HIV DRUG THERAPY GLASGOW 2016 • SATELLITE SYMPOSIUMS AT HIV GLASGOW 2016
REDUCED DRUG REGIMENS AT CROI 2017 • HBV REACTIVATION IN PATIENTS RECEIVING DAAS FOR HCV
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Dear Colleagues

Once again it is my pleasure on behalf of the editorial group to welcome you to the first issue of HIV & Virology News for 2017. We began publishing quarterly in 2011, making this our seventh volume.

As most of you know, the magazine is distributed at no charge to more than 15,000 physicians who are working in the field of infectious diseases in 13 European countries. Although we are financed by advertisements, the content of the journal remains totally independent of our advertisers; they have no influence whatsoever over what we publish. We encourage the free expression of personal viewpoints from all of our editors and contributors, even if those views are controversial. The positive response that the magazine continues to receive, and the fact that it is widely read by European clinicians and researchers in the HIV and hepatitis field, is very heartening. Our commitment is to develop the magazine further, and so we welcome your suggestions of topics or themes for future issues. You can contact the editorial office and share your thoughts with us at editor@hivvirology.com. HIV & Virology News is also available online at www.hivvirology.com.

The annual Conference on Retroviruses and Opportunistic Infections (CROI 2017) was recently held in Seattle, Washington. As usual, a great deal of valuable new data was presented. Although the past few years have seen a trend toward fewer and fewer conference presentations devoted to novel antiretrovirals and drug combinations, the pattern has been broken this year. Several promising studies of new combinations and new drugs were featured, including antiretrovirals with unique modes of action. As José Arribas discusses elsewhere in this issue, two of these presentations pointed out the surprisingly high relative risk of developing INSTI resistance mutation during maintenance monotherapy with dolutegravir. These data will most certainly be the final blow against the use of dolutegravir monotherapy, including its administration as a maintenance regimen. It continues to be recommendable to proceed step-by-step in testing dual therapy before monotherapy. The prospects definitely look better for the use of dual maintenance therapy with 3TC or rilpivirine given together with dolutegravir.

Another trend in HIV drug research appears to be the development of long-acting antiretrovirals for intramuscular and subcutaneous injection, and for oral administration. The first phase III trials (the ATLAS study) testing a long-acting two drug intramuscular regimen of cabotegravir and rilpivirine is currently recruiting participants, and more agents are on the way. A large number of patients continue to voice their desire to free themselves from a daily tablet regimen. PrEP is another attractive target for long-acting drugs. The issue of side effects certainly must be explored carefully, and one needs to take into account the slowly declining drug concentrations after treatment cessation or after a missed dose, all of which could present serious problems for long-acting agents. The development of such long-acting drugs is also in progress in the hepatitis C field. Imagine an injection of DAAs that is effective for three months—only one dose for a hepatitis C cure! That would open up a number of possibilities, such as in the treatment of difficult populations like active injecting drug users.

In addition to much other engaging information, this issue continues the coverage of HIV Glasgow 2016 begun in the previous number. Enjoy your reading!

Magnus Gisslén
Editor
At the end of October 2016, physicians and clinical investigators from around the world gathered in Glasgow (UK) to review current research and discuss implications for HIV management strategies. The Glasgow Congress is given every other year. They were all welcomed by Professor Andrew Phillips, Congress Chair, who at the Opening Ceremony promised them an interesting programme with many new findings.

At the Opening Ceremony, the traditional Joep Lange and Jacqueline van Tongeren Memorial Lecture was given by Dr Anthony S. Fauci. Ending the HIV/AIDS pandemic: Follow the science, was the title of his talk.

1,1 million AIDS deaths in 2015
Dr Fauci began this by presenting two articles written by him in 1981, for the Centre of Disease Control (CDC) weekly report.
– They were rejected for being too alarmist, and did not get published until next year, he told the audience.

In 1982, the second article of his – on Kaposi’s syndrome and opportunistic infections – was finally published in Annals of Internal Medicine.

– We did not call it AIDS then, we only saw the patients. They lived between 8 and 15 months after being diagnosed, Dr Fauci continued.

But the treatment evolved. He presented data on life expectancy for a 20 year old newly diagnosed with HIV in the 1980s and today:
– In the 80s, on no ART, life expectancy was approximately 12 years. Today – on ART – it is 53 years!

In 2015, 17 million individuals are globally on ART. This means that 8.8 million deaths have been averted since the year 2000, Dr Fauci underlined.

Current estimates says that at the end of 2015, globally 36.7 million people were living with HIV. There were 1.1 million deaths in AIDS 2015.
– That is a decline of 43 % since 2003.

But there were also 2.1 million new HIV infections in 2015.

WHO goal reached in Sweden
He continued by presenting what he called “a triad of pivotal ART studies” that have been crucial for treating HIV-infected individuals.
– The SMART study showed that episodic ART is inferior to continuous ART. HPTN 052 study found early ART reduces HIV transmission to uninfected sexual partners by 93 % – and the START study demonstrated that early ART reduces serious illness or death by 57 %.

The foundation for HIV treatment and prevention efforts is HIV testing. If test is positive, then the patient must be in care continuum, Dr Fauci underlined.

But data from CDC from 32 states and DC in the USA shows that 87 % of those with HIV infection are diagnosed, 75 % are linked to care, 57 % are retained in care and only 55 % are virally suppressed (Data from 2013).
– Sweden is the first – and so far the only – country that has achieved the WHO goal of 90-90-90 continuum of HIV care targets. As I put it in an article in the Washington Post: There can be no more excuses – we have the tools to end the HIV pandemic!

Following the science
There are, according to Dr Fauci, two main remaining scientific challenges for HIV research: Addressing HIV persistence, and the development of a safe and effective preventive vaccine.
– Persistence is the stumble for the cure. The HIV reservoir cause viral rebound when treatment is interrupted.

The first sign of efficacy (31 %) in a HIV vaccine clinical trial came with RV144.
-vaccination with ALVAC and AIDSVAX in Thailand. Dr Fauci told the audience that the trial HVTN 702, a modified RV144 prime boost regimen, is now ongoing in South Africa and will enrol 5,400 men and women, 18 - 55 years of age, at risk of HIV.

- There is a theoretical assumption that broadly neutralizing antibodies induced by a vaccine will offer protection against acquisition of HIV.

When summarising his lecture, Dr Fauci said that treatment + non-vaccine prevention + vaccine means implementation of proven scientific tools.

- This can lead to a durable end of the HIV/AIDS pandemic – and that is following the science!

**Increased prevalence of comorbidities**

EuroSIDA is a prospective cohort which collects data from more than 22,000 patients in 35 countries. Ms Sara Lopes presented a study on ageing and the evolution on comorbidities among HIV patients in the EuroSIDA cohort.

- The objective was to characterise the prevalence of non-AIDS related comorbidities and risk factors for the development of renal impairment, bone fractures and cardiovascular events over time, she explained.

9,544 patients were included in 2006 and 11,504 patients in 2014.

- We found that between 2006 and 2014 the HIV population aged. Patients 50 years of age or older are now almost half the population, Ms Lopes said.

The study found an overall increased prevalence of non-AIDS related comorbidities and associated risk factors, particularly for patients that are 50 years or more.

- Careful HIV management, including regular screening and monitoring of the major comorbidities and adequate selection of ART, could lead to a continuous improvement of health outcomes and quality of life in people living with HIV, Ms Lopes concluded.

**A geriatric-HIV scenario**

Successful cART has led to an improvement in survival and an increase in the average age of HIV patients. According to a modelling study, in 15 years multi-morbidity in HIV-positive patients will be the norm.

- In this context, frailty, geriatric syndrome and disability would be relevant outcomes, said Davide De Francesco.

He presented a study that aimed to estimate the level of frailty and its implication for HIV care in Italy up to 2030.

- In 15 years time those over 65 years of age in the HIV population will increase from 4 % to 37 %, Mr De Francesco underlined.

The projected prevalence of clinical outcomes made by the authors shows that, by year 2030, 30 % of HIV patients would report geriatric syndrome and 34 % would have disability.

- The increasing numbers of older patients depict a “geriatric-HIV” scenario. This model suggests that in the early future HIV care will need to draw a multidimensional geriatric assessment, Mr De Francesco stated.

He pointed out, as a limitation, that the model does not simulate the effect of lifestyle factors (diet, exercise etc.) on the development of frailty.

**Cooperation with geriatric medicine and primary care needed**

Another mathematical model on ageing HIV in Italy was presented by Mikaela Smit. The study’s aim was to forecast the future age structure and non-communicable disease (NCD) burden amongst HIV-positive patients on ART.

She reported that HIV patients in Italy are ageing rapidly and will suffer from an increasing NCD burden.

- Particularly with cardiovascular disease and chronic kidney disease.

Trends are similar to the Netherlands, with the exception that chronic kidney disease is expected to contribute a greater burden by 2035 in Italy than in the Netherlands.

- To ensure the best overall long-term health, several strategies are important: Optimal selection of ART and co-medication choice, multi-disciplinary patient management – and an enhanced communication between HIV specialists, geriatric medicine and primary care must be developed, Ms Smit concluded.

**Costs increase with age**

Data on excess non-AIDS related financial burden in people living with HIV are scarce. Dr Eva Wolf presented a study with the objective to compare a German HIV infected population to a matched, non-HIV cohort from the general population in Germany.

The prevalence of non-AIDS related comorbidities and the types of non-AIDS related costs to the German health system were investigated.

1,969 HIV-infected patients met the inclusion criteria and were matched with 3,938 individuals of the non-HIV cohort.

- Overall, yearly costs per patient not related to HIV treatment are higher in an HIV infected population, compared to a matched general non-HIV population in Germany, Dr Wolf said.

These higher costs potentially reflect the higher burden of specific comorbidities observed in the HIV population. Costs tend to increase with age for both groups, but are generally higher for HIV patients, particularly when aged 60 or more.

- Therefore, an adequate HIV management – including regular monitoring, screening for comorbidities, and optimal ART selection – remain critical to achieve continuous improvement of health status of people living with HIV. Also to reduce the burden for the German healthcare system, Dr Wold summarised.
Shorter survival in patients with lymphoma

Survival of HIV-associated lymphoma (Hodgkin and non-Hodgkin) has considerably improved, but the condition still represents a major cause of morbidity and mortality. Data comparing clinical outcomes in HIV-lymphoma with those occurring in the general population are limited and still controversial.

Dr Antonella Cingolani presented a study with the objectives to evaluate overall survival of lymphoma in HIV-infected population, compared to HIV-uninfected. Also to identify the role of HIV infection as predictor of mortality according to lymphoma type.

– A poorer overall survival after a diagnosis of lymphoma was observed in HIV-infected, compared to HIV-uninfected individuals in the unadjusted analysis, she reported.

A shorter survival of HIV-infected people was confirmed for Hodgkin’s disease after adjusting for calendar year, age, standard chemotherapy and lymphoma stage.

– For non-Hodgkin’s lymphoma and diffuse large B-cell lymphoma, HIV status was not longer associated to, or carried an increased risk for, death after adjusting for type of treatment (rituximab) and prognostic index. This suggests a potential detrimental role on survival of more aggressive disease and different chemotherapeutic approach in HIV-infected people, Dr Cingolani said.

She added that unmeasured confounding due to difference in life-style, or other factors not measured in the study, could not be ruled out.

Should she start PrEP?

In an interactive session, Prof Jean-Michel Molina talked about implementation and issues in pre-exposure prophylaxis (PrEP). He started by asking a question, on which the audience had to vote: “Have you read the IAS-USA 2016 treatment and prevention guidelines published in JAMA?”

24 % answered yes, 57 % no and 19 % answered they did not know of these guidelines.

Prof Molina continued with a case, Mrs A, a 30 year old woman married two years ago.

