6TH GILEAD NORDIC SUMMER HIV MEETING · NUCLEOSIDE FREE ZONES · SALT & OLE: “IF YOU CAN BEAT THEM, JOIN THEM” (BUT JUST ONE OF THEM) · THE 4TH EUROPEAN WORKSHOP ON HIV INFECTION IN THE CNS (HANSA) · THE HCV DRUG-RALLY IS ONGOING: SIMEPREVIR AND DACLATASVIR APPROVED BY EMA!
NEWS FROM THE SUMMER/WINTER WORLD AIDS CONFERENCE, MELBOURNE
HIV & VIROLOGY NEWS

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

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Ebola – a serious threat

It has become increasingly obvious that the Ebola outbreak in West Africa has grown out of control. According to WHO, there have been 3052 cases reported up to August 25, 2014, with 1546 deaths. As usual, the epidemic has struck a poor region of the world, affecting countries and cities with huge populations and widespread poverty. In addition, these are areas that have suffered from recent wars and armed conflicts – an ideal environment for microbial spread. The countries affected to date are Guinea, Liberia, Nigeria, and Sierra Leone.

The figures taken from the WHO Ebola Situation Report of August 29, (www.who.int/csr/disease/ebola/en/) show the number of cases reported by country from the beginning of January 2014 (epidemiological Week 1) to August 25 (epidemiological Week 34).

The current outbreak of Ebola virus disease is exceptional in many ways. For one thing, it continues to escalate. Over 40% of the total number of cases have occurred within the past 21 days, and WHO fears that approximately 20,000 people can be infected before the epidemic is under control. Personally, I believe this is an underestimation, and there is an obvious risk that many more will be affected. At present over 240 health care workers have developed the disease in Guinea, Liberia, Nigeria, and Sierra Leone, and above 120 have died (although the survival rate, which is close to 50%, seems higher than in previous outbreaks). A lack of protective equipment, including gloves and face masks, have left medical staff at risk. In addition, several other infectious diseases that frequently need emergency care are endemic to the region and can mimic the initial symptoms of Ebola virus disease. For example, malaria and typhoid fever have sometimes been assumed in patients until health care providers suspected Ebola virus disease.

Médecins Sans Frontières (MSF) has been doing a tremendous job of organizing clinics and trying to limit the epidemic.

However, this crisis is too large to be handled by a single organisation and the international community has a responsibility to respond. Resources from the international political and medical community are urgently needed. It is time to face the fact that the West African Ebola epidemic is a real threat and at this point there is no end in sight. Besides access to protective equipment for health care providers, more effort must be made in case tracing, safe transportation, distributing information, and not least in getting more experienced people working on the ground. This is crucial at this point.

Although Ebola is not the main focus of HIV & Virology News, we will try to cover some aspects of viral hemorrhagic fevers in forthcoming issues. News on new hepatitis C drugs and combinations are continuously arriving. Daclatasvir, the third new drug after sofosbuvir and simeprevir, has recently been approved, making it now possible to cure the vast majority of hepatitis C infected patients with an interferon-free regimen of approved drugs. Only the high price limits its usage.

A new antiretroviral combination pill, Triumeq, has also recently been approved. The combination of abacavir, lamivudine, and dolutegravir is already widely used. While it is an improvement to include all three drugs in a single tablet, it is not a huge difference to take one (Triumeq) instead of two pills (Kivexa and Tivicay) daily. In our experience and that of others, switching for economic reasons from one tablet of Atripla to generic efavirenz (plus Truvada or Kivexa), as discussed in the previous HIV & Virology News Editorial of February 2014, that is, going from one to two pills once a day, has been uncomplicated and does not jeopardize treatment results or adherence. Patients have been very understanding when informed of the reasons.
On June 12th, in the Swedish capital Stockholm, Karolinska University Hospital and Venhälsan presented the 6th Gilead Nordic HIV Meeting. Doctors and nurses working with HIV were invited to participate. In his welcoming address, Prof Anders Sönnerborg was pleased to announce a record-breaking number of 180 attendees.

The Scientific programme consisted of a joint session for both doctors and nurses before lunch. In this, Prof Jens Lundgren was the first speaker, and he talked about HIV and cancer.

– A study from the Danish HIV cohort found that the risk for HIV patients for cancer is 49 % higher, compared to background population. The risk is increased for virally and smoking associated cancers – not other cancers, Prof Lundgren stated. He continued with a list of mechanisms driving the risk for cancer in the immunodeficient host.

– There are pro-oncogenic factors due to lifestyle. The patient’s immunosurveillance is impaired – and a variety of pathologies causes chronic inflammation.

Prof Lundgren also pointed out that high levels of IL-6 at baseline increases the risk for cancer in the long term.

Cancers are becoming dominant cause for morbidity and mortality
Treatment with non-nucleoside reverse-transcriptase inhibitors (NNRTI:s) lowers the risk of cancer more than treatment with protease inhibitors (PI:s) – although PI:s also lower the risk.

– We have to study this more. Prof Lundgren said.

He continued by talking about screening for hepatocellular carcinoma (HCC) in HIV positive patients. If the patient has cirrhosis, an ultrasound should be performed every six months.

– A discussion if we should have increased screening for all HIV patients is ongoing. Certainly we have to ensure that they at least are screened as the background population.

In his summary he underlined that non-AIDS cancers are becoming the dominant cause of morbidity and mortality in HIV positive patients.

– Ageing, continued risk-factor exposure and no clear benefit of ART are main factors associated with a higher risk. Inflammation is also linked to excess risk – and this should be the focus for future studies, Prof Lundgren concluded.

HIV and HPV co-infections
Prof Joakim Dillner talked about HIV and human papillomavirus (HPV) co-infections.

There is a big difference in the global incidence of cervical cancer. These differences attribute to sexual behaviour and organised Pap smear screening programmes.

Prof Dillner also showed data from six
studies that showed an increased rate of HIV acquisition among HPV-positive subjects.

– It will be very interesting to follow what will happen in Sub-Saharan Africa, where many governments now have started HPV vaccination programmes, he said.

There are also much lower HPV clearance rates among HIV-infected subjects. The phenomenon is essentially restricted to subjects with CD4 cell counts of below 200.

– HAART treatment increases the likelihood of HPV clearance.

Prof Dillner also pointed out that virus-associated cancers are increased among the immunosuppressed.

– This is related in particular to decreased cellular immunity – which is known to be important for virus control. Presumably, the cancers that are increased express target antigens recognized by the immune system. The cancer risk is related to CD4 count and use of HAART.

A similar pattern is seen for solid organ transplant recipients.

HIV vaccine prices are dropping

HIV positive patients have a 30-fold excess risk for anal cancer.

– HIV positive women and men who have sex with men (MSM) have high prevalence of anal HPV infection. Even though the risk for anal cancer are particularly high in MSM, they are also significantly elevated in intravenous drug users (IDU) and heterosexuals – and among both men and women, Prof Dillner underlined.

The main preventive tool for HPV is HPV vaccines. They have near complete efficacy against HPV infection – but only if the recipient is not previously infected.

– We have a large experience – more than 100 vaccinations have been performed already. They have shown that they give long-lasting protection. The vaccine prices are dropping rapidly, and are now 20 % or below of original levels.

And they work also among HIV-infected individuals.

Organised HPV vaccination programs are effective for reducing the spread of HPV, and control of some diseases caused by HPV is already seen.

– Several additional cancers – anus, penis, vulva, vagina and tonsil – are also preventable by HPV vaccination. Well organised programmes are predicted to result in HPV elimination, Prof Dillner summarised.

Anogenital warts

Anal cancer was also the topic for the next speaker, Ass Prof Michael Gaisa. He began by telling the audience that HPV are small double-stranded DNA viruses that infect squamous epithelial cells.

– HPV is the most common sexually-transmitted infection in the United States, he continued.

Up to 75 % of new infections occur among persons 15 - 24 years of age. Most HPV infections are asymptomatic and resolve spontaneously. Clinical manifestations of HPV infections include anogenital warts, recurrent respiratory papillomatosis and cancer.

– At any given time, about 1 % of sexually active men in the US have genital warts.

Approximately 90 % of venereal warts are caused by non-oncogenic, low risk HPV types.

– While genital warts generally do not exhibit oncogenic potential, co-infection with more than one HPV type is common – particularly in sexually active men and women with multiple sexual partners, individuals with high-risk sexual behaviours and individuals with HIV, Prof Gaisa stated.

Treatment regimens for anogenital warts include patient-applied modalities, such as topical gels or ointments. Also healthcare professional-applied modalities, such as cryotherapy or surgical interventions. Recurrence of genital warts is common even after complete response to treatment.

– There are no data to suggest that treatment modalities for genital warts should be different for HIV-infected individuals. However, an immunocompromised HIV patient might not respond as well to treatment as immunocompetent persons.

All HIV-infected patients are at risk of high-grade squamous intraepithelial lesion (HSIL) – irrespective of sexual orientation – and should undergo routine screening, was Prof Gaisa's take-home message.

Need to promote testing in Sweden

One third of HIV-positive individuals in Europe are unaware of their diagnosis. Several individuals seek health care for HIV associated conditions, without having an HIV test performed.

Four speakers from four Scandinavian countries talked about this – the hidden HIV epidemic. First was Dr Johanna Brännström from Sweden. She pointed out that in Sweden HIV care is working very well – the challenge is to get patients in care.

– Late diagnosis is a true problem! A majority would clearly benefit from an earlier identification in care. At least 25

Joakim Dillner

Michael Gaisa
% have "missed presentations" within Swedish health care, Dr Brännström said. Swedish born patients are more likely to be missed at presentation with symptoms.

- And a majority of migrants from high endemic areas do not get offered health examination upon arrival in Sweden – and few take an own initiative.

Increased knowledge is needed among the public health care professionals, politicians and policy makers. We need to promote testing and we need to implement indicator guided testing further.

- We also need to increase the offer of health examinations for migrants – and to reduce stigma, Dr Brännström summarised her talk.

Walk-in rapid testing in Denmark
Dr Marie Helleberg talked about late presenters in Denmark.

Presentation with advanced HIV is associated with higher mortality in the following two years, she said.

- But those that survive the first two years have not a higher mortality.

Dr Helleberg continued by describing a walk-in clinic for rapid HIV testing of MSM in Copenhagen (the Danish capital) called Checkpoint.

- 11% of all new HIV cases among MSM in Copenhagen 2008 - 2012 were diagnosed through Checkpoint. 5% of these tested HIV positive, she said.

HIV patients diagnosed in Checkpoint were younger than those diagnosed in healthcare. 97% of those testing HIV positive were successfully referred to care, received ART and achieved viral suppression.

- Patients chose Checkpoint because testing was quick and there was easy access. In 2013 on-site testing was scaled up, and found 3.1% HIV prevalence and 11.7% syphilis prevalence, Dr Helleberg summarised.

