<tr>
<td>I</td>
<td>I</td>
<td>Kidney damage with normal or increased GFR</td>
<td>&gt; 90</td>
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<tr>
<td>II</td>
<td>II</td>
<td>Kidney damage with mildly decreased GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>III</td>
<td>III</td>
<td>Moderately decreased GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>IV</td>
<td>IV</td>
<td>Severely decreased GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>V</td>
<td>V</td>
<td>Kidney failure</td>
<td>&lt; 15 (or dialysis)</td>
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The current approaches to renal monitoring in HIV infected subjects are not appropriately targeted to the main renal toxicities of antiretroviral drugs. This is likely to lead to delayed diagnosis and missed diagnosis of potentially important toxicities. The introduction of new agents, and the recognition of effects with some older antiretrovirals, of important effects on renal transporters leading to alterations in creatinine and eGFR have added urgency to the need to find more targeted and sensitive tools to recognise renal tubular disease in long term ART recipients.

References
1. Reyataz US label

Tubular Bells
As tenofovir is not a glomerular toxin, monitoring its safety with a glomerular test seems pointless. Clinicians are now seeking better makers of tubular dysfunction to look for distress before more serious or severe events arise, essentially to search below the iceberg tip representing bone mineral density may improve [7]. Phosphate loss also reverses [6] and bone mineral density may improve [7].

As tenofovir is not a glomerular toxin, monitoring its safety with a glomerular test seems pointless. Clinicians are now seeking better makers of tubular dysfunction to look for distress before more serious or severe events arise, essentially to search below the iceberg tip representing bone mineral density may improve [7]. Phosphate loss also reverses [6] and bone mineral density may improve [7].

The main tubular makers are low molecular weight proteins that are filtered by the glomerulus but then efficiently resorbed in the proximal tubule leaving minimal amounts in normal urine. As reabsorption is dependent on ATP-dependent transporters resorption is effected by mitochondrial dysfunction. As some drugs have been noted to inhibit renal transporters (although as yet resorption transporters of low molecular weight proteins) results need to be considered in the light of what is known about co-therapies. Finally, some potentially useful proteins are effected by inflammatory and other clinical events so require cautious interpretation of a single sample.

Trends over time are likely to be more important and in a similar way with watching ‘creatinine creep’ is used in current renal monitoring approaches. Increased loss of beta-2-microglobulin and retinol-binding protein (RBP) in the urine, observed in a substantial proportion of recipients, have been associated to TDF administration but appears markedly less common in untreated individuals or those receiving TDF-sparing regimens. The effect appears evident within the first year of administration [2]. Beta-2-microglobulin (and cystatin-C) is acutely affected by HIV and so declines with treatment reduce its suitability as a marker in the first year(s) of treatment.

Together with other tubular parameters or in isolation, both biomarkers could be useful for earlier diagnosis of proximal tubular toxicity or identifying individuals most at risk. Other molecules, such as alpha-1-microglobulin, urinary kidney injury molecule-1, neutrophil gelatinase associated lipocalin, or N-acetyl-b-D-glucosaminidase, are also tubular resorbed proteins that could be used to investigate tubular cell damage and dysfunction.

All of these potential markers lack well established normal laboratory ranges or toxicity grades and will require large scale monitoring studies to find potential cutoffs that associate with or are surrogates for relevant clinical events. While it is clear that RBP is mal-absorbed to a greater extent in subjects receiving TDF relative to abacavir [1] no PRTD events or differences in eGFR were seen in the largest randomised study that has investigated this issue.

A weak association between RBP and fractional phosphate loss and low bone mineral density has been observed in one cross sectional study. It is unclear if fractional phosphate loss can be viewed as a sufficient endpoint, it is more seeking a surrogate of a surrogate. Ideally, both high sensitivity and specificity need to be established to make these potential markers worthy of clinical monitoring.

Data with other markers is a best small scale at present.
News from CROI & EASL on Treatment of Hepatitis C in patients with HIV

Both at CROI in Boston (03/2014) as well as at EASL in London (04/2014) exciting new treatment results of trials in HIV/HCV coinfection were presented which have reported dramatically improved HCV cure rates in this previously perceived difficult to treat patient population and already found their way into the most recent coinfection treatment guidelines. This review aims at summarizing the main findings from these new HCV treatment trials in HIV coinfection as well as to reflect on what practical implications these findings will have on current and future management of HCV in HIV.

Although telaprevir and boceprevir substantially increased sustained virological response rates (SVR) in treatment-naive and experienced genotype 1 patients their use is no longer recommended by recent guidelines in light of the newly registered DAAs which have already come or are about to enter the market and promise much easier administration, less toxicity and at best even enhanced cure rates. Final results of the telaprevir + pegylated interferon + ribavirin ANRS HC26 study in HIV/HCV treatment experienced patients (with 18% patients having F3 fibrosis and 23% F4 fibrosis) showed very high SVR12 and 24 week rates of 80% respectively (1). Most interestingly, efficacy remained high throughout all sub analyses including baseline fibrosis stage, IL28 genotype, background ART and previous HCV treatment response (please note however, that previous null-responders with cirrhosis were excluded from this study).

Clearly, this implies that in countries were because of cost issues new DAAs in particular sofosbuvir are not yet available and probably will not become available for the next years but access to telaprevir and boceprevir exists for patients with more advanced fibrosis, these treatment options still need to be discussed. In the setting of HIV/HCV coinfection both faldaprevir as well as simeprevir, both once daily second wave HCV protease inhibitors, have been studied in combination with pegylated interferon (PEG-IFN) and weight based ribavirin (RBV) in larger trials (faldaprevir trial n=304, simeprevir trial n=106) evaluating tolerability and efficacy of these regimens (2,3). Noteworthy, both trials also addressed the feasibility of rapid virological response (RVR) guided therapy to shorten treatment duration to 24 weeks. Overall HCV cure rate in the faldaprevir trial was 72% (2). SVR rates were higher in relapers (83%) than in treatment naïve (69%), higher in IL28B CC genotype (88%) versus non-CC genotypes (64%) but similar in cirrhotic versus non-cirrhotics, respectively (73 vs 72%). Early treatment success potentially allowing shortened treatment duration was achieved in 80% of patients. Simeprevir 150 mg QD + pegIFN/RBV also led to high virologic response rates in co-infected patients, regardless of prior HCV treatment response (SVR12 77% in treatment-naïve and prior relapers) (3). Relapse occurred only in patients infected with HCV genotype-1a: 5/31 overall population; 3/22 treatment-naïve; 2/9 prior or relapers. 64% of all prior null responders had not experienced failure at the time of the interim analysis. Of 88% of patients who met RVR 75% achieved SVR 12. So in summary both trials show good efficacy rates in HIV/HCV coinfection which are very close to the cure rates obtained in monoinfected subjects.

