HIV AND HEPATITIS NORDIC CONFERENCE 2015 · SATELLITE SYMPOSIUMS AT THE HIV AND HEPATITIS NORDIC CONFERENCE · EACS GUIDELINES 8.0: THE BIG REDUCTION · DOCTOR, I CAN’T SLEEP! LIGHTER ANTIRETROVIRAL THERAPY: WHAT’S NEW FROM EUROPEAN TEAMS
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Guest Editorial

The European AIDS Clinical Society - still a lot to accomplish

Around 2.5 million people live with HIV in the European region and still about 140,000 new HIV infections are encountered in Europe each year. We as the European AIDS Clinical Society – EACS believe that our mission to provide excellence in standard of care, research and education concerning HIV infection and related co-infections, in particular the hepatitis viruses, and to organize the biennial HIV/AIDS Conference remains vitally important.

To provide a best possible basis to fulfill our goals the Society’s structure has been strengthened and new initiatives have been launched. In this context, the newly issued biennial report which can be found on our Society’s webpage www.eacssociety.org gives an excellent overview. Working groups were formed and in the last two years we newly launched programmes for education and training such as the Medical Exchange Programme, as well as the e-learning course being developed by CHIP in Copenhagen in collaboration with WHO Europe. This latter course aims to provide high quality training in the clinical management of HIV to clinicians in Eastern Europe and Central Asia. We are especially pleased that the EACS is broadening its support to the professional life of young colleagues early in their careers with a variety of programmes, building on our many years of experience with the Advanced HIV Course and the European Clinical Research Course. Complementing this, the European Young Investigators course is planned in 2016.

Another new programme is WAVE – Women Against Viruses in Europe that aims to particularly promote the health of HIV-positive women in Europe. We feel that there is still an existing gender issue and that this is an area where the EACS can raise awareness and implement beneficial change. Other new EACS activities relate to collaborations with societies such as the European Society for Clinical Microbiology and Infectious Diseases, the European Association of the Study of the Liver, the European Centre for Disease Prevention and Control (ECDC), the WHO and others. Another highlight was the Standard of Care meeting co-organised by the EACS in the fall of 2014 with stimulating interactions between clinicians, community members, researchers, epidemiologists and public health experts on ways to provide the best possible HIV care. This meeting will again take place in late 2016.

The European AIDS Conference in Barcelona

A forthcoming issue of HIV & Virology News will report about the 15th European AIDS Conference, having taken place in Barcelona, October 21st – October 24th which I had the pleasure and honour to co-chair with José M. Gatell. The conference was attended by over 3,300 participants from 93 countries. More so, there were a record number of abstracts submitted with an extraordinary high level of science from all parts of the world.

The Opening Ceremony with exceptional and inspiring lectures by Michel Kazatchkine, Matthias Egger and Tamás Bereczky superbly set the stage for a very stimulating conference. During the Opening the EACS had the privilege to honour outstanding researchers and clinicians – Jens D. Lundgren, Copenhagen, received the 2015 EACS Awards for Excellence in HIV Medicine, David J. Back, Liverpool, and Jose M. Gatell, Barcelona, the EACS Recognition for Major Lifetime Contributions to the field of HIV/AIDS. New features such as special sessions with a mixture of mini-lectures, original abstracts as well as panel discussions provided a platform to discuss and plan future actions from different interdisciplinary angles. PrEP, hepatitis co-infection, tuberculosis, gender, standard of care or the prospects of cure are examples of topics discussed in depth. Different consortia were affiliated with our conference. Also several joint sessions, e.g. with the WHO or ESCMID are to be mentioned. By closely affiliating the conference with the 17th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV, synergies were created in the thinking about how to address long-term care issues. The EACS seeks to support European researchers and clinicians in the early stages of their career. It was rewarding to see 76 Joep Lange and Jacqueline van Tongeren EACS Scholarships granted at the event.

These were offered to medical doctors, nurses and community members. An outstanding lecture was given by Sheena McCormack to commemorate Professor Martin Fisher, a leading HIV clinician and researcher and firm advocate for high standards of HIV care. The conference also provided a perfect platform to present the 8.0 version of the EACS Guidelines launched in a new complementary format – as a mobile application, freely downloadable. The Conference webcasts are available via our webpage. Many clinicians as well as clinical researchers, and community members contribute to the success of the Society. We are convinced that the EACS should take part in advocating HIV/AIDS health policies in Europe, in particular in Eastern and South-Eastern Europe where the HIV epidemic is still far from being controlled. A lot remains to be accomplished in research, in training and education with respect to both clinical and research skills, and in terms of ensuring optimal access to treatment and care – all over Europe – our mission is far from being accomplished.

Manuel Battegay
President, European AIDS Clinical Society
During the 15th EACS (European AIDS Clinical Society) Conference celebrated in Barcelona last October, the eighth update of the EACS guidelines was presented [1]. The prior version of the EACS guidelines had been updated in 2014. Globally, the HHS [2], the IAS [3] and the EACS guidelines are the guidelines most followed by clinicians taking care of HIV-infected patients in developed countries.

The World Health Organization also produces recommendations on antiretroviral treatment [4]. The WHO guidelines have a public health approach while the other three have an individual patient approach. The HHS guidelines are presented via web page in a very comprehensive and detailed document that was last updated in April 2015. The IAS guidelines are published as a review paper in the Journal of the American Medical Association and were last updated in July 2014. The EACS guidelines are available at the web page of the EACS society and also as a small pocket book that can be carried by physicians in their coats. For the first time this year, the EACS guidelines are available as a free of cost app both for iOS and Android. In the EACS webpage translations of the guidelines are available in different European languages.

In contrast with the other guidelines, the EACS guidelines are designed in a way that makes them useful as a point of care resource that can offer clinicians rapid answers to the most common management questions raised in HIV clinics. To serve this purpose the EACS guidelines are divided into five important sections:

1. Assessment of HIV-infected patients at initial and subsequent visits
2. ART of HIV-positive individuals
3. Prevention & Management of Co-morbidities in HIV-positive persons
4. Clinical management and treatment of HBV and HCV coinfection in HIV-positive persons
5. Opportunistic infections

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

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

**When to start ART: now a very short section**

In part II of the guidelines there are new recommendations about when to start ART. EACS guidelines have acknowledged the important results of the START [5] and TEMPRANO [6] clinical trials. At present ART is recommended for all HIV infected persons regardless of CD4 cell count with the possible exception of elite controllers with high and stable CD4 count. Although ART is recommended for all patients the panel makes a distinction. For symptomatic HIV disease (CDC B or C conditions, including tuberculosis) and for patients with a CD4 cell count of less than 350 cells/μL the wording is “strongly recommended” while for patients with a CD4 cell count of more than 350 cells/μL the wording is simply “recommended” (Table 1). The goal of this distinction is probably to help clinicians prioritize the use of ART, especially in countries where access to treatment remains a challenge. With this update, this is the first time since 2006 that all internationally-written guidelines have agreed on their ‘when to start’ recommendations.

**What to start: fewer regimens**

There is also more consensus among guidelines with regard to recommended in-
Initial ART regimens. In this update of the EACS guidelines, there are important changes on the what to start recommendation:

1. EACS now recommend full regimens instead of the prior approach of selecting two nucleos(t)ides and a third drug
2. Efavirenz is no longer a recommended option. The only recommended non-nucleoside reverse transcriptase inhibitor is rilpivirine
3. Only one boosted protease inhibitor – darunavir/ritonavir – is currently recommended
4. Four regimens including integrase inhibitors are recommended

Since the Spanish GESIDA guidelines [7] started to reduce the number of recommended regimens for initial antiretroviral treatment, other guidelines have followed the same path (Figure 1). GESIDA went from recommending 10 regimens to just three -all integrase inhibitor based- . HHS went from 10 to five and finally the EACS guidelines have gone from 13 to six. In all these three guidelines integrase inhibitor based regimens predominate. This dramatic reduction of the number of recommended regimens has been caused by the results of recent clinical trials comparing integrase inhibitor based regimens to non-integrase inhibitor based regimens [8-11]. In general in these trials outcomes have favored the integrase inhibitor based regimens. The EACS guidelines committee had decided to maintain at least one regimen from each of the three classes of antiretrovirals. He highlighted that the EACS guidelines are important for countries across Europe with a very different levels of access to ART and it is necessary to offer therapeutic possibilities within the three families of drugs.

The current list of alternative regimens includes up to 13 regimens, many of which were preferred in prior versions of the guidelines. It is important to realize that for specific patients these regimens could also be appropriate therapeutic options. The alternative regimens include:

- Integrate inhibitor based regimens: ABC/3TC + RAL
- Non-nucleoside reverse transcriptase inhibitor based regimens: ABC/3TC + EFV and TDF/FTC/EFV
- Protease inhibitor based regimens.

Fig 1. Comparison of recommended regimens in three expert guidelines, years 2014 and 2015.

Switch strategies: dual therapy with 3TC + boosted PI now a possibility
The section of switch strategies for virologically suppressed persons emphasizes the importance of not jeopardizing virological suppression. This is specially important when the switch implies a reduction in the genetic barrier of the regimen. The

### Switch strategies: dual therapy with 3TC + boosted PI now a possibility

The section of switch strategies for virologically suppressed persons emphasizes the importance of not jeopardizing virological suppression. This is specially important when the switch implies a reduction in the genetic barrier of the regimen. The
guidelines for the first time recommend dual therapy with 3TC + LPV/r or 3TC +ATV/r for maintenance of virological suppression. Since this strategy has not been associated with more virological rebounds than triple therapy it might be a better option than boosted protease inhibitor monotherapy.

**PrEP!!!** The other brand new section of this update is the one dealing with Pre-exposure Prophylaxis (PrEP). This is going to be a very important topic all across Europe. Now that the scientific evidence supporting the efficacy of PrEP is overwhelming the critical issue has become implementation. Stay tuned for the heated discussions in different countries.

The EACS guidelines recommend PrEP for adults with high-risk of acquiring HIV infection:

- **Men who have sex with men and transgender individuals who are inconsistent in their use of condoms with casual partners or with HIV-positive partners who are not on treatment.** Guidelines specify that a recent sexually transmitted disease or use of post-exposure prophylaxis may be markers or increased risk for HIV acquisition.

- **PrEP may be also considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and likely to have HIV positive partners who are not on treatment.**

As in prior versions the sections dealing with opportunistic infections and comorbidities provide clinicians with updated information and very practical tables. Now that the majority of patients in our clinics are suppressed we spend most of our clinics time dealing with how to prevent and treat comorbidities. The EACS guidelines stand out among other guidelines in depth of the information provided for each comorbidity: cancer, bone, cardiovascular, neurocognitive etc.

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

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**References**

Lighter Antiretroviral Therapy: what’s new from European teams?

The mood was buoyant among the more than 3000 participants at the 15th European AIDS Clinical Society (EACS) Conference in Barcelona. The sky was bright and the participants young. It was a great pleasure to see a new generation of HIV physicians carrying the torch in the fight against AIDS.

