

## may-june 2016

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## STOP PRESS

### **NHS England confuses arse and elbow: block to PrEP ignores UK HIV crisis and will send PEP services into chaos**

Simon Collins, HIV i-Base

**In an act of breathtaking stupidity, NHS England and its legions of commissioning committees and advisory structures are scrambling to find bureaucratic loopholes to further block access to the most effective way to prevent HIV transmission. [1]**

The decision to prevent doctors from prescribing PrEP to an individual – irrespective of their risk or circumstances – or to identify a rapid way to enable such prescribing will result in thousands of infections in England annually. While World Health Organization recommended PrEP is being integrated into programmes to end AIDS in the US, France, Australia, Canada, South Africa and Kenya, NHS England squabbles to find anyone with the authority to do so here. [2, 3]

If a woman explains to her doctor that her husband refuses to use a condom when they have sex and this has led to her needing treatment for STIs, her doctor will say come back when you are HIV positive, and then I can prescribe HIV drugs for the rest of your life, two of which would have kept you negative if I could have prescribed them today.

And if a 17 year old man with low self esteem, related to a history of childhood abuse, currently has transactional sex with clients who take off condoms, he will be told that he can't be prescribed the same drugs that he has already accessed five times this year as PEP to help stay HIV negative.

Why? Because no one with the authority can find a way to provide care for these people or any of the 7000 who have become HIV positive every year for the last decade.

PrEP was approved in the US in 2012, based on results from large international, randomised, placebo-controlled studies – the gold standard for scientific evidence – showing that PrEP roughly halved the risk of HIV transmission. But further analyses revealed efficacy was actually significantly higher, providing close to 100% protection when people were actually taking the drugs. And for men in the study, even taking four doses a week gave over 95% protection.

The response in the UK was to decide that UK studies were needed. Then, instead of the large, fully powered PROUD study in 5000 people at high risk that was needed, a pilot PROUD study was funded with 500 people. This was a demonstration study, designed to show whether PrEP as a new approach would be acceptable in the UK for people at high risk.

The results from the smaller PROUD study were so significantly effective – in real people in a real world setting of existing NHS clinics and services – that the pilot study had to be stopped early to ensure all participants had immediate access to PrEP. The evidence was so compelling that rollover into the larger study – already funded – was also stopped. All the infections in PROUD were in people who either were not being prescribed PrEP or who for personal reasons had decided not to take it. [4]

Now the NHS are proposing a paltry £2 million to fund yet another demonstration study, two years after PROUD proved PrEP worked in the UK better, faster and more effectively than anyone expected.

PROUD also showed that NHS clinics are able to engage with a group of people at such an alarmingly high risk – approximately 10% per year – that PrEP would be immediately cost effective and could prevent the NHS from lifelong costs from decades of antiretroviral treatment. [5]

As with access to most medical services and prescriptions, deciding who warrants access PrEP requires clinical expertise from a medical doctor. That the NHS currently trusts no doctors to do this is inexcusable – especially given the time that has already been taken to delay PrEP in the UK.

Pirates have hijacked the NHS. Ordinary people dependent on the NHS are having their health jeopardised. Dedicated and committed doctors in the NHS with expertise who care for people are increasingly restricted from helping.

There is an easy answer. The Secretary of State can authorise access to PrEP – which has already passed public consultation and review – and fund it out of the numerous contingency budgets available for crisis situations.



“Pirates have hijacked the NHS.”

“Pirates have hijacked the NHS [ ...] Dedicated and committed doctors in the NHS with expertise who care for people are increasingly restricted from helping.”

And HIV in England is a crisis: 500 people have been diagnosed every month for at least the last decade. PrEP benefits anyone at high risk but by coincidence the highest risk groups are gay men.

Until PrEP is available, people in need of it should continue to access PEP services, with the waste of time and drugs that this entails.

The immediate way for people who cannot afford a private prescription to buy PrEP online from generic pharmacies is to demand PEP for post-exposure prophylaxis now. The decision to provide PEP was made more than a decade ago after the threat of legal action. Similar legal action to demand PrEP is needed now.

In December 2014, UK activists, dressed in PrEP blue lined up outside one of the best and most respected NHS sexual health clinics to demonstrate the NHS provided a PrEP line to nowhere. Similar lines should form outside every Monday morning outside clinics offering PEP. [6]

This fiasco shown that NHS England doesn't know its arse from its elbow; it has disconnected its heart – by showing it cares little for the people PrEP could protect – and it has disconnected its brain – by ignoring its own evidence that proved 18 months ago that PrEP works in the UK.

Current documents for this mess are online. [7]

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#### C O M M E N T

**Following legal advice, the National AIDS Trust have decided to reopen their earlier legal challenge to this decision by NHS England.**

**NAT have launched a crowd funding appeal to help with these costs.**

**<http://uk.virginmoneygiving.com/fund/prep>**

#### Notes:

(i) PrEP stands for Pre-Exposure Prophylaxis. PrEP involves taking an oral tablet that contains two HIV drugs either daily for continuous protection or by event-based dosing (EBD) linked to when you have sex. EBD is only effective to protect against risk from anal sex but can require as few as four tablets. EBD is taken as a double-dose 24-2 hours before and single tablets taken 24 and 48 hours after sex.

(ii) PEP stands for Post Exposure Prophylaxis. PEP involves taking a three-drug combination of HIV drugs for one month after sex. PEP is available on the NHS and includes the two drugs used in PrEP.

(iii) In the UK it is legal to use online pharmacies to buy a three-month supply of generic PrEP for personal use. This is approximately 90% cheaper than using the current brand medicine in the UK.

#### References

1. NHS decision not to fund PrEP  
<https://www.england.nhs.uk/2016/05/prep-provision>
2. World Health Organization (WHO). Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV, (September 2015).  
<http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en> (web page)  
Guideline on when to start ART and PrEP  
[http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf?ua=1) (PDF download)
3. i-Base. Sign-on for PrEP to be raised in Parliament. (23 March 2016)  
<http://i-base.info/sign-on-for-prep-to-be-raised-in-parliament>
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<http://i-base.info/simoncollins/2014/12/nhs-prep-access-act-up-demo-and-community-statements/>
5. McCormack S et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. The Lancet. 2015. (Online 10 September). DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)00056-2](http://dx.doi.org/10.1016/S0140-6736(15)00056-2).  
[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(15\)00056-2/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00056-2/fulltext)
6. Collins S. NHS PrEP access: ACT-UP demo and community statements. Web blog. (10 December 2014).  
<http://i-base.info/simoncollins/2014/12/nhs-prep-access-act-up-demo-and-community-statements/>
7. Report on background to the NHS decision. (31 May 2016).  
<https://www.england.nhs.uk/wp-content/uploads/2016/05/sscc-paper-prep.pdf> (PDF)

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## IN MEMORY

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### **In Memory: Paul Blanchard**

#### **Co-founder of HIV i-Base, Editor of DrFax and HIV Treatment Bulletin**

**It is with immense sadness that we report the death of Paul Blanchard, an inspirational activist, a founder of i-Base, the first editor of HTB, and a long serving member of the HTB editorial board.**

Paul played a unique role in establishing treatment activism in the UK, challenging doctors to continually update their views and practice with evidence from rapidly evolving research.

Before helping to found HIV i-Base, Paul was a leading member of the AIDS Treatment Project (ATP) which was founded in London in 1996, where he edited DrFax, the forerunner to HTB, from 1996 to 2000.

Like many members of ATP, Paul experienced first hand the dramatic benefits of new combination therapy. He was one of the leading activists to recognise the need for using triple combinations to achieve optimal and sustained viral suppression and to avoid drug resistance when UK guidelines - and many other HIV organisations - suggested fewer drugs might be sufficient.

Despite being a generally reserved person, Paul took to the microphone at an early BHIVA conference in 1996, to protest at this apathy among many UK doctors to recognise the need to understand the implications of new treatment.

For most of the last ten years, although Paul continued to be a member of the HTB editorial board after he stepped down as editor in 2003, his primary focus was working at the British School of Osteopathy, where in addition to his teaching practice since 1988, he established the Chapman Clinic, to provide an HIV osteopathy clinic, in association with the Royal Free Hospital.

Paul had a tremendous and steady intellect and a unique critical view that enabled him to comment on new advances and current practice with such masterly understatement that would make disagreeing with his conclusions extremely difficult.

He also had a wicked sense of humour, adding an article on the increases in "internet-related STIs" with a chuckle "because doctors love reading about this sort of thing" or commenting proudly on his own 7-drug salvage regimen in the late 90s that "none of them are made by Glaxo".

i-Base trustee and former ATP member, Hope Mhereza said: "Paul was a big influence on the growth of treatment activism and much of what we know now and do today is owed to his involvement in the early years of HIV, when little was known of how treatments work. We are immensely proud of Paul and the HIV community is poorer without him."

Our thoughts and wishes are with his partner, family and friends.

Paul will be deeply missed.

The BSO website includes a webpage in memory of Paul.

<http://www.bso.ac.uk/bso-news-and-events/recent-news-and-events/in-memory-of-paul-blanchard-1964-2016>

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## EDITORIAL

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### **It is difficult to write this editorial for HTB.**

We learned earlier this month of the death of Paul Blanchard, one of the founders of HIV i-Base, and one of our colleagues from AIDS Treatment Project (ATP) who had a dramatic impact on treatment activism in the UK - and changed the standard of care for people living with HIV.

