THE 7TH GILEAD NORDIC SUMMER HIV MEETING · THREE CLINICAL TRIALS OF ANTIRETROVIRAL THERAPY AT IAS 2015 · NOW IS THE TIME TO START · RISK FOR HEPATOCELLULAR CANCER IN PATIENTS WITH CURED HEPATITIS C · WHEN TO START? THE END OF AN ENDLESS QUESTION
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I recently encountered two HIV cases whose management surprised me and also left me somewhat concerned. Although the vast majority of HIV health care providers are fully aware of basic treatment principles, it might be worthwhile to briefly review these two cases to remind us of what we all know but may sometimes forget. Since antiretroviral treatment nowadays is almost always successful, historical drug resistance and treatment failure may tend to be overlooked.

The first case was that of a middle-aged man who had been infected since he was 19. He was virologically suppressed on boosted Reyataz (atazanavir/ritonavir) and Kivexa (abacavir/lamivudine) for several years and suffered no side-effects. However, he wanted to have an “easier” regimen involving fewer pills. His doctor, therefore, changed the treatment regimen: first to Kivexa + Tivicay (dolutegravir) and later to the combination pill Triumeq when it became available. This worked out quite well. The patient was still virologically suppressed, but was complaining of gastrointestinal discomfort that he and his physician thought might be connected to his new regimen. The treatment was then changed again, this time to Truvada and Isentress (raltegravir). Four months later his viral load showed an increase to about 3,000 HIV-RNA copies/mL, and a resistance test showed multiple resistance mutations against NRTIs. Looking back into the patient’s treatment history showed that he had been on mono- and dual-NRTI therapy for a long period of time at the beginning of the 1990s. There were no resistance tests available then but the virus had most likely developed multi-NRTI-resistance over the course of a long period of ongoing viral replication during suboptimal treatment. The replication was subsequently supressed with PI/r-based treatment, and that remained effective for years. The viral load continued to be supressed with dolutegravir, an integrase inhibitor with a high resistance barrier, but when the treatment was changed to raltegravir a viral breakthrough occurred.

The second case was similar. A man of about 35 years of age had begun treatment approximately 10 years ago with Atripla (tenofovir/emtricitabine/efavirenz). However, his adherence was not perfect and he stopped treatment after approximately 7 to 8 months. A resistance test was taken and revealed an NNRTI mutation (K103N), but no NRTI mutations were detected. Due to a rapid decrease in CD4 cell count, treatment was re-initiated less than one year later with Kivexa and Prezista/Norvir (darunavir/ritonavir), and this time the patient adhered well to treatment. CD4 increased, viral load became undetectable, and it remained so. Treatment in this case was also subsequently changed in order to simplify the regimen and Eviplera (tenofovir/emtricitabine/rilpivirine) was prescribed — not the best choice in this situation. For the first month after the treatment change, HIV-RNA remained below 20 copies/mL, but after three months viral load had increased to 8,000 copies/mL. A resistance test showed no new NNRTI mutations, K103N was still present, however both M184V and K65R (NRTI mutations) were detected. K103N only was detected by the old resistance test, but K103N by itself does not impair the effect of rilpivirine. However, K103N could be seen as more than just a mutation in this case. It should be considered as a marker telling us that the virus has developed drug resistance during treatment and that it is not unlikely that other mutations have also developed. Although not detected they might be present in minor viral populations. It is important to remember that while a positive resistance test confirms mutations, a negative one does not exclude resistance.

Basic information for most of us, but still worth keeping in mind.

Magnus Gisslén
Editor
The 7th Gilead Nordic Summer HIV Meeting

The 7th Gilead Nordic Summer HIV-meeting was held in late May in Malmö, Sweden. The program attracted more than 160 participants and covered the different aspects on the global HIV epidemic and trends in antiretroviral therapy.

Malmö is a city with a rich history. Already in the 1300th century, the city was flourishing and the trademarket with Denmark was intensive.

Today, Malmö is the third biggest city in Sweden with its nearly 281 000 inhabitants.

This year’s Gilead summer HIV-meeting was held in ”Börshuset”, centrally located in the city. In earlier times the building served as a customs house, today it offers spacious conference facilities.

The program for the Meeting included many renowned lecturers from Italy, United Kingdom, Sweden and USA.

One of the head lecturers, Vadim Pokrovskiy from Russia, was unfortunately obliged to cancel his participation due to the alarming HIV-situation in Russia. The same morning as the conference was held, Dr Pokrovskiy was occupied with international media, covered by the BBC’s morning news.

“President Vladimir Putin, who enjoys unstinting support from the Russian Orthodox church, has over the past years been promoting increasingly conservative values in a bid to rally support from his core constituents of middle-aged Russians and blue-collar workers”.

In an interview in the British newspaper The Guardian, Dr Pokrovskiy lambasted the Kremlin’s increasingly conservative agenda, saying the HIV-AIDS epidemic is worsening and at least two million Russians are likely to be infected in about five years. He also declared that the government policies promoting traditional family values had failed to halt the spread of the deadly virus.

Leo Flamholc, member of the Steering Committee and Senior consultant at Skåne University hospital in Sweden, opened the meeting and welcomed the participants in Russian.

He had been given access to Dr Pokrovskiy’s slides and the audience could fortunately take part of the lecture through Dr Flamholc’s improvised talk.

HIV epidemic in Russia

Vadim Pokrovskiy is Professor in epidemiology and the Deputy Director of the Central Research Institute of Epidemiology. He is also head of the Russian Federal Research Centre for AIDS Prevention and Treatment.

Mr Pokrovskiy works on the HIV surveillance and scientific support of HIV/AIDS programs in Russia.

He started HIV researches in 1985 and he found the first AIDS case in the USSR in 1987 - a homosexual male who had been
infected in Zanzibar (Tanzania).

For many years there was a total denial that AIDS existed, the infection disease was regarded as an expression for the decadent European lifestyle.

Finally, in the late 80s, centres for AIDS prevention and care were established in all Russian regions.

Despite preventive measures, a significant increase in HIV rate could be seen from 1995 an onwards. Before that, the annual number of registered HIV-cases was under 200, but after 1995 HIV subtype A and its recombinants started to invade the growing population of homosexual men and intravenous drug users, IVDU, in the former USSR.


Between 1995 and 2010, there was a public reaction. Huge loan programs were launched by The World Bank and Four Global Funds.

Also, national priority plans for AIDS prevention and treatment were implemented between 2007 and 2011. Even though efforts have been done to motivate population to deliberate refusal from models of risky behaviour and to encourage risk groups to voluntary testing and treatment, the alarming situation in Russia has gotten even worse.

The waterfall of HIV

The consequences of a homophobic attitude in Russia and the stigmatization of homosexuals in the society, have created fear among the population of homosexual men (and IVDU) to attend prevention and treatment programs.

Here are some figures to concretize the HIV burden in Russia in 2014:
- Total number of registered HIV cases: 900 000
- Number of alive HIV-positive persons: 700 000
- Estimated number of PLW HIV: 1 300 000
- Number of HIV-positive persons on ART: 170 000

Not only Russia is facing the HIV epidemic. Also surrounding countries such as Armenia, Azerbaijan, Georgia, Kyrgyzstan and Ukraine are facing major problems.

Among countries in Eastern Europe, Estonia has reported the highest rate of HIV-infection.

Also, a huge number of migrant workers who are circulating to Russia and back to their homelands are infected. Work in Russia is a significant risk factor for citizens of Central Asia and Transcaucasia.

Approximately 17% of the migrants are reported to have sex with women abroad.

Russia is in urgent need for special programs in order to tackle the alarming situation. Russia is now facing African levels on AIDS and the situation is going from bad to worst, Leo Flamholc stated.

“The official number of Russians with HIV has grown to some 930 000 people from around 500 000 in 2010. By the end of 2016 the numbers expects to rise to about one million people, as the virus increasingly affects the heterosexual population”.

Vadim Pokrovskiy

HIV care in Ethiopia

Per Björkman, associate Professor at the Department of Infectious Diseases at Skåne University Hospital, Malmö, talked about antiretroviral therapy (ART) in sub-Saharan Africa; from the perspective of Ethiopia, where he is principal investigator for a research project conducted in public health centers since 2010.

Since ART became available in low-income countries around 2003 access to life-saving treatment has increased enormously, and currently 15 million people are estimated to have initiated ART.

– However, even though we have reached far, challenges remain. We are still facing huge numbers of sick patients in need of ART. Patients in low-income countries often have more advanced disease at ART-initiation due to late presentation at HIV diagnosis, Per Björkman commented.

Ethiopia has the second largest population in Africa with 94 million inhabitants. In Ethiopia a free public ART program was introduced in 2005, and by 2012 the estimated ART coverage was 62 percent. As a result, HIV-related mortality has decreased from 132 to 55 per 100 000 population.

In order to continue ART provision in an effective and sustainable way it is necessary to integrate HIV care within the existing primary health care system. There is an urgent need for adapted methods for treatment monitoring and diagnosis of opportunistic infections (OI) for these settings, as well as knowledge on the outcome of ART, especially with regard to drug resistant HIV strains.

– We have to make sure that more patients at earlier stages of HIV infection get on ART. Furthermore, since people living with HIV need life-long therapy it is extremely important to ensure that patients remain in care after having started ART.

At present, one of three patients initiation...
tting ART is lost to follow-up in many programs in sub-Saharan Africa.

**TB/HIV co-infection**

Globally, tuberculosis (TB) is the most common OI and cause of death among PLHIV. TB poses several challenges for health providers in low-income countries, both concerning diagnosis and treatment.