Light seems to have become a word heard more and more in antiretroviral therapy (ART). As worldwide guidelines have extended the range of treating HIV-infections by recommending the initiation of ART in all HIV-infected patients, it has become increasingly important to identify treatment strategies that can exert maximum control over viral replication, yet achieve that goal using a minimal drug burden.

- ART is no longer a question of providing a few years of therapy with a limited follow-up of 5 to 7 years. In the absence of a safe and effective strategy to bring about HIV remission, the disease has to be controlled throughout a patient’s life span. If one considers that globally the median age of ART initiation is approximately 35 years, we are looking at several decades of therapy.
- The anti-HIV drug portfolio is relatively stable and should expand at about the rate it has in the past decade. Pharmaceuticals that can control viral replication are available. Trial results that are impressive enough to justify registering new drugs (such as maturation or attachment inhibitors) have become more difficult to achieve, given the excellent performance of current drug strategies. Clinicians must resign themselves to providing much longer therapy with a fixed portfolio. This is a great incentive for making our armamentarium viable for several decades to come. In order to accomplish this we need to achieve viral suppression with less medication wherever possible.
- The effort to drive individuals who have ignored their HIV infection in the past to seek care is a challenging priority for countries that support the Joint United Nations Programme on HIV and AIDS (UNAIDS) aim of getting “90% of people living with HIV to know they have the virus, 90% of those who know they are infected to be receiving sustainable antiretroviral treatment, and 90% of those people on treatment to have sustainable suppression of their virus by 2020.” The 90-90-90 goal can be reached if treatment is made friendlier and more individualized.
- In the 20 years from 1996 to the present, the gold standard for controlling HIV replication has been the classical regimen of two nucleoside reverse transcriptase inhibitors (2NRTIs) plus a third agent. Now tremendous progress in treatment simplification has been achieved with the licensing of single tablet regimens that have played a major role in improving treatment adherence.

This does not take into account the changing profile of ART-naïve patients:
- Patients nowadays have less severe HIV disease at the time of ART initiation, with a median baseline CD4 count around 350/mm3 and a lower HIV viral load (about 4.0–4.5 log10), according to the most recent registration trials.(1-2)
- Drugs currently available have greater potency and are more robust than their predecessors in the same drug class.

The search for a reduced drug burden that will maximally control HIV will likely become a new field of investigation for patients treated early or those with viral suppression of long duration. Boosted protease inhibitor (PI) monotherapy was the first strategy to demonstrate some efficacy in this application, due to its high potency and strong barrier to resistance.(3) Dose reduction trials such as ENCORE-1 or LASSA,(4-5) or dual strategies such as GARDEL(6) (see HIV & Virology News 2015 No. 3), have also demonstrated their non-inferiority.

Lightening the drug burden

New strategies with dolutegravir (DTG)

The first session ART session at EACS 2015 offered new ways of thinking about DTG, the most recent integrase inhibitor (INI), and one that has moved the field towards lighter strategies.

DTG shares similar characteristics in supporting potential efficacy as maintenance monotherapy:
- High antiviral potency exhibited in a short-course monotherapy study.(7)
- Pharmacological robustness, a long half-life,(8) and a very limited variability in drug concentration in the same individual or within a cohort;
- A high inhibitory quotient.(8)

Some recent studies assessing the efficacy of a simplified DTG-containing regimen were presented at EACS 2015.

The PADDLE Study (11)

Following upon their innovative GARDEL study using dual therapy lopinavir/la-mivudine, Pedro Cahn and his group have...
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1 September – 14 October 2016 £695
presented the interim results of a single-arm Pilot Antiretroviral Design with Dolutegravir Lamivudine (PADDLE) study evaluating a dual therapy with DTG plus lamivudine in naïve HIV-infected patients.

**Study design**
- Twenty ART-naïve patients with HIV-1 RNA 5,000–100,000 cp/mL and CD4+ cell count > 200 cells/mm³ were enrolled sequentially in 2 cohorts of 10 patients each.
- The ART regimen consisted of DTG 50 mg QD plus lamivudine 300 mg QD. HIV-1 RNA was measured at baseline, Days 2, 4, 7, 10, 14, and Weeks 4, 8, 12, and 24.

**End points**
The primary end point was HIV-1 RNA < 50 copies/mL at Week 48 by U.S. Food and Drug Administration (FDA) snapshot analysis. Several discontinuation criteria were included to ensure the safety of the study:
- HIV-1 RNA reduction < 1 log10 copies/mL from baseline to Week 8
- HIV-1 RNA ≥ 1000 copies/mL at Week 12
- HIV-1 RNA ≥ 400 copies/mL at Week 24
- Confirmed viral rebound to > 200 copies/mL after HIV-1 RNA < 50 copies/mL
- Discontinuation at Week 8 if HIV-1 RNA decreases < 1 log10 copies/mL in > 2 of 10 patients in the first cohort

**Study population**
Patients were mostly male (95%), had a median age of 34 years, a median HIV viral load of 24.128 cp/mL (11.686–36.794), and a median CD4+ count of 507 cells/mm³ (296–517).

**Interim Results**
- HIV-1 RNA was < 50 copies/mL by Week 8 in all patients on the DTG plus lamivudine initial therapy
- All patients maintained virologic suppression through Week 24
- Similar results were seen in 4 patients with HIV-1 RNA > 100,000 copies/mL at baseline
- Mean HIV-1 RNA decreased by Day 14 to 2.54 ± 0.27 copies/mL
- CD4+ cell count increased from baseline to +195 CD4 by Week 12, and to +200 cells/mm³ by Week 24.

An improvement in CD4 was already noted at Week 12, with no further significant increase by Week 24.

DTG monotherapy: switch-studies in patients with suppressed viremia

Cohort studies were presented by two groups of clinical investigators involved in the identification of lighter suppressive therapies.

The Spanish group,(12) led by Esteban Martinez of Barcelona, enrolled patients who had been switched from a suppressive regimen to DTG 50 mg QD monotherapy because of toxicity, drug–drug interactions, or potential loss of virologic control due to archived resistance. The end point was the proportion of patients maintaining virologic suppression at Week 24.

**Results**
The 33 patients enrolled were equally distributed by sex, had a median age of 56 years, a long history of HIV infection (average 19 years), and viral suppression for 4 to 13 years (average 8). The baseline ART regimen consisted of PI monotherapy in 67% of the cases; an NNRTI regimen in 27%; and an INI-containing regimen in 6% (two patients).
- **Success:** Virologic suppression was maintained in 97% of all patients at Week 24 (95% CI: 83% to 100%).
- **Failure:** One patient on darunavir monotherapy at baseline had a viral rebound at Week 4, with viral load of 88 copies/mL, 155 copies/mL on a consecutive test, and 101 copies/mL at Week 24. He had a history of reverse transcriptase, protease drug resistance mutations, failure on raltegravir-containing therapy, and no detection of integrase strand transfer inhibitor (INSTI) resistance.
These giants of the animal kingdom need help. Despite their strength and cunning they're no match for a poacher's rifle. For 50 years WWF has been securing protected areas worldwide, but these aren't enough to stop the killing. To disrupt the sophisticated criminal gangs supplying animal parts to lucrative illegal markets, we are working with governments to toughen law enforcement. We’re also working with consumers to reduce the demand for unlawful wildlife products. Help us look after the world where you live at panda.org/50
Dolutegravir monotherapy in patients with suppressed HIV viremia.

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MonoDTG

Virological Efficacy at W24

Proportion of patients with HIV RNA < 50 cp/ml

28 pts

25/28 VL< 50 cp/ml
- All <50c/ml
- All <20c/ml except 37 cp/mL (1)
- 1 blip W4 (52 cp/mL)
3 virological failures
W12 : 1 pt
VL 138/469 cp/mL
W24 : 2 pts
- VL : 2220 cp/mL
- VL : 291 cp/mL

Katlama C et al. EACS 2015 , Oral PSA4/4

Simplification for Dolutegravir as a Mono- or Bitherapy Maintains High Proportion of Viral Suppression Even in Highly-experienced HIV-1-infected Patients

Camelia GUBAVU3, Thierry PRAZUCK1, Mohamadou NIANG3, Jennifer BURET1, Catherine MILLE1, Jérôme GUINARD2, Véronique AVETTAND-FENOEL3,4, Laurent HOCQUELOUXT
only observational and conducted on a limited number of patients, suggest a high rate of efficacy for DTG monotherapy over a period of 24 weeks in a heavily treated ART-experienced population. The regimen was also positively received by patients. This strategy deserves further investigation through larger clinical trials that include more treatment-naive patient populations.

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During three days, from the 30:th of September to the 2:nd of October, more than 250 delegates came to the HIV and Hepatitis Nordic Conference. It was held in the Swedish capital Stockholm.

Prof Magnus Gisslén, Chair of the Organizing Committee, greeted them all welcome.

– We are very pleased to welcome you back to the second Nordic Conference. This year, hepatitis is also included in the Scientific programme, he said.

Prof Gisslén also thanked the sponsors.

– In order to organise this Conference, they are essential.

The sanatorium decade
For the Opening Plenary, Prof Gisslén was pleased to present Prof Jan Gerstoft from Denmark. 35 years of HIV research – problems solved and challenges that remain, was the title of his lecture.

He started his talk with the very first HIV-patients in 1981 – 1983. They were men who have sex with men (MSM) with Kaposi sarcoma. They developed fever of unknown origin, wasting, genital herpes and pneumocystis pneumonia.

– We were surprised to find that all patients had low CD4 count and reduced proliferation to mitogens – and no other causes of immunodeficiency could be identified, Prof Gerstoft said.

The disease was not epidemic then. Soon HIV was identified. This led to what Prof Gerstoft called “the Sanatorium decade”, 1985 – 95.

– The number of patients increased, as did the number of in-patients waiting to die. Opportunistic infections were extremely prevalent.

The treatment options were very few.

– Some patients became demented. Later when therapy became available they got better again – which was very puzzling for neurologists.

During the Sanatorium decade a lot of research was carried out. In 1986 BMJ published that persistent HIV antigenemia and decline of HIV core antibodies was associated with transition to AIDS. In 1989 BMJ published that acute HIV infection predicts course of infection.

– In the isoprinosine study in 1990, 824 HIV-patients were randomized. This was a placebo-controlled study, and AIDS was the endpoint. 17 in the placebo-group got AIDS – versus 2 in the placebo-group, Prof Gerstoft pointed out.

Remaining challenges
In 1996 came cART, and Prof Gerstoft said they saw a sharp decline in viral load when cART was initiated.

– cART works in pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), mother to child transmission (MTCT) and for sexual transmissions. We have seen a decrease in adverse effects gradually over time and a roll out of cART world wide, he continued.
These giants of the animal kingdom need help. Despite their strength and cunning they’re no match for a poacher’s rifle. For 50 years WWF has been securing protected areas worldwide, but these aren’t enough to stop the killing. To disrupt the sophisticated criminal gangs supplying animal parts to lucrative illegal markets, we are working with governments to toughen law enforcement. We’re also working with consumers to reduce the demand for unlawful wildlife products. Help us look after the world where you live at panda.org/50.

Silverback Western lowland gorilla.