– Her husband recently tested HIV-positive in a community-based screening, while she tested negative. Husband’s CD4 count is 830 mm3, and he has not started ART yet. She worries about getting infected, and they have used condoms since he learned he was infected. She would like to conceive, and is ready to follow your advice.

The audience then voted between 6 alternatives, and 43 % (the majority) voted for the option that she should start PrEP and her husband should start ART. 41 % voted for continuing using condoms while he starts ART.

Dr Roy Gulick in the panel commented:
– Her husband should start ART. His viral load is low, so results should come within a month. Since she wants to get pregnant, she then might stop using condoms.

This caused a discussion on treatment as prevention (TasP) and PrEP. Prof Molina showed data from the HPTN 052 study that demonstrated that TasP is effective for discordant heterosexual couples.

Part of a risk-reduction strategy

What happened to this couple? 6 months later the husband has started ART with almost perfect adherence. He has a plasma viral load of 60 copies/ml and a CD4 cell count of 956/mm3. She has not started to use PrEP; they continue to use condoms.

– She wants a baby now, but is concerned about the risk for her and the baby. They come together to seek your advice, Prof Molina continued.

Again the audience was asked, and the majority (53 %) voted that she should start PrEP with daily TDF/FTC to reduce her risk of being infected.

– That is probably the most safe alternative, said Prof Pedro Cahn, Co-Chair for the Session.

He added that in real life we don’t see many parents coming to ask permission to become pregnant...

– Would it be an option to ask her to wait a little longer, until husband is fully undetectable, asked Prof Peter Reiss, the other Co-Chair.

Dr Gulick pointed out that this depends on the patient’s view of risk.

– With husband on 60 copies, there is a risk, however small, he said.

– There is never 0 or 100 in biology. If she wants to be as sure as possible, PrEP is the best option, Prof Cahn commented.

After one more case, Prof Reiss summarised HIV prevention in clinical settings.

– Persons at high risk of HIV should be prioritised for delivery of interventions such as individualised face to face counselling on risk reduction and PrEP, he said.

Daily TDF/FTC is recommended as PrEP for persons at high risk based on background HIV incidence, and/or HIV seronegative partner of HIV-infected person who does not have viral suppression.

– There is a need to rule out HIV-infection before starting PrEP – ideally with a combined Ab-Ag test and regularly thereafter (1 - 3 months).

PrEP should be a part of an integrated risk-reduction strategy, and ongoing use of PrEP should be guided by regular risk re-assessment, were Prof Reiss final comments.

Testing at home

Prof Patrick Sullivan gave a lecture on STI testing and PrEP. He began by showing the use of PrEP in US men who has sex with men (MSM) by year 2012 - 2016.

– It has gone from 1.1 % to 8.3 % – so we’re nowhere near the percentage we need, he said.
So how do we increase scale? Prof Sullivan continued by presenting some ideas on this:

– Integration into routine clinical encounters, self-service options such as mobile phone apps, home delivery of commodities and reminder systems for routine screening.

He described at-home testing. Three kits for HIV, one for STI and two for home PrEP initiation and follow-up are currently under study.

– These systems are acceptable to US MSM and their providers. Return rates for specimens are high, and sample quality is adequate, Prof Sullivan stated.

Mobile apps are highly acceptable as portals for distribution of at-home test kits, condoms and lube, he underlined.

– Further work is needed to assimilate home testing into US payment systems, was Prof Sullivan's last statement.

Ways to dispense ART outside the clinic

Dr Helen Bygrave talked about differentiated ART delivery, and started with the challenges African women face: Monthly visits to collect ART, cost of transport, long queues at the clinic for a 2 minute consultation – which means leaving family and farming activity at home.

– What is differentiated ART delivery, and how can it help this lady?

Dr Bygrave explained that there is a need to separate clinical consultation from a refill. She quoted WHO Guidelines, that recommends less frequent (3 - 6 months) clinical visits for people stable on ART, as well as less frequent medication pickups for this group of patients.

– WHO also states in their guidelines the importance of task-shifting. Trained and supervised community health workers can dispense ART between regular clinical visits.

She presented four examples of this. The first, “individual facility ART refill”, was from Malawi with a 6-monthly (moving to annual) clinical visit with a nurse.

– The second is “individual community ART refill”, taking decentralisation one step further with community pharmacies, Dr Bygrave continued.

Then there is health care worker led group refill – so called “Adherence clubs”, in South Africa and Kenya.

– Finally there are patient led community ART groups that consists of self-forming groups of 4 - 12 stable adults. They meet every three months and check they all are healthy. Then one of them goes to collect all the drugs. Once a year they all go for a clinical check-up and viral load. These groups are to be found in several African countries.

Dr Bygrave ended her talk by pointing out that this is not only quality patient centred care – it is also cheaper care.

– There are patient costs for time and transport to consider – but they are not taken into account in studies.

EACS guidelines address comorbidities

Helping the HIV physician through the challenges of comorbidities in decision making, was the topic for a lecture given by Prof Edouard Battegay. He started by pointing out that multimorbidity is the most prevalent constellation in healthcare.

– Half of the population have one or more disorders! In 9 times out of 10 one of them is hypertension, he said.

In ageing HIV patients, there are multimorbidity clusters. These include vascular risk factors and diseases, heart- and pulmonary disease, major mental disorders, pain, frailty and a broad array of various other medical diseases and conditions, Prof Battegay said.

– The degree of complexity increases exponentially with each diagnosis and interaction. EACS Guidelines, updated October 2016, address this.

He showed how EACS Guidelines are divided in drug-drug interactions, drug-drug-disease interactions and disease-disease-social interactions.

Prof Battegay continued by talking about depression.

– It is a barrier to adherence to HIV drugs.

In a complex patient, describe the pattern and identify medical needs and available knowledge. Then prioritise. Reconcile adverse drug-drug-interactions and find the most suitable, best acceptable therapeutic strategy, he advised.
THE MEETING WILL INCLUDE INTERNATIONAL KEY-NOTE SPEAKERS, POSTER SESSIONS AND SEVERAL SATELLITE SYMPOSIA. THERE WILL ALSO BE AN EXHIBITION AREA IN DIRECT CONNECTION TO THE PLENARY HALL.

SCIENTIFIC AND PROGRAM COMMITTEE 2017:
Magnus Gisslén, Sweden, Soo Aleman, Sweden, Anders Blaxhult, Sweden, Francesca Chiodi, Sweden, Olav Dalgard, Norway, Anne Ma Dythol-Riise, Norway, Leo Flamholc, Sweden, Martti Färkkila, Finland, Jan Gerstoft, Denmark, Magnus Gottfredsson, Iceland, Annika Karlsson, Sweden, Magnus Lindh, Sweden, Arild Maeland, Norway, Helene Mens, Denmark, Matti Ristola, Finland, Veronica Svedhem Johansson, Sweden, Matti Sällberg, Sweden, Anders Sönnerborg, Sweden, Ola Weiland, Sweden, Nina Weis, Denmark, Aylin Yilmaz, Sweden

CONFIRMED SPEAKERS 2017 SO FAR:
Aftab Ansari, USA, Francesca Chiodi, Sweden, Paola Cinque, Italy, Jan Gerstoft, Denmark, Christophe Hézode, France, Malin Maini, UK, Javier Martinez-Picado, Spain, Bart Rijnders, The Netherlands, Johan Sandberg, Sweden, Irini Sereti, USA, Susana Valente, USA and more to come...

MORE INFORMATION AND REGISTRATION, VISIT:
www.hivnordic.se
Communicate medical situation, dilemmas and resolution to the patient in order to allow for shared decision-making. Remember that the EACS guidelines were one of the first to systematically address comorbidities in a specific disease, Prof Battegay finished his lecture.

The most prevalent comorbidities
A study that had investigated the evolution of chronic non-HIV related diseases in a French prospective cohort 10 years apart (2004 and 2014), was presented by Dr Charles Cazanave.

– We found that 72 % of patients achieved CD4 cell counts in 2014 – versus 44 % in 2004, Dr Cazanave said.

He also reported that prevalence of all comorbidities significantly increased between 2004 and 2014.

– Dyslipidaemia and hypertension had the highest increases, and are the most prevalent comorbidities. Comorbidity related medication also increased significantly from 2004 to 2014, except for anti-depressant drugs.

A careful HIV management, including renal monitoring and screening of the major comorbidities, according to current recommendations and adequate selection of ART could lead to an early management of these comorbidities.

– In this context, effective ART options that balance HIV outcomes with fewer long-term impact on cardiovascular, bone and renal events would be beneficial for patient’s care and treatment – in addition to a good control of risk factors, particularly through an improvement of lifestyle, was Dr Cazanave’s conclusion.

Huge gaps in cascade of care for HCV
In a session on co-infections and malignancies, Prof Andri Rauch talked about HCV therapy – what have we achieved, and what are the remaining challenges?

He said that WHO has set a target of 90 % reduction in new cases for 2030.

– The move from interferon to direct-acting-antivirals (DAAs) means that a huge step has been taken forward in treatment eligibility. Cure rates have been much improved – they are from 90 % and up for DAAs, for interferon they were 45 - 50 %, Prof Rauch underlined.

But there are still challenges. Treatment-experienced patients with cirrhosis do not have the same good results, and difficult-to-treat patients also includes those with renal failure.

– Another challenge is that delayed treatment because of late diagnosis or reimbursement restrictions increases the risk of liver-related events.

Comparing HCV and HIV in the cascade of care shows there are huge gaps for HCV.

– High costs for drugs is probably the biggest challenge, he stated.

Great potential for TasP
Prof Rauch summarised the achievements and challenges by using the goals of HCV therapy. The first of these is to cure HCV infection.

– The achievement is that there has been great improvements in treatment efficacy. The challenge is that there are a few difficult-to-treat patients.

Second goal is to minimise adverse events – the achievement is great improvements in tolerability. Here there are no challenges.

– Third goal is to provide universal access to therapy. Here there has been no achievements – barriers are due to access, costs and reimbursement restrictions.

The final goal is to prevent HCV transmissions. There is a great potential of treatment as prevention (TasP), but stabilisation in high-risk behaviour combined with an increase in treatment uptake is required to curb the HCV epidemic among HIV-infected MSM.

– If this can be achieved, TasP can contribute to reaching WHO elimination targets in 2030, Prof Rauch said.

Therapeutical vaccines for HPV in development
Human Papillomavirus (HPV)-associated infections and lesions are more frequent, and their outcome more severe, in persons with HIV, said Dr Deborah Konopnicki.

– 30 % of all cancers from HPV occurs in men, she stressed.

HIV-positive patients have a higher prevalence and incidence of HPV infection. They also have higher prevalence and incidence of precancerous lesions. Among all cancer diagnosed in HIV-patients, 15 % are HPV-related, Dr Konopnicki continued.

Seven studies on HPV preventive vaccine in HIV-positive persons have shown good immunogenicity and anamnestic response, good safety and no deleterious effects on CD4 levels, nor on viral control.

– Preventive vaccine should be proposed to persons living with HIV as primary

Charles Cazanave
Deborah Konopnicki
and secondary prevention strategies.

cART has impact on HPV – but it takes some years before this benefit is seen.

She summarised by stating that implementation or improvement of HPV-related cancer screening should be part of HIV management.

– And therapeutical vaccines are in development. In the future, they could contribute to less ablative therapy for HPV-associated lesions, was Dr Konopnicki’s last statement.

The most effective cancer prevention

Non-AIDS defining cancers have increased. Cancers are a common cause for mortality and disability in HIV, said Prof Jean-Philippe Spano.

There are several reasons for this. The first is that HIV populations continue to age, and they have high prevalence of cancer risk factors, such as smoking.

– Quitting smoking is one of the most effective prevention measures, Prof Spano said.

There may also be inadequate screening programmes.