As treatment duration for the majority of patients is 24 weeks and thereby twice as long as sofosbuvir +IFN + RBV therapy it is unlikely that these treatment regimens will be used much unless sofosbuvir is not licensed or available. It is important to highlight that significant drug interactions exist so that simeprevir cannot be coadministered with a HIV PI. Faldaprevir can be co-administered with boosted darunavir or atazanavir at the dose of 120mg qd. Overall safety of the two new compounds was good and comparable to monoinfection studies. In the faldaprevir trial adverse events leading to treatment discontinuation occurred in 7% of patients, discontinuation because of faldaprevir associated adverse events only in 1% of patients. In the simeprevir trial overall only 4 patients discontinued simeprevir due to adverse events.

**IFN-free HCV therapies**

Most excitingly, at CROI final results from the first IFN-free trial in HIV/HCV coinfection the PHOTON trial were reported (4). The PHOTON 1 study evaluated the safety and efficacy of the oral HCV NS5B inhibitor sofosbuvir (SOF) with ribavirin (RBV) in HIV-seropositive patients coinfected with HCV genotypes 1, 2 or 3 (4). Patients included into the study received SOF 400 mg QD and RBV 1000-1200mg/day; GT 1 treatment-naïve (TN) patients received 24 weeks and GT 2/3 treatment-naïve patients received 12 weeks of treatment. Treatment experienced GT 2/3 patients received 24 weeks of therapy. The study design is shown below in figure 1.

![Figure 1](Image)

**Figure 1:** Study design of the PHOTON-1 trial. Overall, 4% of the treatment –naïve (TN) GT1 patients (n=114), 4% of the TN GT2 patients (n=26) and 14% of the TN GT 3 patients (n=42), respectively had cirrhosis at baseline. 24% of the treatment-experienced GT 2/3 patients had cirrhosis at baseline making this clearly the most difficult to treat patient group. 93-98% of
patients were on ART and had stable HIV disease. Amazingly in this first IFN-free study in HIV/HCV coinfected SVR12 was achieved in 76% (87/114) of TN GT1, 88% (23/26) of TN GT2 and 67% (28/42) in TN GT3, respectively. Extending treatment duration to 24 weeks in treatment experienced GT 2/3 substantially increased response rates (SVR12) in GT3 patients to 94%. Increasing treatment duration in treatment experienced patients with HCV GT2 infection again led to a high cure rate of 92%. These results clearly represent the basis of the guideline recommendations to treat HIV/HCV coinfected patients with GT 2 infection IFN-free with sofosbuvir + ribavirin for 12 weeks and GT3 patients for 24 weeks. However, for GT 1 and 4 patients sofosbuvir and ribavirin combination only would apply in case of IFN-ineligibility as around 25% of patients developed relapse after stopping HCV therapy.

Clearly DAA combination therapy is the way forward for this patient group in order to minimize risk for HCV relapse after treatment discontinuation.

At EASL first results from a sofosbuvir/ledipasvir fix-dose combination trial were reported for coinfected individuals (see figure 2) (5). Fifty HIV/HCV genotype 1, treatment-naive subjects with HAI fibrosis stage 0 – 3 were included into this pilot trial. The IFN/RBV free regimen of LDV/SOF in HIV/HCV coinfected patients resulted in SVR12 of 100% in antiretroviral (ARV) untreated patients and SVR4 of 100% in ARV treated patients. The regimen was well tolerated with no discontinuations.

Clearly, efficacy and safety of this regimen is extremely impressive but still does not answer how this new fix-dose combination may perform in cirrhotic previous non-responders.

More data on DAA combination therapy in HIV/HCV coinfecion came from the C-Worthy study which also included an arm of HIV/HCV coinfected subjects (6). Within the coinfecion arm a cohort of 59 patients with HIV/HCV coinfection who were previously not treated for hepatitis C and did not have cirrhosis were included. The coinfected group was 80% men and mostly white, with a mean age of 45 years. About 75% had HCV subtype 1a, 35% had the IL28B CC variant, and 10% had advanced liver fibrosis. They were on antiretroviral therapy containing raltegravir plus 2 NRTIs and had undetectable HIV viral load and a mean CD4 T-cell count above 600 cells/mm3.

Participants were randomized to received MK-5172 (a HCV protease inhibitor) plus MK-8742 (50 mg) (a NSSA inhibitor), with or without ribavirin, all for 12 weeks. SVR4 rates were 97% for the triple regimen and 90% for MK-5172 plus MK-8742 alone.

There was 1 relapse in the ribavirin arm, and 2 HCV viral breakthroughs plus 1 loss to follow-up in the dual therapy arm. The 2 patients with HCV breakthrough had low blood drug levels suggesting poor adherence. There were no cases of HIV breakthrough.

Overall, safety and tolerability was excellent with no study drug discontinuations because of adverse events or laboratory abnormalities.

These two DAA combination trials with above 95% HCV response rates suggest that indeed for patients with GT1 infection DAA combination therapy will become the new gold standard in the near future. As these combinations are likely to become available by the end of this year or in 2015 (at least the sofosbuvir/ledipasvir fix dose combination as well as the Abbvie combination and the combination of sofosbuvir with either simeprevir or daclatasvir) patients with no or minimal fibrosis and GT 1 or 4 infection should wait for the availability of these new IFN-free regimens.

In patients with more advanced liver disease and less time to wait the currently available options need to be discussed. Please also note that for cirrhotic patients the possibility of receiving daclatasvir over the compassionate use program which has just started in Europe exists (in combination with sofosbuvir which then needs to be prescribed in addition to daclatasvir).

Coinfection guidelines

At EASL for the first time HCV management guidelines were presented which included important statements with regard to coinfection (see box below) (6).