Anonymous testing in Finland
From Finland Dr Pekka Soumalainen reported on an example of how to reach difficult patients groups via the web in South Karelia in Finland. This area has a lot of sex tourism into Russia.

Via the Finnish web portal at www.hyvis.fi citizens can get anonymous advice. No ID is needed and they can chat with an Internet-nurse.

If the patient decides to take a test with his or her ID, registration by electronic ID (web banking codes) or mobile phone ID is possible. When registering, the patient also fills in a STD questionnaire. If the test is negative, information is sent to the patient by the portal’s secure e-mail. If positive, the patient will have a doctor’s appointment at the head centre.

But there is also a way to perform an anonymous rapid HIV test in the communal health care in South Karelia.

- The patient calls the health call center and is given the time and place to go. When they arrive, they also have a 15-minute discussion about HIV infection, risks and prevention of HIV in the future.

After 5 - 10 anonymous tests per month for 18 months, no positive findings have been reported yet.

- We have not reached the older men that have been on sex trips to Russia and Thailand with this kind of testing yet, said Dr Soumalainen.

Testing on venues for MSM in Norway
A community-based HIV testing for MSM in a non-medical setting in Oslo, Norway, was described by Bera Ulstein Moseng, senior advisor in gay and lesbian health, Norway.

- This has been in operation for a year now, and it is the first time we present data, she said.

HIV among MSM continues to rise dramatically in Norway, as in USA and most western European countries. For the first time since the late 1980’s, the practice of safer sex is decreasing. MSM account for more than half of new HIV-infections, and the HIV incidence is 60-fold higher than among heterosexual women or men.

- Barriers to HIV-testing among MSM can be fear of disclosure, not considering oneself to be at risk, having experienced judgemental attitudes or inappropriate counselling as a sexual minority person, Ms Moseng explained.

Therefore testing on venues for MSM (saunas, cruising areas etc) makes it ea-
sier to recruit vulnerable MSM such as heterosexual MSM, MSM with immigrant background etc.

- Evaluation data suggest that trained peers are able to handle the test – and deliver the result of the test correctly. They also manage the task of signposting HIV-positive or MSM at risk to the ordinary healthcare system.

Overall, 573 MSM visited Checkpoint – or Sjekkpunkt in Norwegian – in 2013. 9 men (1,7 %) tested positive for HIV and 15 (4,3 %) tested positive for syphilis. 28 % had not tested for HIV the previous 2 years – and 15 % had never tested before. 63 % reported having unprotected risky sex with one or more partners the last year.

- Testing on venues for MSM effectively removes barriers to HIV testing among this sexual minority – especially among non-gay MSM. Evaluation data documents that most clients, more than 90 %, were very satisfied with peers as testers and counsellors and felt comfortable with a non-clinical setting, was Ms Moseng’s conclusion.

**Different profiles in progression to AIDS**

After this lecture the Meeting was divided into two separate programmes – one for nurses and one for doctors. In the latter, Ass Prof Asier Saez-Cirion talked about the VISCONTI study.

- Viral reservoirs perish in HIV-infected individuals receiving cART. Viral replication resurfaces as soon as therapy is interrupted – to the same level as prior treatment, he pointed out.

There are different profiles of progression to AIDS in the absence of antiretroviral treatment: 10 % have rapid progression (1 - 3 years), 85 % have “standard” progression (7 - 10 years), 5 % have long-term (more than 8 years) non-progression – but a high CD4-count and finally there are less than 1 % who are HIV controllers (HIC = infected individuals spontaneously controlling HIV-1 infection) with an undetectable viral load.

- So is it possible to induce a HIV controller like status? A long term treatment, initiated during primary infection, seems to increase the chances to control viremia. This is was the VISCONTI study aim to find out, Prof Saez-Cirion explained.

**Early treatment limits the viral reservoir**

Post-treatment controllers have low levels of HIV-1 DNA in peripheral blood mononuclear cells (PBMC), which further decreased after treatment interruption in some cases. The VISCONTI cohort consists of 14 French patients.

They were all given ART after being infected with HIV, remained on them for three years and then stopped. They are still doing well, and will be continuously followed.

- Early treatment is limiting the establishment of the viral reservoir, limiting virus diversity, reducing immune activation and preserving and cooperating with immune responses. In addition – treatment is prevention, Prof Saez-Cirion underlined.

He added that however in France, 25 % of HIV infected persons have not been diagnosed – and they are the origin of 60 % of new contaminations. In the world 40 – 50 % of individuals living with HIV do not know they are infected.

- Test and treat early – that will give both individual and global benefits, was his summary.

**Post-treatment controllers**

ART during acute HIV infection is associated with preserved immunity and small reservoir size, and may alter the HIV disease course, Dr Sarah Fidler said in her talk.

- Why can’t ART “cure” HIV? First of all reasons is the viral reservoir – an inaccessible latently infected pool of cells (predominantly CD4 T-cells) that have integrated HIV DNA. These are not recognized by the immune system because they are not actively expressing viral antigens.

And they are not blocked by ART as the current drugs block viral transcription only, Dr Fidler added.

- The reservoir of HIV is less in acutely infected individuals. That is the rationale for targeting these individuals. But they are in small numbers...

She continued by describing the HEATHER study in UK that will try to find biomarkers for finding patients that can stop ART.

- Post-treatment controllers are more common in patients treated during acute infection. Predicators for post-treatment controllers are short interval from HIV onset to ART initiation, long duration of ART and low HIV DNA and high CD4+ T cell count prior to interruption, Dr Fidler summarised and added:

  - Therapeutic HIV vaccines in addition to early ART and new drug classes have an important role in achieving functional cure.

**Probiotics supplementation of HAART**

Dr Jason Brenchley was the final lecturer. **What does the gut do in HIV infected patients** was the title of his talk.

- There are much more CD4 cells in the gut, than there is in blood, he started by saying.

The immunological damage in the gastrointestinal (GI) tract allows microbial products to translocate. Microbial translocation causes immune activation, Dr Brenchley pointed out.

- ART patients still have a shorter life-span than normal population. They die from inflammatory diseases – not the virus!

Probiotics are microorganisms beneficial to the host – via inhibition of pro-inflammatory cytokines, decreased intestinal permeability and production of short-chain fatty acids – which could lead to healing of the epithelium. Dr Brenchley continued with presenting several studies on probiotics in HIV positive people.

- Dysbiosis likely plays a role in microbial translocation. CD4 reconstitution in the GI tract is poor with ARV-only therapy.

Treatment with probiotics improves the anatomy of the GI tract system with increased CD4 reconstitution and decreased fibrosis.

- This suggests that VSL#3 (a probiotic) supplementation of HAART in HIV-infected individuals might improve GI tract immunity and also improve long term prognosis, was Dr Brenchley’s final statement.

Then the Meeting was over. Ass Prof Anders Blaxhult thanked all Speakers, the audience for coming and also Gilead for supporting it.
Evolution tends to work in small steps, a small change here, another there, a further piece acquired from elsewhere. Over time, a complex multicellular beast emerges from a soup of single cells. And so it has been with antiretroviral therapy.

The thymidine nucleoside analogue zidovudine, invented in the 60s as a potential antineoplastic agent, found its use in the 80s as the first antiretroviral. It was the drug waiting for a disease to come along. So when one idea works, people tend to look at variations on the theme, to improve and refine. We then had an adenosine analogue, didanosine, a cytidine analogue zalcitabine and a further thymidine analogue, stavudine.

It is hard to say these drugs represented refinements, as their developments all followed dose de-escalations from the first in man dose due to the development of severe peripheral neuropathy. While much of their use was initially in people who were intolerant or had failed on zidovudine, a small scale study performed at the start of the 1990s suggested incremental benefit could be gained through combining zalcitabine with zidovudine [1]. Combination therapy had begun and the initial single molecule approach underwent its first major evolutionary step towards the successful combination therapies we have today.

These initial combinations suffered from both insufficient efficacy (albeit that the tools to measure efficacy such as viral load assays were not available until the mid 90s) and the burden of combining several agents with established and relatively frequent treatment limiting adverse events. In the mid 90s several key events occurred. Roche and Chiron established viral load assays to replace the rather frequent treatment limiting side effects. Most typically, these were secondary to the nucleoside analogue drugs, where nausea, anaemia, myopathy or neuropathy led to the need for treatment modification. The development of second NNRTI agent, efavirenz, in the later part of the 1990 was the first to challenge the nucleoside analogue paradigm. Nancy Ruiz and Doug Manion at DuPont-Merck, with advice from a number of European physicians including the Frankfurt professor of Medicine Schlomo Staszewski, took the bold step of including a nucleoside sparing arm of Indinavir and efavirenz in their pivotal phase 3 DMP266-006 study. This put a nucleoside sparing regimen up against zidovudine, lamivudine and either indinavir or efavirenz. The results of the study established the hegemony of efavirenz, that is only now fading. Suppression of plasma HIV-1 RNA to undetectable levels was achieved in more patients in the group given efavirenz plus nucleosides than in the group given indinavir plus nucleoside reverse-transcriptase inhibitors (70 percent vs. 48 percent, P<0.001). However, often overlooked from this study is that the efficacy of the regimen of efavirenz plus indinavir was similar (53 percent) to that of the regimen of indinavir, zidovudine, and lamivudine. Indeed in subjects with HIV RNA at baseline <100,000 copies/ml all three regimens were similar in efficacy. It was the high baseline viral load subjects where the 2 nucleoside plus efavirenz group outshone the others [2]. The performance of the nucleoside sparing regimen is all the more remarkable when one considers that there was a considerable drug interaction between efavirenz and indinavir to manage, hence indinavir was dosed as 1000mg three times daily on an empty stomach but as 800mg in the 2 nucleoside arm, this there was a considerable tablet and administrative burden to manage in this arm.

The ACTG5142 study, a decade later, had a near identical design. In this case the superiority of efavirenz and 2 NRTIs was established over the boosted PI lopinavir/r plus 2 NRTIs. The nucleoside sparing arm containing efavirenz and lopinavir/r (again with a dose adjustments for PK issues and the need for 3 daily doses in this arm) performed similarly to the other regimens in the <100,000 copies/ml at baseline subset and similarly to the lopinavir/r plus 2 NRTI arm in the higher viral load subset. It was again at high viral load that the 2 NRTI plus efavirenz arm...
A revival in interest in NRTI-sparing

The next decade of therapy, saw an ongoing focus on nucleoside toxicity with the recognition of a range of clinical toxicities, from the occasionally fatal lactic acidosis to the profoundly stigmatising lipoatrophy. However, the 2 nucleoside paradigm remained largely unchallenged and the toxicity issues with thymidine analogues, didanosine and zalcitabine were managed though a shift to tenofovir DF or abacavir based regimens in combination with a thiazycidine. Subsequently, however there has been a gradual revival in interest in nucleoside sparing regimens due to both some concerns about the long-term nucleoside sparing regimens due to both the profoundly stigmatising lipatrophy and CNS effects ranging from the expected gastrointestinal upsets of lopinavir/r and CNS effects. Boosted PIs remain the preferred PI/s and maraviroc is a CYP3A substrate metabolised, hence no interactions with PI/s and maraviroc is a CYP3A substrate and so is pharmacoenhanced by ritonavir.