– In sub-Saharan Africa integrated TB/HIV care is absolutely necessary. Approximately 85% of the people co-infected with TB/HIV live in this continent, Per Björkman commented.

His research project is based in a field research station in Adama, and involves collaboration with several Ethiopian research institutes. The field sites are located in a region of Central Ethiopia where the prevalence of HIV is high – around 8% of adults are HIV-positive. The project focuses on various aspects of HIV care at health centers in sub-Saharan Africa – the setting where most people living with HIV globally receive treatment. The research questions include:

- How are patients with TB/HIV co-infection managed?
- How can methods for TB screening and diagnosis be improved?
- What are the true outcomes of ART at health centers?

**Need for action**

The prevalence of active TB in a cohort of 812 HIV-positive adults was found to be 18%; among these, less than 10% had been diagnosed with TB previously. The outcome of ART was found to be satisfactory in persons treated at health centers, with similar results in patients with and without TB co-infection. New diagnostic methods and screening algorithms for TB have been evaluated and developed, and could be used as tools for improved management of patients in these settings.

In his conclusion, Per Björkman emphasized the importance of "strengthening the grip" on HIV in Ethiopia. In the current era of ART roll-out, it is critical to monitor the spread of drug-resistant HIV strains, and to understand patterns of remaining HIV transmission, especially in high-risk populations.

For these purposes, large cohorts with clinical and epidemiological data and associated biobank samples, like the one we have accumulated in Adama, can provide important information, Per Björkman concluded.

**The early spread of HIV**

Oliver Pybus, Professor of Evolution and Infectious Disease at the University of Oxford, UK, talked about the early spread and epidemic ignition of HIV-1.

He investigates virus evolution and ecology. Current research includes viral adaption and natural selection.

Oliver Pybus is also Editor in Chief of the journal Virus Evolution.

– Scientific researchers have struggled for a long time in order to present data on the origins of HIV and the AIDS pandemic. Now we have a pretty clear picture on how it arose.

Through history, rather bizarre ideas have been circulating in different societies and countries. Conspiracy theories suggested that Hitler created AIDS virus in order to destroy the US. In certain religious groups, AIDS was supposed to represent the wrath of God.

Lentivirus has been circulating among mammals for more than 10 000 years and there are many different viruses that accompany this family.

– You can find different subtypes of HIV in different localisations, said Oliver Pybus and showed a slide on global patterns of different types of HIV. Each one origin from different animal reservoirs.

The most common types that are responsible for the global epidemic of 60 million cases are HIV-1-M-HXB2 and HIV-1-M-U455.

– We have evidence that shows that chimpanzees and gorillas were infected by two rare HIV-1 viruses in southern Cameroon. We have also identified old viruses in Kinshasa, which suggests that virus moved from Cameroon to Kinshasa.

But how and when did the virus get from animals to humans?

Blood transmissions and hunting, are some of the explanations. Bushmeat is a longstanding source of animal protein and income in the Congo Basin. In Cameroon more than 18 % of non-ape primate bushmeat samples were found to be positive for SIV antibodies (simian immunodeficiency virus).

HIV-infections in Kinshasa were already genetically distinct by the late 1950s. Kinshasa is suggested to be the hub of early viral dispersal of the Democratic Republic of Congo.

Oliver Pybus talked about how researchers have tested the Kinshasa hypothesis in a statistically rigorous way. Overall, 58 percent of total estimated viral movements began from Kinshasa. Brazzaville and the south-eastern part of the Democratic Republic of Congo acted as secondary foci.

In 1920 colonial infrastructure start to connect Central Africa, and Kinshasa became the Regions largest city and a hub for transports, both on land and by rail.
Around 1960 the persons infected by HIV-1 group M tripled. Why?

- We don’t know exactly. Some of the hypothesis suggests an increase in transmission rates. After the independence of Congo there was a change in commercial sex work and a higher rate of partner exchange. One explanation could also be unsafe injections. Hepatitis C is common in Kinshasa and unsafe injections are likely to play an important role.

**HIV transmission risks**

Jan Albert, is a Professor in viral Infectious Disease Control at the Karolinska Institute and a senior consultant at the Department of Clinical Microbiology at the Karolinska University Hospital. His lecture covered HIV transmission risks and follow-up after exposure.

In August 2011, the study “Prevention of HIV-1 Infection with Early Antiretroviral Therapy” (HPTN 052) was published in The New England Journal of Medicine.

- Early therapy showed a 96% reduction of linked transmissions. Thus, ART has a massive effect on transmission risks.

Jan Albert also referred to interim results from the PARTNER-study presented at the CROI conference 2014, which also investigates whether people with HIV become non-infectious if they are on ART. In contrast to HPTN 052, the PARTNER-study includes a significant proportion of MSM (40%). The study had not found any linked transmissions despite around 16 400 MSM and 14 000 heterosexual sexual contacts, of which many were without condom.

- There is a minimal transmission risk if the HIV-infected partner is on effective ART and a condom is used throughout the intercourse. There is also a very low risk of transmission through vaginal and anal intercourse if condom is not used, Jan Albert concluded.

Available data do not contradict the “Swiss statement”, but zero risk is almost impossible to prove scientifically. According to the Swiss statement, a HIV-infected individual on “effective ART” is sexually non-infectious if he or she complies with the therapy, the viral load has been non-detectable since at least six months and there are no additional sexually transmitted diseases present.

Jan Albert also presented the new Swedish recommendation for length of follow-up after HIV exposure. Since 1995, most international and national guidelines recommend 12 weeks follow-up.

- But reviews and recommendations are primarily based on a few old studies and case reports. We have now several studies that suggest shortening the recommended follow-up time after HIV-exposure. The Swedish Reference Group for Antiviral Therapy and the Public Health Agency of Sweden therefore have revised the national recommendations.

- We now recommend 6 weeks follow-up to exclude that transmission has occurred, if a laboratory-based fourth generation assay is used.

Approximately 50% are expected to be positive in Combo-tests 14 days after infection.

Special situations need different management, Jan Albert pointed out.

- Pre and post-exposure prophylaxis (PEP and PrEP) is a daily pill that can prevent HIV infection.
- The recommendation is that the 6 week follow-up should start after prophylaxis has ended.

At the end of the lecture, Jan Albert was asked by the audience if he would use condom if his partner/wife was HIV positive and well treated.

- This is a difficult question. Personally I would probably choose not to use the condom, because the risk is very low, almost none, but this is a very personal opinion.

**Home HIV testing**

Since April 2014, home HIV testing is legal in the UK. The first testing kits were launched in April 2015. The tests are also available on-line and cost about £30.

Michael Brady, a consultant in Sexual Health and HIV at King’s College Hospital in London, talked about “Strategies to curb the HIV epidemic in the MSM (men having sex with men) population”.

- Over the past 10 years we have had about 2 500 new cases of HIV infected among MSM in the UK. The action that has been taken has not been very successful and we need new prevention strategies with greater impact. A combination approach to HIV is essential.

Since 2008, Michael Brady has been the Medical Director of the Terrence Higgins Trust, The UK’s largest HIV and Sexual Health Charity.

A back-calculation estimate of HIV prevalence of undiagnosed infection among MSM during the past ten years, shows a high number of about 8 000 undiagnosed cases per year.

- We can see huge potential in stepping up our HIV testing. But novel testing strategies need to deliver increased testing capacity. We have to develop new models that combine community HIV testing, on-line home HIV sampling and home
HIV testing in order to reduce late diagnosis.

There has been a huge promotion where HIV prevention campaigns have been announced through social media.

– In the current situation, around 36 percent of MSM are diagnosed within a year. If we step up the testing, 60 percent can be diagnosed within a year. If we try even harder and increase the testing rate, 90 percent will be diagnosed within a year, which means an approximately 54 percent reduction in HIV infection in the UK.

Today, individuals can order home HIV sampling through a website (THT-Terrence Higgins Trust) based on the 4th generation dried blood post HIV test.

The samples are posted to a laboratory in Manchester. Test results, if it’s negative, are given by text. If positive, the result is given by phone.

Social media is a key to engaging with MSM and promoting testing. Michael Brady commented. He also emphasized on combining testing with early treatment.

– It is cost-effective. A dramatic increase in HIV testing rates has the potential to have a major impact on the HIV epidemic.

Non-traditional testing reaches those who tend not to test and could encourage regular testing.

Trends in antiretroviral therapy

Dr Graeme Moyle, UK, talked about new drugs and integrase inhibitors. He started by presenting a comparison between the three major guidelines – DHHS (UK), IAS (USA) and EACS (Europe) – on preferred initial regimens 2015.

– They are pretty much the same, he commented.

Dr Moyle continued with new drugs, and told the audience that tenofovir alafenamide fumarate (TAF) from Gilead Sciences (formerly GS-7340) – a nucleotide reverse transcriptase inhibitor and a novel prodrug of tenofovir – has been submitted for approval for use in the treatment of HIV infection.

TAF belongs to a class of HIV drugs called nucleoside reverse transcriptase inhibitors (NRTIs). They block an HIV enzyme called reverse transcriptase. By doing so, NRTIs prevent HIV from multiplying and can reduce the amount of HIV in the body.

– TAF has much less systemic exposure than the current tenofovir prodrug disoproxil fumarate (TDF), Dr Moyle underlined.

At CROI 2015, a study on elvitegravir/cobicistat/emtricitabine/TAF versus elvitegravir/cobicistat/emtricitabine/TDF in treatment-naive adults with more than 1000c/ml HIV-1 RNA was presented, and Dr Moyle presented some of the findings.

– The virologic response rates were high and similar – irrespective of age, sex, race HIV-1 RNA and CD4 cell count. The renal and bone safety was better for TAF, he said.

