CROI 2013 in Atlanta  HIV Cure: Breaking News
Antiretrovirals: New and Old  HIV & Hepatitis News
Declining HIV Drug Resistance in Europe  Letter from the Editor
The (longer than expected?) Path Towards IFN-free Therapy of Hepatitis C
This year marked a jubilee for CROI – it was the 20th time the Conference on Retroviruses and Opportunistic Infections was given. 2013 it was held in Atlanta. Page 3.

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Dear Colleagues,

On behalf of the editorial group, I would like to welcome you to the first issue of HIV & Virology News for 2013. This is the third volume of the magazine that was started 2011, the magazine is also available online at www.hivvirology.com. As many of you know by now, it is published quarterly and distributed for free to about 15,000 physicians working in the field of infectious diseases in 13 European countries. HIV & Virology News is financed by advertisements, but, importantly, the content of the journal is unbound and advertisers have no influence of the content in any way. The editors and other contributors are encouraged to share their personal viewpoints, also if controversial. We are happy about the encouragement and positive response that the magazine has received and we are working hard to develop it further to make it even more interesting for clinicians working in the HIV and hepatitis fields.

Given the fast development in the hepatitis C field we have strengthened the editorial group with Professor Heiner Wedemeyer from the Department of Gastroenterology, Hepatology and Endocrinology at Hannover Medical School, Germany. He is a well-recognized expert in hepatitis and he will cover this interesting and rapidly changing field. I am very pleased to welcome Heiner to the editorial group.

We are also introducing a new section of the magazine called “HIV and Hepatitis News” in where short updates and news will be presented. Dr Leo Flamholc from Skåne University Hospital in Malmö, Sweden will be responsible for this part. Also Leo is warmly welcomed as a writer for HIV & Virology News.

As before, José Arribas from Madrid, Christine Katlama from Paris and Graeme Moyle from London will continue to contribute with well worth reading articles and chronicles.

Enjoy your reading!

Best regards

MAGNUS GISSLÉN
Editor
The Congress had 4,252 registered delegates, and 46% of the attendees came from countries outside USA. 1,063 accepted abstracts (of 1,801 submitted) were presented – 10% oral and 90% on posters.

20 years
These facts were pointed out by Kevin De Cock, Chair of the Scientific Program Committee, at the Opening Session. He then went back in time and presented some highlights from the past 19 Congresses.

– In 1991 controversy erupted on Capitol Hill, the seat of Congress in Washington D.C. They had learned that several hundred US government scientists were travelling to Florence in Italy for a Meeting on HIV. It prompted discussions on the need for a national meeting in the US. The result was CROI – a meeting for US researchers, domestically focused prioritizing basic and clinical science, no commerce, marketing or side-events.

The first CROI was held in 1993 in Washington. 20 years later the Meeting has expanded, and is now attended by doctors and scientists from all over the world, Dr De Cock said.

Paediatric HIV infection
Mother-to-child HIV transmission (MTCT) was a topic that Lynne M. Mofenson talked about during the Opening session. She started this by reminding of the beginning of the HIV epidemic.

– The first case of paediatric AIDS was reported to the CDC in 1982 – 18 months after the first report in adults, she said.

Along with HIV in gay men and blood recipients, a parallel but less perceived heterosexual HIV epidemic was occurring in minority, urban, poor in the US. By 1983, reports of AIDS among children of parents with recognized risk factors were published.

– In the late eighties, one in four HIV-infected mothers transmitted HIV to their infant. By the early nineties more than 16,000 perinatally-infected children had been born in the US – with a critical need for intervention, Dr Mofenson continued.

In absence of treatment, paediatric HIV infection was associated with rapid progression. As shown in a Miami cohort of 172 children with perinatal HIV, 25% of them had died by the age of 2 years.

By 1987, zidovudine (AZT) was first used for the treatment of adults. However, significant toxicity and resistance soon became evident.

CROI 2013 in Atlanta

This year marked a jubilee for CROI – it was the 20th time the Conference on Retroviruses and Opportunistic Infections was given. 2013 it was held in Atlanta.
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August 1, 2013

Late Breaker abstract submission deadline:
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Despite this, given the new availability of AZT, the association of MTCT with viral load and the high mortality of paediatric AIDS, paediatric and obstetric researchers proposed giving AZT to infected women to reduce MTCT.

But giving a potentially toxic drug to pregnant women and exposing their foetuses was highly controversial. However, in 1994 a trial found that AZT regimen gave a 67% reduction in MTCT compared to placebo.

This provided the first demonstration of treatment as prevention, Dr Mofenson continued.

Between 1993 and 1996 surveillance data demonstrate that prenatal AZT increased from 27% to 85%, intrapartum AZT from 5% to 75% and neonatal AZT from 5% to 76%.

In the year 2000 data from the women and infants transmission viral load and study were published, demonstrating that viral load and type of therapy were independent predictors of transmission, with more complex regimens resulting in lower transmission. This led to recommendations of combination regimens in pregnant women.

The finding was rapidly introduced in clinical practice, resulting in a 95% reduction in paediatric AIDS by 2004.

**Efficacy wanes with breastfeeding**

After 1994, as interventions to prevent MTCT in resource-rich countries began to be implemented, attention turned to the developing world – where most paediatric HIV infections were occurring.

By 1994, 1 million HIV-infected infants were estimated to have been born, Dr Mofenson said.

In 1999 CDC published the results of their short course AZT trial in a formula-fed infant population in Thailand. It showed a 50% efficacy.

– This short course AZT regimen was effective and affordable for the developing world – offering the first glimmer of hope for prevention.

Glaxo cut the costs of AZT by 75% for the developing countries. In 1999 Botswana launched Africa’s first program to combat MTCT with short-course AZT.

But while this regimen was effective, breastfeeding caused a loss of efficacy over time. Another study published six months later showed that a single intrapartum or newborn dose of nevirapine (NVP) could almost halve the risk of transmission in a breastfeeding population.

– Providing for the first time a very simple, clearly implementable regimen for Africa. But, as with short AZT regimens, over time efficacy wanes with breastfeeding.

**Combination therapy reduces MTCT**

At the 2000 Durban AIDS Conference, Boehringer Ingelheim announced a five-year nevirapine donation to developing countries for prevention of MTCT.

– The enthusiasm for single-dose NVP was soon tempered by the identification of NVP resistance in mothers. In a meta-analysis of ten studies, resistance was identified in 36% of women exposed to single-dose NVP.

However, a South-African study and then others demonstrated that with the addition of one week of AZT/3TC or other drugs after single-dose NVP reduced the risk of resistance by 90%. The use of a “tail” became a standard recommendation for the use of single-dose NVP.

– Investigators then moved to combine a short course AZT regimen with single-dose NVP. The study on formula-fed infants in Thailand found that combining AZT and NVP was highly effective, reducing transmission by 83% to rates of 1.1%. This is on par with the rates seen with triple ARV in resource-rich countries, Dr Mofenson underlined.

The problem with breastfeeding remains, though.

– Once infant prophylaxis stops, postnatal MTCT resumes for as long as breastfeeding is continued.

**Optimal strategy**

Eliminating paediatric HIV infection – and keeping their mothers alive – is not, and should not, be about how many women take drugs.

– It is about protecting the long-term health, dignity and security of mothers living with HIV and their children, Dr Mofenson stated.

She quoted Jonathan Mann that often stated that the AIDS epidemic exposes inequities in health systems and across societies and flourishes wherever social inequalities are marked and wherever health systems fail to deliver adequate care.

– True elimination is going to require fundamental changes in health systems for women and children.

We must therefore not loose the unique opportunity to build on the prevention of MTCT platform and infrastructure to address other health threats.

– We need to dramatically improve maternal health care and family planning to address this epidemic. To wisely use our resources to strengthen maternal and child health services, we will not only address HIV – but also the major causes for women and child mortality worldwide, Dr Mofenson summarised her talk.

**Promising PrEP agent**

One of the Sessions with oral abstracts at CROI was entitled *HIV Prevention: ARV, Counseling, Contraception, and Condoms*. Chasity Andrews presented a study on GS2126744, an investigational anti-HIV drug included in the integrase inhibitor drug class that exhibits potent antiviral activity following short-term monotherapy in infected patients.

Following a single injection in healthy volunteers, a plasma half-life of 21 to 50
To evaluate GSK744LAP (Long Acting Parenteral) as Pre-Exposure Prophylaxis (PrEP), we designed a study in 16 rhesus macaques, she said. 8 male macaques were injected with the drug at two time points four weeks apart starting one week prior to the first virus exposure. An additional 8 males were untreated and served as placebo controls.

GSK744LAP was well tolerated by all animals. All 8 placebo macaques became infected after a median of 2 rectal exposures. None of the treated macaques had detectable viremia 3 weeks after last virus challenge.

Future studies in macaques will determine the minimum protective dose of GSK744LAP, and also proof of concept PrEP studies in female macaques.

