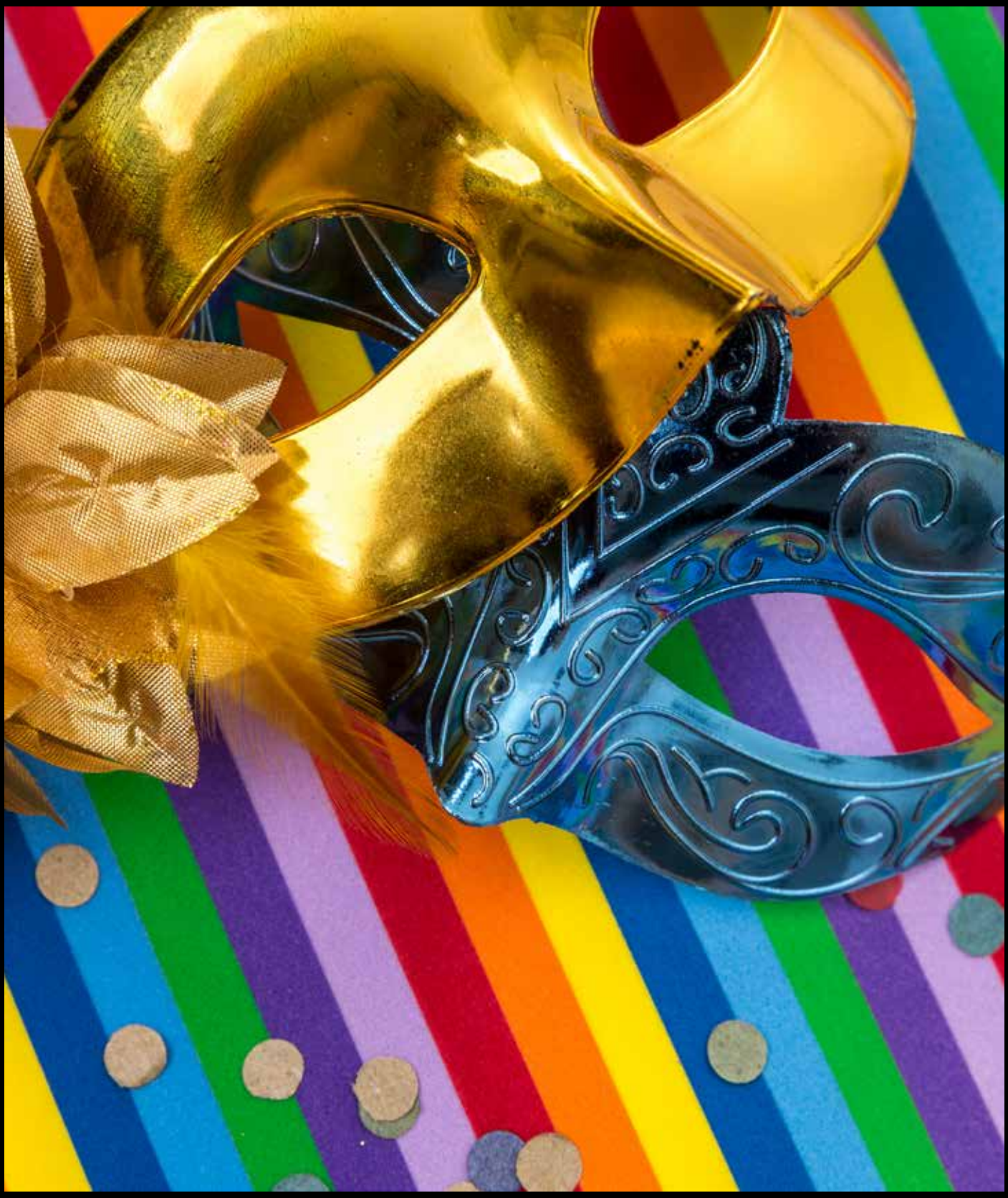
HIV & VIROLOGY NEWS

Issue 1 · 2018



CROI IN BOSTON 2018 · EUROPEAN AIDS CONFERENCE 2017 · SATELLITE SYMPOSIUMS AT THE EUROPEAN AIDS CONGRESS
THE EASL 2017 CLINICAL PRACTICE GUIDELINES ON HBV INFECTION · BHIVA - RESENT EVENTS · THE THIN HARVEST OF STUDIES
OF ANTIRETROVIRAL THERAPY IN NAÏVE · THE BAD OLD DAYS · NOTES 2018 · TOPICAL CONFERENCES 2018

HIV & VIROLOGY NEWS

HIV & Virology News is distributed four times each year, free of charge, to specialists in HIV and virology.

This magazine covers the major congresses and industry symposiums, as well as general news within these areas. It is distributed in April, June, October and December.

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In this issue:

Milano

Dear Colleagues

On behalf of the editorial group, I would like welcome you back to the first issue of *HIV & Virology News* for 2018. This is the eighth volume of our quarterly journal, which was founded in 2011 and is distributed free of charge to approximately 16,000 physicians in the field of infectious diseases in thirteen European countries.

Although the journal is financed by advertisements, its authors are totally independent; advertisers have no influence whatsoever over what we publish. The editors and other contributors are encouraged to share their personal viewpoints, whether controversial or not. We are greatly encouraged by the positive feedback we have received from a wide range of European physicians and clinicians in the HIV and hepatitis field. Our commitment is to develop the magazine further, and so we welcome your suggestions and recommendations for future issues. You may contact the editorial office and share your thoughts with us at editor@hivvirology.com. You can also find *HIV & Virology News* online at www.hivvirology.com.

CROI 2018, the annual Conference on Retroviruses and Opportunistic Infections, was recently held in Boston, Massachusetts, and as usual a great deal of valuable new data was presented. Each year fewer and fewer studies of new antiretrovirals are announced, which is not surprising since we already have access to very potent drugs with generally mild, if any, side-effects. This year considerable attention was given to co-infection with tuberculosis, a major global problem that results in a high burden of morbidity and mortality.

New research data was unveiled in the reservoir and cure field, including promising results about broad neutralizing antibodies (bNAbs). Dan Barouch from Beth Israel Deaconess Medical Center in Boston showed that the V3 glycan-dependent bNAb PGT121, combined with the toll-like receptor 7 (TLR7) agonist GS-962, were able to delay and control viral rebound following ART discontinuation in SHIV-infected rhesus monkeys in whom ART was initiated very early during acute infection. In five out of eleven monkeys whose infections were controlled without viral rebound, adoptive transfer challenges into uninfected recipients were performed without any transmission of virus—a unique development.

CROI 2018 is extensively reviewed in this issue of *HIV & Virology News*. You can also find the second part of our coverage of the European AIDS Clinical Society (EACS) Conference in Milan that began in the previous issue; a summary of the EASL 2017 Clinical Practice Guidelines on the management of HBV infection; and a great deal of other material that we hope you will find informative and stimulating.

Magnus Gisslén
Editor

CROI 2018 in BOSTON

This year CROI celebrated its 25th Conference in Boston, USA. 4,075 registered attendees from 78 countries had come to the North American east coast to participate. They were all greeted welcome by Chair Dr Judith Currier, USA.

During the Opening session, Dr Currier pointed out that there are no commercial activities during the Conference, which sets it apart from many other Meetings.

– The Conference is largely funded by participant registration fees. Other commercial grants are given by supporters from the industry, and we thank them all for their continuous support, she said.

Fewer young choose to study HIV

There are many threats as well as opportunities 25 years into CROI. Funding levels are flat and declining.

– We have done more with less, but we could do so much more with more, Dr Currier underlined.

Treatment and prevention both play a role in ending the epidemic, but there is still a need for a vaccine, a need to expand pre-exposure prophylaxis (PrEP) and other modalities that prevents people to be infected.

– We have a growing youth population in sub-Saharan Africa that is threatening the gains we have made in reducing incidence. And we are not prepared for the ageing population of people living with HIV. Fewer young people are going in to the field of HIV and AIDS research. This is a great concern, coupled with the decreasing investment from the industry as well, she pointed out.

A tool for identifying growing clusters

In a session on new approaches on surveillance and epidemiology, Dr Anne Marie France, epidemiologist at Centres for Disease Control and Prevention (CDC), talked about the rapidly growing HIV transmission clusters in the US 2013 - 2016.

At the end of 2015, an estimated 1,1 million people aged 13 or more were living with HIV infection in USA.

– It is estimated that for each 100 persons living with HIV, there will be 4 transmission events per year. We know however that this transmission rate is not uniform across the population of people living with HIV. It is likely there are some networks with high rates of transmission that are responsible for a disproportionate number of new infections.

Ms France explained that identifying these networks, or clusters, is key to focusing prevention efforts that are effective – such as testing to identify previously undiagnosed infections and ensuring those with diagnosed infection are linked to care.

– Also for providing PrEP and other prevention services for those who are HIV-negative but at increased risk. We would also like to identify factors associated with transmission to guide focused, community-level interventions, she explained.

In the US, HIV drug resistance testing is recommended for all newly diagnosed HIV-infected persons. This generates HIV nucleotide sequence data. Harnessing these data can be used to construct transmission networks that link persons infected with genetically similar variants – a tool to identifying growing clusters that represent active transmission. Such analyses have previously been performed, but have typically been retrospective.

– It has rarely been done prospectively. So we thought to implement routine analyses to identify growing molecular clusters in the US, and to assess transmission rates in these clusters. This for identifying characteristics of growing molecular clusters and persons in these clusters, Ms France said.

Reflect the leading edge of transmission

US HIV Surveillance System is the primary source for monitoring HIV infection ➤

in the US, and HIV nucleotide data are reported to them. They provided data for the analysis that Ms France presented.

– 51,750 persons with HIV were diagnosed from January 2013 to December 2016 with sequences. We identified 60 priority clusters, and these clusters ranged in size from 5 - 42 persons as of December 2016. The clusters were identified in all regions of the country, and involved 20 states, she continued.

Ms France told the audience that the transmission rates for these 60 clusters were 44 per 100 person-years – i.e. *eleven times* higher than the national estimate. She then noted differences in those who were sequenced among persons in the clusters, compared to those who not are in the clusters, by transmission category.

– We see that priority clusters had disproportionally men who has sex with men (MSM) – 83 % compared to 59 % overall. Heterosexual and injecting drug user were less represented in priority clusters.

There was also a difference in age at diagnosis among persons with sequences. In the clusters, 70 % were diagnosed at an age below 30, to be compared with 42 % in all others.

– There was a difference in race and ethnicity: 38 % were Hispanic in clusters, as compared to 27 % in all another. Blacks were 31 % in clusters – and 41 % in all other. For whites the difference was only 1 %.

Anne Marie France

Renee Hefron

These analyses consistently identify clusters across the US with transmission rates far exceeding the national average. These clusters likely reflect the leading edge of HIV transmission, Ms France summarised.

– Prioritizing these networks for public health interventions may increase potential to reduce future infections. CDC continues to run quarterly analyses to identify new clusters and monitor identified clusters. Work to act on these findings to guide prevention efforts is underway, but the work of state and local health departments, and their partner, is essential to translate information on these growing clusters into effective public health action.

Increased risk for HIV during pregnancy

For women of reproductive age, HIV is one of the leading causes of death worldwide. Studies of pregnancy as a risk factor for HIV are conflicting. Dr Renee Hefron, USA, presented a study with the objective to estimate the probability of HIV acquisition per sex act during periods when women were pregnant and postpartum, and compare these possibilities to time periods unrelated to pregnancy.

– We used data from two longitudinal HIV prevention studies, that were randomised trials and included HIV serodiscordant couples, Dr Hefron said.

The investigators found an increased risk of HIV acquisition per sex act that were 3-fold in late pregnancy and 4-fold in postpartum.

– The results accounted for decreases in sexual frequency and condom use as pregnancy progressed. The analysis suggest that biological changes associated with pregnancy and postpartum contribute to increased HIV acquisition. However, we did not directly assess any biological mechanisms for increased HIV susceptibility, Dr Hefron continued.

Her comment was that antenatal care presents tremendous opportunities to promote HIV prevention and care.

– These data highlights the importance of counselling on increased HIV risk during pregnancy and postpartum – and promoting repeated HIV testing during maternal health visits. Not just relying on one test at the beginning of pregnancy!

Dr Hefron also underlined the importance of identifying HIV infected partners and linking them to HIV care and ART initiation.

– Oral PrEP is recommended by the WHO during pregnancy, and it would be a good strategy to promote to pregnant women at risk for HIV infection, Dr Hefron stated.

HIV infection maintained by the proliferation of infected cells

– There has been an ongoing debate on whether the HIV reservoir is sustained through ongoing cycles of viral replication. So we have previously published – along with others – that we have been unable to find evidence for ongoing cycles of viral replication when we look in the blood from patients that have been treated with ART for many years, said Dr Mary Kearney, USA.

But a paper published in 2016 claimed to show evidence of ongoing replication in the lymph nodes, to a level that sustained the HIV reservoir in these individuals.

– We wanted to investigate this. The question was if we could find evidence for ongoing HIV-1 replication in the lymph nodes during suppressive ART.

To do this, they analysed HIV-1 proviral genetics in pre-ART, and after 2 - 13 years on suppressive ART in paired lymph node and peripheral blood samples. This in order if they could see a different dynamics in these two locations, Dr Kearney explained.

– We also analysed HIV-1 integration sites in paired lymph nodes and peripheral blood samples to see if we could find a different profile of integration across these two locations.

Lastly, they analysed HIV-1 RNA expression in single cells in paired lymph node and peripheral blood samples.

The findings she reported suggest that the HIV infection is likely maintained by the proliferation of cells infected prior to ART – not by ongoing cycles of viral replication in either the peripheral blood or the lymph nodes.

Intensifying ART with dolutegravir

Previous studies have clearly demonstra-


Thomas Rasmussen


Dan Barouch

ted that the longevity and also the proliferation of latently infected T-cells are key mechanisms of persistence. But in contrast, whether or not residual replication on ART is also contributing to viral persistence has remained much more controversial, Dr Thomas Rasmussen, Denmark, said.

– The argument against residual replication includes studies that have shown no evolution of virus sequences on ART, no emergence of drug resistance and no change in HIV DNA, he continued.

On the other hand, it was suggested in a recent study that there might be some evolution in virus sequences in ART, but in that study only samples that had been obtained early (6 months of ART) were included and analysed. Another study showed continuous viral production in tissue on ART, but whether this represent actual replication or just production is uncertain.

– And finally, in previous randomised controlled studies on raltegravir intensification, increase in 2LTR circles was seen, Dr Rasmussen said.

He presented a study where the hypothesis was that dolutegravir intensification will inhibit and reveal residual virus replication in individuals on suppressive ART. It was an investigator-initiated, randomised, placebo-controlled, double-blind clinical trial. HIV-infected adults that had been on ART with a suppressed viral load for more than 3 years were enrolled from two centers in Australia.

– This study of dolutegravir intensification showed no change in 2-LTR, which we interpreted as no interference with residual replication during the intervention, he summarised.

The investigators saw no change in cell-associated markers of HIV persistence, and no changes in T-cell activation or in plasma markers of immune activation.

– So we conclude that intensifying ART with dolutegravir did not reveal or impact residual virus replication at least in blood in HIV infected individuals on ART.

bNAbs to target the reservoir

Prof Dan Barouch, USA, presented a Late-breaker on broadly neutralizing antibodies (bNAbs). Previous studies in humans has shown that bNAb administration at the time of ART discontinuation can delay viral rebound, confirming that bNAbs have direct antiviral activity.

– However, whether bNAbs can actually target the reservoir during ART suppression remains unknown, as latently infected cells may not express sufficient envelope on the cell surface for bNAb recognition, he pointed out.

The ability of bNAbs to target the reservoir – rather than just provide antiviral activity – is required for an HIV-1 cure strategy. To assess for anti-reservoir activity, bNAbs need to be administered during ART suppression and no longer be present at therapeutic levels at the time of ART discontinuation.

PGT121 is a recombinant human IgG1 monoclonal antibody that targets a V3 glycan-dependent epitope region of the HIV envelope. GS-9620 is a Toll-Like Receptor 7 Agonist that induces HIV expression and HIV-specific immunity in cells.

– To evaluate a combination of these, we infected 44 rhesus monkeys with SHIV, and then initiated ART (TDF/FTC/DTG) very early at week 1. Then we prolonged the suppression with ART for a long time – 96 weeks, Prof Barouch described the study.