As a consequence of similar SVR rates in DAA based HCV trials (with or without IFN) EASL demands to consider HIV patients just as other HCV patients with regard to treatment indication and regimen choice. However, the EASL guidelines also emphasize the need to check for drug-drug-interactions between HIV and HCV drugs.

- Indications for HCV treatment in HIV/HCV co-infected persons are identical to those in patients with HCV mono-infection (Recommendation A1*)
- The same treatment regimens can be used in HIV-coinfected patients as in patients without HIV infection, as the virological results of therapy are identical (Recommendation A1)
- The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HCV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir (Recommendation A1)
- The daily daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz (Recommendation B2)
- No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs (Recommendation A2)

Grading of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect (A). Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate (B). Low or very low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain (C).

Grading of recommendation:
Strong recommendation warranted Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost (1). Weaker recommendation Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty, higher cost or resource consumption (2).
Conclusions
The time has arrived to stop regarding coinfected patients as a separate risk group which is more difficult to treat but rather demand the inclusion of dually HIV/HCV coinfected subjects into HCV trials irrespective of their HIV infection. Only exception is the need to consider potential drug-drug interactions between HIV and HCV drugs.

IFN free treatment already is the new gold standard for GT 2 and 3 infection, for GT 1 and 4 HCV DAA combinations will offer satisfactory cure rates in the very near future. Hopefully, the comparable cure rates in coinfection will help to decrease the barriers in HCV treatment uptake in coinfection and lead to a more wide-spread use and access of new HCV therapies in this patient group.

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References
I am not aware that it ever happened before that the New England Journal of Medicine published 16 original articles – each of them describing primary data from pivotal phase II and III clinical trials – on one specific disease within less than 17 months. Of note, seven of these papers were printed during just five weeks in April and May 2014.

Numerous additional important trial results on new therapies of chronic hepatitis C were presented during recent months in The Lancet, The Lancet Infectious Diseases, JAMA and Gastroenterology. Considering these overwhelming developments, it became quite difficult even for experts following the field closely to keep track with all important findings in distinct patient subgroups. Are there sufficient data for a specific direct acting antiviral in previous interferon nonresponder patients with liver cirrhosis? What about combinations interferon nonresponder patients with liver cirrhosis? etc. etc. etc.

In light of all these new papers, the field was waiting for a scientific forum to discuss the new findings in more detail. Therefore and not surprisingly, the International Liver Congress (ILC) 2014 organized by the European Association for the Study of the Liver (EASL) was absolutely remarkable and groundbreaking for our discipline. It was not only the largest liver meeting ever with more than 10,800 registered attendees, the field of viral hepatitis C can also be separated from now on in the pre and post ILC 2014 era. Side effect-prone, only partially effective, lengthy and complicated response-guided interferon-based therapies are history. Short-term, side-effect free, easy to apply and always working treatments curing HCV infection in almost every single individual are the future. The meeting was quite exhausting and sometimes almost boring, as it was rather tiring to seeing 95%-100% SVR bars again and again in different sessions and symposia. Frequently, the gap to 100% in the intent-to-treat analysis could be explained only by patients missing follow-up visits rather than by non-response to a distinct antiviral therapy. The most interesting question in future will be to discuss treatment failure in individual cases. E.g., what were the characteristics of the 5 individuals with confirmed virological failures in a 400 patient trial? Resistance? Drug levels? Other specific host or viral factors potentially explaining the lack of sustained response? Scientifically interesting (pooh – we still have something to talk about during future meetings), however, on the larger clinical scale not very important as 395 individuals cured HCV infection within 8-12 weeks without any significant adverse events. Very fortunately, there will be rescue treatments for patients who will not cure HCV infection with the first therapies. Thus, if therapy A fails, treatments B or C should still work.

Does this not sound too good to be true? Will it really happen that we can cure every patient within a few months? Are treatments really as safe as promised? Future will tell us but the meeting presentations and the full paper publications suggest that at least the medical tools will be available within a short time to achieve this goal. There might be few subgroups with areas of uncertainty, e.g. the optimal therapy of HCV genotype 3 infection, management of patients with advanced decompensated cirrhosis or patients after liver transplantation. However, other previously so called difficult-to-treat cohorts such as HCV-coinfected individuals respond nowadays as good as HCV mono-infected patients. The most important questions during the next years will now be if there will be enough resources to pay for the novel drugs and to identify all patients at need who could benefit from antiviral therapy. The ILC2014 was therefore also discussing public health aspects of hepatitis C therapies. These discussion will become more and more important. Access to treatment is the key barrier to overcome in subsequent years.

What are the key findings of the most recent NEJM papers and the respective presentations at EASL? The seven latest publications printed in April and May presented phase 3 trial results on the “AbbVie 3D” combination and the Gilead “Fixed-dose-combination” – all for HCV genotype 1 infection. Overall, 3826 patients were treated in the 8 studies (one paper reported findings from two trials) including 737 individuals being treated with PEG-interferon and ribavirin before...
and 604 patients with liver cirrhosis. Of note, these cirrhotics included many patients with more advanced liver disease than previous trials investigating interferon-containing regimens as the inclusion criteria allowed enrolment of subjects with platelet levels of as low as 60,000/μl. For only 139 of the 3826 subjects no sustained virological response could be documented leading to an overall SVR of 96.4%! The final cure rate might even be higher as several patients were lost to follow-up.

True virological failures were usually associated with the emergence of resistant variants against the respective NS5a inhibitor and for the Abbvie-3D regimen in addition against the protease inhibitor and the non-nucleoside polymerase inhibitor. Post-treatment relapse accounted more often for non-SVR than virological breakthrough during therapy. Of note, the presence of resistant variants against the NS5a inhibitor and the non-nucleoside polymerase inhibitor dasabuvir (Abbvie-studies only) already before therapy was associated with a higher likelihood of not achieving an SVR. This might suggest that testing for baseline resistant variants could have a role in the future management of hepatitis C. However, one has to keep in mind the number needed to test to identify potential treatment failures would be very high as still the far majority of patients would respond to subsequent therapy even if the respective resistant HCV strains would be detectable prior to therapy. On the other hand, the long-term impact of selection of NS5a resistant variants is not clear yet. NS5a resistant strains seem to be more fit than for example the well characterised NS3 resistant mutants which usually become undetectable in the blood after 6-18 months after the end of antiviral therapy. It seems that this is not the case in case of NS5a resistance.