GSK744LAP is a promising next-generation agent that has a pharmacokinetic profile suitable for monthly to quarterly injections, Dr Andrews concluded.

Agents not dependent on daily use are urgently needed
Jeanne Marrazzo presented the VOICE study on PrEP for HIV in women. It is a phase II B randomised, double-blind, placebo-controlled trial of daily use of the following for prevention of HIV acquisition in women: Vaginal tenofovir, oral tenofovir and oral tenofovir + emtricitabine.

We enrolled HIV-uninfected women who reported having had vaginal sex in the prior 3 months, not pregnant or breastfeeding and were willing to use effective contraception throughout the study, Dr Marrazzo said.

They were randomised to once daily use of the above mentioned products including one vaginal placebo arm and one oral placebo arm. Then they came in for monthly visits, at which they were provided comprehensive HIV prevention counselling, condoms, contraception, pregnancy test, STI evaluation and treatment and provision of study product.

The primary study endpoints were HIV infections and safety.

The incidence of HIV in our study was substantially higher than anticipated. No study drug significantly reduced the risk of HIV acquisition, Dr Marrazzo stated.

Adherence to study products was low, especially among younger, unmarried women – who were most at risk for HIV. These results are consistent with another similar study – Fem-PrEP – and clearly support the pursuit of alternate delivery agents that are not dependent on daily use.

– Clearly, understanding HIV risk perception and the determinants of adherence on a multiple level – social and cultural – in this high-risk population is urgently needed, Dr Marrazzo concluded.

Increased risk for HIV with injectable contraception?
Over the last 20 years a number of observational studies have shown that use of hormonal contraception (HC) is associated with an increased risk of HIV acquisition, although the results have not been consistent, said Angela Crook.

She presented a study that aimed to determine the effect of HC use on the risk of HIV, using data from Microbicides Development Programme trial (MDP301) that enrolled 9,385 women in 6 centres from 4 Sub-Saharan African countries 2005–2008.

Injectable HC is the dominant contraceptive method in these countries and in 2012 WHO issued a recommendation that women using progesterogen-only injectable are strongly advised to always use condoms.
This is the largest study to investigate this question to date, she said. Although the crude incidence rates suggests a relatively large increased risk associated with injectable HC, both for injectable depo-medroxyprogesterone acetate (DMPA) and injectable norethisterone enanthate (Net-En). The conclusion of the study was that this was mainly explained by confounding – particularly with age and centre.

– Results were consistent across centers and age groups, Dr Crook explained. Consistent with previous studies, a small increased risk of HIV remained for women using DMPA.

– Although we can't rule out that there are some confounding factors that we haven't been able to accurately account for, she said.

Women on ART

Is DMPA likely to increase infectivity in HIV-positive women receiving ART? A study on this was presented by Summer Day.

– We know that 90% of the 14 million HIV-1 infected women in Sub-Saharan Africa are 15–59 years old – i.e. of childbearing age.

Modern contraception is important to this group – to prevent unwanted pregnancy and to prevent MTCT. It is used by 21% of these women.

– In Kenya, where our study in particular was conducted, 29% of women used HC. A majority of these use DMPA, Dr Day said.

Limiting the use of DMPA has implications – unplanned pregnancies and MTCT, but also on maternal morbidity and mortality, she pointed out.

– Our results suggest that DMPA use may not be associated with increased infectivity in HIV-positive women adherent to effective ART regimens, Dr Day continued.

Therefore consider early initiation of ART in HIV-positive women who desire hormonal contraception, including DMPA, was her conclusion.

Study on HIV and age-related diseases

HIV-infected individuals are living longer, turning HIV infection into a chronic disease. Individuals with chronic diseases are at great risk of age-related diseases – but this is not the same as premature aging.

– Premature aging in a clinical context can be defined as younger age at diagnosis of age-related diseases, said Keri Althoff.

She was talking in a Session on cardiovascular disease and other non-AIDS events.

– The question remains: Are HIV-positive experiencing age-related diseases at similar or younger ages compared to HIV negative individuals?

Dr Althoff presented a study on the subject. More than 84,000 individuals were included.

They found that HIV-positive individuals had greater risk of myocardial infarction (MI), end-stage renal disease (ESRD) and HIV-associated cancers.

– Which suggests greater prevention and screening programs to protect the health for adults living with HIV.

MI and ESRD diagnosis were occurring at similar ages for HIV-infected and uninfected adults, which does not support the hypothesis of premature aging for these two diseases.

– We found a modest difference – 6 months younger in the HIV-positive – for the age of non-AIDS-defining cancers. The clinical and public health significance of this difference is undetermined, Dr Althoff summarized.

Study on awareness of infection

In the US, men who have sex with men (MSM) are disproportionately affected by HIV.

– In 2009, 57% of all persons estimated to be living with HIV were MSM. In 2010 63% of all new HIV infections occurred among MSM, Cyprian Wejnert stated.

Awareness of infection – defined by being aware of ones own status – is a key step toward prevention, he continued.

– Unaware HIV-positive persons are more likely to place their partners at risk. They are also estimated to be responsible for the majority of sexual transmissions of HIV in the US.

The objectives of the study he presented were to describe prevalence and awareness of HIV infection among MSM in 20 US cities in 2008 and 2011 – and to compare prevalence and awareness observed in 2011 to that observed in 2008.

HIV prevalence was highest among black MSM, but remained stable from 2008 to 2011 overall and across all ages and race ethnicity categories, Dr Wejnert reported.

– Awareness of infection was lowest among black MSM, but increased significantly in all categories from 2008 to 2011, he continued.

Reducing disparities

He underlined that there were many limitations in the study: The data are not rep-
The case Dr Persaud presented concerned a functional cure in a newborn child. In his talk at the Opening Ceremony, Kevin De Cock presented some findings that found its way into ordinary news media.

One case presented at the Congress in Atlanta resulted in a very high interest from news media – both television and newspapers. It topped the headline at CNN and other news channels and made the front page of most newspapers.

The case was presented at CROI by Deborah Persaud as a late-breaking abstract, and it concerned a functional HIV cure after very early ART of an infected infant.

– It is important to point out that it is a single case and a proof of concept, Dr Persaud initially said.

There are nearly 70 million individuals infected with HIV over the 20 years of the epidemic – but only one case of HIV cure: The well known so-called “Berlin patient”.

– From that case we have learned that replication-competent HIV reservoirs can be cleared, and long-term virologic control can be achieved in the presence of waning HIV-specific immunity, she continued.

Lost to follow-up
The case Dr Persaud presented concerned a 28-month old girl born at 35 weeks gestation via normal spontaneous delivery. The mother was not engaged in prenatal care, so a rapid test was performed on the mother during labour. The test was positive.

– But no antiretroviral drugs were given, as the delivery was quite precipitous.

The baby was transferred to University of Mississippi Medical Center by 30 hours of age, and two individual blood tests confirmed HIV infection.

– The girl was started on prophylaxis with a three-drug regimen – AZT/3TC/NVP – by 31 hours of age. What’s distinct about this case is the NVP dosage that was given at a therapeutic dose level.

This therapy was continued for 7 days, and then the NVP was changed to lopinavir + ritonavir. Doctors assumed the child would have to require lifetime medication.

But the mother and girl stopped going to their doctor when the girl was 18 months old – and was therefore lost to follow-up. ART was discontinued.

– At 23 months of age the girl was returned to follow-up. The viral load remained undetectable! With treatment being discontinued 5 months previously, this was quite unbelievable, Dr Persaud said.

In addition, standard HIV ELISA testing was negative and the standard HIV-DNA PCR, that is used to diagnose HIV infection in infants, was also negative.

Need for more research
To summarize, Dr Persaud stated that they believed that this is the first well-documented case of a functional cure in an HIV-infected child.

– This, to us, suggests that very early antiretroviral therapy in infants may prevent establishment of a latent reservoir and achieve cure in children.

The finding has potential to transform current treatment practices in HIV-infected newborns worldwide if replicated – especially it could have an impact in development countries where lack of prenatal care fuels a much higher rate of MTCT.

– Clinical trials of prompt antiretroviral therapy have been in development for the past year, with the respect to achieve a curing agenda of paediatric patients in the context of IMPAACT Network, she said.

At the time for the Congress, the time period that had gone since treatment was stopped was 10 months – and the girl was still doing fine.

Efavirenz and zidovudine during pregnancy
The MTCT rates are less than 1% in industrialized countries in the cART era, said Jeanne Sibiude.

– The current issue is access to prevention of mother to child transmission (PMTCT) program, and side-effect of ART in pregnancy, she said.

Dr Sibiude presented a study on birth defects and ARV in a French perinatal cohort, among 13,000 live births from 1994 to 2010.

The recommendation to avoid efavirenz during pregnancy should be maintained in countries with access to other drug options, was one of her conclusions.

– And there is an important need for epidemiological surveillance in coun-
tries where EFV is largely described, she added.

There is an issue raised by the association between first trimester exposure to zidovudine and a higher risk of congenital heart disease.