Then the intervention started, and the monkeys were divided into 4 groups. Group 1 received sham treatment (controls), Group 2 received the TLR7 agonist alone, Group 3 PGT121 alone and the fourth group received both PGT121 and the TRL7 agonist. There were 11 monkeys in each group.

No viral rebound for more than six months

The investigation went on from week 96 to week 114, and the antibody wash-out period lasted from week 114 to 130, when ART was stopped.

– The combination of PGT121 + GS-9620 led to a 5-fold delay in the time to viral rebound as well as substantially reduced viral loads following ART withdrawal, Prof Barouch said.

In the study, 5 of the 11 monkeys that received PGT121 + GS-9620 showed no viral rebound for more than 6 months, with negative adopted transfer studies.

– We believe that residual PGT121 cannot explain the delay in rebound because antibody levels were less than 1 microgram per ml – the previously defined threshold – for a period of more than 2 months prior to ART withdrawal.

The mechanism remains unclear, but might involve activation of CD4+ T-cells by GS-9620, which was documented, followed by potentially enhanced binding and clearance by PGT121. There was no ➤

evidence of a bNAb-induced "vaccinal effect" by the assays that were used.

– Overall, these data suggest that bNAbs combined with an innate immune stimulant may effectively target the viral reservoir, Prof Barouch concluded.

B/F/TAF non-inferior to DTG/ABC/3TC

In a session on new data and insights on ART, a study on switch to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) from dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) in HIV-1 infected adults was presented by Prof Jean-Michel Molina, France.

– As you know, bictegravir is a novel, unboosted, potent integrase strand transfer inhibitor (INSTI) with a high in vitro barrier to resistance and low potential for drug-drug interactions. It is co-formulated with emtricitabine and tenofovir alafenamide as a single-tablet regimen, dosed once-daily with or without food, Prof Molina said.

HIV-suppressed adults on regimen containing DTG, ABC and 3TC, and who were well suppressed, were randomised to either continue the regimen or switch to B/F/TAF for 48 weeks. It was a non-inferiority study with the proportion of patients with HIV RNA higher than 50 copies per ml as its primary endpoint.

– The data show that switching to B/F/TAF was non-inferior to DTG/ABC/3TC. No treatment emergent resistance was observed in neither arm. The switch to B/F/TAF was well tolerated, and the adverse events profiles were comparable between arms at week 48, Prof Molina summarised.

The lipid, bone and renal safety of switching was comparable to remaining on DTG/ABC/3TC.

– So we conclude that B/TAF offers an effective and safe alternative to DTG/ABC/3TC.

Dolutegravir in HIV/TB co-infection

Another session focused on advances in TB treatment. Dr Kelly Dooley talked about a study on the safety and efficacy of dolutegravir ART in TB/HIV co-infected adults.

– Dolutegravir (DTG)-based regimens are now recommended by WHO as alternative first-line regimens. Several countries with high HIV prevalence have adopted DTG-based regimens as first-line treatment, she started by stating.

Characterizing the efficacy, safety, and drug-drug interactions of DTG in patients with tuberculosis (TB) co-infection is a high priority.

– Efavirenz is commonly used, but alternatives are needed – particularly in the setting of adverse events and transmitted drug resistance to non-nucleoside reverse-transcriptase inhibitors (NNRTIs).

Jean-Michel Molina

Kelly Dooley

DTG has some features that may favour its use: Good long term efficacy and favourable safety profile, high barrier to HIV resistance and no impact of primary NNRTI resistance (with a prevalence of around 10 % in some regions). Also, DTG has low potential for drug interactions and is not an inducer of CYP450 enzymes.

– The INSPIRING study is being conducted to estimate the antiviral efficacy and evaluate the safety of DTG in ART-naive adults with HIV/TB co-infection. Today I am going to present the week 24 results, Dr Dooley said.

INSPIRING showed that DTG given at 50 mg twice a day during concomitant rifampin-based TB therapy demonstrated high efficacy and a good immunological response through week 24.

– DTG was well tolerated, the majority of adverse events were grade 1 or 2, with low rates of drug-related adverse events and serious adverse events. No adverse events led to withdrawal. This study provides evidence that DTG is effective and well tolerated in adults with HIV/TB co-infection receiving rifampin-based treatment, Dr Dooley concluded.

Urine-based screening for TB

TB causes 32 - 67 % of deaths in HIV-positive adults admitted to hospitals in Africa, with about half of patients were undiagnosed with TB at the time of death, said Prof Ankur Gupta-Wright, UK.

– This is due to the failure of current diagnostic approach, which relies heavily on test in sputum, he pointed out.

Urine TB-diagnostics have good diagnostic yield, and may reduce deaths and missed TB diagnoses.

Dr Gupta-Wright presented a late-breaking study on rapid urine-based screening for TB, the STAMP trial.

– 99 % of patients were able to produce an urine sample for testing, compared to only 57 % who could produce a sputum sample

The STAMP trial showed that urine-based screening in unselected HIV-positive medical admissions reduced mortality in key subgroups – despite high ART coverage in hospitalised patients.

– Enhanced urine-based TB screening also substantially increased TB diagnosis and treatment, and this benefit was not restricted to subgroups. Note the intervention increased TB diagnosis in patients with CD4 levels more than 100, that were not suspected to have TB by the admitting clinician.

Dr Gupta-Wright's conclusion was that the STAMP trial results support urine-based TB screening in hospitalised TB patients.

Current rifampin doses may be too low

Another late-breaker was a study on a randomised, controlled trial of high-dose rifampin for pulmonary TB. It was pre-

HIV & HEPATITIS NORDIC CONFERENCE

PRELIMINARY PROGRAM

Wednesday	**26-sep**
	Coffe and sandwich will be served from 08.30
09.00-10.00	**Registration**
	Opening session
10.15-10.20	Welcome (Nina Weis, Denmark)
10.20-10.50	**Opening Plenary**
	Progress towards reaching the 90-90-90 HIV target in Europe and beyond (Anastasia Pharris, ECDC, Sweden)
10.50-11.00	Discussion
	Abstract Session I
11.00-11.15	Oral 1 (10 min + 5 min discussion)
11.15-11.30	Oral 2
11.30-11.45	Oral 3
11.45-12.00	Oral 4
12.00-13.00	***Lunch***
	Plenary Session I
13.00-13.30	Plenary 2
	Mortality and morbidity among children and adolescents with perinatal HIV infection (Ruth Goodall, UK)
13.30-13.40	Discussion
13.40-14.10	Plenary 3
	HIV infected women and breastfeeding (Ellen Moseholm Larsen, Denmark)
14.10-14.20	Discussion
14.20-14.35	Short break
14.35-15.50	**BHIVA and HIV Nordic joint session – Aspects on HIV prevention in high-risk-populations**
	Chemsex (Ann Sullivan, UK) PrEP, implementation in Norway (Frank Olav Pettersen, Norway) Declining HIV prevalence among MSM in London (Ann Sullivan, UK)
	Discussion
15.50-16.30	Coffee and exhibition/posters
16.30-17.30	Satellite Symposium I
17.30-17.45	Short break
17.45-18.45	Satellite Symposium II
18.45-	Poster Exhibition with cheese and snacks

Thursday	**27-sep**
08.00-09.00	Satellite Symposium III
09.00-09.10	Short break
	Plenary Session III – Inflammation and reservoirs
09.10-09.40	Plenary 6
	Tissue resident T-cells and immunity during acute and chronic HIV-infection (Mike Betts, USA)
09.40-09.50	Discussion
09.50-10.20	Plenary 7
	Microbial translocation and microbiome dysbiosis in HIV-associated immune activation (Piotr Nowak, Sweden)
10.20-10.30	Discussion
10.30-11.00	Coffee and exhibition/posters
11.00-11.30	Plenary 8
	Is it possible to enhance immune function in HIV-infected persons on ART with immune failure? (Michael Lederman, USA)
11.30-11.40	Discussion
	Plenary Session IV – Living with HIV
11.40-12.10	Plenary 9
	Life expectancy and long-term outlook in PLHIV (Caroline Sabin, UK)
12.10-12.20	Discussion
12.20-12.50	Plenary 10
	Recent achievements in Next-Generation Sequencing (NGS) of HIV and possible clinical implications (Roger Paredes, Spain)
12.50-13.00	Discussion
13.00-14.00	Lunch
	Plenary Session V – Last year's most important achievements in the HIV research field
14.00-14.30	Plenary 11
	Top 5 in basic HIV research 2016-2017 (Jan Albert, Sweden)
14.30-14.40	Discussion
14.40-15.10	Plenary 12
	Top 5 in clinical HIV research 2017-2018 (Anne-Mette Kjær Lebech, Denmark)
15.10-15.20	Discussion
15.20-15.30	Plenary 13
	The history of HIV in Finland (Matti Ristola, Finland)
15.30-15.45	HIV & Hepatitis Nordic Conference 2018 Abstract Award (Matti Ristola, Finland)
15.45-16.15	Coffee and exhibition/posters
16.15-17.15	Satellite Symposium IV
17.15-17.30	Short break
17.30-18.30	Satellite Symposium V
	Conference dinner

Friday	**28-sep**
08.00-09.00	Satellite Symposium VI
	Plenary Session VI – Last year's most important achievements in the hepatitis field
09.10-09.40	Plenary 14
	Top 5 in hepatitis research 2017/18 (Martti Färkkilä, Finland)
09.40-09.50	Discussion
	Abstract Session II
09.50-10.05	Oral 5 (10 + 5 min discussion)
10.05-10.20	Oral 6
10.20-11.00	Coffee and exhibition/posters
	Plenary Session VII
11.00-11.30	Plenary 15
	Update on hepatitis E (Heléne Norder, Sweden)
11.30-11.40	Discussion
11.40-12.10	Plenary 16
	Can HCC surveillance be stopped? / Post SVR surveillance (Sofie Hallager, Denmark)
12.10-12.20	Discussion
12.20-13.20	Lunch
	Plenary Session VIII – Hepatitis C
13.20-13.50	Plenary 17
	HCV treatment in needle exchange programs (Marianne Alanko, Sweden)
13.50-14.00	Discussion
14.00-14.30	Plenary 18
	HCV treatment in the prison systems (Soo Aleman, Sweden)
14.30-14.40	Discussion
14.40-15.10	Plenary 19
	Global Perspectives on HCV Eradication (TBD)
15.10-15.20	Discussion
15.20-15.30	Concluding remarks

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See you in Stockholm!

sented by Dr Gustavo Velásquez, USA.

The standard of care for pulmonary TB is a 6-month, 4-drug regimen that includes rifampin throughout.

– Back in the seventies, when rifampin was an expensive drug, attempts to further shorten TB therapy with higher, intermittent doses of rifampin were unsuccessful due to an apparent increase in toxicity. Later, other controlled trials have evaluated higher daily doses of rifampin, Dr Velásquez said.

But so far none have evaluated concentration-dependent activity in Latin American patients, or looked at efficacy as a function of the pharmacokinetic/pharmacodynamic parameter that is best thought to best predict rifampin activity, which is AUC/MIC.

– So we conducted a blinded, randomised, controlled phase II clinical trial to assess the pharmacokinetics, efficacy and safety of higher *daily* rifampin doses for pulmonary TB. The study was conducted at two hospitals in Peru.

The results showed both dose- and exposure response of rifampin in combination therapy.

– They confirm – at least – dose-proportional increase of rifampin exposures. We did not find a daily dose-dependant toxicity, which is consistent with four other trials. This supports that even higher rifampin doses should be studied. Current rifampin dose may be too low, so it is possible that it could safely be raised to 15 or 20 mg/kg, Dr Velásquez summarised the findings.

Gustavo Velásquez

Sandra Springer

Opioid and alcohol pharmacotherapies included in ART

The UNAIDS goals by year 2020 is that 90 % of all people that are HIV positive should be aware of their HIV status, 90 % of HIV positive people will receive ART and 90 % of those on ART should be virally suppressed.

– These goals can not be achieved without special attention to prisoners and jail detainees, said Dr Sandra Springer, USA.

In the US, HIV is roughly three times greater in prevalence in the prison population compared to the community.

– Although we know that people living with HIV in prisons can receive ART and achieve viral suppression – for the most part prior to their release – that benefit is quickly lost soon *after* they are released.

Relapse to drugs and alcohol use occurs quickly after release, and is associated with loss of viral suppression. A study on this showed that a viral suppression rate on 59 % pre-release, had diminished to 18 % 3 months after release. Loss of viral suppression is associated with morbidity and transmission.

Extended release naltroxene (XR-NTX) reduces relapse to opioid and alcohol use. Dr Springer presented two studies with one specific aim:

– This aim was to evaluate a pharmacotherapy for treatment of opioid use and alcohol disorders with XR-NTX in order to maintain or achieve HIV viral suppression among prisoners and jail attendees with HIV. The study on opioid use disorders is called NEW HOPE, and the study on alcohol use disorders is called INSPIRE.

She reported that the studies had found that XR-NTX is a medication that can be used to reduce alcohol and drug abuse. It can also help stabilize patients coming out of prison and jail, and help to maintain viral suppression.

– I think that to reach the 90-90-90 goal for people living with HIV that are released from prison, high consideration should be given to include opioid and alcohol pharmacotherapies with ART. Future research should involve assessment of XR-NTX in other settings to achieve viral suppression in people living with HIV, as well as for HIV prevention, Dr Springer concluded.

Serious clinical events increase for patients with chronic kidney disease

Chronic kidney disease is becoming increasingly common in the ageing HIV-positive population, with an estimated prevalence up to 30 % in high-risk populations, said Dr Lene Ryom, Denmark.

– Risk factors for chronic kidney disease amongst HIV-positive persons are well established and include traditional renal failure, HIV related renal failure and ART related renal failure, she pointed out.

However, insights into the prognosis after chronic kidney disease in persons with HIV are limited, and require a large dataset with substantial follow-up time. Dr Ryom presented an analysis, based on data from the D:A:D study, with the aim to determine the prognosis and incidence of serious clinical events after diagnosis of chronic kidney disease in people living with HIV, and the role of – if any – modifiable risk factors.

The first conclusion from the analysis was that in an era where many HIV-positive persons require less monitoring due to effective ART, those living with chronic kidney disease have a high burden of serious clinical events – with almost one fifth developing serious clinical events within 3 years, which require closer clinical monitoring.

– We further found that compared to persons living without chronic kidney disease, those living with it have substantially higher rates of organ dysfunction, non-AIDS defined malignancies and non-malignant AIDS events, Dr Ryom said.

The data further suggest modifiable risk factors, including smoking, dyslipidemia, poor HIV control, diabetes and low BMI and low estimated glomerular filtration rate (eGFR).

– These risk factors play a central role for post-chronic kidney disease morbidity and mortality – and highlight the need of

increased awareness, effective treatment and preventive measures for those living with chronic kidney disease, Dr Ryom summarised.

Higher incidence for peripheral artery disease in HIV patients

Dr Andreas Knudsen, Denmark, presented a study on peripheral artery disease in persons with HIV.

– Peripheral artery disease of the lower extremities starts as asymptomatic narrowing of the arteries. With time, it can progress to gangrene and amputation, he explained.

The objective of the study was to determine the prevalence and risk factors of peripheral artery disease in persons living with HIV, compared to uninfected controls.

– We hypothesised that the prevalence is higher in people living with HIV than controls, and that HIV is independently associated with peripheral artery disease, Dr Knudsen explained.

908 people living with HIV were compared to 11,106 uninfected controls. All participants were aged 40 or more.

– There are also some limitations of the study: The cross-sectional design prevents us from drawing any conclusions regarding causality, and we had no information about previous revascularisation, he pointed out.

Dr Knudsen concluded that the prevalence of peripheral artery disease indeed was higher among people living with HIV, compared to uninfected controls. Also that HIV was independently associated with peripheral artery disease.

– And we found some evidence that this relationship was more pronounced in elderly individuals, he said.

Open label extension on dapivirine vaginal ring

Two years ago at CROI, two phase III clinical trials were presented that showed a monthly vaginal ring containing dapivirine was tolerated and reduced HIV-1 incidence by approximately 30 % compared to placebo.

At CROI 2018, Prof Jared Baeten, USA, presented an open-label extension on the trials, called MTN025/HOPE. It is a multi-center, open-label, phase IIIb study of the dapirivine vaginal ring, 25 mg, monthly replaced.

– For new HIV-1 prevention strategies, the pathway from clinical trials to implementation often passes through open-label extensions, Prof Baeten pointed out.

The population in the study is HIV-1 uninfected women who had previously

participated in the MTN020/ASPIRE study. Women may choose to accept, or not accept, the dapivirine vaginal ring at each follow-up visit.