**AbbVie “3D” combination: ABT450r, omibitasvir, dasabuvir +/- ribavirin**

The AbbVie 3D combination was also very well tolerated. Trials in non-cirrhotic patients included a control arm of placebo-treated or untreated controls allowing to determine the true-drug-related adverse event frequency. The two pivotal trials in treatment naïve (Feld et al. NEJM April 24 2014) and previously treated non-cirrhotic patients (Zeuzem et al., NEJM April 24 2014) showed SVR rates of 96.2% and 96.3% respectively. Similar very high response rates were seen in the large trial including patients with liver cirrhosis only (Poordad et al., NEJM April 11 2014). The Pearl trials tested the question if the addition of ribavirin is required for the AbbVie regimen (Ferenci et al., NEJM May 4 2014). Overall, the data suggest that non-cirrhotic patients infected with genotype 1b may not need to be treated with ribavirin when receiving the Abbvie combination while genotype 1a patients and all individuals with cirrhosis should receive ribavirin. If distinct subgroups (genotype 1a previous nonresponder with...
cirrhosis) may benefit from prolonged therapy of 24 weeks as suggested by the trials, will need to be confirmed in future studies.

Other combinations (BMS, Merck, Janssen)

Several promising additional other data on phase II trials were presented from BMS, Merck and Janssen. The final data of the Cosmos trial investigating sofosbuvir plus simeprevir were reported by Mark Sulkowski (SVR12 >95% of different cohorts and subgroups, very few individuals with baseline Q80K variants did not respond to the combination). The Merck Worthy-trials also reported high SVR rates for their combination of a new generation protease inhibitor and a potent NS5a inhibitor. BMS presented data of a phase III trial in HCV genotype 1b patients receiving asunaprevir and daclatasvir. These data have been submitted also for approval to the FDA. Moreover, phase 2 data for the BMS 3D combination asunaprevir, daclatasvir and the non-nuc BMS791325 were presented during the meeting. The daclatasvir-sofosbuvir combination trial was published already in January in the NEJM (Sulkowski et al., NEJM Jan 2014).

References on Treatment of Hepatitis C: 16 x NEJM (January 2013–May 2014)


Integrase Inhibitors in Clinical Practice: Today and Tomorrow

The best event in terms of drug development in the HIV field over the last few years has been the emergence of a new class of antiretroviral (ART) compounds called HIV integrase inhibitors (INI). This has been the result of a long process of basic research. The innovative role of HIV antiviral drug research may someday result in key developments in pharmaceuticals in other areas.

There are currently three drugs available in this class. Two of them – raltegravir (RAL) and elvitegravir (EVG) – belong to the first generation, whereas dolutegravir (DTG) recently licensed in the US and Europe – presents characteristics of a second INI generation.

Prospects for ART

There is little doubt that we will have to focus on suppressing viral loads for decades to come. Despite the intensive search for an HIV cure, the most recent data suggest using a) anti-latency drugs, b) cytokines such as interleukin 7, or c) a vaccine that we are still far from developing. Although these approaches have succeeded in their primary mission of inducing RNA from DNA for histone deacetylase (HDAC) inhibitors or increasing the body’s immune function, they have still been unable to “shake the DNA iceberg”. Therefore, except for the lucky few for whom remission was possible within a specific context or because of a certain genotypic profile, or who had the good fortune to be treated at the time of primary infection (the Visconti cohort), therapy will have to be continued for four or five decades. At present we remain convinced that the best chance for an HIV positive individual, from both a health standpoint and with regard to being contagious, is to receive treatment as soon as the HIV is detected.

INIs: a new key class of drugs

INIs all act on a new target in the HIV life cycle by preventing integration of HIV in the genome of infected cells. Unfortunately, INIs are unable to disintegrate the integrated viruses. There are three main features of the class that make them key components in the HIV armamentarium. INIs are a highly potent, fast acting class of drugs that lead to an approximately 2.0 to 2.5 log reduction of viral load in a very short time—a unique feature in an ART drug. A monotherapy study of 25 patients on different dosages of DTG (10, 20, and 50 mg) showed a viral reduction after 10 days of nearly 2.5 log in HIV RNA in those receiving 50 mg DTG once daily. In assessing the potency and strength of INIs, it was found that 70% of patients with a median baseline viral load of 4.7 log10 had suppressed viremia.

Simple, easy to take drugs, that enable an active lifestyle

EVG is prescribed as 50 mg once daily but requires pharmacokinetic enhancement with cobicistat at this dosage. The triple drug regimen of tenofovir (TFV), emtricitabine (FTC), and EVG is combined with the pharmacokinetic (PK) enhancer cobicistat in the recently licensed Stribild®. Until now, only the single tablet regimen to be taken with food has been available by prescription. Due to its long half-life, DTG is given as 50 mg once daily to patients with no resistance to INI, and as 50 mg twice daily in patients with INI resistant viruses. It does not require PK boosting.

RAL is licensed for administration at 400 mg twice daily. It also does not require boosting. Two studies have been unable to demonstrate the non-inferiority of RAL once daily versus twice daily in terms of virological efficacy.

The QDMRK study showed a 83% success rate with viral load < 50 cp/ml in the RAL 800 mg once daily administration versus an 89% success rate in the 400 mg twice daily arm.

Can RAL be used in a once daily regimen?

There are several arguments in favor of RAL’s potential use as a once daily drug.

Plasma concentrations achieved with once daily administration exceed IC 95% and IC 50% concentrations for inhibition of wild type HIV strains. Despite a relatively short half life, the integration complex has a much longer half life of 27 hours.