BMS-955176 is a second-generation HIV maturation inhibitor. At CROI 2015, a Phase IIa study was presented that demonstrated that supported further clinical development.

– It is now moving into Phase III, Dr Moyle said.

He also talked about fostemsavir (BMS-663068), an experimental HIV entry inhibitor and a prodrug of temsavir. Because it targets a different step of the viral lifecycle, it offers promise for individuals with virus that has become highly resistant to other HIV drugs.

The LATTE trial investigated cabotegravir and rilpivirine as two-drug oral maintenance therapy, and Dr Moyle presented the results from week 96. These showed this regimen to be as effective as an efavirenz-based regimen to keep viral load suppressed.

Doravirine (MK-1439) is a non-nucleoside reverse transcriptase inhibitor under development by Merck & Co. Doravirine demonstrated robust antiviral activity and good tolerability in a small clinical study of 7-day monotherapy reported at CROI 2013. Dr Moyle presented data the 48-week efficacy and safety and early CNS tolerability of doravirine.

– The study was first presented at HIV Drug Therapy Glasgow 2014. Among the findings was that significantly fewer patients on doravirine had more than one CNS event by week 8.

In his summary, Dr Moyle pointed out that in the new drugs coming we see nucleotide reverse transcriptase inhibitors with improved renal and bone safety, non-nucleoside reverse-transcriptase inhibitors, with potential improved CNS safety and without efficacy compromise.

– There will be new classes of drugs – maturation inhibitors and GP120 attachment inhibitors such as fostemsavir. We will also see long-acting injectable therapies, Dr Moyle concluded.

HIV encephalitis

Prof Richard W Price, USA, talked about CNS HIV infections in treated patients.

– Usually, ART is highly successful in suppressing CNS HIV infection. But ART does not always fully normalize CNS, Prof Price pointed out.
This could be due to low residual cerebrospinal fluid (CSF) HIV or residual inflammation and it contributes to persistent CNS impairment.

- Residual CNS inflammation is phenomenally broad, and is associated with levels of residual virus, reduced test performance and decline in neuropsychological test performance.

Most CSF and blood inflammatory biomarkers are reduced, compared to active infection. But several remain elevated compared to HIV negative individuals, he continued.

- This may indicate continued response to the reservoir.

Suppressed individuals can exhibit asymptomatic CNS HIV blips – which mean there is an increase in CSF HIV and in inflammation.

HIV encephalitis is a rare localized CNS HIV breakthrough.

- CNS HIV breakthrough can also result in severe inflammation and a major CNS dysfunction.

Finally, Prof Price suggested that neurosymptomatic escape maybe is caused by an unknown opportunist, stimulating latent HIV pool.

- At our clinic we had a single patient with blood-samples indicating a long-term non-progressor with peripheral viremia below 100 and CD4 higher than 800. However, CSF was drawn because of neurological symptoms, and showed viremia over 5000. We have started treatment, but we have no idea of the rarity of this condition, he summarised.

CNS opportunistic infections

Dr Paola Cinque talked about clinical aspects of CNS opportunistic infections and immune reconstitution inflammatory syndrome (IRIS).

- Most cases of IRIS occur within three months of HAART.

Cryptococcosis is the most common CNS opportunistic infection globally, with a high prevalence in low-income countries. Patients have a high mortality – 17 % at 2 weeks and 34 % at 10 weeks – despite antifungal therapy and eART.

- Cryptococcosis accounts for 20 - 25 % of AIDS-related deaths in Africa, Dr Cinque stated.

Adequate treatment consists of initial treatment with amphotericin B. For prevention a rapid screening test CRAG LFA point-of-care assay is required.

- And IRIS recognition and management is essential.

She also talked about progressive multifocal leukoencephalopathy (PML), a disease of the brain caused by JC virus (JCV).

- cART immune reconstitution is the option in HIV-related PML, but this is often too slow or non-efficient and sometimes the patient gets PML-IRIS.

In her conclusions Dr Cinque stated that CNS opportunistic infections remain highly prevalent in low-income countries and are common in AIDS-presenters in high-income countries. The CNS opportunistic infections – Cryptococcosis and PML in particular – are associated with unacceptable high mortality.

- CNS-IRIS requires prompt diagnosis and management. In PML, in the absence of JCV-specific treatments, alternative prevention and treatment approaches are urgently needed!
Three clinical trials of antiretroviral therapy at IAS 2015

The 2015 International AIDS Society Meeting was held in mostly sunny Vancouver - giving Europeans the chance to enjoy again - after CROI in Seattle - an 8-9 hours jet lag - from July 19th to July 22nd. At this meeting starting the clinical trial was without doubt the most important study presented.

All the discussions about “when to start” are now over since START gave such a clear answer: the sooner, the better. In contrast, the “what to start” and “how to continue” questions are still not over. At IAS three interesting clinical trials help us to be more prepared to answer these two very important questions.

WAVES: Finally an “only women” clinical trial of initial antiretroviral therapy

WAVES (acronym for “Women Antiretroviral Efficacy and Safety”) [1] has undoubtedly won the “prize” for the abstract that without a doubt should have been an oral presentation instead of a poster. I can’t count how many times we have complained about the underrepresentation of women in recent clinical trials of antiretrovirals (typically always less than 10-15%). WAVES is a double-blind randomized clinical trial that included 575 (five hundred seventy five!) antiretroviral naïve women. Well, here you have a very robust trial to try to answer the question of what antiretroviral strategy is preferable in women. The study compared Elvitegravir (EVG) / Cobicistat (COBI) / Emtricitabine (FTC)/ Tenofovir Disoproxil Fumarate (TDF) and Ritonavir Boosted Atazanavir (ATV) plus FTC/TDF in antiretroviral naïve women. In other words is the “female only” version of Gilead 103 [2]. In 103 EVG/c/TDF/FTC showed non-inferiority to ATV/r and TDF/FTC. For the record, in Gilead 103 only 66 women were included.

To be included in WAVES, women had to be antiretroviral naïve, harboring HIV sensitive to FTC, TDF and ATV and with an estimated GFR of at least 70 mL/min. This was an international study that recruited patients from 11 countries but mainly from Russia, Uganda and US. Almost half of patients were black. At baseline median viral load was 4.5-log10 copies/mL and almost one quarter of the women had a viral load above 100,000 copies/mL. Median baseline CD4 cell count was approximately 360 cells/µL.

After 48 weeks of follow-up the snapshot analysis showed the superiority of the EVG/c/TDF/FTC arm over the ATV/r and TDF/FTC (Fig 1). The difference was 87% vs. 81% in favor of EVG/c/TDF/FTC. Mean CD4 cell recovery was similar in both groups. In women with baseline viral loads above 100,000 copies/mL difference in favor of EVG/c/TDF/FTC was larger -90% vs. 78%. Interestingly WAVES is the first trial evaluating EVG/c/TDF/FTC in which not a single virological failure was associated with the detection of EVG, TDF or FTC mutations. As expected no protease inhibitor mutations were detected after virological failure in patients randomized to the ATV/r arm with just three cases of M184V.

Both treatments were well tolerated and again, as expected, 16% of women in the ATV/r arm developed grade 3 or 4 hyperbilirubinemia. Cobicistat interferes with the tubular secretion of creatinine. Patients randomized to EVG/c/TDF/FTC had a decrease in estimated glomerular filtration rate of -6.1 mL/min compared to -2.4 mL/min in the ATV/r arm. Interestingly in Gilead 103, with a predominantly male population the decrease in estimated glomerular filtration rate in the EVG/c/TDF/FTC group was -14.6 mL/min. Decrease in bone mineral density was in line with what was expected in TDF containing regimens (Fig 2) with no differences between arms.

WAVES is the first clinical trial showing an advantage of EVG/c/TDF/FTC versus ATV/r plus TDF/FTC. This is a quite interesting result that add to the controversy about the efficacy of ATV/r in women. In ACTG 5202 [3] women randomized to ATV/r had a significantly shorter time to virologic failure compared to women randomized to EFV. However a systematic review of the efficacy of ATV/r in women [4] did not find a clear answer because of the “lack of randomized clinical trials that recruit women in sufficiently large numbers”. It is going to be very interesting how guidelines response to WAVES provocative results.

GS-US-292-0109: The largest switch trial ever

The open-label Gilead 109 trial [5] explored switching from a TDF-based regimen to a Tenofovir Alafenamide (TAF)-Based Regimen. TAF is the new prodrug of TDF. Tenofovir alafenamide most interesting pharmacokinetic characteristic is that after absorption, blood levels of tenofovir are 90% lower that when tenofovir is administered as difumarate. Lower blood

![Figure 1. WAVES. Virologic Outcomes (HIV-1 RNA <50 c/mL) at Week 48](image)
Face death in a war zone?

Escape, but leave loved ones behind?

What would you do?

For many refugees the choice is between the horrific or something worse. No one chooses to flee to find safety, regain hope and rebuild their lives. 1 family torn apart by war is torn apart by politicians.
levels of tenofovir have been correlated with lower renal and bone toxicity. In contrast with blood levels, intracellular levels of tenofovir diphosphate are 4-5 times higher for TAF than TDF (see HIV & VIROLOGY NEWS 1 · 2015 “In search for better nucleotides. Is TAF the answer?”). In Gilead 109, patients who have been enrolled in other trials and were currently virologically suppressed (for at least 96 weeks) while receiving a TDF-containing regimen were randomized in a 2:1 fashion to switch to EVG/c/FTC/TAF or to continue the TDF-containing regimen (Fig 3). Patients needed to have an estimated glomerular filtration rate above 50 mL/min.