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HELP SAVE THE ‘WOW’

These giants of the animal kingdom need help. Despite their strength and cunning they’re no match for a poacher’s rifle. For 50 years WWF has been securing protected areas worldwide, but these aren’t enough to stop the killing. To disrupt the sophisticated criminal gangs supplying animal parts to lucrative illegal markets, we are working with governments to toughen law enforcement. We’re also working with consumers to reduce the demand for unlawful wildlife products. Help us look after the world where you live at panda.org/50
There are however remaining challenges, and the first on Prof Gerstoft’s list was a prophylactic vaccine – which is really needed.

– I would also like to know about the effectiveness of treatment as prevention. We have not seen a decline in new cases.

Prof Gerstoft also pointed out that there still is no cure.

– Non-smoking, non-viral induced cancers – they are increased in the HIV population, treated or untreated. There are people believing that all cancers increase in all untreated patients.

He ended his talk by calling for regimens with long acting injectable antivirals.

– And we need microbicides that work in real life, such as an antiviral vaginal ring – and they are on their way, Prof Gerstoft said.

HLA genes have the greatest impact
The first Plenary session was on the HIV epidemic. Prof Philip Goulder, UK, talked about the impact of HIV adaptation on virulence. He began this by presenting two studies – with totally different conclusions on HIV virulence.

Of the human factors that influence viral setpoint, HLA genes have the greatest impact, Prof Goulder stated.

– They are concentrated in chromosome G.

He continued to talk about the HIV replicating capacity, which he called virus “fitness”.

– A high percentage of transmissions in acute infection favour selection of fitter viruses. Late – or no – ART decreases the percentage of transmissions in acute infection, and favours selection of lesser fit viruses.

Prof Goulder explained that protective HLA reduce population-level viral fitness is coinciding with reduced protective HLA effect.

– Restricted ART usage to chronically infected subjects with low CD4 counts favours transmissions of low fitness virus. Increasing transmissions in acute infection favours transmission of fitter viruses, he said at the end of his talk.

Very few prevention programs in Russia
An update on the HIV epidemic in Russia was presented by Prof Vadim Pokrowsky.

The number of newly diagnosed HIV infection is rising steeply in the country. 2014 saw 89,342 new cases – a record high.

– The total number of registered HIV cases in the middle of 2015 is 950,000. The estimated number of people living with HIV is 1,300,000. The number of HIV-positive persons on ART is 190,000. All these numbers are in round values, Prof Pokrowsky said.

There are concentrated epidemics among injecting drug users (IDUs) and MSM.

– And there is an ongoing discussion on if we have a generalized epidemic going on.

The main concept in prevention in Russia now is “to motivate population to deliberate refusal from models of risky behaviour” – this was quoted from a speech of the Russian minister of health.

– Very few prevention programs among vulnerable populations were funded in 2010 - 2015, Prof Pokrowsky continued.

He ended his lecture with a proposal for an organisation of a high level national committee and the development of a national strategic plan.

– We need a combination of traditional psychotherapy of drug abusers, with harm reduction programs for all drug abusers and substitution therapy for opium addiction. We also need safe sex education at schools – and for older population at their workplace, Prof Pokrowsky summarised.

A pathogenic cycle
Plenary Session II was on T-cells. Dr Warner Green, USA, gave a lecture on CD4 T-cell depletion in HIV-1 infection.

He described pyroptosis – an intensely inflammatory form of programmed cell death, mediated by activation of caspase-1 in inflammasomes.

– Cell-to-cell pathways are required for induction of pyroptotic cell death pathway. The major “killing unit” of CD4 T-cells during HIV infection is infected cells, rather than cell-free virions, Dr Greene established.

Most CD4 T-cells die during HIV infection because of an innate immune response against the virus, instead of a toxic effect of the virus. Cell death involves caspase-1 dependent pyroptosis.

– A pathogenic cycle of abortive infection, pyroptosis, inflammation and new cell recruitment is established, resulting in a “grist mill” for depleting bystander CD4 T-cells. Caspase-1 inhibitors can break this cycle, and thus form a new, host-directed anti-AIDS therapy complementing virus-directed ART.

DNA-sensing, inflammasome assembly and caspase-1 activation and type I IFN production are all orchestrated by a single protein – IFI16. Blood CD4 T-cells resist pyroptosis apparently due in part to reduced reverse transcription, i.e. less DNA to be sensed, and reduced expression of IFI16.
This likely explains why the pyroptotic death pathway remained undetected so long, Dr Greene said.

His last point was that cell-to-cell transmission is obligately required for the induction of pyroptosis – cell-free virions do not suffice.

The power of multidisciplinary approaches
The last Speaker on the first day was Dr Annika Karlsson, Sweden. She presented data from a study just published the week before the Conference. The topic was the CD4/CD8 ratio as a predictor of T-cell activation in treated and untreated HIV infection.

In her summary, Dr Karlsson said that the CD4/CD8 ratio was identified as the preeminent laboratory predictor for combined T-cell pathogenesis in HIV infection. Markers of immune activation – CD38, HLA-DR and PD-1 – were particularly expressed within these unique T-cell populations.

- Flock analyses showed that it was specific activation and exhaustion profiles of early differentiated memory clusters that were linked to the immunopathogenesis of HIV infection, she continued.

Low CD4/CD8 ratio during ART is associated with persistent immune activation and senescent profiles of T-cells.

- This study highlights the power of multidisciplinary approaches, integrating complex immunological data with bioinformatics, to understand the mechanisms underlying T-cell dysfunction and pathogenesis, was the first of her conclusions.

The CD4/CD8 ratio can be used as an adequate biomarker for monitoring the state of immune dysfunction, and morbidity/mortality in long-term treated HIV-infected individuals, was her second conclusion.

- This multiplex approach is of particular interest for future clinical, therapeutic vaccine or cure studies – in which multiple markers are combined to understand pathological mechanisms of the T-cell repertoire in HIV-infected subjects, was Dr Karlsson’s final conclusion.

Gene therapy using adeno-virus associated vector
Last year’s most important achievements in HIV research were presented in the next Plenary Session. Dr Helene Mens, Denmark, started this by presenting the top 5 basic research.

The first paper was on clonal expansion and persistence of infected cells.

This study was published in Science, July 2014. The authors found 2410 integration sites, and 40 % of integration sites were in clonally expanded cells.

Their conclusion was that some HIV infected cells clonally expand. During cART, all the short-lived infected cells die, however some long-lived infected cells proliferate and the clones can persist for more than 10 years.

The second study was published in Nature, March 5, 2015. It was on gene therapy using adeno-virus associated vector. This was tested in SHIV macaques.

- None of the monkeys became infected after challenge – but all the controls were, she said.

The conclusion was that this was an effective gene therapy for intravenous infection. Some questions remain – about mucosal challenges, and if these findings can be translated into humans. But the findings could be a step towards gene therapy.

The first neutralizing antibody tested in humans
The third study was on whole-body immunopET. The study, published in Nature Methods no. 5 in May 2015, found this to reveal active SIV dynamics in ART treated macaques.

The conclusions were that this is an interesting and new way of measuring SIV replication. It is non invasive, and allows for longitudinal studies. It is however not useful to study the CNS.

- On translational possibilities to humans, there are radiation issues and the different subtypes of HIV to consider. The technique can not measure latent reservoirs – but changes in reactivity, and hence shed light on location, Dr Mens said.

The next study she presented was on the first neutralizing antibody tested in humans. The antibody is 3BNC117. This was presented in a Letter to Nature, June 25, 2015.

- It was tested in 17 patients, and was found to be well tolerated, and have a dose response curve. It effectively – at 30mg/Kg – suppresses viremia temporarily. The real cliffhanger here is if it can be used in a therapeutic setting, or gene therapy – possibly also for a therapeutic vaccine and for eradication.
The last study Dr Mens presented was on pyroptosis, as earlier presented by Dr Green at the Conference. It was published in Nature January 23, 2014.

- Anti-caspase-1 was found to be well tolerated. Could this be used as an addition to cART for CD4 non-responders? she summarised by asking.

Two drugs works as well as three

Dr Arild Mæland, Norway, then presented the top 5 clinical studies from 2014 - 2015. The first of these was from July 1 and published in Lancet Infectious Diseases. It is called the GARDEL study, and investigated whether dual therapy with lopinavir and ritonavir plus lamivudine is non-inferior to standard triple therapy. The findings were that this regimen warrants further clinical research and consideration as a potential therapeutics option for ART-naïve patients.

- My next study is actually two studies – SALT and OLE (both from Lancet Inf Dis 2015; 15).

SALT is a study on dual treatment with atazanavir – ritonavir plus lamivudine. OLE on lopinavir and ritonavir plus lamivudine.

- Again, they show that two drugs works as well as three. Ask yourself when you come to your clinic next week: Is my patient on one drug too many? Dr Mæland encouraged the audience.

The third study was on ledipasvir and sofosbuvir for HCV in patients co-infected with HIV-1, called ION-4. One pill, once daily for 12 weeks resulted in SVR 96 %.

- This result is absolutely fabulous! There is no control arm – these new regimens are so effective that you don’t need that, Dr Mæland stated.

ION-4 was published in August 2015 in New England Journal of Medicine 2015; 373.

All have benefit from early therapy

START was also published in NEJM. As hinted from the title, it was a study on initiation of ART in early asymptomatic HIV infection. 4,685 patients with CD4 above 500 were randomised to treatment or to wait until CD4 had dropped below 350. The endpoints were severe AIDS, severe non-AIDS or death. Both arms were monitored for in median 3 years.

- Is this relevant for my patient – a young Scandinavian woman, for example? No matter if they are young or old, black or white – all have a benefit of early therapy! But the number needed to treat is 120 patients for one year to benefit one endpoint, Dr Mæland underlined.

The final study he presented was very new – it was published online 20 days prior to the Conference (10th of September 2015). It was PROUD – an open label pre-exposure prophylaxis (PrEP) study on Truvada daily for 544 MSM randomised to an immediate arm, or to wait one year.

- The result was 3 versus 20 infections! And importantly – no increase in other STDs was found. The number needed to treat is 13 for one year.

Dr Mæland summarised the arguments against PrEP (drugs to healthy people, low compliance, risk of developing resistance and risky behaviour and no effect against syphilis). He stated that the same things could be said against malaria prophylaxis in the form of mosquito-nets, which rendered him some laughter.

- PrEP is coming to a pharmacy near you – whether you like it or not, he ended his presentation.

A big problem many are working on

Prof Robert Siliciano, USA, talked in the next Plenary session about reversing HIV latency.

- When HIV cells are removed from presenting antigen, they go to rest – and this is causing the latent reservoir, he explained.

He stressed that latently infected cells are a very small proportion of cells.

Prof Siliciano described the famous cases of Boston patient B, and the Mississippi baby – both took a very long time before they rebounded. This is a proof-of-concept for latency.

Can we find drugs to reverse latency without global T-cell activation? Numerous latency reversing agents (LRAs) are identified in studies with transformed cell lines and primary T-cell model systems.

- But few are shown to work ex vivo with cells from patients. In clinical trials, no reduction of the reservoir has yet been demonstrated, Prof Siliciano continued.

There are also several problems how to measure the efficacy of LRAs. This led him to the topic of different assays to do this.