Unboosted PI and Integrase

A range of pilot studies looked at these approaches with a selection of PIs. Once exception was the SPARTAN study which used unboosted atazanavir dosed twice daily with raltegravir, making a nucleoside sparing, ritonavir free regimen. Treatment-naive patients were randomised 2:1 to receive twice-daily ATV+RAL (n=63) or once-daily ATV+r/TDF/FTC (n=31). The proportion of patients with HIV RNA ≤50 copies/mL at week 24 was 74.6% (47/63) in the ATV+RAL arm and 63.3% (19/30) in the ATV+r/TDF/FTC arm. However, the nucleoside sparing regimen had its troubles. The incidence of Grade 4 hyperbilirubinemia was higher on ATV+RAL (20.6%; 13/63) than on ATV+r/TDF/FTC (0%) and virological failure was more common with HIV-RNA values ≥400 copies/mL occurring in 6/63 patients on ATV+RAL, 4 of who had raltegravir resistance, and 1/30 on ATV/ r+TDF/FTC with no emergent resistance [4]. Thus, based on both concerns around efficacy, resistance at failure and excess hyperbilirubinemia events this approach was abandoned.

CCR5 antagonist and PI/r

The combination of maraviroc and atazanavir/r was also subject to a 96 week comparative pilot study. The dose of maraviroc used was at 150mg od, a dose that some may feel underdoses this agent. The trial included 121 treatment-naïve particpants with CCR5-tropic HIV with 1:1 randomisation to either 150 mg once-daily maraviroc or coformulated tenofovir/emtricitabine (Truvada), both with 300 mg atazanavir boosted with 100 mg ritonavir. At 96 weeks, 67.8% of maraviroc recipients and 82.0% of TDF/FTC recipients had HIV RNA <50 copies/ml (P value not calculated). Three people taking maraviroc and 2 on TDF/FTC experienced treatment failure. There were more serious adverse events (22% vs 18%, respectively) and study discontinuations due to adverse events (2 vs 1 patients) in the maraviroc arm than in the tenofovir/emtricitabine arm. Specifically, maraviroc subjects were more likely to develop icterus (17% vs 10%) but showed less decrease in creatinine clearance (5.5 vs 18.0 mL/min, respectively) and lower bone turnover and lower immune activation that TDF/FTC recipients. The relative success of this study led to a larger scale study but using Darunavir/r as the PI partner to avoid this issue of icterus [5].

The analysis of the 48-week results from the double-blind phase III MODERN study comparing maraviroc 150mg od with darunavir/ritonavir (DRV/r) to emtricitabine/tenofovir (FTC/TDF) with DRV/r in antiretroviral-naive subjects was finally presented at the recent IAS conference in Melbourne. The study did not meet the -10% non-inferiority endpoint, meaning the NRTI-sparing arm underperformed the ‘standard of care’ 2 NRTI arm. The proportion of study participants who were with HIV-1 RNA ≤50 copies/mL at week 48 was 77.3% for MVC+DRV/r and 86.8% for FTC/TDF+DRV/r (95% confidence interval -15.0% to -4.4%). The differences were most marked in the high viral load at baseline subset, with 65.4% of MVC and 79.5% of FTC/DRV recipients achieving suppression. Both arms did better in the <100,000 copies at baseline subset, 80.3% vs 88.7%, respectively.

There were more treatment failures in the maraviroc arm (10.1% for MVC and 3.2% for FTC/TDF). There were no reports of viral resistance in subjects who failed in either arm of the study.Discontinuations due to adverse events were 4.8% for MVC+DRV/r and 4.5% for FTC/TDF+DRV/r. The results were similar if a genotypic or phenotypic tropism test was used for study screening [6].

Integrase and PI/r

The other approach has been to combine a boosted PI with raltegravir. While some initial pilots studies were a success (e.g. Progress), others were less so (ACTG 5262) but none really adequately tested the regimens. In Progress, lopinavir/r was used as the boosted PI. At 96 weeks, 66.3% of subjects receiving LPV/r+RAL and 68.6% of subjects receiving LPV/r+TDF/ FTC were responders (plasma HIV-1 RNA levels<40 copies/ml) [7]. However, with a median baseline viral load around 30,000/ ml and few subjects with high baseline viral loads, the regimen was not sufficiently stress tested. Furthermore, in the developed world lopinavir/r with 2 NRTI is no longer considered a preferred regimen, having been found inferior to alternative PIs and efavirenz in comparative studies. In ACTG5262, darunavir/r was used with raltegravir. The study, however, had no comparator arm making interpretation of the (disappointing) results challenging.

Virologic failure rate was 16% by week 24 and 26% by week 48 in an intent-to-treat analysis. Viral load at virologic failure was 51-200 copies/ml in 17/28 failures. Virologic failure was associated with baseline viral load of > 100,000 copies/ml [hazard ratio 3.76, 95% CI (1.52-9.31), P = 0.004] and lower CD4 cell count [0.77 per 100 cells/μl increase (95% CI 0.61-0.98), P = 0.037]. All five participants with integrase mutations during virologic failure had baseline viral load more than 100,000 copies/ml [8].

The larger NEAT 1 study also looked at Darunavir/r once daily with raltegravir twice daily with the comparator of TDF/ FTC once daily in an open label study of 805 treatment naïve individuals. The study used a composite endpoint, similar to some ACTG studies, of time to treatment failure, incorporating 3 virological criteria (switching therapy before week 32 due to insufficient virological response or HIV RNA >50 copies/m at week 32 or at any time thereafter) and 3 clinical criteria (de-
ath due to any cause, any new or recurring AIDS-defining event, or any serious non-AIDS event). At 96 weeks, treatment failure was 17% of raltegravir recipients and 14% for TDF/FTC recipients, with confidence intervals indicating non-inferiority within a 9% delta. Most of the failure was due to viral load >50 copies/mL at week 32 or after. Similar proportions of patients in the raltegravir and TDF/FTC arms achieved HIV RNA <50 copies/ml (89% vs 93%) by a more standardITT analysis. Among people with viral load >100,000 copies/ml at baseline, treatment failure rates were 36% with raltegravir and 27% with TDF/FTC and for those with CD4 counts <200 cells/mm3, failure rates were 39% vs 21%, respectively. The differences in the low CD4 strata reached statistical significance, indicating raltegravir was inferior to TDF/FTC in this subset. Among participants with virological failure who underwent genotypic testing, 5 out of 28 in the raltegravir arm had evidence of major resistance mutations (mostly integrase inhibitor resistance) compared with none in the Truvada arm. Differences in safety parameters were modest, with greater rises in lipids in the raltegravir arm and greater falls in eGFR with TDF/FTC [9].

What went wrong?
Consistently, in initial therapy, NRTI-sparing regimens have underperformed NRTI-based therapy, mainly in subjects with late disease, but the lar...
Nucleos(t)ide sparing regimens has been an important topic of research in the field of antiretroviral therapy. Fifteen years ago the DMP-006 trial [1] explored the combination of Efavirenz and Indinavir in antiretroviral naïve patients. Since then, the search for nucleoside sparing regimens has been quite intense and—to summarize it with one word—disappointing (see accompanying article by Dr. Moyle). Not even the combination of two highly potent drugs such as Darunavir/ritonavir and Raltegravir has been able to beat—or even match—the efficacy of two nucleos(t)ides (tenofovir and emtricitabine) plus Darunavir/ritonavir in patients with high viral loads or low CD4 cell counts [2].

The rationale for nucleos(t)ide sparing regimens relies on finding a regimen that is as efficacious as a nucleos(t)ide containing regimen but offers advantages in terms of toxicity. The three toxicities that matter for most of the clinicians are bone and renal toxicity related to tenofovir, and—possibly—the increased risk of cardiovascular events associated (?) with the use of abacavir. But what about 3TC or FTC? These nucleosides have a great track record of safety and they do not have signature toxicities. Why not use them as the second drug with a boosted protease inhibitor?

This is not—strictly speaking—a nucleos(t)ide sparing regimen but it is a regimen that spares the nucleos(t)ide toxicities that really matter. One of the principal concerns about the use of this dual therapy was the fear that due to the low genetic barrier of 3TC and FTC the risk of development of the M184V mutation would increase.

At the EACS meeting in 2013 the results of the GARDEL study were presented (see HIV & Virology News Issue 4-2013). GARDEL compared in antiretroviral naïve patients Lopinavir/r and two nucleos(t)ides versus Lopinavir/r and 3TC.

To the surprise of many, the dual therapy arm did as well as the triple therapy arm regardless of viral load. There were just two patients in the dual therapy group that had the M184V mutation after virological failure. GARDEL was subsequently published in Lancet Infectious Diseases [3] and the combination of Lopinavir/ritonavir plus 3TC appears as an alternative regimen for antiretroviral naïve patients in the recently published guidelines of the International AIDS Society [4].

It stands to reason that if the combination of a boosted protease inhibitor plus lamivudine has worked in antiretroviral naïve patients regardless of baseline viral load, this combination would also work in patients who have already achieved suppression of viral replication. This is precisely the hypothesis that has been tested in two trials presented at the 20th International AIDS Conference held this past summer in Melbourne. The two trials have catchy acronyms: SALT (Simplification to Atazanavir/Ritonavir + Lamivudine as Maintenance Therapy) [5] and OLE (Only Lopinavir and Epivir) [6].

Both trials are switching trials that have been carried out in Spain (SALT and OLE) and in France (OLE).

SALT

SALT is a 96-week multicenter, randomized, open-label, clinical trial that compares Atazanavir/Ritonavir +3TC with Atazanavir/Ritonavir + two nucleos(t)ides (selected at the discretion of the investigator) in HIV-infected patients on a stable triple drug regimen who switch therapy because of toxicity, intolerance, or simplification. The primary objective of SALT is to demonstrate the non-inferiority of the dual combination at 48 weeks with a non-inferiority margin of –12%.

SALT enrolled 286 patients who had been receiving stable ART for at least one year and who have remained virologically suppressed for at least the prior six months. Important exclusion criteria were previous treatment failure, history of resistance mutation to study medications and chronic hepatitis B.