In a phase III non-inferiority trial comparing the efficacy of RAL once or twice daily, the overall proportion of virological success was 83% in the once daily compared to 89% in the twice daily arm, thus not allowing an assessment of the non-inferiority of either of the two strategies. However, if one considers such a key parameter as the baseline viral load, there is no difference in terms of virological efficacy in patients with less than 100,000 copies/ml (89% with RAL once daily versus 92% with RAL twice daily). At the international Francophone confer-

Structures of anti-integrase inhibitors

Raltegravir
Elvitegravir
Dolutegravir
annons
ence AFRAVIH 2014 at Montpellier in late April Montpellier, F. Caby et al. presented the results of an observational study of 71 patients with suppressed viremia who switched to RAL 800 mg once daily. At baseline, 25% of them were on an RAL 400 mg twice daily regimen. RAL was combined with TDF/FTC or abacavir (ABC)/lamivudine (3TC) in 75% of the patients. Others received atazanavir (ATV) (10%) or non-nucleoside reverse-transcriptase inhibitors (NNRTIs) (15%). The proportion of patients whose viral load remained suppressed at less than 50 copies/ml was 99% [97–100] at W24 and 96% [91–100] at W48. Three patients who failed virologically all had prior failures on a regimen of nucleoside reverse-transcriptase inhibitors (NRTIs). In two cases a prior genotypic resistance test revealed mutations to the backbone of NRTI that were associated with taking RAL once daily, a reasonable explanation for the virological failure.4

**INIs have very limited toxicities**

No INIs have been reported to have overlapped with aging comorbidities or HIV in the form of cardiovascular toxicity, renal impairment, metabolic disorders, or lipohypertrophy.

This is of prime importance, especially for patients who have been on treatment for several years and have accumulated comorbidities and toxicities.

**RAL has beneficial effects on bone mineral density (BMD)**

In an open label randomized pilot study, TNV was switched to RAL in adults on a protease inhibitor regimen (PI/r) with suppressed viremia and a low BMD with a T-score < 1.0. In 37 predominantly male patients with a median age of 49 years who were on TDF for a median time of 3 years, BMD increased significantly at weeks 24 and 48 by 3% (spine) and 2.5% (hip). Bone turnover markers all decreased significantly (p < 0.0017) at week 24.

Once again, this demonstrates that switching suppressed HIV-infected adults who had been on a PI/r from TNV to RAL improved loss of BMD and succeeded in reverting bone turnover markers positively within a short time period.

**RAL has a beneficial impact on inflammation biomarkers**

In the Women, Integrase and Fat Accumulation Trial, 39 women with central adiposity on a 2NRTI + either PI or NNRTI were randomized to substitute the PI or NNRTI for RAL 400 mg twice daily, either immediately or at week 24. While the study was powered to observe a difference of 10% between the two groups, only a 5.4% difference was observed in visceral fat (RAL –3.6%; PI/NNRTI +1.9%), while the observed differences in lipids profile were as anticipated. Given the role of circulating markers of inflammation, including IL6, high sensitivity C reactive protein, and soluble CD14 in predicting all causes of mortality in HIV infection,6 it is important to evaluate whether different ART strategies may have a different impact on these biomarkers. In the above-trial, median sCD14 significantly declined after 24 weeks in subjects switching to RAL (–21% p < 0.001 versus PI/NNRTI –5% p = 0.49). In addition, there was a significant difference between groups. After 48 weeks, this decline was maintained in the group that switched immediately; the delayed switching group experienced it after switching to RAL.7

Although it would be premature to draw any firm conclusions since too few patients have been investigated, it is key to explore the impact of different drug strategies on those biomarker predictors of severe clinical events.

**RAL can be effective in combination with etravirine (ETR) in switch studies**

Because the comorbidities of aging overlaps with HIV and ART drugs such as TNV or PIs in their impact on bone, renal insufficiency, metabolic and cardio vascular risks, one of the preoccupations of HIV physicians is to provide a senior patient with a strategy that will minimize those toxicities and decrease the risk of comorbidities. In this context, it is appealing to think about a strategy that might combine classes of drugs with none of these long-term toxicities, such as NNRTI and INIs.

At present, the combination that has been investigated the most is RAL + ETR.

- At AFRAVIH 2014, R. Calin et al. have updated their initial switch study with the combination of RAL/ETR. This observational study included 91 patients who have been fully suppressed for 4 years with a baseline value of CD4 over 500/ ml. The reason for switching was toxicity in these patients in their mid-fifties [add: average? 53 years] who had been in treatment for 17 years. In a per protocol analysis the success rate of RAL/ETR was 95% (IC 95, 88%–98%) at W48. Three patients who experienced virological failure had previously been replicating on NNRTI with resistance mutations retrospectively identified in a plasma sample.8

- E. Martinez of Barcelona evaluated 25 Spanish patients who had been switched to the combination of RAL/ETR after a median duration of 16 years on ART with a median of 9 regimes. Not surprisingly for this population, 84% had experienced prior virological failure on ART, with 60% having genotypic resistance to either NRTI, NNRTI, or PI. They found very similar results with a success rate of 84% (95% Cl 65.3% –93.6%) by intent-to-treat analysis and 91.3% (95% Cl 73.2%–97.6%) [something missing here that should explain what the 91.3% represents]. One patient previously exposed to nevirapine (NVP) and efavirenz (EFV) failed with 4 resistance mutations associated with NNRTI that made the patient ETR-resistant. In addition to showing a confirmed benefit of RAL on lipids profile, they found a
annons
parallel increase in CD4 (+114/mm³) and a decrease in CD8 (~232/mm³) \( (p < 0.02) \), leading to a CD4/CD8 ratio increase of 0.14 \( (p < 0.001) \).9

These two observational studies lead to the same conclusion. The RAL/ETR combination is effective as long as both drugs are fully active. Prior resistance to NNRTI may be unmasked if minority species or archived resistance mutations are not known.

**EVI**

Two studies presented at CROI 2014 investigated the virological efficacy of switching from a triple drug PI/r of TDF/FTC/NRTI to TDF/FTC/EVG/Cobi.

- In the STRATEGY–NNRTI study, 434 patients on TDF/FTC/NRTI with suppressed viremia were switched to TDF/FTC/EVG/Cobi \( (n = 291) \), while 143 remained on their TDF/FTC/NRTI regimen. The overall virological success rate was 91% in the TDF/FTC/EVG/Cobi arm and 88% in the TDF/FTC/NRTI arm, permitting an assessment of the non-inferiority of the INI strategy.