– Further detailed investigation is needed to clarify this mechanism. And there is also a need for research on NRTI sparing ART for PMTCT in the future.

– However, it is important to keep in mind that the potential risk of birth defects has to be balanced with the major success of current PMTCT strategies, Dr Sibiude underlined.

**Laboratory monitoring in children**

90% of all HIV-infected children are living in Sub-Saharan Africa. But only approx. 28% of those in need of ART are receiving it.

– One potential barrier is the perceived need to provide routine laboratory monitoring of ART, Adeodata Kekitiinwa said.

Trials in adults have shown that routine CD4 monitoring provides small, but significant, benefits on disease progression and death – but routine toxicity monitoring has no impact on toxicity outcomes. No trials have evaluated monitoring strategies in children.

– This raises the question if ART can be provided with clinical driven, rather than routine, laboratory monitoring?

She presented the ARROW trial. In this, 1,206 ART-naive children and adolescents in Uganda and Zaire, meeting WHO 2006 criteria for ART initiation were randomised to two arms: Laboratory and clinical monitoring (LCM) and clinically driven monitoring (CDM).

The 5-year survival in both groups was excellent. Loss to follow-up was very low and adherence to strategy high.

– We conclude that HIV treatment can be delivered safely to children with good quality clinical care, without any need for routine laboratory tests for side-effects on ART, Dr Kekitiinwa stated.

Monitoring of weight gain should be emphasized as an important clinical aid for identifying first-line failure.

– We recommend that resources should be focused on getting as many children onto treatment as possible, rather than providing routine laboratory monitoring to fewer on ART, she summarised.

**Declining mortality**

During one of the Plenary Sessions, Francois Dabis had a talk with the title *Reality check: Is the end of AIDS in sight?*

He began this by taking a brief look at the first 30 years, and apologized for being a bit critical.

– What have we done collectively in 30 years? Although we learned quite soon that antiretrovirals could be used to prevent MTCT, we waited far too long before introducing them in lower-income countries, he said.

Too many years also went before concluding on the protective effect of male circumcision, Dr Dabis added.

– So I believe that the true epidemiological situation is not a fatality, but a direct consequence of our past action – and inaction.

Examining the recent trends may modify this somewhat negative diagnosis, Dr Dabis continued and started with figures on prevalence:

– There have never been more people living with HIV than today – 34 million by the end of 2011. Hopefully we will continue to treat more people more efficiently so they will live longer.

2013 will be the seventh year in a row with declining mortality due to AIDS, mostly due to treatment scale-up.

**Three definitions**

The most important good news comes from figures on incidence trends.

– The speed of the epidemic is changing dramatically. We are already doing well throughout Africa. In other parts of the world – Eastern Europe and central Asia especially – trends are a cause of concern, unfortunately.

President Obama stated in his last State of the Union address “The US will join with our allies to eradicate such extreme poverty in the next two decades… and by realizing the promise of an AIDS-free generation, which is in our reach”.

– We have moved from rhetorics to politics, Dr Dabis said.

He presented three proposed definitions of “the end of AIDS”:

2005 saw the mortality peak in AIDS (2.3 million, including TB-HIV deaths), and he suggested that figure has been reduced to less than 5% (100,000) we can say that HIV has become just a chronic disease.

The peak for sexual and injecting drug use transmission was in 1998 with 3.5 million transmissions.

– May I suggest that we will be close to the end of AIDS when the annual incidence will not exceed 10% (350,000) of the peak worldwide.

The third definition would be to eliminate new HIV infection in children, and it looks like we are on track for this target.

**A matter of quality**

– We also have to base our strategy of disease control on available and sound evidence – and monitor the scientific progress, Dr Dabis continued.

Today’s powerful interventions to tackle HIV include antiretrovirals for PMTCT, medical male circumcision (MMC) and antiretroviral treatment.

Male circumcision has the potential to prevent 1 in 5 new infections in eastern and southern Africa.

– But today we remain far from this target. It is estimated that of 20 million
MMC targeted in Africa by 2015, only 3 million have been performed. Clearly the commitment has been lacking so far.

For the number of people receiving ART in low- and middle-income countries, Dr Dabis thought that we are on track for the target.

– But it is not only a matter of the number of new patients. It is also a matter of quality. We are treating earlier and earlier – but not early enough according to guidelines.

Also linkage and retention in treatment programs are uneven.

Paying now instead of paying forever
He concluded his talk by stating that the end of AIDS is potentially in sight.

– We have a strong approach to eliminate MTCT in the next few years. We have an incredible powerful set of interventions to control the adult epidemic in the next 20 years.

We should now maximise and scale-up MMC in developing counties, and ART up to 500 CD4 everywhere.

– Integration and gains in efficiency will be made, but there is no way this will happen without new resources. Paying now, rather than paying forever was the take home-message of the Washington 2012 Conference, he reminded the audience.

– Reaching the goal of the end of AIDS requires a 20-year global agenda – but that can be shortened by ongoing research, was Dr Dabis last statement.

Child mortality in Africa
The President’s Emergency Plan for AIDS Relief (PEPFAR) is emerging as a central pillar of US global health policy. In this role, PEPFAR’s funding priorities depend on the extent to which its support for HIV programs can be leveraged to improve health beyond HIV.

Eran Bendavid presented a study in which they had examined PEPFAR’s association with changes in under-5 mortality among children of African men and women with HIV.

– Using data on 115,111 parents and 341,357 children from 21 Sub-Saharan countries, we created a longitudinal dataset with monthly survival data on every under-5 child whose mother or father tested for HIV as part of a Demographic and Health Surveys between 1997 and 2010, he said.

Monthly mortality among under-5 children of HIV-positive parents in focus countries decreased from 3.3 per 1000 child-months prior to PEPFAR’s implementation to 2.9 per 1000 child-months during PEPFAR’s implementation.

In non-focus countries, under-5 mortality among children of infected parents increased from 2.5 per 1000 child-months to 2.9 per 1000 child-months over the same time periods.

The conclusion of the study was that PEPFAR was associated with relatively greater all-cause mortality decline among children of HIV-positive parents, but not among children of HIV-negative parents.

– This could be due to reduced mother-to-child transmission or the parents’ improved health and welfare. This is the first study to quantitatively measure PEPFAR’s effect on child mortality, Eran Bendavid summarised.

Omitting NRTIs
Complete viral suppression is the goal of ART. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are frequently included when constructing new ARV regimens for patients with virologic failure.

Karen Tashima presented the OPTIONS study.

– Our hypothesis for the study was that omitting NRTIs would be non-inferior to adding NRTIs in treatment-experienced subjects starting a new optimised regimen, she said.

OPTIONS enrolled subjects with viral failure who had protease inhibitor (PI), Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) and NRTI experience and/or viral resistance into a randomised, non-inferiority trial comparing omitting NRTI versus adding NRTI to a new regimen. 360 subjects were randomised.

The study had two endpoints – primary efficacy endpoint and primary safety endpoint.

In her summary, Dr Tashima said that regimen failure was not more likely among those omitting NRTIs versus adding NRTIs to an optimised new regimen.

– HIV RNA and CD4 cell responses were similar.

Her conclusions were that in this population, NRTIs can be safely omitted without compromising regimen failure.

– Potential benefits of omitting NRTIs is reduced pill burden and cost. These results should be considered when recommending new regimens for treatment-experienced patients, she stated.
Declining HIV Drug Resistance in Europe

There appears an increasing diversion between the HIV epidemics in the US and Europe. A decline in the proportion of new infections acquired by injection drug use has been noted especially in Southern Europe, with associated declines in the persons co-infected with Hepatitis C.

Europe’s epidemic is also a much greater mix of B and non-clade B viruses compared to the almost homogeneous clade B epidemic in the US. This reflects the US epidemic being a predominately ‘homegrown’ epidemic whereas the European epidemic is more a mix of locally acquired infections and infections acquired abroad (and local transmission of infections acquired abroad). Furthermore, rates of reported resistance at diagnosis are notably divergent between the two regions as are the prevalence of resistance in experienced patients. These differences are one of many potential contributors to the higher rates of treatment success observed in European cohorts relative to the USA.

Primary drug resistance first emerged in the mono and dual therapy era of the early 1990s. Transmitted resistance to all drug classes including integrase inhibitors and recently approved agents such as rilpivirine, have been reported. Transmitted drug resistance is associated with narrower treatment choices and poor virologic responses when antiretroviral therapy is used. While it is often thought that there is a single ‘founder’ variant of HIV, hence the persistence of transmitted resistance in the absence of drug pressure as compared to wild-type outgrowth that may mask acquired or treatment emergent mutations after selection pressure is removed, recent data suggest at least some transmissions include multiple founders [1].

