CROI 2014 NEAT 991 AND ACTG 5257 SPARING
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WITH INTERGRASE INHIBITORS THE EUROPEAN SOFOSBUVIR LABEL: FROM
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At the Opening Session at CROI 2014 4,103 final registrants were welcomed to the city.
Dear Colleagues

On behalf of the editorial group, I would like to welcome you to the first issue of HIV & Virology News for 2014. This is the fourth volume of the magazine, which began in 2011.

It is published quarterly and distributed at no charge to about 15,000 physicians who work in the field of infectious diseases in 13 European countries. Although the journal is financed by advertisements, its contents are totally independent; our advertisers have no influence over what we publish in any way. We are greatly encouraged by the positive response that the magazine has received and by indications that it is widely read by European physicians and clinicians in the HIV and hepatitis field. HIV & Virology News is also available online at www.hivvirology.com.

The annual Conference on Retroviruses and Opportunistic Infections (CROI) was recently held in Boston. This issue of HIV & Virology News covers several aspects of the conference with a number of reports.

In my opinion one of the most important clinical presentations at the conference was an interim analysis of the PARTNER study, an observational assessment of the risk of sexual HIV transmission from an HIV-positive person on antiretroviral treatment (Abstract #153LB). While condomless sex has also been practiced in HIV sero-discordant couples who have participated in previously published studies (for example, several pregnancies were noted in the HPTN 052-study), this has not been consistently followed and reported, nor has the frequency of anal sex.

By contrast, the PARTNER study provides information on the risk of HIV transmission through condomless sex, including both straight and gay anal sex. By November 2013, 1,110 couples had been recruited and followed for a total of 1,151 years of follow-up. The interim results from 767 couples who contributed 894 eligible couple years of follow-up (586 in heterosexual couples and 308 in gay male couples) showed that no linked transmissions have occurred thus far from an HIV-infected partner with a plasma viral load < 200 copies/mL. The upper 95% confidence interval (CI) limit for the risk of overall transmission by any type of sex was 3.9% over a 10-year period. If one looks only at anal sex, the upper 95% CI was 9.2% over 10 years. Couples in the study will continue to be followed, and more gay couples will be recruited into PARTNER 2.

CROI 2014 covered HIV infection of the central nervous system more comprehensively than in previous years, something very pleasing to note. Several abstracts from high-quality studies were presented. One significant finding reported that early antiretroviral therapy during acute infection appears to normalize intrathecal immune activation (#30 and #31), as opposed to initiating treatment during chronic infection. In the latter case, CNS inflammation initially decreases significantly, but then almost half of all subjects end up with a stable increase in intrathecal immune activation, despite receiving suppressive antiretroviral treatment for years.

Other studies presented at the conference indicated that increased intrathecal immune activation during treatment was linked to a higher risk of depression (#33) and impaired cognition (#490). This corroborates recent research in non-HIV depressive disorders, indicating that inflammation is an important etiologic factor—a significant insight.

Increase in cerebrospinal fluid (CSF) viral load is correlated with increased CNS inflammation and, similar to what is seen in blood, viral blips are also common in the CSF (#442 and #443). However, CSF blips do not seem to be associated with an increased risk of persistent CSF viral escape (#445).

Abstracts, posters, and webcasts from CROI 2014 may be found at www.croi2014.org. Enjoy your reading!
In 2014 CROI was held in Boston. It is the capital and largest city of the state of Massachusetts – and one of the oldest cities in the United States, founded in 1630.

At the Opening Session, Kevin DeCock, who was the Chair for the Meeting, greeted 4,103 final registrants welcome to the city.
– There are 85 countries represented among you, and 47 % of registrants come from countries outside the US, he said.

Dr DeCock also told the audience that 1,936 general abstracts and 217 late breakers were submitted to CROI.
– Approximately 48 % of the general and 34 % of the late breakers was accepted.

He also introduced the Vice Chairs Dr Scott Hammer and Dr Julie Overbaugh.
Dr Hammer has overseen the clinical science for the Meeting, and Dr Overbaugh the basic science.

Similar social and political issues are arising
CROI was established in 1993 and has its focus on basic science, clinical medicine and epidemiology and appropriate interventions.
– An emphasis on science above all, synergy and a multidisciplinary approach characterises this Meeting. We believe that CROI is the pre-eminent and most important conference addressing the science of AIDS in the world, Dr DeCock continued.

CROI is not a commercial undertaking. It is administered by the CROI foundation, a charitable non-profit organisation that operates exclusively for the charitable and educational purpose of organising, promoting and presenting the conference on retroviruses and opportunistic infections.

– Nothing endures but change – Heraclitus wrote that 500 years B.C. It applies to society and organisations, as it does to the Darwinian evolution of viral genetics, he continued.

One programme change in CROI is an increased emphasis on TB and on hepatitis – especially hepatitis C. Some of the therapeutic evolutions in hepatitis C science are reminiscent of those in HIV 20 years ago.

– Similar social and political issues as we saw with HIV are arising – around drug pricing, drug access in low- and middle income settings, availability of generic medication, questions around intellectual property and the public health approach in scaling up treatment where it is needed.

Research in Senegal led to first description of HIV-2
In the Plenary Session that followed, Professor Souleymane Mboup gave a lecture on the application of scientific knowledge and evidence to limit the progression of HIV and AIDS in West Africa.

He started by reminding that the first global program on AIDS biomedical research in Africa already started in 1989.
– This program in 1989 found in a study that there were low and stable HIV infection rates in Senegal. Was this due to the natural course of the epidemic – or instead

CROI 2014
Adeeba Kamarulzaman talked about HIV in people who use drugs. She started by describing the global burden of HIV due to illicit drug use.

Research to inform the national effort was critical. This was set up and led to the first description of HIV-2, which was the initial HIV-virus in the country. The first HIV-1 case was not observed until 1986.

Important discovery
Studies revealed that HIV-1 was more infectious than HIV-2, and also that there were differences in mother to child transmission (MTCT). HIV-1 showed in studies in Gambia, Guinea-Bissau, Ivory Coast and Senegal a rate for MTCT of 20 – 45 %, whereas for HIV-2 the rate was 0 – 5 %.

The AIDS-free survival was also shown to be considerably much higher in those infected with HIV-2.

- HIV-1 and HIV-2 are highly related, they have common virus properties. But they show different biology in people – in terms of epidemiology, transmission and disease progression. The interaction of two virus types shows viral immunity and protection, Prof Mboup said.

He continued by describing the development of research in Senegal, and pointed out that this has been a major focus for their work for over 30 years.

- The first countries that had success in HIV prevention were Uganda, Thailand and Senegal, and they were all characterized by a very strong research activity.

The discovery of HIV-2 has been very important.

- Important as a model for international and long term collaboration and partnership – and even more important for public health measures. We need creation of centers of excellence to use the opportunities provided by this research – with state-of-the-art technologies, collaboration and technology transfer, Prof Mboup concluded.

Needle and syringe programmes and opiate substitution
In the Plenary Session next morning, Prof Adeeba Kamarulzaman talked about HIV in people who use drugs. She started by describing the global burden of HIV due to illicit drug use.

Of the estimated 16 million people infected by HIV in the world, 3 million are so due to injecting drug use. In countries where HIV incidence is rising, 70 – 80 % of HIV cases are among people who are injecting drugs, Prof Kamarulzaman said.

- Certainly injecting drug users remain a problem.

She presented a review of the evidence of effectiveness of interventions to prevent HIV and Hepatitis C in people who inject drugs. Both needle and syringe programmes (NSP) and opiate substitution programmes (OSP) have showed sufficient evidence to support their effectiveness.

- Due to the fact that these programs have so many disbelievers, they are probably the most studied tools we have - there are 43 studies on NSP and 35 on OSP!

However, much as we know that they are effective, globally only an estimated 8 for every 100 of people injecting drugs are receiving opioid substitution therapy, and even much less are given a clean syringe.

Adolescents have poor access to services
Within the group of marginalised drug users, there are three groups that are further marginalised. First there are the female drug users.

They have been found to have a higher prevalence of HIV, compared to their male counterparts.

- Gender-specific drivers that increase vulnerabilities to HIV – structural “risk environments” – include intimate partner violence, gender norms and gender imbalances in the drug culture, and lack of woman-specific drug treatment and services, Prof Kamarulzaman continued.

The other group that escapes attention is adolescents. Though a global population size estimate for people who inject drugs under the age of 18 is unavailable, it is known that in some countries significant proportions of people who inject drugs are adolescents.

- In Nepal they are 20 %. In a study in Indonesia, they found in Jakarta that more than 50 % of people between the age of 15 and 19 shared needles.

In Ukraine a study from 2012 found that of an estimated number of 50.500 adolescent injecting drug users, less than 1.000 were reached by harm reduction services.

- Universally, adolescents have poor access to these services.

An epidemic of imprisonment
The third group Prof Kamarulzaman focused on was men who have sex with men (MSM) who are also drug users. What is known about this group is that the use of drugs varies widely.

- The prevalence of use is higher in further marginalised or minority groups – such as ethnic minority gay men in USA. It is also higher in younger men, and among men living in large urban centers.

Traditionally we know what to do for harm reduction – clean syringes and opioid substitution – but we need to bear in mind that these services need to be tailored to the different groups we try to serve, she reminded the audience.
- Context is a key factor in harm reduction for people who use drugs.
- But a presentation on HIV and drug use would be incomplete if it did not include the problem of prisons and people who use drugs.
- Since Nixon declared a war on drugs in 1971 there has been an epidemic of imprisonment.

**Prisons – a terrible incubator**

A lot of these prisoners are imprisoned for personal, non-violent drug use. In one prison in Malaysia – Prof Kamarulzaman’s home country – these accounted for 60% of those sentenced for drug-associated crimes.

