HIV & Hepatitis Nordic Conference 2017

In September 27-29, the 4th Nordic Meeting on HIV and hepatitis took place in Stockholm. Delegates from all Nordic countries were greeted welcome by Prof Magnus Gisslén, Sweden, who together with Prof Nina Weis, Denmark, was Chair for the Scientific Committee.

In his welcoming address, Prof Gisslén thanked the sponsors, and encouraged all delegates to ask questions and participate in the discussions.

Immune activation remain altered in spite of early ART

The first Speaker was Prof Francesca Chiodi, who talked about persistent immunological problems in the ART era.

She started by pointing out that abnormal immune activation and inflammation have a central role in HIV pathogenesis.

– Today I will concentrate on immune activation. But there is some confusion on this term: Immune activation is *affected* by many parameters – such as microbial translocation, co-infections and altered Treg/Th17 to name a few. It is *reflected* in many parameters – lymph node fibrosis, T-cell exhaustion and local inflammation driven by monocyte activation – resulting in impaired CD4 T-cell recovery and end-organ disease.

CD8+ T-cells of patients starting ART during the acute phase of infection still display perturbated expression of molecules linked to immune activation and exhaustion, Prof Chiodi said.

– Despite effective ART, HIV-infected patients remain at increased risk of non-AIDS morbidity and mortality, she continued and presented studies establishing this.

HIV reservoirs may be the source of production of inflammatory cytokines. The role of supporting cells in maintenance of inflammation in tissue during HIV infection has been poorly studied.

– Does the virus activate programs for production of inflammatory cytokines from supporting cells in affected tissues? And which cytokines are produced by these cells? This has been very poorly studied.

For some of these cells there is no clear evidence of complete HIV replication – they have however the capacity to trap virus particles with the potential to spread HIV to other cells.

– So my conclusion is that many parameters on immune activation remain altered in spite of early ART. We only have data for the first 24 months, hopefully we will see a decline after that, Prof Chiodi said.

Underlying opportunistic pathogens

IRIS stands for immune reconstitution inflammatory syndrome. It is a condition seen in some cases of immunosuppression in which the immune system begins to recover, but then responds to a previously acquired opportunistic infection with an overwhelming inflammatory response – that paradoxically makes the symptoms of infection worse.

Dr Irini Sereti talked about IRIS in HIV infection, and presented some challenging cases from her clinic.

– Antigen-driven activation and expansion of CD4+ T-cells are more pronounced in IRIS patients, and are driven by the underlying opportunistic pathogens, she said.

There is a role for monocytes in pro- ➤

duction of inflammatory mediators and accumulation of primed macrophages, Dr Sereti continued.

– Inflammatory biomarkers are important predictors, with a potential role for IL6/CRP/TNF in early diagnosis.

In her conclusions she stated that opportunistic infections and mortality in HIV remain a reality in the US and worldwide.

– So there is a need for improved earlier diagnosis, linkage and retention to care.

New targeted preventive and therapeutic strategies are needed – on cytokines and metabolic pathways.

– Finally, predictors of IRIS and death – biomarkers and composite risks – may help guide clinical trial design, Dr Sereti summarised.

IRIS occurs frequently in late HIV presenters

Is the use of integrase inhibitors (INI) a risk factor for IRIS? The question was the headline of Dr Bart Reijnders' lecture.

INI-containing cART enables a faster HIV-RNA decline and a faster CD4 T-cell recovery, compared to protease inhibitors/non-nucleoside transcriptase inhibitors (PI/NNRTI), he started by saying.

In HIV late presenters, with CD4 less than 200 and/or an opportunistic infection, the use of INI-cART may increase the incidence of IRIS.

Irini Sereti

Jan Gerstoft

– In the phase III registration trials of INI, patients with opportunistic infections were explicitly excluded. No large randomised controlled trials that included a significant number of late presenters has compared INI with non-INI and reported on IRIS incidence, Dr Reijnders said.

However, a HIV cohort may give useful information, he added.

He presented a study with the primary objective to identify independent risk factors for the occurrence of IRIS, as well as IRIS within the first 12 months of cART.

– It included 672 HIV patients, all late presenters, for analysis. 155 on INI, and 517 on non-INI.

The conclusion he presented was that in HIV late presenters in a resource rich setting, IRIS occurred frequently (10-30 %). *Mycobacterium avium* complex and cryptococcal meningitis were associated with IRIS.