US surveillance data reported at this year’s CROI described a convenience sample of persons newly diagnosed with HIV-1 infection who did not have evidence of prior ART use. The study covered 10 HIV surveillance areas in the United States from 2007 to 2010, reported to CDC through June 2011. Sequences collected from 18,144 (23.3%) of 77,887 persons newly diagnosed with HIV-1 infection and found that 2932 (16.2%) of 18,144 sequences contained 4788 transmitted drug-resistance associated mutations for NRTI, NNRTI and PI classes. Of these 2461 (13.6%) had resistance to a single drug class, 386 (2.1%) 2 class resistance and 85 (0.5%) 3 class resistance. The most common mutations reported were associated with NNRTIs, present in 1464 (8.1%) samples with NRTI resistance in 1206 (6.7%), and PI resistance in 818 (4.5%) sequences. They noted a significant increasing trend for a single drug class- and NNRTI-associated transmitted resistance from 2007 to 2010 [2].

This contrasts with regional surveillance across Europe where transmitted resistance is in decline. In Spain during a similar period (2007–2010), transmitted drug resistance in 1,864 antiretroviral-naïve patients an overall prevalence of 8.58% was observed with 3.92% samples NRTI resistant, 3.86% NNRTIs resistant and 2.31% PI resistant. A significant decreasing trend over time for NNRTIs (5.53%, 2007; 2.45%, 2010; p for trend=0.044) was observed. Non-B subtype prevalence was 15.93%, with a significant increase over time (11.95%, 2007; 18.14%, 2010; p for trend=0.018). Non-B subtype significantly reduced the risk of transmitted to...
NRTIs (OR, 0.27) [3]. For the UK similar trends were observed, even when just the clade B subtypes are considered. Of 1654 (11.3% of 14,584 patients infected with HIV-1 subtype B virus) samples with one or more mutations associated drug resistance, the prevalence was found to decline from 15.5% in 2002 to 9.6% in 2007, followed by a slight increase to 10.9% in 2009 (P=0.21). This later rise was mainly a result of increases in resistance to NRTIs (from 5.4% in 2007 to 6.6% in 2009, P=0.24) and protease inhibitors (1.5% to 2.1%, P=0.12). Thymidine analogue mutations, including T215 revertants, remained the most frequent mutations associated with NRTI, despite a considerable fall in stavudine and zidovudine use between 2002 and 2009 (from 29.4% of drug regimens in 2002 to 0.8% in 2009, from 47.9% to 8.8%, respectively) [4].

For Italy, the prevalence of transmitted drug resistance in 3163 antiretroviral-naive HIV-1-infected patients, with a genotypic resistance test (GRT) performed ≤6 months before starting cART between 2000 and 2010 was 12%. Subtype B was the main subtype (69%) and was associated with transmitted resistance, the prevalence being 13.2% against 9% for non-B samples. During the study period transmitted resistance significantly declined overall and for each of the single drug classes [5].

Finally, in Sweden samples from 1,463 patients newly diagnosed with HIV-1 infection between 2003 and 2010, found 82 subjects with transmitted resistance, a prevalence of 5.6% without any significant time trends or differences between patients infected in Sweden or abroad. 68% of samples showed single mutations but 5 subjects had multidrug resistant viruses [6].

Even in treated patients in Europe there is decline observed resistance. A recently published retrospective analysis involving 20,323 samples from ART-experienced patients revealed that, despite increasing overall drug exposure, the prevalence of resistance mutations decreased between 1997 and 2008. HIV genotype data on samples obtained from ART-experienced patients in the U.K., Italy, Portugal, Germany, Sweden, Spain, and Belgium between 1997 and 2008. Overall, 16,278 samples (80%) showed at least one resistance mutation. Resistance to NRTIs was most common (67%), followed by NNRTIs; 51% and PIs; 33%, resistance to one, two, and three of these drug classes was seen in 26%, 38%, and 16% of the samples, respectively. For NNRTIs, the most common resistance mutations were M184V/I and thymidine analogue mutations; for NNRTIs, K103N, Y181C/I, and G190A; and for PIs, L90M, M46I/L, V82A/F/L/S/T, and I84V. The proportion of samples with at least one resistance mutation declined over time, from 81% in 1997 to 71% in 2008 with NRTI and PI mutations showing the most substantial decreases. This was despite NRTI use remaining near ubiquitous (98% of the patients in 1997, 94% in 2008.

A key factor in the declining risk of PI resistance (and hence option exhaustion) is likely to be the shift from unboosted PI use (55% in 1997 to 77% in 2008) to boosted PI use increased (from 1% in 1997 to 48% in 2008). Importantly, the proportion of sampled patients judged as having exhausted available drug options dropped dramatically, from 32% in 2000 to 1% in 2008. Similarly to trends in transmitted resistance factors associated with detection of resistance included MSM, non-B subtype virus, history of suboptimal therapy, failure of a greater number of regimens, and longer duration of ART exposure [7].

The declining HIV drug resistance, both transmitted and acquired, in Europe is good news for managing the HIV epidemic in this region. The success treatment-as-prevention schemes require high levels of treatment success to reduce transmission, something that would be challenged but high or rising rates transmitted and acquired resistance. The reasons for success in Europe are unclear but is likely to reflect success with safe sex messaging, high levels of adherence and success amongst treated subjects, and use of boosted PI regimens that protect against resistance emergence at failure as key factors. The introduction of more single tablet therapies in 2013 is likely to further support patient adherence and acceptability of early treatment but these advantages will need to be counterbalanced with the low genetic barriers and high rates of 2 class resistance seen in the few virological failures in studies with some of these combinations.

Finally, the European (and Canadian, Australian) social systems that address social ills and aid access to and retention in care are critical. The lack of such a system in the US and the demographics driving the US epidemic (poverty, drug use) are likely to mean ART resistance will remain a tale of two regions.

Conflict of Interests
Dr Moyle has received research grants from Abbott, Ardea Biosciences, Bionor, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies and Tibotec.

He has received honoraria as speaker and/or advisor from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Theratechnologies, Tibotec and ViIV Healthcare.

References:
1. Song H, Cai F, Ganausov V, et al. Recombination Shapes Viral Evolution during Early Infection in Individuals Infected with Multiple Transmitted/Founder HIV-1. CROI 2013; abstract 244.
The latest data on the potential for such an outcome were presented and the consensus was that there are several reasons why HIV cannot yet be cured, despite years of advances in suppressive therapy. Those limitations are the following:

- The latency of HIV integrated into host DNA in cells that are mainly long resting memory T-cells. This integrated cell-associated DNA is called a reservoir and it differs from anatomical HIV compartments such as those in the central nervous system.
- The persistence of low-level HIV replication, which may continuously fuel the HIV reservoir.
- The persistence of immune activation, which may consistently induce a low level of replication.

Clinical research has begun to evaluate various strategies to purge or decrease HIV reservoirs.

**Treatment intensification**

Following the hypothesis that persistent HIV replication continues despite viral suppression under conventional antiretroviral therapy (ART), one of the initial research questions has been to determine whether an intensification of ART therapy could block the subliminal production of virus. The results have been inconclusive, with most studies showing no advantage in adding raltegravir or maraviroc, whereas others indicated some benefit [1].

Hiroyu Hatano, a member of Deeks’s group in San Francisco, partially clarified the controversy over Buzon’s findings with regard to the positive effect of raltegravir in inducing the production of LTR circles – those virus elements that are released before viral integration, indicating a persistent but minimal level of replication [1]. In a double blind placebo-controlled study including 31 long-term ART patients (15 randomized to raltegravir intensification and 16 to placebo), it has previously been reported that intensification was neither linked to a decrease in ultra-sensitive assay results, nor to cell-associated PBMC [2]. By contrast to their apparently negative results with regard to the potential benefit of raltegravir intensification, a significant increase (similar to Buzon’s findings) in 2 LTR production in patients given raltegravir (9/15) compared to placebo (3/15) was reported at CROI 2013, with an effect ranging from 3 to 8 times higher during the 24 weeks of the study [3]. This effect was mainly observed in patients receiving a regimen containing PI, suggesting that residual viral replication may occur in compartments less accessible to PI.

Furthermore, adding raltegravir to a suppressive led to a significant decrease in D Dimers, a marker of coagulation and inflammation associated with increased morbidity and mortality in SMART, and contrasting with the absence of benefit shown on markers for endothelial function, as assessed by flow-mediated vasodilation (FMD) of the brachial artery [4].

The key message, as outlined last year by Flechner [5], is the importance of further evaluating the impact of different classes of drugs in terms of viral compartments, viral reservoirs, and immune activation and inflammation markers beyond the plasma suppression achieved by most of the current ART strategies.

**Can the latent virus be purged out of resting T-cells?**

Latency remains the main obstacle to curing HIV. Infected cells containing replication-competent provirus are transcriptionally silenced by corepressor complexes containing histone deacetylases (HDAC), histone methyltransferases, and heterochromatin proteins. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues, resulting in an open chromatin structure and transcriptional activation. HDACs can activate HIV proviruses ex vivo [6]. Several drug companies have already launched intense research programs aimed at discovering anti-HIV latency agents.