- Very similar data in terms of efficacy were observed with the parallel STRATEGY–PI study that included 433 patients randomized to TDF/FTC/EVG/Cobi \( (n = 293) \), with 140 remaining on their TDF/FTC/Pi regimen. The success rate of maintaining plasma viral suppression < 50 HIV RNA copies/ml was similar in the two arms, which was 94% in the EVG regimen compared to 87% in the PI/r. There was no emergence of mutations in any arm. The benefit of switching from a lopinavir (LPV) regimen to EVG was a mild decrease (~16 mg/dl) in triglycerides and cholesterol. In patients receiving ATV or darunavir (DRV), no significant benefit in lipids profile was observed.10

The strategy of switching to TDF/FTC/EVG/Cobi was virologically simple, consisting of a single tablet regimen. The impact on comorbidities of switching to a classical NNRTI regimen or a PI/r have not yet been convincingly demonstrated.

**INIs have different profile in terms of drug–drug interactions**

(see article by G. Moyle in HIV Virology News 2014 No. 1)

The most favorable profile in terms of didanosine (DDI) is RAL, which is metabolized only through the UGT1A hepatic pathway. This is of clinical importance in light of the various situations in which ART has to coexist with other mandatory therapies (such as immunosuppressive or cancer chemotherapies) in the context of organ or bone marrow transplantation, cytokine therapies, or anti-hepatitis C virus (HCV) therapies. There has been less experience with DTG and the potential for a moderate rate of interaction through CYP3A. In terms of ARV drug–drug interactions, DTG should not be combined with ETR, whereas combination with rilpivirine (RPV) is possible. EVG and DTG induces a mild increase in serum creatinine that should not be seen
as a renal toxicity but as the result of a competitive inhibition of renal transportation of creatinine.

Future strategies with INI regimen
Considering the potency, tolerability profile, and virological robustness of DTG, building ART strategies for the coming decades is of great importance.

The main questions to be solved are the following:
- With patients starting ART earlier in the course of their HIV infection (e.g., at lower viral loads and higher CD4), and given the higher potency of ARV drugs currently in use, should we continue the dogmatic approach of a triple drug regimen for all individuals, independent of their baseline viral loads and CD4 lymphocytes?
- Can patients who have been suppressed for several years through nucleoside analogues and NNRTI or PI therapy be safely switched to a different strategy that may use fewer drugs with a different toxicity profile to prevent comorbidities? Can we build NNRTI and PI-free regimens?

Ongoing studies in Europe
A DTG + RPV Switch Study (DORISS) has been designed as a pilot and non-inferiority trial comparing DTG + RPV vs. continued Highly Active Antiretroviral Therapy (HAART) in patients with plasma HIV RNA ≤ 50 copies/mL for at least two years. The study should commence in mid-2014. This strategy will explore the benefits of a strategy free of NRTI and PI.12

NEAT022 from the new European clinical consortium NEAT ID is an open label, randomised, non-inferiority 96 week switch study with early or 48 weeks delayed switching from a boosted PI + 2 NRTIs HAART regimen to DGV, in addition to maintaining NRTIs in 420 patients with suppressed viremia. The main objectives of this study will be the efficacy of the DTG strategy and its impact on metabolic and cardiovascular risk. It is also planned to start in mid-2014.

ETRAL ANRS 163 is an open label, pilot, switch study that will evaluate the virological safety and metabolic and BMD benefits of a dual combination of RAL and ETR in 160 patients over age 45. It has a starting date of June 2014.

Conclusion
INIs represent a key class of drugs in the armamentarium of ART, given their potency, robustness, and the simplicity of their regimen. They are currently indicated for both naive and experienced patients who are beset by treatment failure. In addition to their potency, one of the greatest advantages of this class is their tolerability. They have shown none of the comorbidities that overlap with those of HIV, NRTIs, PIs, or aging. Several switch strategies are already planned for clinical investigation to determine their future place in long-term HIV strategies.

References
3. Fabienne C, Bonmarchand M, Soulie C, et al. Efficacité du raltegravir 800mg une fois par jour chez des patients infectés par le VIH-1 en suc-

11. Dolutegravir + Rilpivirine Switch Study (DO-RISS) available at:
annon
HIV and Subclinical Coronary Atherosclerosis.

Do HIV infected men have more atherosclerosis than uninfected men? 1001 men from the MACS cohort between 40 and 70 years of age underwent cardiac computed tomography of which 759 had a coronary CT angiography. 618 men were HIV-infected and 383 uninfected.

The prevalence of calcified and non calcified plaques was evaluated and a “plaque score” was calculated for each participant. A greater prevalence and extent of non-calcified plaques was found among the HIV-infected men.

The difference remained after adjustment for well known risk factors. Lower nadir, CD4 count and years on HAART were positively associated with increased likelihood of coronary artery stenosis greater than 50 %.


Comment: As nadir CD4 is associated with increased risk of atherosclerosis one may hope that early HAART will have a protective effect on the development of atherosclerosis.

It is also important not to forget the importance of life style factors like smoking.

Hepatitis a bigger killer than HIV in Europe.

The Global Burden of Disease Study 2010 (GBD 2010) is a study of causes of human deaths worldwide. Mortality attributed to HBV, HCV and HIV/AIDS across Europe was estimated. In the European Union (EU) mortality from HIV/AIDS has decreased significantly and it was calculated that 8 000 deaths in 2010 were caused by HIV/AIDS.

The corresponding figures for hepatitis B was about 31 000 and 57 000 for hepatitis C. Altogether viral hepatitis caused more than ten times as many deaths as HIV/AIDS in the EU according to the study.

Cowie et al. Abstract 086:The International Liver Congress 2014

Comment: There is hope that vaccination and improved management of hepatitis B together with the availability of effective directly acting antivirals for hepatitis C will have a significant long term impact on hepatitis related mortality.

Ribavirin for chronic hepatitis E in transplant recipients.

In a retrospective French study 59 transplant recipients with chronic hepatitis E were treated with ribavirin monotherapy for a median of three months.

The median daily dose was 600 milligram. Genotyping was performed in 54 of the patients and all had genotype 3. At the end of therapy hepatitis E was cleared in 95 %. In ten patients with end of treatment clearance the virus recurred after cessation of therapy.

In total 46 of the 59 patients had undetectable HEV-RNA 6 months after discontinuation of ribavirin therapy. Of the ten patients whose virus recurred 6 were retreated of which 4 cleared the virus after prolonged retreatment.

As expected anemia was the major side effect with ribavirin dose reductions in 29 %, erythropoetin treatment in 54 % and blood transfusions in 12 %.