After 48 weeks of follow-up, maintenance of virological suppression occurred more frequently in the EVG/c/FTC/TAF than in the TDF-containing regimens (97% vs. 93%, treatment difference: 4%; 95% CI: +1.6%, +5.6%), meeting superiority criteria. Superiority results in open label trials could have important confounders. Patients might for example be disappointed if they are not randomized to the new experimental regimen.

In Gilead 109 patients randomized to EVG/c/FTC/TAF experienced higher increases in lipid fractions since the “lipid-lowering” advantage of TDF is lost. It is interesting that while bone mineral density in spine/hip remained stable in the TDF group, there was a 1.8%/1.4% recovery in the TAF group. The number of patients with a normal spine T-score increased from 59% to 64% in the TAF group while it remained stable in the TDF group (56%), a difference that was also statistically significant. Similar results were seen in the hip. With regard to renal safety results there were statistically significant differences between treatment arms in favor of the EVG/c/FTC/TAF group in urinary albumin/creatinine, protein/creatinine, retinol binding protein/creatinine and beta-2 microglobulin/creatinine ratios (Figure 4). There were no cases of Fanconi Syndrome on E/C/F/TAF but one case in the TDF-based arm. In summary, results of Gilead 109 support differences in bone and renal toxicity in favor of TAF, a finding that corroborates in suppressed patients what have been found in antiretroviral naïve individuals [6].

**Doravirine: a new non-nucleoside reverse transcriptase inhibitor**

After 30 years of antiretroviral therapy it can be argued that we still do not have the perfect non-nucleoside reverse transcriptase inhibitor. Efavirenz is no longer recommended as a preferred option in treatment guidelines due to its central...
nervous system adverse events and possible association with an increased risk of suicidality (see HIV & VIROLOGY NEWS 2 · 2015 “Efavirenz: too much of a good thing?”). Rilpivirine is better tolerated than Efavirenz but its use in antiretroviral naïve is restricted to patients with viral loads below 100,000 copies/mL and CD4 cell counts above 200 cells/µL. So the unmet need is clear, we need a non-nucleoside reverse transcriptase inhibitor as well tolerated as rilpivirine and as efficacious as efavirenz. Could doravirine be the answer?

In Vancouver we could see the week 24 results of protocol 007, a comparison of the efficacy and safety of Doravirine 100mg (QD) vs Efavirenz with TDF/FTC in antiretroviral naïve patients [7]. This analysis was part of a dose-finding clinical trial. The comparison included 108 patients per group. Take home messages:

- Virologic response at 24 weeks was very similar when the < 200 or the < 40 copies/mL cutoff was used (88.9/73.1% for Doravirine and 87/77.2% for Efavirenz) using a non-completer = failure, approach (Fig. 5)
- The number of virologic failures was higher in the Doravirine group (21 vs 11). Of the 21 virologic failures in patients receiving doravirine, 19 had viral loads between 40 and 200 copies/mL and none had experienced a rebound. These data along with the lack or detection of resistance suggest that viral loads were still on their way down.
- Doravirine had significantly fewer treatment-emergent CNS adverse events by week 24 than efavirenz

So, this is preliminary data. We would have to wait for the phase III –already enrolling patients- to have a definitive answer about the role of doravirine as a therapeutic agent.

Figure 3. GS-US-292-0109. Study design

Figure 4. Switch to E/C/F/TAF in Suppressed Adults: Effect on Tubular Proteinuria

Figure 5. Protocol 007. Patients with HIV RNA <40 c/mL, % (95% CI) Non-completer = Failure Approach

References
Now is the time to start

‘The White Rabbit put on his spectacles. ‘Where shall I begin, please your Majesty?’ he asked. ‘Begin at the beginning,’ the King said gravely, ‘and go on till you come to the end; then stop.’

This advice was all very well in the looking glass world of Alice in Wonderland. However, the world of HIV treatment has been troubled since its dawn by never quite knowing where the beginning was. Before viral load testing began in the mid 1990s, studies on timing of therapy used mainly CD4 cell counts and clinical progression or death as endpoints. The largest and longest trials of this era, ACTG 019, EACG020 and Concorde, drew somewhat differing conclusions about starting AZT monotherapy below or around CD4 500/mm³, meaning that rather like the Red Queen in Alice’s adventures, it took all the running we can do to keep in the same place. Predominately, the studies found some short term advantages to early treatment, less progression to AIDS or symptomatic disease, but with little or no survival advantage. As AZT caused a burden of side effects including anaemia, neutropenia, nausea, myopathy (lipoatrophy was not recognised at that time) any benefit on reducing disease was counterbalanced by a burden of toxicity.

Triple therapy regimen questions

With the development of triple therapy regimens questions around the timing of treatment and the need for continuous treatment began to be re-evaluated. Initially, timing of therapy continued to be juxtaposed with the side effects of new regimens (such as severe rash and fulminant hepatitis with nevirapine, abacavir hypersensitivity, PI (especially ritonavir)-related dyslipidemia, and subsequently the recognition of lipoatrophy with thymidine nucleosides) and convenience of administration issues that came to dominate recipients’ lives (fasted three times daily dosing with indinavir being the apothecosis of this). Thus, the potential for benefits from earlier treatment remained obfuscated by the impact on quality of life and stigmatising side effects from treatment.

Several things have changed over the last decade that have shifted thinking around a more universal treatment approach, indefinite treatment from early diagnosis. Pivotal to this has been the evidence for treatment as prevention (TasP) particularly data from HPTN052 and the UK Partners study. Final data from HPTN 052 were reported at the IAS conference in Vancouver. HPTN 052 began in 2005 and enrolled over 1,750 mostly heterosexual serodiscordant couples at 13 sites in 9 countries. Over the course of the study, there were a total of 46 virologically-linked (verified by molecular testing) transmissions from the HIV-positive partner to the HIV-negative partner. Three transmissions occurred among couples who started ART immediately, 43 occurred in couples who started ART when symptomatic or their CD4 cell count fell below 250 cells/mm³. None of the people who transmitted HIV were virologically suppressed at the time when the transmission occurred. Transmissions in the immediate arm occurred either within a few weeks of initiation when suppression was not complete or during treatment interruptions [1]. Thus, the estimate that early ART reduces transmission risk by 93% may well underestimate the true power of TasP. Similar data have been reported previously in Partners, which examined a range different sex acts in straight and gay HIV serodiscordant couples but did not observe any transmissions [2]. While these data don’t absolutely rule out the possibility of transmission with an undetectable viral load, they underline the potential for universal ART as a public health intervention that could rapidly change the shape of the future HIV pandemic. Of course to achieve this programs to diagnoses HIV infection and retain people in care are needed. Both family practitioners and hospital doctors in both medical and surgical specialties remain poor at offering HIV tests to people who argue have HIV indicator diseases (this would include most skin problems, diabetes, cardiac disease, malignancy, GI upset etc ad infinitum) missing opportunities for early diagnosis. This is clearly negligent, and should be taught as such in Medical schools and medical education programs across specialties. Furthermore, many health care systems, most notably the US, are poor at retaining people in care so finish up doing poorly when it comes to the numbers in the treatment cascade who actually have undetectable viral loads. Most European (and Australia, Canada) healthcare systems which don’t place access, insurance or cost obstacles in the way of retention do vastly better.

Dramatic improvements in tolerability

A second key factor is the dramatic improvements in tolerability and convenience of administration of ART. The shift to non-thymidine nucleosides has eliminated most mitochondrial toxicities and the HLAB*5701 test has eliminated abacavir hypersensitivity from clinical practice. Reformulation of tenofovir as an alafenamide fumarate (TAF) is likely to reduce the renal and bone toxicities of the current TDF formulation. A shift is some guidelines (US DHHS, Spanish GESIDA) to (near) universal recommendation of integrase inhibitors is a reflection of the improvements in tolerability and more rapid virological responses that these agents bring to therapy. Integrase inhibitors have proved marginally better in efficacy against old standards in some trials (Dolutegravir vs Efavirenz in Single, Raltegravir vs Efavirenz in StartMRK, Raltegravir vs

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The START study

PIs in ACTG 5257, Dolutegravir vs Darunavir/r in Flamingo and Stribild vs Atazanavir/r in the women only WAVE study reported at Vancouver [3]. A report on clinical experience with the different integrase inhibitors from the HIV service in St Paul’s Hospital Vancouver reported at the IAS meeting showed adjusted adverse event rates (ADR) (CI 95%) per 100 person-years were Raltegravir 1.88 (0.72-4.93), elvitegravir-cobicistat 5.76 (2.14-15.49), and dolutegravir 3.34 (1.19-9.40) [4], underlining that the high levels of mainly short-term tolerability in trials appear to translate into practice. However, one key obstacle to universal treatment raised by many cohort studies, most notably D:A:D, remained the long-term risk of ART, what role drug choice may have in risk of specific events such as myocardial infarction, renal and bone disease.

SMART

Furthermore, clinical studies such as SMART, which compared continuous viral suppression with CD4-guided therapy, showed that that untreated HIV infection or uncontrolled viremia was associated with development of many non-AIDS-defining diseases, including cardiovascular disease (CVD), kidney disease, liver disease, and malignancies, possibly through inflammatory drive [5]. This underlined the need to target viremia, rather than the former goal of maintaining CD4 cell counts above a certain threshold, 200, 350, 500/mm³ all being used at various times. In some ways this was not surprising as the ‘wait and see’ model is generally not a part of infectious disease management. We don’t wait, for example, for a certain number of colony forming units to be present before treating a bacteremia. Additionally, clinical trial and cohort studies identified that the CD4 at start of therapy was critical to where CD4 count ended up many years after starting therapy, that there appeared to be a limit to the extent of numerical and functional immune restoration. So a CD4 number on the way down may be different from the same number on the way up. If a CD4 threshold was critical to maintaining immune surveillance against both AIDS and non-AIDS illnesses it made sense to keep it high with early treatment.