**HDACs inhibitors**

Vorinostat inhibits the enzymatic activity of histone deacetylases HDAC1, HDAC2, and HDAC3 (Class I), and HDAC6 (Class II) at nanomolar concentrations (IC50 < 86 nM).

D. Margolis’ group has recently published their finding that a single dose of Vorinostat, a drug licensed for chemotherapy of cutaneous lymphoma (Zolinza® from MSD), was able to induce a transcription of virus [7]. This year, Sharon Lewin from the Mac Burnet Institute in Melbourne reported the results of a pilot study aimed at evaluating whether multiple doses of Vorinostat (at two-week administration of 400 mg daily) would be both safe and capable of inducing viral transcription from latently infected cells as measured by unspliced RNA [8]. The 20 patients they enrolled in a single arm study had an excellent current HIV infection status, with a median CD4 of 721 cells/mm3 and a median time of 5 years of viral suppression.

The main results are as follows:

- Overall, Vorinostat appears reasonably well-tolerated, with no unexpected side effects, other than mostly grade 1 or 2 (diarrhoea, nausea, fatigue).
- A positive induction of viral transcription with a significant and sustained increase in cell-associated unspliced RNA in 18/20 patients, with a 2.65 fold increase from baseline during the on-drug period and a transient increase in RNA in some patients.
- Despite the transient reversion of latency, there was no change in HIV DNA throughout the study, indicating that more drugs or additional strategies to eliminate latently infected cells were needed.
Other HDACIs are currently under investigation, such as Rhomidepsin (RMD), a cyclic peptide HDACi approved for the treatment of lymphoma, which in vitro and ex vivo studies have shown to induce an expression of latent HIV more effectively than Vorinostat at clinically achievable concentrations [9].

Interleukin 7 and Intensification

The approach in the Eramune 01 study [10] was to combine strategies that would first intensify ART with a combination of raltegravir and maraviroc, and secondly modulate the immune system using interleukin 7 to stimulate CD4 lymphocytes and purge them from latent viruses. Unlike the previous study, the primary objective here was to decrease HIV DNA. As the study design was very similar to the oncology approach, one patient with at least a 0.5 log₁₀ decrease in HIV DNA PBMC would be enough to declare the strategy of further scientific interest.

Twenty-one patients selected as perfectly controlled in terms of viral load and CD4 (median values of 558 cells/mm³), having an HIV DNA reservoir of between 50 and 1000 copies per million PBMC (median value 360 copies/10⁶), were randomized to receive either raltegravir/maraviroc intensification alone for 56 weeks (14 patients) or intensification plus IL-7 administered as 3 weekly injection at W8, W9, and W10 (15 patients).

In summary, dual RAL/MVC intensification over 56 weeks with or without IL-7 was unable to decrease the total HIV-DNA reservoir in peripheral blood cells.

The massive CD4 T-cell expansion induced by IL-7 primarily involved the central memory. T-cells (Tₘ₉) responsible for the transient increase in the HIV-DNA copy numbers may have masked the expected effect of IL-7 on reactivation of HIV in latently infected cells.

HIV functional cure: The first demonstration of a functional cure after very early ART in a perinatally infected child

During the same session we all applauded the very exciting and joyful case reported by Deborah Persaud on behalf of the team in charge of the first infant in remission from HIV infection [11]. The infant had been perinatally infected (probably in utero) by an untreated HIV-positive mother with a relatively low viral load. He received standard treatment with oral AZT/3TC/NVP beginning as early as 31 hours of age for one week, followed by an AZT/3TC/LPV regimen until 18 months of age. The viral load declined under therapy from 19,812 copies/ml HIV RNA to 2,617 copies/ml (3.4 log) at 15 months. The infant remained free of virus for 19 days, followed by a typical biphasic decay in plasma viral load on ART.

to 2617, 516, 265, and then < 40 copies at age 18 months. He was then lost to follow-up and did not return to care until 23 months of age. At that time, five months after ART discontinuation, the standard viral load HIV RNA was repeatedly undetectable. Further attempts were unable to detect any positive ELISA test. The standard DNA PCR was also negative. Multiple virological assessments, similar to the ones performed on the Berlin patient, failed to detect any HIV-specific CD4 or CD8 immune responses. The infant was CCR5 delta 32 wild type and had no specific HLA profile that could have been protective against HIV infection.

Caution is indicated since the follow-up has only been 10 to 12 months after discontinuing ART, and the absence of virus detected cannot preclude subsequent viral rebound in the future. However, the clear message from this isolated case strongly suggests that the early administration of ART may be capable of preventing the establishment of a latent reservoir and may contain the potential for a cure.

Is it possible to limit the establishment of an HIV reservoir?
Perhaps it is possible to initiate ART so early that establishment of an HIV DNA cell-associated reservoir can be limited, as in the case of the “cured baby.” It may be possible!

The SEARCH study presented by Jintana Ananworanich [12] of Thailand investigated the relationship between the size of the cellular reservoir and the initiation of ART at the time of a primary infection. Seventy-five patients were started on ART soon after HIV penetration into the body, with a median delay of 15 days of infection.

Two sets of data appear highly significant with regard to the DNA viral reservoir:

Prior to any therapy there was a clear difference in DNA reservoir, depending on the time of infection: at the earliest stage (Fiebig I RNA pos, p24 neg 3°gen EIA neg) the reservoir was the lowest; then followed by Fiebig II RNA pos, p24 pos 3°gen EIA neg; then Fiebig III RNA pos, p24 pos 3°gen EIA neg WB.

Almost all Fiebig I subjects showed negative unintegrated DNA and DNA in biopsies, indicating that at the time of primary infection a very rapid enrichment of the reservoir occurs.

Following ART initiation there was a decrease in HIV DNA in patients, with reservoirs very similar to doses of elite controllers. These data strongly suggest that early initiation of therapy represents a unique opportunity to limit the reservoir.

Conclusion
Since the field is undergoing rapid changes, we need to better understand what is going on at the reservoir level—not only in primary infections, but at other stages of HIV disease as well. As clinicians we must realize that it is likely the measurement of viral reservoirs may be a key marker. When considering therapeutics to purge the cellular reservoir or enhance immune responses for control, the smaller the cellular reservoir, the better the chance there may be for success, at least in the early stages of fundamental research.

Conflict of Interests
Professor Katlama has received research grants from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, and Tibotec. She has received honoraria as speaker and/or advisor from Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Tibotec and ViV Healthcare.

References:
3. HIroyo Hatano, M Strain, R Scherzer, et al. Increase in 2-LTR Circles after Raltegravir Intensification in HAART-suppressed Patients with High CD4+ T Cell Counts: A Randomized, Controlled Trial. 20th Conference on Retroviruses and Opportunistic Infections, CROI 2013, Atlanta GA 2013, Abstract 42
10. Christine Katlama, S Lambert, I Assoumou, et al. Impact of Interleukin-7 and Raltegravir + Maraviroc Intensification on Total HIV DNA Reservoir: Results from ERAMUNE. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta GA 2013, Abstract 170aLB
Antiretrovirals: New and Old

Report from the 20th Conference on Retrovirus and Opportunistic Infections

The 20th Conference on Retroviruses and Opportunistic Infections (CROI) was held in surprisingly chilly Atlanta from March 3th to March 6th. This year the meeting was dominated by research on HIV cure and advances in the treatment of Hepatitis C infection. There were also several relevant presentations focused on new and old antiretroviral drugs.

NEW ANTIRETROVIRALS

Dolutegravir

SAILING is a double-blind clinical trial [1] that included 715 antiretroviral experienced patients who were integrase inhibitor naïve. To be included in the trial patients needed to have in the background regimen one fully active antiretroviral agent plus no more than one second single agent which may or may not have been active. Then patients were randomized to receive dolutegravir 50 mg qd or raltegravir 400 mg bid. Median HIV-RNA level was approximately 4.2 logs and median CD4 cell count was approximately 200 cells/μL. Almost half of the patients had triple class resistance. After 24 weeks of follow-up proportions of patients with HIV-RNA less than 50 copies/mL were 79% and 70% for dolutegravir and raltegravir respectively (Fig 1). This result supports the superiority of dolutegravir (p=0.003). Differences were larger in patients with baseline viral load >50.000 HIV-RNA copies/ml (70% vs. 53%) and when darunavir was compromised by the presence of primary mutations (79% vs. 67%).

For patients failing therapy dolutegravir was associated with a lower frequency of viruses with evidence of integrase resistance (dolutegravir 2/354: 0.6% vs. raltegravir 10/361: 2.8%, p = 0.016). In the dolutegravir group, two patients developed one integrase resistance mutation (R263K). In each case fold change IC50 for both dolutegravir and raltegravir was less than two.

Take home message: SAILING clearly supports the use of dolutegravir in ART-experienced, integrase naïve patients. Expectations about dolutegravir remain very high. First trial including patients naïve to integrase inhibitors in which dolutegravir has selected integrase mutations.