Paul taught us to focus on the science in order for our activist demands to be more than just a wish list. Virtually no-one at ATP had a scientific background and we had to learn how to understand how to critically evaluate evidence - good and bad - from scientific research. This training - supported by some of the UK's leading doctors and researchers - enabled ordinary people to have the power to question advice and opinions from doctors and friends and to distinguish both from pharmaceutical company marketing.

In 1996, the information we gave to people calling the ATP phonenumber who were only being offered two rather than three-drug ART, included how to register at a clinic that would provide the best care - because the evidence supported using at least three drugs.

i-Base is an activist organisation, so it is particularly difficult when NHS England ignores best scientific evidence - or worse in the case of the decision to block access to PrEP - and constructs bureaucratic reasons to restrict drugs that are increasingly available globally.

However difficult and high a person's individual HIV risk, UK doctors are unable to prescribe commonly used drugs for a new indication. This challenges a doctor's duty of care when sitting with a person that they strongly believe will become HIV positive within the next year.

It is similar to telling a doctor that they can prescribe ART to an HIV positive person to prevent HIV transmission but not for their own health care if their CD4 count is above 350. Oh, wait, that is currently the case too.

So while being HIV positive doesn't necessarily mean someone will live a shorter life, an HIV diagnosis is still a life-changing traumatic event. It also makes someone dependent on medical care, that will probably be lifelong.

As a result of the decision to block PrEP, services for PEP are likely to be further destabilised. Even with the waste this involves, i-Base supports this way to access PrEP - similar to the information in 1996 to change clinics to get better care. The NHS does run on a postcode lottery for treatment and finding the right clinic is an important individual option when the NHS bureaucracy squabbles.

We include a new "UK guide to PrEP" as a supplement with this issue of HTB. Although originally written to support people buying generic PrEP online, it is just as appropriate for people accessing PrEP from PEP clinics.

Further news in this issue includes conference reports from four medical conferences: BHIVA, EASL, CROI and the HIV and Women Workshop. And global news about access to better treatment - notably integrase inhibitors for HIV and direct acting antivirals for HCV.

Our fight to use best available scientific evidence to drive better medical care continued in large part due to the example and inspiration from Paul Blanchard, and it is in a very small way, our tribute to a colleague and friend who we will miss deeply.

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## CONFERENCE REPORTS

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### **22nd Annual BHIVA Conference**

**19-22 April 2016, Manchester**

#### **Introduction**

This year the annual BHIVA spring conference was held in Manchester.

There were numerous important presentations – with extensive webcast coverage available for all oral presentations.

<http://www.bhiva.org/Presentations160420.aspx>

The programme and abstract book are also available to download from the BHIVA website.

<http://www.bhiva.org/AnnualConference2016Presentations.aspx>

The following brief reports are selected highlights from the oral presentations and invited lectures.

- New HBV drugs and non-viral liver disease in HIV positive people
- Non-AIDS mortality in England and Wales in HIV positive vs general population
- High prevalence of multiple high-risk HPV infections in young HIV positive gay men
- Anal cancer and HPV screening in HIV positive people
- Increasing demand for community treatment information services
- Non alcohol fatty acid liver disease: an emerging problem
- HIV positive people on ART have impaired alveolar immunity

## **New HBV drugs and non-viral liver disease in HIV positive people**

**Gareth Hardy, HIV i-Base**

**Chronic hepatitis B (HBV) infection affects 350 million people worldwide and causes more than 600,000 deaths per year. Despite the prevalence of this virus, it is still poorly understood. Several challenges include achieving a cure, understanding the natural history and reducing the risk of hepatocellular carcinoma.**

In a session on hepatology highlights for HIV doctors, Patrick Kennedy from Queen Mary College London reviewed the current understanding of chronic HBV infection, as well as advances in treatment.

The immune response to HBV characterises different phases of the natural course of infection, which includes: 1) immune tolerance; 2) immune clearance; 3) immune control; and then typically 4) immune escape.

Dr Kennedy proposed that the immune regulatory marker PD1 might be involved in the establishment and maintenance of immune tolerance to HBV as both HBV antigen and T cells are present in the liver during the tolerant phase, but inflammatory cells fail to be recruited to the tissue. PD-1 expression on T cells is high in these patients. During this phase damage occurs to the liver that involves collagen deposition. Therefore, these phases should be regarded as non-inflammatory and inflammatory, rather than tolerant and active.

Current therapies are non-curative for the majority of people and include pegylated interferon (peg-IFN) and nucleoside analogues. While treatment can bring about long-term viral suppression, sustained immune control is limited. In contrast to single drug therapy, sequential nucleoside therapy with peg-IFN results in a greater decline in tissue HBV surface antigen as well as increasing the function of NK cells.

New classes of therapies are in development for chronic HBV. These include antiviral drugs that target sites in the viral life cycle: viral entry; clearance of viral cccDNA from the nucleus; and suppression of HBV DNA, RNA and/or proteins. Other therapies for HBV might utilise boosting HBV-specific adaptive immunity by blocking PD-1, or with HBV therapeutic vaccines, or engineered T cells that have high affinity receptors for HBV. Another approach is the development of antibodies tailored to deliver cytokines, such as interferon, to the interior of hepatocytes, making them resistant to infection. Clinical trials of these approaches are currently ongoing.

The end of the presentation included a brief overview of non-alcohol fatty liver disease (NAFLD), which is an emerging problem in long-term HIV infection and was the subject of considerable discussion at this conference. As much as 30% of the population may have NAFLD, which is thought to be caused by high blood lipids. Of those, 12-40% may develop non-alcoholic steatohepatitis (NASH), which probably results from inflammation or inflammatory mediators (though not necessarily originating in the liver). Approximately 15-20% of people with NASH develop liver cirrhosis, which is fatal in 50% of cases and a further 7% may then develop hepatocellular carcinoma. The main interventions are management of metabolic syndrome, and management of cardiovascular risk factors.

### Reference

Kennedy P. Hepatitis B virus - the role of new drugs and non-viral liver disease in HIV. 22nd Annual BHIVA Conference, 19-22 April 2016, Manchester. Invited lecture.

<http://www.bhiva.org/documents/Conferences/2016Manchester/Presentations/160419/PatrickKennedy.pdf> (PDF slides)

<http://www.bhiva.org/160419PatrickKennedy.aspx> (webcast)

## **Non-AIDS mortality in England and Wales in HIV positive vs general population**

**Gareth Hardy, HIV i-Base**

**Sara Croxford from Public Health England (PHE) presented an analysis of non-AIDS mortality in England and Wales among HIV positive people diagnosed from 1997 to 2012.**

This is the first UK study to categorise national HIV deaths using the Coding Causes of Death in HIV Project (CoDe) protocol and to compare mortality to the general population.

All-cause deaths of people living with HIV in England and Wales are recorded by direct reporting to PHE by doctors and by linkage to the National Mortality Register at the Office for National Statistics (ONS).

Of 88,994 people diagnosed between 1997 and 2012, a total of 83,276 were included in the analysis who had at least one attendance at an HIV clinic or who had died by end of 2012.

There were 5,302 deaths (6.4%) from 443,818 person years of follow-up. Of these, 58% were AIDS-related and 42% were non-AIDS related. The highest proportions of non-AIDS deaths were caused by cardiovascular disease or stroke (19%), non-AIDS malignancies (19%) and non-AIDS-defining infections (18%), followed by liver disease (12%).

To compare deaths in people living with HIV against those of the general population, a standardised mortality ratio (SMR) was calculated by dividing the deaths in the cohort by expected deaths according to age and sex matched ONS population data. A value of 1.0 would denote there is no difference between the two populations.

Strikingly, the all-cause SMR was substantially higher in the HIV positive cohort, at 5.7. This figure rose to 9.0 when looking at women alone.

Non-AIDS infections and liver disease accounted for the highest differences with the general population, with SMRs of 11.0 and 3.7 respectively. Again, these values increased substantially for women who had an SMR of 18.0 for non-AIDS infections and 4.5 for liver disease.

In this historical cohort that included the first years of combination therapy, mortality rates amongst people with HIV were significantly higher than for the general population, even when AIDS-related deaths are excluded.

#### Reference

Croxford S et al. Non-AIDS mortality among people diagnosed with HIV in the era of HAART compared to the general population: England and Wales, 1997 – 2012. 22nd Annual BHIVA Conference, 19-22 April 2016, Manchester. Oral abstract O1.

<http://www.bhiva.org/documents/Conferences/2016Manchester/Presentations/160420/SaraCroxford.pdf> (PDF slides)

<http://www.bhiva.org/160420SaraCroxford.aspx> (webcast)

## High prevalence of multiple high-risk HPV infections in young HIV positive gay men

Gareth Hardy, HIV i-Base

**Corinna Sadlier from Trinity College Dublin, investigated whether the baseline epidemiology of HPV infection in young HIV positive MSM may help guide primary and secondary prevention strategies.**

The study recruited 50 HIV positive 18-26 year old MSM and conducted oropharyngeal, anal and penile swabs and tested serum for anti-HPV 16/18 antibodies.