So the stage was set for the START (Strategic Timing of AntiRetroviral Treatment) trial to investigate the role of immediate ART versus delayed (to CD4 350/mm³ or clinical disease) ART on its impact on ‘serious AIDS events’ (CDC AIDS events plus Hodgkin’s lymphoma) and ‘serious non-AIDS events’ (major cardiovascular disease events, end-stage kidney disease, liver disease and non-AIDS-defining cancers). The data and safety monitoring board required a significant reduction in both types of events to be achieved to eliminate the possibility that treatment reduced the risk of AIDS events but caused an increase in non-AIDS events.

The START trial enrolled 4,685 HIV-infected men and women >18 years (median age of 36 years) who had CD4+ T-cell counts above 500 cells/mm³, no symptoms of HIV infection, and had never taken antiretroviral therapy. The average duration of known HIV infection was around 1 year. Twenty-seven percent of the participants were women, and about half were gay men and the study population was drawn from across the globe, including 215 sites in 35 countries. The initial antiretroviral drug regimen was chosen freely at the site from a list of drugs based on the treatment guidelines of the U.S. Department of Health and Human Services (DHHS). Treatment changes were permissible without consequence to the subjects’ participation. Medication
and follow-up care was provided free to all study participants, a key issue to study retention. The most common first line choice was TDF/FTC+Efavirenz, 73% in the immediate and 51% in the deferred group, consistent with WHO recommendations. Study participants were followed at one month, four months, and every four months thereafter for an average of three years.

**CD4**
The median CD4 count at study entry was 651/mm3 and viral load 13000 copies/ml. The arms were well matched. The median time to ART in the deferred group was 3 years and over the duration of follow up the spent on therapy was 94% in the immediate and 28% in the deferred groups. Despite the high baseline CD4 counts, the numbers rose further with treatment and at 60 weeks was a mean 194 cells/mm³ higher in the immediate treatment arm relative to the deferred arm.

For the primary combined endpoint of AIDS and serious non-AIDS events, there were 42 (1.8%) in the immediate group for a rate/100 patient years of follow up of 0.6 and in the deferred group 96 (1.4%) for a rate of 1.38/100pyrs. This gave a hazard ratio of 0.43 (95%CI 0.3-0.62 p=0.001). For individual endpoints the rates of serious AIDS was 14 events (0.2/100pyrs) vs 50 events (0.72/100pyps) (HR 0.28 95%CI 0.15-0.5, p=0.001) and serious non-AIDS 29 events (0.42/100pyrs) vs 47 events (0.67/100pyrs) (HR 0.61 95%CI 0.38-0.97, p=0.04). Thus both endpoints were significant albeit the impact on AIDS events differed little between groups [6]. The majority of events occurred when the number of new infections. This involves a massive mobilization of skills, infrastructure, logistics and a substantial increase in the production of ART to avoid stock outs, but most of all it requires belief from governments, healthcare professionals, and people with and affected by HIV that it can be done. As such, this represents another turning point in the fight against HIV. Let's begin at the beginning and keep going until HIV comes to an end.

**Summary**
In summary, treatment of HIV at high CD4 cell counts reduces risk of AIDS events and non-AIDS events and shows a trend towards fewer deaths. Treatment (most commonly with TDF/FTC+efavirenz) does not burden subjects with additional grade 4 events (of note, suicide did not differ between groups). While the number needed to treat to benefit was not reported, my estimate is that it is about 180 persons treated for 1 year to prevent an event. While that may look expensive, the costs are firstly partially offset by preventing serious and expensive disease in young economically productive people, and most notably reducing TB events which may affect the wider community. Secondly, any consideration not to treat is made moot given the added TasP benefits of early treatment as defined by HPTN 052 and Partners. In practice what it means is we need to offer treatment to everyone with identified HIV infection and, as shown in SMART, maintain that treatment lifelong. This is a very simple public health message. Test, be treated, protect yourself and your partners. It means we will no longer send people away from clinic suggesting that they are ‘all right for now’ only to find them lost to future follow up or subsequently presenting symptomatic. It also means we need to redouble our efforts to find people with HIV through testing programs and pro-selytising the benefits of testing and early diagnosis to our colleagues and the media.

There remain some unanswered questions, most notably around the burden of lower grade adverse effects of treatment, the impact on laboratory changes and other drug-related effects that may take longer than a mean 3 years follow up in young people to manifest as clinical events and the issue of why so many clinical events occurred in people with apparently normal (>500/mm3) CD4 cell counts regardless of whether treated or not. This underlines the need for greater understanding of the immune profiles we use in daily practice, the potential for additional markers and how limited the value of CD4 counts may be above (say) 350. As many have clinics have shifted to infrequent (annual) CD4 testing this looks like money well saved.

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**The START study**
Hepatitis C

We have certainly seen a true revolution within treatment for hepatitis C virus (HCV) infection, since the launching of direct acting antivirals (DAAs) during 2014.

Treatment against HCV can now be given without frequent adverse events associated with interferon (IFN)-containing regimen, and it does not exclude any special patient groups as previously, especially patients with Child Pugh class B or C patients. The chance of achieving sustained virological response (SVR), i.e. cure of the HCV infection, has increased dramatically from approximately 30-50% to 80-99% in cirrhotic patients with usage of DAAs. The number of cirrhotic patients with SVR is therefore expected to increase steeply with introduction of DAAs.

Long-term overall survival
In the last few years, we have gained knowledge about the long-term overall survival benefit of achieving SVR in cirrhotic patients after IFN based treatments [1, 2]. Decreased risks for liver complications, liver-related and overall mortality have been seen, compared to those with non-SVR [3-5]. These data derived mainly from patients with compensated liver cirrhosis, although beneficial effect in survival has also been reported in patients with decompensated liver disease [3].

The risks for hepatocellular carcinoma (HCC) and liver complications decreased after achievement of SVR, as seen in Figure 1 [2]. The risks are though not totally abolished, and a remaining risk persisted in patients with pre-treatment liver cirrhosis [1, 2, 4, 5]. The substantial hazard often leading to liver-related mortality in these patients was the risk for development of HCC. In parallel with increasing number of cirrhotic patients achieving SVR, the number of developed HCC in patients with SVR is also expected to increase.

International guidelines recommend therefore continued, in practice lifelong, surveillance with ultrasound every sixth months, after achievement of SVR in patients with liver cirrhosis prior to treatment [6, 7]. With prolonged survival and increased number of cirrhotic patients reaching SVR, these recommendations can be a quite challenge for physicians to adhere, due to limited resources and lack of knowledge about the cost-effectiveness and the needed duration of such a program. In the light of the new knowledge we have gained in the last years about the reversibility of cirrhosis to lower fibrosis stages in as much as 60% of patients, clinicians are really questioning about whether the patients with regressed cirrhosis should really be subjected to continued surveillance for HCC.

The questions are therefore:
1. How high is the risk for HCC in cirrhotic patients with SVR, and for how long does the risk persist for and need continued surveillance?
2. Can we stop the surveillance in patients with regressed cirrhosis?

Cost-effectiveness for continued surveillance
Firstly, several cohorts have shown a remaining yearly risk for HCC after SVR of 0.6-1.2% in patients with pre-treatment compensated liver cirrhosis [1, 2, 4, 5]. Whether this incidence is high enough regarding cost-effectiveness for continued surveillance with ultrasound is unknown at the present. The incidence of HCC for cost-effectiveness of surveillance in cirrhotic patients of any etiologies has been estimated to be 1.5%/year or more [8]. On the other hand, for hepatitis B carriers without cirrhosis but of Asian and African origin, the surveillance could be cost-effective at a low incidence as 0.2%/year [6].

The threshold for cost-effectiveness for patients with pre-treatment cirrhosis and HCV-SVR needs therefore to be explored.

We do neither have any knowledge about how long this risk for HCC persists, or if it decreases with time. In our

Figure 1. Kaplan-Meier curves showing the risk for being free from risk for hepatocellular carcinoma (HCC) and other complications in patients with non-SVR (=sustained virological response), SVR and untreated hepatitis C infected patients. Significantly reduced risk could be seen in patients with SVR, compared to non-SVR patients.

Risk for hepatocellular cancer in patients with cured hepatitis C
These giants of the animal kingdom need help. Despite their strength and cunning they’re no match for a poacher’s rifle. For 50 years WWF has been securing protected areas worldwide, but these aren’t enough to stop the killing. To disrupt the sophisticated criminal gangs supplying animal parts to lucrative illegal markets, we are working with governments to toughen law enforcement. We’re also working with consumers to reduce the demand for unlawful wildlife products. Help us look after the world where you live at panda.org/50.
published cohort study from Sweden, the events of HCC after SVR occurred in two patients within two years after SVR, while the others occurred 2.4, 7.4, 7.6 and 7.6 years after achievement of SVR [2]. There are anecdotal cases of late HCCs reported, and in Karolinska University Hospital we have seen two patients who have developed HCC at 12 and 15 years after SVR (not published data). One might speculate that the risk will decrease with time, as it has been shown for patients with chronic hepatitis B infection [9]. The reductive effect of antivirals on the incidence of HCC in these patients was noticeable at approximately 2 years of therapy and further decreased with time.