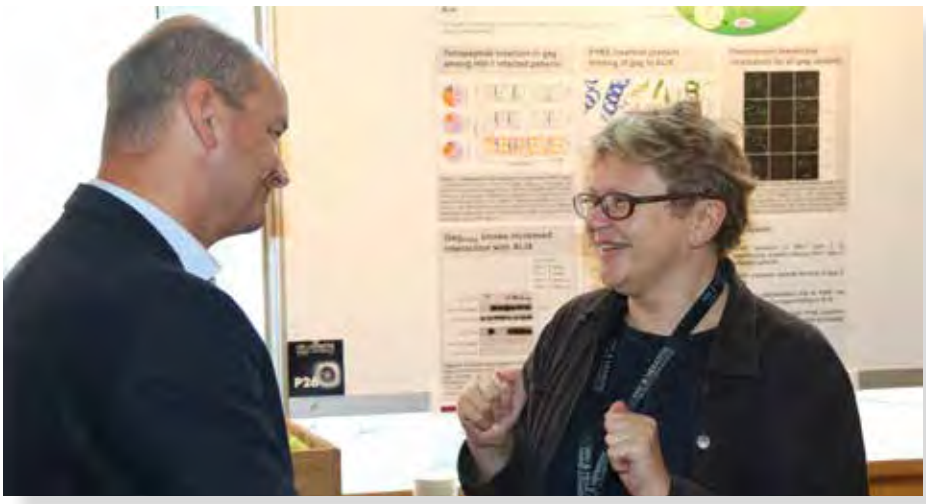
– IRIS may occur more frequently in patients who have started an INI. However, data are insufficient to draw any definite conclusions. A large pragmatic randomised trial is needed in HIV late presenters, on INI versus non-INI, where IRIS should be predefined as an endpoint, Dr Reijnders underlined.

Potential problems with long-acting injectables

In a session on ART, Prof Jan Gerstoft talked about long acting injectables.

– Long acting antivirals are characterized by a low daily dose, long half-life and low solubility. They are not associated with serious adverse events, and there is some experience of long acting drugs from anti-psychotics and injectable contraceptives, Prof Gerstoft initially said.

Cabotegravir and rilpivirine is an example on long acting injectables that have been evaluated in the LATTE- 2 study.



The question he presented was how many patients that will actually prefer a long acting regimen.

– There are no daily compliance issues, and perhaps a feeling of less stigmatization. But the patient will have to see a health professional every 1-2 months – instead of every 6th month. There will also be some injection site reactions, Prof Gerstoft continued.

Also there are some other potential problems: There is a long tail if the regimen is discontinued – 1 year. Resistance development is almost certain if the tail is not covered. It is also difficult or impossible to *remove* the regimen if there are side effects – hence a need for an oral lead-in, in order to rule out side effects.

– And what do we do if the patient gets pregnant?

But he concluded that in a few years long acting injectables is likely to be an option for treatment in a limited section of patients.

– Also these drugs have the potential to boost PrEP (pre-exposure prophylaxis) in developing countries, as demonstrated in the FEM-PrEP trial on at-risk HIV non-infected African women. But resistance is a risk, Prof Gerstoft ended his lecture.

Global action plan on HIV drug resistance

Dr Silvia Bertagnolio from WHO talked about the threat of increasing HIV drug resistance.

A systematic review had found a strong effect of non-nucleoside transcriptase inhibitors pre-treatment drug resistance (NNRTI-PDR) on treatment outcome compared to no NNRTI-PDR when people initiate a NNRTI-based regimen.

– People with NNRTI resistance who initiate NNRTI-based first line ART are less likely to achieve viral suppression and maintain it, and more likely to experience virological failure, she said.

They are also more likely to discontinue ART and more likely to acquire new HIV drug resistance mutations. This can threaten programmes sustainability, Dr Bertagnolio pointed out.

– With higher levels of HIV drug resistance, more resources would be needed to treat the same number of patients, or – more likely – *fewer* patients could be treated with the same resources.

WHO has therefore presented The Global Action Plan on HIV drug resistance 2017 - 2021.

– It aims to raise awareness of the need to prevent, monitor and respond to HIV drug resistance. Also to provide a frame-

Silvia Bertagnolio

Tina Carlander

work of actions for all stakeholders in order to ensure that HIV drug resistance does not threaten achieving global targets to end AIDS.

A way forward Dr Bertagnolio pointed out in her conclusions is a rapid transition from efavirenz to dolutegravir.

– The action plan provides a framework for action – to address new questions and promote high impact interventions, she ended her talk.

A delayed establishment of CNS HIV reservoir

– As you all know, latent reservoir is in resting CD4 T-cells – but also in central nervous system (CNS). However, we lack good methods to measure the reservoir in CNS, said Prof Magnus Gisslén.

There are cellular reservoirs in dormant memory T-cells in lymph node and blood. Anatomical reservoirs are in genital tract, the gastrointestinal tract – and in CNS.