HPV DNA was detected in 68% of study participants. High-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) were found in anal swabs from 46% of participants, in penile swabs from 4% of participants and were not found at all in oropharyngeal swabs. Antibodies to HPV-16 were found in serum from 44% of participants while antibodies to another high-risk type, HPV-18, were found in serum from 26% of participants. Antibodies to both types were found in serum from 16% of participants. A detectable HIV viral load was associated with high-risk HPV detection ( $p=0.04$ ).

Importantly, DNA from high-risk HPV types 51, 56 and 59, were frequently found in swabs, and these HPV types are not included in either the 4- or 9-valent vaccines. This demonstrates a need for improved primary and secondary prevention interventions in HIV positive MSM.

The four-valent HPV vaccine Gardasil confers protection against HPV types 6, 11, 16 and 18.

Merck's 9-valent vaccine for HPV, Gardasil-9, which includes HPV types 31, 33, 45, 52, and 58 as well as 6, 11, 16 and 18 was approved in the US in December 2014 and in the EU in June 2015. Vaccination can greatly reduce the burden of HPV disease, especially as HPV-16 is highly associated with anal cancer.

#### Reference

Sadlier C et al. Prevalence, type and factors associated with HPV infection at multiple sites in young HIV positive MSM. 22nd Annual BHIVA Conference, 19-22 April 2016, Manchester. Oral abstract O9.

<http://www.bhiva.org/documents/Conferences/2016Manchester/Presentations/160421/CorinnaSadlier.pdf> (PDF slides)

<http://www.bhiva.org/160421CorinnaSadlier.aspx> (webcast)

## Anal cancer and HPV screening in HIV positive people

Gareth Hardy, HIV i-Base

**Anal cancer is a serious issue in people with HIV even after long term ART.**

One third of MSM worldwide are infected with HPV type 16, which is responsible for 80 to 90% of anal cancers. Charles Lacey from University of York discussed approaches to prevent HPV associated anal cancer in HIV positive people.

Current prevention strategies against anal cancer in HIV positive people include vaccination against HPV in adolescent boys, vaccination in MSM aged 16 to 45, starting ART at higher CD4 counts, maintaining prolonged HIV suppression with ART and stopping smoking. The Joint Committee on Vaccines and Immunisation has recommended that

vaccination of MSM aged 16 to 45 would be cost effective, but the Department of Health, Public Health England and NHS England have yet to make a decision on its implementation.

Dr Lacey discussed various studies that have assessed risk factors for anal cancer and anal intraepithelial neoplasia (AIN). These studies showed that the risk of cancer decreased significantly for those who maintained an undetectable viral load at least 60% of the time (OR 0.51), and for those with higher CD4 count nadirs (above 350, OR 0.34). In contrast current smoking was significantly associated with higher risk of anal cancer (O.R. 2.59).

Screening programmes for anal cancer include anal cytology which is currently the screening test of choice, digital ano-rectal examination (DARE), which may be cost effective if used to screen HIV positive men older than 50 years every four years, and serial HPV viral load testing which may predict anal disease evolution.

Treatment options for AIN2/3 include ablation (laser, electrocautery, or infrared coagulator), imiquimod, or 5-FU. While these treatments can result in complete responses in percentage of cases, 66% of patients experienced recurrences at 1.5 years.

Finally, Dr Lacey discussed 'good', 'better' and 'best' prevention strategies for anal cancer in HIV positive MSM. The latter of these includes vaccination, initiating ART at HIV diagnosis, discouraging smoking, DARE-screening, and HPV-16 DNA and viral load testing, as well as a new effective treatment regimen that combines ablation with therapeutic vaccination.

#### Reference

Lacey C. Anal cancer prevention strategies including screening for HPV-related diseases in HIV-positive patients. 22nd Annual BHIVA Conference, 19-22 April 2016, Manchester. Invited lecture.

<http://www.bhiva.org/documents/Conferences/2016Manchester/Presentations/160421/CharlesLacey.pdf> (PDF slides)  
<http://www.bhiva.org/160421CharlesLacey.aspx> (webcast)

## Increasing demand for community treatment information services

Gareth Hardy, HIV i-Base

**The treatment information services provided by HIV i-Base and their use over the last year, were covered in a presentation Robin Jakob.**

i-Base aims to enable HIV positive people to take an active role in their health care by providing up to date information, in non-technical language, using various formats.

Jakob reviewed the ways in which HIV positive people can contact i-Base with specific treatment and health related questions. These include a free-to-call phone line, an email service and an online Q&A forum on the i-Base website. Comments on this forum by other users are also answered individually.

Importantly, from 2014 to 2015, there was a substantial increase in the demand for these services. Over the last year, demand across all services rose by 30%, with email enquiries increasing by 52% and phone line enquiries increasing by 22%.

The majority of enquiries were from men, who made of 82% of enquiries. Enquiries from the London area made up 60%. There was an even distribution of age range (mainly between 30 and 60 years old) among those using the services. The vast majority of enquiries, 98%, were from HIV positive people calling for themselves.

The biggest proportion of calls were in relation to side effects, 17%, followed by concerns about transmission, 13%, and then treatment access, 12%. Enquiries by phone often included secondary topics.

The presentation emphasised the adaptability of the services provided by i-Base for new and rapidly changing topics of concern from callers. This was underscored by the number of calls i-Base has taken regarding PrEP. In summary these numbers demonstrate the continued need for community treatment support services, such as i-Base.

#### Reference

Jakob R et al. HIV treatment information and advocacy 2014/15: continued demand for community support services. 22nd Annual BHIVA Conference, 19-22 April 2016, Manchester. Oral abstract 05.

<http://www.bhiva.org/documents/Conferences/2016Manchester/Presentations/160420/RobinJakob.pdf> (PDF slides)  
<http://www.bhiva.org/160420RobinJakob.aspx> (webcast)



## Non alcohol fatty acid liver disease: an emerging problem

Gareth Hardy, HIV i-Base

**Lucy Garvey from St Mary's Hospital, London, presented an excellent overview on the emerging issue of non-alcohol fatty liver disease in HIV positive people.**

This topic has been a growing concern for a number of years and Dr Garvey's lecture provides an update on our current understanding.

NAFLD is of great concern because 10-20% of those who are affected by it will progress to more serious liver disease and as many as 5% will develop cirrhosis within 10-20 years. In HIV positive people, liver disease is the third greatest cause of death, compared to the 13th greatest in the general population. The risk factors for NAFLD are obesity, dyslipidaemia (high triglycerides, low HDL cholesterol), type-II diabetes, metabolic syndrome and a larger waist circumference.

Garvey reviewed the prevalence of NAFLD and non-alcoholic steatohepatitis (NASH), which is secondary to NAFLD, in the general population and in HIV positive people, as well as the increasing incidence of obesity in the UK.

The pathogenesis of NAFLD is not well understood, but there are a number of different factors that are considered likely to be playing a role. These include genetic factors, a high fat diet, insulin resistance, microbial translocation across the intestinal wall (an effect of HIV infection) as well as the possibility that HIV itself, immune activation and possibly some antiretroviral drugs may play a role. One other consideration is that there may be a role for alcohol consumption, especially as HIV positive people appear to have reduced tolerance and metabolism of alcohol compared to HIV negative people.

The most successful treatment interventions involve lifestyle changes in diet and exercise. Exercise for 30-60 minutes at least three times per week substantially reduces liver fat, while a 7-10% fall in body weight improves steatosis and NASH.

Similarly a 5% reduction in body weight significantly reduces serum ALT, which is a marker of liver disease. A number of drugs are being considered for treatment of NASH including insulin-sensitisers, vitamin E and statins, as well as an anti-fibrotic monoclonal antibody, and the anti-fibrotic drug cenicriviroc which blocks the chemokine receptors CCR2 and CCR5.

### Reference

Garvey L et al. NAFLD (Non alcohol fatty acid liver disease): an emerging problem. 22nd Annual BHIVA Conference, 19-22 April 2016, Manchester. Plenary lecture.

<http://www.bhiva.org/documents/Conferences/2016Manchester/Presentations/160421/LucyGarvey.pdf> (PDF slides)

<http://www.bhiva.org/160421LucyGarvey.aspx> (webcast)

## HIV positive people on ART have impaired alveolar immunity

Gareth Hardy, HIV i-Base

**Professor Paul Collini from University of Sheffield presented some interesting immunological results that suggest that macrophages in the lungs of HIV positive people may be impaired, even after viral suppression on ART.**

The risk of invasive, pneumococcal disease and declining lung function contributing to conditions such as chronic obstructive pulmonary disease (COPD) are increased in HIV positive people, even during the ART era. Dr Collini investigated whether there is a persistently altered virologic and immunologic environment in the lung during ART that impairs apoptosis-associated pneumococcal killing by alveolar macrophages.

In this study HIV positive people were either ART naive or had an undetectable viral load for a median of 87 months. The researchers found that alveolar macrophages had an impaired ability to kill pneumococci bacteria and that even in people on ART there is a persistent lymphocytosis in the alveoli of the lung. A much higher proportion of these cells were CD8 T cells than is the case in healthy control subjects.