Does the risk for HCC decrease with fibrosis regression? There are no data, but in the French study by Mallet V et al, no liver complications including HCC was seen during the up to 10 years of follow-up time among 18 pre-treatment cirrhotic patients who have regressed in their fibrosis to at least stage two or fewer METAVIR units in the post-treatment liver biopsies [10]. In the last years, liver elasticity measurements have mainly replaced liver biopsy for estimating the degree of fibrosis. In the abstract of Sultanik P et al, liver stiffness measured by Fibroscan could not predict occurrence of HCC in patients with SVR [11]. However, liver stiffness measurement has been shown to have poor correlation with regression from cirrhosis in liver biopsies of patients with SVR [12].

Older age, low platelet count, increas-
ed AFP levels, moderate-heavy alcohol consumption, high AST or ALT levels and hepatic steatosis have been associated to increased risks for HCC in Asian patients with SVR [13, 14]. In Western patients, age, platelet count and diabetes mellitus were shown to be risk factors for HCC in the abstract of multicenter Western study by van der Meer et al [15]. In the future, we may be able to better identify the subgroups of patients with pre-treatment cirrhosis who do need continued surveillance after SVR, with cost-effectiveness, depending on the risk factors.

Conclusion
In summary, we do have a growing group of cirrhotic patients with SVR in the era of new DAAs at risk for developing HCC, but there are large knowledge gaps about which subgroups or for how long the surveillance for HCC should be continued after achievement of SVR. Cost-effectiveness analyses are needed. Until we have more data, we should be on the conservative side and continue the surveillance with ultrasound for HCC after SVR in all patients with pre-treatment cirrhosis, regardless of fibrosis regression.

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References
When to initiate antiretroviral therapy (ART) has been controversial since the 1980s. Recommendations made by various guidelines committees have fluctuated widely. Some groups have even changed their views over time.

However, an accumulation of data suggests that untreated patients or those who have discontinued therapy experience deleterious biological events such as heightened inflammation and an increase in coagulation markers that result in cardio-vascular events. As seen in SMART. [1] In addition, a massive 95% reduction in the transmission rate has been recorded in discordant couples in which there is one uninfected male or female partner. Control of viral replication following ART has been clearly linked to a reduction in the transmission rate of HIV-AIDS of over 90%. [2,3]

Several guidelines from the US or countries in Europe have recommended that virtually all HIV-infected persons, regardless of CD4+ cell count, be treated. [4,5] Still, up until 2015 other guidelines continued to recommended waiting until cell count was < 500 or < 350 cells/mm³ before initiating ART. It was argued that there was insufficient clinical endpoint data from randomized trials to establish the benefits of early treatment. [6,7]

START (see the article by Graeme Moyle in this issue of HIV NEWS) is a large, randomized, international study that demonstrates the clinical benefits of initiating ART in patients with a CD4+ count > 500 cells/mm³, these benefits being a reduction in serious AIDS-related and serious non–AIDS-related events, compared to deferring the ART until the CD4+ count was < 350 cells/mm³. This finding was observed in all patient categories, independent of age, sex, geographical region, CD4+ count, viral load, or risk factors for serious non-AIDS diseases.

TEMPRANO
The TEMPRANO ANRS12136 trial that began in 2008 and ended in 2015 sought to determine the efficacy of administering early ART along with isoniazide as a prophylaxis against the devastation spread of tuberculosis in Africa. The question was whether this would be clinically beneficial to HIV-infected patients in a sub-Saharan African country such as Ivory Coast, where prophylaxis was not systematically prescribed earlier. The study has been continued despite the politically troubled times in Ivory Coast in recent years.

**Study design**
Subjects were randomized to one of four arms:
- **Arm 1:** Deferred ART initiation
- **Arm 2:** Deferred ART initiation + 6 months isoniazid preventive therapy (IPT)
- **Arm 3:** Immediate ART initiation
- **Arm 4:** Immediate ART initiation + 6 months IPT

- During the seven years of the trial, the criteria for beginning ART were adapted to the most recent WHO guidelines: CD4+ < 200/mm³ from March 2008 to December 2009, CD4+ < 350/mm³ from December 2009 to July 2012, and CD4+ < 500/mm³ from July 2012 to December 2014.
- Follow-up: 30 months
**Drugs:** INH was given 300 mg/day for 6 months. ART consisted of:
- TDF + FTC + efavirenz
- TDF + FTC + lopinavir/ritonavir
- TDF + FTC + zidovudine

**End points**
The primary end point was a composite of death from any cause, AIDS-defining disease, non-AIDS-defining cancer, or non-AIDS-defining invasive bacterial disease. The main secondary end points included grade 3 or 4 illness, including all events with a grade of 3 or 4 according to the ANRS grading table.

**Results**
A total of 2,076 patients were randomly assigned to treatment groups; 2,056 of them (99%) were included in the analyses. They were mostly females (78%) with a median age of 35 years. The median baseline CD4+ cells count was 465 CD4+/mm³ (IQR: 369–573), viral load 4.7 log10 (4.0–5.3). Approximately 90% received cotrimoxazole.

In the early ART arm, 1,033 (100%) received ART; 58% received ART in the deferred arm. ART consisted mainly in TDF/FTC plus EFV (70%) and TDF/FTC plus LPV (30%). The rate of attendance at clinics was excellent: 93% at 3 months and 86% at 30 months.

Overall, the probability of starting therapy within the 30 months of follow-up was 63%, suggesting that the time prior to initiation of ART is short and represents a small fraction of the patient's lifetime, considering how young the population is.

The response rate to ART was excellent with a viral suppression rate of 84% at month 12 in the 1,033 patients assigned to the early ART arm, and 83% among the 872 patients in the deferred arm at month 24.

**End points**
A total of 204 primary end-point events were recorded in 175 patients. There were events at all CD4+ levels, with a higher number, as expected (depending of the degree of immune suppression) in patients with 2.8 events, 4.1 events, and 6.8 events per 100 person-years (95% CI, 5.0–8.6) in the > 500 CD4+, 499/mm³, 350/mm³, and < 350/mm³ groups.

The 30 month probability of a primary end-point event was:
- 11.4% in the deferred ART strategy
- 6.6% among patients in the early ART strategy,
- 10.7% among patients in the no IPT strategy, and 7.2% among patients in the IPT strategy

Thus, the early initiation of ART and 6 months of IPT independently resulted in a 44% decreased risk of severe HIV-related illness and a 35% decreased risk of death, in comparison with deferred initiation of ART and no IPT.

The year 1983 marked the discovery of HIV; 1986 marked the start of antiretroviral drugs development with the transient positive results of zidovudine; and 1996 is forever linked to the end of a nightmare with the advent of highly active triple drug therapy. We expect 2015 to symbolize a new era in which we all recognize that ART is highly beneficial for controlling HIV in all HIV-infected patients.

There is no longer any doubt that controlling a virus that replicates a billion times daily is better that letting it grow. There are not only general health benefits to the individual patient. Private sexual life can be pursued with confidence since the virus is suppressed and one is no longer a source of contagion, reducing anxiety for both partners and avoiding the risk of stigmatization.

Overall, a normal life is possible, including undertakings that extend over many years, parenting, and aging. It is a relief that the question “To treat or not treat at any CD4+ count?” has been put to rest and the debate is over.

**Time to concentrate on treatment optimization**
Resolving one question opens others. The next decade will have to determine which treatment options are the best and can be recommended worldwide, not only for initiation, but for treating long-term suppressed patients as well, perhaps by individualization of ART.

Given the greater potency of new drugs, the robustness of new compounds, and the less severe HIV parameters in naïve patients with higher CD4+ and lower viral loads, the question is whether a patient with 780 CD4+/mm³ and a viral load.
of 12,000 cp/ml requires the same treatment as a late presenter with less than 50 CD4+/mm² and several hundred thousand copies of HIV RNA.

Additional major challenges face the medical community in the coming months and years:

- Testing has to be promoted among the 35 million individuals estimated to be HIV infected, since there is a proven benefit to controlling viral replication.
- Information and education regarding ART has to be presented in a more positive way, stressing a simple regimen and conveying a hopeful perspective on the future.
- Since treatment must be maintained lifelong in the absence of current strategies for cure or remission, we must optimize ART to provide maximal viral suppression with minimal drugs.

One way to optimize antiretroviral strategy is by reducing the dose of antiretroviral drugs. The rationale is that when new drugs are developed, the highest tolerated doses in phase II are often selected for phase III and approval. In some cases lower doses might have had equivalent efficacy and better tolerability.

An extended follow-up from ENCORE19 has provided 96 week data showing that a lower dose of efavirenz (EFV) is not inferior to the currently approved regimen. New results continue to appear.[10]

The LASA study: Low dose Atazanavir/r vs. standard dose Atazanavir/r

Also in the field of dose reduction, Thai researcher Torsak Bunupuradah has presented the strong LASA study on behalf of the Thai national collaboration at IAS in Vancouver.

The study investigated whether a reduced dosage of atazanavir/ritonavir 200/100 mg could be as effective as atazanavir/ritonavir 300/100 mg in virologic suppressed HIV-infected Thai adults.

This multicenter, randomized, open-label trial enrolled 560 patients with an undetectable viral load who were on a 2 NRTI + PI (protease inhibitor) regimen. They were then switched to an ATV/r 300/100 mg (n = 280) or to an ATV/r 200/100 mg (n = 279) regimen. The primary end point was the rate of viral suppression at Week 48. The study found that the proportion of viral suppression < 50 cp/mL remained high, with over 90% viral suppression at Week 48, as shown in Figure 2.

If there is no difference in terms of virological success between the ATV 200 mg and ATV 300 mg by intent to treat and per protocol analysis, the lower dose of atazanavir can be assessed as non-inferior to the higher dose. Overall, by snapshot analysis, ATV 200 mg was even superior to ATV 300 mg, due to the better tolerability of the lower dose and a reduced discontinuation rate.