– Primary objectives are to assess adherence and safety in an open-label setting.

ASPIRE reported its primary results in February 2016, and HOPE began in August 2016. Enrolment concluded in September 2017 and HOPE will be ongoing until October 2018. Data presented at CROI this year were from October 2017, the last Study Monitoring Committee review.

– Returned, used rings are tested for residual levels of dapivirine. Rings with levels under 23.5 mg of dapivirine are defined as indicating at least some adherence during the month, thus it does not necessarily indicate consistent use, Prof Baeten continued.

He said that to date, 89 % of returned rings had levels less of 23.5 mg – compared to 77 % in ASPIRE.

– These interim results suggest important HIV-1 prevention effectiveness of the dapivirine vaginal ring when used by African women in an open-label setting, was Prof Baeten's conclusion.

ART initiation at young age

Dr Marta Massanella, USA, presented a study on ARV prophylaxis and ART initiation at birth in Thai children.

– As you all know, early ART initiation and virologic control during the first years of life limit the size of the HIV reservoir, she said.

The aim of the study was to identify predictors of the HIV reservoir size in the paediatric population.

– One thing we wanted to analyse was the impact of age at ART initiation has on the HIV reservoir. We found that infants who started ART before 6 weeks of age show lower levels of all markers of HIV

Andreas Knudsen

Marta Massanella

persistence, Dr Massanella reported.

In her conclusions she stated that controlling viral replication limits the size of the initial HIV reservoir. Also that direct transition from prophylactic antiretroviral to ART, and ART initiation at a younger age, are associated with lower HIV reservoir.

– Importantly, early ART (less than 6 weeks) dramatically restricts the pool of cells harbouring total and integrated HIV DNA, as well as the inducible reservoir.

Time to rebound after stopping ART in children

The CHER trial, presented by PhD Man Chan, UK, had investigated the time, and factors associated with time, to viral rebound after stopping ART in children treated from infancy.

The study found that after stopping ART, estimated cumulative probability of viral rebound was 80 % by 4 months, and 99 % by 8 months.

– Interestingly, one child remained suppressed until the end of follow-up, Ms Chan said.

Higher baseline CD4 percentage, higher birth weight and faster viral suppression were independently associated with longer time to viral rebound.

– Age at ART initiation and length of therapy were not significantly associated with longer time to rebound. However, we ➤

should interpret these results with some caution: Age at ART start only ranged from 6 to 12 weeks.

She concluded that the results suggest that pre-treatment immune function and birth health may influence viral control after treatment discontinuation.

Grazoprevir/elbasvir as effective as 12 weeks

In a session on hepatitis virus C (HCV) and HIV-associated malignancies, Dr Anne Boerekamps, the Netherlands, presented the DAHHS 2 study. It was a single-arm, prospective, open-label multicenter phase IIb trial on 8 weeks of grazoprevir plus elbasvir for acute HCV genotype 1 or 4 infection.

– In the Netherlands, the group with the highest number of HCV infections are HIV-infected men who have sex with men (MSM). Although we saw a significant decline of HCV infections last year in Dutch MSM after a very rapid treatment of direct-acting-antivirals (DAAs) for chronic HCV, our results were not confirmed by a recent French study – despite a similar treatment uptake. So additional interventions are needed, Dr Boerekamps said.

One such additional intervention could be to treat patients with acute HCV infection *immediately* after diagnosis, instead of waiting for spontaneously clearance occurs. The DAA labels only talks about chronic HCV as an indication, and this has resulted in reimbursement restrictions in many countries for acute HCV infection with DAAs.

– Therefore we feel that convincing evidence is needed to support cost-effectiveness and efficacy of DAA therapy for acute hepatitis C.

Based on the results so far, the study showed that an 8 week course of grazoprevir/elbasvir for acute HCV was safe and effective, and non-inferior compared to 12 weeks for chronic HCV.

– Our study is the first study that included a substantial number of genotype 4 patients (29), a substantial number of patients with a high viral load – more than 1,000,000 IU/ml (19) and our sample size is sufficient to draw conclusions of non-inferiority, she stated.

The study also had some limitations. It was on a non pan-genotype regimen, so genotyping was still needed.

– And keep in mind that sustained virological response of 17 patients are still pending, The final results will be available in July 2018, Dr Boerekamps ended by pointing out.

Anne Boerekamps

Christoph Boesecke

Spontaneous clearance is rare

Dr Christoph Boesecke, Germany, talked about the rates of spontaneous clearance of HCV infections.

– Several clinical trials have shown comparable sustained virological response (SVR) rates in the treatment of acute HCV co-infection with DAAs, compared with chronic HCV co-infection, he said.

With no DAA currently being licensed for the treatment of acute HCV infection, and with high drug prices, the question becomes eminent which patients will resolve their infection spontaneously – and which patients should be offered timely treatment, Dr Boesecke continued.

He presented the PROBE-C study that aimed to evaluate rates of spontaneous clearance of acute HCV co-infection in a large European cohort. It included HIV positive patients with a diagnosis of acute HCV infection from many countries, with 3 years of individual follow-up.

– The summary of our findings is that spontaneous clearance in this setting is a rare event! Almost 90 % of acutely infected patients face a chronic course, Dr Boesecke underlined.

A less than 2 log drop in HCV RNA 4 weeks after diagnosis in the cohort was strongly predictive of a chronic course, allowing for early treatment intervention

– EACS guidelines have recently been amended to support early usage of DAA in acute HCV co-infection in a high-risk population, he ended by pointing out.

Domestic or internationally acquired infection?

A study on international versus domestic HCV transmission in MSM, was presented by PhD Luisa Salazar-Viscaya, Switzerland.

– Scale-up DAAs are national, but transmission of HCV is international, she said.

The higher the level of international transmissions, the lower the projected impact of national therapy will become.

The aims and objectives of the study she presented was to classify incident HCV infections in HIV-positive MSM as domestically or internationally acquired – and to locate incident infections in transmission clusters. This was done by viral sequencing of incident infections.

Swiss-domestic transmissions of HCV subtype 1a is ongoing. National treatment scale-up is therefore expected to reduce incidence among HIV-positive MSM, she reported.

– But we estimate that 14 % to up to 44 % of sequenced infections were likely acquired by contacts with MSM not living in Switzerland – which suggests that international transmission networks need to be taken into account, Ms Salazar-Viscaya said.

No trace of HCV transmission bridging between persons who inject drugs and MSM in Switzerland was found.

– We believe joint European scale-up schemes – and co-ordination between them – may boost the effect of national ones towards HCV elimination. Time-updated phylogenies for the whole of Europe may be valuable for monitoring the impact of national DAA scale-up programs, she concluded.

This ends *HIV & Virology News* report from CROI 2018. Next year the Congress is held in Seattle, USA, March 4 - 7.

Per Lundblad

European AIDS Conference 2017

The 16th biannual European AIDS Conference was given in the city of Milan from October 25 to 27. The Meeting had attracted 2,845 delegates from 85 countries to come to the Italian city.

The Conference is organised by the European AIDS Clinical Society (EACS), established in 1991. It is currently chaired by Prof Fiona Mulcahy, Ireland with Prof Jürgen Rockstroh, Germany, as Vice-President.

– EACS has always been a clinical organisation for delivering clinical care, Prof Mulcahy pointed out at the beginning of the Congress.

A city of education

At the Opening session, all were greeted welcome by Prof Mulcahy and local Chair Prof Antonella D'Armino Monforte.

– It is the second time EACS is here in Milan. The first time was 1994 – in the dark age of aids, she said.

Prof D'Armino Monforte continued by underlining there is still a lot of work to be done.

– We have to ensure that *all* infected can get care, and this is important work for Europe too. So I welcome you all to Milan!

She continued by describing Milan as the capital of AIDS in Italy. The country had 70,000 cases of AIDS in 2015, with 9,000 cases in Milan.

– It is also the first city for new HIV diagnoses in 2015 – Milan had 11.7 % of the total of new diagnoses in Italy. A project to meet this challenge is ongoing, she said.

But there is more to Milan than this – Prof D'Armino Monforte talked about a city of education where the present meets the future. She also showed some sights in Milan, with old and new architecture.

Costs for PrEP reduced

EACS award for Excellence in Medicine was presented during the Opening session. It was presented to Prof Jean-Michel Molina, France. After receiving it, he continued with a lecture on the feasibility and durability of pre-exposure prophylaxis (PrEP) in Europe. He began with an update of PrEP implementation in Europe as of October 2017.

– It is pretty good in the West, but there is still an important need in East Europe, he said.

Prof Molina described the IPERGAY and PROUD trials on PrEP, and summarised the results from them:

– It was established that there is an high incidence of HIV infection among men who have sex with men (MSM) in the UK, France and Canada. Also that daily, and on-demand, PrEP with oral tenofovir disoproxil fumerate/emtribicitabine (TDF/FTC) is highly effective in high risk MSM. The safety of PrEP was found to be good, and PrEP also removed fear during sexual activity.

The main concern of PrEP, which has been limiting the implementation, is the cost of drugs. But, following the introduction of generics in 2017, this has been reduced by 50 %. Prof Molina presented data from a Dutch study that showed PrEP to be cost-effective, and this finding was backed up by a French study.

In his conclusions, Prof Molina underlined that recent efforts to reduce HIV incidence among high-risk individuals are not sufficient – we need to do more.

– PrEP is an additional tool to prevent HIV infection, and people at risk should be aware of – and have access to – PrEP. The implementation is feasible and life-saving!

A close partnership with the community and political support is needed to facilitate PrEP implementation.

– Europe should unite for PrEP access and implementation, he ended his lecture.

Fiona Mulcahy

Jean-Michel Molina

The importance of early testing and diagnosing

The Dean Street model of testing in the UK was then presented by Dr Emma Devitt. The location of the clinic was chosen so they could target key populations, she explained.

– It opened in 2009 in Soho, central London. The focus was on reducing undiagnosed HIV.

In 2016, the clinic accounted for 25 % of all STI tests in MSM in England. Dr Devitt talked about their new quick design for testing – with video-guidance for self-testing and a rapid result that is texted to the individual person.

– If it is positive, a link is provided to come to the clinic for treatment. This has meant that the time attendance to informing result has come down from 183 hours to 3.8 hours – and the time attendance to treatment from 238 hours to 48 hours.

A reduction in HIV infections has been established. This is due to frequent testing and early diagnosis, Dr Devitt stated.

– Also to rapid ART initiation, treatment-as-prevention (TasP), rapid STI diagnosis and treatment – and PrEP.

Mr Gus Cairns is editor of Aidsmap, and coordinator for PrEP in Europe, a partnership of European organisations dedicated to increasing access to PrEP throughout the European region.

– We need champions to spread the message of PrEP in society, he said.

PrEP – or the promise of it – leads to more frequent testing. More frequent tests lead to earlier diagnoses and better PrEP adherence, Mr Cairns pointed out.

– Earlier diagnoses leads to quicker treatment – and this in turn, plus PrEP, leads to *fewer* diagnoses, he explained.

PrEP means sex without fear, but Mr Cairns stressed that it does not lead to irresponsible sex.

The Opening session then ended with a panel discussion including all the speakers.

An important milestone

The second day of Congress started with a lecture given by Prof Roy Gulick, USA, on the future of HIV therapy. This he started with a summary of 114 trials being performed on HIV up to 2012.

– In 1995, 48 % of patients participating in trials reached virologic remission. In 2012, 78 % did, he said.

Multiclass failure of treatment is uncommon, but these patients do exist.

– They should be treated with new classes of drugs – and luckily such drugs are on their way, he continued.

Fostemsavir is an oral HIV attachment inhibitor. It is a prodrug of temsavir and inhibits CD4 by binding to gp120 (a glycoprotein exposed on the surface of the HIV envelope). The drug was awarded with break-through status by FDA in 2015, and a phase III trial was presented at EACS 2017.

Ibalizumab is a HIV entry inhibitor – a parenteral monoclonal antibody that binds to the CD4 receptor.

– These two drugs will address the multi-resistant patients, Prof Gulick stated.

A new class in development are HIV maturation inhibitors. And an even *newer* class is HIV capsid inhibitors. Prof Gulick described them, and continued with alternative ways of drug distribution.

– The future of our field are injectables and implants, he said and presented a study on long-acting subdermal implants of tenofovir alafenamide (TAF) in dogs.

In year 2000, 28.9 million people were living with HIV, and 770,000 of them were on ART. Those receiving treatment has since then been escalated: In 2015, 36.7 million people were living with HIV – and 17 million were receiving treatment.

– In 2017, 19.5 million people were receiving ART. That is an important milestone – more than *half* of HIV patients are now on ART! The costs are also going down.

This has naturally influenced life expectancy, which has increased.

– ART in the future will be better for those with multidrug resistance, will be safer and better tolerated, be more convenient, have greater affordability and accessibility – and continue to increase life expectancy, Prof Gulick said in his conclusions.

51 % still diagnosed late

Dr Anastasia Pharris from the European Centre for disease prevention and control, talked about the epidemiological challenges in Europe.

– It is a very diverse picture. In the WHO European region, there are more than 150,000 new diagnoses which translates into 17.6 per 100,000 inhabitants – but 79 % of these are in the East, 18 % in the West and 3 % in the centre of Europe, she said.

Estimated new HIV infections are decreasing globally, but *increasing* in WHO European region, Dr Pharris continued.

– In Eastern Europe, it is an intravenous drug user (IDU)-driven epidemic with increasing heterosexual transmission. In Central Europe it is a MSM/heterosexual-driven epidemic – and in Western Europe MSM is the only group where infections have increased. However, migrants play an important role in some European countries.

UNAIDS goals for Europe and Central Asia are to reduce new infections to fewer than 63,000 by 2020, to reduce AIDS-related death and to eliminate HIV-related stigma and discrimination by 2020.

– So how are we doing? Sweden and Denmark have reached this target, other countries have not, she pointed out.

In the WHO European region, 51 % of those with a CD4 count reported are diagnosed late. And despite decades of evidence, harm reduction coverage such as opiate substitution treatment and needle and syringe programme coverage, remain low in parts of Europe.

– A 32 % decrease in London is linked to increased testing, immediate ART and PrEP. And 2 out of 3 countries report that funds available for HIV prevention are insufficient to reduce the number of new HIV infections, Dr Pharris told the audience.

HIV will be more concentrated in some populations

At the end of her lecture, Dr Pharris said there are several factors that will affect our work in the coming decade: Political instability and austerity, health care system re-structuring and migration, are some of them.

– Also an ageing cohort of people living with HIV, changes in drug markets and patterns of use and mobile technology.

In her conclusions she underlined that Europe, as a region, is lagging behind in its response to the HIV epidemic and is not on track to reach the 2020 targets.

– Effective interventions – frequent testing, immediate linkage to care and ART initiation, PrEP – are not being applied at scale in many European countries. But there are some good news – a reduced incidence in MSM in selected countries, mother to child transmission and IDUs.

In the next decade – as HIV incidence declines in some populations and regions

Emma Devitt

Roy Gulick

– HIV will be concentrated in even harder to reach populations and spaces.

– Uneven application of evidence-based prevention and treatment policies may further exacerbate existing inequalities in HIV incidence and outcomes in Europe. We *have* the sufficient tools to eliminate new infections in Europe, Dr Pharris ended her lecture.

Pros and cons of dual therapies

For many years, 3-drug combinations have remained unbeatable in achieving and maintaining HIV-RNA suppression, Dr Ignacio Perez Valero, Spain, said. He was giving a talk on optimising antiretrovirals using non-standard regimens.

– There are side-effects of triple therapy, such as lipodystrophy, kidney-, heart- and bone disease. There is a complexity, and also interactions, to consider, Dr Valero stated.

He reminded the audience that the panel of Antiretroviral guidelines for adults and adolescents emphasises that monotherapy with any antiretroviral drug should not be used due to increased risk of virologic failure and drug resistance.

– But in long-acting dual therapies, results are encouraging, Dr Valero said.

Do we still need non-standard ART? According to him the answer is both yes and no.

– Yes: Some patients cannot receive conventional ART, and the least toxic drug is the one you do *not* take. Long acting combinations are needed in some patients – and two drugs may be cheaper than three.

On account for *no*, dual therapies may not be enough to control virus and may be associated with higher levels of immune activation.

– And dual therapies may condition higher rates of biological ageing, Dr Valero summarised.