All patients included in SALT switched their current ART regimen to Atazanavir/ritonavir and two nucleos(t)ides during a transition or lead-in phase that lasted four weeks. The goal of this transition phase was to guarantee that patients tolerated Atazanavir/ritonavir. After this phase half of the patients switched their nucleos(t)ides to Lamivudine 300 mg QD. The majority of the included patients were male (73%) with a high baseline CD4 cell count (median 583 cells/µL), who have been virologically suppressed for more than two years (median 28 months).

Approximately two thirds of the patients switched away from another boosted protease inhibitor based regimen and one third switched away from a non-nucleoside reverse transcriptase inhibitor-containing regimen.

In SALT treatment failure was defined as two consecutive HIV RNA levels above 50 copies/mL at week 48, loss to follow-up, >
or discontinuation/ modification of randomized treatment. Using these criteria, treatment efficacy was 83.6% for Atazanavir/ ritonavir plus 3TC and 78.4% for Atazanavir/ ritonavir plus two nucleos(t)ides. (Figure 1). The lower extreme of the 95% CI went down to -4.8% clearly showing the non-inferiority of the dual combination. At week 48 there were nine virological failures; five in the Atazanavir/ ritonavir plus 3TC arm and four in the Atazanavir/ ritonavir plus two nucleos(t)ides arm. Only one patient in the triple therapy arm developed resistance mutations (M184V). There were no differences between arms in toxicities. As expected the most common adverse event was hyperbilirubinemia and jaundice. Changes in renal function, bone density, and fat gain/ distribution between groups were similar.

**OLE**

OLE is a 48-week multicenter, prospective, randomized, open-label, non-inferiority trial. (Disclosure: I am one of the co-chairs of the study).

In contrast with SALT to be enrolled in OLE patients had to be already receiving treatment with Lopinavir/ ritonavir and two nucleos(t)ides for at least four weeks.

Patients had to be virologically suppressed for at least six months and could not have prior resistance to Lopinavir/ ritonavir or Lamivudine. Chronic hepatitis B was also an exclusion criterion.

The primary endpoint was the proportion of patients free of therapeutic failure at 48 weeks defined as two consecutive viral load measurements above 50 copies/mL, death, progression to new AIDS defining disease, loss to follow-up or change or permanent discontinuation of any antiretroviral treatment for any reason. There were also purely virological endpoints. The non-inferiority margin was also 12%.

As in SALT, the majority of patients enrolled in OLE were male with a good immunological status (median CD4 cell count 610 cells/µL). Patients have had undetectable viral loads for a median of almost four years (47 months). The most common nucleos(t)ides used were TDF/ FTC (61%) and ABC/3TC (26%).

In the intention to treat population proportion of patients free of therapeutic failure at week 48 were 82.8% in the dual therapy arm and 86.6% in the triple therapy arm (Figure 2). The lower extreme of the 95% CI was -1.2% which clearly demonstrates the non-inferiority of the experimental dual therapy.

In OLE we have performed multiple sensitivity analysis to support the main endpoint analysis. Looking at proportions of patients with protocol defined virological failure (two consecutive viral loads of 50 copies/mL or above), blips or the combination of virological failures or blips the 95% CI again showed the non-inferiority of the dual therapy arm. We found no differences between arms in lipid or creatinine changes. There were no significant differences in the incidence of adverse events or laboratory abnormalities.

The M184V mutation was found after virological failure in one patient randomized to the dual therapy arm.

**Summary**

OLE and SALT results certainly supports the use of a boosted protease inhibitor plus Lamivudine as a switch strategy in patients who have achieved virological control. Results were expected given the good outcomes seen in the GARDEL study with Lopinavir/ ritonavir and Lamivudine in antiretroviral naïve patients. In contrast with GARDEL, Lamivudine was used once daily both in SALT and OLE. Importantly, in both trials the control arm included nucleos(t)ides recommended by expert guidelines. GARDEL results have been questioned because a large proportion of patients in the control arm received Zidovudine and therefore results are not immediately applicable in the developed world. This is not the case in SALT and OLE.

Although it is true that none of the trials have shown a benefit of the dual therapy strategy in terms of avoiding toxicity we should not forget that the toxicities we try to avoid occur long term and cannot be captured in trials of short duration. In contrast with monotherapy studies, the dual combinations using 3TC did not show an increased risk of low-level viral rebound and the risk of selecting for the M184V mutation appears to be minimal. Since efficacy has been matched, the burden of the proof can be transferred to the triple therapy defenders: why should I add TDF of ABC to a boosted protease inhibitor plus 3TC? One final question is if the results would be applicable to Darunavir/ ritonavir: most likely, but if you want empirical evidence the DUAL study (DarU navir And Lamivudine) is already enrolling patients in Spain [8].

**Figure 2**

![Figure 2](image-url)

**References**


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The 4th North European Workshop on HIV Infection in the CNS (HANSA)

The 4th North European Workshop on HIV Infection in the CNS was held 9–10 May 2014, once again in Berlin. The meeting is organized as a collaboration between the University of Gothenburg and Abbvie. The numbers of participants and countries represented have increased each year. If you want to hear the latest about ongoing HIV CNS research and learn about how to translate this into clinical management, this is the meeting to go to. Focus this year, besides clinical complications and management of HIV CNS infection, was on CNS infection, inflammation and injury in treated HIV patients, and the CNS as a reservoir and implications for cure.

There was a very appreciated session where participants contributed with interesting case reports, and we could learn about things like Alice in Wonderland syndrome (could be associated with EBV encephalitis), inclusion body myositis, CNS escape, psychosis caused by efavirenz (most likely), and CNS manganosis in an intravenous drug user (look it up, if you have not heard of it!)

HIV CNS infection, inflammation, and injury in treated HIV
Steve Deeks, USA, the first speaker of the workshop addressed the issue of inflammation and ageing. Antiretroviral treatment (ART) results in rapid control of HIV replication and partial restoration of immune function, leading to prevention of the various complications that define AIDS. However, several studies have demonstrated that treatment does not fully restore health. Figure 1 illustrates the causes and consequences of HIV-associated inflammation. HIV-infected adults who have durable ART-mediated suppression of HIV replication are at risk for developing several non AIDS disorders, including cardiovascular disease, cancer, kidney disease, liver disease, osteopenia/osteoporosis, and neurocognitive disease.

The impact of HIV on risk for cardiovascular disease in some studies is comparable to traditional risk factors including hypertension, diabetes mellitus, and hyperlipidaemia. Why is it that antiretroviral-treated adults have an excess risk of these seemingly unrelated non-AIDS events? Traditional risk factors, antiretroviral drug toxicity, and metabolic changes do not fully explain all the excess risk for non-AIDS morbidity. Many markers of inflammation are higher in antiretroviral-treated adults than in age-matched uninfected individuals. Small rises in many of these biomarkers (for example interleukin 6, CD14, and CD163) are associated with dramatic increases in the risk of subsequent disease, including all-cause mortality. Whether HIV leads to accelerated or premature ageing depends on how one defines ageing, but HIV infection and its treatment has been shown to affect the biology of ageing (inflammation, cellular senescence, telomerase/telomeres, mitochondrial disease).

Many HIV-associated factors could affect healthy ageing (Figure 2), and preventing age-associated complications might be easier than reversing them. Dr Deeks rounded up his presentation by sharing what he does with his patients; putting everyone on ART and talking about exercise and food with his patients.

CNS compartmentalization
Ron Swanstrom, USA, talked about the difficult to pronounce phenomenon of CNS compartmentalization. Compartmentalization is indicative of local CNS replication, and late in disease is linked to HIV-associated dementia. Compartmentalized viral populations can comprise either CCR5-using T cell-tropic or macrophage-tropic virus. Macrophage-tropic HIV-1 variants are characterized by the ability to infect cells with low CD4 surface expression, are poorly represented in blood, are not transmitted, and decay slowly following initiation of ART,
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unlike the rapid decay of virus replicating in activated CD4+ T cells in blood. In heterosexual transmission 80% of infections are initiated with a single virus variant and all evolution in the individual evolves from this single variant. The remaining 20% are infected with two or more variants. Dr Swanstrom presented data on viral compartmentalization of 43 HIV-1 subtype C-infected children. About half of the children under 18 months of age had an intermediate level of compartmentalization. Vertically transmitted viruses are often highly homogeneous, representing infection seeded by a single variant and characterized by low diversity, but in some of the children two variants were transmitted from the mother. In several of these cases one of the transmitted viruses was replicating in the CNS while the other was found predominantly in the blood/periphery. The results that Dr Swanstrom presented suggests that compartmentalized CSF/CNS populations can be detected in up to 50% of children by year three, either established early in the infection or through sequestration of a transmitted variant within the CNS.

**ART simplification and the CNS**

Alan Winston, UK, has participated in all four HANS A meetings, talked about ART simplification and the CNS during this 4th workshop. The reasons for ART simplification are several; patient preferences, adherence issues, end organ toxicities, polypharmacy, and costs. Dr Winston guided the audience through the various ways of simplification that have been studied. The first one is to switch therapy whilst maintaining nucleosides, for example to switch the fixed-dose combination with efavirenz/tenofovir/emtricitabine (since efavirenz is associated with neurotoxicity) to the fixed-dose combination with rilpivirine/tenofovir/emtricitabine or elvitegravir/cobicistat/tenofovir/emtricitabine. These studies were however unblinded and the placebo effect could have contributed to the results. Are we using to high doses of antiretroviral drugs? A second strategy to simplify treatment could be to reduce the doses. One example is efavirenz, where the same antiviral effect is reached with 200 mg, 400 mg, and 600 mg once daily. The third alternative is by excluding (for example the NEAT trial with darunavir/r + raltegravir versus darunavir/r + tenofovir/emtricitabine) or limiting (for example reyzataz/r + lamivudine in the AtLaS study) use of nucleosides in the ART regimen. The fourth, and most drastic simplification strategy is by using PI/r monotherapy.

Dr Winston presented results from the PIVOT trial, which included 587 patients from 43 sites in UK. Main inclusion criteria were (1) on 2 NRTIs + PI/r or NNRTI for > 24 weeks, (2) plasma HIV RNA < 50 copies/ml for 24 weeks, and (3) CD4 > 100. Participants were randomized to switch to PI/r monotherapy or to continue with triple therapy. Almost all patients in the PI/r monotherapy arm were on darunavir/r or lopinavir/r. Five cognitive domains were tested at baseline and yearly thereafter. Patients were followed for five years. Regarding neurocognitive function, there was no difference between the two groups at the final visit (Figure 3).

Approximately one third of the patients on PI/r monotherapy had virological failure, all of these were re-suppressed after the addition of two nucleoside analogues. There is a CSF substudy of the PIVOT trial that is still ongoing. Dr Winston summarized by saying that the results of the PIVOT trial shows that PI/r monotherapy is safe if used in selected patients, but that we have to be careful in choosing the right patients. There are many unanswered questions, such as if there are any effects of viral rebound on neurocognitive function. We are eagerly waiting for the results of the CSF substudy of the PIVOT trial that is still ongoing.