Since HIV infection of macrophages in the lung is minimal, Dr Collini proposed that this pathology might have an indirect mechanism. The researchers then demonstrated that despite ART, the HIV protein gp120 persists in the lung and is detectable in broncho-alveolar lavage fluid. They further demonstrated that treatment of macrophages with gp120 inhibits their ability to kill cells infected with pneumococcus. In conclusion, alveolar macrophages have an impaired apoptotic response to pneumococci and the immune environment of the lung fails to correct ART, possibly playing a role in HIV-associated lung disease.

Ref: Collini P et al. Healthy HIV sero-positive individuals have impaired alveolar immunity despite HAART. 22nd Annual BHIVA Conference, 19-22 April 2016, Manchester. Oral abstract O10.

<http://www.bhiva.org/documents/Conferences/2016Manchester/Presentations/160421/PaulCollini.pdf> (PDF slides)

<http://www.bhiva.org/160421PaulCollini.aspx> (webcast)

## CONFERENCE REPORTS

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### **International Liver Congress (EASL) 2016**

**13-18 April 2016, Barcelona**

#### **Introduction**

**The International Liver Congress took place this year from 13 to 18 April in Barcelona.**

Although there is a searchable programme from this meeting on the conference website, very few of the conference materials are available online.

<https://events.easl.eu/EventProgramme/ILC2016.aspx>

The two reports in this issue of HTB are both related to treatment access.

- High cure rates using generic hepatitis C drugs bought online: EASL supports lower cost access for high-income countries
- Studies of new generic \$300 HepC combination of sofosbuvir and vildagliacin for low income countries

### **High cure rates using generic hepatitis C drugs bought online: EASL supports lower cost access for high-income countries**

**Simon Collins, HIV i-Base**

**A new way to access excessively priced drugs in high-income countries, including the UK, was presented today in an oral late-breaker study at the 2016 International Liver Congress (EASL) currently being held in Barcelona.**

**Just as importantly, this approach to access treatment was officially supported by EASL.**

James Freeman from GP2U Telehealth and colleagues presented interim results from an international cohort of people using generic HCV drugs bought online using a web-based community project in Australia (FixHepC.com). [2]

Countries with people enrolled into FixHepC.com programme.

The high prices charged for new HCV drugs has enraged many doctors, researchers and people living with HCV, who in good faith supported the drugs' research and development, with the expectation that people in the countries where this was conducted would widely benefit.

Instead, the research showing extraordinarily high efficacy and safety – curing more than 95% of patients within a few months of easy-to-take treatment – led to drugs that, post-approval, remain out-of-reach, with access filtering through to only a few of the most sick or richest.

The unethical nature of this example of pharmaceutical pricing is highlighted by the production and manufacturing costs, which for all of these HCV medicines are incredibly low, together with the unmet medical need by 150 million HCV positive people globally. Last year, more people died from HCV-related complications than were treated with these medicines.

Another presentation at the conference on the cost of HCV drugs, by Andrew Hill from the Chelsea and Westminster Hospital in London, showed that the raw material for the combination of sofosbuvir plus daclatasvir was less than \$100 for a three month course of treatment but this is priced at US \$84,000 in the US and about US \$50,000 in the UK, France and Australia. [3]

As a result, even after being recently approved by NICE in the UK, only the sickest people will be treated, while everyone else waits for trickle-down access over years or decades.

But, it is legal in the UK, Australia and some other countries, for citizens to import generic medicines bought online, so long as this is for their personal use. Personal use is defined as being for three months or less. Many other countries allow generic medicines to be imported personally when carried by the individual who is using treatment. This is included in the TRIPS agreement (article 60) in reference to patent agreements. A community web-based project in Australia (FixHepC.com) was set up to help facilitate this access.

FixHepC.com first validated the quality of generic sofosbuvir, ledipasvir, daclatasvir and ribavirin using high performance liquid chromatography (HPLC) and mass spectrometry. So far, 448 people have enrolled and been helped through the steps needed to import medicines. Clinical assessments were made before, during and after treatment using a telemedicine platform (gp2u.com.au).

This is an international cohort with people enrolling from the UK, Europe, Australia, the United States, Thailand, Africa and South America. Mean age was 54 and almost half were women (46%). Baseline genotype (G) was approximately 64% for G1, 5% G2, 27% G3, 3% G4 and <1% G5/6. Half the participants were treatment naive (51%) and almost one-third (31%) had cirrhosis. Mean HCV viral load was 6.46 log IU/mL.

Treatment results were available for about half of the cohort. End of treatment (EOT) and sustained viral response rates at week 4 (SVR4) were 99.6% (220/221) and 94.2% (129/137) respectively. SVR4 results were 94.2% (129/137) overall for G1-6. By regimen, G1 results were 93.2% (55/59) using sofosbuvir plus ledipasvir and 97.4% (37/38) for using sofosbuvir plus daclatasvir.

SVR4 results by genotype, recognising there are very low numbers in some groups, were 95% (92/97) for G1, 100% (6/6) for G2, 90% (26/29) for G3, 100% (3/3) for G4 and 100% (2/2) for G5/6.

Tolerability was good, with no new side effects and headache, fatigue and insomnia being most reported.

Three people with compensated liver disease temporarily decompensated after starting treatment but continued with treatment.

Four people died, all from hepatic cellular cancer (HCC), one before starting treatment, two people discontinued treatment for palliative care, and one died before reaching the SVR4 timepoint.

The study concluded that results using generic imported HCV drugs are at least as effective and seen in clinical trials and that mass global treatment is feasible and a legal alternative for many people when high prices prevent access to originator drugs.

An official conference press release quotes Professor Laurent Castéra, EASL Secretary General in support of this study: "There is a clear role for generic treatments such as these for people with hepatitis C across the world. The implications of increased availability of these drugs could be enormous, presenting more people with the possibility of a 'cure' for what is often a debilitating condition." [4]

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#### C O M M E N T

**These results are important for indicating that generic HCV drugs purchased online using the FixHepC web service produced cure rates that are comparable to those reported in clinical studies of originator drugs.**

**Even though limited data are available from this interim analysis of an open-label study, the results also highlight that people in high-income countries are dying from HCV-related complications due to limited access to new treatment.**

**Although in the UK, the NHS should provide these drugs, the lack of government action to negotiate appropriate prices for medicines and the constrained NHS budgets that cannot afford current prices, mean that people might have to buy their own medicine to guarantee short-term access. Under these circumstances, as with PrEP for HIV prevention, the NHS should at least provide the monitoring needed to use these treatments safely.**

**At some point the originator manufacturers will reduce prices because their business models allow much lower prices to still generate vast profits from HCV drugs.**

**But companies will only do this if they are forced to and unfortunately the UK has shown no leadership for this to happen so far.**

**The support from EASL for using online generic medicines to access treatment is significant. There is little point in international meetings showcasing clinical results, however impressive, when these medical advances are being undermined by prices that prevent doctors from prescribing these medicines.**

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4. EASL press release. Low-cost generic direct-acting antiviral treatment for hep C is equivalent to branded formulations: New data indicate that generics are a feasible alternative to support access to direct-acting antiviral treatment for hepatitis C sufferers. 16 April 2016.  
[http://www.eurekalert.org/pub\\_releases/2016-04/eaft-lgd040816.php#.VxH\\_PRMb3lo](http://www.eurekalert.org/pub_releases/2016-04/eaft-lgd040816.php#.VxH_PRMb3lo)

## Studies of new generic \$300 HepC combination of ravidasvir and sofosbuvir for low-income countries

### DNDi press statement

#### **Drugs for Neglected Diseases initiative (DNDi) issued a press statement at EASL 2016 about a new HCV combination that is entering studies for pan-genotypic HCV in Malaysia and Thailand.**

DNDi and the Egyptian manufacturer Pharco Pharmaceuticals, are launching studies to compare sofosbuvir with ravidasvir compared to sofosbuvir plus daclatasvir. If effective, the new combination will be available at less than \$300 for a standard course.

Ravidasvir is an NS5A inhibitor, one of a new generation of direct-acting antivirals (DAAs) that are revolutionizing the treatment of hepatitis C. In a Phase III clinical trial in Egypt, conducted by Pharco, ravidasvir showed cure rates of up to 100% in patients with genotype 4 when used in combination with sofosbuvir, which also is a DAA.

These studies will enrol approximately 1,000 participants and will evaluate the efficacy, safety, and pharmacokinetics of the sofosbuvir plus ravidasvir combination in patients with various levels of liver fibrosis, various genotypes, and with/without HIV co-infection.

Malaysia and Thailand are among the many middle-income countries that are excluded from the voluntary licensing agreements that Gilead and Bristol-Myers Squibb, the intellectual property holders of the hepatitis C drugs sofosbuvir and daclatasvir, respectively, have concluded with generic companies. Of the up to 150 million people infected with chronic hepatitis C globally, approximately 75% live in middle-income countries.

DNDi has licensed rights for ravidasvir in low- and middle-income countries from Presidio Pharmaceuticals.

#### Reference

DNDi press release. Drugs for Neglected Diseases initiative and Pharco Pharmaceuticals to test affordable hepatitis C regimen with support of Malaysian and Thai governments. (13 April 2016)

<http://www.dndi.org/2016/media-centre/press-releases/dndi-pharco-hepc-malaysia-thailand>

## CONFERENCE REPORTS

### **23rd Conference on Retroviruses and Opportunistic Infections (CROI 2016)**

**22 – 25 February 2016, Boston**

#### **Introduction**

#### **Every year, CROI brings more than 5000 researchers, doctors, community activists and other health workers meet for one of the most scientifically important HIV conferences.**

This year the meeting was in Boston and with over 1000 studies presented, there is far more to report than the key studies that make headline news.