He presented a hypothesis that states that anti-HIV antibody reflects the size of the reservoir.

– The magnitude of antibody production reflects the amount of antigen.

Using archived samples and two individuals who failed PrEP, individuals without ART followed longitudinally and the cured Berlin patient, a study had been performed by Prof Gisslén and colleagues. The first conclusion he reported was that serum and cerebrospinal fluid could be used for monitoring the systemic and CNS HIV reservoirs.

– Our data suggests that there is a delayed establishment of the CNS HIV reservoir compared to the systemic reservoir. Also that early treatment have a greater impact on long-term CNS infection compared to its systemic counterpart – and maybe even *prevent* the establishment of a CNS reservoir if started very early, Prof Gisslén said.

He added that the significantly lower antibody level in the CSF in treated early-infected subjects – even years later – points to the stability and durability of ART protection.

ART effective against cervical cancer

Do women living with HIV in Sweden have a poorer outcome after treatment of cervical intraepithelial neoplasia grade 2+ (CIN2+) than HIV-negative women of the same country of birth? And which are the predictors of treatment failure and recurrence among women living with HIV?

Dr Tina Carlander presented a study that aimed to answer these questions.

– Women living with HIV have a higher risk of developing cervical cancer, she started by saying.

The study population was taken from three registries: The Swedish National HIV Registry, where all women living with HIV 1983 - 2014 in the cities Stockholm and Gothenburg were linked to Swedish National Cervical Screening Registry (NKCx) – and all HIV negative in the two cities with CIN2+ during the same time were drawn from the Swedish Population Registry and also linked to NKCx, matched 2:1 and country of birth.

– We found that both suppressive ART and CD4 counts of 500 or more are associated with an effective treatment of CIN2+, said Dr Carlander.

She concluded that early HIV diagnosis, immediate ART and continuum of care are all essential to reach successful CIN2+ treatment.

New mechanisms found?

A session with the top 5 abstracts in basic HIV research and in clinical research is a tradition in the Nordic Conference.

Professor Johan K Sandberg presented the top 5 in basic research.

– They are selected from my perspective as an immunologist, he explained.

Prof Sandberg started with a study on integrin α4β7 – an integrin important for homing and retention of T-cells in the gut mucosa. Treatment with anti-α4β7 antibodies can give partial protection from infection and progression in non-human primate models. The data from the study suggests virion incorporation of integrin α4β7 facilitates HIV-infection and intestinal homing.

– HIV-1 exploits a mechanism of cellular homing as a virulence factor to facilitate its own spread and pathogenesis. This mechanism may be particularly important for infectivity during acute infection, were the study's conclusions.

Next study was on gut-homing delta 142PD1+VΔ2 T-cells, that were found to promote innate mucosal damage via TLR4 during acute HIV1 infection.

– The data may suggest a new mechanism for initiation of inflammation in the small intestines during acute HIV infection.

Broadly neutralizing antibodies

The third study was on the latent reservoir. This is vast, but only a fraction of it is functional.

– Data from the study suggest that CD32a is a possible biomarker to identify the majority of persistently infected CD4 T-cells on ART. But this need to be repeated and verified, also in lymphoid tissue.

Study number four aimed to investigate if a combination of therapeutic vaccination and innate immune stimulus could boost immunity enough to allow virus control after ART discontinuation. 36 rhesus macaques were infected with SIVmac251, and put on ART on day 7.

– Data demonstrated proof-of-concept that this combination can improve virus control after ART discontinuation.

The last study had broadly neutralizing antibodies (bnAbs) targeting three main neutralization sites.

– BnAbs are rare, take long time to develop in natural infection, and are hard to induce by vaccination. Identification, production and engineering of bnAbs may be a good tool for passive immunization against HIV, Prof Sandberg said.

The conclusion was that trispecific antibodies exhibited higher potency and breadth than any single bnAb and conferred complete protection against challenge with mixture of SIVHs in non-human primates.

– This finding has made it into the news, Prof Sandberg ended his lecture.

Enhanced antimicrobial prophylaxis reduces rates of death

Dr Aylin Yilmaz then presented the top 5 clinical abstracts. This she began with a non-scientific paper – the UNAIDS annual report of the status of the HIV/AIDS epidemic.

– In eastern and southern Africa AIDS-related deaths was nearly halved in the past 6 years. The decline was more rapid in women and girls, she pointed out to the audience.

New HIV-infections are declining, but are far off the pace needed for the 2020 target, Dr Yilmaz continued.

And there are regional differences – a decline in Africa, but in eastern Europe and central Asia there has been an *increase* with 60 % since 2010.