- Defective proviruses accumulate rapidly in acute HIV infection. DNA PCR assays are widely used for reservoir ana-
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lisis – it mainly detects provirus with profound defects that arise during reverse transcription, he said.

Defective proviruses may respond differently to different eradication strategies. Assays involving a single round of T-cell activation miss some inducible replication-competent viruses.

– With current assays, we can bracket – but not precisely measure – the latent reservoir. It is a big problem, but many people are working on it, Prof Siliciano summarised.

Cancer and HIV cure research agendas are converging

HIV immunotherapy - Lessons from Oncology, was the title of Prof Steven Deeks, USA, lecture.

– When used optimally, ART can control HIV indefinitely, restore health and prevent transmission. But ART is not curative, he pointed out.

Despite effective viral suppression with reasonable benign ART, people remain at risk for a number of co-morbidities, including coronary artery disease and cancer. Chronic inflammation persists during ART and predicts these events.

– Multiple factors cause persistent inflammation during ART, he explained.

Cancer cells and HIV-infected cells are both “foreign” and should be readily cleared by the immune system. HIV disease is an inflammatory disease marked by potent immunosuppressive counter-regulatory responses. Immuno-inhibition is generally dominant over immuno-stimulation, and hence a more effective target, Prof Deeks continued.

The cancer and HIV cure research agendas are converging, with advances in cancer immunotherapy dramatically reshaping how we approach HIV disease, according to Prof Deeks.

– Interruption of the pathways that contribute to chronic inflammation during ART should reduce the immunosuppressive environment in tissues, thus allowing the adaptive immune system to work better.

The immune evasion mechanisms are remarkably similar: ICB upregulation, release of immune suppressive cytokines and expansion of immune suppressive cells.

– Immunotherapy is revolutionizing cancer therapy, and could have comparable effects on HIV, he concluded.

Successful ageing

Prof Giovanni Guaraldi, Italy, talked about HIV and ageing. He started by underlining that there are approximately 4.2 million persons aged 50 years or older living with HIV today – and half of them live in sub-Saharan Africa.

– And people acquire HIV at an older age. In 2003, the median age at HIV diagnosis was 35 years. In 2012 it was 43 years, Prof Guaraldi said.

When we today state that life expectancy for a HIV-infected individual will be close to what is expected in the normal population, there may be a survival bias: The current older population of HIV-infected individuals, survived the pre-ART and early ART eras, and may be enriched for favourable host genetics and healthier lifestyles than the general population, Prof Guaraldi said.

– All the others have died!

He urged the audience to look for frailty in their patients, as this is an indicator of the patient’s biological age.

– A study showed that frailty index predicts survival and incident multimorbidity independently from markers of HIV disease severity among people ageing with HIV. But frailty is not mentioned in our guidelines...

Prof Guaraldi ended his lecture by talking about successful ageing.

– It is not only all about disease, but also about the absence of cognitive, physical, spiritual and emotional co-morbidities.

Resistance testing is valuable

Transmission of HIV with resistance mutations is very clinically relevant, since they may compromise first line treatment. They are detected by sequencing of pol gene.

The prevalence of transmitted drug resistance (TDR) is 10 - 15 % in Europe and USA. In Sweden 2003 - 2010 the prevalence was 5.6 %. We see an increasing prevalence in Eastern Africa (7.4 %) and in Southern Africa (3.7 %). Non-nucleoside reverse-transcriptase inhibitors (NNRTIs) mutations are the most common, said Dr Emmi Andersson, Sweden.

She presented a study that had investigated the prevalence, characteristics and trends of TDR in ART naïve patients diagnosed in Sweden 2010 - 2014.

– We found an overall prevalence higher in MSM. Nucleoside reverse transcriptase inhibitors (NRTIs) surveillance drug resistance mutations (SDRMs) are more common in patients infected in Sweden, whereas NNRTI SDRMs are more common in patients infected in sub-Sahara, Dr Anderson reported.

There was a significant increase in TDR over the study period. This is due both to clonal spread of virus with NRTI muta-
tions among MSM in Sweden, and increase of TDR among migrants from Sub-Saharan Africa.

- It is easy to conclude that resistance testing is valuable in both MSM in Sweden and in patients infected in sub-Saharan Africa, Dr Andersson summarised.

**HIV established as an endemic infection in Iceland**

The reporting of HIV in Iceland started in 1985. By the end of 2014 there had been 321 infections, 67 cases of AIDS and 39 deaths. The molecular epidemiology of HIV-1 in Iceland has not been characterized so far.

Dr Malik Sallam, Sweden, presented a study that aimed to do this. Partial HIV-1 pol sequences were generated from 230 Icelandic samples collected between 1996 and 2013, representing 77% of all HIV infected individuals reported in Iceland between 1985 and 2012.

In his conclusions, Dr Sallam stated that HIV-1 has been established as an endemic infection.

- HIV-1 was introduced there at least 144 times as early as in the 1970s. Its genetic diversity increased significantly over time. It is still dominated by subtype B for domestic spread among MSM and intravenous drug users. The recent increased incidence in the latter group was due to two separate introductions, Dr Sallam summarized the findings.

**Tracing transmission clusters in the Nordic countries**

*HIV-1 transmission from MSM to heterosexuals and increasing proportions of circulating recombinant forms in the Nordic countries* was the title of a study presented by PhD Joakim Esbjörnsson, UK/Sweden.

The study aims were several: To combine epidemiological and sequence information to study subtype distribution and time trends, cluster types and dissection of geographic and transmission group dispersion.

HIV-1 pol sequences and clinical data of 51% of all newly diagnosed HIV-1 infections in Sweden, Denmark and Finland were analysed.

- Subtype B is still the most common HIV-variant. Even if it seems to decrease over time, it is still the dominating form of HIV-1 in the Nordic countries, Dr Esbjörnsson said.

He also told the audience that their results indicated several cases of MSM to heterosexual HIV-1 transmission.

- Analysis of sequence data, combined with clinical and epidemiological data, can be used to dissect and trace the HIV-1 transmission history on the country level – to inform and make future prevention strategies more effective, was his conclusion.

**The evolutionary process of HIV**

Prof Jan Albert, Sweden, presented a study on whole-genome population genomics of intrapatient HIV-1 population.

Within an infected host, HIV-1 rapidly accumulates mutations – in part to evade immune recognition. To characterize this evolutionary process, they performed whole genome deep sequencing of HIV populations in 9 untreated patients with 6-12 longitudinal samples, spanning 5-8 years of infection.

- This project is one of the most complete portraits of intrapatient evolution of HIV-1 to date, Prof Albert established.

Intrapatient variation mirrors global variation. Cytotoxic-T-lymphocyte (CTL) escape is an important driver of evolution.

- We have a very high rate of reversion towards global consensus following transmission to the new host. HIV-1 is an extensively recombining population – in a constant battle between immune evasion and maintenance of virus function.

Prof Albert finished his talk by saying that further analyses are ongoing, and that website access to processed data is planned.

**No difference for STRs versus three tablets**

Dr Andrew Hill, UK, gave a lecture on cost savings from switching to generic antiretrovirals.

Basic drug patents last for 20 years. Additional “evergreen” patents can extend the time when only pharmaceutical com-
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panies can sell drugs, he said.

- There are "evergreen" patents on co-formulation of drugs, which can last for over 10 years after the patents on the individual drugs have expired. That "evergreen" patent is important for HIV, Dr Hill continued.

He described a systematic PUBMED/EMBASE search that had identified open-label randomised trials comparing co-formulated antiretrovirals with individual components.

- We compared single tablet regimens (STRs) versus three pills per day, Dr Hill explained.

The conclusion was that if you look at virological failure, there was no difference for STRs versus three tablets.

- Pharmaceutical companies have not conducted randomised trials to evaluate the potential benefits of using STRs versus individual drugs in naïve patients. The only available evidence from switch studies suggests no benefit for STRs in terms of virological failure or drug resistance. Evidences from cohort studies are conflicting, and subject to biases in patient selection, Dr Hill said.

The use of generic individual antiretrovirals could potentially save the National Health Service in UK 1.25 billion pounds over the next five years, compared with the use of patented high-cost STRs.

- The cost-effectiveness of STRs versus 2 - 3 pill combinations of generic antiretrovirals has not been established, Prof Hill stated at the end of his lecture.

Wide variation in the prevalence of TDF resistance

The largest study ever undertaken on tenofovir (TDF) resistance was presented by Dr Ravindra Gupta, UK.

- TDF is now the preferred NRTI as first line cART, and also the preferred anti-HBV drug. In addition, TDF is used in PrEP and multiple STRs contain TDF. A scale up for TDF globally is occurring, Dr Gupta pointed out.

It was a retrospective, multi-centre study that aimed to quantify regional prevalence of TDF resistance, identify risk factors for TDF resistance and to assess transmission potential of TDF resistance.

- We found a wide variation in the prevalence of TDF resistance, sub-Saharan Africa has the highest burden. Applying published estimates for virological failure, 9 - 21 % have high level TDF resistance after 1 year in sub-Saharan Africa, Dr Gupta said.

The study found that the immune status predicts risk of TDF resistance. Nevirapine versus efavirenz carries higher risk for TDF resistance, and so does lamivudine versus emtricitabine.

- We have also shown that TDF resistance viruses have similar in vivo fitness as TDF sensitive viruses. Finally, TDF resistant viruses usually carry multi-drug resistance, was Dr Gupta's conclusions.

IDUs achieve similar SVR and compliance rates

The last day of the Conference was dedicated to Hepatitis C (HCV). The first speaker was Dr Hannah Woodall, UK, who talked about HCV treatment as prevention among injection drug users (IDUs).

The main interventions for this group are needle and syringe provision (NSP) and opiate substitution therapy (OST).

- But on HCV transmission there is weak evidence that NSP and OST are effective, she said.

However, according to pooled survey data from England, Wales and Scotland an ongoing systematic review suggests that OST decreases HCV transmission risks by
58%, and NSP by 61%.

Few (less than 1%) of IDUs have been treated for HCV with previous regimens. The reason for this has been concerns over potential non-compliance and re-infection, Dr Woodall explained.

- However, the evidence say that IDUs achieve similar sustained virologic response (SVR) and compliance rates as non-, or ex-IDUs, she underlined.

**Current treatment regimens need to be scaled up**

Dr Woodall presented a model that estimated the impact of current and scaled-up treatment rates on chronic HCV prevalence in 11 selected countries. The model used collected site specific data to estimate key parameters, including people with injecting drug use, OST/NSP coverage and treatment rates.

She then continued by presenting some examples from some countries, and started with Norway.

- Continuing treatment at current levels project a 0.8% decrease in chronic prevalence. Switching to direct-acting antivirals (DAAs) increases this decrease to 2%. Switching to DAAs and doubling current treatment levels projects a 6.1% decrease in chronic prevalence in 10 years.

Dr Woodall compared this with Czech Republic. There the model predicted a decrease by 18.6% at current levels, switching to DAAs increases this to 33.3% – and doing this and also doubling current treatment, projects a decrease of 81.5%.

- Across most sites in Europe, it is likely that current treatment regimens will need to be scaled up in order to have a large impact on chronic prevalence, she summarised.