– For screening guidelines, some factors remain useful: Age, CD4, viral load, cART and oncogenic virus, he underlined.

Early diagnosis and cART reduce risk of NHL and HL

The objective for the D:A:D study was to identify risk factors associated with developing non-Hodgkin’s lymphoma (NHL) or Hodgkin’s lymphoma (HL) in HIV-positive people.

– It found that NHL incidence was associated with lower current CD4, and higher current and historical exposure to viral replication. This indicates that ongoing viral replication may play a part in NHL development alongside current immunodeficiency, said Ms Leah Shepherd.

HL incidence was elevated in those with current-immunodeficiency, but current and historical exposure to uncontrolled HIV replication were not associated. Factors involved in pathology of HL are less clear.

– Preventive measures should include identification and management of persons with HIV to minimise exposure to uncontrolled viremia and advanced immunodeficiency. Our results highlight the importance of early diagnosis and early cART initiation, Ms Shepherd concluded.

Study on resistance patterns for INI

Integrase inhibitors are the latest antiretrovirals introduced in clinical practice and are becoming widely used. The integrase inhibitors (INI) raltegravir, elvitegravir and dolutegravir resistance have been extensively studied in vitro and in clinical trials with a limited number of failures.

– There is a need to get more data about resistance to compounds of this class in the clinical setting, said Prof Anne-Geneviève Marcelin.

She presented a multicenter, observational study with the primary objective to characterize resistance patterns in case of virological failure to INI-based regimen in a clinical setting from the French ANRS network. Secondary objectives were to identify factors associated with selection of INI resistance mutations, and to identify new INI associated resistance mutations.

– A large cohort of 439 patients failing INI-based regimens have been followed in hospital clinical care. Inclusions are still ongoing until 31/12/17, and 1,000 patients are expected, Prof Marcelin told the audience.

Resistance robustness of dolutegravir confirmed

Among the patients followed so far, 36 % harboured viruses with at least 1 INI resistance mutation, Prof Marcelin continued.

– That is close to the previous result of 39 % failing raltegravir-based regimen, shown by Fourati et al. 2015.

Among patients failing to raltegravir, 32 % harboured a virus resistant to raltegravir. Among patients failing to elvitegravir, 41 % harboured a virus resistant to elvitegravir.

– We also observed a high level of cross resistance between raltegravir and elvitegravir, she continued.

Among all patients failing to dolutegravir (as the first INI, or in patients previo-
usly exposed to raltegravir or elvitegravir containing regimen), 18 % harboured a virus resistant to dolutegravir once or twice per day.

– However, in patients failing to dolutegravir when used as first INI (i.e. INI naive patients), no major resistance to INI was detected at failure. This confirms resistance robustness of dolutegravir, Prof Marcelin concluded.

**Monotherapy a promising treatment option**

DOMONO is a non-inferiority clinical trial investigating dolutegravir monotherapy in virologically suppressed HIV-1 infected adults. The study was presented by Prof Bart Rinjders.

– cART has been standard for 20 years. But is this really needed in 2016? Monotherapy means reduced toxicity, reduced costs and smaller pills he started by saying

DOMONO is a randomised open label multicenter trial. Dolutegravir was given as monotherapy 50 mg for 48 weeks with or without a meal.

– If HIV-RNA became detectable at any level over 20 copies/ml, the patient is instructed to take dolutegravir with a meal, Prof Rijnders explained.

He told the audience that the study found that in patients selected on virological, immunological and good compliance criteria, switching to dolutegravir monotherapy is a promising treatment option.

– However, external validity outside clinical trial remains to be demonstrated. 2 of 85 patients had virological failure at week 24, and 4 of 96 patients on dolutegravir within the available follow-up had virological failure overall so far.

Prof Rijnders underlined there was little – if any – loss of future treatment options.

– Longer follow-up is needed for more definite conclusions, he ended his talk.

And with that, *HIV & Virology News* also ends the report from Glasgow.

**Per Lundblad**
Senior writer

(Per Lundblad is a Journalist specialising in medical subjects and Senior writer for *HIV & Virology News*. He is employed by the publisher of the Magazine, Mediahuset i Göteborg AB. He has no other affiliations with, or involvement in, any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in his articles.)
Five satellite symposiums were held at the Congress in Glasgow, and HIV & Virology News sat in on three of them.

A new backbone to our HIV story, was the title of a satellite symposium sponsored by Gilead Sciences. Dr Jonathan Schapiro was the Chair.

The first Speaker was Dr Chloe Orkin. She said that for 20 years triple therapy has been underpinned by a dual nucleoside reverse transcriptase inhibitors (NRTI) backbone.

– Although the dual NRTI backbone has delivered durable viral suppression, it has also been associated with toxicities, she pointed out.

Dr Orkin presented an overview of studies on NRTI-reducing therapies, and their outcomes in comorbidities. So far, they have told us that triple therapy, with a dual NRTI backbone, remains the standard of care.

– We need better powered studies with correct comparators, longer follow up – most of those we have are for 48 weeks only – and more subanalyses for adverse events and toxicities, Dr Orkin said.

Advancing clinical practice with the backbone

Dr Andrew Ustianowski then talked about tenofovir alafenamide (TAF). He pointed out that TAF has shorter half-life in plasma and is accumulated in cells, so therefore less drug is needed.

He presented several studies that show that TAF has durable viral suppression, less impact on kidneys and bone, and is well tolerated.

– It is important to remember that these are data from studies. So for the future, we also want to see if it is possible to experience the same results in everyday clinical practice, Dr Ustianowski said.

Prof Jürgen Rockstroh then talked about Descovy (emtricitabine and TAF) backbone as part of triple therapy in an everyday clinical setting. He presented four different clinical cases, that were all shifted to treatment with Descovy.

– All patients should have proactive treatment reviews to ensure long-term health. Real-world clinical experience reflects the efficacy and tolerability of Descovy based treatments. We are going to see a lot of it in the next 10 years, Prof Rockstroh summarised.

Barriers to address mental health

UNAIDS 90-90-90: Helping patients stay the course, was a satellite symposium sponsored by MSD, and Dr Mark Nelson was the Chair.

In his welcoming address, Dr Nelson talked about the need to individualise the treatment to the patient.

Dr Brian Pence described mental health concerns in people living with HIV. He presented data that showed that HIV-infected women had much higher percentage of childhood abuse – sexual and physical – compared with national sample. A meta-analysis showed that depression affects adherence to ART in a negative way.

There are barriers to addressing mental health concerns among people living with HIV, and Dr Pence described some of them.

– There is a lack of mental health expertise in HIV care settings, and stigma remains around the topic of mental health services.
He described a model of care that included a depression care manager.

- This person can follow-up patients, and assess how they are doing – and give decision-support to the HIV care manager. A psychiatrist supervises, and give quality assurance.

"We may be the only place of reference"

Physicians and health care providers must be aware of the social determinants of the health of their HIV positive patients, said Mr Moisés Agosto-Rosario.

- Encourage patient-centered communication that incorporates every point along the HIV care continuum – and closely work with patient’s health navigator, case manager and or community health worker, he continued.

Physicians as well as their staff must learn to be culturally competent on the communities they serve, Mr Agosto-Rosario added.

Our HIV positive patients are experiencing a cultural shift in behaviours, societal norms, technologies, recreational drug use and changing HIV stigmas, said Dr David Stuart.

- Let us be aware of their holistic needs – invite them to disclose to us, and be confident to refer to appropriate support. In a complicated and changing gay world, we may be the only place of reference, as our patients go through changing seasons of sexual and general well-being, he said.

In his closing comments, Dr Nelson underlined that the patients put their trust in us.

- Ask your patient what they want from their therapy, he stated.

Drug-drug interactions influence choice of ART

In a satellite symposium sponsored by Viiv Healthcare, different regimens in challenging scenarios were discussed. Dr Anton Pozniak was the Chair.

80 people are diagnosed with HIV every day in the EU. Two thirds of these are men. 47% are diagnosed late and are at a higher risk of dying, he said.

Prof José Arribas continued by presenting a case – an older female patient with multiple comorbidities. During the case presentation, the audience was invited to participate with voting for ART regimen.

- A range of ART regimens are recommended for use in HIV-infected women, Prof Arribas stated in his case summary.

Drug-drug interactions influence choice of ART, particularly in patients with comorbidities.

- And a range of new ART regimens have demonstrated efficacy as switch options in virologically suppressed patients, he said.

Offer substitution therapy to injection drug user

Prof Daniel R. Kuritzkes then presented a case on initiating ART in a male patient with advanced HIV disease.

- ART should be started as soon as possible in most patients presenting with an acute opportunistic infection, Prof Kuritzkes underlined.

A boosted PI or dolutegravir should be used as empiric ART while awaiting results of resistance testing.

- TDF/FTC or TAF/FTC should be used as the NRTI backbone while awaiting results of HLA-B*5701 testing, and HBV testing, he continued.

Treatment can be modified, if desired, once test results are available.

Prof Fiona Mulcahy presented the third and last case: A young female patient at risk for nonadherence. She was an injection drug user.

- Patients for whom adherence is a concern should be offered support when starting ART. Injection drug users should be referred for opioid substitution therapy and harm reduction measures where possible, Prof Mulcahy stressed.

Drug-drug interactions influence choice of ART, eg: Between oral contraceptives and boosted PIs, EVG/COBI, NNRTIs – and between methadone and boosted PIs, NNRTIs.

- ART is recommended for all HIV-positive patients, including pregnant women. Women planning – or becoming – pregnant on ART should maintain existing therapy unless contraindicated, Prof Mulcahy summarised.
Symposium on HIV eradication in Aarhus

How can HIV be eradicated – current strategies and challenges was the title for a symposium with several international Speakers, given January 31 in Aarhus, Denmark. The scientific content of the Meeting was organised by Dept of Biomedicine, Aarhus University and Dept of Infectious Diseases, Aarhus University Hospital. The Meeting was founded by an unrestricted educational grant from Gilead Sciences Nordic.

Doctors, Nurses, Researchers and students with an interest in HIV were invited, and they were greeted welcome by Prof Lars Østergaard.
– I want to thank the moderators for putting together the program, the international lecturers who travelled to Denmark and Gilead for supporting the Meeting, he said.

Various forms of CD4 T-cell death
The first Speaker was PhD Giliad Doitsh, San Francisco.
– The hallmark of AIDS is the progressive depletion of T-cells over time. But what is the mechanism by which HIV-1 depletes CD4 T-cells in human lymphoid tissues? This has been an open question over the decades, Mr Doitsh said.

Lymphoid tissues contain more than 98 % of the body’s CD4 T-cells, and are the primary site of HIV replication in HIV-infected patients.
After describing the HIV life cycle, he said that HIV may induce various forms of CD4 T-cell death.
– It could be via apoptosis, a programmed process of cell death that avoids eliciting of inflammation. Or via pyroptosis – a highly inflammatory form of programmed cell death, mediated by inflammasome-associated caspase-1, Mr Doitsh explained.

The mode of HIV-1 spread determines the outcome
VX-765 (an orally absorbed prodrug of VRT-043198, a potent and selective inhibitor of caspases belonging to the ICE/ caspase-1 subfamily) protects CD4 T-cells from depletion following R5-tropic HIV infection of humanized mice.
– It also dramatically reduces the levels of IL-18 in blood of HIV-infected humanized mice. Also important is that levels of viremia are similar in VX-765 and vehicle treated mice, indicating that the effects of VX-765 on CD4 T-cell recovery can not be explained by an antiviral effect of VX-765, Mr Doitsh continued.

These findings could open the door to an entirely new class of “anti-AIDS” therapies, that act by targeting the host rather than the virus.
– By altering the host response to tolerate the virus, rather than suppressing its replication, VX-765 or related drugs may mimic the evolutionary strategy observed in natural hosts – where a stable equilibrium has been established between viral growth and host survival, he said.