Comment: Chronic hepatitis E in immunedeficient patients is an emerging disease with fast progression to cirrhosis. As there is no established therapy for hepatitis E until now this study is a valuable contribution to the management of hepatitis E.

Renal events among women treated with tenofovir/emtricitabine with lopinavir/r vs nevirapine

When tenofovir (TDF) is co-administered with ritonavir boosted protease inhibitors the exposure raises 20 - 30 %. From a randomized study comparing nevirapine to boosted lopinavir (LPV/r) in women who had previously received single dose nevirapine (NVP) the incidence of renal events was analysed (ACTG A5208). All patients received TDF/emtricitabine.

Renal events were defined as a confirmed drop in creatinine clearance associated with a serum creatinine grade 2 or higher, or that leading to treatment modification. The study included 741 HIV-positive women from southern and eastern Africa who were randomized to either NVP or LPV/r in combination with TDF/emtricitabine.

Participants were followed until the last patient had reached 48 weeks.24 women (3.2 %) had renal events, 18 in the LPV and 6 in the NVP group. In multivariate analysis the use of LPV/r was statistically significantly associated with increased risk of renal events.

Mwafongo et al. AIDS 2014, 28:1135–1142

Comment: The overall incidence of renal events was low. However, the observation time was rather short and the study population was young.

One cannot rule out the possibility that renal events would have
been more common in an older population with longer follow up. The use of TDF in combination with boosted protease inhibitors may be an important risk factor for renal events.

HIV or malaria?

Febrile patients in many parts of Africa are often assumed to have malaria. Other causes of fever are easily overlooked. In a study of young adults (< 30 years) 3602 febrile patients (≤ 37.5°C, axillary) in a Kenyan coastal town were evaluated for acute HIV infection (AHI) and malaria. A scoring system was used for inclusion. Body pains, diarrhea, history of multiple partners and symptoms of STIs were used as screening criteria for AHI. The study was performed in 5 health facilities and patients were also referred from 5 pharmacies. AHI was diagnosed using p-24 antigen in HIV negative patients. Overall HIV prevalence was 3.9 %. Among patients who fulfilled AHI criteria according to the scoring system 1% had acute HIV infection. The malaria incidence was of similar magnitude at 1.7 %. Sanders et al. AIDS 2014, 28 000-000 ännu inte i tryck, referens kan uppdateras när artikeln är i tryck

Comment: Patients with AHI are highly contagious and early diagnoses and prompt initiation of ART may be an important factor in limiting the spread of HIV. The “rapid tests” used to diagnose HIV infection do usually not include antigen testing and in many of the “rapid combo tests” the performance of the antigen test has not been reliable. In the present study the samples were analyzed in a central laboratory. Improved rapid combo test would improve the possibilities to diagnose AHI.

Clearance rate of serum hepatitis B surface antigen (HBsAg).

2112 Japanese patients with chronic hepatitis B were followed for at least 15 years from 1968. Patients with monoinfection without any history of HCC or any other liver disease were included. Almost 80 % had genotype C. About two thirds were men and the median age was 37 years. 982 patients received treatment with interferon, nucleotide analogues or prednisolon. The overall annual clearance rate of HBsAg was 1.75 %. In the 1130 untreated patients the annual clearance rate was 1.65 % and 2.05 % in the treated patients.

A similar analysis in treated patients showed an association between negative HBeAg and absence of HBV infection in the family with clearance. Interferon treatment was significantly more likely to be associated with clearance compared to other treatment. There was a numerical but not a statistically significant difference in HBsAg clearance between treated and untreated patients.


Comment: In this very long term observational study treatment was not statistically associated with HBsAg clearance compared to no treatment. However, it is an observational non randomi-zed study with baseline differences between the groups and the groups are thus not comparable.

The association between HBsAg titer and clearance is another indication of the importance of including HBsAg titer as a part of routine management of chronic hepatitis B.

HIV transmission risk estimates.

The last Centers for Disease Control and Prevention (CDC) es-timate of HIV transmission rates was published 2005. A new estimate was done with the addition of data published since 2005. The analysis also includes the effect of modifiable factors like condom use, antiretroviral therapy (ART) and male circumcision. Compared with previous estimates the estimate for re-ceptive anal intercourse increased. The estimated risk for HIV transmission from sexual intercourse with the combined use of ART and a condom decreased by 99.2 %.

The probability of acquiring HIV in unprotected receptive anal intercourse was estimated to be 138 per 10 000 acts. The estimation for insertive anal intercourse is much lower with 11 trans-missions per 10 000.

The corresponding risk estimates for insertive and receptive penil-vaginal intercourse are 4 and 8 per 10 000 acts. The risk for both receptive and insertive oral sex is too low to be estima-ted. Factors that increase the probability of transmission include high plasma viral load, genital ulcer disease, acute versus asympto-matic disease and late versus asymptomatic disease.

Patel et al. AIDS 2014 28:000-000 Finns ännu så länge bara på nåtet, behöver kompletteras

Comment: The risk estimates have major limitations with large confidence intervals and the changes compared to earlier esti-mates fall within the confidence intervals. In the perspective of the recently presented “Partner Study” one would expect the protective effect of ART and condom use to be even higher than 99.2 %

Increased risk of HIV infection after vaccination!

HVTN 503/Phambili was a double blind, placebo controlled vac-cine trial of HIV uninfected sexually active adults aged 18-35 in South Africa. A recombinant adenovirus vector was used in the trial expressing HIV gag/pol/nef subtype B. The same vaccine was used in the Step trial where mainly MSM and at-risk women in the Ame-ricas, Caribbean and Australia were included. The Step trial was stopped when prespecified futility rules were met. Subgroup analyses from the Step trial showed an increased risk of HIV acquisition in men who had been vaccinated compar-ed to those who received placebo. Also the HVTN 503/Phambili trial was stopped and the partici-pants were followed. 800 patients were enrolled in the study. Of the 400 individuals in the vaccination arm only 29 had received three doses while 259 got 2 vaccinations and 112 one dose before the trial was stopped. After follow up for 42 months a total of 100 participants in the study were HIV infected. Of these 63 had received vaccine and 37 placebo. The differ-ence is statistically significant. There was no difference in CD4 decline or viral load set-point between the HIV positives who had received vaccine compared to the HIV infected who had re-ceived placebo. The increased HIV acquisition was noted in all subgroups. No correlation between the number of injections and
the risk of HIV infection was seen. A meta analysis of combining the results with the Step study gives a hazard ratio of 1.41 (CI 1.11 – 1.78). It is speculated that the vaccination may increase the number of HIV-1 target cells.