- Prisons are a high-risk environment for ongoing transmission for HIV. TB is also rampant – in Malaysia’s largest prison we found undiagnosed TB in 15 of 125 inmates. That is a prevalence of 12%! Prisons represent a terrible incubator for HIV, TB and many other diseases.
- We have, as she already had stated in her lecture, evidence that needle and syringe programmes and opiate substitution programmes are effective – albeit with some extra changes for people who use drugs – for providing good care. Prof Kamarulzaman also showed data that they make economic sense by preventing transmission of HIV.

So why is this not more widespread?
- I believe that the end of AIDS will not come until we see the war on drugs – and the end of the war on drug users, she stated and received applause from the audience. In spite of this war on drugs, global heroin supply increased by 380% from 1980 to 2010, and the price of heroin in Europe has decreased by 79% in the same time period, she pointed out.

**“Science can be a catalyst for the realisation of human rights”**

- In Portugal in 2001 they decriminalised personal possession of all illicit drugs, but continued prosecution of dealers and traffickers.
- They also expanded treatment and harm reduction. The incidence of HIV and AIDS among drug users was reduced by approximately 45% from the year 2000 to 2008. If we could follow their example, we would see fewer people infected by HIV.
- Prof Kamarulzaman also talked about stigma – opioid use disorder as a medical illness is still overshadowed by its misconception as a moral weakness or a wilful choice.
- We have to address stigma and discrimination – and begin with the medical and scientific community!
- She ended her highly appreciated talk with the following quote:
  - Science can be a catalyst for the realisation of human rights. And human rights can accelerate the translation of scientific knowledge into practice and society!

**Simeprevir once-daily dosing**

The first oral abstract session was on hepatitis.
- Prof Douglas Dieterich presented a study on simeprevir (SMV) plus PegIFN/ribavirin (PR) in HCV genotype-1 and HIV-1 co-infection.
- SMV is a single-pill, once daily, oral HCV protease inhibitor approved in Japan, Canada and the US. It is under regulatory review in Europe and other regions.
- The study found that SMV once daily dosing plus PR led to a high sustained viral response (SVR) in HCV genotype-1/ HIV-1 co-infected patients, regardless of prior HCV treatment response with overall rates of 74%. Baseline characteristics seemed not to have an impact on SVR rates, Prof Dieterich said.
- 89% of treatment-naïve and prior relapers without cirrhosis met response-guided therapy criteria and were eligible to shorten therapy to 24 weeks, with 87% achieving SVR12. HIV virologic suppression was maintained during SMV therapy.
- SMV once-daily dosing was well tolerated – with a safety profile similar to that in mono-infected patients, Prof Dieterich concluded.

**BMS-791325**

A Phase 2B open-label study on an all-oral combination of daclatasvir, asunaprevir and BMS-791325 for HCV genotype 1 infections was presented by Dr Trevor Hawkins.
- Daclatasvir (DSV) is a non-structural protein 5A replication complex inhibitor, asunaprevir (ASV) is a NS3 protease inhibitor and BMS-791325 is a non-structural protein 5B polymerase inhibitor, Dr Hawkins explained.
- The 12-week, interferon- and ribavirin-free regimen achieved SVR12 in more than 90% of patients – despite high prevalence of genotype 1A, advanced fibrosis and cirrhosis and two thirds of patients having non-CC genotypes. Virologic failures were infrequent.
- We could not find a pattern of baseline polymorphisms that were predictor of failure. The regimen was well tolerated, with low rates of adverse events and treatment discontinuations, regardless of BMS-7913-25 dose.
- These results supports Phase III trials which are already fully enrolled – UNITY 1 and UNITY 2 – with a twice-daily fixed dosing of DCV/ASV/BMS-791325 at the 75 mg dose level, Dr Hawkins concluded.

**Treatment for HCV in six weeks**

A late breaking abstract had the final results of the SYNERGY trial. This was designed to use combination therapy with multiple direct-acting antivirals targeting different stages of HCV lifecycle to shorten the duration of therapy to achieve sustained viral response, said Dr Anita Kohli.
- In the first arm, patients were treated with sofosbuvir and ledipasvir for 12 weeks. In the second and third arm, GS-9669 (a non-nucleoside inhibitor) and GS-9451 (a protease inhibitor) was added and the duration of treatment was reduced from 12 to 6 weeks.
- What we found in the study was that hepatitis C can be successfully and safely treated in 6 weeks using three direct acting agents with different mechanisms of action, she continued.
- Addition of a third direct-acting antiviral enabled a shorter duration of therapy.

Douglas Dieterich
Trevor Hawkins
Reduced brain volume in individuals on ART
In a Plenary Session Ass Prof Serena Spudich gave a lecture in which she provided an overview of Neuro-HIV in 2014.

She started this by pointing out that a number of different studies have suggested that there are still persistent milder forms of HIV-associated neurocognitive disorders (HAND) in 18 – 50 % of individuals on ART.

And a lot of different studies have shown – either with structural imaging, or more functional imaging, suggesting how the brain can operate – a reduced brain volume in individuals on ART compared to HIV-uninfected controls.

Perturbations in the CNS are evident in some individuals in the setting of suppressive ART.

CNS abnormality may derive from a confluence of viral, immune and co-morbid factors during ART – one question that remains to be answered is if the damage is ongoing. Or it may derive from the accrual of injury during the early stages of HIV – prior to ART. The unanswered question here is if the damage is irreversible.

HIV invades the CNS early, and initiates local infection and immune activation, potentially establishing a compartmentalized viral reservoir, Prof Spudich finished her talk.

The Long Beach Baby
When scientists at CROI 2013, as reported in last years HIV & Virology News, made the announcement that a baby girl seemed to have been cured from HIV there was a lot of media interest.

To recap – a case of HIV-1 remission in a 26 month old perinatally HIV-infected child who received very early cART (AZT, 3TC and nevirapine) initiated at age 31 hours was inadvertently stopped at 18 months of age. The cART cessation did not lead to rebound viremia for 12 months (at 30 months of age), said Dr Deborah Persaud.

The child is known in media as “The Mississippi Child” and when Dr Persaud presented her report at this year’s CROI she said that the baby now has had 23 months off cART.

– The child remains in remission! There are no replication-competent CD4+ T-cell reservoirs detected today, and this supports our hypothesis that very early cART may form a barrier to long-lived HIV-1 reservoir in perinatal infection.

Dr Persaud also presented a second case – a 9 month old who received a three drug ART-regimen starting at four hours of age, who remains on ART. In media this child is called “The Long Beach Baby”.

Maternal tenofovir use affects neonatal bone density
Dr George Siberry presented a study on tenofovir impact on bones in newborn children – i.e. what impact the treatment of the mother has on the foetus.

– The primary objective was to compare the bone mineral content (BMC) of newborns exposed to tenofovir in utero to the BMC of newborns who were not exposed to tenofovir in utero, he explained.

It was a paediatric cohort study in two arms. The whole body BMC was obtained at age 2 weeks. This showed that maternal tenofovir use is associated with a significantly lower neonatal BMC that persists, despite adjustment for other factors.

– The duration and clinical significance of this finding should be evaluated in longitudinal studies. We do have a study in our IMPACT network – P1084s – taking place in several sites in Africa that performs serial infant dual energy X-ray absorptiometry (DXA) after randomised assignment of maternal tenofovir, versus no tenofovir, he continued.

This is fully approved, and Dr Siberry said that we should have results within two years.

– In addition, there are plans for testing of stored specimens to help explore the mechanisms that may help to explain the effect observed of maternal tenofovir on infant bone mineral content, Dr Siberry concluded.

Age disparities
Social epidemiologist Guy Harling talked about age-disparate relationships and HIV incidence amongst rural South Afri-
can women.
– The background for this analysis is that older male partners are considered a risk factor for HIV, particularly for younger women. As a result, numerous governments have been targeting these kinds of relationships with an effort to stigmatise them and reduce them, he said.

Dr Harling illustrated this with a photo on a campaign billboard that stated that “older men + young girls = teenage pregnancy and AIDS”.

However, there hasn’t actually been an analysis of age disparities and subsequent HIV infections. The existing evidence is focussing on prevalent HIV and age disparity. Furthermore there has been no analysis of women older than 30 years of age.

– The aim of this study is to fill these gaps, Dr Harling continued.

**Change of policy needed**
The study was set up by Africa Centre for Health and Population Studies. In a rural area, north of Durban, with a high prevalence for HIV, health interviews and HIV tests have been taken annually from 2005 to 2012. This in order to build a cohort of initially seronegative women, and then to follow them forwards to see if they became infected.

The research found that age disparities are present, but they are not associated with a higher risk for HIV infection.
– One reason for this could be that young women are aware of the high prevalence for HIV and therefore select older partners more carefully.

Another reason could be that older partner relationships are different.
– Younger men are considered to be abusive and disrespectful, and this could lead to sexual behaviour that younger women are not looking for – and would not prefer to have, Dr Harling said.

A third possibility is that in a poor setting there is limited economic motivation for a young girl to choose her partner – the older man is also poor.

Dr Harling therefore called for a change of policy.

– Stigmatizing age-disparate relationships for young women may be inefficient – and for older women it may be harmful. Instead we need more research on who is at risk, and take action to the relevant parts of the population!

**Package for increase of viral suppression**

Dr Ruanne Barnabas presented a study on community HIV testing and linking to care in South Africa and Uganda.
– ART has the potential to decrease HIV incident cases, but requires high coverage of HIV counselling and testing (HCT), high linkage of HIV positive persons to care, high ART initiation and adherence – and high levels of viral suppression at population level, she said.

The aims of the study was to estimate the impact of a package of interventions (community-based home HCT, CD4-testing, referral to care and follow-up visits) on linkage to HIV clinic, ART initiation and viral load suppression 12 months after testing.
– We found that this package achieved high testing coverage in South Africa and Uganda. It identified HIV positive persons unaware of serostatus and at high CD4 count, and facilitated linkage to HIV care and ART initiation. We also saw a significant increase in viral suppression at population level, Dr Barnabas said.