There was also a significant difference in hyperbilirubinemia, with a lower total bilirubin level (1.9 vs. 2.2 mg/dL) and less grade 3-4 hyperbilirubinemia in the low dose atazanavir group compared to standard dose (17% vs. 32%).

A positive collateral side effect of dose reduction, in addition to better tolerability, which ensures heightened compliance and reduces the rate of discontinuation, is its lower cost. A projected cost savings of 58 million dollars over 5 years to treat 20,000 patients is reported with LASA. Nevertheless, the results of the LASA study are not at present generalizable to other populations, such as non-Thai, naïve, or failing first-line patients. [11]

These results add to the new era of reducing dosage of antiretroviral drugs opened years ago with stavudine, and recently with efavirenz in the ENCORE study. They are highly encouraging for long term management therapy. Drugs such as PIs with high plasma concentration in comparison to IC 90% of sensitive HIV strains, a high robustness, and unprecedented high genetic barrier to resistance represent an antiretroviral class that cannot be discarded too quickly. The use of low doses of the most currently used PIs worldwide, such as lopinavir in developing countries, atazavir or darunavir have yet to be investigated.

In the same area of dose reduction, several trials are going in France whose goal is to improve long term management. DARULIGHT ANRS 165 is an on-going
trial to evaluate viral suppression rates after switching from darunavir/r 800/100 mg to darunavir/r 400/100 mg in fully-suppressed patients on a standard 2 NRTI plus standard darunavir/r 800 mg and no resistance. [12]

ATALOW is a non-comparative study that starts mid-June 2015 - evaluate viral suppression rates after switching from standard atazanavir /r 300/100 mg/d to atazanavir /r 200/100 mg in patients already successfully controlled on a standard 2 NRTI+ atazanavir 300/100 mg regimen. [13]

PIs hold a special place in our drug armamentarium against HIV due to their wide availability and proven robustness. Since their development occurred when long-term safety concerns extending over decades was not an issue, and at a time high dosages were given priority in naïve or failing patients, we must reevaluate their use in present and future applications in the context of long-term patient management.

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References
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The persistent HIV reservoir
Invitation for
the 2nd Nordic Meeting on Women
Living with HIV

- Scientific meeting

December 9th 2015 at Hilton Copenhagen Airport,
Copenhagen, Denmark

We welcome you to this 2nd Nordic meeting, in which we will explore the challenges faced by women living with HIV.

Nordic Program Committee: Dr. Inka Abu, FIN. Dr. Pia Kivelä, FIN. Dr. Katarina Westling, SWE. R.N. Midwife, Lena Rolffsmo, SWE. Dr. Kristina Elfström, SWE. Dr. Leo Hoemhals, SWE. Dr. Nina Weis, DK. Dr. Terese Katzenstein, DK
## Program for doctors and nurses:

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<td>9.30-10.00</td>
<td>Arrival, registration and coffee</td>
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<td>10.00-10.15</td>
<td>Welcome and review of agenda</td>
<td>Program committee</td>
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<tr>
<td>10.15-10.30</td>
<td>A history from the real world...</td>
<td>Kristina Thorsteinsen, DK</td>
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<td>10.30-11.00</td>
<td>Osteoporosis in HIV infected individuals</td>
<td>Maria Wessman, DK</td>
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<td>11.00-11.15</td>
<td>Mode of delivery in women living with HIV in Denmark</td>
<td>Mathilde Ørbeak Jensen, DK</td>
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<td>11.15-11.45</td>
<td>Mode of delivery, complications and outcome in women living with HIV in Sweden</td>
<td>Stina Bornhede, SE</td>
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<td>11.45-12.00</td>
<td>Hospitalizations among HIV-exposed uninfected children</td>
<td>Ellen Moseholm Larsen, DK</td>
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<td>12.00-12.45</td>
<td>LUNCH</td>
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<tr>
<td>12.45-13.45</td>
<td>Choosing the right antiretroviral agent for women living with HIV across their lifespan</td>
<td>Sharon Wallmsley, Canada</td>
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<td>13.45-14.30</td>
<td>HPV infection in women</td>
<td>Susanne Krüger Kjær, DK</td>
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<td>14.30-14.45</td>
<td>Coffee break</td>
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<td>14.45-15.45</td>
<td>Monitoring HPV infections in the Nordics</td>
<td>Inka Aho, FI.</td>
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<tr>
<td>15.45-16.00</td>
<td>Closing remarks</td>
<td>Christina Carlsson, SE. Kristina Thorsteinsen, DK</td>
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<td></td>
<td>Safe trip back home and sandwich</td>
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## Registration:

To register for this meeting please mail to: caroline.holbek@bms.com

Please register before Friday November 6th

The meeting is sponsored by Bristol-Myers Squibb

Dina personuppgifter: I samband med din anmälan till/ditt deltagande i ovanstående aktivitet samt Bristol-Myers Squibb AB (BMS) innehåller personuppgifter. Dessa uppgifter används för att hantera din anmälan/ditt deltagande samt för att utvärdera och förbättra våra aktiviteter. Genom att fylla i formuläret medger du att personuppgifterna får användas och sparas av BMS för ovan nämnda syften. Sådana medgivande omfattar hela BMS-koncernen samt några av utvalda leverantörer som BMS använder sig av i samband med aktiviteten. Du har rätt att begära en kopia av dina personliga uppgifter, till dessa korrigerade och/eller motsatta dig fortsatt behandling av dina personuppgifter genom att kontakta BMS på 08-704 71 00 eller infosverige@bms.com.
Entecavir resistant hepatitis B

In a Korean study 90 patients with entecavir (ETV) resistant Hepatitis B were randomized to tenofovir disoproxil fumarate (TDF) as monotherapy or the combination of TDF and ETV. All patients had at least one resistance-associated mutation and detectable HBV-DNA at baseline. The median baseline HBV-DNA was 4.02 log10 IU/mL and 89% were HBeAg positive. After 48 weeks of therapy there was no difference in the number of patients achieving HBV-DNA < 15 IU/mL (71 vs 73%). Median HBV change from baseline was – 3.7 log10 IU/mL and residual HBV-DNA level in patients who did not achieve undetectability was 1.79 log10 IU/mL. No development of new resistance mutations was observed and safety profiles were similar in the two groups.


Comment: The study results confirm the lack of cross resistance between entecavir and tenofovir. Monotherapy was as effective as combination therapy. However, the results should be interpreted with some caution as 48 weeks may be too short to detect potential differences in outcome.

Double dose Hepatitis B vaccine in HIV-positive non-responders?

178 HIV-positive individuals with at least 200 CD4 cells who were non responders to 2-4 doses of Hepatitis B vaccination were randomized to receive revaccination with 3 doses of standard (20 µg) or double dose (40 µg) vaccine. Before randomization all participants were given one booster dose of 20 µg. Those who responded to the booster dose were excluded from the study. 411 received the booster dose before randomization. Doses were given at week 0, 4 and 24. The primary endpoint was the proportion of responders at week 28. Response was defined as having an anti-HBs titer of at least 10 mIU/mL. The response rate was 67 % with single dose versus 74 % in the double dose arm (p=0.334). The difference was not statistically different. Local reactions were more common with double dose. However, the titers among the responders were higher in the double dose arm. At week 72 the response was lost in 56 % of the initial responders in the standard dose versus 23 % in the double dose study arm.

Rey D, et al. Lancet Infect Dis 2015, Published online August 7, 2015

Comment: This ambitious study does not give us any real clue on how to best manage non responders to Hepatitis B vaccination. One surprising finding was that 218 of 411 (53 %) “non responders” responded to one standard dose of vaccine and were excluded from the randomized part of the trial. The figure is much higher than expected in non responders. In the paper the authors discuss the effect of three doses but actually all randomized participants received 4 doses including the initial booster dose. Already at 72 weeks a substantial proportion of the responders in both arms had titers below 10mIU/mL. In healthy adults no revaccination is recommended despite waning titers. Should HIV positive individuals be revaccinated when anti-HBs titers are waning?

The effect of Isoniazid Preventive Therapy and ART in combination

In a large retrospective non randomized cohort study the composite endpoint of tuberculosis (TB) and death was compared in HIV-positive patients who received both ART and Isoniazid Preventive Therapy (IPT) compared to ART only. The cohort included patients with HIV who had been treated in an Ethiopian University Hospital. Of 4091 patients 1922 patients were included in the final analysis. The most common reason for exclusion from the study was loss to follow up. Before initiating IPT active TB was ruled out. ART was started in patients with WHO stage III disease or CD4 count below 200. A majority of the patients had less than 200 CD4. 374 patients received both ART and IPT while 1548 had only ART. The uptake of IPT was low despite WHO guidelines recommending IPT to all patients without active TB. Median follow up duration was 839 days and the total observation time was 5491 person years. In total 110 patients developed TB and 149 died during the course of the study. After adjustment for baseline confounders the hazard for TB/death was 60 % lower for those receiving both ART and IPT compared to those receiving ART only.


Comment: Despite showing a statistically convincing risk reduction for TB/death with the combination of IPT and ART...
versus ART only, there are several limitations in the interpretation and application of the results. First and foremost it is a retrospective non randomized study with potential confounding factors that may be difficult to adjust for. Secondly there is a large loss to follow up and thirdly ART is started at much higher CD4 counts today compared to when the study was performed. In the discussion the potential risk of resistance development with IPT is not mentioned.