Dual therapy non-inferior to triple

Dual therapy with ritonavir-boosted protease inhibitor (PI/r) + lamivudine has shown non-inferiority versus PI/r + two nucleoside reverse transcriptase inhibitors (2N(t)RTIs) in four clinical trials using a non-inferiority margin of 12 %. These sample trials had a sample size of less than 150 patients per group.

– It remains to be seen if dual therapy is efficacious in specific subgroups such as women, HIV co-infection, or if all the PIs have same efficacy in the context of dual therapy, said Dr Jose Perez-Molina, Spain.

He presented a individual patient data-analysis of 1,051 participants from 4 studies. This showed that dual therapy was non-inferior to triple therapy using both current and past FDA endpoints for trials of antiretroviral therapy switch.

Ignacio Perez Valero

Jose Perez-Molina

– The effect of switching to dual therapy is not affected by patient's gender, active HIV infection status or type of protease inhibitors.

The switch to dual therapy did not affect the CD4 cell count.

– While renal function improves slightly in patients randomised to dual therapy, blood lipids had mild increases, Dr Perez-Molina said.

Dolutegravir monotherapy stopped in trial

Two speakers talked about dolutegravir-based simplified strategies. The first was Dr Marta Buzzi, Switzerland, who presented an analysis from 14 studies with the objective to provide estimates of the virological failure rate on a dolutegravir-based (mono and dual) maintenance therapy. She underlined that the study had limitations: It was based on mostly small observational studies, and short follow-up, which could affect the robustness of estimates.

– Dual therapy for maintenance had better virological outcomes compared to dolutegravir monotherapy. No dolutegravir/integrase inhibitor resistance occurrence was detected and is therefore a promising strategy for treatment simplification. Large and randomised trials with long-term follow-up are ongoing and could provide confirmation of these results, Dr Buzzi concluded.

Prof Esteban Martinez, Spain, talked about the DOLAM study. In this, patients on triple cART were randomised to either continue on the same cART, to switch to dolutegravir + lamivudine or to switch to dolutegravir monotherapy. The Data Safety Monitoring Board would review the data if the proportion of confirmed virological failure in any of the two experimental arms reached 5 % or more – which it did in the monotherapy arm.

– So they recommended stopping the dolutegravir monotherapy arm and continuing the study with the control and dolutegravir + lamivudine arms. The conclusion of the study is that in contrast with the dolutegravir + lamivudine arm, dolutegravir monotherapy in patients with sustained viral suppression led to an unacceptable risk of viral failure with development of resistance complications, Dr Martinez reported.

Same drugs can have different resistance behaviour

A study that aimed to measure resistance selected in patients treated by triple and dual regimens, experiencing virological failure, was presented by Prof Vincent Calvez, France.

– The robustness to antiretrovirals resistance is driven by several factors – such as the number of resistance mutations to get a significant resistance level, plasma or intracellular half-life of active forms and target binding half-life. Also by the type of combination, he established.

465 patients at more than 30 centres in Italy and France were studied.

– The conclusions are that in case of virological failure, same drugs can have *different* resistance behaviours according

to type of combination. Some nucleoside reverse transcriptase inhibitors (NRTIs) based triple combinations are more effective. For 2NRTIs + PI/r, or 2 NRTIs + dolutegravir a lack of any resistance in the vast majority of cases was found, Prof Calvez said.

Some NRTI based triple combinations are less protective – 2 NRTIs + NNRTIs. Failure on a dual regimen is globally associated with higher resistance selection.

– Less resistance protection is observed for the associated drugs when PI/r or dolutegravir are used in a dual regimen, was his final message.

Linos Vandekerckhove

Vincent Calvez

New drug reduces reservoir

ABX464 is a first-in-class antiviral drug candidate. It is an orally available small molecule that blocks HIV replication through an entirely novel mechanism – inhibition of Rev activity (Rev activity determines sensitivity of HIV-1-infected primary T cells to cytotoxic T lymphocyte killing).

This was described by Dr Linos Vandekerckhove, Belgium who presented the ABX464-004 study.

– It is a multicenter, randomised, double-blind, placebo-controlled study in Spain, Belgium and France. The primary endpoint was to evaluate the safety of ABX464 versus placebo when administered on top of boosted darunavir, he said.

The most common adverse events noted were abdominal pain and headache. All events except one were grade 1 or 2. One patient discontinued treatment prior to day 28 due to abdominal pain (grade 2) and epigastric pain (grade 1), considered related to study drug by the investigator. There were no serious treatment-emergent adverse events.

– So the conclusion is that ABX464 was well tolerated in fully suppressed patients on boosted darunavir.

A mean decrease of 186 (38 %) copies of total HIV DNA/Mio peripheral blood mononuclear cell was demonstrated in ABX464 responders, and a mean decrease of 131 (55 %) of integrated HIV DNA was observed in responders.

– Despite the important decrease of the HIV reservoir, this was not yet sufficient to delay the time to viral load rebound. But to our knowledge this is the first time a signal has been observed demonstrating the reduction of HIV reservoirs in patients with a therapeutic candidate, Dr Vandekerckhove told the audience.

The next steps are to confirm this study and to perform larger studies.

– ABX464-005 will investigate ABX464 given in addition to triple therapy, -006 to evaluate how to achieve maximal reduction in HIV reservoir in chronically infected, well suppressed, HIV patients. -007 will evaluate time needed to achieve maximal reduction of HIV reservoir in early treated, well suppressed, HIV patients, he ended his lecture.

EACS Guidelines updated

One of the highlights at the European AIDS Congress is the presentation of the updated Guidelines. In Milan, version 9.0 was presented at a special session.

Chairs Prof Manuel Battegay, Switzerland, and Dr Lene Ryom, Denmark, and started the session by thanking the panel chairs for their work with creating the Guidelines.

– The panels are focused on producing comprehensive and user-friendly guidelines. All recommendations are evidence-based whenever possible, and based on expert opinions in the rare instance where adequate evidence is unavailable, said Dr Ryom.

The Guidelines show that the diagnosis and management of HIV infection and related co-infections, opportunistic diseases and co-morbidities still requires a multidisciplinary effort – for which the EACS Guidelines will provide an excellent basis, Prof Battegay said.

– The EACS mission will use the Guidelines to increase the level of care throughout Europe in particular, for example by using direct links to video teaching lessons, he added.

This new edition took into account new scientific evidence, said Dr Anton Pozniak, UK.

– Our recommended initial treatments have more details regarding the use of backbone drugs. Important issues, highly relevant to women, were also revised – especially in regard to which drugs we recommend during pregnancy and to which special monitoring is needed, Dr Pozniak highlighted.

As antiviral therapies improve and people with HIV get older, accompanying health conditions and diseases become more important, Dr Georg Behrens, Germany, pointed out.

– Recommendations for chronic lung disease, solid organ transplantation and non-alcoholic liver disease were included, in order to address the increased risk for these comorbidities, he explained.

Available in different languages online

The eradication of HCV co-infection in people living with HIV is now an achievable goal and all co-infected persons should be considered fro treatment, according to the new guidelines, Dr Massimo Puoti, Italy, stated.

– Two recently approved pan-genotypic anti-HCV combination treatments – with simplified treatment indication and a shortened treatment duration, have been included among the anti-treatment options. Thanks to its dual activity against HBV and HIV and the absence of renal and bone toxicities, tenofovir alfenamide has been considered as a feasible treatment option, Dr Puoti said.

Dr José Miro, Spain, talked about the changes in the opportunistic infection section.

– The new edition includes new strate- ➤

gies for the prevention and treatment of Cryptococcal meningitis when flucytosine is not available.

He also said that new approaches exist for the treatment of tuberculosis. These include a highly new effective new combination for shortening the therapy of multidrug resistant and extensively drug resistant TB.

Finally, Dr Catia Marzolini, UK, team member of the Liverpool HIV/HEP Drug Interactions website, said this new edition expanded the drug-drug interactions (DDIs) section for polymorbid individuals.

– Also, DDI tablets were revised to include the most recently approved HCV drugs and to further discriminate DDIs associated with a risk of contraceptive failure, she underlined.

The guidelines are easily available on the web for free. Go to *www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html*. Apart from English, they are also available on this site in Chinese, French, German, Portuguese, Russian and Spanish.

Effective treatment is not sufficient

Hepatitis C virus (HCV) and HIV co-infection increases the risk of hepatic and extra-hepatic complication. Co-infection is therefore a major cause of morbidity and death among people living with HIV, said Dr Andri Rauch, Switzerland.

– The new direct-acting antivirals (DAAs), with their specific and highly efficient inhibition of the HCV life cycle was a breakthrough in treatment of HCV and holds the key to HCV eradication, he continued.

Dr Rauch also stressed that deferring HCV therapy increases the risk for liver-related complications and reduces cure rates.

– DAAs are also much better tolerated than previous interferon-based regimens, so they have a much better uptake – also in HIV cohorts.

There are different trends in HCV prevalence among people with injectable drug use and MSM. It is decreased in the former group, but increases in MSM. According to Dr Rauch, these diverging trends can at least partly be explained with drug users have a better uptake of treatment – via clean syringe programmes etc.

A hurdle to HCV elimination is access to therapy, affordability and reimbursement restrictions.

– Reimbursement restrictions lead to an increased risk for morbidity and mortality and for onward HCV transmission.

Fear of re-infections is not an argument for not upscaling treatment, Dr Rauch stressed.

He made an analogy with other infectious diseases and showed that availability of effective treatments is not sufficient to achieve elimination.

– It has to be combined with an upscale of counselling and other interventions.

In Dr Rauch's summary he underlined that cure of HCV infection improves health, prevents deaths and eliminates onward transmission. Early diagnosis and therapy prevents complications and is required to reduce incidence.

– Central elements for HCV elimination include optimised screening and diagnosis strategies, optimised prevention and counselling and increased treatment uptake and access to interferon-free DAA for all at affordable prices. Also, coordinated national and international HCV strategies and leadership is required!

Treatment of HIV-2

Prof Sophie Matheron, France talked about HIV-2.

HIV-1 and HIV-2 are two different viruses. HIV-1 is the main family of HIV and accounts for 95% of all infections worldwide.

– HIV-2 only has a limited number of patients. There are 1 - 2 million cases in West Africa, and approximately 1,000 cases in Portugal and France, she explained.

HIV-2 patients have a slow disease progression and a low viral load. There are few therapeutic alternatives and a high level of antiretroviral cross-resistance and a poor immunological response.

– So we have several challenges. The first is to define the best evidence-based treatment, next is to design and set up randomised trials. This is not possible in Europe, so we have to rely upon observational studies and pilot trials,

Andri Rauch

Sophie Matheron

Prof Matheron said.

However, there is an ongoing randomised trial in West Africa, ANRS12294 FIT-2, on first line treatment for HIV-2, and she presented it in more detail.

Treatment guidelines for HIV-2 recommend as first line two nucleoside reverse transcriptase inhibitors – tenofovir alafenamide/tenofovir disoproxil fumarate or abacavir + emtricitabine/lamivudine – in combination with one protease inhibitor (darunavir/ritonavir or lopinavir/ritonavir) or one integrase strand transfer inhibitor – raltegravir, elvitegravir/cobicistat, dolutegravir.

Clinical trials urgently needed

Dr Diana Póvoas, Portugal, presented a retrospective analysis of the clinical records of HIV-2 patients.

– Portugal is one of the European countries with the highest prevalence of HIV-2 infection, she said.

The analysis showed that patients with HIV-2 infection are an heterogeneous and ageing population of difficult management. Suboptimal adherence to regular follow-up may be due to socioeconomic factors and differences in disease perception.

– Although ART may sometimes be controversial in HIV-2 infection, it is still advisable since it is associated with immune

recovery and clinical positive outcome, Dr Póvoas pointed out.

Based on their experience, lopinavir/ritonavir, saquinavir/ritonavir, darunavir/ritonavir, raltegravir and dolutegravir are good options in HIV-2 treatment, she continued.

– However, clinical trials on HIV-2 treatment are urgently needed, was Dr Póvoas' last message.

Study on new STR

The AMBER study is a Phase III randomised, double-blind trial in ART-naive HIV-1 infected adults. It evaluated the efficacy and safety of the once-daily single-tablet regimen (STR) of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/c/F/TAF) versus standard therapy with darunavir and cobicistat (DRV/c) plus emtricitabine and tenofovir disoproxil fumarate (F/TDF). 725 patients were randomised 1:1 and treated.

Chloe Orkin

Teymure Noori

At the Conference, the results from week 48 were presented by Dr Chloe Orkin, UK.

– D/c/F/TAF is the first once-daily STR containing boosted darunavir, she pointed out.

TAF provides similar efficacy to TDF, with improved renal and bone safety markers, Dr Orkin added.

Conclusions were that through week 48 , D/c/F/TAF resulted in high virologic suppression in treatment-naive patients that was non-inferior to DRV/c + F/TDF. There was no development of DRV, primary protease inhibitors or TDF/TAF resistance-associated mutations.

– There were few serious adverse events, grade 3 or 4 adverse events or adverse events-related discontinuations – and no discontinuations due to bone, renal or CNS adverse events. Bone, renal and lipid safety was consistent with known profiles of TAF and cobicistat, she said.

Dr Orkin's summary was that D/c/F/TAF combines the efficacy and high genetic barrier for resistance of darunavir with the safety profile of tenofovir alafenamide for treatment-naive, HIV-1 infected patients.

An alternative backbone

The 48 week analysis from a randomised, double-blinded trial of a switch from abacavir/lamivudine (ABC/3TC) to tenofovir alafenamide/emtribitacine (TAF/FTC) in suppressed individuals were presented by Prof Alan Winston, UK.

– TAF/FTC was non-inferior to ABC/3TC in maintaining virological suppression in combination with a variety of third agents. There were no differences in renal and bone biomarkers versus ABC/3TC – suggesting that TAF is kidney- and bone neutral, similar to ABC, Prof Winston reported.

TAF/FTC also had a similar lipid profile versus ABC/3TC.

– Overall, in virologically suppressed people TAF/FTC provides an alternative backbone to ABC/3TC with similar effects on kidney and bone, was his conclusion.

Inequalities in access still a barrier

Teymure Noori is HIV expert at the European Center for Disease Prevention and Control (ECDC).

– According to our most recent data on the continuum of care monitored by ECDC in Europe and Central Asia, 1.2 million people live with HIV, 75 % of whom have been diagnosed, Ms Noori said at the last day of the Conference.

She continued by pointing out that among these diagnosed cases, about 1 in 4 is not receiving any treatment.

– Although HIV treatment is effective, 2 out of 5 people with HIV have not achieved viral suppression. This means that a substantial proportion of people in Europe and Central Asia do not benefit from the highly effective HIV treatments, and that HIV transmission continues – especially among key populations, Ms Noori underlined.

On this last day, focus was also on the eradication of HCV.

It has been a fact estimated that 2.3 million patients are concomitantly infected with HIV and HCV worldwide. Most of them have a history of injectable drug use. With the introduction of antivirals for the treatment of HCV, the eradication has become an achievable goal – and yet the proportion of people who reach sustained virological responses after HCV therapy in Europe continues to be low, thereby emphasizing the barriers to access to HCV care and a strong need for improvement in this area.

– Indeed, a first analysis from the Netherlands has shown that, after 75 % of all HIV-infected MSM with HCV have been cured following HCV DAA therapy, the number of new acute HCV infections has dramatically dropped by more than 50 %, said Prof Jürgen Rockstroh.

This clearly underlines and emphasizes that HCV elimination is reachable in the special population of HIV/HCV co-infected individuals.

– Nevertheless, inequalities in access to HCV diagnostics and treatment in Europe are still a dreadful barrier against any successful elimination strategy – and this needs to be pointed out! Only through a combined effort – which should include al stakeholders in the HCV arena – does HCV eradication appear possible by 2030, according to WHO's ambitious goal, Prof Rockstroh ended by stating.

And with these words, *HIV & Virology News* also ends the report from the 16th European AIDS conference. Next time it will be held will be in Basel, Switzerland on November 6 - 8, 2019.

Per Lundblad

BHIVA - resent events

BHIVA Hepatology Highlights for the Healthcare Specialist in collaboration with the British Viral Hepatitis Group – 15th November 2017

This evening programme run by BHIVA and BVHG included talks on HCV resistance, fibrosis after treatment and HCV elimination.