This model could be utilized by the existing cadre of community health workers in both settings.
– We also found that despite high HIV clinic attendance, ART uptake did lag in those persons with a high CD4 count. Strategies for these could include a client support and follow-up, messaging about the benefits of ART when asymptomatic and care provider training.

Additional strategies are needed to reach youth, men working away from homes – and to promote couples testing and disclosure, Dr Barnabas concluded.

**The XTEND trial**
– Improved diagnosis of TB is a global priority for TB control, Prof Gavin Churchyard stated.

The Xpert MTB/RIF is a cartridge-based, automated diagnostic test that can identify Mycobacterium tuberculosis (MTB) and resistance to rifampicin (rifampicin). It has greater sensitivity than sputum smear microscopy and provides an immediate rifampicin resistance result, he continued.

– In 2013 WHO issued a conditional recommendation that Xpert MTB/RIF should be the initial diagnostic test for adults investigated for TB. However, the
impact of Xpert MTB/RIF will depend on the health system of which it is used. South Africa has the third largest number of TB cases globally. The Xpert MTB/RIF program is the largest in the world, and accounts for more than 50% of all cartridges procured globally.

Prof Churchyard presented the XT-END trial. Its primary objective was to evaluate the effect of Xpert MTB/RIF implementation on mortality among adults investigated for TB.

- We found that the mortality for these persons was high – and it was not reduced after implementation of Xpert MTB/RIF. Important determinants of mortality included having an unknown HIV status or being HIV-positive, but not taking ART.

People being investigated for TB should know their HIV status, and linkage to HIV care should be improved.

- The relatively constant death rate over six months of follow-up suggests opportunities to intervene, particularly at those at high risk of death which includes older age and multiple TB symptoms, Prof Churchyard underlined in his conclusion.

Refocus on TB as an infectious disease

Prof Peter Godfrey-Faussett talked about population-level control of HIV-related TB.

- We seem to be doing a good job – there is a global decline in TB-associated AIDS deaths, he initially said.

But he reminded the audience that from most places where people are dying from HIV-associated TB, we don’t have vital registration statistics.

- The accuracy of TB/HIV burden estimation depends on quality of HIV/TB surveillance data. We have insufficient data on contributory causes of AIDS deaths. The percentage of AIDS deaths due to TB are pooled from autopsy studies from only 10 countries that are non-representative and with geographical heterogeneity, he pointed out.

Prof Godfrey-Faussett stated that in population control of HIV-related TB we face enormous health system challenges.

- Things that work well on paper works less well than expected, largely due to health-system reasons.

We need to focus on delivery mechanisms. Since TB is an infectious disease, there is a need for structural and social change.

- It is clear that quality assured expansion of ART will have an impact on TB. Scaled up combination HIV prevention – not only relying on treatment – will also have an impact on controlling TB.

We still need to find and treat TB, and implement a wider use of intermittent preventive treatment.

- But perhaps the message that I want to put across the most – to stimulate young researchers on where to go next on HIV and TB on a population level – is to refocus on TB as an infectious disease again! How we detect and understand transmission events – and subsequently how we can interrupt those events, Prof Godfrey-Faussett summarised.

Fewer than three doses of vaccine for HPV

As pointed out by Dr DeCock in his opening speech, also talks on human papilloma virus (HPV) were included in CROI:s program.

In a Plenary Session, Dr Douglas Lowry from the National Cancer Institute talked about HPV vaccines.

- There are two goals for HPV vaccination: To directly reduce the risk of infection and disease in vaccines. But – at least as important – to indirectly reduce these risks by reducing the prevalence of vaccine types in the general population, so called herd immunity, he established.

In his summary Dr Lowry pointed out that HPV causes several different cancers as well as genital warts and other benign diseases.

- The HPV vaccine can prevent the benign, premalignant and malignant diseases induced by the HPV types targeted by the vaccines.

Second generation HPV vaccines with an activity against a broader range of HPV types should achieve an even greater reduction in HPV-associated disease.

- The high immunogenicity of the vaccine implies it should be possible to induce long-term protection with fewer than three doses. This is already possible from a regulatory perspective in Europe, but not in the US at present. We think this could have a big impact in the developing world, Dr Lowry concluded.
annons
The 2014 Conference on Retroviruses and Opportunistic Infections (CROI) was held in extremely cold Boston from March 3rd to March 6th. In this year meeting two very large randomized clinical trials focused the attention of attendees interested in the field of antiretroviral therapy.

NEAT 001. Looking deep into a nucleoside sparing regimen in antiretroviral naïve patients

NEAT 001 has been a massive undertaking. The trial included patients from 78 sites in 15 European countries. Trials of this magnitude are exceptional in Europe. This open-label trial included 805 antiretroviral naïve patients [1]. The trial compared a nucleoside-sparing regimen - Darunavir/r QD and Raltegravir BID- versus a nucleoside-containing regimen – Darunavir/r QD and TDF/FTC. ACTG 5262 [2] a previous study of Darunavir/r QD and Raltegravir BID had reported a higher than expected rate of virological failure, especially in naïve patients with baseline viral loads above 100,000 copies/mL.

However, since ACTG 5262 was a single arm study results could not be considered definitive. Therefore NEAT 001 was eagerly awaited. NEAT 001 was designed to prove the non-inferiority of the nuc-sparing combination with a non-inferiority margin of 9%.

Patients included in NEAT 001 had CD4 cell counts close to 350 and approximately one third had viral loads at baseline above 100,000 copies/mL. The primary endpoint of the trial was a composite endpoint at 96 weeks that included the following virological and clinical components:

**Virological endpoints:** < 1 log10 copies/ml HIV RNA reduction at week 18, HIV RNA ≥ 400 copies/ml at week 24, HIV RNA ≥ 50 c/ml at or after week 32.

**Clinical endpoints:** death, AIDS event or serious non-AIDS event.

At week 96 the estimated proportion reaching primary endpoint (Figure 1) was 17.4% for RAL and 13.7% for TDF/FTC with an adjusted difference of 3.7% (95% CI: -1.1, 8.6%). This result proves the non-inferiority of the Raltegravir combination.

Two additional sensitivity analyses supported the non-inferiority of Raltegravir in NEAT 001. Considering only the virological components of the primary endpoint the estimated proportion reaching endpoint was 15.4% for RAL and 11.8% for TDF/FTC (95% CI: -0.8, 8.1%). Adding to the primary endpoint discontinuation of any component of the randomized regimen for any reason as failure, the estimated proportions were 22.8% for RAL and 19.5% for TDF/FTC (95% CI: -1.9, 8.4 %).

In other pre-specified analysis investigators looked at primary endpoints by baseline characteristics. In patients who started the trial with a viral load ≥ 100,000 copies/mL RAL did not achieve non-inferiority. Also in patients with baseline CD4 cell counts < 200/µL RAL was inferior to TDF/FTC (Fig 2). In the TDF/FTC arm not a single patient had virological failure with resistance development. In the RAL arm one patient had K65R and five patients had N155H conferring resistance to RAL.

Regarding adverse events and laboratory abnormalities, the RAL arm had higher increases from baseline in total cholesterol, LDL cholesterol and HDL cholesterol. The TC/HDL ratio did not differ between groups. Creatinine clearance changes from baseline showed stability in the RAL arm with a mean change from baseline of +0.9 mL/min and a small decrease in the TDF/FTC arm of -3.8 mL/min. This difference is statistically significant but probably not important clinically.

In my opinion NEAT001 results shows that the nuc-sparing combination of boosted Darunavir/ritonavir and Raltegravir could be a viable option only in the very infrequent case that the patient is not a good candidate for starting a nucleoside-containing regimen. This regimen is not appropriate in patients with very high viral loads or late presentation with severe immunodeficiency. I am still surprised that a combination that mixes the high genetic barrier of a boosted protease inhibitor and the extreme potency of an integrase inhibitor has such a hard time matching the efficacy of boosted protease inhibitor and two nucleosides. When NEAT 001 was designed the expectation was that the nuc-sparing regimen was going to be extremely efficacious even in late presenters.
ACTG 5257
Looking deep into non-nucleoside sparing regimens in antiretroviral naïve patients ACTG 5257 [3] is another large randomized clinical trial that clearly adds to our knowledge of the activity of three antiretroviral regimens that are recommended in all expert guidelines as preferred regimens in antiretroviral naïve patients. The three regimens are TDF/FTC and Raltegravir, TDF/FTC and Darunavir/ritonavir and TDF/FTC and Atazanavir/ritonavir. ACTG 5257 fills two gaps in our knowledge of initial antiretroviral therapy. First, Raltegravir had never been compared with protease inhibitors. Second, Darunavir/ritonavir and Atazanavir/ritonavir had never been compared head to head in a large randomized clinical trial. ACTG 5257 included 1809 antiretroviral naïve patients with a median CD4 cell count of 308 cells/µL and a median viral load of 4.6 log10 copies/mL.

This open label study had two primary endpoints:

1) Virological Failure: Time to HIV-1 RNA >1000 copies/mL at week 16 to before week 24, or >200 copies/mL at or after week 24.

2) Treatment failure: time to discontinuation of randomized component for toxicity.

In addition, ACTG 5257 had a pre-planned composite endpoint defined as the earlier occurrence of either virological failure or treatment failure in a given participant. The study was designed as an equivalence study with an equivalence limit of ±10% Table 1 shows results for these endpoints at week 96.

In the more “classical” snapshot analysis—which is also a combination of virological efficacy and discontinuations due to toxicity—proportion of patients with viral loads <50 HIV-RNA copies/mL at week 96 were: 63% for Atazanavir/ritonavir, 80% for Raltegravir and 73% for Darunavir/ritonavir.