In his summary, he stated that the mode of HIV-1 spread determines the outcome form of cell death.
– Cell-to-cell spread of HIV-1 is required to deplete non-permissive lymphoid CD4 T-cells via capase-1-dependent pyroptosis. Infection with free HIV-1 particles causes the small fraction of permissive cells to die via caspase-3-dependent apoptosis, Mr Doitsh finished his lecture.

Not just an academic dilemma
There are two theories to explain residual viremia in patients on ART: Residual viremia represents ongoing replication cycles (infection of new cells) that continue at low levels despite ART – or ART stops all virus replication, and residual viremia reflects virus release from stable reservoirs due to cellular reactivation, said Dr Alexander Pasternak, The Netherlands.
– This is not just an academic dilemma. A number of HIV eradication strategies are based on purging the virus from latency by induction of virus production from latently infected cells. If infection of new cells is completely inhibited, such strategy
will result in death of productively infected cells - and eradication of HIV, Dr Pasternak pointed out.

However, if infection of new cells is not completely inhibited, such strategy will result in further dissemination of HIV reservoir, instead of virus eradication, he added.

Unspliced RNA a marker of active reservoir
The only way to know if a patient is cured is to stop ART, and Dr Pasternak said that is a tough decision for a clinician to take.

– For the improved design of strategies towards HIV-1 functional cure, it is important to identify biomarkers that could predict the duration of post-treatment virological control.

He said that cell-associated HIV-1 unspliced RNA level independently predicts both time to virological suppression and time to virological rebound in patients treated with temporary early ART. Cell-associated HIV-1 multiply spliced RNA independently predicts disease progression (CD4+ T-cell loss) after interruption of early ART, while unspliced RNA was not predictive.

– It looks like reactivation of HIV after therapy is interrupted and subsequent CD4+ T-cell loss are driven by different mechanisms.

HIV DNA is a marker of total reservoir (mostly defective).

– Unspliced RNA is a marker of active reservoir. It overestimates, but might correlate with functional reservoir. Multiply spliced RNA is a marker of “hyperactive reservoir” – cells with high multiply spliced RNA levels, a subset of active reservoir. The relative size of this “hyperactive reservoir” may drive HIV pathogenesis, determining the rate of CD4+ T-cell loss, was Dr Pasternak’s summary.

A major obstacle
Lymphoid organs are the primary anatomical compartments for HIV replication and spreading. Lymph node (LN) PD-1 cells (cells that express programmed cell death) and T follicular helper (Tfh) cells are enriched in inducible replication competent and infectious HIV in treated aviremic HIV-infected subjects, said Prof Matthieu Perreau, Switzerland.

– LN PD-1+/Tfh cells serve as the major source for active and persistent virus transcription after long-term ART. And they support the existence of persistent HIV-1 replication during ART, he stated.

LN PD-1/Tfh cells therefore may represent a major obstacle for HIV functional cure or eradication.

– This provides the scientific rationale for the development of therapeutic intervention targeting PD+/Tfh cells through armed anti-PD-1 antibodies, Prof Perreau concluded.

HIV-1 infected cells are highly glycolytic
Natural HIV controllers possess strong and efficient HIV-specific CD8 T-cell responses, said Prof Asier Sáez-Cirión, France.
- HIV-1 infection of CD4+ T-cell subsets is dependent on intrinsic properties of these cells, CD4+ T-cell subsets have different metabolic states that are also differently modulated after T-cell receptor activation, he continued.

HIV infected cells have higher basal metabolism. In particular, an important glycolytic function is detected. Inhibition of glycolysis blocks HIV infection and promotes the death of HIV-1 infected cells.

- Glucose dependency of HIV-infected cells could be used as a therapeutic target to eliminate infected cells, Prof Sáez-Cirión said.

In his summary he highlighted that deprivation of nutrients in infection sites may negatively impact the functionality of HIV-specific CD8+ T-cells.

- Control of infection could be associated with an optimal utilization of metabolic resources by HIV-specific CD8+ T-cells from HIV controllers!

HIV-infected cells are highly glycolytic. Glucose may become limited in sites of HIV replication.

- Metabolic requirements of infected cells offer opportunities to target them, Prof Sáez-Cirión ended his lecture.

Interesting data from BCN 02

The role of therapeutic vaccines in current eradication strategies was the topic of Dr Beatriz Mothe’s, Spain, lecture.

She talked about new T-cell vaccine concepts, and how to improve immunogenic design.

- Approach one is to cover all possible diversity. The other approach is entirely different: Circumvent viral diversity by excluding it. The rationale is to avoid filling the immune space with decoy responses and to profit from a focus of selected HIV viral targets – where the virus is most vulnerable, Dr Mothe explained.

All strategies being tested are still in early proof of concept studies.

- No one has been “cured” so far with this kind of strategy. However, data from BCN 02 (a study on a combined “kick and kill” strategy) shows for the first time a potentially induced virologic control in a few individuals.

Reducing the viral reservoir needs to go along with improved immune control - either by therapeutic vaccines, immune checkpoints etc. Characteristics of T-cell responses needed include strength, breadth, functionality and focus on non-escaped and vulnerable targets.

- Any strategy aimed for a functional cure need to be scalable, cost-effective and safe in long term – in the context of effective and safe current ART, was her last conclusion.

12 candidates for the new "Berlin patient" assembled

Prof Javier Martinez-Picardo, Spain, talked about stem cell therapy.

- Allogenic hematopoietic stem cell transplantation (allo-HSCT) is feasible in HIV-positive cART-treated subject with haematological malignancies, although morbidity and mortality is important and greater than in subjects that do not have HIV, Prof Martinez-Picardo told the audience.

The allo-HSCT is currently the only clinical intervention demonstrating a substantial reduction of the viral reservoir, he added.

Prof Martinez-Picardo described IciStem, that systematically monitors the patients included for extensive periods of time to better understand the biological clues leading to viral reservoirs reduction, and potential cases of HIV-1 eradication/remission among these patients.

- IciStem was originally set up for cancer purposes, but includes patients with HIV. It is an observational project to investigate cases of allo-HSCT in HIV-positive subjects – and to understand the unique case of HIV-1 cure, i.e. the Berlin patient.

IciStem has assembled an unpreceden-
ted cohort of 12 potential candidates to be the new Berlin patients.

It has more tasks: To systematically trace reservoir changes and immune recovery, to generate a registry of CCR5Δ32 (a genetic mutation responsible for the two types of HIV resistance that exist) HSC donors, both adults and cord blood – and to explore the role of HIV activity.

– Gene therapy might offer the autologous transplant with CCR5Δ32 a feasible and scalable intervention, Prof Martinez-Picardo stated.

"Make everyone an elite controller"

Only 17 million of the 36.7 million people globally infected with HIV have access to ART, said Prof Warner Greene, USA, who was the last Speaker at the Symposium.

– And the majority of people accessing ART are not “on therapy” – i.e. have linkage and retention in care and adherence to ART.

This lead to the conclusion that an HIV cure may be Africa’s best hope in the battle against HIV/AIDS, he continued.

For HIV latency, the best characterised reservoir is in resting memory CD4 T-cells. Latently infected cells are rare – about 1 in a million.

– But that means 300 - 600 million latently infected cells in the body – and those we have to get rid of, Prof Greene said.

Personally, he did not think that eradication is going to be possible, so reduce and control should be the strategy and first goal.

– We should aim to make everyone a HIV “elite” controller.

Detailed studies of elite controllers, and post-treatment controllers, suggest that a sustained viral remission will require: Low amounts of virus, low inflammation – and sustained T-cell responses that reside in tissues, target the right parts of the virus, and are primed to attack when the virus threatens to rebound.

– That is what it will take to consistently get to a sustained viral remission off ART, Prof Greene pointed out.

He finished describing their ongoing research for a safe but effective latency reversing agent.

– The road to an HIV cure will twist and turn, and potholes are to be expected. However, gratifying progress is being made and is cause for optimism, was Prof Greene’s final message.

And on this positive note, the Symposium had come to its end.

Per Lundblad
Reduced Drug Regimens at CROI 2017

The 2017 Conference on Retroviruses and Opportunistic Infections (CROI) was held in pleasant Seattle from February 13th to February 17th. CROI 2018 would be back in Boston (March 4th to 7th).

Antiretrovirals are back! One of the main messages of this, in general, excellent CROI is that antiretrovirals are back in the scientific program. In contrast with past CROI conferences we have seen a flurry of presentations about clinical trials and cohort studies looking at the efficacy of different antiretroviral combinations. We have seen data on new triple drug combinations including a new non-nucleoside reverse transcriptase inhibitor, Doravirine [1] and a new non-boosted integrase strand transfer inhibitor, Bictegravir [2]. There was also a very interesting presentation data about a new family of drugs, capsid inhibitors with long acting potential [3]. In this article I am going to focus on those antiretroviral combinations that involve less than three drugs. I have been writing for a while about reduced drug regimens, in general to inform of many disappointing results. This time is different.

Sword cuts deep

Biggest news at CROI 2017 in the field of antiretroviral therapy were the good –better than anticipated -results of the SWORD trials [4]. Josep Llibre from Barcelona presented the pooled results of two identical open-label clinical trials that include HIV infected participants who were receiving their first or second antiretroviral regimen with no prior virological failure. They needed to be HBsAg negative. The studies also requested virological suppression for at least one year. Participants were receiving antiretroviral therapy with two nucleoside reverse transcriptase inhibitors and a third drug that could be a protease inhibitor (26%), a non-nucleoside (54%) or an integrase inhibitor (20%) (Figure 1)

The 1024 participants in SWORD were randomized to continue their suppressive regimen or switch entirely to a new combination with only two drugs: rilpivirine and dolutegravir. Approximately 75% of participants were male, with a good CD4 cell count (median around 624 cells/µL). Around 70% of the participants were taking a TDF containing regimen. The primary endpoint of the study was at week 48. After week 52, all participants were offered switch to the dual regimen (Figure 1).

By the FDA snapshot analysis after 48 weeks of follow-up, 95% of patients in each randomization group were still below 50 HIV-RNA copies/mL. This results prove the non-inferiority of the dual regimen combining dolutegravir with rilpivirine. The lower limit of the 95% confidence interval, -3%; is far from the -8% pre-established non-inferiority margin (Figure 2). Results of each individual trial showed almost identical results. A more detailed analysis of the FDA snapshot analysis showed an imbalance in the groups with “no virological data” (Figure 3). While in the dolutegravir and rilpivirine group there were 17 participants (3%) who discontinued due to adverse events or death (only two deaths in the study, both unrelated to the study drugs) there were only 3 (<1%) in the triple therapy group. In contrast, there were 7 participants (1%) in the dolutegravir and rilpivirine group who discontinued therapy for other reasons while there were 16 (3%) in the triple therapy group. In brief, discontinuations for other reasons in the triple therapy group canceled out the discontinuations due to adverse events in the dual therapy group.

Only two patients per group withdrew from the study due to confirmed virologic failure. In total there was just a single participant in the dolutegravir and rilpivirine...
A group who developed a non-nucleoside mutation, K101K/E. This mutation was found after the participant stopped study drugs and experienced a very high virological rebound with a viral load of 1,059,711 HIV-RNA copies/mL. K101K/E confers only a 1.2-fold change of susceptibility to rilpivirine. Interestingly this participant was resuppressed with dolutegravir and rilpivirine.

As mentioned, in terms of adverse events there were more discontinuations in the dual therapy group. Nine participants discontinued due to central nervous system adverse events. Changes in lipids were very similar in both groups. After 48 weeks the total cholesterol: HDL ratio was identical in both groups, 3.7. Interestingly, patients randomized to dolutegravir plus rilpivirine showed an improvement in bone turnover biomarkers. A bone mineral substudy using DEXAs will be presented in an upcoming conference.