To view the presentations follow this link: www.bhiva.org/2017-hepatologyhighlights.aspx

BHIVA Autumn Conference - 16th-17th November 2017

The conference programme covered a wide range of topics relevant to HIV medicine including premature ageing, anti-inflammatory agents, point of care diagnostics, PrEP, HIV and neglected tropical diseases, TB, and the effects of ageing on the HIV population. The conference also contained lectures on best practice management, interactive clinical conundrums and clinico-pathological and pregnancy and breastfeeding case presentations, which were presented during the very popular BHIVA lunchtime workshops. The BHIVA Foundation Lecture covered 'How to survive a sexual health tender: the HIV clinic perspective'. Our international speakers included Dr Keri Althoff from the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.

For more details and to view the presentations, follow this link:
www.bhiva.org/AutumnConference2017.aspx

BHIVA World AIDS Day Event - 1st December 2017

BHIVA held a well-attended showing of the renowned play, 'The HIV Monologues" written by Patrick Cash and directed by Luke Davies at the National Gallery.

For more details, follow this link: www.bhiva.org/world-AIDS-day-2017.aspx

Forthcoming events:
BHIVA 'Best of CROI' Feedback Meetings - March 2018

These meetings will provide an independent, unbiased and impartial review of the key presentations held at the annual Conference on Retroviruses and Opportunistic Infections (CROI) in Boston, Massachusetts, USA from 4-7 March 2018.

An experienced working party was convened, made up primarily of BHIVA Executive Committee members, to review presentations and collate the most relevant slides and material for feedback to those working in the field of HIV medicine in the UK.

BHIVA will hold six Feedback Meetings during March 2018; the first in London with subsequent regional meetings in Birmingham, Haydock, Cardiff, Wakefield and Edinburgh.

For more details please follow this link: www.bhiva.org/BestofCROI2018.aspx

BHIVA Hepatology Highlights for the Healthcare Specialist in collaboration with the British Viral Hepatitis Group – 17th April 2018

This programme run by BHIVA and BVHG will include talks on improving access to HCV treatment for hard to reach populations, non-infectious liver complications of HIV and lessons on HCV elimination from Scotland.

For more details, follow this link: www.bhiva.org/hepatology-highlights-2018.aspx

The 4th Joint BHIVA/BASHH Conference - 17th – 20th April 2018

The Fourth Joint Conference of the British HIV Association (BHIVA) with the British Association for Sexual Health and HIV (BASHH) will be held at the Edinburgh International Conference Centre, UK.

Highlights include

<u>BHIVA Keynote Lecture:</u>

HIV cure strategies: interventions, endpoints and ethics.

Professor Sharon Lewin, The Peter Doherty Institute for Infection and Immunity, Melbourne, Australia

<u>BHIVA Invited Lectures:</u>

- Telling the truth: issues around disclosure of sexually transmitted infections. Dr Andreas Wismeijer, Tilbury University, The Netherlands
- How can primary care work more closely with sexual health services to deliver appropriate testing, prevention and care for STIs and HIV. Professor Jackie Cassell, Brighton and Sussex Medical School
- Harnessing molecular technology to inform our understanding of HIV and STI epidemics. Ms Katy Town, National Institute for Health Research (NIHR)
- Refugees, migrants and healthcare access: key issues in the response to HIV, STIs and TB. Dr Fionnuala Finnerty, Brighton and Sussex University Hospitals NHS Trust and Dr Yusef Azad, National AIDS Trust

<u>The Launch of the BHIVA Standards of Care For People Living with HIV.</u>

For more details about the conference, follow this link:
www.bhiva.org/AnnualConference2018.aspx

Satellite symposiums at the European AIDS Congress

Several industry sponsored satellite symposiums, covering a wide range of topics, were given in adjunction to the Congress.

Catia Marzolini, Gabriele Arendt, Jordi Blanch and Esteban Martinez.

Fabio Vescini, Bruce Hendry, Aoifi Cotter, Giovanni di Perri and Jürgen Rockstroh.

A *Penny for your thoughts: HIV and the brain* was the title of a symposium sponsored by MSD. Prof Esteban Martinez (Spain) was the Chair.

– We all know that CNS health is important for our patients, Prof Martinez said when he greeted delegates welcome.

Chronic inflammation often associated with depression

The first Speaker was Dr Jordi Blanch, Spain. He stated that psychiatric disorders are very prevalent in HIV disease, and these have a very negative impact on HIV illness.

– HIV-infected persons with depression show decreased survival, decreased adherence to ART, increased risk behaviours and have longer hospital stays and more frequent medical visits, Dr Blanch said.

However, depression is seldom screened and diagnosed in HIV clinics – and once diagnosed, it is seldom treated, he continued.

– Chronic inflammation is often associated with the emergence of depression symptoms. Depressed patients show increased levels of circulating cytokines.

Differential diagnosis of depression in HIV-infected patients is quite difficult.

– Cognitive/affective and non-symptomatic symptoms should be taken into account for diagnosing depression in HIV. They should be treated in your clinic – the patient won't go to a psychiatrist! Selective serotonin reuptake inhibitors (SSRIs) are the treatment of choice for depression in HIV, Dr Blanch said.

Diagnostic criteria for HAND

Even long lasting aviremic patients can suffer from HIV-associated neurocognitive disorder (HAND), Prof Gabriele Arendt, Germany, underlined.

– Patients complaining of cognitive deficits should be at least short-diagnosed for the presence of HAND, she stated.

cART remains the best and most needed treatment for HAND, however it may not always be sufficient. Future studies should tell whether early cART will prevent HAND.

– Putative cART neurotoxicity may be an issue, and additional studies are warranted – especially in early treated patients, Prof Arendt said.

In addition to cART, neuroprotective drugs are needed, but so far trials have been disappointing.

A consensus research definition on HAND was articulated in 2006 at Frascati, Italy, with sub-classifications created that include asymptomatic neurocognitive impairment, mild neurocognitive disorder and HIV associated dementia.

– Frascati is the valid diagnostic criteria for HAND, and it should be revised in the nearer future, was Dr Arendt final conclusion.

More CNS adverse events with dolutegravir

CNS adverse events are subjective and diagnosis is established in the clinic. Different factors may impact on detection – so be open not to miss them, said Dr Catia Marzolini, Switzerland.

– EACS and other guidelines recommends to screen neuropsychological health in HIV-positive patients, she pointed out.

All three currently available integrase strand transfer inhibitors (INSTIs) may have CNS adverse events, but they seem to be more common with dolutegravir.

– So levels of dolutegravir and patients' characteristics may be risk factors for adverse events.

Dr Marzolini concluded that we need to improve the collection of CNS adverse events in clinical cohorts of patients treated with INSTIs.

– Pathophysiological studies are also needed.

Consider comorbidities

Seeing the whole picture was the title of a symposium sponsored by Gilead. Prof Giovanni di Perri, Italy and Prof Jürgen Rockstroh, Germany, were the Chairs.

Between 1996 and 2010, life expectancy of HIV-positive individuals was increased by 9 years in women and 10 years in men, Prof di Perri started by pointing out.

– Even in the late ART era, survival continues to improve – likely reflecting the transition to less toxic antiretroviral drugs, improved adherence, prophylactic measures and management of comorbidity, he continued.

Individuals with HIV are more susceptible to developing cardiovascular disease, bone fractures and renal failure than HIV-negative people. Prof di Perri presented a mathematical model to forecast clinical events in the HIV-positive population in Italy between 2015 and 2035.

– In the next 20 years, burden of cardiovascular disease is predicted to double – and burden of diabetes and chronic kidney disease will almost *quadruple*! Data from USA show an increasing mortality due to cardiovascular disease in people living with HIV between 1999 an 2013.

There is an need to act *now*, he summarised.

– We need to carefully manage our patients as a whole – going beyond undetectable, in order to prevent their overall health.

– Consider comorbidities – prevent and treat. Counsel on lifestyle and risk factors, and a careful selection of ART that balances HIV efficacy, durability and toxicity, Prof di Perri finished.

Kidney and bone

Three cases were then presented. First a 52 year old male, living with HIV for 27 years. He had several comorbidities: Diabetes, hypertension, hyperlipidemia and proteinurea. The audience was asked to vote on several questions on how to manage the patient, and the results of the votes were displayed and commented by the panel.

The discussion centred on kidney side effects of treatment. Tenofovir alfenamide (TAF) is now recommended for patients with kidney problems.

– Patients on tenofovir disoproxil fumarate (TDF) that switch to TAF quickly reduces the stress on the kidney caused by the TDF regime, said one of the panel members.

– I think this gentleman represents a kind of patient we will see more of in the future, said Prof Bruce Hendry, UK commented.

Via a case of a 47 year old female living with HIV for 10 year, presented by Dr Aoifi Cotter, Ireland, the discussion shifted to the importance of bone health being considered at all stages of life.

– Her current regimen – efavirenz/emtricitabine/tenofovir disoproxil fumarate – should be bone friendly, Dr Cotter said.

She also underlined that virological suppression can be maintained when switching regimen. The objectives for switching should be to eliminate or improve adverse events, facilitate treatment of comorbidities and improve quality of life.

– Switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide has demonstrated statistically significant superior efficacy in treatment-naive patients, and for experienced patients switching regimens in comparison with initiating, or remaining on, TDF-based regimens.

Start after diagnosis

The third patient was a 23 year old newly diagnosed with HIV, and this case led to a discussion on when to start ART. The panel's answer was that treatment should start as soon as all clinical data are gathered.

Data from San Francisco on same-day observed ART initiation versus standard of care showed a significantly shorter time to viral suppression in same-day ART versus universal ART. The safety and tolera-

Sanjay Bhagani, Fiona Marra, Anca Streinu-Cercel, Saye Khoo and David Back.

bility was similar between the two groups.

– I would be reluctant to start the same day as diagnosis, because I want to have data on renal function first, said Prof Hendry.

Dr Cotter underlined that guidelines recommend starting treatment as soon as possible, regardless of CD4 cell count.

– Selection of initial ART should focus on achieving viral suppression and minimising adverse reactions in the short and long term. And throughout a patient's life, we need to consider the risk of developing comorbidities, she summarised.

DDI's in pregnancy and contraception

A symposium entitled *Liverpool drug interactions session: Key pharmacology issues of current and future ART* was sponsored by ViiV Healthcare. The audience was greeted welcome by Prof David Back, UK who first talked about the Liverpool drug-drug interaction (DDI) registry. This can be accessed online at *www.hiv-druginteractions.org* in pdf format.

He then introduced Prof Saye Khoo, UK who held a mini lecture on contraception and pregnancy. She first talked about DDIs between HIV drugs and hormonal contraception.

– Tailor ART around contraceptive choice where possible, Prof Khoo advised.

For hormonal contraception there is a potentially higher risk of failure of progestin implants with efavirenz.

– One must carefully balance between benefits, choice and risk, she stressed.

For dolutegravir in pregnancy preliminary, short-term data, are reassuring.

– But we need more data – e.g. on women initiating in the third trimester, IRIS, breast-feeding, infant exposures and washout etc.

Nevertheless, Prof Khoo stated that it seems reasonable to continue dolutegravir in a woman if pregnancy develops.

HIV/HBV and TB co-infection

Two cases were then presented. The first by Dr Sanjay Bhagani, UK, on a 37 year old man from Sierra Leone who worked in the UK as a taxi driver. He presented with advanced HIV in February 2013, and was found to have a hepatitis B co-infection. He also had renal impairment, but completed 24 months of anti-MAI/MAC therapy in February 2015.

– In January 2017, things are looking good. The patient is on tenofovir/emtricitabine/raltegravir. However, he has had new thoracic back pain for two months. He puts this down to his driving position, and wants a referral to physiotherapy, Dr Bhagani said.

But an expert confirms mycobacterium tuberculosis (mTB).

– We opted to go for standard quadruple anti-TB treatment – isoniazid/rifampicin/pyrazinamide and ethambutol. But we need to take into account DDIs, renal impairment and HBV co-infection. So we looked it up at the Liverpool website.

There they found that isoniazid and pyrazinamide are not a problem, and that they can use rifampicin with raltegravir.

– But we can't use TAF (yet), and we can't use TDF due to low, but fluctuating, eGFR.

Their decision was to switch TAF/emtricitabine to abacavir/lamivudine, continue raltegravir and add-in entecavir (renal dose-adjusted).

– For TB treatment we chose isoniazid/rifampicin and pyrazinamide for two months. Ethambutol was continued until mTB confirmed to be fully sensitive. Then isoniazid/rifampicin for 10 months, Dr Bhagani summarised.

HIV/HCV co-infection

Ms Fiona Marra, UK, is a Master of Pharmacy at the Liverpool University. She presented a case of a 43 year old MSM diagnosed with hepatitis C (HCV) /HIV co-infection.

– So what should we do – should we choose a direct-acting-antiviral (DAA) to fit around antiretroviral (ARV) combination? Or should we change ARVs to allow for DAA of choice, she asked the audience.

The majority voted for the second alternative.

– Grazoprevir/elbasvir is encouraged as first line in treatment of HCV in guidelines. But does this go with ART? We checked the Liverpool website, and fond that it doesn't, Ms Marra continued.

So they decided to switch to Triumeq (abacavir, lamivudine, dolutegravir) for treatment of HIV.

– For HCV we chose 12 weeks Epclusa (sofosbuvir/velpatasvir + ribavirin). SVR 12 was achieved. The patient was on omeprazole, which was stopped, and the hepatic function remained stable, Ms Marra said.

Prof Back then asked Dr Anca Streinu-Cercel, Romania, who was on the panel, how these cases would be managed in Romania.

– All new drugs are not available in Romania yet, but I hope they soon will be – so we also could have a happy end in cases like these, was her answer.

Per Lundblad

The EASL 2017 Clinical Practice Guidelines on HBV infection

The European Association for the Study of the Liver (EASL) published its most recent clinical practice guidelines on the management of hepatitis B virus (HBV) infection in the *Journal of Hepatology* in August 2017. The most important aspects and changes from previous guideline versions will be discussed in this report.

Worldwide, approximately 240 million people are chronic HBV surface antigen (HBsAg) carriers who are at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma. Prevalence rates vary greatly across Europe. However, prevalence and incidence rates may increase even in countries with a low seroprevalence (e.g. Germany and Italy) due to recent migration movements.

New Definition of HBV Disease Phases

To better guide clinicians on treatment indications, the new EASL guideline contains a new nomenclature of the different disease phases of HBV infection (Table 1). The nomenclature no longer uses the term "immune tolerant phase". Instead, the natural course of chronic HBV infection is now classified according to disease activity. There are five phases of chronic HBV infection. In HBsAg-positive patients there are four phases, including chronic infection (normal transaminases) or chronic hepatitis (elevated transaminases) with or without HBeAg positivity. The different phases do not necessarily constitute a continuum and require frequent monitoring of biochemical, serological and molecular markers. The fifth phase is characterised by negative HBsAg and positive antibodies to HBcAg. This phase is usually associated with the absence of HBV DNA. However, immunosuppression may lead to HBV reactivation in these patients.

Aim of Antiviral Therapy

While HBV cure is virtually impossible with currently available antiviral agents, the main goal of therapy is to improve survival by preventing disease progression, and HCC development. Additional goals of antiviral therapy include the prevention of mother-to-child transmission, hepatitis B reactivation in immunocompromised people, and treatment of HBV-associated extrahepatic manifestations.

	HBeAg-positive		HBeAg-negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	high	High/intermediate	Low	Intermediate
HBV DNA	$>10^7$ IU/mL	10^4-10^7 IU/mL	<2,000 IU/mL	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated
Liver injury	None	Moderate/severe	None	Moderate/Severe

Table 1. Natural history of HBsAg-positive chronic HBV infection (adapted from EASL Clinical Practice Guidelines on the management of hepatitis B virus infection; J Hepatol 2017)

Condition	EASL recommendation
Women of childbearing age who plan pregnancy (no advanced fibrosis)	Consider to delay treatment until child is born
Pregnant women with advanced fibrosis/cirrhosis	Treat with TDF
Pregnant women on NUC therapy	Continue or switch to TDF
Pregnant women with HBV DNA >200,000 IU/mL	Start TDF at week 24-28 of gestation Continue for up to 12 wks. after delivery
Breast feeding	Not contraindicated in untreated women or TDF treated women

TDF, tenofovir disoproxil

Table 2. Indications for antiviral treatment/prophylaxis during pregnancy (adapted from EASL Clinical Practice Guidelines on the management of hepatitis B virus infection; J Hepatol 2017)

Condition	EASL recommendation
HBsAg loss with/without anti-HBsAg seroconversion	Stop NUC therapy
HBeAg seroconversion in non-cirrhotic HBeAg-positive patients and undetectable HBV DNA for >12 months	NUCs can be discontinued*
Non-cirrhotic HBeAg-negative patients with undetectable HBV DNA >36 months	NUC discontinuation may be considered*

*close post-withdrawal monitoring is required

Table 3. Recommendations for Discontinuation of Nucleos(t)ide Therapy (adapted from EASL Clinical Practice Guidelines on the management of hepatitis B virus infection; J Hepatol 2017)

Indications for Antiviral Therapy

Indications for antiviral therapy have not changed compared to the previous guideline edition. In brief, treatment should be initiated in all patients with HBeAg-positive or -negative chronic HBV, defined by HBV DNA >2,000 IU/ml, elevated ALT and/or moderate liver necroinflammation or fibrosis. In addition, all cirrhotic patients with replicative HBV DNA should be treated, regardless of ALT levels. In patients with HBeAg-positive HBV infection with persistently normal ALT levels and very high HBV DNA levels, treatment may be initiated if patients are older than 30 years to decrease the HCC risk in this particular patient population.