Results of the trial
Results of the ACTG 5257 trial were clearly influenced by discontinuations associated to toxicity of each regimen. These discontinuations were higher (16%) in the Atazanavir/ritonavir group than in the Raltegravir (1%) or Darunavir/ritonavir (5%) groups. Of note, most of the discontinuations in the Atazanavir/ritonavir group were due to jaundice/hyperbilirubinemia or gastrointestinal toxicity.

In ACTG 5257 rates of resistance were quite low in all three arms but as expected higher in the Raltegravir arm (3%) than in the boosted protease inhibitors arms with 1.5% in the Atazanavir/ritonavir arm and less than 1% in the Darunavir/ritonavir arm.

LDL-cholesterol and triglycerides levels increased with Darunavir/ritonavir and Atazanavir/ritonavir but not with Raltegravir from baseline to week. There were no significant differences in lipid increases between the two boosted protease inhibitors [4].

A substudy exploring changes in bone mineral density [5] showed similar losses at the lumbar spine and total hip with both protease inhibitors while raltegravir had significantly less bone mineral loss at these sites. Total body BMD loss was slightly greater with Atazanavir/ritonavir than Darunavir/ritonavir.

In my opinion ACTG 5257 results reinforces the use of integrase inhibitors such as Raltegravir in antiretroviral naïve patients. Despite the BID dosing of Raltegravir and the QD dosing of Atazanavir/ritonavir and Darunavir/ritonavir, the combined endpoint analysis clearly favored the Raltegravir group. In addition lipids and bone mineral changes also favored Raltegravir.

With regard to the comparison between Atazanavir/ritonavir and Darunavir/ritonavir it is important to realize than in the context of an open label trial there is always the risk of a lower threshold by clinicians to discontinue selectively one of the randomized regimens. In ACTG 5257 almost 8% of patients discontinued Atazanavir/ritonavir due to jaundice/hyperbilirubinemia. In the recent double-blind Gilead 103 trial only 1.7% of patients randomized to Atazanavir/ritonavir discontinued due to jaundice at week 96 [6]. For this reason it is difficult to interpret the results of the combined endpoint in patients randomized to Atazanavir/ritonavir.

Summary
In summary, everybody interested in antiretroviral therapy would have to remember these two trials: NEAT 001 and ACTG 5257. Without a doubt its results would influence expert guidelines of antiretroviral treatment.

Table 1. ACTG 5257. Comparisons of the three different endpoints at week 96

<table>
<thead>
<tr>
<th>Virologic Failure</th>
<th>ATV/r vs RAL</th>
<th>DRV/r vs RAL</th>
<th>ATV/r vs DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>3.4%</td>
<td>5.6%</td>
<td>-2.2%</td>
</tr>
<tr>
<td>97.5% CI</td>
<td>-0.7% - 7.4%</td>
<td>1.3% - 9.9%</td>
<td>-6.7% - 2.3%</td>
</tr>
<tr>
<td>Favors</td>
<td>Equivalent</td>
<td>Equivalent</td>
<td>Equivalent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tolerability Failure</th>
<th>ATV/r vs RAL</th>
<th>DRV/r vs RAL</th>
<th>ATV/r vs DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>13%</td>
<td>3.6%</td>
<td>9.2%</td>
</tr>
<tr>
<td>97.5% CI</td>
<td>9.4% - 15%</td>
<td>1.4% - 5.8%</td>
<td>5.6% - 13%</td>
</tr>
<tr>
<td>Favors</td>
<td>RAL Superior</td>
<td>RAL Superior</td>
<td>DRV/r Superior</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative Failure</th>
<th>ATV/r vs RAL</th>
<th>DRV/r vs RAL</th>
<th>ATV/r vs DRV/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>16%</td>
<td>7.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>97.5% CI</td>
<td>10% - 20%</td>
<td>3.2% - 12%</td>
<td>2.3% - 13%</td>
</tr>
<tr>
<td>Favors</td>
<td>RAL Superior</td>
<td>RAL Superior</td>
<td>DRV/r Superior</td>
</tr>
</tbody>
</table>

DR. JOSE R ARRIBAS
Servicio de Medicina Interna, Unidad VIH Hospital La Paz, IdiPAZ. Madrid, Spain
annons
References


Dr Graeme Moyle was born in Australia, and he studied medicine in the city Adelaide on Australia’s southern coast.

– I decided to become a doctor when I was five years old, he says.

This early interest came from the fact that he, already at this time, thought medicine to be an interesting subject and that he was good at science in school. Dr Moyle won an award for being the top biology student in school when he left college.

After graduating medical school, he worked as a doctor in Australia.

– I did my internship there, and was finished at the end of 1986.

He explains that in those days one could use a degree in medicine as a passport. Dr Moyle decided to go to the UK.

– I knew the language, it was simple to register and straightforward to get employment. UK was also a good starting point for travelling the world – which is something I still enjoy doing.

Friends died young

Upon arrival in London in 1988, Dr Moyle did a variety of general medical jobs before he started to work at what is now known as Chelsea Westminster Hospital in 1989 and began working in HIV and Sexual Health medicine. He has been there ever since.

– I became a specialist in sexual health, but I was already interested in HIV before that, Dr Moyle continues.

He explains that when he started his studies in medicine, several of the new friends he got to know in “the new world” in University were gay men.

– In our second year, one of them ‘came out’ to me – he told me he was gay, so I introduced him to some of my other gay friends. He took a year off studies, after that.

Over the following years this friend became sick, and eventually died, before Dr Moyle finished his internship.

– I also knew some more people in my social milieu that acquired the disease – one of them was an ex-girlfriend! She eventually died, but some others of them are still alive thanks to the treatments we have helped pioneer over the last 25 years.

Early AIDS clinic in London

He says that when studying medicine, you get to go to other parts of the world to work. In Dr Moyle’s case he went to India for three months.

– There I mostly worked with infectious diseases. I was generally interested in that subject.

After finishing the internship he considered two options: Either to do infectious diseases – or tropical medicine.

– But I ended up in a clinic for sexual health. It gave me a slightly broader outlook then just STD.

The clinic was the site for testing for HIV at the time. It was situated at the heart of the old gay community in London, and had pioneered testing for the virus in the British capital.

– One year earlier the clinic had started the first trial of AZT.

In 1990 Dr Moyle got his first research opportunity: To give the first European dose of didanosine (DDI), the second antiviral drug to be approved.

An extraordinary time

– I wrote my PhD thesis on that study. I created a survival database and compared the data with the previous years’ survival of our HIV cohort (who had not had DDI).

The study contributed to the approval of the drug in the US and Europe. DDI added approximately 6 months of survival.

– One of the patients I met in those years was Freddie Mercury (legendary vocalist in the rock group Queen). I was one of his physicians until his death in November 1991.

He explains that this was an extraordinary time in his life. Dr Moyle was named on the front page of the English tabloid The Sun, among others.

– This was a time when a lot of people were dying, so I took two years off to work in the pharmaceutical industry. I moved to Basel in Switzerland, in order to work for Roche on the first protease inhibitors.

The Lazarus effect

Protease inhibitors could be combined with antivirals to suppress viral replication.

– At Roche they also developed viral load assays. These new treatments and diagnostics revolutionised management of HIV and stopped AIDS and death from being the endpoint in studies...

Then came Vancouver 1996 – the congress when everything changed.

– It was however Merck’s drug Indinavir that proved the importance of measuring viral suppression – with viral load assays pioneered by Roche, Dr Moyle underlines.

He then returned to clinical practice at the end of 1994, and there he ran protease inhibitor clinical trials.

– I was able to observe what we called the “Lazarus effect”. We had patients that we expected to die within weeks or months – instead we saw them gain weight and strength and to be restored! And – in patients who tolerated the drug – the effect lasted!

The era of STRs

Dr Moyle continued to work both in clinical practice and with clinical trials.

– Around 1998, a group in Australia reported the first description of lipodystrophy (a body change due to loss of fat under the skin) which became the key stigmata for people with HIV.

This caused a change of direction for Dr
Moyle’s research – he became focused on finding a management approach for lipo dystrophy. It included the first study on changing the drug Thymidine to Tenofovir or Abacavir, which led to recovery of subcutaneous fat.

I did some studies of plastic surgical interventions on the face that led to the approval of Poly-L-Lactic Acid (Sculptra, New-Fill). I also worked with studies leading to the US approval of growth hormone in the treatment of AIDS wasting syndrome.

At this time Dr Moyle also worked on the combination tablet Kivexa, which was the first once daily, fixed-dose tablet for HIV. It heralded the era of once-daily dosing treatment regimens for people with HIV and eventually single tablet regimens.

Some individuals with HIV will eventually be cured

At present, Dr Moyle is part of a team looking after the largest cohort of patients in Europe – more than 6,000 HIV-patients. He is still involved in early and late stage developments of drugs, and in drug pharmacology studies.

He is taking an active role in describing the phenomenon on ageing with HIV, and how the virus may accentuate the process of ageing.

Some of this problem appears to be related to the inflammation in HIV, and some seems to be related to other risk factors that are common for people with HIV.

Dr Moyle states that we are going to have a population that will get old with HIV, and this has to be addressed with earlier preventive measures and earlier diagnosis and treatment for HIV.

That may also have an additional general health benefit, such as preventing further transmission.

He finishes by saying that he believes that before he is retired, some individuals with HIV actually will be cured.

If so, I will have gone full circle – from a disease that brought death, to a cure. That would be a remarkable medical journey, Dr Moyle says.
Superior to PI-based regimens in maintaining virologic suppression at week 48 in a recent study presented at CROI8

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References

Drug Interactions with Integrase Inhibitors

The recently revised DHHS guidelines now recommend as preferred all the approved integrase strand transfer inhibitors (INI), raltegravir, elvitegravir and dolutegravir as part of initial therapy regimens. Thus, as many integrase inhibitors are recommended as agents in all other classes, one NNRTI, efavirenz, and two PIs, atazanavir/r and darunavir/r. Additionally, with 4 recommended integrase-based regimens, out of 7 in total, more integrase-based regimens are recommended than all other classes combined.