Gray et al. Lancet Infect Dis 2014;14:388-96

Comment: The HIV vaccine development has so far been very unsuccessful. Not only was there no protective effect of the vaccine but increased risk. These very discouraging results must be taken into account when future vaccine trials are designed.

Faster progression to AIDS with recombinant subtype

In a cohort of police officers in Guinea-Bissau that was started in 1990, blood samples and follow up visits have been scheduled every 12-18 months. Seroconversion date was defined as the midpoint between the last negative and first positive test. Inclusion and follow up was temporarily interrupted during a civil war from 1998 to 2002. Antiretroviral therapy became available 2006.

In this study the time from seroconversion to AIDS/AIDS-related death was the primary endpoint. Of 225 HIV positive individuals samples from 191 individuals were available. Of these 152 could be amplified and sequenced for the C2-V3 region. Five cases could not be assigned a subtype/circulating recombinant form (CRF). Of the remaining 147 samples 78 were classified as CRF02_AG, 42 as subtype A3 and 22 as a recombinant of A3 and CRF02_AG.

In 19 of the 22 samples the first part of the C2-V3 fragment was of subtype A while the remaining 3 samples had a different pattern and were excluded from further analysis together with 5 other samples with different subtypes. The median time from estimated seroconversion to AIDS was 5.6 years. Kaplan-Meier analysis showed that the estimated time to AIDS/AIDS-related death was 7.2 years for individuals infected with A3, 6.2 years for CRF_AG and 5.0 years for A3/CRF02_AG.

Time to death showed a similar pattern with 11.3, 9.0 and 8.0 years in the three groups. The authors conclude that the A3/CRF02 recombinant is associated with a faster progression to AIDS and death compared with subtype A3.

Palm et al. JID 2014;209:721-728

Comment: To what extent HIV subtype influences the progression to AIDS has been widely discussed. It has been claimed that subtype D is associated with faster progression than subtype A. In this study a shorter time for the recombinant A3/CR0F-AG virus is observed. One possible confounding factor is that the median estimated date of seroconversion for the individuals infected with the recombinant virus was January 2000 compared to January 2005 for the A3 group.

Nevirapine (NVP) versus boosted lopinavir (LP-V/r) as first line ART in resource-limited setting

425 treatment naïve patients in Democratic Republic of the Congo (DRC) were randomized to either NVP or LPV/r together with zidovudine/lamivudine or tenofovir/emtricitabine. The study was open label and the nucleoside backbone was randomly chosen. About 70 % of the patients were female and the baseline median CD4-count was about 165. The inclusion criteria followed the DRC national guidelines for initiation of HIV therapy; WHO clinical stage 3 or 4 or CD4< 200. The study was designed before efavirenz became the preferred NNRTI (WHO). Trimethoprim/sulfamethoxazole prophylaxis was systematically given.

Therapeutical failure was defined as the occurrence of WHO stage 3 or 4 events or death or discontinuation of study drugs for toxicity. At 48 weeks there was no difference in the rate of therapeutical failure between the arms. However, there was significantly more virological failure and resistance development in the NVP arm at the time of failure. In the NVP arm 27 patients failed virologically of which 22 had genotype available at failure. 3 of the 22 had baseline mutations. Of the remaining 19 patients all had NNRTI associated mutations and 15 had NRTI associated mutations including 7 K65R. In the LPV/r arm none of the 13 virologically failing patients developed a major PI mutation and only 2 patients had NRTI associated mutations (M184V).

Clumeck et al. AIDS2014;28:1143-1153

Comment: WHO recommends NNRTI (efavirenz) for first line therapy in resource limited settings. As is clearly demonstrated in this trial the risk of resistance development and thus limitations of future treatment options is much greater with NNRTI based regimens. Resistance develops not only to the NNRTI but also to the backbone NRTI:s. A switch from NNRTI to PI-based first line therapy would reduce the risk of resistance and long term clinical failure.
Topical Conferences in 2014

**June 25–26**
2nd International Conference on HIV/AIDS, STDs & STIs
Valencia, Spain
http://72.167.32.140/hiv-aids-std-conference-2014/

**July 18–19**
6th International workshop on HIV Pediatrics
Melbourne, Australia
http://www.virology-education.com/

**July 20–25**
20th International AIDS Conference
Melbourne, Australia
http://www.aids2014.org/

**September 5–9**
Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)
54th ICAAC, Washington DC
http://www.icaac.org

**September 12–13**
AASLD/EASL HCV Special Conference
New York, USA
http://www.aalsd.org

**September 24–27**
Southern African HIV Clinicians Society Conference 2014
Cape Town, South Africa
http://www.sahivsoc2014.co.za

**October 2–3**
HIV Nordic Conference
Stockholm, Sweden
http://www.hivnordic.se

**October 6–8**
16th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV Workshop
Philadelphia, PA, United States of America
http://www.intmedpress.com/comorbidities/

**October 8–13**
The Modes of Action of Vaccine Adjuvants
Seattle, Washington, USA
http://www.keystonesymposia.org/meetings

**October 12–14**
3rd Antivirals Congress 2014
Amsterdam, Netherlands
http://www.antivirals.elsevier.com/index.html

**October 27 - 29**
2nd International Conference on HIV/AIDS, STDs & STIs- 2014 Conference
Las Vegas, United States of America
http://72.167.32.140/hiv-aids-std-conference-2014/

**November 2–6**
HIV Glasgow
Glasgow, United Kingdom
http://www.hivglasgow.org

**November 5 - 6**
1st International Hepatitis Cure & Eradication Meeting 2014
Toronto, Canada
http://www.virology-education.com/event/upcoming/1st-international-hepatitis-cure-eradication-meeting-2014/

**November 7-11**
AASLD
Boston, MA, USA
http://www.aalsd.org

**2015**

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

**April 26 - May 1 2015**
Host Response in Tuberculosis
Boston Park Plaza, Boston, Massachusetts, USA
http://www.keystonesymposia.org