**Psychiatric complications in treated HIV**

HIV infection has evolved from being a fatal disease to a chronic manageable condition. With this change has also fol-
lowed new challenges in the management of our patients. HIV infected individuals, however, still continue to face extensive social challenges, stigma and discrimination, and social isolation. Adriana Carvalhal, Canada, focused her presentation on the most common psychiatric disorders associated with HIV, namely mood disorders and substance abuse. Depression is more prevalent among HIV infected individuals (life time prevalence 22–45%) compared to the general population (life time prevalence 15%). An HIV infected individual with depression is less likely to receive ART and more likely to engage in risk behavior. Figure 4 lists risk factors for depression in HIV-infected individuals. HIV-associated depression remains poorly understood, but there is probably a complex interaction between psychosocial factors, viral toxicity, and neuroinflammation. When it comes to treatment of depression in HIV-infected patients, the first choice is the SSRIs. They have been shown to modulate immune activity and, theoretically at least, depressed patients with inflammatory conditions (such as HIV) could potentially benefit from anti-inflammatory therapy such as the SSRIs.

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Risk Faktors for Depression
- Number of years living with HIV
- Avoidance vs. active coping style
- Excessive rumination about health-related problems
- Past history of depression
- Other psychiatric disorder - SUD
- Personality disorders
- Low social support
- Low education
The HCV drug-rally is ongoing: Simeprevir and Daclatasvir approved by EMA!

The first step towards the long-awaited interferon-free therapy of hepatitis C was the approval of the HCV polymerase inhibitor sofosbuvir in January 2014. However, sofosbuvir combined with the old friend (or foe?) ribavirin was still suboptimal and many patients with advanced liver disease could not be cured by this first IFN-free approach. Therefore it is very fortunate for many patients that the European Commission approved two new HCV drugs which are targeting other viral enzymes allowing very potent new combination therapies.

The HCV protease inhibitor simeprevir (Olysio®, Janssen-Cilag) – which has become available in the US and in Japan already during the second half of 2013 – was approved in Europe in May 2014. Daclatasvir (Daklinza®, BMS), the first-in-class HCV NS5A inhibitor, was granted marketing authorisation in August. Remarkably, both new drugs can be used with interferon alpha in combination with sofosbuvir even though only small phase 2 data are available for each IFN-free regimen.

These approvals represent major steps forward on the pathway towards highly effective therapies against hepatitis C. In principle, we have now tools to cure almost every hepatitis C patient. Different combinations are now possible and additional options may become available during the next months with the expected marketing authorisations for the Gilead single-tablet regimen ledipasvir/sofosbuvir and the “Abbvie-3D” regimen.

Further programs are ongoing by Merck, BMS, Gilead, Abbvie, Achillon and others.

Simeprevir

Simeprevir (formerly called TMC-435) is the third HCV protease inhibitor (PI) that has been approved in Europe. However, in contrast to the “first generation” PIs boceprevir and telaprevir, simeprevir can be dosed once daily and the safety profile is much better. Thus far, the compound did not show any relevant haematological side effects and also dermatological adverse events were much more favourable as compared to telaprevir. Mild photosensitivity can be managed easily by sun-blockers, and 97% of rashes in phase 3 trials (reported for about one quarter of patients) were very mild with grade 1 or 2.

Four years ago a “classical” phase 3 program has been initiated investigating simeprevir in combination with PEG-interferon alfa and ribavirin. Triple therapy was given for 12 weeks followed by a PEG-IFNa/ribavirin tail of additional 12-36 weeks depending on early on-treatment responses – “response guided therapy” based on rapid virological responses at treatment week 4.

Importantly, more than 85% of patients achieved a RVR defined as an HCV RNA value of <25 IU/ml and thus qualified for a short overall treatment duration of 24 weeks. SVR rates were 88% in these patients (1,2). The European label recommends not to continue therapy if treatment HCV levels are >25 IU/ml at week 4. This early “stopping rule” is very helpful in the management of patients as patients may try 4 weeks of triple therapy. Nine out of ten patients can continue and most of these patients will eventually cure HCV infection. Moreover, non-RVR patients have been exposed for only 4 weeks to the drugs and unnecessary prolonged therapies can be avoided. Simeprevir is recommended for HCV genotype 1 and 4 infections. The drug is ineffective against HCV genotypes 3 and 5.

The main disadvantage of PEG-IFNa/ribavirin/simeprevir triple therapy is that patients have to be treated with PEG-IFNa for 24 weeks while sofosbuvir-based triple therapy is 12 weeks only for all patients independently from on-treatment HCV RNA kinetics.

In addition, patients with HCV genotype 1a scheduled for simeprevir in combination with PEG-IFNa/RBV should be tested for a specific HCV variant (“Q80K”) since simeprevir is not active against this variant. Q80K can be detected in 30%-50% of all patients infected with HCV genotypes 1a. Thus, PEG-IFNa/ribavirin/simeprevir is not recommended as a preferred first-line treatment option by most international guidelines.

However, simeprevir is recommended in combination with sofosbuvir without interferon and even without ribavirin. The European approval is based on the Cosmos phase 2 study which investigated simeprevir + sofosbuvir with or without ribavirin for 12 or 24 weeks. 167 patients were recruited in two cohorts based on the fibrosis status and previous exposure
The HCV drug-rally

to PEG-IFNa/RBV therapy (3). Study results were remarkable even for previous PEG-IFNa/RBV treatment failures with liver cirrhosis. More than 90% of patients cured HCV infection across all study arms and different cohorts irrespectively from treatment duration (12 vs. 24 weeks). The administration of ribavirin did also not increase SVR rates.

Interestingly, the far majority of patients carrying the Q80K variant were cured when simeprevir was combined with sofosbuvir suggesting that the presence of resistant-associated variants (RAVs) before therapy is of minor relevance if a DAA is combined with a potent nucleotide with a high barrier to resistance. Even though exciting, these data need to be confirmed in much larger cohorts.

Moreover, we do not know yet if 12 weeks SIM-SOF without ribavirin are sufficient for patients with more advanced liver disease (e.g. Child-Pugh B cirrhosis). Finally, it is not clear yet how simeprevir must be dosed in patients with decompensated cirrhosis as drug levels may be difficult to predict in patients with severely impaired liver function. Phase 3 studies are ongoing and some of these questions should be answered within the next 6–9 months.

The label recommends simeprevir and sofosbuvir for patients who are intolerant to interferon and if there is an urgent need for therapy. Thus, in most countries and settings, this treatment option cannot be used yet for HCV-infected patients without liver cirrhosis or other distinct reasons for antiviral therapy.

**Daclatasvir**

Daclatasvir is a very potent and first-in-class “NS5A-inhibitor”. The HCV NS5a protein has multiple functions in the HCV life-cycle; e.g. NS5A is involved in replication and packaging of the virion. More than 5000 patients have been treated already with daclatasvir as part of various investigational regimens. The clinicaltrials.gov registry lists combination therapies of daclatasvir with PEG-IFNa and ribavirin, PEG-IFN lambda, the BMS protease inhibitor asunaprevir, asunaprevir + BMS791325 (a non-nuc), sofosbuvir, VX-135, and even simeprevir.

The “Command” phase 2 program investigating daclatasvir in combination with PEG-IFNa and ribavirin revealed that addition of daclatasvir may increase response by 20%-50% in genotype 1 or 4 patients as compared to the old PEG-IFNa/RBV combination therapy (4). Of note, response were better in HCV genotype 1b vs. 1a (“b=better” in genotype 1!!).

This notion is also inline with combination therapies of daclatasvir with asunaprevir, the BMS protease inhibitor. This was the very first publication on cure of chronic hepatitis C by an IFN-free regimen which was published by Anna Lok in February 2012 in the New England Journal of Medicine (5).

Two out of nine genotype 1a patients and both genotype 1b patients were cured in that pilot trials. Subsequently, a phase 3 program was initiated with asunaprevir and daclatasvir in genotype 1b patients only. The Hallmark study was just recently published in the Lancet and the combination has been approved in Japan in August 2014 (6). Asunaprevir+daclatasvir has also been submitted for review by the FDA.

The development of daclatasvir was different in Europe. Last November, the European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) advised to use daclatasvir in combination with sofosbuvir in a compassionate-use-program.

This recommendation was based on request for a CHMP opinion by Sweden and supported by data from a phase 2 study (“the 040 study”) (7). This phase 2 study included roughly 200 patients who were treated for 12-24 weeks with daclatasvir and sofosbuvir with or without ribavirin. It is important to note that cirrhosis was an exclusion criterion. However and im-
The HCV drug-rally

portantly, 41 patients were included who were treatment failures to triple therapy regimens with boceprevir or telaprevir. Very interestingly, only one single patient with HCV genotype 3 infection had a confirmed virological failure in this study. 6 additional patients without a documented SVR-12 in the intent-to-treat analysis did either miss the follow-up week 12 visit, had an HCV reinfection with another viral strain (1 patient) or were treated with PEG-IFNa/RBV when not being HCV RNA negative at week 8 (1 patient).

All other patients cured the infection. BMS submitted these phase 2 efficacy data in combination with the large safety data set to EMA and the European Commission approved daclatasvir for hepatitis C in combination with other antiviral drugs in August 2014.

The label suggest to treat HCV genotype 1 infection without cirrhosis with daclatasvir and sofosbuvir for 12 weeks while patients with liver cirrhosis and patients with genotype 3 infection should receive 24 weeks of therapy. Phase 3 data are ongoing to investigate if 12 weeks of therapy are sufficient even in patients with advanced liver fibrosis and also in patients after liver transplantation.

Hopefully, we will see also “real-world” efficacy and safety data of this promising combination during the next 6 months also to answer the question if ribavirin is still needed for this combination in particular settings.

Simeprevir plus daclatasvir?

When both simeprevir and daclatasvir can be combined with sofosbuvir with great success, an obvious question is if simeprevir and daclatasvir can also be used together. This has been studied in the LEAGUE-1 study mainly in patients with genotype 1b but also in few patients with genotype 1a (here in combination with ribavirin).

However, daclatasvir was used here at a lower dose with 30mg QD only (instead of 60mg QD as in all other trials) (8). SVR-12 rates were between 65% and 95% in the different treatment arms indicating efficacy but also emergence of treatment failures in substantial number of patients. If higher doses of daclatasvir would also fail in substantial number of patients. If higher doses of daclatasvir would also fail in substantial number of patients. If higher doses of daclatasvir would also fail in substantial number of patients. If higher doses of daclatasvir would also fail in substantial number of patients. If higher doses of daclatasvir would also fail in substantial number of patients. If higher doses of daclatasvir would also fail in substantial number of patients.