A combination of OST and NSP and HCV treatment can have a substantial impact on decreasing prevalence, Dr Woodall added.

**Attempt to eradicate HCV from an entire country**

In Georgia they are working on a program to eliminate HCV.

- Georgia will be the first country free of HCV, said Dr Lali Sharvadze, Georgia.

The country has an area of 69,700 km2, and a population of 3.7 million. The prevalence of HCV is 6.7%.

The pharmaceutical company Gilead’s CEO John Martin and Prime Minister of Georgia Irakli Garibashvili signed a memorandum of understanding on the 21st of April 2015. In this, Gilead committed to provide sofosbuvir and ledipasvir/sofosbuvir free of charge to this program.

- The rationale for choosing Georgia as a model country for HCV elimination is that there is a high prevalence of HCV infection in the general population, Dr Sharvadze explained.

It is also a small country, has a strong governmental commitment for controlling the HCV epidemic, all modern HCV diagnostic and treatment methods are available and Georgia has a strong human resource capacity in the field of HCV.

The goal is simple: Elimination of HCV infection in the country – i.e. zero new infections! This shall be done through identifying and treating all HCV patients, and through wide-scale implementation of prevention interventions.

- The program has two phases. Phase 1 is the development and implementation of the initial and urgent activities. Phase 2 is the development and implementation of a long-term strategic plan of action, Dr Sharvadze said.

At present (i.e. 2015) they are in Phase 1. This includes treating 5 000 patients – those with F3 or F4 fibrosis, severe extrahepatic manifestations and those with HIV/HCV co-infection.

Phase 2 is going to last from 2016 – 2020. Then a large scale combination HCV prevention strategy will be implemented – including seeking, testing and treating.

**Testing more - finding fewer**

Dr Sofie Hallager, Denmark, presented a study on the prevalence of HIV co-infection among patients newly diagnosed with chronic hepatitis B (HBV) and HCV in Denmark. It was a nationwide cohort study.

- HIV, HBV and HCV have shared routes of transmission. Co-infection with HIV leads to a more rapid progression of liver disease. But there are few studies estimating the HIV prevalence in viral hepatitis patients, she said.

The conclusions were that the prevalence of HIV co-infection was relatively low, especially in recent years. HIV prevalence fell over time – from 7.9% in 2002 to 1.3% in 2012.

- We saw an improved testing frequency in the same period. The take home message is that we are testing more individuals, and finding fewer, Dr Hallager pointed out.

**Care centre causes good retention to care**

Dr Susan Simola described a care model with good retention yielded to control the...
HIV outbreak among IDUs in the Helsinki area.

Before 1998 there were very few cases of HIV among IDUs in the Finnish capital. An outbreak that year changed this, she told the audience.

– At the end of the year 2000, a comprehensive care centre for HIV infected IDUs was opened in Helsinki.

The aims of the centre were to provide a place where IDUs were welcomed and not condemned for their lifestyle, to make contact with them. The Munkkisaari care centre provided a basic package with all the essential services – including washing facilities, nursing services, addiction- and infectious diseases physicians among others.

– The immediate effect of the opening of the centre was a sharp rise of patients retained in care. 53 % were retained in care before the end of December 2000. Over 90 % were retained by 2003, Dr Simola reported.

The coverage of ART in the cohort exceeded 50 % by 2005, and retention in care has since then remained over 90 %. In 2014, the coverage of ART was higher than 90 %.

– An increasing number of patients are transferring from the centre to the clinic. Those who still use the centre are the most at risk of falling out of care – these patients need constant support in carrying out HIV treatment, Dr Simola stated.

All possible influencing factors should be considered before starting treatment

Optimal HCV regimen for care, was the title of a lecture given by Dr Johannes Vermehren, Germany.

– We have all been overwhelmed by the success of the DAAs, he said.

Approved DAAs have a good safety profile, are well tolerated and have very high SVR. The only exceptions are patients with genotype 3 and cirrhosis.

– There’s a gap in the results there. They have a lower chance – 60 - 70 % – to achieve eradication, Dr Vermehren continued.

How to make the new DAAs accessible and affordable is the main obstacle to overcome at present.

Patients with resistance associated variants (RAVs) have a higher chance to reach SVR. Baseline RAVs are present in 10 – 30 % of untreated patients. RAVs are common after DAA failure.

– Resistance testing should probably not be performed in all patients. But it may be feasible especially in patients with planned short treatment, with cirrhosis and in those with treatment experience.

Ribavirin is still required in many subgroups, and may be required for all, or most, DAA failures. Long treatment duration is rarely needed, but probably standard in DAA failures, Prof Vermehren said.

– To sum it up, all possible influencing factors should be considered before starting treatment: Resistance, HCV subtype, cirrhosis, prior treatment, use of ribavirin and treatment duration. The first treatment is the optimal regimen for cure, he ended his talk.

Treating mild HCV makes sense

– The new drugs are spectacular, said Prof Graham Foster, UK.

He added that this is now being confirmed by data from the real world.

– But they are going to cause many more patients in our wards – and it is going to be very hard to convince politicians to treat them.

The title of Prof Foster’s talk was Expanding HCV therapy to mild disease.

– The virus causes progressive disease – the more you wait, more patients will get cirrhosis, and then you’re in trouble, he said.

Progression can be slow, then flare up and progress quickly. Therefore all patients need follow-up.

Treating mild HCV makes clinical, economic and public health sense. A NICE review 2015 supports treating early disease.

A research article published in Journal of Hepatology concluded that HCV eradication has a beneficial effect on cerebral metabolism and selective aspects of neurocognitive function, and is an important factor when contemplating anti-viral therapy in HCV, especially in those with mild disease.

Prof Foster also reminded the audience that HCV is infectious.

– All those who are infected are worried about transmitting HCV to their loved ones. Dead virus doesn’t transmit – so why don’t we kill them all?

Prof Foster ended by saying that we can not treat everyone at once.

– We will therefore need some degree of prioritisation.

IFN or NUC therapy for HBV

Prof Pietro Lampertico, Italy, talked about treatment for hepatitis B virus (HBV) in 2015.
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– There are two therapeutic strategies: Short term “curative” treatment with interferon (IFN), or long term “suppressive” treatment with a nucleos(t)ide analog (NUC), he said.

Quantification of HBsAg levels is an accepted clinical tool to determine response to treatment. Regular monitoring is recommended by both EASL and NICE guidelines. HBsAg seroconversion is considered the optimal goal of antiviral treatment – it indicates resolution of chronic HBV infection.

IFN therapy for 48 weeks gives a sustained response in 20 – 40 % of patients. There are week 12 stopping rules, based on HBsAg levels. The therapy reduces complications and improves survival.

NUC therapy (5 - 7 years with entecavir or tenofovir) results in more than 95 % of viral suppression and 85 % with normal alanine aminotransferase (ALT) levels. Decompensation and portal hypertension are improved.

– PegIFN is aimed to clinically cure HBV. NUC therapy is aimed to suppress HBV, Prof Lampertico underlined.

There are two European multicenter studies on adding a PEG in long-term NUC treated patients. They demonstrated continued.

– Therefore surveillance is needed in patients with high risks, Dr Aleman continued.

EASL and AASLD guidelines recommend HCC surveillance with ultrasound every 6th month for patients with F3 fibrosis and F4 cirrhosis.

Antiviral therapy has a protective effect against HCC. For patients with liver cirrhosis and achieved SVR, the HCC risk decreases from 4 % to below 1 % per year.

– This is low, but there is a remaining risk for HCC patients with liver cirrhosis prior to treatment. They should therefore continue with HCC surveillance after SVR, she pointed out.

This will be a growing problem in the era of DAAs. Only time will tell how risk prevails after SVR.

– Among cirrhotic patients with SVR, the risk of HCC was associated with age, severity of liver disease and diabetes mellitus, Dr Aleman ended her talk.

Health systems barriers in low-resource settings

The last speaker at the Stockholm Conference was Prof Anna Mia Ekström, Sweden. Her topic was HCV and HIV in resource limited countries.

– 185 million people in the world are living with HCV, and there are 3 - 4 million newly infected every year. 36.9 million are HIV-infected, and 2 million are newly infected every year, Prof Ekström said.

Approximately 700,000 dies from HCV and 1,200,000 from HIV.

– While some efforts have been made to reduce the price for drugs for low-income countries, without uniform strategies to make these medicines more affordable globally the potential for public health gains will be reduced considerably, Prof Ekström quoted WHO assistant director-general for health systems.

She described the health systems barriers in poor resource settings. They need effective policy implementation, financing at district or hospital level, drug distribution systems procurement and information systems.

– They also need trained staff. How much can unpaid community health workers really be expected to do? They also need lab capacity – viral loads take 2 - 16 weeks to measure.

We also need to come away from monthly refills – time and income is lost through transport and queuing. Stock-outs still occur – which causes resistance and patients to give up.

– We need medical-pharmaceutical break-through innovations: Monthly injections, point of care tests of viral loads, a cure or vaccine also for HIV and more effective procurement systems!

She ended her talk by reminding that prevention is always more cost-efficient than treatment.

Then the Conference was over. Professor Anders Sönnerborg from the Organizing Committee thanked all Speakers and delegates that had come to Stockholm.

– We have decided to come back next year for a new HIV and Hepatitis Conference in Stockholm 28 - 30 September. Read more on www.hivnordic.se. We are looking forward to see you then!
Satellite Symposiums at the HIV and Hepatitis Nordic Conference

At the Conference in Stockholm six industry sponsored were held.

In the first of these, Dr Allison Ross Eckard, USA, talked about Inflammation and immune activation in HIV. It was sponsored by Gilead.

Long-term ART may increase cardiovascular risk
For every decade, people with HIV develop more co-morbidities compared to the general population, Dr Ross Eckard started by saying.
- HIV infected with well controlled disease have greater arterial inflammation – so they are at higher risk for cardiovascular disease. Lipopolysaccharid levels are also higher in treated HIV, versus controls, Dr Ross Eckard continued.

Circulating microbial products, derived from the GI tract, are a cause of HIV-related systemic immune activation.
- Effective ART partially reduce microbial translocation, but it does not go away.

HIV infection is an independent risk factor for many comorbidities. Increased inflammation and immune activation underlie many of these conditions.
- Combination ART partially decreases inflammation and immune activation, but levels do not return to normal, Dr Ross Eckard said.

Hence long-term ART may increase cardiovascular risk.

Dr Ross Eckard talked about the Gilead 102 sub-study, which showed there is a more favourable effect of elvitegravir compared to efavirenz on immune activation that may affect vascular inflammation.
- So certain antiretroviral drugs may be associated with a differential effect on comorbidity risk. This effect may be partly mediated via inflammatory and immunologic abnormalities.

Comorbidity risk assessment should be considered when choosing an antiretroviral regimen for patients, was her conclusion.

The Swedish cascade of care
The evolution of modern HIV treatment – factors that influence and what it means in clinical practice, was the title for a symposium. It was sponsored by Janssen.