The second paper Dr Yilmaz presented was on the REALITY study, a factorial, open-label, muliticentre randomised controlled trial designed to evaluate strategies for reducing the risk of death in people who start antiretroviral treatment with very low CD4 cell counts (i.e. below 100).

– It found that among HIV-infected patients with advanced immunosuppression and enhanced antimicrobial prophylaxis combined with ART resulted in reduced rates of death at both 24 weeks and 48 seeks – without compromising viral suppression or increasing toxic effects. It was also inexpensive.

Aylin Yilmaz

Johan K. Sandberg

On demand PrEP is effective

The LATTE-2 study had compared three ways of drug-dosing.

After a induction period of 20 weeks of cabotegravir 30 mg + abc/3TC 600/300 mg once daily with addition of rilpivirine 25 mg once daily at week 16 309 patients were randomised to three arms. 115 went to intramuscular injections with long acting (LA) cabotegravir 400 mg + LA rilipivirine 600 mg every 4 weeks, the other arm had intramuscular injections with LA cabotegravir 600 mg + LA rilpivirine 900 mg every 8 weeks. 115 patients were in each of these arm.

The third arm (56 patients) continued the induction regimen once daily.

– The two-drug combination of all-injectable, long-acting cabotegravir plus rilpivirine every 4 week or 8 weeks was as effective as the daily three-drug oral therapy at maintaining HIV viral suppression through 96 weeks, and was well accepted and tolerated, Dr Yilmaz summarised the findings.

On-demand PrEP is an open-label extension of the IPERGAY trial.

– On demand PrEP is highly effective at preventing HIV-infection among high risk men who have sex with men, and therefore represents an alternative to daily PrEP, Dr Yilmaz said.

She finished with a phase I dose ranging study on long-acting rilpivirine as PrEP – the MWRI-01 study.

– Their finding was that a single-dose administration of LA rilpivirine is safe and acceptable. Exposure to LA rilpiviri-

ne as associated with prolonged pharmacokinetics and viral suppression in colorectal – but not cervicovaginal – tissue, Dr Yilmaz reported.

Atazanavir reduces risk of cardiovascular disease

Both HIV infection and antiretrovirals increase the risk for cardiovascular disease (CVD), said Prof Ann-Brit Eg Hansen.

– Earlier studies have demonstrated associations between cumulative use of first generation protease inhibitors (PIs) and CVD. Is the cumulative use of contemporary PIs ritonavir boosted atazanavir (ATV/r) and darunavir (DRV/r) independent-

ly associated with increased risk of CVD?

Prof Eg Hansen continued by stating that in the D:A:D cohort, cumulative use of DRV/r, but not ATV/r, was independently associated with a small – but gradually increasing – risk of CVD by 59 % per 5 years exposure.

In large cohort studies, use of ATV has not been associated with an increased CVD risk.

– In the VA cohort use of ATV was associated with 41 % and 36 % *decreased* risk of myocardial infarction and stroke, respectively. And use of ATV/r is associated with decreased progression of carotid intima-media thickness in both randomised controlled studies and small observation studies.

She ended by stating that we have to remember that the rate of myocardial infarction and stroke remains relatively low in more recent years.

– This can be due to earlier initiation of cART, less toxic drugs and management of modifiable risk factors.

71 million individuals infected globally

The last day of the Conference was on hepatitis. This day also had a presentation of a selection of the best published studies, presented by Prof Soo Aleman.

– WHO has a plan to eliminate viral hepatitis by 2030. One important step is to assess the global burden of HCV infection, she underlined.

This took Prof Aleman to the first study – on global prevalence of hepatitis C virus (HCV) infection. It is a modelling study, developed by systematic reviews of 6,754 studies, and by input from country-specific experts. The study reported that around the world 71 million persons are estimated to be infected with hepatitis C.

– This is lower then previous figures. Why? Mainly it is due to lower prevalence estimates in China, India and Africa. Also the total number of viremic HCV infections has been decreasing.

Although there are high cure rates for HCV, there are several challenges ahead to achieve the WHO elimination goal.

HCV-affected organs for transplant

Do direct-acting-antivirals (DAAs), used to eradicate HCV, increase the risk for hepatocellular carcinoma (HCC) occurrence or recurrence? There have been conflicting results in mainly small cohort studies. Prof Aleman's second study was a systematic review, meta-analysis and meta-regression on the subject.

– It *did* see a higher risk in DAA treated, but this is explained by older age and more advanced cirrhosis. They found no increased risk for HCC recurrence or occurrence after DAA treatment. Still, more data are needed, she said.