The drugs are approved – can we use them in clinical practice?

EMA has to be congratulated that two innovative drugs were approved based on limited phase 2 efficacy data but with a large set of safety data generated in different combinations. The new treatment options can potentially save many lives and help many patients. However, these new medicines are not for free. E.g., daclatasvir plus sofosbuvir for 24 weeks would be now the preferred treatment option for HCV genotype 3 infection in patients with cirrhosis.

In Germany, this combination would cost up to 200.000 Euro! Even if costs are lower for different clinical situations and in other countries, there is an enormous economical pressure on all health systems. There is no easy answer and but physicians are certainly responsible to use the new medicines in a responsible way. Most likely we will have to prioritize therapies by urgency for some years before HCV can be eradicated by treatment!

HEINER WEDEMAYER

References


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The long-term control of HIV infection with mandatory antiretroviral therapy (ART) has raised new challenges. The main question patients in our clinic are asking is “Doctor, is there any good news from the big Australian conference to give us hope that we will be able to be cured someday and not need our medication?”

Among our clinical challenges, finding a path toward an HIV cure is one of the greatest and most anticipated worldwide. Along the way there remain many questions that have no clear answers. We especially need a better understanding of why immune activation and inflammation persists once a virus is suppressed in plasma. This question is not only of interest to immunologists and basic researchers, but also to clinical therapists, since this state of hyperinflammation is not only of interest to immunologists and basic researchers, but also to clinical therapists, but also to clinical researchers, but also to clinical therapists, but also to clinical therapists.

Each international conference resolves a piece of the puzzle and fills in some of our missing knowledge. Basic science was not at the centre of the International AIDS Conference (IAC) held in Melbourne this year, but let’s look at some of the contributions from there.

The Search for the Cure: some good and some bad news

The bad news: viral rebound for the Mississippi baby. A few days prior to the conference, those clinicians and researchers who had started to believe in the possibility of a functional cure, as encouraged in part by the “Mississippi baby” [1], were saddened and disappointed to learn that the famous baby had rebounded.

Everyone recalls the hopes raised by this baby, who was born prematurely in a Mississippi clinic in 2010 to a mother who had not been diagnosed with HIV and therefore did not receive antiretroviral (ARV) prophylaxis until the time of delivery. The infant was started on triple drug therapy at 30 hours and had an excellent viral response to HIV replication, rapidly showing full viral suppression.

The baby continued on ART until 18 months of age, when she was lost to follow-up and so no longer received treatment. When she was brought back to the hospital five months later, no HIV could be found in her plasma, nor were HIV-specific antibodies detected. The child continued to do well in the absence of ARV medicines and remained free of detectable HIV. About 2 years later, at a routine visit where her viral load was monitored, plasma HIV RNA was detected at a level of 16,750 copies/mL and confirmed at 10,564 copies/mL of virus. As expected following the resumption of viral replication, antibodies reappeared and CD4 lymphocytes declined. At that point the child, who is now 4 years old, was off therapy for nearly 2 years and had been considered functionally cured. She was now restarted on ART. Genetic sequencing of the virus indicated that the child’s HIV infection was the same strain as that acquired from her mother.

Although these developments might have been predicted from the beginning, as time passed everyone wanted to believe in the amazing story of the Mississippi baby. The case indicates two things: first, that a prolonged period off therapy is possible if treatment is initiated very early and limits reservoir and immune function disruption. Second, that the child was able to control viral replication for nearly 2 years without the specific anti-HIV immune responses with which we are familiar.

This presents a unique situation for Deborah Persaud of Johns Hopkins Children’s Center in Baltimore and Katherine Luzuriaga at the University of Massachusetts Medical School. They must now try to understand what could have triggered the replication of cells in the first place.

Today, the only ones who have remained functionally cured are the Visconti cohort. As in the case of the Mississippi baby, they were treated at the time of primary infection, but for a longer period of about 3 to 4 years [2]. As the elite controller group, they shared the virologic characteristic of having very low blood cell-associated HIV DNA, along with the Mississippi baby.

A low reservoir alone was clearly not enough for the Mississippi baby. Will this be different in the case of chronically-infected adult patients? What is the missing factor that the Visconti patients possess? Perhaps next year will bring more news about this exciting and difficult research problem.

Good news from Aarhus University

After first introducing it at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI), the Danish team of Infectious Diseases and Clinical Immunology from Aarhus University has come up with promising data about panobinostat.
(PNB), a new histone deacetylase inhibitor (HDACi) [8].

**Background**

The “shock and kill” strategy aims to disrupt HIV by “shocking” it out of latency, then making the “kill”. Identifying a relatively safe modality to reactivate latent HIV in memory cells is an important step toward an HIV cure. The maintenance of latency is a complex process involving several mechanisms that restrict viral replication. One of them is the modification of the long terminal repeat (LTR) by methylation and alteration of the chromatin environment by histone deacetylation (HDAC) or other epigenetic modifications.

While acetylation of the lysine residues on the histone tails relaxes the chromatin structure and allows for gene expression, deacetylation of those tails leads to condensation of the chromatin structure and the silencing of gene expression. In accordance with this mechanism, HDACIs have been shown to induce HIV transcription in latently infected cells. Many HDACIs have considerable differences in their effect on HIV gene expression [4].

**Panobinostat**

Earlier this year, Rasmussen [3] presented the results of a non-randomized interventional phase 1/II trial designed to evaluate the effect of PNB (20 mg 3 times weekly every other week for 8 weeks) on the latent HIV-1 reservoir in 15 aviremic HIV-infected patients on ART. In brief, the results were a reactivation by PNB of latent HIV with a significant increase in cell-associated RNA. However PNB had no impact on the a production of plasma HIV RNA, suggesting that the reactivation was not potent enough to induce active viral production. Importantly, other compounds of the HDACi class are in development, as can be seen in the latest trials with romidepsin (RMD).

**Romidepsin**

RMD is licensed in the US by the Celgene Corporation for the treatment of cutaneous T-cell lymphoma. In an in vitro T-cell model, RMD was the most potent inducer of HIV (EC50 = 4.5 nM), compared to vorinostat (VOR) or PNB. While the increase in intracellular HIV RNA was 2- to 3-fold with VOR or PNB, RMD led to a 6-fold increase with persistent activity over 48 hours. Such an effect was observed at concentrations lower than the plasma levels achieved in patients treated for T-cell lymphoma [5].

Next came the clinical study presented in July 2014 by Sogaard et al. [6]. This was a non-randomized interventional trial in 6 chronically infected middle-aged (54 year old) HIV-1 patients on ART for a median time of 9.5 years with a median CD4+ cell count of 760 cells/mm3 (range 510-1000). RMD was given as an IV infusion of 5 mg/m2. Each a dose was the equivalent of one-third of the standard dosing used in cancer treatment on days 0, 7, and 14.

**Safety**

RMD appears to be globally well-tolerated and requires no treatment discontinuation. Reported adverse effects were mostly mild abdominal symptoms and fatigue that spontaneously resolved within a few days. A mild decrease in peripheral blood cells following RMD infusion returned to baseline after 7 days.

**Efficacy**

The quick increase in the degree of histone acetylation that followed 1 to 2 hours after infusion confirmed the pharmacodynamic effect of an HDACi on cells.

**Effect on cell-associated RNA**

A first approach toward evaluating whether the compound was effective in releasing HIV from HIV transcription within CD4 cells was measuring the cell-associated HIV RNA observed in all 6 patients. The greatest increase was noted after the second and third infusions.

**Impact on HIV RNA**

The next challenge for an HDACi is to release viral particles from the cells into the blood. Two assays for HIV RNA measurements were employed: the Cobas standard assay with a cut-off at 20 copies/ml, and a qualitative Transcription-Mediated Amplification (TMA) assay used by blood banks for screening donor blood for early signs of HIV infection. After the first infusion, 3 of 6 patients had HIV RNA that became quantifiable; at the second infusion, 5 of 6 patients had a release of HIV RNA plasma that returned to baseline after 7 days. The third infusion was slightly less productive. Overall, 5 of 6 patients reached quantifiable RNA plasma levels during the 3 infusions. TMA showed that the proportion of patients with positive samples increased from 50% at baseline to 90% 3 days post-infusion.

Overall these data favour the use of RMD as a reactivating agent that “kicks” the latently infected cells out of latency.

**Impact on CD4/CD8**

RMD immediately induced changes in the composition of the peripheral CD4+ and CD8+ compartment, causing a shift toward a larger proportion of naïve cells and fewer effector and central memory cells. However, the changes had almost reversed by day 10, and CD4 T-cell activation as measured by CD69 increased.

Moreover, these encouraging results on the ability of RMD to release viral particles from latent virus did not translate into any change in total HIV DNA.

**HDAC inhibitors and activation/inflammation**

HIV infection is characterized by a state of inflammation and immune activation that may not normalize with suppressive ART and may contribute to the development of end-organ disease in HIV-infected people. Recently, circulating markers of inflammation (including interleukin-6 [IL-6], high-sensitivity C-reactive protein [hs-CRP], and soluble CD14 [sCD14]) have been shown to predict all-cause mortality in cases of HIV infection, enhancing interest in biomarkers as predictors of morbidity and mortality in this patient population. Several compounds are currently being studied to evaluate their impact on inflammation and immune activation markers.

In addition to their potential role in disrupting HIV latency, HDACIs exert potent anti-inflammatory effects. Therefore, the Danish group hypothesized that the HDACi PNB would reduce inflammation in carefully monitored HIV patients [7]. The 15 patients in the PNB pilot study mentioned above have been on ART for a median of 3.2 years with a median 935 CD4 cells/mm3.

Plasma levels of 8 soluble biomarkers were determined a) at baseline, b) 4 days after initiating treatment, and c) 4 weeks after completing treatment using an enzyme-linked immunosorbent assay (ELISA) and Luminex. Gene expression in peripheral blood mononuclear cells (PBMCs) was analyzed on a Human Transcriptome Array (HTA) 2.0 chip (Affymetrix).

Multiple significant changes from baseline in plasma inflammation were observed during and after PNB treatment (see table below). Notably, hs-CRP decreased by a mean of 50% during treatment, and this change persisted 4 weeks post-treatment. Plasma levels of IL-6, MPP-9, sE-selectin, and sCD40L also decreased, while sCD14 increased. On day 4, IL-1β gene expression levels were downregulated 2-fold (p = 7.9×10−9, FDR = 4.1×10−6) and IL-8 expression levels 4-fold (p = 1.1×10−6, FDR = 0.00016), compared to baseline.

We must ask ourselves if there is a difference in terms of activation/inflammation...
Employee of the month:
Age 9

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between different ARV drugs. Persistent immune activation in HIV-infected patients on ART may be the result of one or more stimuli such as concomitant infections or comorbidities, enterocyte damage leading to microbial translocation, or medication-specific toxicities. Determining how markers of monocyte activation and inflammation change following ART initiation could help define the mechanism driving these changes.