Dr Anton Pozniak, UK, talked about factors that influence treatment.
- We now know that the START trial has established that ART should be started at any CD4 count. It is important to recognize that the absolute risk of deferring therapy may be one that an HIV-positive individual is reasonably prepared to accept in the short term, he said.

Dr Pozniak pointed out that women are usually under-represented in clinical trials. He also said that non-inferiority trials – of which there are many ongoing now – carry several challenges.
- It requires a high quality trial! Poor execution and weak control favours non-inferiority!

He talked about the problem with snapshots from trials.
- It could be taken during a blip – then the result is a failure. It could be after a rebound – then it shows a success!

Prof Magnus Gisslén, Sweden, talked about the Swedish cascade of care.
- The public health agency of Sweden have recently approximated that more than 90 % of all HIV-infected in Sweden are currently diagnosed by using ECDC estimating tools, he said.

The linkage to care is very high – 99.9 %. - The Swedish Communicable Diseases Act states that patient must attend the repeat visits and tests which the doctor considers necessary. We have the capability to force them into care!

More than 90 % stays in care. The dropouts are patients that move abroad, die or are lost to follow up. At the time for the Conference, 6 902 patients were in care in Sweden.
- 95 % of all patients in care are on treatment and of those 95 % have a viral load <50 copies/mL in a snapshot ana-
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lysis. Most of the others probably had a blip. With those calculations, 81% of all estimated HIV-cases in Sweden have suppressed viral load – which means that Sweden meets the UNAIDS 90-90-90-targets, Prof Gisslén ended his talk.

Positive action for adolescents

In a symposium sponsored by GlaxoSmithKline and ViiV healthcare the STRIVING study was presented. It was conducted to evaluate the efficacy, safety, tolerability and treatment satisfaction of switching to Triumeq in subjects stable and suppressed on a variety of regimens.

Triumeq is the first tenofovir-free single pill regimen that contains dolutegravir.

The conclusions from the study were presented by Dr Els Hollanders, Belgium.

– Switching to Triumeq met non-inferiority endpoints for all population analyses, and was demonstrated to be safe and effective, she said.

No subjects met the protocol-defined virologic failure endpoint through 24 weeks. Discontinuations due to adverse events in the Triumeq arm were infrequent and mostly due to low grade adverse events.

– Greater improvements in treatment satisfaction were demonstrated in subjects switching to Triumeq, was Dr Hollanders last conclusion.

Anna Lawson spoke about Positive Action Europe.

They support patient advocacy groups focused on patient empowerment and education, increasing testing for early diagnosis and addressing emotional and societal issues.

– A new ViiV healthcare grant programme was launched this year – positive action for adolescents, she continued.

Most adolescents are unaware of their HIV status. The programme is focussed on key adolescents in South Africa and sub-Saharan Africa.

– The grants are to support evaluation of the impact of new behavioural and service delivery interventions in specific areas of focus, and to build capacity of adolescent community leaders.

The symposium ended with a patient’s story from Ms Ophelia Haanyama.

– First of all I’d like to say that I’m still alive – not only alive, but actually living, she said.

Ms Haanyama ended the symposium by speaking with both pathos and frankness about how she got her HIV infection, and her experiences from living with it.

New direct acting antivirals 2015

Prof Mark Nelson, UK, talked about HIV/HCV co-infection in a symposium sponsored by Abbvie.

– Things change. We don’t talk about death at HIV congresses any longer. Patients die with HIV – not from HIV. That is an enormous difference, he said.

Today patients die from other causes – co-morbidities. The liver is constantly under attack, Prof Nelson continued.

Patients with HCV can get their liver decompensated, risk hepatocellular carcinoma or other liver-related events. Data shows that in HIV/HCV co-infected subjects SVR is associated with decreased morbidity and mortality.

– So it is important to treat these patients.

Direct-acting antivirals (DAAs) against HCV can be divided in three categories: Protease inhibitors (‘...previrs). NS5A inhibitors (‘...asvirs”) and polymerase inhibitors (‘...buvirs”).

– When choosing a drug, we need to have a high resistance barrier, Prof Nelson underlined.

He presented new DAAs available from 2015. For genotype 1 - 4, there is a fixed dose combination of dasabuvir, ritonavir and ombitasvir, with or without ribavirin available. For multigenotypic there is a fixed-dose combination of sofosbuvir and ledipasvir, with or without ribavirin.

– In clinical trials, there is no difference in SVR between HCV co-infected and HCV mono-infected patients.

He ended by presenting a calculation of the future toll of illness if we don’t treat HCV. By 2035, the most common health complications associated with HCV will increase by 89% for compensated cirrhosis, 80% for decompensated cirrhosis, 160% for liver-related deaths and 205% for liver cancer.
Action speaks louder than words – we must test and treat HCV, was Prof Nelson final message.

**Strategies in Spain and Scotland**

National action plans on the fight against HCV were presented in a symposium sponsored by Gilead. First Dr Maria Buti, Spain, presented the Spanish strategy. The aim is to reduce HCV morbidity and mortality in the Spanish population.

- Restriction on access for new drugs caused demonstrations and high media attention. Scientific associations called for a national plan for HCV. In January 2015, the new Minister of Health decided to change the direction of HCV policy – a national plan, Dr Buti explained.

786 million euro in additional investment has been reserved for 2015 - 2017, when the plan is in its first phase.

Scotland has now reached the fourth phase in its HCV action plan. Professor David Goldberg, UK, talked about lessons learned and future approach.

He presented a modelled incidence of advanced liver disease among those with chronic HCV in Scotland, according to different treatment strategies. This showed that if the annual number initiated on therapy from 2015 and onwards is 1500, a decrease of liver cancer and end-stage liver disease will decrease by 75 %.

The plan has been in place since 2008, and Prof Goldberg presented some selected key principles, based on their experience.

- Prioritise initiatives to diagnose and re-diagnose those in most urgent need of therapy. Only optimal therapies should be offered, and aim to deliver in community settings!

Phase 4 of the plan will continue until 2020.

- The overall strategy is to make progress in eliminating Hepatitis C as a serious health concern, said Prof Goldberg.

**High SVR rates in difficult to treat patients**

Real world data on treatment of chronic HCV patients – advanced disease and genotype 3, was the title of the last satellite symposium. It was sponsored by Bristol-Myers Squibb.

Prof Olav Dalgard, Norway, talked about genotype 3 infection. He presented a study on the effect of sofosbuvir containing regimens with HCV genotype 3 infection – a Scandinavian real-life experience.

- The primary aim was to assess the effect of these regimens seen in our daily practices. The secondary aim was to identify potential predictors of treatment failure.

All patients seen at one of the 16 participating hospitals in Norway, Denmark, Finland and Sweden who received at least one dose of a sofosbuvir containing regimen were included.

- SVR4 was achieved in 213 of 232 – which is 92 %, Prof Dalgaard said.

Prof Ola Weiland, Sweden, talked about real world clinical experience of daclatasvir.

- The all or allal regimen of daclatasvir + sofosbuvir with or without ribavirin achieved high SVR rates in HCV genotype 3-infected patients with high risk of hepatic decompensation or death, he said.

Prof Weiland underlined that 91 % of patients with cirrhosis – which included patients with decompensated cirrhosis and treatment-experienced patients – achieved SVR12. There was no virologic breakthrough.

- The regimen was generally safe and well tolerated, with few discontinuations due to adverse events.

These preliminary results show that the all oral regimen of daclatasvir + sofosbuvir, with or without ribavirin, represents a safe and effective treatment for patients with genotype 3, including those most difficult to treat, he concluded.

- Further evaluations will provide additional insights on the optimal duration of treatment, and the role of ribavirin in patients with advanced cirrhosis.
The T-shirt needs help. Because the cotton crop it’s made from absorbs thousands of litres of water. WWF is helping farmers grow thirsty crops, like cotton, rice and sugarcane, more sustainably with less water. This takes the pressure off freshwater ecosystems, benefiting people and nature. We also help businesses understand the amount of water in their raw materials and final products, so they can be more efficient, and look after nature as well as their bottom line. Help us look after the world where you live at panda.org/50
I can’t sleep

Sleep is that golden chain that ties our health and our bodies together. The Dalai Lama has described sleep as the best meditation. Yet, commonly, our patients complain of sleep disturbances.

Attempts to estimate the prevalence of sleep disturbance suggest sleep problems amongst people with HIV are more common than in the general population [1]. Many factors are at play and the high prevalence of reports of sleep disturbance suggest both disease and treatment factors may be critical. Additionally, insomnia has been associated with poorer disease outcomes because it adversely affects immune status and medication adherence. Furthermore, poor sleep is associated with increased fatigue and comorbid psychiatric disorders including anxiety and depression, leading to reduced quality of life.

The most commonly used scale to investigate sleep disturbance and insomnia is the Pittsburgh Sleep Quality Index (PSQI) or variations of it. Polysomnography has rarely been conducted in HIV patients and those that have, including our own [2], suffer from small sample size, lack of comparator arm and probability of repeat administration effects (the subject has more disturbed sleep the first time they sleep with the probes on, making the baseline assessment an overestimate of sleep disturbance and potentially missing treatment effects).

Mood Disorders
Psychiatric symptoms and mood disorders are common amongst people with HIV for a constellation of reasons and may be both a cause and effect of sleep problems. Individuals with any chronic illness have more anxiety and depression than the general ‘well’ population but this is further exacerbated by the perceived stigma of HIV infection. HIV infection is over-represented in subgroups of society that may further be stigmatised, such as migrants, LGBT and individuals with a history of injection drug use. These groups may also suffer relative social isolation and in some cases marginal housing and low income that further add to the risks of mental illness.

Substance abuse is a particular risk factor for sleep disorders and mental illness, be it the use of excess alcohol, heroin, powder and crack cocaine or as more recently seen with the rise of ‘chem sex’ amongst (mostly) a subset of urban gay men, drugs including crystal methamphetamine, mephadrone, GHB, amphetamines, ketamine and various other previously obscure chemicals. Many of these chemicals are associated with unfavourable changes in sleep architecture (alcohol, marijuana), insomnia and diminished sleep (cocaine, amphetamines, ecstasy) and hallucinogenic effects (ketamine, marijuana). Additionally, mental illness and substance abuse are often interrelated in a ‘chicken and egg’ way, as mental illness may lead to substance abuse and visa versa.

Thus a ‘perfect storm’ of factors for mental illness and sleep disturbance exists in many people affected by HIV.

Mood disorders commonly present as sleep disorders and sleep disorders may contribute further to low mood and anxiety as well as the fatigue, inertia and anhedonia that accompany depression. Some of these symptoms are thought to be related to the role of serotonin in sleep regulation, patients often reporting a rapid improvement in sleep and psychomotor retardation after starting on a SSRI antidepressant. Laboratory induced sleep deprivation leads to both low mood and proinflammatory cytokine profiles underlining the close inter-relation between sleep and mood. Furthermore, the perception of being ‘stressed’, another common self-report amongst people with HIV, may also manifest as sleeplessness.

Addressing sleep disorders is a key component of managing anxiety and depression and may help prevent mood disorders and assist in the management of substance abuse problems. Resolution of sleep problems is often a clear sign of improvement in mood and well-being.