This year, major studies present research on basic and clinical science relating to prevention, new treatment and global access.

The programme and abstracts are posted to the conference website, with many posters also available as PDF files.

<http://www.croiconference.org/electronic-materials>

Although the programme is now online, abstracts are not publically available until after the conference ends.

<http://www.croiconference.org/abstracts/search-abstracts/>

Webcasts are now also online and were posted very soon after the oral presentations.

<http://www.croiconference.org>

Reports in this issue of HTB are:

- No effect of tenofovir on infant bone mineral content in African study
- Use of modelling to predicting paediatric dosing of long acting antiretrovirals

- Nevirapine dosing for treatment of neonates
- START substudies: increased quality of life from earlier treatment but no impact on vascular function or cardiovascular markers
- Six-week ledipasvir/sofosbuvir in HIV positive patients with acute HCV

CROI 2016: PAEDIATRIC CARE

## No effect of tenofovir on infant bone mineral content in African study

Polly Clayden, HIV i-Base

**A report from the PROMISE study showed no adverse bone mineral effect, linked to maternal tenofovir disoproxil fumarate (TDF), in exposed infants. [1] But starting a lopinavir/ritonavir (LPV/r)-containing regimen during pregnancy might lead to lower newborn bone mineralisation.**

George Siberry presented data from a sub-study of PROMISE (Promoting Maternal-Infant Survival Everywhere/IMPAACT P1084) at CROI 2016.

Results from the main study were presented at CROI 2015. [2,3] The study showed that taking a three-drug ART regimen in pregnancy was more effective in preventing mother-to-child transmission than taking one antiretroviral drug during pregnancy, another in labour and two after delivery.

PROMISE was a multinational study to which asymptomatic women with  $>350$  cells/mm<sup>3</sup> (or above the local threshold for starting ART at the time) were enrolled. At 14 weeks of pregnancy women were randomised to: Arm A – AZT plus single-dose nevirapine at delivery plus TDF/ FTC tail vs Arm B – AZT/3TC plus LPV/r vs Arm C – TDF/FTC plus LPV/r.

At the study's interim review the DSMB reported that the pre-specified efficacy boundary for this part of the study was crossed and there were safety differences between arms. The rate of vertical transmission at 14 days postpartum was significantly lower in the pooled triple ART arms (Arms B and C) compared with Arm A.

The P1084s infant DXA substudy compared newborn bone mineral content (BMC) by exposure to maternal antiretroviral regimens at  $>14$  weeks gestational age (GA). The primary comparison was between the triple ART arms but the investigators also made secondary comparisons between each triple ART arm and Arm 1. P1084s participants were enrolled at eight African sites (Malawi, South Africa, Uganda and Zimbabwe) with DXA capacity within 21 days of PROMISE enrolment and before the onset of labour.

The infants had whole-body (WB) and lumbar spine (LS) DXA BMC measurements 28 days of age. Training was standardised. Analysis was standardised and performed centrally at UCSF.

The accrual target of 150 infants per arm was based on 80% power to detect a pair-wise difference of 4–5% in mean WB-BMC (121 evaluable per arm) and 6–7% in mean LS-BMC (140 evaluable per arm). The investigators compared mean BMC differences using Student's t-test.

As mothers enrolled in the substudy after PROMISE randomisation, the investigators used multivariable linear regression to adjust for baseline maternal factors and infant factors at time of DXA scan.

Of 452 eligible mothers, data from 426 infants were available for analysis after accounting for twins (6 pairs), foetal (8) or neonatal death (10) and those that dropped out of the study (15). About 15% of infants did not have an evaluable DXA within the time frame. Arms 1, 2 and 3 had 118 (117 LS-BMC and 99 WB-BMC), 129 (127 LS-BMC, and 104 WB-BMC) and 115 (113 LS-BMC and 96 WB-BMC) infants with evaluable data respectively.

Overall mothers of infants with a DXA scan were median age of 26 years (range 18–43), and a median CD4 count of 543 cells/mm<sup>3</sup> (range 350–1493), entered the study at a median of 28 weeks (range 13.7–39.3) of pregnancy and 19% reported alcohol use. The infants were 51% female, with a median GA of 40 weeks (32–43), a median length at birth of 49 cm (IQR 47–50), and weight of 2990 gm (IQR 2700–3210).

Mothers in the triple ART arms were slightly older 25.5 vs 27 years ( $p=0.03$ ). Infants in the ART arms had slightly lower birth weight 2990 vs 2920 gm ( $p<0.001$ ) respectively.

In Arms A, B and C, mean LS-BMC were 1.73 vs 1.64 vs 1.72g; and WB-BMC were 73.1 vs 65.1 vs 63.3g respectively.

LS-BMC pairwise comparisons revealed some borderline differences. Mean difference adjusted for maternal factors at baseline and infant factors at time of DXA: Arm B vs Arm C, -0.08 (95% CI -0.16 to 0.0),  $p=0.04$ ; Arm A vs Arm C, +0.01 (95% CI -0.07 to 0.09),  $p=0.79$ ; and Arm A vs Arm B, +0.07 (95% CI -0.01 to 0.15),  $p=0.09$ .

But significant differences in WB-BMC between Arm A and each triple ART arm persisted after adjustment. Mean difference adjusted for maternal factors at baseline and infant factors at time of DXA: Arm B vs Arm C, +1.22 (95% CI

-2.31 to 4.75),  $p=0.5$ ; Arm A vs Arm C, +8.69 (95% CI 4.78 to 12.60),  $p<0.001$ ; and Arm A vs Arm B, +5.82 (95% CI 2.10 to 9.54),  $p=0.002$ .

Dr Siberry explained that there were some limitations to the study: higher rates of neonatal death in Arm C (TDF/FTC backbone) in the parent study; both ART arms used LPV/r, limiting extrapolation to most women in African countries who receive efavirenz (EFV)-based regimens; and women in PROMISE had high CD4 counts. He noted that the clinical significance and persistence of these findings are unknown.

But P1084s also had a number of strengths: maternal regimens were randomly assigned; the ART regimens only differed between two backbones; women started antiretrovirals in pregnancy; the sample size was large; and DXAs were standardised.

The study did not show an impact of maternal TDF on infant BMC. But, compared to AZT (plus single dose nevirapine plus TDF/FTC tail), LPV/r-based ART in pregnancy was associated with significantly lower WB-BMC, even after adjustment.

#### C O M M E N T

**These data are reassuring as TDF is widely used in pregnancy and they also reinforce current WHO and national first-line recommendations.**

**One of the reasons for this substudy was that previous US observational data from PHACS found lower newborn BMC after maternal TDF use. [4] So much of the discussion after the presentation was about this contradiction. It is possible that different TDF-containing regimens or US versus African settings might make a difference. Also PHACS women started ART before conception or early in pregnancy whereas PROMISE women started from the second trimester onwards.**

**Other mediating factors are also being analysed including the effect of HIV. Dr Siberry pointed out that we have the advantage of other studies that are ongoing or planned in which it will be possible to look at HIV negative women receiving TDF as PrEP in pregnancy, as well as one in Thailand looking at TDF for the prevention of hepatitis B transmission.**

**A further important finding from the PROMISE substudy is that infant DXAs are feasible in African clinical research and 6-month LS results are also in analysis.**

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## Use of modelling to predicting paediatric dosing of long acting antiretrovirals

Polly Clayden, HIV i-Base

**Physiologically based pharmacokinetic (PBPK) modeling can help predict dosing strategies for long-acting (LA) antiretrovirals, according to data presented at CROI 2016.**

LA antiretrovirals could provide an important option for children and adolescents. LA regimens have the potential to simplify regimens, reduce drug costs and improve adherence to both treatment and PrEP.

Paediatric dose optimisation is complicated due to differences in anatomical and physiological processes compared with adults. PBPK modelling is a mathematical approach to predict pharmacokinetics (PK) using the description of molecular and physiological processes defining drug disposition. This modelling can be used to identify promising paediatric dosing strategies.

Rajith Jajoli and colleagues from the Department of Molecular and Clinical Pharmacology at University of Liverpool showed data from a study designed to simulate the PK of LA antiretrovirals in children and adolescents and predict optimal doses using PBPK modelling.

The investigators integrated in vitro PK data from cabotegravir (CBV) and rilpivirine (RPV) into their models. These models were validated against available clinical data for the doses of LA formulations in adults: 800 mg CBV and 900 mg RPV. The investigators extrapolated the rate of drug release from injection sites for the two drugs from clinical data in adults.

The anatomy and physiology of children aged 3–18 years was validated against data available in the literature. World Health Organization (WHO) weight band recommendations were used. The investigators simulated PK for 200 paediatric patients for each weight band after intramuscular (IM) injection of LA CBV and RPV.

They validated weights and blood flow rates of children and adolescents at different ages using available anatomical and anthropometric data. And they validated parameters of existing available adult IM formulations of CBV and RPV against available clinical data.