Expanded Indication for Initiating Treatment for the Prevention of Mother-to-Child Transmission

The current clinical practice guideline has also expanded indications for initiating antiviral therapy in order to prevent mother-to-child transmission (Table 2). There is now increasing evidence that tenofovir disoproxil (TDF) can be safely ad-

ministered during all phases of pregnancy (2). Accordingly, it is now recommended that pregnant women already on nucleotide therapy with TDF should be continued while other NUCs such as entecavir (ETV) should be switched to TDF. Moreover, in untreated pregnant women with high HBV DNA levels (>200,000 IU/mL) or HBsAg levels >4 $\log_{10}$ IU/mL, antiviral prophylaxis with TDF should be started at week 24–28 of gestation and continue for up to 12 weeks after delivery. A recent meta-analysis showed that this approach significantly decreased the risk of mother-to-child transmission in addition to passive and active HBV vaccination of new-borns within 12 hours after delivery (2). Finally, the EASL guidelines also state that breast-feeding is not contraindicated in HBsAg-positive untreated women or in those on TDF-based treatment or prophylaxis.

What is the role of tenofovir alafenamide (TAF)?

Importantly, the 2017 EASL guidelines no longer recommend the use of lamivudine, adefovir or telbivudine in patients with chronic HBV infection. Instead, the preferred regimens are either TDF, ETV or tenofovir alafenamide. Among these, TDF is the only NUC that is recommended during pregnancy or breast-feeding (see above).

The EASL guidelines were the first international guidelines to include tenofovir alafenamide (TAF) into current treatment algorithms. TAF, a prodrug of tenofovir with improved safety profile, has been reviewed in detail in the second issue of the 2017 edition of *HIV & Virology News*. The EASL guidelines recommends to select TAF or ETV over TDF in older patients (>60 years), patients with bone disease (e.g. osteoporosis or history of fragility fracture) or those with chronic kidney disease with an estimated glomerular filtration rate below 60ml/min/1.73m^2.

NUC Discontinuation

It is common practice to discontinue NUC therapy following confirmed HBsAg loss, with or without anti-HBs seroconversion. Moreover, treatment may also be discontinued in HBeAg-positive patients following stable HBeAg seroconversion. However, there is increasing evidence that long-term NUC therapy may also be stopped in HBeAg-negative patients (3). For the first time, The EASL guidelines clearly state that discontinuation of NUC therapy may be considered in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (at least 3 years) HBV DNA suppression by continuous NUC therapy (Table 3). This recommendation is based on data suggesting that virologic remission, defined as HBV DNA <2,000–20,000 IU/mL, will be maintained in approximately 50% of patients three years after stopping NUC therapy. However, close biochemical and HBV DNA monitoring is required in these patients, as severe hepatitis flares have occasionally been reported following NUC withdrawal. Moreover, such an approach should not be considered in patients with advanced liver fibrosis or cirrhosis, as this was associated with adverse outcomes. Of note, increase in HBV DNA levels is observed much later following ETV treatment as compared to TDF following drug withdrawal.

Prevention of HBV reactivation

The risk of HBV reactivation during direct antiviral therapy for HCV has been addressed in a recent issue of *HIV & Virology News*. The EASL guidelines recommend that HBsAg-positive patients undergoing DAA therapy should be considered for NUC prophylaxis until week 12 following DAA therapy. This recommendation is supported by results from a recent meta-analysis that showed a HBV reactivation rate of 24% in HBV/HCV co-infected patients (4).

In HBsAg-positive patients who are candidates for chemotherapy or immunosuppressive therapy, prophylaxis with a potent nucleos(t)ide analogue is also recommended. In contrast, antiviral prophylaxis is only recommended in HBsAg-negative patients if they are at high risk (>10%) of experiencing HBV reactivation (e.g. following rituximab therapy).

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(Consultancies and/or lecture fees: Abbott, AbbVie, Bristol-Myers Squibb, Gilead, Medtronic, and Roche.)

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The thin harvest of studies of antiretroviral therapy in naïve

The 2018 Conference on Retroviruses and Opportunistic Infections (CROI) was held in snowy Boston Seattle from March 4th to March 7th. CROI 2018 would be back in Seattle (March 4th to 7th, 2019).

This was not the year of antiretrovirals at CROI. There were few presentations, however I consider some of them interesting for the clinicians.

Is penetration of antiretrovirals in lymph node tissue relevant?

Dr. Courtney Fletcher and collaborators presented a provocative study [1] looking at tissue penetration of the three integrase inhibitors currently available in the majority of countries: raltegravir, elvitegravir and dolutegravir. This research group had reported in 2014 that compared to average PBMC concentrations, the average concentrations in lymph node tissue were 80% lower for tenofovir diphosphate, 66% lower for FTC triphosphate, 100% for atazanavir, 99% lower for darunavir and 94% lower for efavirenz [2]. Authors correlated these low lymphatic tissue levels with persistent HIV replication in lymph nodes 6 months after starting antiretroviral therapy. At this year CROI Fletcher and collaborators have presented a study including 34 volunteers receiving treatment with nucleos(t)ide reverse transcriptase inhibitors and either dolutegravir (n=11), elvitegravir/cobicistat (n=17) or raltegravir (n=6). These participants volunteered for lymph node, ileum and rectum biopsies for determination of intracellular concentrations (mononuclear cells) of the integrase inhibitors. As summarized in Table 1 the inhibitory quotients values in PBMC for dolutegravir, elvitegravir and raltegravir were 6-fold or more above the IC90-95. However, in lymph node tissues median IQ values were lower than in PBMCs except for elvitegravir in the ileum and rectum. Of note, only elvitegravir achieved IQ values greater than 1 in lymph nodes.

The clinical relevance of these findings is unknown and possibly not very important in the setting of triple therapy. However, I think penetration in lymph nodes could be an explanation for the in general disappointing results of nucleos(t)ide sparing regimens. Dr. Fletcher also presented an in vitro model to predict lymphoid tissue bioavailability (Table 2). Interestingly both darunavir and raltegravir have low penetration in lymph node tissue and this combination underperformed in the NEAT001 clinical trial [3]. In contrast dolutegravir and rilpivirine has medium and high penetrance respectively. The combination of these two drugs matched the efficacy of triple therapy in the SWORD clinical trials [4].

During the Q&A time Dr. Fletcher explained that as a class nucleos(t)ide reverse transcriptase inhibitors have better penetrance in lymph node tissue.

Drug	Inhibitory Quotient (intracelular concentration/protein binding corrected IC_{90-95}) Median and Interquartile Range		
	DTG	EVG	RAL
PBMC	5.24 (3.32, 13.23)	16.46 (10.76, 25.93)	6.08 (0.94, 14.14)
LN	0.44 (0.26, 0.66)	1.85 (1.51, 2.15)	0.28 (0.26, 0.48)
Ileum	0.43 (0.35, 9.95)	39.88 (7.28, 105.41)	Not done
Rectum	0.41 (0.33, 0.99)	16.97 (7.87, 39.83)	2.71 (2.62, 5.91)

Table 1. Inhibitory Quotient Values

Hi (>67th %ile)	Medium (67->33rd %ile)	Low (<33rd %ile)
RPV	RTV	ATV
EFV	TDF	DRV
EVG	DTG	RAL
Cobi	MVC	FTC
		ABC

Table 2. In Vitro Model of Lymphoid Tissue Bioavailability Using Human Lymphatic Endothelial Cells

	Global (n=145)	Triple Therapy (n=70)	Double Therapy (n=75)
	33.1±9.9 30 (25.5-39.5)	32.5±8.4 30 (26-38)	33.7±11.1 30 (24-92)
Males	131 (91%)	61 (88%)	70 (93%)
Hispanic/Latino	102 (71%)	49 (71%)	53 (71%)
MSM/Bisexual	101 (73%)	48 (71%)	53 (76%)
CDC Stage B	11 (8%)	5 (7%)	6 (8%)
Viral Load (log)	4.5 (4.0-5.0)	4.5 (3.9-5.0)	4.6 (4.1-5.1)
CD4 Count	383 (286-562)	366.5 (275-544)	419 (290-564)
CD4 %	19 (14-25)	19 (14-25)	19 (14-25)
VL > 100000 c/mL (Baseline)	35 (24%)	15 (22%)	20 (27%)

Table 3. ANDES Clinical Trial. Baseline Characteristics.

Five rhesus macaques cured with PGT121 combined with GS-9620.

The field of HIV cure has not had good news in recent years. In the "Boston patients" [5] and the "Mississippi" baby [6]

	Global	Triple Therapy	Double Therapy	Difference
Primary Outcome: VL<50 c/mL at Week 48				
ITT Snapshot, (n=145)	136 (94%)	66 (94%)	70 (93%)	-1.0% (-7.5; 5.6%)
ITT Snapshot, Baseline VL>100,00 c/ml (n=35)	32 (91%)	12 (92%)	20 (91%)	-1.4% (-17.2; 14.4%)
Observed (n=140)	136 (99%)	66 (99%)	70 (100%)	-1.5% (-0.9; 3.9%)
Adverse Events				
Rash		7%	8%	
Gastrointestinal		14%	7%	
Total Cholesterol (Change from BSL)		4%	19%	p:0.01
LDL-Cholesterol		6%	14%	
Triglycerides		14%	25%	

Table 4. ANDES Clinical Trial. Results at 48 weeks

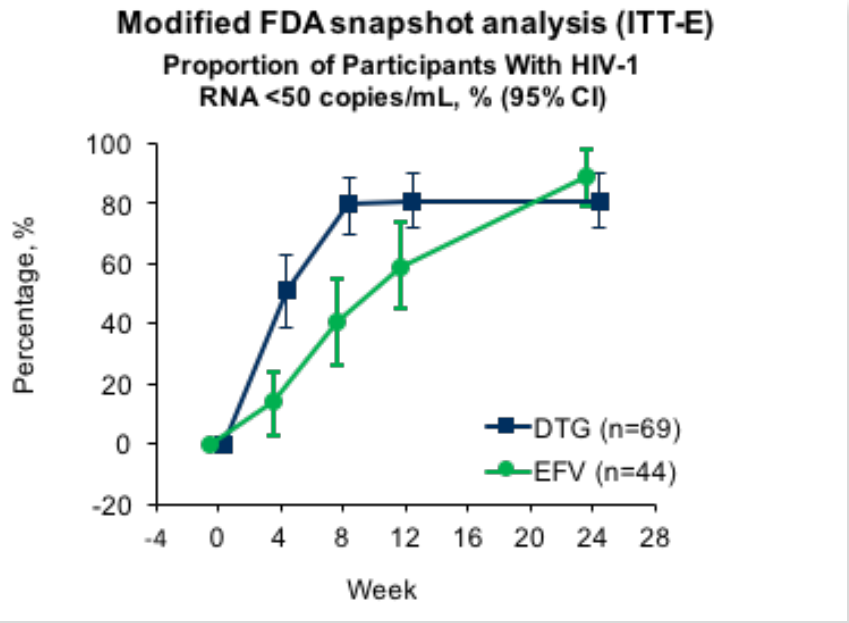

Figure 1. INSPIRING Study resutls

HIV rebounded after prolonged periods of remission in the absence of antiretroviral therapy. One of the most exciting presentation at this year CROI has been a study in rhesus macaques infected with SHIV [7]. In this study 5 macaques have been apparently cured of SHIV infection. Forty-four monkeys were infected with SHIV, a virus combining parts of the HIV and SIV genomes. As soon as 7 days after the infection antiretroviral treatment with TDF, FTC and dolutegravir was started and maintained during 96 weeks. After this period of treatment monkeys were equally divided in four groups that received, in addition to antiretroviral therapy, placebo, the TLR7 agonist GS-9620, the broadly neutralizing antibody PGT121 or the combination of GS-9620 and PGT121. A TLR7 agonist works by helping to release antiviral and proinflmmatory cytokines such as type I interferons involved in immune responses to infections, including HIV. Besides, GS-9620 is able to reactivate expression of the latent HIV reservoir. PGT121 is a broadly neutralizing antibody that binds to gp120. After a period of 20 weeks all therapies were stopped. As expected 11/11 monkeys receiving ART plus placebo rapidly rebounded compared to 10/11 that received GS-9620 and 9/11 that received PGT121. Rebounds after PGT121 were lower and occurred later than in monkeys receiving placebo. The big news is that only 6/11 monkeys that received the combination of GS-9620 and PG121 rebounded. Investigators performed later adoptive transfer of lymph node mononuclear cells and PBMC from 5 monkeys without rebound (4 from the PGT121 + GS-9620 group and 1 from the PGT121 alone). None of them transmitted SHIV to the receptor monkey suggesting that they in fact had been cured from SHIV infection. These are good news in the cure field. Caveats are that this is an animal model and that monkeys started ART very soon after infection, most likely with a low reservoir. Nevertheless, this is an exciting development. Trials in humans using GS-9620 and PGT121 are ongoing. Stay tuned for their results.

ANDES: more data supporting dual therapy with boosted protease inhibitor and lamivudine

The only dual regimen that has proven similar efficacy than triple therapy in naïve patients is the combination of lopinavir/ritonavir and lamivudine in the GARDEL clinical trial [8]. Lopinavir is no longer a recommended drug in expert guidelines so this result has little practical consequence. At CROI this year, Figueroa et al [9] from Pedro Cahn's research group presented the 48 weeks results of the ANDES trial that explored the dual combination of darunavir/ritonavir and lamivudine administered as a generic fixed dose combination. This dual combination was compared with triple therapy with darunavir/ritonavir and TDF-3TC in 145 antiretroviral naïve participants. Mean CD4 cell count was 383 and approximately one quarter of participants had viral loads above 100,000 copies/mL (Table 3). At week 48, the proportion with HIV-RNA less than 50 copies/mL by snapshot analysis were 93% and 94% in dual and triple therapy respectively. In participants with high viral loads at baseline, proportions with suppression were 91 and 92% (Table 4). Only one patient in the triple therapy arm developed protocol defined virological failure. The only statistically significant difference in laboratory adverse events was a higher total cholesterol in the dual therapy arm. Although sample size was small, ANDES further support the notion that dual therapy with boosted darunavir ➤

and 3TC is efficacious both in naïve and in suppressed patients [10]

Dolutegravir: another alternative for naïve patients with active tuberculosis?

For HIV-infected persons who need to initiate simultaneously antiretroviral therapy and antituberculous treatment, the current recommendation is to use either efavirenz or raltegravir although there is more experience with efavirenz. At CROI this year, the first data of what can become a new alternative; dolutegravir, were presented [11]. The INSPIRING study is a Phase 3b, non-comparative, active control, randomised, open-label study in HIV-1-infected ART-naïve adults with drug-sensitive tuberculosis, 96% pulmonary TB. In this trial participants receiving rifampin-based tuberculous treatment for up to 8 weeks were randomised (3:2) to receive dolutegravir at a dose of 50 mg twice daily or efavirenz 600 mg once daily. Both groups also received two nucleos(t)ide reverse transcriptase inhibitors. At baseline, median CD4 cell count was approximately 200 cells/μL and 60% had viral loads above 100,000 copies/mL. By modified FDA snapshot analysis proportions of participants with HIV-RNA less than 50 copies/mL were 89% and 81% for dolutegravir and efavirenz respectively (Figure 1). Of note, the majority of snapshot non-responders in the dolutegravir group were due to discontinuation for non-treatment-related reasons, mainly lost to follow-up while suppressed. Only one participant in the efavirenz group had virological failure with resistance development. INSPIRING also included a pharmacokinetic substudy showing that despite the use of rifampin, plasma dolutegravir concentrations when given as 50 mg BID were well above the target Ctrough. Rates of immune reconstitution syndrome were similar in both groups. This result is in line with what has been reported, also at this CROI, by investigators in the REALITY trial who showed that adding raltegravir to standard triple therapy with efavirenz did not increase the rates of immune reconstitution syndrome [12]. Although INSPIRING is a small study these initial results suggest that dolutegravir might be used along with rifampin in HIV-infected patients with active tuberculosis.