Tenofovir alafenamide fumarate (TAF)

TAF is is a prodrug of tenofovir with increased delivery to lymphoid cells and hepatocytes. In comparison with 300 mg of tenofovir disoproxil fumarate, 25 mg of TAF leads to increased intracellular tenofovir diphosphate levels by approximately 7-fold and decreased circulating plasma tenofovir levels by approximately 90%. It is expected that the lower plasma levels of tenofovir would translate in lower bone and renal toxicity. When combined with cobicistat the exposure to TAF further increases approximately 2.2 fold and doses as low as 10 mg can be used.

The GS-US-292-0102 phase II clinical trial [2] compared the fixed dose combination of tenofovir disoproxil dilefumarate/emtricitabine/elvitegravir/cobicistat (TDF/FTC/EVG/c) versus tenofovir alafenamide fumarate/emtricitabine/elvitegravir/cobicistat (TAF/FTC/EVG/c) in 170 antiretroviral naïve patients. After 24 weeks of follow-up proportion of subjects with HIV-1 RNA less 50 HIV-RNA copies/mL were 89.7% for TDF and 87.5% for TAF. As expected tenofovir plasma levels were substantially decreased in the TAF group by approximately ten-fold while tenofovir diphosphate intracellular levels were increased by five-fold.

Interestingly the lower plasma levels of tenofovir in the TAF group appear to translate into lower renal and bone toxicity. At week 24 median changes from baseline eGFR (Cockroft-Gault) were -11.8 mL/min and -4.8 mL/min in the TDF and TAF groups respectively (p=0.04). By bone densitometry mean percentage change in bone mineral density in spine/hip were -2.5/-2 and -0.8/-0.3 in the TDF and TAF groups respectively (p=0.002 and 0.001. Fig 2). Lipid changes (total cholesterol, LDL and HDL) were significantly higher in the TAF group, which suggest that the lipid lowering advantage of TDF might not exist with TAF. Finally there were more cases of neutropenia in the TAF group although it is still unclear if this occurred just by chance.
Another study evaluated the efficacy of doravirine in different subgroups of patients of the well-known SPRING 2 (comparative with raltegravir) and SINGLE (comparative with TDF/FTC/EFV) clinical trials [4].

Main conclusion: regardless of the accompanying nucleosides -ABC/3TC or TDF/FTC- doravirine is as efficacious as the comparator in patients with baseline CD4 cell counts of less than 350/µL or viral loads above 100,000 HIV-RNA copies/µL. Adverse events leading to withdrawal of study medication are comparable to raltegravir and significantly lower than with efavirenz.

There was an interesting oral presentation about a new non-nucleoside reverse transcriptase inhibitor called MK-1439 [5]. MK-1439 lacks the central nervous system adverse events characteristic of efavirenz, is active against viruses harboring common non-nucleoside reverse transcriptase inhibitor mutations such as K103N, G190A and Y181C and has the potential to be administered once-daily. In a phase I study MK-1439 was well-tolerated and showed antiviral activity at doses of 25 and 200 mg QD.

Cenicriviroc is a CCR5 receptor antagonist than also antagonizes the CCR2 receptor. The CCR2 receptor and one of its ligands (MCP-1) are involved in the tissue recruitment of monocytes and macrophages. Cenicriviroc potentially could combine antiviral and anti-inflammatory properties. In a phase 1b trial that was presented as a late breaker [6] cenicriviroc at 100 and 200 mg doses combined with TDF/FTC showed antiviral efficacy similar to efavirenz, significant increases in plasma levels of MCP-1 and significant decreases in plasma sCD14. Importantly, elevated sCD14 level was a predictor of mortality in the SMART clinical trial.

Nucleosides: gone with the wind?
One question that HIV clinicians have been discussing for a long time is if N(t) RTIs regardless of activity should be maintained in a salvage regimen. In the ACTG OPTIONS study [7] patients failing current protease inhibitor-based regimen and with prior N(t)RTI and NNRTI resistance and/or experience underwent resistance and tropism testing. An expert group performed a regimen recommendation. The recommended regimen always had a phenotypic susceptibility score higher than 2. Patients were randomized to add or omit nucleosides from the potent recommended regimen.

In the OPTIONS study, the most commonly selected N(t) RTIs were TDF/FTC (82%) and TDF/FTC/ZDV (12%). In 12% of the cases none of the N(t)RTIs were active, in 57% only one NRTI was active and in 31% two or more NRTIs were active. The most frequently recommended regimen was the combination of boosted darunavir, etravirine and raltegravir (58% of the cases). The median number of active antiretrovirals in the rescue regimen was 3. In the primary endpoint analysis, omitting N(t)RTIs was non inferior to adding N(t)RTIs. Proportions of patients with Week 48 plasma HIV RNA <50 copies/mL were 64% and 66% in the groups without and with N(t)RTIs respectively. There was a significant higher number of deaths in the N(t)RTIs group however deaths do not appear to be related to the use of N(t)RTIs.

Take home message: Options clearly shows than in the context of a potent background regimen with three active antiretrovirals N(t)RTIs can be safely omitted without compromising treatment success.

The SECOND-LINE study also explored the importance of recycled N(t)RTIs but in a different scenario: patients failing their first N(t)RTIs+NNRTI regimen in low and middle-income countries [8]. In SECOND-LINE patients were naïve to boosted protease inhibitors and integrase inhibitors. Five hundred and forty one patients were randomized to received lopinavir/ritonavir plus two or three recycled N(t)RTIs or lopinavir/ritonavir plus raltegravir. Of 492 patients with baseline genotypic resistance testing 89% had ≥1 N(t)RTI resistance mutation and 60% had M184V plus one or more additional N(t)RTI mutations. Therefore SECOND-LINE is comparing fully active lopinavir/ritonavir plus partially active N(t)RTIs versus fully active lopinavir/ritonavir plus fully active raltegravir. Surprisingly in the primary endpoint raltegravir was “only” non-inferior to the control arm. Proportion of patients with less than 200/50 HIV-RNA copies/mL were 82.6/71.7% and 80.8/70.5% in the N(t)RTIs and raltegravir arms respectively. Detailed analysis based on NRTI resistance at baseline is still pending.

Take home message: SECOND LINE shows that lopinavir/ritonavir plus raltegravir is clearly an option after failure of an N(t)RTI+NNRTI regimen. However in this scenario it appears that if the boosted protease inhibitor is completely active, partially active N(t)RTIs might also do the job.
Conflict of Interests
Dr Arribas has received advisory fees, speaker fees and grant support from Tibotec, Janssen, Abbott, BMS, Gilead, MSD. He has received advisory fees and speaker fees from Viiv.

References:
5. Anderson M et al. Safety and Antiviral Activity of MK-1439, a Novel NNRTI, in Treatment-naive HIV+ Patients. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, abstract 100, 2013

Topical Conferences in 2013

May 10–11, 2013
2nd Asian Conference on Hepatitis and HIV
Beijing, China
http://www.virology-education.com/

May 14–17, 2013
7th INTEREST Workshop
Dakar, Senegal
http://www.virology-education.com/

May 30–31, 2013
9th International Workshop on HIV & Hepatitis Co-infection
Rome, Italy
http://www.virology-education.com/

June 2–4, 2013
8th International conference on HIV Treatment and prevention adherence, International Association of Physicians in AIDS Care (IAPAC)
Miami, FL, USA
http://www.iapac.org/

June 4–8, 2013
Toronto Canada
www.informedhorizons.com

June 18–21, 2013
6th SA AIDS Conference
Durban, South Africa
http://www.saaids.co.za/

June 26–27, 2013
8th International Workshop on Clinical Pharmacology of Hepatitis Therapy
Cambridge, MA, USA
http://www.virology-education.com/

June 27–28, 2013
8th International Workshop on Hepatitis C. Resistance & New Compounds
Cambridge, MA, USA
http://www.virology-education.com/

June 30 – July 3, 2013
7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS)
Kuala Lumpur, Malaysia
http://www.ias2013.org/

October 16–19, 2013
14th European AIDS Conference, European AIDS Clinical Society (EACS)
Brussels, Belgium
http://www.eacs-conference2013.com/

July 14–17, 2013
STI & AIDS World Congress 2013
Vienna, Austria
http://www.stiwienna2013.com/

October 21–23, 2013
The 2013 Australasian HIV/AIDS Conference
Darwin, Australia

December 3–6, 2013
6th International Workshop on HIV Persistence, Reservoirs and Eradication Strategies Conference
Miami, FL, USA
http://www.informedhorizons.com/persistence2013

December 8–12, 2103
Big Island, Hawaii, USA
www.informedhorizons.com
**Functional cure in HIV-infected infant**

A child whose mother had an unknown HIV-infection and had not received any ART during pregnancy had positive HIV-RNA and HIV-DNA in very early samples. 31 hours after birth triple therapy ART was started. Therapy was discontinued by caretaker at 18 months. At 24 months virus was undetectable by standard and ultrasensitive HIV-PCR and Western Blot was negative for reactive bands. Ultrasensitive HIV-DNA was however positive at 4 copies at 26 months. The child is considered to be functionally cured.