According to the models, mean values for 800 mg CBV quarterly IM injection were: AUC 4467 vs 5257 ug.h/mL, Cmax 3.3 vs 3.54 ug/mL and Ctrough 1.1 vs 1.2 ug/mL. Mean values for 900 mg IM RPV monthly administration were: AUC 74,420 vs 91,087 ng.h/mL, Cmax 168 vs 168.7 ng/mL and Ctrough 79.1 vs 78.3 ng/mL.

The models predicted optimal antiretroviral doses with which at least 95% of patients achieved Ctrough over the cut-off values for quarterly CBV or monthly RPV IM injections. Table 1 shows predicted CBV and RPV doses for all WHO weight bands.

**Table 1: Optimised doses of CBV and RPV LA formulations for WHO weight bands**

Age (years)	Weight (kg)	Rilpivirine		Cabotegravir	
Duration		1 month		3 months	
Cut-off limit (ng/mL)		20.3 (PAIC90)	80 (MEC)	166 (PAIC90)	664 (MEC)
3–5.75	14–19.9	180	720	30	110
5.75–7.75	20–24.9	190	720	30	130
7.75–9.4	25–29.9	190	730	35	150
9.4–10.75	30–34.9	200	735	35	160
10.75–11.9	35–39.9	200	770	45	170
11.9–12.8	40–44.9	210	790	45	180
12.8–13.7	45–49.9	220	810	50	190
13.7–14.75	50–54.9	225	825	50	200
14.75–15.75	55–59.9	230	840	55	210
15.75–17.25	60–64.9	240	860	55	220
17.25–19.5	65–69.9	240	880	60	240

The investigators noted that the roles of transporters, the immune system, and drug diffusion through the lymphatic system during long-term treatment are potential limitations that they did not consider in these PBPK models.

But they conclude that PBPK models can help predict dosing strategies and could provide innovative ways to optimise dose requirements in special populations such as paediatrics.

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## Nevirapine dosing for treatment of neonates

Polly Clayden, HIV i-Base

**Nevirapine (NVP) clearance is low immediately after birth and increases dramatically over the first months of life. Population modelling and pharmacokinetic (PK) simulations shown at CROI 2016 predicted dosing regimens to achieve target NVP treatment concentrations in term and late preterm infants.**

NVP clearance is low in term neonates, and lower still in preterm ones, because of immaturity in CYP2B6 and CYP3A4 activity. Clearance is also autoinduced in proportion to the size of the NVP dose in the first years of life.

PK data are available to guide NVP dosing for treatment of HIV in infants after one month of life: trough concentration target 3.0 ug/mL. But NVP PK studies in infants less than one month old are limited to evaluations of dosing regimens for prevention of vertical transmission: trough concentration target 0.1 ug/mL.

Increasing evidence for early treatment and trends on early infant diagnosis – as well as a paucity of other antiretroviral options in this age group – has led to considerable interest in the use of NVP as part of ART regimens for neonates.

Mark Mirochnick and colleagues from the IMPAACT network presented findings from a study that used population modelling to evaluate proposed NVP dosing regimens to meet target concentrations in term and late preterm infants (34–37 weeks gestation) from birth to 6 months old.

The investigators developed a NVP population PK model using NONMEM. The model included data from 192 infants (1121 plasma NVP concentrations) from US, Africa and Brazil in five PACTG or HPTN studies.

CYP286 metaboliser status, rate of autoinduction, and preterm effects were estimated from published literature. Dosing regimens from birth through 6 months of age were evaluated using simulations. Simulations were used to evaluate proposed NVP doses of 6 mg/kg twice daily for term infants and 4mg/kg twice daily for one week followed by 6 mg/kg twice daily for late preterm infants. The target was to meet trough concentrations of > 3.0 ug/mL.

The investigators used a one-compartment model with first order absorption. Clearance was scaled allometrically and volume of distribution scaled linearly for weight. It was modelled to mature with age and autoinduction as a linear function of dose. The investigators inputted effects of prematurity and maturation of CYP2B6 and CYP3A4 activity on NVP clearance from published data.

They noted that typical NVP clearance (L/hr/kg) in term infants increased by nearly 6 fold from birth to 6 months due to maturation and by an additional 79% due to induction. The final simulations used term infant doses of 6 mg/kg twice daily and late preterm infant doses of 4mg/kg twice daily for one week followed by 6 mg/kg twice daily. In these simulations, the dosing regimens achieved NVP targets.

The investigators concluded that NVP dosing regimens in neonates must take into account the impact of maturation, auto-induction and prematurity on NVP clearance.

**C O M M E N T**

**There is increasing interest in using ART regimens early in life in HIV infected neonates and those at high risk of infection. NVP is one of the few antiretrovirals with some PK and safety data in this age group and formulations for neonates. The dosing regimens in these simulations and NVP PK in preterm infants are being evaluated in the IMPAACT 1115 and 1106 trials.**

**Table 1 shows the lack of antiretroviral options for neonates and includes ongoing and planned IMPAACT trials that will provide some data to guide dosing. Without better data and formulations it is unclear how very early treatment of neonates will be achieved.**

**Table 1: Antiretrovirals available for neonates (including ongoing and planned IMPAACT trials)**

Drug	Preterm	Term	2 weeks
Nucleos(t)ide Reverse Transcriptase Inhibitors			
ABC	P1106 < 2500 g		
AZT	√	√	√
ddl			√
d4T	P1106 < 2500 g	√	√
FTC		√	√
TAF	P1026s washout	P1026s washout	
3TC	P1106 < 2500 g	√	√
Non-nucleoside Reverse Transcriptase Inhibitors			
Doravirine	P1026s washout	P1026s washout	
EFV	P1026s washout	P1026s washout	
ETR	P1026s washout	P1026s washout	
NVP	P1106 < 2500 g	P1115 >34 weeks GA	√
RPV			



Protease Inhibitors			
ATV			
DRV	P1026s washout	P1026s washout	
LPV	P1026s washout P1106 <2500 g	P1026s washout	√
Integrase Inhibitors			
DTG	P1026s washout	P1026s washout P1093 dosing (in development)	P1093 dosing (in development)
EVG	P1026s washout	P1026s washout	
RAL	P1097 washout	P1097 washout P1110 dosing	
CCR5 Receptor Antagonist			
Maraviroc		In development	

Adapted from Ruel T. IMPAACT 2015

Reference

Mirochnick M et al. Nevirapine dosing for treatment in the first month of life. Conference on Retroviruses and Opportunistic Infections. 22-26 February 2016. Boston. Poster abstract 440.

<http://www.croiconference.org/sessions/nevirapine-dosing-treatment-first-month-life-0> (Abstract)

[http://www.croiconference.org/sites/default/files/posters-2016/440\\_0.pdf](http://www.croiconference.org/sites/default/files/posters-2016/440_0.pdf) (Poster)

<http://www.croiwebcasts.org/console/player/29499?mediaType=slideVideo&> (Themed discussion)

CROI 2016: ART COMPLICATIONS

## **START substudies: increased quality of life from earlier treatment but no impact on vascular function or cardiovascular markers**

**Gareth Hardy, HIV i-Base**

**A number of sub-studies from the START trial were presented at CROI 2016 that continue to show results that were not widely predicted.**

START has already showed effects of initiating ART immediately versus deferring (when CD4 count falls to 350) on various non-AIDS associated morbidities.

The first sub-study – on quality of life (QoL) – was presented by Alan Lifson from University of Minnesota. [1]

QoL assessments consisted of three different tests: a visual analogue scale (VAS) for self-assessment of overall current health and then three measures of quality of life based on results from the Short-Form 12-Item Health Survey version 2 (SF-12v2): General health perception (GHP); physical component summary (PCS), and mental component summary (MCS).

Data was collected from 4561 START study participants, who had a median baseline CD4 count of 651 cells, median age 36 years, and 27% of which were female, with 46% from high-income countries.

All quality of life measures improved for the immediate treatment group versus the deferred treatment group, from month 4 to 12 (all  $p < 0.001$ ). Differences between the treatment groups during follow-up were estimated as: VAS=1.9 (95% CI 1.2-2.5); GHP=3.6 (2.8-4.5); PCS=0.8 (0.5-1.1); MCS=0.9 (0.4-1.3). Although these differences were significant, they were also modest. It was noted that improvements in physical and mental health assessments occurred in equal measure.

A second sub-study looked at artery elasticity in 332 START participants, randomised to either immediate ART or deferred ART. The investigators assessed diastolic blood pressure waveform contour, which they have previously shown is altered in HIV positive people who are not on ART and also in those with advancing age. [2]

The median age of sub-study participants was 33 years, 70% of participants were male. Cardiovascular risk factors were considered to be low in this cohort at study entry.

No differences were found in small or large arterial elasticity between or within either group during the study. Dr Baker noted that the follow up duration remains modest for assessment of potentially cumulative effects of ART toxicity, when considering the time frame for development of CVD.

Finally, also presented by Jason Baker in a poster, a third sub-study looking at differences in cardiovascular factors between the immediate vs deferred ART groups.

The baseline characteristics of participants in this sub-study were similar to those in the vascular function sub-study described above.

All lipid parameters (total cholesterol, low-density lipoprotein [LDL]-cholesterol, high-density lipoprotein [HDL]-cholesterol, total cholesterol to HDL-C ratio) and fasting glucose increased significantly in the immediate treatment group compared to the deferred treatment group (all  $p < 0.001$ ). Incident dyslipidaemia was also greater among the immediate versus deferred treatment group (HR 1.62, [95% CI: 1.33-1.94]). There were no changes in incident diabetes or hypertension between the groups.