Results of the combined SWORD studies are big news in the field of antiretroviral therapy. After almost a decade of research we have for the first time a completely nucleoside-sparing and booster-sparing combination that matches the efficacy of triple antiretroviral therapy. The 95% efficacy rate for maintenance of virological suppression is as good as the most successful switch regimens using triple antiretroviral therapy. It is true that a few patients would develop adverse events when exposed to this combination but the number is relatively small. Dolutegravir is going to be combined with rilpivirine in a small pill that would be attractive for patients given its good tolerance.

Where this combination is going to be situated in the upcoming landscape of ART is difficult to say. Somewhat paradoxically, the biggest competitor of the dolutegravir and rilpivirine formulation is going to be another dual therapy regimen, the combination of dolutegravir and lamivudine that would have the added advantage of cost, since lamivudine is already a generic drug. My opinion is that the combination of dolutegravir and rilpivirine would be quite appropriate for patients with multiple comorbidities in whom we want to avoid at the same time tenofovir disufarate and ritonavir or cobicistat. One weakness of this regimen is the interaction of rilpivirine with omeprazole and the need for taking it with food.

**Figure 3. SWORD Studies. FDA snapshot outcomes**

<table>
<thead>
<tr>
<th>Early Switch Phase</th>
<th>DTG + RPV (n=513)</th>
<th>CAR (n=511)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic success</td>
<td>486 (95)</td>
<td>485 (95)</td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>3 (&lt;1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Data in window not &lt;50 c/mL</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Discontinued for lack of efficacy</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Discontinued while VL not &lt;50 c/mL</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Change in ART</td>
<td>0</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>No virologic data</td>
<td>24 (5)</td>
<td>20 (4)</td>
</tr>
<tr>
<td>Discontinued due to AE or death</td>
<td>17 (3)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Discontinued for other reasons</td>
<td>7 (1)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>
These giants of the animal kingdom need help. Despite their strength and cunning they’re no match for a poacher’s rifle. For 50 years WWF has been securing protected areas worldwide, but these aren’t enough to stop the killing. To disrupt the sophisticated criminal gangs supplying animal parts to lucrative illegal markets, we are working with governments to toughen law enforcement. We’re also working with consumers to reduce the demand for unlawful wildlife products. Help us look after the world where you live at panda.org/50.
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the possibility of monotherapy because of its high genetic barrier. In clinical trials of antiretroviral naive participants who received dolutegravir as part of a triple therapy regimen there was not a single case of resistance development. However, this has not been the case when dolutegravir has been used as single drug for maintenance of virological suppression.

1 Wijting and colleagues conducted a carefully designed clinical trial, the DOMONO study [6] in which aviremic HIV infected participants were switched to dolutegravir monotherapy. To be included in the trial patients needed to be virologically suppressed for at least 6 months. The study excluded participants with pre-ART viral loads above 100,000 HIV-RNA copies/ml, nadir CD4 cell count below 200 cells/µL, baseline resistance or prior virologic failure. During the course of the study eight out of 77 (10%) participants developed virologic failure, three of them with resistance to integrase inhibitors (S230R, K263R, N155H).

Blanco and colleagues presented the results of a retrospective cohort involving three large HIV clinics. The study focused on patients who had been prescribed dolutegravir monotherapy for maintenance of virological suppression [7]. In this study 11 out of 122 patients (9%) experienced virological failure while on dolutegravir monotherapy. Unfortunately, 9 patients developed integrase inhibitor resistance. Of these nine patients, four were naive to integrase inhibitors. The mutations selected after failures of dolutegravir monotherapy involved different pathways of resistance: 92Q,118R,148X and 155H.

Given the results of these two studies I think that dolutegravir monotherapy should be abandoned even as a research strategy. The risk of virological failure and resistance development is unacceptable high and is in sharp contrast with other reduced drug regimens such as dolutegravir and rilpivirine or dolutegravir and lamivudine.

Dolutegravir and lamivudine for maintenance of virological suppression: so far, so good

Joly et al presented the results of LA-MIDOL, a non-comparative open-label, single arm, multicenter trial that included 110 participants who switched their current triple antiretroviral regimen to first, dolutegravir and the two nucleoside reverse transcriptase inhibitors that the patient was taking and then, if viral load was still suppressed eight weeks after the initial switch, they were switched again to dual therapy with dolutegravir and lamivudine [8].

To be included in LA-MIDOL, participants needed a CD4 cell nadir above 200 cells/µL, lack of prior resistance, and demonstrable viral suppression for at least two years. After 40 weeks of follow-up only one of the 110 participants developed virologic failure at week 12. Patient had a low level virologic rebound with a maximum viral load of 100 HIV-RNA copies/mL. Genotyping could not be performed.

The results of LA-MIDOL, combined with the impressive results of PADDLE [9] support further research with this combination that has the potential to be a “game changer” in antiretroviral therapy. Dolutegravir plus lamivudine would be an attractive regimen given its good safety profile, the lack of relevant pharmacological interactions, the low cost of generic lamivudine and the need of very infrequent monitoring. However, we have to recognize that dual therapy regimens have a lot to prove. More than twenty years of antiretroviral therapy cannot be changed if we do not have definitive proof that dual therapies based on integrase inhibitors offer the same benefits. This is especially true since we have now available triple drug combinations that include non-toxic nucleoside reverse transcriptase inhibitors such as TAF. Be ready for a very interesting debate in the upcoming months. At the beginning of this debate we would focus on virological efficacy but I bet that we would start a long discussion about cost-efficacy, toxicity benefits, residual replication, persistent inflammation, penetration in reservoirs...(to be continued).
HBV Reactivation in Patients Receiving DAAs for HCV

FDA Black Box Warning: A so-called “black box warning” issued by the United States Food and Drug Administration (FDA) made the news in October 2016, warning about the risk of hepatitis B reactivation in patients treated with direct-acting antivirals (DAAs) for hepatitis C.

The FDA reported on 24 post-marketing cases of HBV reactivation in patients who had received second-generation DAAs (http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm).

A more detailed analysis comprising 29 patients was presented during the Liver Meeting in Boston in November 2016 (1). Data had been drawn from the FDA’s own Adverse Event Reporting System database which has to rely on voluntary reporting. In brief, HBV reactivation usually occurred within 4-8 weeks of starting DAA therapy (mean time from start of therapy until reactivation: 53 days). All DAAs available at the time (November 2013 – October 2016) were involved. Among the 29 cases, 2 patients died, 1 patient had to undergo liver transplantation, 6 were hospitalized, and 10 discontinued DAA treatment (Table 1). More importantly, HBV treatment was delayed in 7 of the 16 (44%) treated cases despite a known HBV status and clinical signs of reactivation. Interestingly, the vast majority of cases were reported from Japan (n=19) and only 5 were from the US. Against the background of approximately 240,000 treated patients in the US in 2015 alone, HBV reactivation must be considered a very rare event! Of the 17 patients with known HBsAg status, 13 were HBsAg positive, whereas 3 were HBsAg negative and HBV DNA negative at baseline. Thus, most patients were HBsAg carriers or even had chronic HBV infection. It is of course a well-known fact that HBV DNA flares may occur in these patients at any time, particularly during immunosuppression and/or chemotherapy. Therefore, given the lack of a control group, the causal relationship between DAA treatment and HBV reactivation has yet to be proven. Nevertheless, following these observations, the FDA recommends that all patients should be screened for current or prior HBV infection before starting treatment with DAAs and close monitoring of these patients should be performed during treatment and post-treatment follow-up.

Antiviral therapy in patients with HBV/HCV co-infection

Just to make things clear from the start: HBV reactivation in co-infected patients treated for HCV is no news! HBV/HCV co-infection is not a common sight in most Western countries (2) but it is more frequently found in HBV endemic areas including many Asian countries as well as in high-risk populations, including patients who inject drugs, haemophiliacs and those with HIV co-infection. Moreover, co-infection is associated with an increased risk of fibrosis progression and HCC development (3).

Several studies have shown that both viruses interact in co-infected patients and HBV reactivation has been commonly observed after successful HCV eradication with Interferon-based therapies (4). HBV DNA levels are typically low or even undetectable in co-infected patients but large fluctuations may still be possible. As co-infected patients were excluded from DAA approval studies, it comes as little surprise that cases of HBV reactivation are now reported in the post marketing setting. There are only few and mostly anecdotal data on DAA treatments in patients with co-infection. However, there is one small study by Edward Gane et al. that showed increased HBV DNA levels in seven of the eight DAA-treated patients but no clinical HBV flares were seen and no HBV treatment had to be initiated (5).

Screening for the presence of HBV serologic markers before initiation of HCV therapy has been common practice for many years and has also been recommended by clinical practice guidelines. The cases of HBV reactivation reported by the FDA and others reaffirm this approach. There is no doubt that patients with co-infection who meet the criteria for starting treatment in mono-infected patients (i.e. HBV DNA >2000 IU/mL) should also be treated whereas close monitoring of HBV DNA and ALT levels should be perfor-
med during DAA treatment in patients with low-level HBV viremia according to current AASLD/IDSA guidelines (6).

In contrast, the current EASL guidelines even recommend nucleoside/nucleotide treatment during DAA therapy in any HBsAg-positive patient, regardless of HBV DNA level (7; Figure 1).

Is there a risk for HBV reactivation in patients with resolved HBV infection?

It is a well-known fact that HBsAg-negative, anti-HBc-positive patients who undergo immunosuppressive therapy are at risk of HBV reactivation. Most cases involved treatment with rituximab (black box warning issued by the FDA in 2013) but other agents have also been involved (8). However, it comes as a surprise that the aforementioned FDA report also involved three cases of HBV reactivation in HBsAg-negative, anti-HBc-positive patients undergoing DAA treatment. This is somewhat worrying as the percentage of anti-HBc-positive patients is potentially very large among HCV-infected patients, even in Western countries. During the Liver Meeting it was revealed that one of the three patients was receiving rituximab therapy at the time. Therefore, with so little clinical background information, it is currently unclear how these patients should be monitored and/or treated for HBV infection. The presented data do not warrant universal nucleoside/nucleotide treatment in patients with resolved HBV infection but ALT monitoring should certainly be performed during and even after DAA treatment.

A recent retrospective study of 173 patients treated with DAAs in an HBV endemic area (Korea and Taiwan) revealed that 103 (60%) had been previously infected with HBV but none showed evidence of reactivation (9). To better understand the risks of HBV reactivation in anti-HBc-positive patients, more real-world data are required.

### Table 1. Demographic and clinical parameters of HBV reactivation cases (n=29) reported by Bersoff-Matcha et al. (1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total: n=29</th>
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<tbody>
<tr>
<td>Median age (range)</td>
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</tr>
<tr>
<td>Male gender, n (%)</td>
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<tr>
<td>Country of report, n (%)</td>
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<td>Japan</td>
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</tr>
<tr>
<td>USA</td>
<td>5 (17)</td>
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<tr>
<td>Other</td>
<td>5 (17)</td>
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<tr>
<td>Days to event, median (range)</td>
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</tr>
<tr>
<td>Treatment delay, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes/Possible</td>
<td>14 (48)</td>
</tr>
<tr>
<td>No treatment given/stated</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Baseline HBsAg, n (%)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Negative</td>
<td>4* (14)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (41)</td>
</tr>
<tr>
<td>Outcome, n (%)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Transplant</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>6 (21)</td>
</tr>
<tr>
<td>DAA treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>Discontinued</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Completed</td>
<td>13 (45)</td>
</tr>
<tr>
<td>Not reported</td>
<td>6 (21)</td>
</tr>
</tbody>
</table>

*includes one without known other baseline HBV viral parameters incl. HBV DNA

References

More sleepless nights

As described in my previous article in HIV & Virology News, (‘Doctor I can’t sleep’ issue 4/2015) sleep problems in people with HIV are common and arise from a panoply of potential causes. Mood disorders and psychiatric problems may be both a cause and consequence of these sleep problems as well as related to both endogenous and exogenous triggers, drug use and the burdens of a chronic stigmatising illness disproportionately affecting some already marginalised groups in society.