Other observations

Investigators from the AMBER study reported a subgroup analysis of the comparison of darunavir/cobicistat/emtricitabine/tenofovir alafenamide fixed dose formulation vs. darunavir/cobicistat plus emtricitabine/tenofovir difumarate. AMBER showed that darunavir/cobicistat/emtricitabine/tenofovir alafenamide was non-inferior to the comparator arm. This result was not impacted by age (above or below 50), gender or race [13].

In the DRIVE-AHEAD trial doravirine, a new generation non-nucleoside reverse transcriptase inhibitor, combined with tenofovir disoproxil fumarate and lamivudine showed non-inferiority versus efavirenz/emtricitabine/tenofovir disoproxil fumarate in antiretroviral naïve patients. This difference was not affected by baseline CD4, viral load, viral subtype, hepatitis B or C coinfection, age, gender or race [14]

Clinical trials of the fixed dose combination of bictegravir/emtricitabine/tenofovir alafenamide requested participants to have sensitivity to emtricitabine and tenofovir alafenamide. Testing for integrase resistance was not compulsory at baseline. Investigators from these trials have analyzed the impact of baseline resistance to integrase inhibitors (approximately 1%), nucleoside resistance (approximately 1%) or non-nucleoside resistance (approximately 12%) upon virological response to bictegravir/emtricitabine/tenofovir alafenamide. The short answer to this question is: resistance has no impact. Even one patient with transmitted integrase resistance caused by the G140S/Q148H mutations achieved virological suppression [15]. These results suggest that the need for baseline resistance testing is questionable when using high genetic barrier drugs.

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The bad old days

Back in the later half of 1980s, when I saw my first patient with AIDS, treatment was limited to the recently licensed, toxic and difficult to adhere AZT. New diagnoses, commonly in a symptomatic state, were common and testing limited to a few settings such as sexual health clinics.

Hospital wards across the developed world were increasingly occupied with HIV positive individuals with multiple health problems and a range of previously exotic opportunistic infections and malignancies. We treated these infections, often with initial success only for the same individual to present soon after with a new and more severe and less treatable infection. HIV was viewed as a progressive disease with AIDS and death an inevitable end. Indeed, clinical trials routinely used the composite endpoint of AIDS and death to define outcomes. The first decent disease surrogate that addressed HIV as a viral disease, HIV RNA testing, did not become available in clinical practice until 1996. The lack of surrogates hampered the speed of research, which relied on p24 antigen testing that was only positive in a minority of subjects and CD4 cell counts. Physicians, scientists and dedicated, articulate treatment advocates chased government bodies and pharmaceutical companies for funding for research into HIV. A trickle of new drugs, all NRTIs with their own problems, reached the market in the early 1990s following large scale studies with AIDS/death endpoints but which made only limited and transient impact on survival and no impact on transmission. The situation in the vast swathes of the world where HIV was most prevalent was even worse.

In London, and many other cities, new charities sprung up to assist people with HIV deal with discrimination and stigma (as documented in Tom Hanks portrayal of an HIV positive man in the film 'Philadelphia'), advocate for research (such as ACT-UP, Treatment Action Group) and provide care for people with HIV. In the UK and other countries, private funding, eventually with some government assistance and contracts, established respite, convalescence and end of life facilities for people with HIV. Organisations in the UK such as the London Lighthouse and the Griffin Project, both of which I was privileged to work for, provided these services in the face of established services for terminal care that were at best reticent about taking in people with HIV. Many friends and patients died of AIDS in these facilities which increasingly specialised in end of life management and palliative care. The care process for someone with HIV followed a path of firstly managing quality of life to then managing quality of death as HIV teams became skilled in palliative care, symptom management, pain relief and accepting the disease had won and amazingly brave people said goodbye to their loved ones way before their time.

Up to 70% of our local community of gay men died during that time and HIV infection shortened the average life expectancy for these individuals by 45 years. Haemophilia populations were devastated as they dealt with both HIV and Hepatitis C epidemics. Parts of Africa saw average life expectancy across whole communities decline dramatically. Deaths for AIDS peaked in 1996 in the developed world and the arrival for viral load testing and triple therapy led to a gradual decline in deaths and hospitalisations over the later part of the 1990s. Some patients were deemed 'Lazarus' patients after the Biblical story of him rising from the dead. While medications had many problems, challenging schedules and even more challenging side effects, from kidney stones to lipoatrophy via peripheral neuropathy and lactic acidosis, remarkable numbers of people managed somehow to get through it, albeit all to commonly bearing the stigmatising scars to prove it.

As deaths and hospitalisations declined the need to convalescence and terminal care facilities went into, well, terminal decline. Facilities such as the London Lighthouse temporarily functioned as community centres for people with HIV offering a stigma free environments, counselling, occupational therapy for the disabled and benefits and retraining advice on those seeking return to work. The residential units closed as needs and funding dried up. Eventually, the services closed entirely and the buildings were sold off and repurposed for things unrelated to HIV.

Growing Old with HIV

The 'naughties' and into the 2010s saw considerable refinement to antiretroviral treatments, with fewer adverse effects, once daily dosing and complete regimen single tablets. Deaths related to HIV continued to decline and the impact of treatment availability in the developing world was also witnessed. People who had survived the 80s and 90s often returned to work and celebrated birthdays they had never expected to reach. Sadly, those birthday celebrations were also tinged with the recollection of many absent friends and lovers.

A research trend began into understating the experience of aging with HIV. Areas of interest included the role of HIV

per se and contributions of ART to observed clinical events. For a generation exposed to thymidine NRTIs and other mitochondrial toxic NRTIs as well as long periods of immune deficiency it was suggested that aging may have been accelerated or at least accentuated, with events such as diabetes, metabolic disorders, cardiovascular disease, neurocognitive disorders, renal and bone disease as well as certain malignancies (anal cancer, lymphoma, lung cancer) all seen more commonly and added to the burden of residual disabilities related to prior AIDS events (such as visual impairments from CMV, memory problems from toxoplasma) and NRTI toxicities (particularly lipoatrophy and peripheral neuropathy).

More recently, the EU-funded four-year COBRA project which has focused on age-related disorders in persons living with HIV relative to well matched HIV negative controls concluded that the added risk of developing aging-related conditions may have been overemphasised, and that any added risk stabilises once patients receive effective treatment and conditions such as memory loss decline at the same rates as age and lifestyle matched controls. However, at the start of the study, the HIV-infected group on average already demonstrated evidence of being biologically older than their actual age would indicate, compared to the group without HIV.

Thus, individuals who are now treated early with test and treat approaches and receive well the current generation of preferred agents are probably in a much better situation. This suggests that for people living with HIV, there needs to be a focus on lifestyle factors, smoking, alcohol, drugs, diet, exercise and sleep quality so they limit the impact on and rate of progression of pre-existing conditions.

As HIV was seen as a chronic manageable condition, and many people had recovered sufficiently to return to work Government benefits systems began to withdraw support. Healthcare assessments, often done by people with limited knowledge of HIV or understanding of a person's medical history deemed many disabled people with HIV fit for work based on current CD4 values and undetectable viral loads. As these assessments rose in frequency and strictness, they unleashed a new wave of anxiety and depression amongst a group of people carrying the burdens of chronic illness, disease stigma, stigma related to sexuality or migration, polypharmacy and who had commonly lost much of their social support network through HIV related deaths in the 80s and 90s. Patients began saying the previously unsayable, confiding that they often wished they had not survived the past given the vicissitudes they faced now.

Dying of 'Old Age'

Many clinical cohorts now includes many individuals in their 70s, 80s and even 90s who have lived to or beyond the average life expectancy of the general population, let alone their own expectancy upon HIV diagnosis. As with my parents who both have lived into their 90s, these people have often outlived everyone in their generation. They became the last man or woman standing. Stephen Crohn, the man in whom the CCR5 delta 32 mutation was discovered, similarly articulated the consequences, psychologically, of surviving the HIV plague. Stephen was never infected with HIV but was greatly affected by HIV, eventually taking his own life as he was left growing old in a shrunken and narrow world with photo albums full of dead friends and old diaries of telephone numbers that if called would go unanswered. Furthermore, may individuals enter old age after years of disability and prolonged time out of the workforce so commonly have limited financial resource with housing and income dependent increasingly tight public support. Again, charities which once helped people with HIV with grants for things such as washing machines have vanished so when things breakdown individuals start to go without.

Clinical practice now involves seeing many people with the diseases of old age. HIV Doctors are now 'morphing' into geriatricians with a sideline in managing drug interactions between HIV drugs and the polypharmacy of diseases not simplified by polypills and single tablet regimens. Clinical events such as heart attacks, strokes, end stage diabetes, prostate and lung cancer, Alzheimer's disease, now fill wards once filled with patients with opportunistic diseases. The HIV ward, if it still exists, looks after the same diseases as the other general medical wards, the HIV disease being just a footnote on the list of presenting complaints. The differences with the people on the general wards are that those wards at visiting time are full of friends who came to see them, family who ran errands for them. All too often people who have survived with HIV are reaching old age with no children, or children in a far away land, and with a social network that is again either distant, disabled or already dead. Upon discharge back 'home', support is provided by the cold hand of the state, 'carers' that stay ➤

only a matter of minutes and change everyday, the gourmet delights of 'meals on wheels'. When winter comes, the choice between food and heating begin to bite at limited resources.

General practice appears ill-prepared for dealing with HIV. Often family doctors have had little formal training in HIV and next to no knowledge about the antiretrovirals prescribed in specialist practice. Sometimes attitudes to people with HIV, especially gay men, are reported by patients as being unhelpful at best. The regular letters sent to general practices are not matched with communication back, often making it a struggle to determine what 'the small white pill' that was recently commenced might be. Letters certainly require attention to use the Liverpool drug interactions website or contact details for specialist pharmacists who can advise before prescriptions or written.

There comes a time in old age when individuals can no longer manage independently. Many people in the general population transition from independent living, perhaps via a 'retirement village' to supervised semi-independent care and eventually nursing homes. These are all generalist facilities that commonly are best suited to the dominant population group but unsuitable for people from racial or sexuality minorities. A survey by Stonewall UK suggested 'elderly gay and lesbian people are almost twice as likely as their heterosexual peers to expect to rely on medical, housing, care and home help services. However, they often struggle to find providers who will understand their needs.' Gay men are met with outdated attitudes still prevalent in the older generation. People who migrated to the UK 30 or more years ago find that they have nothing in common with their fellow residents. People are left lonely in facilities where some in the general population find a new range of friends and activities. Staff in nursing homes are generally unfamiliar with HIV and the homes have no policies in place to avoid discrimination. Thus, anxieties about transmission, despite our best explanations that undetectable means non-transmissible, result in our patients experiencing a pariah status where that are managed with stigmatising glove and mask hygiene and other indignities exclusive to them. This of course unmasks them as 'different' to other residents who then avoid and ostracise them at meal times and in social activities again leading to a spiral of isolation [1].

Ultimately, as the Institute of Medicine has defined a good death is "one that is free from avoidable distress and suffering, for patients, family, and caregivers; in general accord with the patients' and families' wishes; and reasonably consistent with clinical, cultural, and ethical standards." This is something we need to stave to offer our patients.

What is needed?

Recently in Australia and the US, the first retirement villages targeted to the LBGT community have opened. Linton Estate [2], 30 miles west of Melbourne, Australia claimed at its 2015 opening to be 'the world's first residential village for gay, lesbian, bisexual, transgender, intersex community and like minded people, with the flexibility to be a weekend retreat or a place to retire. It has all what a retirement village has and more' including access to a hospital with specialist age care facilities and a large GP practice.

Australia has been particular progressive in facing the issues around aging in the LBGT community. the In 2012, the Australian Government recognised this invisibility of the community in planning around aging and the importance of challenging approaches that assume all people are heterosexual and not trans resulting in legislative reforms recognising older LGBTI people as a Special Needs Group and providing protection against discrimination on the basis of sexual orientation and gender identity including in the provision of aged care services. Similar legislation and recognition is widely lacking across Europe.

The US has also seen this trend developing with more than 20 retirement facilities for LBGT communities now being open [3] with some services targeted to those with low incomes. Following Australia's lead California in October 2017 signed into law a 'Lesbian, Gay, Bisexual and Transgender Long-Term Care Facility Residents' Bill of Rights' to protect LGBT older adults in the state from discrimination or mistreatment in assisted living communities and nursing homes.

The time has come for governments and entrepreneurs in Europe to address the needs of both the LBGT community but also, and at least partially intertwined with this, people living with HIV to establish specialist retirement options and nursing care facilities to those who survived the worst of times and can retire and eventually die in safe, dignified and supportive environment.

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3. https://money.usnews.com/money/blogs/on-retirement/articles/2016-11-03/20-retirement-communities-for-lgbt-seniors

Other Reading

- http://journalofdementiacare.com/we-are-still-gay-the-needs-of-lgbt-australians-with-dementia/
- Gay Men's Working Lives, Retirement and Old Age By Peter Robinson (Springer 2012)

Notes 2018

Retreatment of hepatitis C genotype 1 and 4

In a prospective study of previous treatment failures participants were randomized to 16 or 24 weeks of treatment with the combination of sofosbuvir, weight based ribavirin and grazoprevir/elbasvir. Patients who had previously failed treatment with sofosbuvir with or without ribavirin together with simeprevir, daclatasvir or ledipasvir and who had documented resistance-associated substitutions (RASs) were included. Patients with all stages of fibrosis with the exception of Child B or C were eligible for inclusion. 28 patients with NS3 or NS5A RASs were randomized. The most common genotype was 1 B. 13 patients had cirrhosis (liver stiffness > 14.5). A majority (18/28) had previously been treated with sofosbuvir and ledipasvir. Two patients withdrew consent. 1 patient with a history of hepatocellular carcinoma (HCC) was hospitalized for chemoembolism of residual HCC and liver transplantation discontinued treatment after 12 weeks due to worsening renal function and hepatic dysfunction and died five weeks later. All other patients achieved SVR 12 with 16 or 24 weeks of therapy.

Lédinghen et al. Clin Infect Dis 2018;66:1013-1018

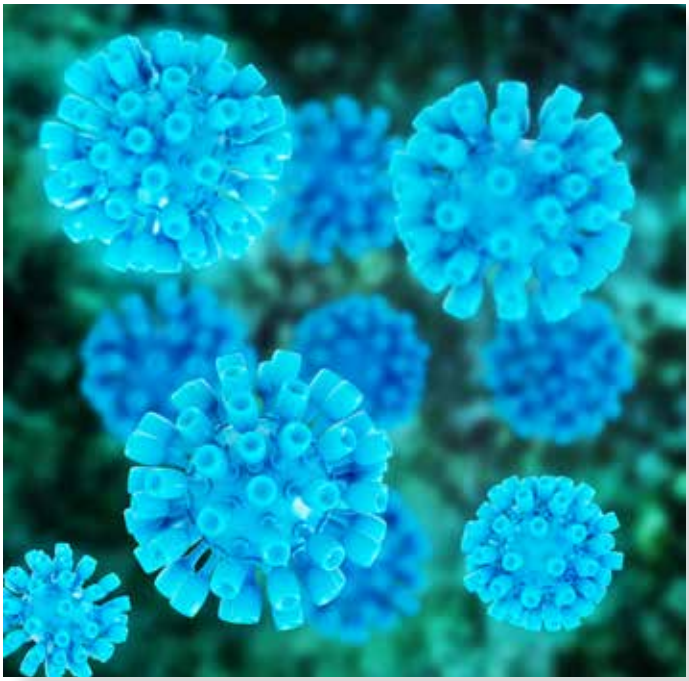
Comment: Even in patients who have previously failed hepatitis C treatment with directly acting antivirals very high rates of sustained viral response can be achieved. 16 weeks of quadruple treatment with sofosbuvir, grazoprevir/elbasvir and weight based ribavirin cleared the virus in all patients.