Although immediate ART was associated with increases in LDL-C and dyslipidaemia, concurrent increases in HDL-C and other mixed effects meant that there was no consistent difference in CVD risk scores between the groups over time.

#### Reference

1. Lifson A et al. Increased quality of life with immediate ART initiation: results from the START trial. 23rd CROI, 22-25 February 2016, Boston. <http://www.croiconference.org/sessions/increased-quality-life-immediate-art-initiation-results-start-trial> (abstract)  
<http://www.croiconference.org/sites/default/files/posters-2016/475.pdf> (PDF poster)
2. Baker JV et al. Early antiretroviral therapy does not improve vascular function: A START substudy. 23rd CROI, 22-25 February 2016, Boston. Poster abstract 475.
3. Baker JV et al. Changes in CVD risk factors with early and deferred ART in the START Trial. 23rd CROI, 22-25 February 2016, Boston. <http://www.croiconference.org/sessions/changes-cvd-risk-factors-early-and-deferred-art-start-trial> (abstract)  
<http://www.croiwebcasts.org/console/player/29442> (webcast)

CROI 2016: HEPATITIS C

## Six-week ledipasvir/sofosbuvir in HIV positive patients with acute HCV

Gareth Hardy, HIV i-Base

**Jürgen Rockstroh from University of Bonn, Germany, presented data on using the combined ledipasvir/sofosbuvir (LED/SOF) for only six weeks in a small group of HIV positive people diagnosed with acute HCV.**

LED/SOF was a fixed dose combination (90 mg/400 mg) taken once-daily. The primary efficacy was the proportion of patients with SVR12 (sustained virological response 12 weeks after the end of treatment). Safety and tolerability data were also collected.

The study enrolled 26 participants with acute HCV infection (defined as within 24 weeks) and chronic HIV infection. All participants were male, 92% were white, with a mean age of 42 years. Mean HCV viral load at baseline was 5.2 log IU/mL (range <LLOQ to 7.3 log). Mean CD4 count was 675 cells/mm<sup>3</sup> (range 275 to 1291). All except one participant were on ART.

After 4 weeks of LED/SOF, 85% of patients experienced a SVR (22/26). Of the four virologic failures without SVR at week 4, three relapsed and one was re-infected with HCV after completing the 6 week treatment course. By 12 weeks, there were no additional virologic failures, but two patients had been lost to follow up, causing an SVR-12 response rate of 77%. None of the patients developed any resistance-associated variants.

Of the three patients who experienced virologic relapse by week 4, two had been HCV-infected for more than 22 weeks, bringing them to the cusp of acute HCV infection definition. These three participants who experienced viral relapse had the highest baseline HCV viral loads (all >7.0 log) after the person with re-infection, suggesting that baseline HCV viral load may be a determinant of viral relapse.

Adverse events were reported in 85% of study participants, 2 (8%) of these were grade 3 or 4 events. There were no discontinuations of the drugs and no deaths in the study. There were also no renal abnormalities and no graded creatinine elevations.

The study concluded that shorter course HCV treatment might be a cheaper option in people with acute HCV and lower HCV viral load.

#### Reference

Rockstroh J et al. Ledipasvir/sofosbuvir for 6 weeks in HIV-infected patients with acute HCV infection. 23rd CROI, 22-25 February 2016, Boston. Oral late breaker abstract 154LB.

<http://www.croiconference.org/sessions/ledipasvirsofosbuvir-6-weeks-hiv-infected-patients-acute-hcv-infection> (Abstract)

<http://www.croiwebcasts.org/console/player/29747> (webcast)

## CONFERENCE REPORTS

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### 6th International Workshop on HIV & Women

20 – 21 February 2016, Boston

#### Introduction

**This annual meeting focuses on the latest developments in research and treatment of HIV positive women from a global perspective and is now in its sixth year.**

The meeting provides an interactive programme that includes: overview talks, oral abstract presentations, Q&A sessions, poster sessions and case studies.

The oral presentations are online at:

<http://www.infectiousdiseasesonline.com/6th-hiv-women-videos> (Webcasts)

<http://www.infectiousdiseasesonline.com/6th-hiv-women-presentations> (Slides)

The abstract book is available at:

[http://regist2.virology-education.com/Abstractbook/2016\\_1.pdf](http://regist2.virology-education.com/Abstractbook/2016_1.pdf)

The two reports in this issue of HTB are related to contraception and pregnancy respectively:

- Doravirine can be co-administered with oral contraceptives
- No increased risk of birth defects with darunavir: findings from the Antiretroviral Pregnancy Registry

### Doravirine can be co-administered with oral contraceptives

Polly Clayden, HIV i-Base

**Multiple dosing with doravirine does not change the plasma pharmacokinetics (PK) of a single dose of ethinyl estradiol (EE) or levonorgestrel (LNG) to a clinically important extent, according to data shown at the 6th International Workshop on HIV and Women.**

Doravirine is a novel non-nucleoside reverse transcriptase inhibitor with an anticipated once daily dose of 100 mg. This drug is primarily metabolised by CYP3A4 but shows no inhibitory or inductive potential on CYP3A4-mediated metabolism in clinical studies. Doravirine has shown no interaction with the enzymes responsible for the metabolism of either EE or LNG.

Investigators from Merck conducted a study to assess the effect of doravirine on the plasma PK of an EE and LNG-containing oral contraceptive.

The study was an open-label, two-period, fixed-sequence design with a seven-day washout between Periods 1 and 2, conducted in HIV negative women. In Period 1 participants received a single oral dose of 0.03 mg EE/0.15 mg LNG. In Period 2 they received 100 mg doravirine once daily for 17 days, with a single dose of EE/LNG co-administered with doravirine on day 14.

The study enrolled 20 post menopausal or oophorectomised women aged 42–65 years. Plasma samples were taken for up to 96 hours post dose in each period.

The investigators reported no serious adverse events (AEs) during the study. One participant discontinued due to a non-serious AE, not considered to be related to any study drug.

Twelve participants reported 27 post dose clinical AEs: three were considered to be associated with study drugs, two doravine (mild erythematous rash, oral herpes) and one both doravirine and EE/LNG (nervousness). One participant reported one laboratory AE associated with both doravirine and EE/LNG (red blood cells in urine). All AEs were transient and judged to be mild or moderate.

The geometric mean ratio (GMR) for EE, EE/LNG + doravirine: EE/LNG was: 0.98 (90% CI 0.94–1.03) for AUC<sub>0-inf</sub> and 0.83 (90% CI 0.80–0.87) for C<sub>max</sub>. GMR for LNG, EE/LNG + doravirine: 1.21 (90% CI 1.14–1.28) for AUC<sub>0-inf</sub> and 0.96 (90% CI 0.88–1.05) for C<sub>max</sub>.

Although the upper bound of the 90% CI for LNG AUC<sub>0-inf</sub> was outside the pre-specified bioequivalence interval (0.80–1.25), the investigators noted that the 90% CI for AUC<sub>0-last</sub> fell within the bounds: GMR 1.15 (90% CI 1.10–1.21). Although the upper bound of the 90% CI for LNG AUC<sub>0-inf</sub> slightly exceeded 1.25, this slight mean increase of 21% would not be expected to affect the efficacy of EE/LNG.

The investigators also reported that although bioequivalence criteria were met for C<sub>max</sub> of EE coadministered with doravirine, 8 out of 19 participants had individual GMR ratios below 0.80 – they suggested that this was unlikely to have a clinically significant effect on the contraceptive efficacy of OC/LNG as this is dependent on the progesterone component of the combined pill. The investigators did not observe corresponding reduction in either AUC parameter.

As a result of this PK evaluation there are no restrictions in the use of oral contraceptives in the phase 3 trials of doravirine.

#### Reference

Anderson M et al. Effect of doravirine (MK-1439) on the pharmacokinetics of oral contraceptive (ethinyl estradiol [EE] and levonorgestrol [LNG]). 6th International Workshop on HIV & Women. 20-21 February 2016. Boston. Poster abstract 19.

## No increased risk of birth defects with darunavir: findings from the Antiretroviral Pregnancy Registry

Polly Clayden, HIV i-Base

**The Antiretroviral Pregnancy Registry (APR) found no apparent increase in the frequency of specific birth defects with first trimester darunavir (DRV) exposure. These findings were presented at the 6th International Workshop on HIV and Women.**

DRV has recently been added to the US pregnancy guidelines list of preferred antiretrovirals for the treatment of women during pregnancy.

Preclinical DRV studies showed no embryotoxicity or teratogenicity in animal models. Human pregnancy studies have focused on pharmacokinetics.

The APR is designed to identify teratogenetic signals in infants exposed to maternal antiretrovirals. The registry receives reports of women taking antiretrovirals in pregnancy, their pregnancies are followed and the outcomes recorded. Reporting is voluntary.

Data from approximately 1300 pregnant women from the US (15% of the 8,700 HIV positive pregnant women who give birth each year worldwide) and 200 women from other countries are reported to the APR annually.

The analysis presented was conducted to evaluate: birth outcomes for ART regimens including and not including DRV; prevalence of birth defects for regimens including DRV; and prevalence for regimens including other protease inhibitors (PI) by earliest trimester of exposure.