The large ACTG 5257 study is a Phase III, prospective, multi-centre, open-label trial that has randomized 1809 HIV+ ART-naïve subjects into 3 randomized 1:1:1 non-nucleoside reverse transcription inhibitor-sparing (NNRTI) ARV regimens (TDF/FTC plus raltegravir [RAL], or plus atazanavir [ATV]). It has demonstrated the virological efficacy of those regimens. The objective of a sub-study (ACTG A5260s) was to evaluate whether various ART strategies would have different impacts on biomarkers of systemic inflammation, macrophage, and T-cell activation.

It remains unclear whether integrase inhibitors such as RAL may reduce inflammation and immune activation compared to other ARTs, including protease inhibitors (PIs) or NNRTIs. The study has enrolled 328 patients selected from the baseline population who have no known cardiovascular disease (CVD), diabetes mellitus, or use of lipid-lowering medications. In order to avoid bias from patients who may not have reached full virologic suppression status, only 234 patients with HIV RNA > 50 copies/ml at Week 24 and thereafter were analyzed: 109 in the atazanavir/raltegravir (ATV/r) group, 106 in the RAL arm, and 113 in the darunavir/ritonavir (DRV/r) arm.

Biomarkers were assessed at baseline, Week 24 (cellular markers), Week 48 (plasma markers), and Week 96. These included markers of

- inflammation and coagulation: hs-CRP, IL-6, D-dimer
- macrophage activation: sCD14, sCD163, %CD14+CD16+ of monocytes
- T-cell activation: sIL-2r, %CD38+HL-ADR+ of CD8+ T-cells
- Changes were measured as the ratio of follow-up to baseline (mean fold change) at 24 and 96 weeks for cellular biomarkers and 48 and 96 weeks for plasma biomarkers. Ratios of 1.0 indicate no change.

A total of 234 mostly male patients, with a baseline CD4 and HIV RNA participated in the study. The overall results can be summarized as follows:

- Biomarker changes varied by regimen
- Hs-CRP declined with ATV/r and RAL for 96 weeks
- IL-6 declined with RAL (but not with ATV/r and DRV/r) at 96 weeks
- D-dimer declined with ATV/r and DRV/r
- After ART initiation, both T-cell activation and sCD163 (but not sCD14) declined similarly across groups
- Over a 96 week follow-up period, RAL had no differential effect on systemic inflammation and immune activation compared to PIs

These results suggest an incomplete reversal of inflammation and immune activation due to effective treatment with these different therapeutic agents. Longer follow-up may better define regimen differences and correlations between these markers and long-term complications. This is of particular importance at a time where options for effective ART have expanded. Is early ART capable of reversing persistent gut inflammation and CD4 cell depletion? The gastrointestinal (GI) tract is an early site of viral replication and pathology in HIV infection. HIV induces depletion of the lamina propria (LP) and CD4+T-cells, and causes GI epithelial barrier damage that leads to microbial translocation and associated inflammation. This is one of the potential mechanisms of persistent inflammation during the course of treating HIV infection [8].

A scientific team from the Frederick National Laboratory for Cancer Research, together with the RV254 team in Thailand, explored whether early ART initiation at the time of primary infection could prevent those early pathologic disorders in the gut. They analyzed GI LP CD4+T-
cell population size, GI damage, and other aspects of GI immunity before and after the initiation of early highly active antiretroviral therapy (HAART) in a cohort of 30 untreated acutely HIV-infected individuals (10 Fiebig I (FI), 4 FII, 12 FIII, and 4 FIV/V), 5 untreated chronically HIV-infected patients, and 10 HIV-uninfected people. Intestinal biopsies for immunohistochemistry and cell quantifications were made on days 0, 6, and 24 months to measure GI damage (MPO staining), inflammation (MxA, TNFa), immune activation (KI67), and CD4+T-cell population size in the LP.

- Does early ART prevent or restore CD4 T-cells in LP?
- No. There was no significant recovery of CD4 cells in the LP following early ART initiation.
- Does early ART prevent GI tract damage?
- Yes. GI tract damage, as measured by polymorphonuclear cells, was positively influenced by early ART initiation in all patients.
- Does early ART prevent or restore CD4 T-cells in LP?
- – Yes. There was a drastic reduction in immune activation and inflammation following ART.

Early ART at the time of primary infection was highly beneficial in reducing GI damage and inflammation. However, early HAART intervention was not able to prevent the depletion of LP CD4+T-cells, nor was it able to restore CD4+T-cells after 24 months on HAART.

Maintaining normal weight after initiation of ART to avoid CVD and diabetes risk. The D:A:D cohort [9] was established to prospectively evaluate adverse events associated with ART. It enrolled 49,717 HIV-infected patients, including 14,108 who had initiated first-line ART. In order to evaluate the relationship between weight gain following ART initiation and the subsequent risk of CVD and diabetes, the analysis focused on the risk associated with body mass index (BMI) change 1 year following ART initiation in patients with no history of CVD. Short-term gains in BMI after 1 year on ART were associated with increased risk of CVD and diabetes. Overall, the vast majority of the 9321 patients analysed had a BMI in the normal range (median) before beginning ART.

Younger patients generally had a lower frequency of CVD risk factors, except for individuals with a high rate of smoking, which was more commonly the case in the lower BMI category. After adjusting for confounding factors, the relationship between BMI gain following ART initiation and CVD risk varied according to pre-ART BMI.

- In patients with normal pre-ART BMI, the CVD risk increased by approximately 18% per BMI unit gain (p = 0.041). In underweight, overweight, or obese individuals there was no significant relationship between BMI gain and CVD risk.
- Diabetes risk increased by approximately 10% to 11% per BMI unit gain following ART initiation, regardless of pre-ART BMI.
- The rate of CVD events was 2.21/1000 person-years (95% CI: 1.76–2.68) and that of diabetes was 2.89/1000 person-years.
- Rates of CVD and diabetes increased as pre-ART BMI baseline level rose.

**Summary**

- While results remain speculative in terms of viral remission, the family of HDAC inhibitor compounds continues to show promising results with the introduction of RMD.
- ART initiation remains the major issue for best preserving the future and massively decreasing immune activation and inflammation over 2 years.
- Better evaluation and understanding of how each type of ARV strategy affects inflammation and immune activation will undoubtedly be a part of future trials.
- The preservation of CD4 is the best option for optimal survival.

**References**

The lipstick you love contains palm oil. Don’t love lipstick? How about crisps? Ice cream? Soap? About half the products in the supermarket contain this versatile oil. Soon it may even power your car. But palm oil often comes at the expense of tropical forests and the wildlife that lives in them. Rather than asking consumers to ditch these useful products, WWF is working to make them more environmentally friendly. Manufacturers, retailers and consumers should insist on certified sustainable palm oil. Help us look after the world where you live at panda.org/50.

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The Scientific Programme for HIV Drug Therapy Glasgow promises to be relevant, meaningful and topical, reflecting recent progress in the research and treatment affecting the management of HIV infection. Despite significant advances in treatment, challenges still remain. This Congress will provide practical advice and guidance to clinicians in the day-to-day treatment of their patients.

The programme will offer a mix of presentation types and styles, from keynote lectures to practical case-based presentations, within a single-session plenary format. Networking and Scientific Posters will be a key aspect of the meeting.

**PROGRAMME TOPICS**

- Treatment strategies (naïve, experienced, switch, simplification, late presenters, etc)
- New treatments and targets
- Adverse events (renal, cardiovascular, bone, metabolic, etc)
- HIV-related infections, co-infections (opportunistic infections, hepatitis, tuberculosis), and cancers
- Non-AIDS morbidities and mortality, and ageing
- Laboratory monitoring
- HIV management in resource-limited settings
- Women, MTCT and children
- Community initiatives
- Resistance
- Clinical pharmacology

**DATES FOR THE DIARY**

- Last date to register
- Friday 24 October 2014

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Early establishment of viral reservoir.

20 rhesus monkeys were inoculated rectally with SIV. ART (tenofovir, emtricitabine and dolutegravir) was initiated on day 3, 7, 10 or 14 after inoculation. In the monkeys that received ART on day three no viral RNA or proviral DNA could be detected in blood samples. It also blocked the emergence of SIV specific humoral and cellular response. Proviral DNA could not be found in PBMCs but was found in the gastrointestinal mucosa and in lymph nodes. In monkeys receiving ART at later time points there was an exponential increase in viral load until therapy was initiated and these monkeys did develop humoral and cellular responses.

Suppressive therapy was given for 24 weeks and no virus could be detected during therapy. After the cessation of therapy viral rebound occurred in all monkeys. All the 4 monkeys that received ART on day 3 rebounded although it took longer time to develop viraemia compared to the monkeys that were started on therapy after 7 – 14 days. The study results indicate that viral seeding occurs early before the development of viremia.


Comment: There was a hope that the “Mississippi baby” was cured with very early antiviral therapy but just like in this experiment the virus rebounded even though it took a very long time. One may wonder at what time point it is too late to give post exposure prophylaxis (PEP)? US Public Health Service Guidelines do not specify when it is too late to start but recommend that PEP should start within hours and that animal studies demonstrate that PEP is likely to be less effective when started after 72 hours. It is still not possible to define when it is too late to give prophylaxis but this study indicates that 72 hours may already be too late to prevent viral seeding.

Could antiviral therapy of hepatitis B be stopped after prolonged anti-viral suppression?

A single-centre retrospective review of patients with chronic hepatitis B who stopped therapy after viral suppression for 4–5 years was performed at Beth Israel Deaconess Medical Center in Boston. Patients who had stopped antiviral therapy who were e-antigen negative, without cirrhosis and who were not coinfected with HIV or hepatitis C were identified. All patients had abnormal ALT and viral load > 20 000 IU/ml or viral load > 2000 IU/ml together with abnormal ALT and biopsy proven necroinflammation prior to therapy. 33 patients were identified. Virological relapse was defined as an increase in viral load to >2 000 IU/ml and T and biopsy proven necroinflammation. 33 patients were identified. Virological relapse was defined as an increase in viral load to >2 000 IU/ml and another 5 patients were restarted on therapy without meeting the criteria for the composite endpoint. All patients who restarted therapy normalized ALT and achieved undetectable viral load. Patients who remained off therapy had a median follow up time of 36 months after discontinuing treatment. The authors conclude that cessation of antiviral therapy in e-antigen negative non-cirrhotic patients following prolonged therapy is safe and effective and may be considered in the absence of surface antigen seroconversion.