Efavirenz (and a structurally related NNRTI briefly investigated by DuPont and BMS) has been associated with a fairly well defined CNS syndrome that typically occurs within few hours of starting therapy, occurs in most patients and seems to at least partially settle over several weeks of continued dosing. The syndrome has been linked with an efavirenz interaction with a serotonin receptor, where it acts as a serotonin 2A receptor partial-agonist. After 20 years of widespread use, efavirenz was eventually associated with an increased risk of attempted or completed suicide and sidelined in most developed world guidelines. Further effects of efavirenz on glutamine and GABA neurotransmitters have been suggested in animal studies and changes in sleep architecture have been documented. As noted in the START study, where possible physicians avoid the use of efavirenz in subjects with active or even a history of mental health problems. Typically, subjects commencing efavirenz report a range of sleep problems, most typically vivid dreams, which may wake them during the night, increased and sometimes intrusive dream recollection, both somnolence and insomnia, a feeling of intoxication after dosing and a morning hangover or sluggishness. Anxiety and low mood may accompany the syndrome although this was difficult to document relative to comparators in clinical trials.

More recently, expended use of integrase inhibitor drugs (INSTI) interest in a possible CNS ‘syndrome’ with Dolutegravir has arisen. The first reports of mood disorders and sleep problems with Dolutegravir, arose from short case series and subsequently larger clinical cohorts, which have reported data on their clinical experiences with this agent, including relative to other Integrase inhibitors. To date, no studies looking at the impact of dolutegravir on neurotransmitters or receptors have been published and systematic sleep studies have not been conducted.

Dolutegravir is structurally unrelated to efavirenz so understanding any CNS events or ‘syndrome’ with this agent will require systematic investigation.

This article will look at the available data on dolutegravir and CNS events reported in clinical trials and the larger cohort and case series reported.

Randomised Cohorts
Adverse events or any central nervous system ‘syndrome’ with dolutegravir, or perhaps more commonly with the abacavir/lamivudine/dolutegravir single tablet, are currently less well defined than the efavirenz events and CNS events were only systematically sought in the SINGLE trial relative to efavirenz. Data presented from the 4 phase 3a/3b naive clinical trials (SINGLE, Spring-2, Flamingo and the all-female ARIA) by ViiV/GSK at Glasgow 2016 did not support the idea of an excess of CNS or neuropsychiatric events with dolutegravir relative to comparators including efavirenz, raltegravir, darunavir/ritonavir and atazanavir/ritonavir (1). The report looked at insomnia, anxiety, depression, nightmares/abnormal dreams and ‘suicidality’. Of note, data on headaches, a commonly described event with dolutegravir regimens in cohort studies, and fatigue, often a symptom of poor sleep quality, were not included in the report. Furthermore, safety data from the STRiVing study, which looked at switch off a range of treatments to ABC/3TC/DTG and observed multiple discontinuations for insomnia, mood disorders, fatigue and headaches were not included in the analysis. It is often informative to look at what is not reported as well as what is. Only in SINGLE, versus efavirenz was a meaningful difference in insomnia (17% with ABC/3TC/DTG vs 12% with TDF/FTC/EFV) reported although in each of the other studies there was a 1% greater number of insomnia reports with DTG relative to comparator. The difference in SINGLE may have been driven by a relationship between ABC/3TC/DTG and insomnia but it could also be that as efavirenz commonly causes somnolence, subjects on TDF/FTC/EFV fell asleep more readily but then went on to experience a marked excess of nightmares/abnormal dreams (10% with ABC/3TC/DTG vs 21% with TDF/FTC/EFV). Of course if you are lying awake with insomnia you can’t have abnormal dreams! The observed frequency of insomnia was much higher in SINGLE than other studies due to several reasons including extensive details about efavirenz side effects in the consent
form and specific questioning about sleep related issues in the follow-up. It is also worth noting that SINGLE exclusively used the ABC/3TC backbone, whereas in FLAMINGO and SPRING-2 only around a third of subjects used this backbone. The two dolutegravir switch studies, STRiiVing and SWORD provide some further insights but are complicated by fact that most patients started other new agents as well as dolutegravir, ABC/3TC in STRiiVING and Rilpivirine in SWORD. Rilpivirine, in particular, is known to interact with some neurotransmitter receptors and the Abacavir US labelling lists headache, nausea, dizziness and fatigue as ‘common’ (1-10%) adverse effects of this agent.

The STRiiVING study, which was designed to assess switching off virologically suppressed, HLA-B*5701 negative patients on either PI, NNRTI or integrase inhibitors could be successfully and safely switched to DTG/ABC/3TC (Triumeq). The majority of patients switched all 3 parts of their regimen as over 70% were also on TDF/FTC as their NRTIs at baseline. The first 24-week phase of the study showed that viral suppression was maintained after switch but that switch introduced new adverse events, notably nausea, insomnia and mood disorders. The study included 553 patients, randomized 1:1, with 85% of those randomized to switch, and 88% that remained on their previous regimen, still suppressed at week 24. After 24 weeks, subjects who had not initially switched, also changed over to DTG/ABC/3TC. The delayed switch appeared better tolerated than the immediate switch with only 4 subjects (2%) discontinuing over 24 weeks follow up, versus 10 (4%) in the immediate switch phase. Insomnia was reported as an adverse event after switching by 4% of subjects in each phase but no new ‘episodes’ of insomnia occurred beyond 24-weeks post switch, suggesting either an ascertainment effect (subjects at risk of insomnia continue early due to insomnia or another reason, leaving only those who don’t experience this effect) or insomnia is an early side effect that either undergoes tachyphylaxis or settles with simple advice such as changing to morning dosing.

The two SWORD studies, are the 2 large cohorts (plus some smaller ones) that have reported discontinuation events with dolutegravir, in 3 cases with data comparing against other integrase inhibitors. A report of 157 patients commencing on Dolutegravir in Belfast, Northern Ireland reported that 25% of subjects complained of difficulty with low mood, anxiety or sleep disturbance and 10% discontinued dolutegravir, 8% due to ‘intolerable side effects’. (4).

Outcomes for 556 patients commencing dolutegravir have been reported from Amsterdam, Holland. 102 (18.4%) were ART-naïve at initiation of dolutegravir, the remaining mostly switch. Subjects were followed for a median 225 days. Overall, 85 patients (15.3%) stopped dolutegravir. In 76 patients (13.7%), this was due to adverse events that included. insomnia and sleep disturbance (5.6%), gastrointestinal complaints (4.3%) and neuropsychiatric symptoms such as anxiety, psychosis and depression (4.3%). Regimens in which abacavir/lamivudine was co-prescribed, were more frequently discontinued (adjusted relative risk 1.92, 95% confidence interval 1.09-3.38, p log-rank 0.01) (5).

The experience with all integrase inhibitors was been reported from British Columbia, Canada. Analyses used exposure adjustments to account for the longer availability of raltegravir. The cohort included 1044 INSTI-treated patients, 75 (7.2%) of whom contributed data for ≥2 INSTIs, providing 1122 distinct patient-INSTITI records: 522 received raltegravir, 301 elvitegravir/cobicistat and 299 dolutegravir regimens. After controlling for baseline factors and adjusting for sex, antiretroviral treatment experience and hepatitis C co-infection, adjusted adverse event rates (with 95%CI) per 100 person-years were: raltegravir 1.88 (0.72-4.93), elvitegravir-cobicistat 5.76 (2.14-15.49), and dolutegravir 3.34 (1.19-9.40). Raltegravir was the most well tolerated agent with the adjusted RR of ADR relative to raltegravir was 3.06 (2.97-3.14) for elvitegravir-cobicistat and 1.78 (1.65-1.91) for dolutegravir. CNS side effects were the most common reason for discontinuation with dolutegravir (2.8%) albeit CNS related discontinuations were also recorded with the other INSTI. GI disturbances were predominate with elvitegravir/c. (6).

Similarly, the Hamburg and Cologne, Germany, cohorts compared discontinuation rates due to adverse events (AEs) within 2 years of starting treatment regimens with dolutegravir, raltegravir or elvitegravir/cobicistat and provided some additional insights into the clinical experience with these adverse effects. Of 1950 INSTI-based regimens initiated in 1704 patients eligible for analysis. The estimated rates of any AE and of neuropsychiatric AEs leading to discontinuation within 12 months were 7.6% and 5.6%, respectively, for dolutegravir (n = 985), 7.6% and 0.7%, respectively, for elvitegravir/c (n = 287), and 3.3% and 1.9%, respectively, 2017 29
for raltegravir (n = 678). Neuropsychiatric AEs leading to dolutegravir discontinuation were observed more frequently in women [hazard ratio (HR) 2.64; 95% confidence interval (CI) 1.23–5.65; P = 0.012] in patients older than 60 years (HR: 2.86; 95% CI: 1.42–5.77; P = 0.003) and in HLA-B*5701-negative patients who initiated abacavir at the same time (HR: 2.42; 95% CI: 1.38–4.24; P = 0.002). Considering the entire observation period, 6.8% of patients discontinued dolutegravir due to any AE and 5.0% due to neuropsychiatric AEs. The median time between dolutegravir start and discontinuation was 3.1 months and most discontinuations, 38 of 49 (78%), occurred within 6 months. The most frequent symptoms included insomnia and sleep disturbances as well as dizziness and paraesthesia. No symptoms were life-threatening or led to hospitalization and most symptoms resolved promptly on discontinuation of dolutegravir. In 32 of 37 (86%) patients followed for at least 3 months after dolutegravir discontinuation, the subsequent antiretroviral regimen was tolerated and effective. In six patients who interrupted dolutegravir, neuropsychiatric adverse effects recurred in all six cases upon re-exposure. Of note, the observations remained consistent when patients initiating dolutegravir in 2016 were excluded, suggesting other case reports did not lead to a reporting bias.

Finally, at CROI 2017, the Spanish PISCIS cohort reported no differences in discontinuation rates between INSTIs. The PISCIS Cohort is an ongoing observational study that includes about 21,000 HIV-infected patients aged 16 years from 10 hospitals in Catalonia and 2 in the Balearic Islands (Spain). All subjects who had started one of 5 regimens including DTG in all six cases upon re-exposure. Of note, the observations remained consistent when patients initiating dolutegravir in 2016 were excluded, suggesting other case reports did not lead to a reporting bias.

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Globally, exclusive breastfeeding reduces morbidity and mortality in both HIV exposed and HIV unexposed infants in low and middle-income countries (LMIC). It has been estimated that overall, breastfeeding could prevent half of diarrhoeal and a third of respiratory illnesses in infants living in LMIC.[1].

There is no doubt that in settings with high HIV prevalence and where formula feeding is not available, feasible, affordable, sustainable, and safe, breastfeeding improves HIV-free survival by improving nutrition and growth and protecting against serious infections.[2]. The current WHO guidance recommends that all women with HIV take combined antiretroviral therapy (cART) and are supported to breastfeed their babies until 12 months of age (exclusively for the first six months) [3]. The WHO guidance is adopted primarily by LMIC countries with high rates of diarrhoeal illnesses and mortality in infancy. Currently, guidance for women living with HIV in the UK and other high-income countries (HIC) advises avoidance of breastfeeding to reduce the risk of transmission via breast milk.[4].

What are the health benefits of breastfeeding in the general population?