*Abstract 48LB CROI 2013, Atlanta Georgia.*

*Comment:* Until now only “the Berlin man” has been considered to be cured from HIV. It is debatable if functional cure is the most appropriate term that applies to this case. Will this case change the way we manage newborns with HIV-infected mothers? In cases where the mother received ART during pregnancy we have no reason the change the present guidelines. If the maternal infection is detected during labour triple ART therapy for the child should be initiated immediately in any case so despite being a very interesting case it will probably not affect the management of newborns with HIV-positive mothers.

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**New PEP guidelines**

The New York State Department of Health AIDS institute in collaboration with Johns Hopkins University Division of Infectious Diseases has issued new guidelines for HIV prophylaxis following occupational HIV exposure. A regimen consisting of tenofovir and emtricitabine in combination with raltegravir for four weeks is the recommended regimen. Testing is recommended after 4 and 12 weeks. Routine testing 6 months post-exposure is no longer recommended. Prophylaxis should be initiated as soon as possible and preferably within 2 hours.

*New York State Department of Health AIDS Institute: www.hivguidelines.org*

*Comment:* The suggested regimen is far better tolerated than previously recommended drug combinations. It is also reasonable to shorten the unnecessary follow up period that has been practised until now.

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**Cryptococcal meningitis and the initiation of ART (COAT study)**

In a study of cryptococcal meningitis (CM) in Uganda and South Africa patients were randomized to early initiation of ART within 2 weeks or deferred therapy until at least 5 weeks after diagnosis. Amphotericin B together with fluconazole was given for 14 days followed by fluconazole. The intention was to include 500 patients but the study was stopped by DSMB after 177 patients were included as mortality was significantly higher in the early treatment group with 40/88 deaths versus 27/89 in the arm with deferred ART.

*Conference on Retroviruses and Opportunistic Infections; March 3-6, 2013; Atlanta, Georgia. Abstract 144*

*Comment:* The optimal timing of ART in patients with CM has been unknown with conflicting results in smaller earlier studies. Based on the study results deferred initiation of ART must be recommended. It is however important to not to generalize these results to all opportunistic infections as earlier studies have shown a survival benefit with early initiation of ART in other opportunistic infections.

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**Treatment of acute HCV in HIV-infected men with Telaprevir in combination with peginterferon/ribavirin**

20 HIV infected MSM with acute HCV GT 1 infection were treated with a triple combination of telaprevir in combination with peginterferon/ribavirin for 12 weeks. Treatment was initiated within 6 months of acute HCV-infection. End of treatment response was 85% (17/20) and SVR24 was 79% (14/17). The authors concluded that this triple drug therapy is a substantive improvement in the treatment of acute GT 1 infection in HIV infected men.

*20th Conference on Retroviruses and Opportunistic Infections; March 3-6, 2013; Atlanta, Georgia. Abstract 156LB*

*Comment:* The conclusion is perhaps somewhat premature. High SVR is to be expected in the treatment of acute HCV also with standard therapy and it is unclear to what extent telaprevir contributes to improved outcome even though treatment was shorter than standard therapy. In the present study 11/20 patients had a favorable IL28 polymorphism (CC). To draw any firm conclusions a larger randomized study comparing different regimens is necessary.

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**A Tenofovir (TDF) intravaginal ring protects non-human primates against SHIV in vaginal challenge**

A polyurethane vaginal ring containing 130 mg of TDF made of hydrophilic elastomer showed complete protection in 6 female macaques that were challenged for up to 16 weeks with SHIV. In contrast 11/12 control animals became infected.

*20th Conference on Retroviruses and Opportunistic Infections; March 3-6, 2013; Atlanta, Georgia. Abstract 25LB*

*Comment:* Insufficient adherence has been the major reason for the negative results in VOICE and other PREP studies. Whether a vaginal TDF containing ring will improve adherence remains to be proven.

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**Sofosbuvir in combination with Simeprevir with or without Ribavirin in HCV GT 1 infection**

A total of 80 patients with HCV GT1 monoinfection with previous null response to standard therapy were included in a four arms randomized study of sofosbuvir and simeprevir with or without ribavirin for 12 or 24 weeks of therapy. Patients with metavir score of F0-F2 were included. In the patients who reached 8 weeks post therapy SVR 8 was achieved by 4/6 vs. 5/5 (66.7 % vs. 100%) in the patients treated for 24 weeks with or without ribavirin and in 26/27 and 13/14 (96.3 % vs. 92.9 %) in patients with a and without ribavirin.

*20th Conference on Retroviruses and Opportunistic Infections; March 3-6, 2013; Atlanta, Georgia. Abstract 155LB*

*Comment:* These preliminary results are extremely promising in a difficult to treat population and further results are eagerly awaited.
Telaprevir dosing: BID or TID?
In the Optimize study twice daily telaprevir was compared to the approved dosage of three times daily in treatment naïve GT 1 patients in combination with pegylated interferon and ribavi- rin (n=740). Triple therapy including telaprevir was given for 12 weeks followed by treatment with ribavirin and pegylated interferon. Duration of therapy was response guided with 24 weeks of therapy in patients with rapid viral response (RVR) and total treatment time of 48 weeks in patients without RVR. Patients were stratified for fibrosis stage and IL28 GT. There was no difference in outcome (SVR12) or safety and tolerability between the different arms.

AASLD 2012. Abstract LB-8

Comment: Twice daily telaprevir seems to be as effective as thrice daily telaprevir. BID therapy may improve adherence and quality of life.

Management of anemia
Patients with GT1 infection treated with boceprevir in combi- nation with ribavirin and pegylated interferon who developed anemia with HbG less than 10 g/dl were randomized to either erythropoetin or reduced dose ribavirin. Outcomes expressed as SVR was not different between the 2 arms. Only total ribavi- rin dose less than 50% of per protocol total dose was associated with worse outcome.

AASLD 2012. Abstract 154

Comment: With triple therapy including a protease inhibitor it does not seem as important as with standard therapy to main- tain a high ribavirin dose to achieve SVR. To reduce the ribavi- rin dose in these patients instead of initiating erythropoetin is an acceptable way of managing anemia.

Does food influence the result of Transient Elastography (TE)?
Patients with chronic hepatitis C in different stages of fibrotic evolution underwent TE after overnight fasting and 15, 30, 45, 60 and 120 minutes after a standardized liquid meal. Liver stiffness (LS) values increased 15 to 45 minutes after the meal and returned to pre-meal levels within 120 minutes. The increase in LS values was progressively more marked with increasing stages of fibrosis. The authors suggest that a fasting period of 120 minutes should be observed before TE.


Comment: TE is widely used to detect liver fibrosis. To improve the accuracy it seems reasonable to perform TE in standardized fashion after at least 120 minutes of fasting.

Should ART be initiated during primary infection?
366 patients with HIV seroconversion within 6 months were randomised to three arms; No treatment, 12 weeks of ART and 48 weeks of ART. The primary endpoints were CD4 decline to less than 350 or initiation of long term ART. Median follow up time was 4.2 years. The primary endpoint was reached in 61, 61 and 50% in the three arms. In the 48 weeks treatment arm the median time to the primary endpoint was 65 weeks longer in the arm without treatment and in the 12 weeks ART arm the difference was 27 weeks.


Comment: The delay until the primary endpoint with treatment compared to no treatment is slightly longer than the duration of treatment. This rather small difference is probably of minor clinical importance. The reasonable approach is continuous therapy once ART is initiated and perhaps all patients with primary in- fection or recent seroconversion should be offered ART?

High dose vitamins and HAART
3418 HIV positive patients were enrolled in a study of high dose versus standard dose vitamin supplementation. The study was performed in Tanzania in patients that initiated HAART. High doses of vitamin B complex, vitamin C and vitamin E were com- pared to standard levels of the recommended dietary allowance. The study was randomised and double blind. There was no dif- ference in mortality, CD4 count, viral load, BMI or haemoglobin levels. However, there was a significant increase of ALT in the group that received high dose supplement. The study was inter- rupted because of the increase in ALT.

Effect of high-dose vs. standard-dose multivitamin supplemen- tation at the initiation of HAART on HIV disease progression and mortality in Tanzania: a randomized controlled trial. JAMA. 2012 Oct 17;308(15):1535-44

Comment: No benefit with high doses of vitamins.

Heterosexual transmission of hepatitis C
The long term heterosexual partners of 500 HCV-positive, mo- noinfected individuals were studied in a cross sectional study. In HCV-positive partners genotype was determined and in geno- type/serotype-concordant couples sequencing was performed to determine the relatedness of virus isolates. Overall prevalence of HCV-positivity was 4% (n=20). In 9 couples there was con- cordant genotype/serotype and in three of these couples the vi- ruses were closely related. Based on 8377 person-years of follow up the maximum rate of HCV-transmission was estimated to be 0.07% per year.