Physicians usually tell a patient that is cured from HCV that they are not allowed to donate blood. The third study was on the use of HCV-positive organs to HCV-negative recipients.

– The waiting time for a kidney transplant is at least 3 - 5 years, and more than 500 high-quality kidneys from HCV-positive donors are discarded annually in the US alone, Prof Aleman pointed out.

It was a proof-of-concept study, in which 10 patients received HCV-infected kidneys. All received antiviral treatment approximately at day 3 after transplantation, and all reached sustained virological response at week 12 (SVR12).

– However, more data are needed to define safe and effective use of HCV-positive organs.

Ann-Brit Eg Hansen

Soo Aleman

High replication, low replication stage

The fourth study was on hepatitis B infection (HBV) on the concept of immunotolerance.

– The immuno-tolerant phase, the first of the three phases of chronic HBV infection, is thought to lack disease activity. This study was of HBV-DNA integration and immunological responses in patients in this phase, Prof Aleman continued.

A high number of HBV-DNA integrations, randomly distributed among chromosomes, was found in all patient groups.

– The authors' conclusion was that this could indicate that hepatocarcinogenesis could start even in young patients with considered immune tolerant phase. They propose that this early phase should be called a high-replication, low-inflammation stage (HRLI).

Data from Nepal

Finally, she talked about hepatitis D (HDV) and E (HEV).

– HDV is a more severe form of viral hepatitis with rapid progress to liver cirrhosis. Peg-IFN is the only available treatment, but with poor response. There are several drugs in pipeline, but still depressingly low treatment response rates.

The country Nepal has experienced a number of HEV outbreaks. The devastating earthquakes in 2015, where 8,891 people lost their lives, left expectations f a high burden of HEV in the aftermath. A post-earthquake study on seroepidemiology for HEV among blood donors in the country did – unexpectedly – not provide evidence of a sizeable outbreak of HEV.

– High antibody levels due to previous outbreaks could have provided immunity against re-infection. Also 390,000 individuals left Kathmandu region immediately following the earthquakes – decreasing HEV population susceptibility, Prof Aleman said.

She summarised by stating that there is an increasing awareness of high prevalence of HEV in certain areas.

Cirrhosis regression is a slow process

Dr Magnus Hedenstierna presented a study on risk factors for persisting advanced fibrosis after HCV eradication.

– The aim was to assess fibrosis with

liver elasticity measurements long term after SVR of chronic HCV, and to identify risk factors associated with persisting fibrosis, he explained.

It was a cross-sectional study on patients with pre-treatment F3 or F4 fibrosis that had achieved SVR for chronic SVR between 1992 and 2013. They were offered a follow-up visit with liver stiffness measurement (FibroScan).

– Fibrosis and cirrhosis regressed substantially in a majority of patients after SVR, Dr Hedenstierna reported.

Pre-treatment cirrhosis, high age and BMI were found to be important risk factors for persisting advanced fibrosis.

– Liver stiffness at follow-up was significantly lower for patients with pre-treatment cirrhosis and longer follow-up time – indicating that cirrhosis regression is a slow process that continues over time, was his conclusion.

Covalently closed circular DNA in HBV

Prof Magnus Lindh talked about hepatitis B (HBV).

– There are approximately 250 million people with chronic HBV infection globally, and 20 - 25 % develop significant liver disease – such as chronic inflammation, cirrhosis and HCC, he pointed out.

650,000 die every year from cirrhosis or HCC. Vaccine – HBsAg – is good, but has a slow impact. Treatment with antivirals is increasingly used of fear for HCC.

Chronic infection with HBV is characterized by the persistence of the episomal viral genome, the covalently closed circular DNA (cccDNA), which forms a stable minichromosome in the nuclei of infected hepatocytes. HBsAG correlates with HBV DNA and might reflect cccDNA.

HBeAg is a viral protein and an indicator of active viral replication.

– HBsAg remains remarkably high in HBeAg-carriers, Prof Lindh continued.

HBsAg quantification may not represent cccDNA, but can still be useful – for identification of inactive carriers, prediction of spontaneous HBsAg loss and assessment of treatment response.

How can cccDNA be reduced? According to Prof Lindh there is no drug with direct action on cccDNA.

– But it can be reduced by mitosis.

He ended his lecture by stating that maybe nucleoside analogues have a rather good effect on cccDNA, and showed an example of a patient with 99 % cccDNA reduction in one year.

Pro and contra for HCV vaccine

An overview of HCV vaccine development was presented by Prof Judith Gottwein.

The Conference Abstract Award was awarded to Frideborg Bradley.

Magnus Lindh

Judith Gottwein

– There is an unmet need for a prophylactic HCV vaccine to control HCV on a global scale, she established.