Emerging evidence suggests that even in high-income countries (HIC) where morbidity due to infections is less of a problem, breastfeeding may improve child and maternal health. A recent Lancet review and meta-analysis found that breastfeeding in the general population was consistently associated with reductions in the incidence of otitis media in under-2s (OR 0.62, 95% CI 0.62-0.72), and in the prevalence of obesity in later life (a pooled reduction of 20%, which fell to 13% when restricted to high quality studies).[1]. The meta-analysis described a reduction in later type 2 diabetes in breastfed children (OR 0.65, 95% CI: 0.49-0.86), however when the analysis was restricted to the three highest quality studies, the association was no longer statistically significant. Associations were described between intelligence in later life and breastfeeding - a pooled gain of around three intelligence quotient (IQ) points. Other smaller meta-analyses have suggested less clinically relevant findings such as a 36% lower risk of sudden infant death syndrome, a 58% decreased risk of necrotising enterocolitis and a 19% reduction in childhood leukaemias.[5]. In terms of maternal health, a clear reduction in the risk of breast and ovarian cancer has been demonstrated for women who breastfeed.

Data on the health effects of breastfeeding are largely observational, and therefore subject to confounding. Within HIC, there are many socio-demographic factors associated with breastfeeding that are also associated with long-term health outcomes - not all of these are readily measurable. Longitudinal data from a cohort of around 7,000 children in the US analysed the association of breastfeeding with long-term health and educational benefits[6]. When the effect of breastfeeding between families was examined, multiple positive health outcomes were associated with breastfeeding, including emotional attachment and educational attainment. In the same study, when analyses were restricted to siblings (including families where siblings were fed differently), and adjusted to account for within-family effects, these associations largely disappeared.

What is the risk of HIV transmission through breastfeeding, and how does it occur?

The risk of postnatal HIV transmission in untreated women is cumulative, and estimated to be 5-10%[7] and it is higher with mixed feeding than exclusive breastfeeding[8–10]. In women not receiving effective ART, the complete avoidance of breastfeeding reduces the rate of mother-to-child HIV transmission (MTCT) [11] and can eliminate the risk of postnatal MTCT. However, given the clear health and mortality benefits of breastfeeding HIV-exposed infants in LMIC, there are an increasing number of studies examining the postnatal transmission rates in breastfeeding women on combined ART which report transmission rates of less than 1% at six months (see Table 1). Most recently, the PROMISE study, a multicentre randomised controlled trial with more than 1000 mother-infant pairs, reported a postnatal transmission rate of three per

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**Table 1. Comparison of postnatal MTCT rates at 6 months after delivery in studies with mothers on cART [12,30-35]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Setting</th>
<th>Enrolment</th>
<th>Number of mother-infant pairs</th>
<th>cART regimen</th>
<th>Estimated postnatal transmission rate (les births)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitra Plus</td>
<td>Prospective cohort</td>
<td>Tanzania</td>
<td>2004 -2006</td>
<td>378</td>
<td>ZDV/3TC/NVP</td>
<td>10 per 1000</td>
</tr>
<tr>
<td>Marazzi et al</td>
<td>Prospective cohort</td>
<td>Mozambique</td>
<td>2005 - 2007</td>
<td>313</td>
<td>ZDV/3TC/NVP</td>
<td>6 per 1000</td>
</tr>
<tr>
<td>Amato</td>
<td>Prospective cohort</td>
<td>Rwanda</td>
<td>2005 - 2007</td>
<td>227</td>
<td>D4T/3TC/NVP or ZDV/3TC/EFZ</td>
<td>5 per 1000</td>
</tr>
<tr>
<td>Mena Bana</td>
<td>RCT</td>
<td>Botswana</td>
<td>2006 - 2008</td>
<td>263</td>
<td>ZDV/3TC/LPV r</td>
<td>3 per 1000</td>
</tr>
<tr>
<td>IAN</td>
<td>RCT</td>
<td>Malawi</td>
<td>2004 - 2008</td>
<td>803</td>
<td>ZDV/3TC + NVP or NVP or LPV/r</td>
<td>26 per 1000</td>
</tr>
<tr>
<td>Kosbo Borgu</td>
<td>RCT</td>
<td>Burkina Faso, Kenya, South Africa</td>
<td>2005 - 2008</td>
<td>349</td>
<td>ZDV/3TC/LPV r</td>
<td>16 per 1000</td>
</tr>
<tr>
<td>PROMISE</td>
<td>RCT</td>
<td>Sub-Saharan Africa (13 centres), India (1 centre)</td>
<td>2011 - 2014</td>
<td>1220</td>
<td>TDF/FTC/LPV r</td>
<td>3 per 1000</td>
</tr>
</tbody>
</table>

RCT: randomised controlled trial; cART: combined antiretroviral therapy, ZDV: zidovudine; 3TC: lamivudine, NVP: nevirapine; D4T: stavudine; EFZ: efavirenz; LPV/r: ritonavir-boosted lopinavir; NFV: nelfinavir; TDF: tenofovir disoproxil; FTC: emtricitabine

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**Should we encourage women to breastfeed?**

HIV & VIROLOGY NEWS 1 · 2017

Breastfeeding

[1] The risk of postnatal HIV transmission in untreated women is cumulative, and estimated to be 5-10%[7] and it is higher with mixed feeding than exclusive breastfeeding[8–10]. In women not receiving effective ART, the complete avoidance of breastfeeding reduces the rate of mother-to-child HIV transmission (MTCT) [11] and can eliminate the risk of postnatal MTCT. However, given the clear health and mortality benefits of breastfeeding HIV-exposed infants in LMIC, there are an increasing number of studies examining the postnatal transmission rates in breastfeeding women on combined ART which report transmission rates of less than 1% at six months (see Table 1). Most recently, the PROMISE study, a multicentre randomised controlled trial with more than 1000 mother-infant pairs, reported a postnatal transmission rate of three per...
1000 live births at six months after delivery with women on protease-inhibitor based cART [12].

Although the precise mechanisms of HIV transmission through breastfeeding are incompletely understood, transmission most likely occurs through multiple pathogenic pathways relating to high levels of both[13] cell-free and cell-associated virus. High levels of cell-associated virus may be more strongly linked with transmission in women not on cART[14].

There is evidence that cART does not entirely suppress cell-associated HIV DNA in breast milk despite suppression in plasma[15,16], and activated CD4+ T-cells producing HIV have been detected in the breast milk of women on cART with undetectable plasma viral load [17], possibly because mammary epithelial cells may represent a non-T cell reservoir of HIV[18]. However, in a recent study of 221 breastfeeding mothers in Malawi looking at paired plasma and breast milk RNA, none of the mothers with suppressed plasma virus transmitted to their babies[19]

Are we preventing MTCT in HIC?

In Europe, MTCT rates in women diagnosed with HIV before delivery are consistently less than 1%[20–22]. In the UK, around 1100 pregnancies are reported in women with diagnosed HIV each year in whom the overall transmission rate has fallen to 0.27% (see Figure 1) and falls to 0.14% in those who are virologically suppressed at delivery [23,24]. The HIV testing offered to all women antenatally has resulted in 85% of pregnant women being diagnosed before conception, and over 70% have conceived on cART. [25]. The clear benefit of cART regardless of CD4 count will mean that the proportion of women conceiving on cART will further increase, as will the proportion taking life-long cART after delivery.

The postnatal period is a uniquely challenging time

The period after women give birth can be a difficult time in which to maintain cART adherence and engagement with HIV services [22]. A comparison of women in the UK Collaborative HIV Cohort study and women reported to the National Study of HIV in Pregnancy and Childhood found a higher rate of viral rebound in women who were in the postpartum period than age-matched non-postpartum controls[26]. The reasons are most likely multifactorial, including sleep deprivation, disrupted routines, caring for other children, attending HIV services which are rarely baby-friendly, and inconvenient
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Breastfeeding

Is there a cost to women with HIV of avoiding breastfeeding?

Women delivering in the UK are surrounded by images of breastfeeding promotion, and may have very strong cultural breastfeeding norms. A qualitative study of pregnant and postnatal women in London found that the decision to abstain from breastfeeding was often fraught and characterised by feelings of guilt, sorrow and fear[27]. The majority of women with HIV having babies in the UK are of African ethnicity, in whose cultures breastfeeding may be highly valued. Women also expressed concerns that formula feeding would interfere with maternal-infant bonding, and that it would lead to suspicions around their HIV status. Costly formula feeding requires adherence to strict sterilisation guidance, with inconsistent locally-provided financial assistance for formula to women living with HIV in the UK.

Weighing the risks and the benefits of breastfeeding for women with HIV in HIC

On one hand, the risk of postnatal transmission from women on cART is extremely low; on the other, even the lowest MTCT rates in exclusive breastfeeding studies are around double the 0.14% rate in non-breastfeeding women suppressed on cART in the UK. As the proportion of women on lifelong cART rises, the number conceiving while virologically suppressed on cART will also rise, thereby reducing the number of in utero or peripartum transmissions even further. There are valid concerns that breast milk may be a reservoir for HIV despite suppressed plasma viral load, and there are also concerns around potential long-term effects of prolonged ART exposure of infants via breast milk. HIV-exposed but uninfected infants can be exposed to ART in utero, via breastfeeding and through post-exposure prophylaxis; there is currently very limited data on long-term outcomes in these infants[28]. Although observational studies in HIC have described improved health outcomes for children of breast-feeding HIV-negative mothers, the strength of these associations is relatively weak for the most clinically relevant and prevalent conditions of diabetes and obesity.

Despite the improvements in health and mortality for perinatally-infected children[29], the acquisition of HIV at the beginning of life remains a very serious but preventable outcome. For some women, the small but nonetheless significantly higher risk of breastfeeding will be outweighed by other powerful drivers such as cultural norms, fear of HIV-related stigma and the association between breastfeeding and mother-infant bonding. We are edging closer to the tipping point, we might not be ready to recommend breastfeeding, but we can and must provide support to those women who have made the informed and personal choice to breastfeed.

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**Hepatitis B vaccination in People who inject drugs (PWID)**

In a needle exchange program in southern Sweden, all participants who were hepatitis B susceptible were offered a standard three doses vaccination schedule with a commercially available vaccine. Those who had no serological response (anti-HBs < 10 mIU/mL) were given up to three booster doses with measurement of serological response after each dose. 1142 individuals initiated vaccination. Of these, 898 received three doses. Among the 244 who did not receive three doses, 30 cases were due to seroconversion with either HBsAg positivity or development of antibodies to HBsAg or HbcAg before completion of the vaccination program. Of the participants with available post-vaccination serological tests 74.8 % responded to standard vaccination. 34.5 % responded to the first booster dose, 44.9 % responded to the second booster and 38.5 % responded to the third booster dose.

Higher age and positivity for hepatitis C antibodies were associated with non-response. 18 cases of HBV infection were observed among 202 non-responders to at least three doses of vaccine. Three cases of development of anti-Hbc were coincidentally found in participants with prior vaccination response with documented anti-HBs >10 mIU/mL.

**Comment:** It is well known that PWID have lower response rates to hepatitis B vaccination compared to the general population. According to the results of the present study it seems worthwhile to give at least up to three booster doses in non-responders.

Another potentially important finding from the study is that three cases of seroconversion to anti-Hbc positivity were detected in individuals with prior response to vaccine with documented anti-HBs > 10 mIU/mL (none of the three seroconverters had any known history of clinical hepatitis). Although sometimes debated the common belief is that a positive titer to HBs after vaccination provides lifelong protection against hepatitis B and that no booster doses are required even if the anti-HBs titer is gradually declining. If these results are confirmed that belief may be questioned.