Ribavirin-free retreatment of hepatitis C

In another retreatment study of patients who had failed treatment with at least one NS3/4A- and/or NS5A- inhibitor patients with genotype 1 and 4, were randomized to 12 or 16 weeks of ribavirin free therapy with glecaprevir/pibrentasvir. 91 patients with compensated liver disease with or without cirrhosis were included. A vast majority had genotype 1 (87/91). The remaining four patients had genotype 4. 89 % (39/44) of the patients who received 12 weeks of therapy and 91 % (43/47) of the patients who were treated for 16 weeks achieved SVR. 4 of 5 who failed 12 weeks of therapy had virologic relapse while the four failures in the 16 weeks arm all had on treatment failure. Past treatment with NS5A- but not NS3/4A- inhibitors was associated with a higher risk of failure. Patients who had no baseline RASs or NS3/4A RASs only, had 100 % SVR in both arms. The authors conclude that 16 weeks of glecaprevir/pibrentasvir achieves a high cure rate in patients with previous failures on either NS5A or NS3 inhibitors.

Poordad et al.Hepatology 2017: https://doi.org/10.1002/hep.29671

Comment: It is of course very attractive to use a ribavirin free regimen even in patients with previous failures. There was no statistically significant difference between SVR in 12 and 16 weeks of therapy but relapses occurred only in the 12 weeks arm while on treatment failures were more common in the 16 weeks arm. Patients without any baseline RASs had 100 % SVR with both 12 and 16 weeks of therapy. 12 weeks of therapy may therefore be an



attractive alternative in patients with previous failures without baseline RASs.

Drug interactions between dolutegravir, isoniazid and rifapentine

Once weekly isoniazid and rifapentine for 3 months (3HP) is an alternative treatment for latent tuberculosis. In trials comparing it to nine months of isoniazid treatment higher rates of adherence and treatment completion were achieved. Despite this, it has not been widely used in HIV-infected patients partly due to lack of limited data on drug interactions with antiretroviral therapy. In a study of healthy volunteers drug-drug interactions between dolutegravir and 3HP were examined. Each subject received 4 days of only dolutegravir followed by the combination of dolutegravir and once weekly isoniazid and rifapentine. Serial blood sampling was performed on day 4, 14 and 19. The study was terminated after two of four subjects developed serious toxicities after the third isoniazid/rifapentine dose. Both subjects developed flulike symptoms with elevated transaminases. Interferon-γ and other cytokines were elevated. The elevation of cytokines was temporally associated with the flulike symptoms. Area under the curve (AUC) for dolutegravir was decreased 46 % following the second isoniazid/rifapentine dose. The levels of rifapentine and its metabolite were comparable to reference values but isoniazid AUC was up to 92 % higher in subjects who developed toxicities.

Brooks et al. Clin Infect Dis 2018 Feb 3. doi: 10.1093/cid/ciy082. [Epub ahead of print]

Comment: As dolutegravir is now recommended as first line therapy in many countries with high prevalence of tuberculosis this is important information. The combination of dolutegravir and once weekly isoniazid and rifapentine should be avoided. ➤

Abacavir use and risk of recurrent myocardial infarction (MI)

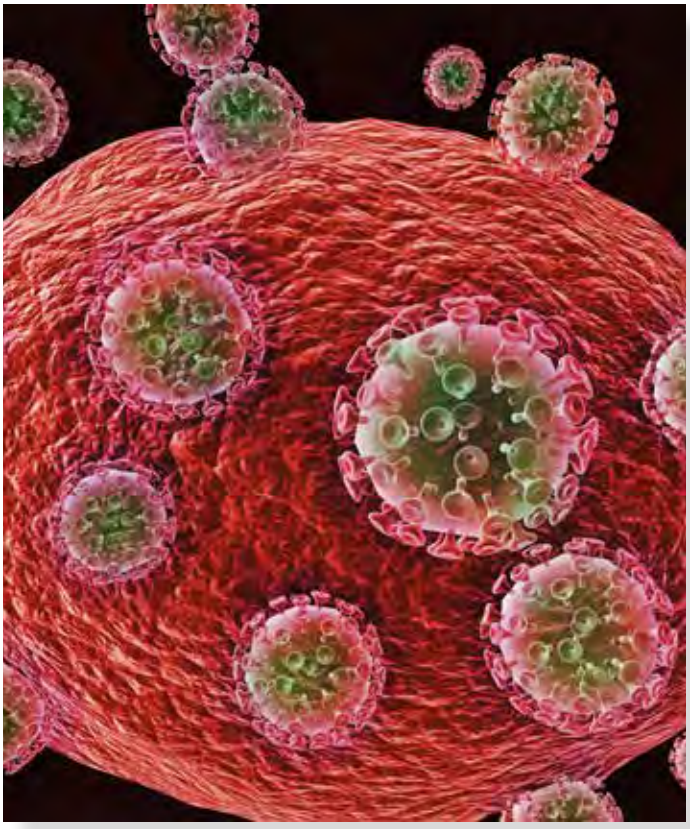
In 2008 data from the D:A:D study reported that current or recent use of abacavir in HIV-treatment was associated with a 90 % increased risk of MI. In an international multicohort collaboration follow up study the risk of recurrent MI with use of abacavir was investigated. 984 individuals who had an index MI were followed for 5,312 person-years. There were 136 recurrent MIs corresponding to 2.56/100 person-years. No associations between current use or cumulative exposure to abacavir and risk of recurrent MI were found.

Sabin et al. AIDS 2018:32;79-88

Comment: The fact that there was no association between the use of abacavir and risk of recurrent MI seems to contradict earlier reports of the increased risk of MI in patients with recent or current abacavir treatment. In the discussion, the authors suggest that the contradictory findings may be explained by post-MI interventions and the use of antiplatelet therapy with aspirin with or without the addition of clopidogrel. A suggested mechanism explaining the increased risk of MI in abacavir use is increased platelet activation. If this is correct perhaps aspirin should be prescribed for patients on abacavir treatment with risk factors for MI?

Bacterial vaginosis, hormonal contraception and risk of HIV acquisition

In a longitudinal cohort of serodiscordant heterosexual couples with an HIV-positive male the risk of seroconversion was evaluated in relation to the use of hormonal contraception and bacterial vaginosis. The cohort was recruited in Zambia between 1994 and 2002. Genital tract examination and HIV-testing were performed quarterly. Among 564 discordant couples (1,137 couple years of observation) with an HIV positive male 106 seroconversions occurred. Unadjusted seroincidence/ couple years of observation during bacterial vaginosis was 8.2 for non-hormonal or no contraception, 20.8 for injectable hormonal contraception and 31.0 for oral hormonal contraception. During periods without bacterial vaginosis there was no statistically significant difference between the groups (8.2, 9.7 and 12.3, respectively)



Haddad et al. AIDS 2018:32;595-604

Comment: Several studies have shown that the risk of acquiring HIV increases with the use of hormonal contraception. In this study it is the combination of bacterial vaginosis and hormonal contraception that synergistically increase the risk of seroincidence. The underlying mechanism is not clear and further studies are required to understand the potential interaction between hormonal contraception and bacterial vaginosis.

A new treatment option for HIV

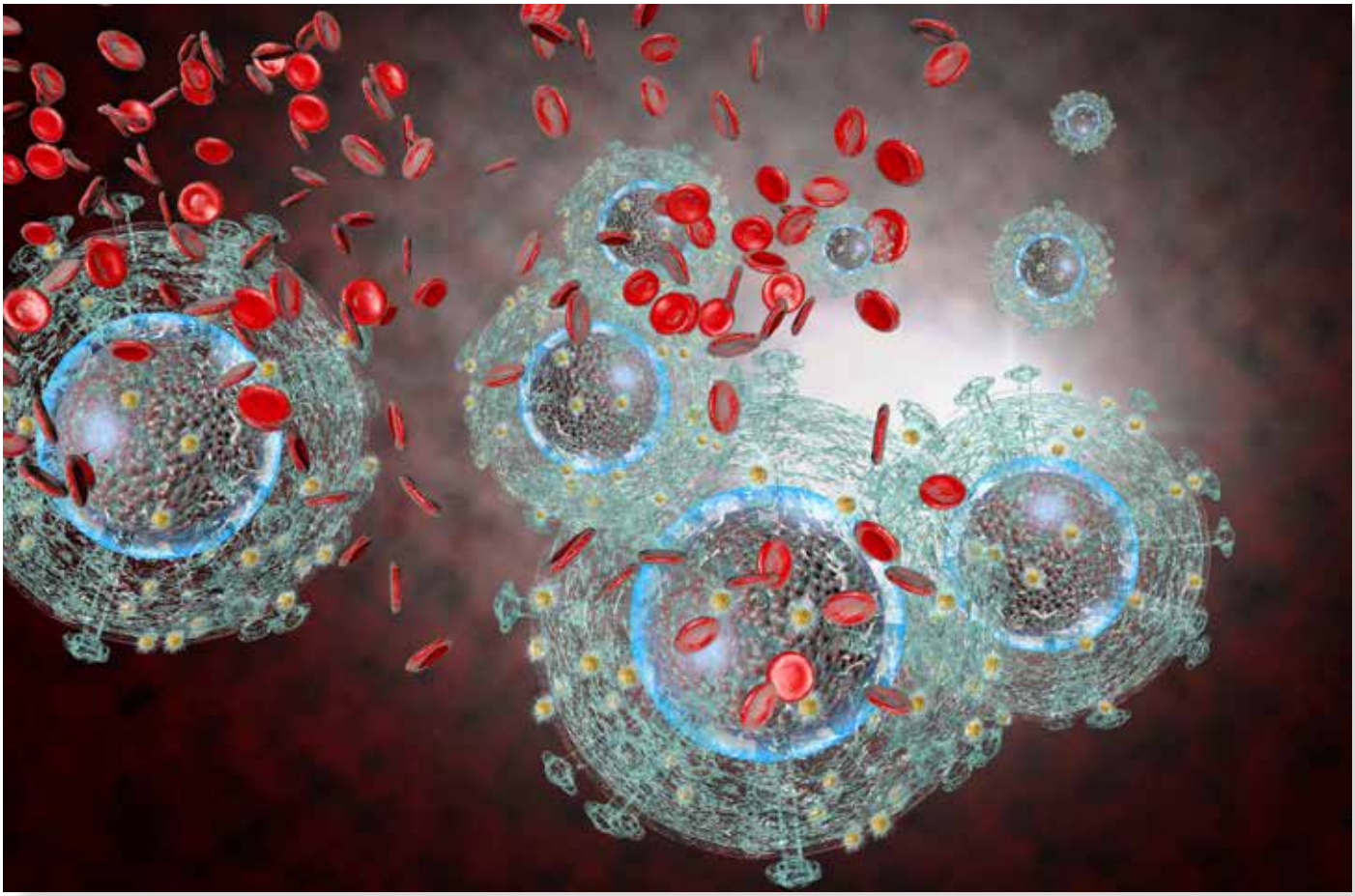
Doravirine is a new non-nucleoside reverse transcriptase inhibitor (NNRTI) suitable for once daily dosing with good activity against the most common NNRTI-resistant HIV-variants. In a non-inferiority trial, doravirine in combination with two investigator-selected nucleoside reverse transcriptase inhibitors (NRTI) was compared to ritonavir-boosted darunavir together with two NRTIs. The study was double blind, placebo-controlled and primary endpoint was proportion of patients with HIV viral load less than 50 copies at 48 weeks according to snapshot analysis. Treatment-naïve patients with HIV-RNA > 1,000 copies/ml without hepatitis or treatment with immunosuppressive drugs were eligible for inclusion. 769 patients were randomized 1:1. After 48 weeks 84 % in the doravirine arm and 80 % in the darunavir arm had HIV-RNA < 50. Most failures were due to patients lost to follow up. One patient in the doravirine arm who discontinued treatment at week 24 because of non-compliance developed genotypic resistant mutations to doravirine and emtricitabine. Adverse events including rash and neuropsychiatric symptoms were similar between the two arms. Total and LDL cholesterol and triglycerides were higher in the darunavir arm. In summary doravirine together with two NRTIs was non-inferior after 48 weeks with similar adverse events and a more favorable lipid profile compared to ritonavir boosted darunavir.

Molina et al. Lancet HIV: Published on line March 25 2018: https://doi.org/10.1016/S2352-3018(18)30021-3

Comment: A new NNRTI without the neuropsychiatric side effects of efavirenz is a welcome addition to the available treatment regimens for HIV. Doravirine is also developed as a single tablet regimen in combination with lamivudine and tenofovir disoproxil fumarate (TDF). As both lamivudine and TDF are available as generics one can perhaps hope for a competitive price?

Increase in transmitted drug resistance in migrants from sub-Saharan Africa (SSA)

In the Swedish data base "InfCare" all patients diagnosed with HIV in Sweden are included. The majority of newly diagnosed HIV patients are migrants. 1713 pol sequences from 2010-2016 in newly diagnosed patients were analyzed for resistance muta-



tions. Resistance to NNRTIs increased from 1.5 % in 2010 to 6.2 % in 2016. The increase in resistance is associated with migrants originating from SSA. In newly diagnosed MSM there was no increase in transmitted drug resistance, rather a slight decline.

Andersson et al. AIDS 2018:32;877-884

Comment: NNRTIs have been used as first line therapy in SSA. The increased rate of resistance in newly diagnosed HIV-infected migrants from SSA in Sweden illustrates the situation in SSA. The recent WHO recommendation to use dolutegravir as first line therapy is a welcome and necessary change in light of the increasing prevalence of NNRTI resistance.

Microbial translocation biomarkers and risk of ADS-related non-Hodgkin lymphoma (NHL)

The development of NHL in HIV infection is preceded by chronic immune activation. The underlying mechanism is not known. Biomarkers of microbial translocation including bacterial receptors/antibodies, intestinal barrier proteins and macrophage activation associated cytokines and chemokines were measured in 200 men from the Multicenter AIDS Cohort Study (MACS) who subsequently developed NHL. The median time from measurement to NHL diagnosis was 3.9 years. For each case a matched HIV-positive person from the MACS-cohort who did not develop NHL was selected. Both microbial translocation biomarkers and macrophage associated cytokines and chemokines were significantly higher in patients who developed NHL compared to the controls. The authors conclude that the systemic immune activation in chronic HIV infection plays an important role in the development of NHL and that microbial translocation may explain the immune activation.

Epeldegui et al. AIDS 2018:32;945-954

Comment: If these results can be verified new therapeutic approaches to reduce microbial translocation have to be explored. Does the gut microbiome play a role in microbial translocation and can we find ways of modifying the chronic immune activation? Many unanswered questions remain to be answered before these very interesting observations will result in changes in clinical management.

DR. LEO FLAMHOLC
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Topical Conferences 2018

16-18 May
Isheid, Hiv Hcv emerging infecious diseases
Marseille, France
www.isheid.com

16-18 May
14th edition of the International Workshop on Co-infection: HIV, Hepatitis and Liver Disease
Seville, Spain
www.virology-education.com/event/upcoming/14th-co-infection-workshop-2018

22-24 May
The International Workshop on Clinical Pharmacology of Antiviral Therapy 2018
Washington DC, USA
www.virology-education.com/event/upcoming/antiviralpk-workshop-2018

30 may-1 June
16th European Meeting on HIV & Hepatitis: Treatment Strategies & AntiviralDrug Resistance
Rome, Italy
www.virology-education.com

9-10 June
7th Asian Conference on Hepatitis and AIDS (ACHA)
Beijing, China
www.emedevents.com

20-21 July
10th International Workshop on HIV Pediatrics
Paris, France
http://www.virology-education.com/event/upcoming/10th-workshop-hiv-pediatrics

23-27 July
22nd International AIDS Conference (AIDS2018)
Amsterdam, Netherlands
www.aids2018.org

6-9 September
21st Annual United States Conference on AIDS (USCA)
Orlando, Florida, United States
http://2018usca.org

13-15 September
1st Conference on Liver Disease in Africa (COLDA)
Nairobi,Kenya
www.emedevents.com

26-28 September
5th HIV & Hepatitis Nordic Conference
Stockholm Sweden
www.hivnordic.se

1-2 October
9th HIV & Aging Workshop 2018
New York, NY, United States
www.virology-education.com

3-7 October
ID Week 2018
San Francisco, CA, USA
www.idweek.org

29-30 October
6th International Conference on HIV/AIDS, STDs and STIs
San Francisco, USA
https://hiv-aids-std.conferenceseries.com

9-13 November
The Liver Meeting (American association for the study of liver diseases, AASLD)
San Francisco
www.aasld.org/events-professional-development/liver-meeting

21-25 October
HIV Research for Prevention (HIVR4P) 2018
Madrid, Spain
www.hivr4p.org

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