So is this feasible? Prof Gottwein first underlined that protective immunity against HCV does exist.

– We see viral clearance in up to 30 % of acute infections, and protection from re-infection in individuals who have cleared their infection. We have also seen that protective immunity can be induced in chimpanzees, were some of the items on her "pro" list.

But Prof Gottwein also presented a "contra" list. In this she underlined the genetic heterogeneity of HCV.

– There are 6 epidemiologically relevant genotypes, and genotype 1, 2 and 3 cause more than 80 % of infections. Also HCV immune evasion is a barrier – mutational escape, decoy epitopes and epitope shielding.

Various approaches are investigated, and candidates in clinical trials have shown protective effect in chimpanzees. Prof Gottwein presented ongoing work in her own lab, and the technology and processes it includes.

– But additional candidates are needed. A development of cell culture systems and a basic approach on HCV facilitates vaccine design. And we have to show optimisation of whole virus inactivated prior to clinical testing, was her summary.

And after her lecture, the Nordic HIV & Hepatitis Conference 2017 had come to an end. It will return in 2018, 26-28th of September. Save the date, and read more on **www.hivnordic.se**.

Per Lundblad

Satellite symposiums at the HIV & Hepatitis Nordic Conference

In adjunction to the scientific program at the Conference, several satellite symposiums were held.

The first of these had the title *Dolutegravir – from development to real-life safety and universal access*, and was sponsored by ViiV Healthcare.

Annemiek de Ruiter and Eva Fernvik

Paola Cinque, Erika Ahlgren, Aylin Yilmaz, Steffen Leth and Lars Østergaard

Stigma and discrimination remain prevalent

Dr Annemiek de Ruiter presented a case, with a 35 years old woman who tested positive for HIV.

– There are so many considerations for her to make – reproductive wishes, cultural norms and stigma to name only a few. It is not very helpful for her mental health, Dr de Ruiter underlined.

The patient's problems also might be disclosing to her partner on the infection. Her partner could be tested along with her family members if she does – but also there is a fear of being stigmatized and abandoned.

Dr Ruiter presented a survey from India, in which 305 doctors had participated.

– 13 % thought that health care personnel should have the right to refuse to treat people living with HIV (PLWHIV). 55 % had the view that HIV positive women should not be allowed to have children – and 40 % that PLWHIV should not be allowed to marry, she pointed out.

Stigma and discrimination around HIV remain highly prevalent, and disclosure remains difficult for many PLWHIV.

– Mental issues can impact on adherence, and co-morbidities and poly-pharmacy are increasing issues in an ageing population.

Drug-drug interactions are a significant concern, and Dr de Ruiter ended her talk by pointing out that dolutegravir based regimens are efficacious, convenient and well tolerated – with few drug interactions and a high barrier to resistance.

Working on information is important

PhD Eva Fernvik, scientific advisor for HIV at ViiV Healthcare and Chair of the satellite symposium, then talked about a Pharma company's responsibility.

– It goes beyond the drug supply, she stated.

Positive action is a programme addressing the needs of key affected populations. It is globally ongoing, the majority of programmes are in Africa and Asia.

Dr Fernvik presented a survey that had explored five different types of stigma – physical, verbal, institutionalised, social and self stigma – that PLWHIV may have experienced in the past 12 months.

– 82 % had experienced a form of stigma related to their HIV in this timeframe.

How can the feelings of stigmatisation be reduced?

– 67 % (643) of PLWHIV in eight countries believe that better education for the general public was the number one way to address the issue. In an Italian sur-

Christina Carlander and Teresa Katzenstein

vey, 62 % (75) believe that better teaching in schools was the best way, Dr Fernvik said.

Her conclusion was that working on information is important.

PML

CNS complications in HIV patients was the topic for a symposium sponsored by Janssen Pharmaceuticals. Chair Lars Østergaard greeted all welcome to an interactive symposium where two cases were presented.

Dr Paola Cinque began by describing the most important CNS lesions in HIV.

First case was diagnosed as PML, and the patient was prescribed steroids, which later were stopped. The patient was treated with Rezolsta (darunavir/cobicistat). Maraviroc + Triumeq were added, which led to improved cognition and better strength in right hand and arm.

Day 315 after treatment initiation, the plasma viral load was less than 20 copies per ml, and the CD4 count was 200. Rezolsta was then stopped, and the patient continued with Maraviroc and Triumeq.

Dr Cinque recommended in her comment that the patient should be monitored in the future.

Alzheimer's disease

The next case concerned a 66 year old woman, diagnosed with HIV at 54 years of age. At a regular visit she told that for the two past years, she has had problems with her memory and ability to concentrate. At first she thought it had to do with her work, but the symptoms had not improved since she retired almost one year ago.