Patwardhan, et al. Aliment pharmacol Ther; Article first published online: 11 AUG 2014 | DOI: 10.1111/apt.12908

Comment: The optimal duration of antiviral therapy in e-antigen negative, non cirrhotic hepatitis B patients remains unclear. For firm conclusions greater number of patients and longer follow up is necessary. Most physicians would discontinue antiviral treatment only after surface antigen seroconversion. Prospective long term studies to define the optimal strategy are badly needed but extremely difficult to perform. Perhaps the inclusion of surface antigen titers as a clinical tool will improve our ability to define patients that may safely discontinue antiviral treatment?

A step towards a cure for HIV?

Romidepsin is an HDAC (Histone deacetylase inhibitor) inhibitor used to treat cancer. At Aarhus University Hospital in Denmark 6 HIV positive virologically suppressed patients on stable antiretroviral therapy received three infusions of romidepsin over 14 days in an attempt to “purge” the virus from latently infected cells. In 5 of the 6 patients the viral load became measurable. However, no reduction in the size of the HIV reservoir was observed in the 6 patients.


Comment: This is so far the most successful attempt to activate latently infected cells even though no reduction in the size of the HIV reservoir was observed.

When should antiretroviral therapy be given in HIV/Tuberculosis (TB) coinfection?

In a randomized placebo-controlled trial of early versus delayed antiretroviral therapy (ART) in HIV/TB coinfected patients 1675 patients were included. 26 centres in South Africa, Tanzania, Uganda and Zambia participated in the study. HIV positive patients with culture proven tuberculosis and CD4 count of at least 220 were included. After 2 weeks of TB-therapy patients were randomized to either antiretroviral therapy or matching placebo. The placebo recipients were given antiretroviral therapy after completing 6 months of TB-therapy. The median baseline CD4 count was 267. 8.5 % in the early ART group versus 9.2 % in the delayed ART group reached the primary endpoint which was death, TB treatment failure or recurrence. After 24 months there was no statistically significant difference in mortality between the two groups. Interestingly there was no difference either in
the occurrence of the Immune reconstitution inflammatory syndrome (IRIS) between the groups. The authors recommend that ART should be delayed until after the completion of 6 months of tuberculosis therapy in patients with CD4 > 220.

Mfinanga et al. Lancet Infect Dis 2014;14:563-71

Comment: WHO guidelines recommend that all patients with HIV and tuberculosis should receive antiretroviral therapy. Even though the study did not show any advantage with early versus delayed therapy intuitively it seems like a reasonable strategy to start ART as soon as possible. We will have to wait and see if these results will impact future guidelines.

Switching from entecavir to interferon in e-antigen chronic hepatitis B

In a Chinese study 200 chronic hepatitis B patients on entecavir therapy who were e-antigen positive prior to initiation of entecavir therapy were randomized to continue entecavir or to receive 48 weeks of PegIFN α2a. The primary endpoint was HBsAg seroconversion after 48 weeks. HBsAg seroconversion was significantly more common in the interferon group (14.9 % versus 6.1 %). HBsAg loss occurred only in patients randomized to interferon (8.5 %) and HBsAg seroconversion was achieved in 4, 3 % at 48 weeks. Significantly more patients who switched to interferon had low levels of HBsAg at the end of therapy. As may be expected adverse events were more common in the interferon group. Low levels of HBsAg were associated with increased likelihood of e-antigen seroconversion and loss of surface antigen.

Ning et al. J Hepatol (2014) http://dx.doi.org/10.1016/j.jhep.2014.05.044

Comment: These results are preliminary as only week 48 week results are included. Genotypes are not known in this investigation. Different genotypes may respond differently to interferon therapy.

Perhaps a low HBsAg titer in combination with knowledge of subtype could identify patients who would be most likely to benefit switching to interferon.

Are two drugs as effective as three drugs?

In the GARDEL study naïve HIV positive patients were randomized to dual or triple therapy. The dual therapy was a combination of boosted lopinavir together with lamivudine. In triple therapy boosted lopinavir was combined with a fixed dose combination of two NRTI (abacavir/lamivudine or tenofovir/emtricitabine). The primary endpoint was proportion of patients with viral load less than 50 copies after 48 weeks. After 48 weeks 88.3 % in the dual arm versus 88.7 % in the triple arm met the primary endpoint. 4.7 % in the dual arm and 5.9 % in the triple arm had virological failure.

Cahn et al. Lancet Infect Dis 2014;527-80

Comment: Triple therapy has been generally recommended in HIV treatment. In the GARDEL study 2 active drugs are non inferior to the combination of 3 drugs. Both boosted lopinavir and lamivudine were dosed twice daily. As there are many alternatives available with once daily therapy it is unlikely that this combination of two drugs will be widely used in the future. However, the concept is interesting and perhaps other more conveniently dosed combinations with only 2 drugs may be as effective as the traditional 3 drug combinations.

Risk of non-Hodgkin lymphoma in the HAART era

Data from the US HIV/AIDS Cancer Match Study from 1996 to 2010 was used to calculate the occurrence of subtypes of non-Hodgkin lymphoma (NHL) in the HIV positive population compared to the general population. The total risk was 11 times higher in the HIV positive population but varied by subtype. The risk compared to the general population was 17 times higher for all AIDS defining subtypes (diffuse large B-cell lymphoma, Burkitt, Central nervous system and NHL-not otherwise specified). There was also a higher risk in those who had developed AIDS relative to those who were HIV positive without a history of AIDS.


Comment: Despite HAART lymphoma is still much more common in HIV infection compared to the general population. As there is a correlation between the level of immunodeficiency and the risk of lymphoma one may hope that earlier initiation of HAART will lead to a decrease in the risk of lymphoma.

HIV and ischemic stroke

The rate of ischemic stroke was compared between 24 678 HIV positive and 257 600 HIV negative controls from 1996 – 2011 in “Kaiser Permanente Northern and Southern California”. The mean follow up was 4.9 and 5.9 years in the HIV-cohort and the controls. The overall stroke rate was 125 per 100 000 person-years in HIV positive versus 74 in HIV-negative. In HIV positive individuals with a recent CD4 count above 500 or HIV-RNA below 500 copies/ml there was no increased rate compared to the HIV-negative controls.

Marcus et al. AIDS 2014, 28:1911-1919

Comment: In this very large comparison of HIV positive individuals with a control group the overall risk for ischemic stroke was clearly higher in the HIV-cohort. However, this difference disappears for those with CD-count above 500 or viral load below 500. In other words it appears as if antiretroviral therapy has a protective effect. There is no information about what regimen the patients are using and no conclusion on the influence of different therapies can be drawn. In any case these results can be interpreted as another argument favoring early therapy.

Lambda Interferon?

In a randomized, blinded study 525 patients with hepatitis C were treated with either 120/180/240µg of lambda interferon or peginterferon α2a 180 µg. All patients received ribavirin. Treatment was given 24 weeks for genotypes 2+3 and 48 weeks for genotypes 1+4. Complete early viral responses (cEVR) were significantly higher with all doses of lambda interferon in genotype 1 and 4 and similar in genotype 2 and 3 compared to peginter-
feron alfa-2a. Sustained viral response after 24 weeks (SVR 24) was however numerically but not statistically significantly higher for neither genotypes 1+4 or 2+3. No obvious difference in efficacy between the different doses of lambda interferon. Side effects were generally milder with lambda interferon with markedly less hematotoxic and general adverse events.

Muir et al. J Hepatol http://dx.doi.org/10.1016/j.jhep.2014.07.022

Comment: Lambda interferon appears to be at least as effective as pegylated interferon with fewer and milder side effects. It is however very doubtful whether there will be any place for lambda interferon in the treatment of hepatitis C taking the already available and future directly acting antivirals into account.

HIV and MS?

A single HIV patient with concomitant multiple sclerosis (MS) was started on antiretroviral therapy after which his MS symptoms totally disappeared. This prompted a Danish team to analyze the incidence of MS in the Danish HIV cohort and to compare it with the general population. The result was that the incidence ratio for MS in the HIV positive group was 0.38 relative to the controls. The material was not big enough to show a statistically significant difference. A similar but bigger study has therefore been conducted in UK where information from the “Hospital Episode Statistics” was used to evaluate the incidence of MS in the HIV infected cohort and compare it to a large control group. The total number of patients in the HIV-cohort was 21,207 and the control group consisted of over 5 million patients. The result was similar to the Danish study with a relative risk of 0.38 in HIV cohort which was statistically significant.

Gold et al. Neurol Neurosurg Psychiatry jnpn-2014-307932Published Online First: 4 August 2014

Comment: Is MS caused by a retrovirus? Is there really a causal protective effect of HIV or perhaps HIV therapy? There are of course many alternative explanations. One potential explanation is that the relative impairment of the immune system in HIV protects against the development of MS. There may be many more potential explanations but in any case it is an interesting observation that may be an important observation in the quest for understanding the cause of MS.
Topical Conferences

September 18
18th Annual Resistance and Antiviral Therapy Meeting
London
www.mediscript.ltd.uk

October 2-3
HIV Nordic Conference
Stockholm, Sweden
www.hivnordic.se

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

October 8-13
The Modes of Action of Vaccine Adjuvants
Seattle, Washington, USA
www.keystone-symposia.org/meetings

October 9-10
BHIVA Autumn Conference, 2014
London
www.bhiva.org

October 12-14
3rd Antivirals Congress 2014
Amsterdam, Netherlands
www.antivirals.elsevier.com/index.html

October 20-21
5th International Workshop on HIV & Aging
Baltimore, USA
www.virology-education.com

October 25-26
9th International Workshop on HIV Transmission Principles of Intervention
Cape Town, South Africa
www.virology-education.com

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

November 2-6
HIV Glasgow
Glasgow, United Kingdom
www.hivglagow.org

November 2-6
12th Intern. Congress on Drug Therapy in HIV Infection
Glasgow
www.hiv11.com

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

November 7-11
AASLD
Boston, MA, USA
www.aasld.org

December 8-9
Five Nations Conference on HIV and Hepatitis
London
www.bhiva.org

December 8-11
7th International Workshop on HIV Persistence during Therapy
Miami
www.hiv-persistence.com

2015

January 22-27
Host Response in Tuberculosis
Santa Fe, New Mexico, USA
www.keystone-symposia.org/meetings

February 21-22
XXIV International HIV Drug Resistance Workshop
Seattle, Washington USA
www.informedhorizons.com/resistance2015/

February 21-22
5th International Workshop on HIV & Women, from Adolescence through Menopause
Seattle
www.virology-education.com

February 23-26
22nd Conference on Retroviruses and Opportunistic Infections (CROI 2015)
Seattle
www.croi2014.org

April 25-28
ECCMID
Copenhagen, Denmark
www.eccmid.org

April 26-May 1
Host Response in Tuberculosis
Boston Park Plaza, Boston, Massachusetts, USA
www.keystone-symposia.org