Dolutegravir has the added distinction of providing NRTI ‘backbone’ flexibility, being recommended with both TDF/FTC and ABC/3TC, regardless of baseline viral load [1]. Elvitegravir is only available in the EU as part of a fixed dose formulation coformulation with the pharmacoenhancer cobicistat and TDF/FTC. The recent outcomes of the ACTG 5257 ARDENT study [2] (which compared raltegravir, atazanavir/r and darunavir/r) and those in the dolutegravir programme suggest that these integrase inhibitors may have significant advantages over NNRTI and PI/r regimens in terms of speed of antiviral response and rates of discontinuation due to drug related adverse events. Results from the elvitegravir/c/TDF/FTC programme showed this product has non-inferior efficacy to preferred NNRTI and PI regimens. Rates of resistance at failure, at least for raltegravir and elvitegravir are higher than with PI based regimens but similar to NNRTIs.

Not food or acid dependent
One prescription niche established by the first INI raltegravir was in persons where significant interactions via cytochrome (CYP) enzyme interactions were likely with NNRTI or PI/r based therapy, such as people with malignancies or hepatitis C requiring therapy, in persons with polypharmacy or who were talking ‘recreational’ (usually illicit) substances with unknown sites of metabolism. Raltegravir is metabolised primarily by UGT1A1 and as such has a low risk of drug interactions at the level of metabolising enzymes. The interactions that do occur (modest boosting by atazanavir, a 50% exposure reduction with rifabutin) may not be clinically relevant as doses 50% above (600mg bd) the approved 400mg bd dose were similarly well tolerated and 50% below (200mg bd) were similarly effective in phase 2b studies. Furthermore, raltegravir’s absorption is not food or acid dependent and it does not significantly interact with renal transporters limiting unexpected interaction risk. Recent data do indicate that raltegravir should be separated from metal (aluminium, magnesium) containing antacids as these appear to chelate raltegravir in the gut [3]. As INIs work via attachment to a Mg++ group in the integrase enzyme such an interaction with bivalent cations is not surprising. A similar chelation effect has been reported with dolutegravir [4], where dose separation from a range of metal based preparations, right down to multivitamin and mineral preparations is recommended. The same is likely to be true with elvitegravir but has not been formally investigated. Other metal cations that may chelate INI include iron, zinc, selenium and calcium. Patients should be advised to separate preparations containing these metals, many of which are over the counter, from their antiretrovirals. Amongst other drugs, ciprofloxacin is known to be chelated by several metals, and we have recently reported zinc co-administration reduced atazanavir exposures and bilirubin levels by up to 25% [5], an interaction that may be harnessed as a management tool for clinically evident hyperbilirubinemia in subjects on atazanavir. As bilirubin levels correlate with drug exposure, a modest reduction in atazanavir levels in individuals with grade 3 or 4 bilirubin would not be expected to be unfavourable for efficacy.

<table>
<thead>
<tr>
<th>Table 1</th>
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<table>
<thead>
<tr>
<th></th>
<th>RALTEGRAVIR</th>
<th>ELVITEGRAVIR/c</th>
<th>DOLUTEGRAVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU Status (Rx naive)</td>
<td>Approved</td>
<td>Approved</td>
<td>Approved</td>
</tr>
<tr>
<td>Dosing</td>
<td>400mg BD</td>
<td>In single tablet OD with TDF/FTC/c</td>
<td>50mg OD (in initial therapy)</td>
</tr>
<tr>
<td>Food</td>
<td>Regardless</td>
<td>With food</td>
<td>Regardless</td>
</tr>
<tr>
<td>Metabolism</td>
<td>UGT1A</td>
<td>CYP3A, induces 2C9 /c inhibits 3A &amp; 2D6, P-gp, BCRP, OAT1, MATE1</td>
<td>UGT1A1 &gt; CYP3A, Substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro</td>
</tr>
<tr>
<td>Drug Interaction Potential</td>
<td>Low</td>
<td>High via P-gp, CYP and MATE1</td>
<td>Moderate via CYP3A, P-gp, OCT2</td>
</tr>
<tr>
<td>Renal effects</td>
<td>Nil</td>
<td>Raised creatinine via MATE1 inhibition</td>
<td>Raised creatinine via OCT2 inhibition</td>
</tr>
<tr>
<td>Data in women, &gt;50yrs, Low CD4/high VL</td>
<td>Some</td>
<td>Few</td>
<td>Few</td>
</tr>
</tbody>
</table>
Key characteristics
Table 1 details the key characteristics of the absorption, metabolism and transporter interactions of the three approved integrase inhibitors [6-8]. The relative absence of data in women and older individuals for elvitegravir and dolutegravir is notable as cyclical hormonal effects in women, declines in CYP enzyme expression and renal function with age may affect handling of drugs. Raltegravir has been the subject of specific study in individuals over 60 years with no observed differences in exposure seen relative to younger individuals. Similarly, as raltegravir and dolutegravir do not interact with the oral contraceptive pill, alterations in the normal female menstrual cycle and interaction with other hormonal contraceptives or HRT would not be expected (see table 3). Two women receiving TDF/FTC/EFV/G/c have been reported from a single US clinic to have experienced breast pain and discomfort after starting medication possibly due to elevations in natural progestogens leading to premenstrual type symptoms. More study of the effects of antiretroviral regimens on the normal female menstrual cycle and the impact of cyclical changes in CYP enzymes on antiretroviral pharmacokinetics are needed. Of further note, cobicistat, while having no interaction with ritonavir, interacts differently with cellular pumps (such as PGP), renal transporters (notable MATE1) and CYP enzymes, hence the type and magnitude of interactions will not be the same as those seen with ritonavir.

Table 2 details the interactions between INI and other antiretrovirals [6-8]. Where not listed no interaction is anticipated. As elvitegravir is only available as a fixed formulation co-administration with other antiretrovirals is not recommended and 3 way (or more) interactions with cobicistat, elvitegravir and other drugs insufficiently investigated.

Table 3 details the interaction with the oral contraceptive pill. Dosing of EVG/c/TDF/FTC with the pill may be considered with a >30µg oestrogen pill to adjust for lower oestrogen exposures.

However, as the interaction indicates, progestogen levels may be markedly elevated. Interactions with ritonavir based therapy and depoprovera indicate that a marked increase in progestogen exposure occurs with this booster and is also likely with cobicistat.

As both a consequence of aging and accentuated risks related to HIV and past or current antiretrovirals a range of metabolic disorders, hyperlipidemia, diabetes mellitus and possibly hypertension are more common in persons with HIV at any age. The most widely used statins, all calcium channel blockers and some antidiabetic medications may interact with antivirals. An interaction via renal transporters OCT2 (dolutegravir) and MATE1 (cobicistat) is anticipated with metformin. The magnitude of the interaction is not known at present, hence co-administration caution is warranted especially in older subjects where risk of hypoglycaemia (and falls) is greatest. Table 4 outlines the known or expected interactions with common metabolic drug classes. These interactions are at best representative only. For example, the extent of CYP3A metabolism of atorvastatin is greater than for rosuvastatin hence the interaction with EVG/c/TDF/FTC is likely to be greater than that reported with rosuvastatin. Dolutegravir, as a partially CYP3A metabolised agent, is likely to modestly interact with atorvastatin although it would be anticipated that this is unlikely to be a clinically significant risk. Interactions with amiodipine will not be the same with, for example, diltiazem. As calcium channel blockers are widely recommended as first or second line antihypertensives more work on this drug class and antiretroviral drugs is needed. Interactions with corticosteroids are anticipated with CYP3A metabolised agents. Interactions with oral, inhaled, intra-articular and conjunctivally administered corticosteroids have been reported with ritonavir based regimens and are anticipated with cobicistat based therapy. The interaction

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>RALTEGRAVIR</th>
<th>ELVITEGRAVIR (with TDF/FTC/c)</th>
<th>DOLUTEGRAVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirine</td>
<td>No dose adjustment</td>
<td>As a complete regimen, not be administered with other ARV</td>
<td>Should not be used without coadminist. of atazanavir/r, darunavir/c or lopinavir/c</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>No dose adjustment</td>
<td>As a complete regimen, should not be administered with other ARV</td>
<td>Dose adjustment to 50mg BID or alt. combinations to be considered</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>No dose adjustment</td>
<td>As a complete regimen, should not be administered with other ARV</td>
<td>Should be avoided</td>
</tr>
<tr>
<td>Fosamprenavir/r ; tipranavir/r</td>
<td>No dose adjustment</td>
<td>As a complete regimen, should not be administered with other ARV</td>
<td>Dose adjustment to 50mg BID or alternative combinations to be considered</td>
</tr>
<tr>
<td>Other ARV</td>
<td>No dose adjustment</td>
<td>As a complete regimen, should not be administered with other ARV</td>
<td>Limited data</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>RALTEGRAVIR</th>
<th>ELVITEGRAVIR (with TDF/FTC/c)</th>
<th>DOLUTEGRAVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinyl Oestradiol</td>
<td>Unchanged</td>
<td>Reduced x 0.75</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>Unchanged</td>
<td>Increased x 2.26</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>
potential with corticosteroids and dolutegravir is considerably lower but worthy of investigation. The anticipated interaction of drugs via renal transporters is a new area of pharmacokinetic interest and one that is not yet well understood. Caution therefore should be exercised when using renally excreted agents with cobicistat or dolutegravir.

Summary

This article provides an introduction to the extent of interactions with INI agents and formulations and in by no means a comprehensive guide. Further details of anticipated or known interactions can be found at http://www.hiv-druginteractions.org/.