A CT scan of the brain and a simple bedside test were performed.

Their results was summarised by Dr Aylin Yilmaz.

– The bloodwork was normal, and also evaluation for depression. The brain MRI was also normal.

But the woman had problems finding words and finding her way around. Later on she displayed change in temper and less tolerance for stress.

– The neuropsychological assessment showed abnormal performance in spatial short-time memory and spatial episodic memory. FDG-PET revealed decreased glucose uptake bilaterally in the parietal lobes, in the left anterior cingulum and in the right posterior thalamus. Everything consistent with Alzheimer's disease, she said.

The woman started treatment with a cholinesterase inhibitor. For her HIV, she was on tenofovir/emtricitabine/efavirenz, which was going to be changed.

No gender differences for PrEP

A symposium sponsored by Gilead was entitled *HIV and women*. Dr Christina Carlander was the Chair.

Dr Teresa Katzenstein was the speaker, and started by asking if PrEP also is for women.

A study from 2016 found that PrEP significantly reduced the risk of HIV acquisition, and no significant difference in effectiveness according to gender. The study's result also underlined that adherence is of major importance.

– Long-acting regimens are also relevant in PrEP. There are many issues though: A better understanding of PrEPs barrier is needed, and we need long-acting compounds, Dr Katzenstein continued.

On transmission, she said that studies have found that women in general have lower viral load compared to men. Why this is so has not been answered.

– But it does not matter in treatment terms – everyone should start treatment.

There are no gender differences in time from eligibility to HAART initiation, nor in treatment modification within the first year – and no differences in response CD4 and viral load.

Focus on osteoporosis needed

– However, loss of estrogens at menopause intensifies bone loss. Accelerated bone loss is compounded by the fact that women typically have reduced skeletal mass due to smaller, thinner bones, Dr Katzenstein pointed out.

Exposure to TDF – both current or ever – is an independent risk factor for fractures. This is different with TAF.

Her conclusions were that PrEP also for women need to be optimised.

She also pointed out that women have lower viral loads.

– This is intellectually challenging, but maybe not of major clinical impact.

Per sexual transmission risk shows differences in high and low income countries – with a lower risk in high income countries.

– It seems to vary by "economy".

A focus on osteoporosis is needed for both sexes.

– Problems with ART and hormonal contraception have to be weighted against risk of unplanned pregnancies. The rates of unintended pregnancy has gone down in the US, but remains on 45 % – which still is very high. However, a study showed that ART did not reduce the impact of contraceptives, Dr Katzenstein finished her lecture.

"The last generation of HCV treatments"

The era of pangenotypic next-generation HCV treatment was the headline for a symposium sponsored by Abbvie.

Chair Prof Ola Weiland stated that the next generation also will be the last generation. He continued by presenting the presently available DAA classes.

– All treatments have a NS5A inhibitor as its backbone, that can be combined with several other types of drugs, he said.

There are 8 combinations – with or without ribavirin – in EASLs guidelines. They differ from each other when it comes to effect on various viral genotypes.

– NS5A inhibitors, NS3 protease inhibitors and non-nucleoside RdRp inhibitors are low-barrier-to resistance drugs – nucleotide analogues are high-barrier-to resistance drugs.

High SVR rates across all genotypes

Prof Jean-Michel Pawlotsky then continued by explaining that the new drugs are pangenotypic.

– Glecaprevir have a high resistance profile – and pibrentasvir an even better profile, he underlined.

He presented data from trials on both treatment-naive and treatment-experienced, non-cirrhotic patients treated with glecaprevir/pibrentasvir for 8 weeks. For genotype (GT)1 (N=351) the success rate was 99 %, for GT3 (N=157) the rate was 95 % and for GT 4, 5 and 6 (N=203) it was 97 %.

– In a Phase III trial on GT1-2-4-5-6 in compensated cirrhosis for 12 weeks the overall success rate was 99 %.

New pangenotypic "next generation" DAA-based regimens have been approved in Europe, and will be available soon, Prof Pawlotsky said.

– These regimens are safe and yield high SVR rates with 8 - 12 weeks of administration in all groups of patients – including special populations, such as HIV co-infected, chronic kidney disease and transplanted – and DAA-exposed patients.

Unfortunately, the presence of a protease inhibitor precludes their use in patients with decompensated cirrhosis (Child-Pugh B or C).

– Now that the technical HCV challenge has been solved, the new challenge is access to care and elimination, Prof Pawlotsky ended the symposium.