**Simplification from triple therapy to dual therapy in virologically suppressed patients (OLE)**

250 HIV-positive patients from 32 HIV units in Spain and France were included in a simplification study. Eligible patients were treated with lopinavir/r and 2 NRTIs and had viral load less than 50 copies/mL for at least 6 months. Patients were randomized 1:1 to continue the same therapy or to switch to dual therapy with lopinavir/r twice daily and lamivudine once daily. Patients with hepatitis B were excluded and so were patients who had failed virologically while receiving a regimen containing lopinavir, lamivudine or emtricitabine. The primary endpoint was treatment response after 48 weeks. According to intention to treat 86.6% in the triple arm and 87.8% in the dual-treatment arm fulfilled the criteria of treatment response. There were no statistically significant differences in adverse events between the two treatment arms. One patient had resistance mutations at failure but the same mutations were found retrospectively in a saved pre-study sample. The number of “blips” did not differ between the arms. In summary non-inferiority for dual treatment with lopinavir/r and lamivudine was shown.


**Comment:** Even though there were no obvious differences in adverse effects between the arms during the study in the long term it may be beneficial to avoid abacavir and tenofovir thus avoiding potential toxic effects. Using dual therapy may also be a way of reducing costs taking the fact that lamivudine is a generic drug into consideration. However, twice daily dosing may be a less attractive option for simplification when most regimens are given once daily.

**Simplification from triple therapy to dual therapy in virologically suppressed patients (SALT)**

In a similar study design 286 HIV positive patients from 30 hospitals in Spain were randomized 1:1 to triple therapy with atazanavir/ together with two NRTIs or dual therapy with atazanavir/r together with lamivudine. Patients with stable antiretroviral therapy and viral load less than 50 copies/mL during the preceding 6 months could be included. Hepatitis B, Gilbert’s syndrome, previous virological failure and switch of antiretroviral therapy within the last 4 months were exclusion criteria. At baseline 65% were on a boosted PI regimen while 33% were on an NNRTI regimen. After 48 weeks 83% of the patients in the dual therapy arm had viral load less than 50 versus 78% in the triple arm. Non-inferiority was shown. Viral blips were noted in both arms with 15 and 17% having at least one “viral blip” not leading to treatment interruption. One patient on triple therapy developed a resistance mutation in M184V. Treatment interruption was more common in the triple therapy arm with 7% versus 2%. Adverse events were evenly distributed.


**Comment:** As in the OLE trial dual therapy was as effective as triple therapy in the SALT trial. Dual therapy with atazanavir/r and lamivudine once daily may be a more attractive option than twice daily lopinavir/r with lamivudine. It is however important to remember that both studies were done in patients with suppressed viral loads and no previous virological failure.
Hepatitis B Surface Antigen (HBsAg) levels predict fibrosis in e-antigen positive Hepatitis B

A total of 1175 patients from two different studies of patients with e-antigen positive hepatitis B were retrospectively analyzed for predictors of liver fibrosis. All patients were Asians and had genotype C or D and all had undergone liver biopsy. Baseline HBsAg levels were measured retrospectively in frozen serum samples. Two different scoring systems were developed (PS1 and PS2). In PS1 age (<30 vs >30), ALT-level (<3fold vs >3 fold upper normal level) and HBsAg level (<17.500 vs >17.500 IU/ml) were used and in PS2 the score was based on only age and HBsAg-level. The scores were compared with biopsy results. PS1 identified patients with F0-F1 (Metavir score) vs F2-F4 with more than 87 % specificity and positive predictive value >75. It identified patients with F0-F2 vs F3-F4 with 95 % specificity and 97 % positive predictive value. PS2 was less accurate in predicting F0-F1 vs F2-F4 but identified F1-F2 vs F3-F4 with the same high sensitivity and positive predictive value as PS1.


Comment: Could be a useful, simple and inexpensive method to distinguish patients with no or minimal fibrosis who do not require immediate antiviral therapy from those with more advanced disease in which antiviral therapy should not be delayed.

A scoring system to predict HBsAg clearance

2491 HBsAg positive individuals with negative e-antigen were followed for a median of 10.1 years. They all had genotype B or C. A scoring system based on age, HBV-DNA levels and HBsAg titer was constructed. Clearance was defined as two negative tests for HBsAg one year apart. No patients on antiviral treatment were included in the study. The prediction score ranged from 0 to 27. Age less than 40 gave a score of 0 points, age 40-49 1, 50-59 2 and over 60 3 points. HBV-DNA > 2 000 IU/ml gave a score 0 points, 200-1999 2 and less than 200 6 points. HBsAg titer > 1000 IU/ml gave a score 0, 100-999 9 and <100 18 points. The maximum score was thus 27. 5 year probability of HBsAg clearance ranged from 0.97 with 0 points to 30.5 with 27 points. The 10 year probability of clearance ranged from 2.6 to 62.5. The scoring system was also used in a “validation cohort” with somewhat different characteristics than the original cohort. Despite inherent differences between the 2 cohorts the model performed well in the validation cohort.


Comment: HBsAg seems to be the strongest predictor of seroclearance of HBsAg. It seems reasonable to include HBsAg titers in the routine management of hepatitis B. The study does not include patients who received antiviral therapy. It is unclear what if any impact on the probability of seroclearance antiviral treatment has.
Multivitamin supplementation in HIV-infection?

400 Ugandan HIV patients who were initiating or who had been on antiretroviral therapy for less than 6 months were randomized to supplementation with multivitamins or placebo. The multivitamin contained recommended daily allowances of vitamin B-complex, vitamin C and vitamin E. Patients were followed for up to 18 months. Primary endpoints were changes in CD4 levels, weight and quality of life. Secondary endpoints were new or recurrent HIV disease event, switch from first to second line antiretroviral therapy and occurrence of side effects including severe anemia, nausea/vomiting, diarrhea and peripheral neuropathy. The observed average increase of CD4 was 141 in the multivitamin arm and 147 in the placebo arm. Average weight increase was 3.9 kg in the multivitamin arm and 3.3 kg in the placebo arm. There were no statistically significant differences in any of the primary or secondary endpoints. Neither were there any differences in adverse effects between placebo and multivitamins.


Comment: No added value with multivitamin supplementation. Effective ART and proper food is good enough!

Lower dose of efavirenz non inferior to standard dose

In the ENCORE trial treatment naïve HIV positive patients with CD4 cells between 50 and 500 were randomized to 400 or 600 mg of efavirenz together with fixed dose combination of tenofovir and emtricitabine. 630 patients were included at 38 different sites. The trial was double blind. The results after 48 weeks were published last year and showed that the 400 mg arm was non-inferior to the 600 mg arm. 96 weeks follow up has now been published. The results confirm that 400 mg is non-inferior to 600 mg. At 96 weeks 90.1 % in the 400 mg group and 90.6 % in the 600 mg arm had viral load below 200 copies/mL. Patients reporting an adverse event that was definitely or probably related to efavirenz was significantly higher for the 600 mg arm (48 % vs 39 %, p=0.03). The number of serious side effects did not differ between the groups.

ENCORE study group. Lancet Infect Dis 2015 Jul;793-802

Comment: Despite the fact that efavirenz is no longer a preferred first option in all guidelines it is still globally the most widely used “third agent”. Even though there is no dramatic difference in side effects it is hard to understand why these convincing results should not be applied in clinical practice. It is hard to see any valid reason not to introduce fixed dose tablets containing 400 mg efavirenz instead of 600 mg.

The survival benefit of sustained viral response (SVR) in hepatitis C

A meta-analysis of studies of hepatitis C assessing all-cause mortality in SVR and non SVR was performed through a search of Medline and EMBASE from 1990 to November 2014. 31 studies were identified with sufficient data to be included in the analysis with a total of 33,360 participants. The 31 studies were divided into three categories. The studies were classified as general, cirrhotic and coinfected. The general studies included patients with any stage of liver fibrosis (n=28,398). 9 studies were in cirrhotic patients (n=2,604) and the remaining 5 studies were in HIV/HCV coinfected patients (n=2,358). The median follow up time was 5.2 years in the general studies, 6.8 in the cirrhotics and 5.0 years in the coinfected. Among the patients in the general studies 502 of 12,140 who achieved SVR died compared to 1708 of 16,258 who did not achieve SVR. This corresponds to 0.4 deaths/100 person years of follow up (PYFU) compared to 1.6/100 PYFU. The corresponding figures among the cirrhotic patients was 1.0/100 PYFU for those who achieved SVR vs 3.4/100 PYFU in those who did not achieve SVR and among coinfected it was 0.3 vs 2.4/100 PYFU. The survival differences in all-cause mortality was statistically highly significant in all three categories. The largest protective effect of SVR was in the coinfected group. After adjusting for potential confounding factors, SVR was associated with 50 %, 74 % and 79 % decreased risk of all-cause mortality.


Comment: It is not a big surprise that achieving SVR reduces mortality significantly but it is still reassuring to see the magnitude of the improvement. As we now can cure almost all patients that receive treatment this kind of analysis will be difficult to perform in the future. The median follow up time after SVR was 5.0 to 6.8 years. It is very likely that longer follow up would result in an even more dramatic improvement in survival after achieving SVR compared to those who did not achieve SVR.
Topical Conferences

October 5-6
6th International Workshop on HIV & Ageing
Washington DC

October 7-11
IDWeek 2015
San Diego, CA, USA
https://www.idweekinternational.com

October 8-10
NeuroHIV 2015. 6th International Meeting
On HIV Infection and the Central Nervous System
Matera, Italy
www.neurohiv.com/

October 21-24
15th European AIDS Conference (EACS)
Barcelona, Spain
www.eacs-conference2015.com

November 13-17
AASLD - The Liver Meeting 2015
San Francisco, California, USA
www.aasld.org/

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

December 10-11
European HIV Hepatitis Coinfection (EHHC) Conference
London, UK
www.bhiva.org

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

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

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