The metabolism of INI differs between individual drugs or formulations and therefore interactions cannot be considered on a ‘class’ basis. Raltegravir has the lowest potential for drug interactions. Dolutegravir with a low proportion of metabolism via CYP3A and low/no induction or inhibition has few known or anticipated interactions. The need for a pharmacoenhancer with elvitegravir results in a wide range of anticipated interactions with this agents, an issue that is currently underinvestigate

<table>
<thead>
<tr>
<th></th>
<th>RALTEGRAVIR</th>
<th>ELVITEGRAVIR (with TDF/FTC/c)</th>
<th>DOLUTEGRAVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Unchanged</td>
<td>Unknown</td>
<td>No studies with statins</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>None anticipated</td>
<td>Unchanged (+26%)</td>
<td>No studies with statins</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Unchanged</td>
<td>Unknown (Label warning)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Metformin</td>
<td>None expected</td>
<td>Unknown/Expected (Label warning)</td>
<td>Unknown/Expected (Label warning)</td>
</tr>
</tbody>
</table>

GRAEME MOYLE

References

1. DHHS Guidelines http://aidsinfo.nih.gov/guidelines

5. Isentress US package label
6. Stribild US package label
7. Tivicay US package label

Table 4
The European Sofosbuvir Label: From Evidence-based to EMA-based Medicine

The new era of hepatitis C therapy started in Europe officially on the 17th of January 2014 with the approval of sofosbuvir. This approval by the European Commission was long expected but included also some surprises.

The European Medical Agency (EMA) label is to large extent in line with the FDA label. The FDA approved sofosbuvir in November 2013. Both labels considered data from the available pivotal phase 3 trials but also recognized preliminary evidence from phase 2 trials. Overall, the agencies provided rather straightforward and clinically practical recommendations, even in the absence of proven evidence generated in large prospective trials.

HCV Genotype 1 infection
HCV genotype 1 infection should be treated with sofosbuvir, ribavirin and pegylated interferon alfa for 12 weeks. The rationale for this recommendation is based on findings from the Neutrino study published last May in the New England Journal of Medicine (1). This new triple therapy is straightforward as there is no longer a need for “response-guided therapy” in contrast to previous therapies with 1st generation protease inhibitors. Very importantly, this triple therapy should also be used in patients who failed a previous course of IFNa-based therapies – even though no prospective data are available for genotype 1 nonresponder patients as the Neutrino study included only treatment-naïve patients! The assumption made by the agencies was that a trial in previously untreated patients would also include subjects who would have failed PEG-IFNa/ribavirin therapy. Considering the very high overall SVR rate of 90% in the Neutrino study and the fact that 86% of patients with the unfavourable IL28b “TT” genotype achieved a SVR, it is very reasonable that also PEG-IFNa nonresponder patients would benefit from PEG-IFNa/ribavirin/sofosbuvir triple therapy. Still, more data in previous non-responder patients with other negative response factors (e.g. liver cirrhosis) would be needed to determine the real benefit of the new triple in particular difficult to treat individuals.

A big surprise is the suggestion that treatment may be extended from 12 weeks to 24 weeks in patients “who have one or more factors historically associated with lower response rates to interferon based therapies (e.g. advanced fibrosis/cirrhosis, high baseline viral concentrations, Black race, IL28B non-CC genotype, prior null response to PEG-IFN and RBV therapy)”. This suggestion is not supported by any data and it is rather questionable if SVR rates can be really increased in these patients. Payers in most countries will certainly not follow this recommendation as costs would be doubled without any scientific evidence. One also has to keep in mind that almost all patients carry at least one of these factors as patients with an IL28b-CC genotype usually have a high baseline viral load and thus one would theoretically be allowed to extend treatment to 24 weeks in nearly every case.

The recently launched AASLD practice guidelines do not recommend to extend triple therapy with sofosbuvir beyond 12 weeks and I certainly agree with this recommendation.

Patients who are ineligible or intolerant to PEG-IFNa can be treated for 24 weeks with sofosbuvir and ribavirin only. There is no phase 3 trial available investigating sofosbuvir-ribavirin therapy in patients with HCV mono-infection. The main evidence for the EMA recommendation was generated in the Photon-1 study which included 114 HCV-HIV coinfected patients achieving a SVR in 76% of genotype 1-infected patients (2). Moreover, an investigator initiated study performed at the NIH in more difficult-to-treat patients achieved an SVR of 68% in 25 patients receiving sofosbuvir and weight-based ribavirin for 24 weeks (3). Considering these promising data, the agencies took a very reasonable decision to support PEG-IFNa/sofosbuvir/ribavirin therapy for interferon intolerant patients in the absence of other alternatives. Patients with advanced cirrhosis are at very high risk to experience hepatic decompensation without therapy.

We need to offer antiviral therapy to these patients and it is therefore very good that sofosbuvir-ribavirin therapy is now backed by the official label even in the absence of a large prospective phase 3 trial. In fact, it is the first in the drug HCV development process that a label for mono-infected patients is mainly based on evidence generated in coinfected individuals. However, the decision to use this reasonably effective but still not perfect treatment regimen may change with the approval of simeprevir in May 2014.

The Cosmos study investigated simepre-
annonns
viral load monitoring may provide reliable and female gender. If early on-treatment in infection were absence of liver cirrhosis factors associated with SVR in genotype 3 infected in two thirds of patients. Independent therapy but where 12 weeks are sufficient. Overall, 12 weeks of treatment maybe enough in two thirds of patients. Independent factors associated with SVR in genotype 3 infection were absence of liver cirrhosis and female gender. If early on-treatment viral load monitoring may provide reliable additional information to individualize treatment durations remains to be investigated in future trials.

The label offers an alternative treatment option for genotype 3 infection with 12 weeks of triple therapy with PEG-IFNa, ribavirin and sofosbuvir. Again, there is no data from phase 3 trials supporting this recommendation and only very limited evidence was generated in a phase 2 trial performed in Texas. 24 genotype 3-infected nonresponder patients were treated with triple therapy including 12 patients with cirrhosis. Importantly, 20 patients (83%) achieved a SVR and response rates were not lower in cirrhotics. Thus, this shorter therapy seems to be a very reasonable alternative for patients who can tolerate interferon. Gilead is running currently performing a respective trial to generate more data. So far, no data are available with European patients treated for 12 weeks with this regimen.

Another future alternative for the most difficult to treat genotype 3 infection will be combination therapy of sofosbuvir and daclatasvir. A recent NEJM paper showed very high response rates above 90% also for genotype 3 (6). The only patient that did not achieve a SVR had a daclatasvir-resistant variant present already before therapy was initiated. Optimal treatment duration needs to be defined (12 vs. 24 weeks) and also the question if ribavirin is still needed in this combination should be investigated in future trials.

HCV Genotype 4, 5 and 6 infection
EMA recommends the same treatment regimen for HCV genotypes 4, 5 and 6 as for HCV genotype 1. In vitro studies confirmed pan-genotypic activity of sofosbuvir. Indeed, clinical evidence confirmed efficacy beyond genotype 1. The Neutrino study included also 28 patients with HCV genotype 4 with 27 achieving a SVR and thus it is very reasonable to apply the identical triple therapy with PEG-IFNa, ribavirin and sofosbuvir also to genotype 4 patients. Of note, EMA (but not the FDA!) suggests this treatment also for HCV genotypes 5 and 6 even though only 1 patient with genotype 5 and 6 patients with genotype 6 were recruited in the Neutrino study. All genotype 5 and 6 patients cleared HCV in the study. Even though the evidence for the label is very limited considering these small numbers, the agency has to be congratulated to give clear recommendations to physicians and patients. However, more data is certainly needed to really support triple therapy of hepatitis C also for these rare genotypes.

Summary
Physicians treating hepatitis C can be grateful to the European Medical Agency that the label gives us flexibility to provide optimal individual therapies to our patients – at least in countries where sofosbuvir is already available and reimbursed. However, the specific implications will be valid only for a rather short time as more compounds and treatment regimens will receive market authorisations during the next 12 months. Simeprevir received a positive opinion by the Committee for Medicinal Products for Human Use (CHMP) for the use of simeprevir in combination with other medicinal products and thus should be officially approved in May 2014. The next compound to follow will be the NSSA inhibitor daclatasvir during Q3 2014. Later this year or early 2015 we can expect the Gilead fixed-dose combination of sofosbuvir with ledipasvir and the Abbvie regimen (ABT-450/r/ombitasvir and dasabuvir with ribavirin) – both achieved cure rates of 90-99% in different HCV genotype 1-infected populations with treatment durations between 8, 12 and 24 weeks. Even more compounds and combinations will follow later during 2015 and 2016 by BMS, Merck and others and thus it should be possible to cure HCV infection in almost every individual. The big question will be if all individuals at need in Europe will get access to these therapies which can save lives. The evidence has been generated. It is now in the hands of decision makers, insurers and politicians that we do not miss the unique opportunity to dramatically reduce the disease burden and complications caused by a severe chronic infection.

References
(2) Sulkowski MS, et al. AASLD 2013. Washington, DC. Oral #212
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HEINER WEDEMEYER

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Our annual CROI meeting is traditionally held in early March. It is really the place to be - so much to see and think about. The studious, industrious British atmosphere of CROI is very compatible with Boston, a city much more suitable than other places where we have met.

The oral communication format at CROI clearly favors the US style of doing things. Early in the morning and late in the afternoon one strolls among the vast aisles of posters, soft carpet underfoot and an ice cream distributed at tea time to improve your disposition. The posters are full of treasures - just the sort of investigations you always wanted to conduct but never had time to do. It is a joy to come upon exactly the kind of results you had hoped to find . . .

You have been there since early morning and grow tired. You want to have a look outside but there are no windows, and anyway it is too cold out there. Let us take a walk instead along the poster session.

New strategies

1. OPTIPRIM

Is it better to give more drugs in a context of primary infection?

The landscape of the cure agenda has been mitigated by some disappointments from anti-latency agents where, despite a limited production of HIV RNA that is thought to derive from integrated DNA, there has been no effect on decreasing viral reservoirs.