Comment: These results confirm the low rate of heterosexual transmission of hepatitis C in contrast to reports on sexual trans- mission in MSM.

Conflict of Interests
Dr Flamholc has received honoraria as speaker and/or advisor from Abbott, Bioinvent, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck, Pfizer, Roche and Janssen.
Drug development against hepatitis C is an extremely dynamic field. At least 50 different direct acting antivirals (DAA) against the hepatitis C virus (HCV) are in clinical development and it is almost impossible to follow all the latest news for each compound. Every month we can read press releases presenting exciting data with cure rates close to 100% (suggesting that the only remaining question is when we will reach response rates above 100% and boosting stock values of the respective companies involved...). On the other side, unexpected funerals of promising new compounds or treatment strategies occurred quite frequently in recent years. The graveyard of anti-HCV DAAs burying billions of dollars of investments is impressive and it is more than likely that we have to face more (bad) surprises in the future.

Just two years ago in May 2011, the first two HCV protease inhibitors boceprevir and telaprevir were approved by the FDA. Shortly before, during the International Liver Congress in Berlin in April 2011, Anna Lok presented for the first time data from a phase II pilot trial showing cure of persistent HCV infection in 4 out of 11 patients treated with an IFN-free combination of an HCV protease inhibitor and an HCV NS5A inhibitor (published later in the New England Journal of Medicine [4] and confirmed by a separate trial performed in Japan [5]). Since then, various studies exploring a wide range of treatment strategies were presented during scientific meetings or in press releases confirming that it is indeed possible to eradicate HCV by a combination of DAAs without administration of type I interferons even in individuals with chronic hepatitis C. This development generated a lot of hope. Some colleagues even started to think moving to other research fields as the “hepatitis C game” seemed to come to an end rather soon. However, during recent months it became clear that it is unlikely that there will be a “one size fits all” therapy and that special populations might still require more intense treatment approaches. E.g. we had to learn from Gilead press-releases that a three months course of sofosbuvir plus ribavirin will likely be not sufficient for many HCV genotype 3-infected patients with liver cirrhosis.

Physicians treating hepatitis C need to be aware of the most important developments as knowledge about potential short-term and mid-term treatment options influences current treatment decisions: If treatment will be extremely easy in 24 months from now, why start a complicated therapy potentially being associated with severe side effects now? On the other hand, if the “magic pills” will not hold strong promises for every patient, can we afford to delay therapy? And if so, in which patients?

In a series of three articles I will try to summarize the emerging data on DAAs against HCV. Real-world studies on current triple therapy regimens data are discussed in this issue of the magazine. In the next issue most recent results of various IFN-free DAA therapy regimens presented at the International Liver Congress organized by EASL (April 24–28, Amsterdam) will be included. It is expected that several pivotal phase III data will be shown for the first time in Amsterdam. In the September issue I will then discuss challenges to implement the new therapies in current public health systems and address the role of preventive and therapeutic immunotherapies of hepatitis C including vaccination.
Five pivotal phase III studies on triple therapy of chronic hepatitis with PEG-IFNa, ribavirin and either boceprevir or telaprevir were published in the New England Journal of Medicine during the year 2011 [6]. Response rates in treatment naïve subjects increased by about 25–30% and by 3–4 folds in nonresponder patients. Most recommendations and guidelines consider previous relapser with some level of fibrosis or cirrhosis as ideal candidates for triple therapies as 70–85% will achieve a sustained virological response (SVR) [7,8]. However, cure rates are still very disappointing (<15%) in previous nonresponder with cirrhosis and other poor response factors. During the last two years various baseline and on-treatment parameters were identified as associated with SVR in triple therapy, which can be used to individualize therapy (Table 1). E.g., a patient with previous null-response, HCV genotype 1a infection and liver cirrhosis has certainly a very low chance to achieve a sustained virological response. Still, a PEG-IFNa/ribavirin “lead-in” phase may identify if the patient as a minimal IFN response which could justify an attempt of a protease inhibitor therapy.

Well-selected patient cohorts are treated in phase III trials usually excluding subjects with comorbidities. Moreover, hepatitis C registration studies included only a rather small proportion of patients with liver cirrhosis who are at most urgent need of therapy but who also may suffer most from therapy-associated side effects. Experiences from real-world settings were therefore eagerly awaited for triple therapy of hepatitis C.

In France, an early access program for boceprevir and telaprevir in patients with liver cirrhosis was initiated already in February 2011 (several months before final EMA approval). More than 600 patients were included in this so called “CUPIC” cohort within one year. Interim reports on the safety and efficacy of triple therapy in this “difficult-to-treat” population were reported during the last European and American liver meetings (e.g. Hezode et al., J Hepatol 2012; 56 (Suppl. 2): S4). Overall, treatment-related serious adverse events were much more frequent than in the registration trials and occurred in about 40–50% of patients treated with boceprevir or telaprevir. Approximately one quarter of patients discontinued therapy early during the first 16 weeks of therapy. Importantly, the French investigators even reported fatal cases (about 2% of all patients treated), mainly due to serious infectious complications. Anemia represented a very frequent side effect, which occurred both during boceprevir and telaprevir therapy. Grade 3 or 4 anemia was observed in about 10% of patients despite very frequent use of erythropoietin (56–66%) and blood transfusions were necessary in up to 15% of cases. However, despite all these challenging side effects, preliminary antiviral efficacy data were good and well in line with the phase III studies.

SVR data are expected to be presented during the International Liver Congress in Amsterdam in April.

**Table 1:** Triple therapy of chronic hepatitis C: factors being associated with SVR [6].

<table>
<thead>
<tr>
<th>Baseline factors</th>
<th>Response to previous therapy</th>
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<tbody>
<tr>
<td>Stage of liver disease (poorer responses in advanced fibrosis/cirrhosis)</td>
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<tr>
<td>HCV genotype (poorer responses in genotype 1a vs. 1b)</td>
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<tr>
<td>IL28b genotype (less important as in dual therapy)</td>
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<tr>
<td>Very high viral load</td>
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<td>LDL levels (telaprevir studies only)</td>
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</tbody>
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<table>
<thead>
<tr>
<th>On treatment factors</th>
<th>Response during PEG-IFNa/ribavirin lead-in therapy</th>
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<tbody>
<tr>
<td>Week 4 response during PI therapy (response guided total treatment duration based on response after 4 weeks of triple therapy)</td>
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<tr>
<td>Anemia during therapy (higher response rates in patients a &gt;3g/dl haemoglobin decline)</td>
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**Figure 1.** Schematic figure summarizing arguments to start treatment or to wait.
During the last American Liver Meeting in Boston, a large number of additional abstracts was presented showing first triple therapy experiences from several different countries. Most studies gave similar messages: antiviral efficacy of triple therapy seem to hold promises but side effects are more frequent than in the phase III studies and in particular anemia management is time consuming and costly. Infectious complications were a particular concern in cirrhotics. However, we still lack full publications for most studies and it is therefore difficult to draw final conclusions. In February 2013, we published our first experience for triple therapy regimens from Hannover Medical School in PlosOne [9]. Two main messages were drawn from this study: (i) more than half of the patients evaluated for protease-inhibitor therapy were actually not treated for a wide range of reasons including too advanced liver disease on the one hand and very early stages of fibrosis on the other. (ii) a careful patient selection is absolutely crucial to improve safety and efficacy of triple therapy. Management of side effects required enormous efforts and resources as patients were seen at least every two weeks and hospitalizations were required in almost 20% of patients during the first months of therapy. Interestingly, platelet counts <110x10^3/nl were associated with treatment failure or hospitalization suggesting that low platelets are a sensitive marker of too advanced liver disease where triple therapy can be particularly dangerous.

**Overall, the increasing number** of preliminary reports from real-world settings suggests that the safety profile of the triple therapy is poorer as compared with phase III trials. There is clearly an increased rate of SAEs in particular in patients with liver cirrhosis. Patients with compensated cirrhosis should be treated cautiously and infectious complications are a particular concern. Anemia is frequent and can be difficult to manage. Still, reasonably high rates of virologic response justify antiviral therapy but more factors such as platelet counts are needed to identify patients with poor chances of treatment success. Nevertheless, a large proportion of patients with chronic hepatitis C is not eligible for triple therapy highlighting the urgent need for alternative treatment options which should ideally be IFN-free. The advances in development of IFN-free treatment options which should ideally be IFN-free. The advances in development of IFN-free treatment regimens for chronic hepatitis C will be discussed in the next issue of the magazine!

**Conflict of Interests**

Honorary for consulting or speaking (last 5 years): Abbott, Abvie, Biolex, BMS, Boehringer Ingelheim, Gilead, ICS, ITJ/ Janssen-Cilag, Medgenics, Merck/Schering-Plough, Novartis, Roche, Roche Diagnostics, Siemens, Transgene, ViV.

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