Physical problems
People with HIV may have a range of physical ailments, sometimes as a result of past HIV-related illness that may disturb sleep. Chronic pain problems, such a neuropathic pain, may be particularly problematic and require specialist intervention to manage. Fat loss and loss of muscle mass may make it difficult to find comfort in bed and may further increase the risk of mechanical pain such as back or knee...
pain. Furthermore, diabetes is more common in persons with HIV and sleep broken by the need to micturate may signal the onset of the osmotic symptoms of diabete. Naturally, as our patients age male subjects may also be prone to prostatism with nocturia, again symptoms that warrant investigation due to the high rate of prostatic malignancy generally that may be higher amongst men with HIV. Finally, aging itself is associated with greater periods of nocturnal wakefulness, shorter sleep cycles and diurnal sleepiness that may present in the clinic as sleep or mood disorders or reports of cognitive impairment.

**HIV and effects of immune deficiency and cytokines on sleep**

HIV infection is associated with immune dysregulation and a ‘cytokine storm’. The immune system is connected to the sleep regulatory system [3] and actions of the immune system in response to infection affect sleep architecture and duration possibly through altered metabolism of neurotransmitters [4]. This may explain evidence that sleep disorders being exacerbated by advanced HIV disease. Similarly, sleep restriction and deficit increase vulnerability to disease. Sleep is regulated partly by cytokines. The immune system has a circadian rhythm with CD4+ T-cells and levels of proinflammatory cytokines being high during the night and leukocytes and the anti-inflammatory cytokine IL-10 rising during daytime. The rise in proinflammatory cytokines triggers fatigue and may encourage resting as an adaptive response to infection, but this becomes counter productive in chronic illness. Inflammatory cytokines are also likely to be responsible for the sleep-disrupting night sweats often reported by people with HIV infection regardless of CD4 cell count. Higher levels of IL-1 and TNF-alpha are known to reduce REM sleep and may make sleep lighter and less restful. Cytokines may also play a role in apnea during sleep, a major cause of chronic diurnal fatigue and a risk factor for myocardial infarction. Treatment of HIV, and a reduction in the proinflammatory state may therefore potentially help sleep.

Poor sleep also affects immune responses, most notably to vaccinations and has been associated with a range of conditions seen at increased frequency in people with HIV including diabetes mellitus, cardiovascular disease and malignancies. These events are increasingly seen as the main causes of morbidity and mortality, suggesting that managing sleep disorders may be a key contributor to improving overall health and reducing morbidity in people with HIV.

**Antiretroviral therapy**

Randomized studies and case reports have consistently described a variety of sleep disturbances with the use of antiretrovirals, in particular the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz and more recently with the integrase strand transfer inhibitor (INSTI) dolutegravir. It is to be expected that sleep changes after the initiation of therapy as starting therapy may be stressful, may necessitate changes in eating habits or other daily activities and clearly alters the cytokine environment. Treatment initiation may also be associated with other ‘health-seeking’ behaviours such as reducing alcohol or drug use and with accessing social security benefits that may reduce social and financial stresses.

The effect of efavirenz (and a structurally related NNRTI evaluated in phase 1/2) on sleep was noted in ‘entry into man’ studies and most commonly includes reports of insomnia, somnolence, dizziness, increased dream recollection, vivid or intrusive dreams and morning ‘hangovers’. Psychiatric disorders were also reported. ACTG 5095/5097 found sleep disorders, were more common with efavirenz based regimens, mainly in the first 4 weeks of therapy, relative to an all nucleoside regimen, AZT/3TC/ABC. The patients were tested at baseline, and then again at weeks 1, 4, 12 and 24 of therapy. The investigators found no significant differences in changes in neuropsychological testing at any time point among the patients who received or did not receive efavirenz. The symptom questionnaire, which was specifically designed to detect potential efavirenz-related side effects, detected significant increases in neurological symptoms at week one (P<0.001), but not at weeks 4, 12 or 24. Similarly, the Pittsburgh Sleep Questionnaire (PSQI) revealed more “bad dreams” at week one in the efavirenz-treated patients (P=0.038), but there was no difference between the groups at weeks 4, 12 or 24. Notably, relatively better global PSQI scores and “sleep quality” were found in the efavirenz-containing arm at week four, but again the significance of this finding disappeared by week 12. At no time point was there a significant difference between the patients who received or did not receive efavirenz regarding depressed mood or anxiety, nor in the proportion of subjects with clinically significant anxiety or high levels of depressive symptoms and there was no correlation between plasma efavirenz levels and mood [5]. However, increased risk of discontinuation of EFV was noted in a range of studies in individuals with a polymorphism in CYP2B6 associated with slower efavirenz clearance and higher exposure [6]. More recently, collated data from 5 randomised ACTG studies, have found efavirenz use to be associated with ‘suicidality’ (suicidal thoughts, attempted or completed suicides)[7]. This has not been observed in cohorts such as D:A:D, or other safety surveillance data. The differences in observation may relate to patient selection in clinical cohorts.
rather than random allocation in clinical trials and the patient demographics from which the ACTG draws its trial participants. Younger individuals with psychiatric illness and substance abuse problems were also independent risk factors for suicidality. This has lead to a change in DHHS guidelines, dropping efavirenz to an alternative, a move followed by the EACS guidelines committee. Efavirenz remains WHO recommended, in part due to cost and logistic reasons.

The mechanism by which CNS effects occur with efavirenz is not known, it interacts with serotonin type-2 as a partial agonist [8] and may alter neuronal bioenergetics. Data from sleep polysomnography studies suggested commencement of efavirenz was associated with greater amounts of time spent in phase 2 ‘light’ sleep and reduced deeper sleep phases [2, 8]. Phase 2 sleep is typically associated with ‘hypnagogic’ experiences, often recalled as dreams, which may be suggestible or semi-controllable, a typical report of efavirenz recipients. These effects were noted to persist on polysomnography at 3 months into therapy, despite an apparent ‘tachyphylaxis’ of clinical symptoms [2].

It is clear, however, from switch studies and indeed dose reduction studies such as the Encore 1 study with 400mg or efavirenz and a Taiwanese switch study which, pragmatically, used halved tablets (approximately 300mg) that the CNS effects of efavirenz are dose or plasma exposure dependent and readily reversible. Removal of efavirenz in switch studies leads to a reduction, but of course not elimination, of a wide range of symptoms including sleep disturbances (both insomnia and hypersomnia), dream recollection, dizziness, impaired concentration and mood disorders. These improvements do not seem to be only seen in subjects who report these symptoms, but apparently ‘normal’ subjects, individuals not overtly aware of any efavirenz effects, anecdotally, report a new and preferred normal after the replacement of efavirenz with alternatives such as rilpivirine, etravirine, raltegravir or Stribild. These observations are likely to lead to a steady decline in established efavirenz prescriptions as physicians encourage patients to move to newer alternatives.

The Single Study, a blinded placebo controlled study comparing ABC/3TC + dolutegravir (DTG) with TDF/FTC/EFV was notable in the excess of insomnia events in the dolutegravir arm (15% vs 10%) along with a range of other CNS disturbances in both arms albeit mostly at a lower frequency with dolutegravir then observed in the efavirenz arm [9]. Subsequently, a case series from France reported psychotic episodes in 4 subjects started on dolutegravir [10]. The EU and US labels for dolutegravir containing preparations including warnings around headache (listed as very common in the EU SPC), insomnia, abnormal dreams, dizziness and depression (listed as common in the EU SPC) and suicidal ideation (rare). More recently the ‘Striving’ switch study, which moved subjects off PI, NNRTI or INSTI regimens (mostly with TDF/FTC) to ABC/3TC/DTG also saw discontinuations after switching for insomnia, depression, headache and euphoric mood as well as an excess of ‘fatigue’ as an adverse experience relative to the control subjects (7% vs 1%) [11]. This points to dolutegravir having an associated CNS syndrome, distinct from EFV but with overlapping features and a greater prominence of insomnia. Switch studies involving removing subjects from dolutegravir have not been performed, but anecdotally these symptoms resolve spontaneously when subjects use an alternative INSTI. The mechanism by which these events occur with dolutegravir is not known but requires intensive investigation lest dolutegravir becomes ‘the new efavirenz’.

Managing sleep disorders

A range of different approaches can be employed to help improve sleep duration and architecture. Clearly this begins with addressing the underlying causes of sleep disorder and initially treating insomnia or broken sleep as a symptom not a disease. Sleep is a habitual process so regularizing bedtime and pre-bed routine is useful. ‘Sleep hygiene’ involves creating an environment conducive to sleep. This may include avoiding caffeine for 6-8 hrs before sleep (the half life is caffeine is about 4 hrs), not exercising or eating for at least 3 hrs before sleep (due to exercise and diet induced thermogenesis), reducing or eliminating alcohol, turning off TV, internet and email an hour before and dimming bedroom lights. Reading, meditation or breathing-focused relation techniques in low light may assist. Sleep is better in cool rooms with ventilation. Reducing environmental noise, including managing a partner’s snoring, such as using earplugs may also help along with blinds and curtains that black out light. Diagnosing and addressing underlying mental health disorders and substance abuse issues may go a long way to help, albeit that individuals withdrawing from substance abuse may experience acutely disturbed sleep and thus require substantial support during these times. Cognitive behaviour therapy may also be useful in establishing more productive less ruminant thinking. Drug interactions with antidepressant and pain medications should be taken into account before these medications are commenced.

As outlined above, choice of ART, most notably the avoidance or elimination of efavirenz and, for a subset of individuals at least, dolutegravir may substantially improve sleep. RCTs and dose reduction studies have clearly demonstrated advantages in moving away from efavirenz.
on sleep and general well being, with the impression that these benefits extend beyond those reporting apparent symptoms.

A range of sleep aids can be used to help short term. These include the ‘traditional’ approaches such as non-caffeinate milk drinks (possibly due to high levels of L-tryptophan in milk) and chamomile tea (as advocated by Peter Rabbit in Beatrix Potter’s books) or preparations of Valerian root have anecdotal benefits but are not subject to RCTs and regulatory assessments nor drug interaction studies. St John’s Wort or Hypericum is a CYP3A inducer and may reduce levels of many drugs including PIs, elvitegravir and dolutegravir. A large ‘placebo effect’ from traditional sleep remedies may be relevant in relaxing into sleep.

The variety of pharmacological interventions is quite wide without resorting to the extremes used by Michael Jackson's physician. Tricyclic antidepressants, benzodiazepines and non-benzo sleeping tablets all have short term roles in habituating sleep patterns. Subjects should be counseled about the habituation risks of these products, avoiding nightly dosing, avoiding alcohol, using at intervals rather than daily or only at times when sleep is likely to be poor (such as when traveling), using only for short terms such as a maximum of 3 consecutive days. Patients should be watchful for memory or cognitive side effects including somnambulation, side effects which may be most readily recorded in the morning or observed by partners. Drug interactions and diurnal drowsiness may be additional side effects as may be a rebound in anxiety. Zopiclon users commonly report a metallic taste the next morning and most non-benzo sleeping medications have been associated with nocturnal activities (notably somnambulation) and morning amnesia. Sleep architecture remains abnormal with sleeping tablets underlining that they are not a complete solution. Suvorexant, an orexin-inhibitor (orexin is involved in the wakefulness part of the sleep-wake cycle) has recently (august 2014) been approved by the FDA but is not approved in the EU. Polysomnographic studies with this medication suggests a promotion of both deeper non-REM and REM sleep suggestive of a more normal sleep cycle.