Until now, the most impressive news has come from studies of patients treated at an very early stage of infection. Every team involved has been excited to find those patients in a state of functional cure.

The research idea behind OPTIPRIM was to address two principal questions

1. Can we get a better decrease in HIV reservoirs by using a treatment strategy employing four classes of drugs that target all key enzymes of the HIV replication cycle, namely, reverse transcriptase, protease, integrase, and CCR5 co-receptor, compared to a standard triple drug approach with RT and protease inhibitors?

2. After two years of therapy and a viral load durably suppressed, is it possible to identify post-treatment controllers after ART discontinuation in those patients?

OPTIPRIM has been designed as a randomized controlled study to compare the impact of a five drug regimen compared to a triple drug therapy in patients initiating ART while they have a primary infection. Patients were included if they had HIV-1 western-blot (WB) ≤ 4 antibodies and positive HIV-RNA, and CD4 <500/mm3 in case of asymptomatic PHI.

The primary endpoint was the between-arm difference in HIV-DNA levels at M24. After 24 months, all patients with suppressed viremia were offered the opportunity of discontinuing therapy for 6 months if HIV-RNA< 50 copies/mL and [CD4 ≥ 500/mm3 or CD4 ≥ 30%]. Treatment re-initiation was recommended if HIV-RNA ≥ 50 000 copies/mL or CD4< 500/mm3 and CD4< 30%.

A total of 90 patients were enrolled in the study. The median interval from the estimated time of infection was 35 days; 40% had an acute primary infection syndrome. The median CD4 cells number was 470/mm3 and median viral load was 5.4 log 10.

OPTIPRIM: Study Design

Result 1: At month 24 there was no statistically significant difference in total HIV-DNA levels between the two treatment arms in ITT (Figure 1).

The largest decrease occurred during the first 3 months. HIV-DNA levels continued to decline until month 24, with similar slopes in both arms. The decrease in HIV-DNA was higher than in the previously reported studies with a median – 1.70 log in HIV DNA at month 24 compared to values around 1 log in (- 0.91 in Primoferon study and – 1.14 log10 copies/106 PBMC in ANRS PRIMO cohort). At month 12, HIV-DNA change was – 1.33 and -1.25 compared to -0.75 in the Quest study.

Result 2: In terms of HIV RNA viral load, a virological success was observed in both arms with 91% and 93% responses at < 50 copies/mL at M24. However, kinetics of HIV RNA viral load decline differed between the two arms with a more rapid decline in arm 1 which included raltegravir as expected.

The rate of maximal viral suppression < 50 cp/mL was subsequently lower in the five drug arm, compared to the three drug arm, a result that was unexpected.

Result 3: After 24 months, 29 patients in the five- drug arm and 34 patients in the three- drug arm agreed to discontinue their treatment. Of these, 19 and 11 patients, respectively, resumed treatment within 6 months. One patient per arm maintained viral control (<400 copies/mL) for 12 months after treatment interruption.

Viral load remained below 50 copies/mL until 18 months in patient #1 who may be classified as a post-treatment controller. None of the patients showed any specific protective HLA profile such as HLA-B27/B57 alleles. Viral load in patient #2 reached 530 copies/mL 18 months after treatment interruption.

Expert opinion: This is another demonstration that early treatment decreases HIV reservoirs and that five drugs are not necessarily better than three. Is there some unexplained finding about the lesser viral efficacy of the raltegravir-maraniroc...
arm? The most important result is the ability to identify patients who can control their HIV infection for one year without treatment intervention. Might this be a track toward a functional cure?

2. The PIVOT trial
Protease inhibitor monotherapy has been investigated for several years now as a means of reducing the burden of antiretroviral therapy in terms of drug molecule intake and cost. However, such protocols are still very confidential and have not yet changed treatment strategies in practice.

As stated in their poster, (N. Paton et al.) British team investigators decide to evaluate, at the national level, what the impact of a mono PI strategy on meaningful long-term outcomes. The Protease Inhibitor monotherapy Versus Ongoing Triple therapy (PIVOT) was designed as a five-year randomized controlled open-label strategy performed at 43 centres in the UK.

Patients were enrolled if they were on a stable NNRTI or PI, based regimen with a suppressed viremia < 50 copies/ml for greater than six months and if their CD4 cell number was > 100/mm³.

Patients were randomised to maintain ongoing triple therapy (OTT) or switch to a PI monotherapy strategy (PIm) using a ritonavir-boosted PI (physician’s choice of drugs) with a prompt reintroduction of NRTIs if unable to maintain VL suppression < 50 copies/ml. VL was measured every 12 weeks, with resistance testing for all confirmed VL rebound (≥ 50 copies/ml × 3, including 1 re-test of the same sample)

The meaningful primary end-point chosen was the loss of future drug options, defined as new intermediate/high level resistance to ≥ 1 drugs to which the patient’s virus was considered to be sensitive at trial entry. Secondary outcomes included serious disease complications (AIDS, serious non-AIDS, all-cause death), total grade 3/4 adverse events and neurocognitive function change.

Results:
A total of 587 patients were followed for a median of 44 and a maximum of 59 months; patients were mainly gay men (60%) with a median CD4 number of 513 cells/mm³.

Median time on ART was 4 years. Patients were either on a PI regimen (47%) or NNRTI (53%).

Results:
• PI monotherapy was non-inferior on the primary outcome of loss of future drug options even though a VL rebound was much more common in PI monotherapy, but all rebounds on PIm re-suppressed either spontaneously or with NRTI reintroduction.
• Sequences were obtained in 83% of confirmed VL rebounds. Few new resistance mutations were seen in either arm and of those observed, most appeared to have been archived prior to PIVOT entry.
• There were no significant differences in serious disease complications or neurocognitive function between the arms.
• Of those in PIm 58% remained on monotherapy at the end of the trial.
• Overall drug costs were substantially lower in the monotherapy arm.

PIVOT Trial: Main Outcomes

Expert opinion
PIVOT confirms what we knew from all PI
monotheray trials: slightly less antiviral potency leads to greater numbers of viral loads rebounds or blips. This is an expected effect if one balances one antiretroviral drug against three. However, in none of the rebounds were there any deleterious consequences in terms of resistance and loss of drug options which represent the real pragmatic consequences. Thus, it confirms that mono PI strategies are safe and beneficial in terms of long terms side effects. Furthermore, the PIVOT authors will probably analyze at some future time what can be the predictors of virological success. In MONO1 study, the duration of viral suppression and the total DNA content were the two predictors of remaining suppression. On the other hand, the PIVOT trial can be considered as a non-event by conservative HIV clinicians who prefer a triple drug approach extending over decades with a minimized risk of rebound. Nevertheless, a monotherapy approach is a potential strategy by physicians and health authorities to whom the issue of minimizing drug therapy without jeopardizing ART success matters.

3. Should we use statins in HIV infected patients?

There are several potential arguments for using statins in HIV infected patients with persistent inflammation and immune activation despite viral suppression on cART.

However, a short eight week course of statins only leads to a modest decrease in CD8 activation. A month administration succeeded in modestly decreasing some inflammation parameters. Given the importance of determining if there could be an improvement in persistent inflammation and immune activation despite suppressed viremia, the answers given by the SATURN-HIV trial (Stopping Atherosclerosis and Treating Unhealthy bone with Rosuvastatin) are significant.

SATURN-HIV has been designed as a randomized double-blind placebo-controlled trial whose primary objectives are to measure the effect of 10 mg rosuvastatin daily on inflammation and immune activation markers and on the progression of subclinical vascular disease and skeletal health. Secondary objectives included changes in systemic and vascular inflammation, coagulation, and monocyte and lymphocyte immune activation. Randomization was stratified by PI use at entry. A total of 147 subjects were enrolled (72 on rosuvastatin and 75 on placebo), while they are on stable ART with HIV-1 RNA < 1,000 copies/mL. All patients had evidence of heightened T-cell activation (CD8+CD38+HLA-DR+ ≥ 19%) or increased inflammation (high sensitivity C-reactive protein (hsCRP ≥ 2mg/L) at baseline and LDL-cholesterol (LDL-C) ≥ 130 mg/dL. Patients were mostly male (80%), African-American (70%), smokers (60%), with suppressive viremia.

The main results of the study show that rosuvastatin decreases: inflammation markers with a significantly decrease in sCD14 (p = 0.006), Lp-PLA2 (p = 0.0007), and IP-10 (p = 0.03) levels; lymphocytes activation markers with a significant, more pronounced decrease in CD4 and CD8 activation markers, namely, CD38+ DR+ in the rosuvastatin group (about a 35% decrease) compared to placebo (about 20% decrease); and monocytes activation markers with a decrease in sCD163 and fibrinogen within the statin arm (p = 0.001 and p = 0.015) Within the statin arm, treatment reduced proportions of TF+ monocytes among all three subsets (CD14+CD16-, p = 0.002, CD14+CD16+ and CD14DimCD16+, p < 0.0001 for both). Since statins boost expression of the bone morphogenetic protein 2, which enhances bone formation, Grace McComsey, the principal investigator of Case Western University Cleveland, Ohio, found modest BMD gains with statins. However, this trial is the first to evaluate the impact of statins on BMD in HIV-positive patients. Another concern with statins has been the conflicting reports of the impact of statins on glucose, insulin, and diabetes risk.

SATURN-HIV demonstrated that over 48 weeks rosuvastatin

1. Induced a modest but significant rise in total hip bone mineral density BMD (+0.6% in the rosuvastatin group compared to -0.6% in the placebo group; p = 0.017), an increase of BMD measured at trochanter (+ 0.9% in statin group versus - 0.7% in placebo group; p = 0.04).

2. However, there was a significant increase in fasting glucose 8% (p = 0.017 versus baseline, p = 0.217 versus 3.3% rise with placebo), fasting insulin 52% (p = 0.0006 versus baseline, p = 0.0055 versus 5.5% rise with placebo), and insulin resistance as measured by HOMA-IR 72% (p = 0.0015 versus baseline, p = 0.068 versus 14.5% rise with placebo). These changes were related to changes in inflammation or lymphocyte, monocyte activation. Diabetes developed in only one patient from the placebo group.