**Hepatitis B vaccination in neonates**

In two Chinese provinces children of Hepatitis B surface antigen positive/hepatitis E antigen negative (HBsAg+/HBeAg-) mothers were vaccinated against hepatitis B with or without Hepatitis B immune globulin (HBIG). This was an observational non-randomized study but the two groups were comparable. The perinatal transmission rate was 1/752 (0.1%) in neonates who received both vaccination and HBIG and 0/132 in neonates who received only vaccination. The response rate to vaccination was similar in the 2 groups but the anti-HBs titers were significantly higher in the vaccine only group.

**Comment:** Adding HBIG to vaccinated neonates born to hepatitis B infected mothers without e-antigen does not seem to confer any benefit compared to vaccine only. On the contrary the anti-HBs-titers were significantly higher in children who did not receive HBIG.

**Lower risk of bacterial infections with immediate initiation of antiretroviral therapy in HIV**

In the large START study immediate versus delayed initiation of antiretroviral therapy was compared in patients with CD4 counts above 500 cells/µL. Patients were randomized to immediate therapy or deferred therapy until the CD4 count was lower than 350. Immediate therapy decreased the risk of serious morbidity including AIDS-related and non-AIDS related events and all-cause mortality. In a preplanned analysis of the START study the risk of severe bacterial infections was compared between the groups. Of a total of 120 severe bacterial infections during a median of 2.8 years of follow up 34 were in the immediate group and 86 in the deferred group. The difference was highly statistically significant (p<0.0001). In the immediate group the average CD4 count was 194 cells higher and the neutrophil count was also higher. The most common bacterial infections were tuberculosis (n=26) and bacterial pneumonia (n=48). 20/26 cases of tuberculosis and 34/48 cases of bacterial pneumonia occurred in the deferred group.

**Comment:** The study results are a reminder of the fact that not only “classical” opportunistic infections are more common in HIV-related immunodeficiency but also infections that are seen in non-HIV infected. One such example is pneumococcal pne-
monia and sepsis. In the pre-antiretroviral era such infections were reported to be up to several hundred times more common in HIV-infected than in the general population. The results of this study illustrate that also a rather modest immunodeficiency is associated with increased risk of bacterial infections. This is yet another argument for initiating antiretroviral therapy immediately in all patients.

More coffee!

A retrospective cross-sectional study of 1018 patients with non-alcoholic fatty liver disease (n=155), hepatitis C (n=578) and hepatitis B (n=485) showed that coffee intake is associated with lower liver stiffness.

Tea and coffee intake was assessed and transient elastography was performed in all patients. Univariate and multivariate regression models were performed. Those who drank at least 2 cups of coffee per day had significantly lower liver stiffness (p=0.044). Intake of tea had no effect.


Comment: A growing number of studies come to the conclusion that intake of coffee is associated with decreased inflammation and fibrosis development. Perhaps it is time to do a dose response study? What is the optimal intake of coffee and what kind of coffee should be recommended?

Lower levels of CNS inflammation marker with immediate initiation of antiretroviral therapy

YKL-40 is a biomarker of microglial cell activation. In a cross-sectional study the level of YKL-40 was measured in cerebrospinal fluid in two groups of HIV positive patients before initiation of therapy. The first group consisted of patients with acute infection (n=33) and the second group were patients with chronic infection (n=34). In a subset of the patients serial measurements were performed after initiation of therapy. 18 HIV-uninfected controls were included in the study.

Untreated patients with chronic infection had statistically significant higher baseline levels of levels of YKL-40 than patients with acute infection and HIV-uninfected controls. There was no significant difference between uninfected controls and patients with acute infection. In patients for whom serial CSF data were available the difference in YKL-40 concentration remained significant between the two groups. The authors conclude that YKL-40 may be a valuable marker in understanding HIV neuropathogenesis and that immediate therapy is associated with lower levels of microglial activation.

Peluso et al. AIDS 2017;31:247-252

Comment: Better understanding of the neuropathogenesis of HIV is urgently needed and the availability of improved biomarkers may improve our understanding. The study also illustrates the protective effect of immediate therapy.

Proton pump inhibitor (PPI) with ledipasvir and sofosbuvir (LDV/SOF)

In an earlier report it has been suggested that the concomitant use of PPI with LDV/SOF may lead to decreased rates of sustained viral response (SVR). A real life observational study of 1979 patients treated with LDV/SOF was performed to evaluate the effect of PPI on SVR. SVR24 was achieved in 441 (97.1 %) of PPI recipients and in 1497 (98.2 %) not receiving PPI. Neither low nor high dose PPI was associated with decreased SVR. However, twice daily intake of PPI in patients with cirrhosis was associated with lower SVR. The author’s conclusion is that PPI can be taken together with LDV/SOF but that the intake should be limited to one daily dose of the equivalent of 20 mg of omeprazole.

Tapper et al. Hepatology 216;64:1893-1899

Comment: It is reassuring that more than 97 % of those taking PPI together with LDV/SOF achieved SVR. However, it is important to time the intake of drugs correctly. A concomitant intake of 20 mg omeprazole and LDV/SOF leads to a modest decrease of LDV Cmax and AUC. If omeprazole is taken 2 hours before LDV/SOF the decrease in LDV Cmax and AUC is much more pronounced. The message is that omeprazole and LDV/SOF should be taken at the same time and preferably on an empty stomach.

6 weeks of ledipasvir/sofosbuvir (LDV/SOF) in acute hepatitis C infection

In a German study of acute hepatitis C treatment with fixed dose LDV/SOF was given for 6 weeks. Acute HCV infection was defined as a known seroconversion to HCV within 4 months or known or suspected exposure to HCV within four months and ALT-level at least ten times above the upper normal limit at screening or within the last four preceding weeks and HCV-RNA > 10 000 IU/mL. 20 male patients were included with 11 genotype 1 a and 9 genotype 1 b. 19 patients had symptomatic disease and 8 had jaundice with bilirubin > 2.5 times the upper normal limit. All 20 patients cleared the infection with negative SVR at 12 weeks or later.

Deterding et al. Lancet Infect Dis 2017;17: 215-222

Comment: The spontaneous clearance rate in hepatitis C is estimated to be at least 15-20%. In symptomatic patients the rate may be substantially higher. In the present study all but 1 patient had symptomatic disease. With the availability of extremely potent drugs against chronic hepatitis C and the high cost of treatment it seems reasonable to defer treatment until spontaneous clearance has been ruled out.

6 weeks of sofosbuvir and ribavirin in recent hepatitis C infection.

In a study from Australia/New Zealand 19 patients with recent hepatitis C infection were treated with sofosbuvir and weight based ribavirin for 6 weeks. Recent hepatitis C was defined as a duration of infection < 12 months. 14 of the participants were HIV-infected on stable antiretroviral therapy. 6 patients had an asymptomatic seroconversion while all other had symptomatic disease. With the availability of extremely potent drugs against chronic hepatitis C and the high cost of treatment it seems reasonable to defer treatment until spontaneous clearance has been ruled out.
was demonstrated with a shift from genotype 3a to genotype 1a between weeks 4 and 12 posttreatment.

Martinello et al. Hepatology 2016;64:1911-1921

**Comment:** 6 weeks of sofosbuvir in combination with weight based ribavirin is obviously insufficient for treatment of recently acquired hepatitis C.

**Effect of antiretroviral therapy on malaria incidence in HIV-infected Ugandan adults**

Data from a cotrimoxazole cessation study in Ugandan HIV-positive adults was used to evaluate the effect of antiretroviral therapy on the incidence of malaria. Patients with more than 250 CD4+ cells/µL were randomized to receive placebo or cotrimoxazole. Irrespective of cotrimoxazole use they were categorized into three groups according to antiretroviral therapy; nucleoside reverse transcriptase inhibitor (NRTI) only, non nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen or protease inhibitor (PI)-regimen. Blood slides for malaria microscopy were examined at scheduled visits and at unscheduled visits when the participant felt sick. The original purpose of the study was to evaluate if cotrimoxazole could be safely discontinued in HIV-positive adults with more than 250 CD4+ cells/µL. The trial enrolled 2180 participants. A vast majority of the patients started on an NNRTI-containing regimen in accordance with WHO recommendations. 86 patients (4 %) were on a PI-containing (mostly lopinavir/ritonavir) regimen at study inclusion and 1 % were treated with NRTI only. During the study 10 patients switched to a PI-containing therapy. 447 episodes of malaria were observed during the study. Malaria incidence per 100 person years was 9.9 in the NRTI only group, 9.3 in the NNRTI group and 3.5 in the PI group. Due to the low number of participants the confidence interval for the PI group was wide and the difference just reached statistical significance. Stratification for cotrimoxazole gave similar results.

Kasirye et al. AIDS 2017;31:577-582

**Comment:** The positive effect of protease inhibitor use on malaria in African children has been reported in earlier studies. The present study was not originally designed to evaluate the effect of different antiretroviral therapies on the malaria incidence. Nevertheless the study results indicate that the choice of antiretroviral regimen in malaria endemic regions may have important impact on public health not only from a strict HIV-perspective.

**Prognostic value of transient elastography (TE) in HIV/HCV infection**

1292 coinfected Spanish patients were included in a retrospective study of the prognostic value of TE. All patients had undergone at least one examination with TE after it was introduced as a routine procedure to evaluate liver fibrosis in coinfected patients 2006. The primary outcome was the occurrence of liver related events (LRE) defined as decompensation or hepatocellular carcinoma. 90 patients experienced LRE. The median follow up time was 5.8 years. In a subgroup of 957 patients who did not achieve sustained viral response or end of treatment response the TE result was evaluated to predict LE. A cutoff value of 12 kPa was established as a predictor of the risk of developing LE. The negative predictive value of a value below 12 kPa was 98 %. In patients with TE scores above 12 kPa there was a proportional increase hazard ratio of LE. For each kPa the hazard ratio increased 1.07 (1.05-1.08) and for 5 kPa increase above 12 the hazard ratio was 1.38 (1.31-1.46).


**Comment:** The usefulness of transient elastography to classify fibrosis and predicting the risk of hepatic decompensation and hepatocellular cancer is confirmed in this important study. It is of course desirable to treat all hepatitis C infected patients as fast as possible but taking the high negative predictive value of a TE result below 12 kPa into account it seems acceptable to postpone treatment somewhat in patients with low TE scores.
Topical Conferences 2017

9-12 May
11th INTEREST workshop
Lilongwe, Malawi
www.virology-education.com/event/upcoming/
interest-workshop-2017/

20-21 May
Asian Conference on Hepatitis and AIDS 2017
Shenzhen, China
www.virology-education.com/event/upcoming/acha2017/

May 25-28
The 29th Annual National Conference on Social Work
and HIV/AIDS Exit Disclaimer
Atlanta, GA, USA
www.bc.edu/schools/gssw/academics/ce/conferences.html

7-9 June
15th European Meeting on HIV & Hepatitis: Treatment
Strategies & Antiviral Drug Resistance
Rome, Italy
www.virology-education.com/event/upcoming/
15th-european-meeting-hiv-hepatitis-2017/

11-13 June
The Viral Hepatitis Congress
Frankfurt, Germany
www.viral-hep.org

9-12 July
STI & HIV World Congress
Rio de Janeiro, Brazil
http://stihivrio2017.com/

23-26 July
9th IAS Conference on HIV Science (IAS 2017)
Paris, France
www.iars2017.org/

27-29 September
4th HIV & Hepatitis Nordic Conference
Stockholm, Sweden
www.hivnordic.se

4-8 October
ID Week 2017
San Diego, United States
www.idweek.org/

12-14 October
NeuroHIV 7th International meeting on HIV Infection
of the Central Nervous system
Sicily, Italy
www.neurohiv.com

20-24 October
The Liver Meeting 2017 - American association for the
study of liver diseases 68th annual meeting 2017
Washington, United States
www.aasld.org/events-professional-
development/liver-meeting

25-27 October
16th European AIDS Conference (EACS 2017)
Milan, Italy
www.eacs-conference2017.com/