In summary, sleep disorders are common in persons with HIV and may be a key indicator of undiagnosed mental health problems or unreported substance abuse but may also be a consequence of HIV-induced cytokines and some antiretrovirals. The management of sleep problems should begin with addressing underlying disorders and should include a multidisciplinary approach.

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References
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23–26 October 2016
Scottish Exhibition and Conference Centre, Glasgow, UK

www.hivglasgow.org

Registration Fees
Up to 31 May 2016 £520
1 June – 31 August 2016 £610
1 September – 14 October 2016 £695
Hepatitis B reactivation during treatment of Hepatitis C

During treatment for hepatitis C (HCV) with sofosbuvir and simprevir two patients reactivated hepatitis B. The first case was a 55 year old man with chronic e-antigen negative hepatitis B and genotype 1 HCV. He had evidence of cirrhosis and portal hypertension. During treatment with sofosbuvir and simprevir he developed jaundice, malaise, increased liver function tests (LFTs) and tender hepatomegaly. Hepatitis B viral load (HBV-DNA) increased from about 2000 IU/ml at baseline to 22 million IU/ml. HCV treatment was stopped after 8 weeks and treatment with tenofovir/emtricitabine was initiated. Symptoms resolved and LFTs returned to normal. HCV- RNA remained undetectable. The second case was a 57 year old man with HCV genotype 1 who was negative for hepatitis B surface antigen but had a positive hepatitis B core antibody test and positive HBV-DNA below the level of detection. During treatment for hepatitis C with sofosbuvir and simprevir the HBV-DNA increased to more than 11 000 IU/ml. The patient remained asymtomatic but tenofovir was added and HBV became undetectable. HCV remained undetectable.


Comment: Comment: It has been reported earlier that HCV can suppress HBV. In the first of the described cases the patient should have had treatment for hepatitis B anyway. The second case was less obvious with negative HBsAg. Patients with hepatitis C should be tested not only for HBsAg but also for anti-HBc. It seems reasonable that patients with positive HBsAg or anti-HBc should be monitored for hepatitis B reactivation during HCV therapy.

How long should the follow up time after HIV-1 exposure be?

When commercial tests for HIV antibodies became available in 1985 it was unclear how long it takes from infection to seroconversion. A follow up time of 6 months after HIV exposure was recommended. Gradually the recommended follow up time was shortened but there has been no consensus on the optimal follow up time. With more sensitive antibody tests and the introduction of combination tests for both antibody and antigen the accuracy has improved. In a position statement from the Public Health Agency of Sweden and the Swedish Reference Group for Antiviral therapy a six week follow up time after HIV-1 exposure was recommended when a combination test is used.


Comment: A six week follow up time actually includes a safety margin as the time from infection to positive test is shorter than 6 weeks. It is however important to be aware of the fact that so called rapid tests and home based tests are less sensitive in early infection and should not be used to diagnose suspected primary infections.

Hepatitis C treatment in advanced kidney disease – the C SURFER study

The treatment options for patients with advanced kidney disease and hepatitis C are limited. In a study of the combination of a protease inhibitor (grazoprevir) and an NS5a inhibitor (elbasvir) patients with stage 4-5 kidney disease with or without haemodialysis were included. Both drugs have a very limited kidney elimination and dosing does not need to be modified according to kidney function. The study was placebo controlled. Patients randomized to placebo were offered deferred treatment. Treatment was given for 12 weeks. Of 122 patients who were assigned to immediate therapy 6 were excluded due to various non virological reasons. All patients had genotype 1 with an equal proportion of 1a and 1b. 7 patients had cirrhosis. All 116 patients achieved non detectable viral load at the end of treatment. One patient relapsed after week 12 post therapy. The SVR rate is thus >99 %. Frequencies of adverse effects were similar between the placebo arm and the treatment arm.

Roth D et al. www.thelancet.com; Published online October 6 2015

Comment: Very encouraging results in a difficult to treat group.

Prenylation inhibitor for Hepatitis delta infection (HDV)

In a proof of concept study the prenylation inhibitor lonafarnib in two different doses was compared to placebo in patients with HDV. Patients were given 100 mg, 200 mg or placebo twice daily for four weeks. HDV titers declined significantly in a dose dependent fashion compared to placebo. Mean log decline was 0.73 ➤
in them 100 mg group versus 1.54 in the 200 mg group. Titers returned to baseline level within 4 weeks after therapy was stopped. A trend for increasing HBV-DNA during therapy was observed. Abdominal side effects including nausea and diarrhoea occurred in several patients. Prenylation is a post-translational lipid modification process.


Comment: HDV infection is perhaps the most serious of the different forms of hepatitis. The only available therapy for HDV infection is interferon with only very limited effect. Better treatment is badly needed and this study may be a first step in that direction.

Raltegravir (RAL) in patients on Rifampicin

Coinfected patients with tuberculosis (TB) and HIV were included in a study of raltegravir treatment during rifampicin containing TB therapy. After a median of six weeks of TB therapy patients were randomized to open label therapy with standard dose raltegravir 400 mg twice daily, double dose 800 mg twice daily or efavirenz (EFV) 600 mg once daily. All patients received lamivudine and tenofovir in standard dose. A total of 37 patients received raltegravir. Patients who received double dose raltegravir switched to standard dose after rifampicin was discontinued. Raltegravir levels were measured and as expected were lower during rifampicin therapy. The inter- and intraindividual variations were large. Geometric Mean Ratio (GMR) for raltegravir levels was 0.67 during rifampicin treatment compared to the concentration after rifampicin was stopped. However the GMR:s for AUC and Cmax were close to 1 and all but one samples were above the IC95 concentration for raltegravir. The higher dose of 800 mg twice daily fully compensated for the rifampicin effect. All patients were successfully treated for tb. At week 48 18/21 (86 %) and 11/16 (69 %) in the 400 mg and 800 mg RAL groups had viral load less than 50.


Comment: Although there were no differences in clinical outcome between standard dose and double dose of raltegravir this study is not sufficient to clearly state that standard dose is as effective as double dose in combination with rifampicin. The individual differences are large. Until further results are available double dose raltegravir in combination with rifampicin should probably remain the preferred option.

Is benign prostate hypertrophy (BPH) more common in HIV infected men?

In a nationwide study the incidence of BPH in 4633 HIV positive Danish men was compared to three different control groups. The first control group consisted of 46330 age matched men, the second group of 1585 fathers of HIV positive men and the third group of 20 449 fathers of the age matched men. These kinds of comparisons are possible to do in Denmark based on the fact that every person in Denmark has a unique 10 digit personal identification number that can be used to track individuals in different registries like the Danish Prescription registry, Hospital registry etc. In summary the results showed no increase in BPH in HIV positive men compared to the control groups.

Glindvad M et al.AIDS 2015, 29:2315-2322

Comment: The Danish system with personal identification numbers that can be used to track individuals in all kinds of registries makes it possible to perform detailed epidemiological studies that are unique. In this study it was shown that the incidence of BPH is similar in HIV-positive and negative individuals. As the authors conclude BPH is an age related condition and the results of the study do not indicate accelerated aging in HIV infection.

The end of HIV-2?

In the district of Caïo in Guinea-Bissau in West Africa the incidence and prevalence of HIV-2 was measured 1990, 1997 and 2007. A mathematical model of the spread of HIV-2 was used to predict the future of the HIV-2 epidemic. The studies were done before the introduction of antiretroviral therapy. The prevalence in adults declined from 8.3 % in 1990 to 4.7 % in 2007. The prevalence remained higher in older adults (age >45) while the decrease was more dramatic in young adults (15-35). In older adults the prevalence decreased from 22 to 12 % while young adults had a decrease from 3 to 0.9 %. The pace of decline was greater from 1997 to 2007 compared to 1990 to 1997. The mathematical model that was applied predicts that HIV-2 prevalence will continue to decline and that HIV-2 will become extinct before the end of the century! By 2050 the prevalence is expected to fall below 0.1 %. Though the study and the model were based on one district the authors believe that the model is representative for the whole country.


Comment: Before any widespread use of antiretroviral therapy was introduced HIV-2 incidence decreased significantly in Guinea-Bissau. The biology of HIV-2 is different from HIV-1 with lower viral load and lower transmission rate. It is of course very good news that HIV-2 may disappear within the foreseeable fu-
The combination of ritonavir boosted paritaprevir together with ombitasvir and dasabuvir is very effective in hepatitis C genotype 1 treatment including patients with cirrhosis. For genotype 4 the combination without paritaprevir is also very effective. The pharmacokinetics of the different components in the combination were studied in patients with hepatic impairment and compared to healthy controls. A single dose was given to 7 HCV infected individuals with Child-Pugh A, 6 with Child-Pugh B and 5 with Child-Pugh C. Plasma samples for pharmacokinetic evaluation were followed until 144 hours after administration. In mild to moderate hepatic impairment (Child-Pugh A and B) Cmax and AUC were minimally different from healthy volunteers for all three drugs with the exception of 62 % increase in AUC for paritaprevir (+950 %) and dasabuvir (+320 %).

Khatri A et al. J Hepatol 2015;63:805-812

**Comment**: It is important to emphasize that this drug combination is not recommended in patients with Child-Pugh B and C. Recently FDA issued a safety warning that this combination can cause serious liver injury in patients with underlying advanced liver disease. It seems plausible that the higher drug levels seen in patients with advanced underlying liver disease may contribute to the liver injury. In patients with cirrhosis without any decomposition there is no contraindication to use this drug combination.
Topical Conferences

February 20-21, 2016
6th HIV & Women workshop
Boston, Massachusetts, USA
www.virology-education.com

February 20-21, 2016
XXV International HIV Drug Resistance Workshop
Boston, Massachusetts, USA
www.informedhorizons.com/resistance2016/

February 22-25, 2016
23rd Conference on Retroviruses and Opportunistic Infections (CROI 2015)
Boston, Massachusetts, USA
www.croiconference.org

March 20-24, 2016
Keystone Symposia: HIV Persistence: Pathogenesis and Eradication (X7) and HIV Vaccines (X8)
Olympic Valley, California, USA
www.keystonesymposia.org/

April 13-17, 2016
EASL - The International Liver Congress 2016
Barcelona, Spain
www.easl.eu/

19-22, April 2016
22nd Annual Conference of the British HIV Association (BHIVA)
Manchester
www.bhiva.org

17-22 July, 2016
21st International AIDS Conference (IAS 2016)
Durban
www.aids2016.org

28-30 September, 2016
3rd Nordic HIV & Hepatitis Conference
www.hivnordic.se
Stockholm, Stockholm

23-26 October, 2016
Congress on HIV Therapy (Glasgow 2016)
Glasgow
http://hivglasgow.org

November 11-15, 2016
AASLD 2016, 67th Annual Meeting of the American Association for the Study of Liver Diseases
Boston, MA, USA