This study cannot discern whether the changes seen are unique to rosuvastatin or apply to other statins as well. These data highlights the need for close glucose and insulin monitoring in HIV-positive people taking statins.

With regard to potential clinical benefits from BMD data, larger and more extensive studies will be needed to determine, whether statins can prevent fractures. A SATURN-HIV follow-up is continuing for 96 weeks.

References

1. Cheret al. Paradoxical impact of intensified HAART started during primary HIV infection: Results of the OPTIPRIM-ANRS 147. CROI 2014 Abstract 549LB.


CHRISTINE KATLAMA
Prolonged Co-trimoxazole in HIV-infected children in Africa.

758 HIV-positive children in Uganda and Zambia were randomized to continue or stop co-trimoxazole prophylaxis after receiving ART for at least 96 weeks. All children received insecticide treated bed nets. The median age was 7.9 years. The primary end points were hospitalization or death and severe side effects. The children who stopped co-trimoxazole had significantly higher rates of hospitalization or death. The major difference was a higher rate of hospitalization for malaria (49 vs. 21 events) and other infections (53 vs. 25). More grade 4 adverse events were reported in the children who continued co-trimoxazole with anemia accounting for the difference. The authors recommend continued co-trimoxazole prophylaxis beyond 2 years but do not specify when prophylaxis should be discontinued.


Comment: Would the results be very different if a similar study had been performed in children without HIV-infection?

Risk of hepatitis C reinfection after treatment in i.v. drug users.

With the availability of more effective and better tolerated drugs for hepatitis C treatment of active i.v. drug users has been debated. It has been shown that good treatment results can be achieved also in patients who continue to use i.v. drugs. One argument against treatment for this group is the risk of reinfection. In a review of reinfection in treated i.v. drug users it was concluded that there certainly is a risk of reinfection but that the risk is relatively small and that spontaneous clearance of reinfection occurs. The authors speculate that a certain immunity develops in patients who have cleared the virus after treatment. The overall conclusion is that reinfection is rather uncommon and that treatment for hepatitis C in active drug users should not be withheld due to concerns about reinfection.

Grady et al. CID 2013;57 (suppl 2)

Comment: To successfully stop HCV-transmission and to achieve long term eradication of HCV treatment of active drug users is necessary.

Normal lifespan in HIV-infection with ART?

Despite effective ART and prolonged life expectancy mortality seems to be higher in HIV-infected individuals. The question is if this is caused by HIV or by non-HIV related factors? In a review by Sabin it is pointed out that individuals with HIV-infection tend to exhibit lifestyles and behaviors that place them at increased risk of mortality. There still may be a slightly higher mortality in the HIV-infected population but with more appropriately matched control group most of the difference would likely disappear. To further improve life expectancy in HIV-infected individuals life style issues like smoking and drug use have to be addressed.


Comment: It is still a bit too early to definitely conclude that the life expectancy is the same in ART treated HIV-infected individuals as non-HIV populations but with more carefully matched control groups it seems likely that much of the difference would disappear.

Smoking and HIV

The association between smoking and mortality was estimated in almost 18 000 patients from 8 cohorts in Europe and North America followed for almost 80 000 person-years. All patients were on ART and the presumed transmission route was other than i.v. drug use. Rates of death from cardiovascular disease and non-AIDS cancers were substantially higher among ever smokers compared to never smokers (6.28 vs 2.67). Excess mortality/ per 1000 patient years associated with smoking was 0.6 at 35 years and increased to 43.6 at age > 65. The loss of life years associated with HIV in ever smokers and never smokers was estimated at age 35 compared to a French background population resulting in the conclusion that more years of life are lost through smoking compared to HIV.

Hellberg et al. CROI 2014, Abstr 101

Comment: We have come a long way in HIV-treatment when smoking is a bigger threat than HIV to the health of an HIV-infected individual! Strategies to reduce smoking should be prioritized.

Beneficial effect of tenofovir in Hepatitis Delta.

In a retrospective analysis of patients coinfected with HIV and hepatitis B with Hepatitis delta the effect of tenofovir on hepatitis delta was evaluated. All HIV infected patients in Spain with hepatitis delta on tenofovir therapy were retrospectively identified. HBV-DNA and HDV-RNA was quantified and liver fibrosis was measured with elastometry. A total of 19 patients were identified and all had hepatitis delta genotype 1. After a median tenofovir exposure of 58 months all achieved undetectable HBV-DNA and 10/19 had HDV-RNA < 10 copies/mL. The median time to undetectable HDV-RNA was 54 months. In those with detectable HDV-RNA there was a median drop of 2.42 log/mL. Significant liver fibrosis regression was defined as a 30% decrease in liver stiffness. 6/10 patients with non-detectable HDV-RNA had a significant decrease in liver stiffness in contrast to 0/9 patients with detectable virus. Median liver enzymes declined but did not normalize completely. The investigators conclusion is that long term exposure to tenofovir significantly reduces serum HDV-RNA and that this is accompanied by significant liver fibrosis regression.
Sierra-Enguita et al. CROI 2014, Abstr 700

Comment: Interferon has been the only but not very effective treatment option for hepatitis delta. Hepatitis delta may cause a severe hepatitis. If the beneficial effect of tenofovir on hepatitis delta can be confirmed it is a major improvement in the management of hepatitis delta.

HCV cured in 6 weeks!

In the Synergy trial treatment naïve patients with Hepatitis C genotype 1 monoinfection were treated 6 or 12 weeks with interferon free therapy. A majority of the participants had Genotype 1a. The study had 3 different arms with 20 patients in each arm. In the first arm patients with all stages of fibrosis were included. Treatment with the combination of Sofosbuvir and Ledaspavir was given for 12 weeks. In the two other arms a third agent was added. Either GS-9669, a non-nucleosid polymerase inhibitor or GS-9451, a protease inhibitor was added and treatment was given for 6 weeks. The SVR-12 was 100, 95 and 100 % in the three treatment arms. All three regimens were well tolerated without any serious side effects.

Kohli et al. CROI 2014, Abstr 27LB

Comment: 59 out of 60 patients achieved SVR 12. The results of this small study is overwhelmingly impressive. Not long ago a cure rate of almost 100 % seemed totally unachievable. Not only is the cure rate extremely high but it is achieved in no more than 6 weeks in most patients.

The Photon study.

HIV infected patients coinfected with hepatitis C genotype 1, 2 or 3 were included in a non randomized trial of Sofosbuvir in combination with weight based ribavirin. Patients with cirrhosis or low platelets were not excluded from the study. Treatment naïve patients with genotype 1 were given treatment for 24 weeks. Genotype 2/3 patients who were treatment naïve were treated for 12 weeks while treatment experienced patients were treated for 24 weeks. In genotype 1 SVR 12 was 76 %. In genotype 2 88 % of naïve and 92 % of experienced patients had SVR12, while genotype 3 patients had 67 and 94 % SVR12. The most common laboratory abnormality was anemia. Very few participants discontinued due to adverse events.

Naggie et al. CROI 2014, Abstr 26

Comment: It has been confirmed in several trials that 12 weeks of Sofosbuvir and ribavirin is not enough for genotype 3. Otherwise high cure rates were achieved in all treatment arms. Coinfected patients seem to respond similarly to monoinfected patients in this and other hepatitis C treatment studies.

Injectable PrEP drug?

GSK744LA is a long acting injectable integrase inhibitor that was given as a single dose to 8 macaques while a control group of 4 macaques did not receive any drug. All 12 macaques were given weekly challenge doses of SHIV. All four monkeys who did not receive any drug got infected after one to seven challenges while non of the monkeys that were injected got infected before 6 weeks and the last got infected after 17 weeks. Drug levels were measured and no macaque got infected while the drug level was above 3 times IC90.


Comment: The major obstacle to effective PrEP in trials has been the low adherence. With a long acting injectable drug one may achieve a much more effective PrEP strategy.

Female to female transmission of HIV.

Female to female transmission of HIV has rarely been described. In a case report in MMWR a likely case of female to female sexual transmission of HIV is reported. A woman with recently acquired HIV infection reported no other risk factors for HIV infection than having an HIV positive female partner. Viruses from the two women showed a very high degree of sequence identity which made it very likely that the virus in the woman with the recently acquired infection came from her partner. The couple reported oral and vaginal contact including use of sex toys and “rough” sex and sex during menstruations.

MMWR March 14, 2014, 63(10);209-12

Comment: Female to female transmission of HIV may not be a major problem but it is still valuable to be aware of the fact that it may occur.
annons
Topical Conferences in 2014

April 9–13
The International Liver Congress (EASL)
London, United Kingdom
http://www.ilc-congress.eu

May 7–10
2014 HIV in the Americas
Rio de Janeiro, Brazil
http://www.hivamericas.org/

May 9–11
HANSA 2014 (North European Workshop on HIV Infection in the CNS)
Berlin, Germany
http://www.seeuthere.com/2014/HANSA-Berlin

May 19–21
15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy
Washington DC, USA
http://www.virology-education.com

May 22–25
26th Annual National Conference on Social Work and HIV/AIDS
Denver, CO, United States
http://www.bc.edu/schools/gsw/academics/ce/conferences.html

June 3–7
International Workshop on Antiviral Drug Resistance: Meeting the Global Challenge
The Grand Hyatt Berlin
Berlin, Germany

June 12–13
10th HIV and Hepatitis Coinfection Workshop
Paris, France
http://www.virology-education.com

June 18–20
6th Conference on Peer Education, Sexuality, HIV & AIDS
Nairobi, Kenya
http://www.nope.or.ke/conference

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

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

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

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

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

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

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

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

November 7–8
AASLD
Boston, MA, USA
http://www.aasld.org