Ola Weiland and Jean-Michel Pawlotsky

Have to find the patients where they are

Many people that inject drugs do not receive care for HCV. How can they be optimally helped? This was the title of a symposium sponsored by Gilead. Barbro Westerholm, Swedish MP, was the Chair.

– Improve screening and linkage to care for this patient category, by optimisation of the cooperation between infectious disease departments, psychiatric departments the criminal ward, social authorities and other acting parties, Prof Fred Nyberg said.

He also advocated to treat HCV at other health care units than infectious disease and gastroenterology departments, such as opioid substitution therapy (OST) units.

– However, it is important to have access to, and to consult, infectious disease specialists, Prof Nyberg added.

Dr Anders Nystedt, department of communicable disease control, stated that we need a strategy – a plan – for elimination of HCV.

– The tools – we have them. But we need to find the patients that are hidden to us. That means we have to go where they are – which means we have to find new arenas. Prisons are an ideal place – and forensic psychiatric hospitals.

Lars Håkan Nilsson, Marianne Alanko Blomé, Fred Nyberg, Barbro Westerholm, Anders Nystedt and Martin Kåberg

Development of needle exchange programmes in Sweden has been slow

Dr Martin Kåberg talked about patients on opioid substitution therapy.

– DAA therapy is effective in people receiving opioid substitution therapy, and people with a history of injecting drug use. This is evidence-based, he pointed out.

SVR rates among patients on opioid agonist therapy are similar to those of the general population.

– Treating these patients is feasible – for patients with ongoing drug use a multidisciplinary approach is needed.

In order to achieve HCV elimination by 2030, we need scaling up screening and linkage to care. This is essential, Dr Kåberg underlined.

– Reimbursement restrictions must be omitted, and a national HCV elimination strategy is needed.

Dr Marianne Alanko Blomé talked about needle exchange programs as a valuable tool. She described the centre for this in Malmö that has a long history.

– But the development of these centers in other areas of Sweden has been slow.

Finally, senior medical adviser Lars Håkan Nilsson talked about the prison and probation service as an arena to treat HCV.

– Approximately 8.500 persons are im-

Olav Dalgård, Hannah Fraser, Lars Peters, Henrikki Brummer-Korvenkontio, Knut Boe Kielland and Martin Kåberg

prisoned each year, and half of them have sentences long enough to enable a treatment of HCV. The prison services has a structure that makes such a treatment possible, he said.

The costs for persons with a substance use disorder is high, but if it creates an incitement for a life without drugs, the gains for the individual patient and society are considerable, was his last message.

Elimination is possible – in a model

Towards elimination in the Nordics, was the title of the last symposium. It was sponsored by MSD. The question debated was how to eliminate HCV in the Nordic countries, which was discussed by invited speakers from these countries.

Prof Olav Dalgård, who was the Chair, began by reminding the audience on the goal from WHO to eliminate HCV in 2030.

Dr Hannah Fraser first talked about modelling elimination of HCV. This is possible in the Nordic countries with scale-up treatment, but also with scale-up of opioid substitution therapy and needle syringe programmes.

– Robust HCV surveillance data among people who inject drugs is imperative, Dr Fraser also said.

Dr Martin Kåberg stressed that elimination in Sweden is possible – but not in 2030 with current strategies.

– With current strategies, elimination is not ever possible. Neither is it possible if we only scale up treatment, he said.

Denmark, Finland and Norway

Dr Lars Peters talked about Denmark.

– Even in a treat-all scenario, HCV elimination would be challenged by a lack of overview of the problem, and low testing rates and linkage to care. We have a centralized HCV treatment and the care system for HCV is not adopted to the needs of the majority of infected persons, Dr Peters stated.

In Finland, a strategy for HCV 2016 - 2019 by a multidisciplinary working group was published in November 2016, said Mr Henrikki Brummer-Korvenkontio.

– In Finland 1,200 new infections are notified every year. It is estimated that 20,000 persons carry the virus in Finland, but in 2016 some 400 cases were treated.

There are several major barriers for elimination of HCV in Finland, according to Mr Brummer-Korvenkontio: A high number of chronic infections, identifying those infected and building an infrastructure for linkage and treatment assessment.

– Also reinfections. And there is a need for lower drug prices.

Plans for elimination of HCV in Norway are basically non-existent, but there are probably no fibrosis-limits for DAA treatment from 2018 – depending on drug prices, said Dr Knut Boe Kielland.

– If so, intensive DAA treatment efforts are expected – including residential drug abusement institutions, prisons, low threshold treatment facilities and among patients on opioid substitution therapy. Also among other patients – former and current people who use drugs and immigrants – via a public campaign, Dr Kielland ended the symposium.

Per Lundblad