The analysis included data from 17,332 women: 535 received ART regimens containing DRV and 16,797 ART regimens excluding DRV.

The women were a median age of 28 years (range 13–55), 57% black and 18% Hispanic and 15% white. CD4 count at the start of pregnancy among women with available data were: 17% <200 cells/mm<sup>3</sup>, 48% 200–499 cells/mm<sup>3</sup> and 35% ≥ 500.

Of 17,330 birth outcomes, 542 were exposed to DRV and 17,088 were not. There were no differences in still births, induced abortion and preterm birth among women exposed or not exposed to DRV. There was increased risk of spontaneous losses and low birth rate: relative risk (RR) 1.60 (95% CI 1.05–2.44), p=0.0348, and RR 1.39 (95% CI 1.10–1.76), p=0.008, respectively.

The overall prevalence of birth defects with DRV exposure was 2.81% (14 out of 498 live births) and without DRV exposure 2.8.6% (456 out of 15, 930 live births), RR 0.98 (95% CI 0.57–1.68), p=1.0.

The prevalence of birth defects in pregnancies with first trimester exposure to a PI was 2.89% (122 defects out of 4,224 live births) and with second or third trimester exposure the prevalence was 2.95% (168 birth defects out of 5,703 live births).

For DRV, the relative risk of birth defects with earliest exposure during the first trimester of pregnancy vs the second or third trimester was 1.75 (95% CI 0.47–6.55),  $p=0.55$ .

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C O M M E N T

**The authors noted that one of the limitations of this analysis is the small number of women in the APR who used DRV-containing regimens – the threshold for detection of birth defects is 200 cases.**

**They also added that the analysis is not adjusted for maternal age, CD4 count or HIV clinical category and the groups receiving regimens including and excluding DRV were different sizes.**

**Another limitation was the lack of information on any previous exposure to antiretrovirals earlier in pregnancy for women starting a PI in the second or third trimesters.**

**Other limitations are similar to any voluntary reporting to a registry: differences in reporting, different assessments of birth defects and loss to follow up, as well as possible under reporting of women with early terminations or losses.**

**Nevertheless it is important that doctors caring for HIV positive pregnant women report to the APR – particularly outside the US, which still contributes the majority of the data and that from other countries remains scarcer.**

Reference

Short WR et al. Use of antiretroviral regimens including darunavir during pregnancy: findings from the Antiretroviral Pregnancy Registry. 6th International Workshop on HIV & Women. 20-21 February 2016. Boston. Poster abstract 23.

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## ANTIRETROVIRALS

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### FTC/TAF dual-nuke approved in the US and Europe

Simon Collins, HIV i-Base

**The new dual-NRTI coformulation of emtricitabine (FTC) plus tenofovir alafenamide (TAF) was approved by the FDA and EMA on 4 April and 25 April 2016 respectively.**

Although the EU approved two doses of F/TAF: 200/10 mg and 200/25 mg, the US FDA only approved the 200 mg formulation.

TAF is a new prodrug of tenofovir which achieves greater intracellular concentrations but with lower plasma drug levels compared to tenofovir disoproxil fumarate (TDF).

The EU indication is for the treatment of adults and adolescents (ages 12 years and older with body weight at least 35 kg) and creatinine clearance greater than or equal to 30 mL per minute, in combination with other HIV antiretroviral agents.

Manufactured by Gilead Sciences the brand name is Descovy.

For further details please see the full prescribing information.

References

1. Gilead press statement. U.S. Food and Drug Administration approves Descovy (emtricitabine, tenofovir alafenamide), Gilead's third TAF-based HIV therapy. (4 April 2016).  
<http://www.gilead.com/news/press-releases>
2. Gilead press statement. European Commission Grants Marketing Authorization for Gilead's Fixed-Dose Combination Descovy (Emtricitabine, Tenofovir Alafenamide) for Treatment of HIV. (25 April 2016)  
<http://www.gilead.com/news/press-releases>

## Paediatric labeling expanded, and additional tablet strengths for FTC/TDF

Simon Collins, HIV i-Base

The combined formulation of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) tablet label was recently updated to expand the indication to include paediatric patients weighing at least 17 kilograms

New strength tablets are available: 100/150 mg, 133/200 mg and 167/250 mg.

A summary of the changes is included below but please see prescribing information for full details.

### Recommended dose

The recommended oral dose for pediatric patients weighing greater than or equal to 17 kg and who are able to swallow a whole tablet, is one low strength FTC/TDF tablet (167 mg/250 mg, 133 mg/200 mg, or 100 mg/150 mg based on body weight) taken orally once daily with or without food.

The recommended oral dosage of TRUVADA low strength tablets is presented in Table 1. Weight should be monitored periodically and the dose adjusted accordingly.

**Table 1. Dosing for paediatric patients weighing 17 kg to less than 35 kg using FTC/TDF low strength tablets**

Body weight (kg)	Dosing of FTC (mg)/TDF (mg)
17 to less than 22	one 100/150 tablet once daily
22 to less than 28	one 133/200 tablet once daily
28 to less than 35	one 167/250 tablet once daily

### Dose forms and strengths

TRUVADA tablets are available in three new dose strengths:

- Tablet: 100 mg of FTC and 150 mg of TDF (equivalent to 123 mg of tenofovir disoproxil): blue, oval-shaped, film-coated, debossed with "GSI" on one side and with "703" on the other side.
- Tablet: 133 mg of FTC and 200 mg of TDF (equivalent to 163 mg of tenofovir disoproxil): blue, rectangular-shaped, film-coated, debossed with "GSI" on one side and with "704" on the other side.
- Tablet: 167 mg of FTC and 250 mg of TDF (equivalent to 204 mg of tenofovir disoproxil): blue, modified capsule-shaped, film-coated, debossed with "GSI" on one side and with "705" on the other side.

### Reference

Truvada (emtricitabine/tenofovir disoproxil fumarate) pediatric labeling expanded, & additional tablet strengths added.

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/021752s047lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021752s047lbl.pdf) (PDF)

## TREATMENT ACCESS

### Timeline for access to generic dolutegravir: what still needs to be done

Polly Clayden, HIV i-Base

**Dolutegravir (DTG) is widely predicted to both provide better antiretroviral options for low-income countries (LMICs) and reduce the cost of global ART. But a number of steps need to happen before DTG is widely available and recommended for all populations.**

The originator (ViiV Healthcare) manufacturer's DTG 50 mg single tablet was approved a few weeks ago in South Africa. It is now approved or under regulatory review across the African continent and in many LMICs.

The DTG price in South Africa will be around R770 per month (approx US \$600 pppy) and it should be on the shelves in early June.

ViiV licensed DTG to Aurobindo in 2014 and subsequently, through the Medicines Patent Pool (MPP), to other generic manufacturers. [1, 2, 3]

Several Indian companies have also completed the development of generic DTG.

The Aurobindo single DTG 50 mg tablet is currently under review for tentative approval with the US Food and Drug Administration (FDA) and there should be an answer from them very soon. This version will be available to generic accessible countries for about US \$44 pppy under an agreement with ViiV and the Clinton Health Access Initiative (CHAI). [3]

Other generic companies will follow suit.

The Aurobindo fixed dose combination (FDC) of DTG/tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) is expected be filed with the FDA in the third quarter of this year and there are other similar generic products on the way. [4]

Assuming all goes according to plan, countries could begin procuring DTG/TDF/3TC in 2017, with World Health Organization (WHO) pre-qualification and FDA approval by end 2017.

One concern for access to the Indian generics is that the department within the Indian Central Drugs Standard Organisation of the Ministry of Health responsible for regulating medical devices and drugs, the Drug Controller General of India (DCGI), requests clinical trials in India for all new drugs. This request can also affect the export of new drugs. [5]

The use of Indian generics to treat HIV is global: Mylan has 30% of the most recent South African tender, covering the three-year period from 1 April 2015 to 31 March 2018. [6]

Indian approval of DTG is sufficiently critical to the success of treating everyone with HIV worldwide. The DCGI waived the local clinical trial requirement for sofosbuvir for hepatitis C, for example, [7] and DTG represents a clear case for such an exception.

Generic manufacturers expect to make the first DTG-based FDCs available for a similar price to EFV-based ones – about US \$100 pppy. Active pharmaceutical ingredients (API) and manufacturing costs for DTG and later tenofovir alafenamide (TAF) will help get this down to about \$85 for DTG/TAF/FTC by 2018/19.

### Missing information and ongoing or planned clinical trials

DTG is now recommended by WHO as part of an alternative adult first-line regimen with restrictions, notably use in pregnancy and with concomitant rifampicin-based treatment for TB. It will not be a preferred regimen until we have more data to guide ART in low-income countries (LMICs), particularly in these two populations.

Several studies designed to address these evidence gaps are ongoing or planned. These include a three-arm, non-inferiority study comparing DTG/TAF/FTC with either DTG/TDF/FTC (currently a recommended first-line regimen in most high-income countries) or EFV/TDF/FTC (currently recommended in WHO guidelines and the most widely used first-line ART globally). The inclusion criteria will reflect clinical practice and populations in LMICs. Other studies will look at the interaction with rifampicin and DTG use in pregnant women.

Our next annual update of ART optimisation trials and generic products in the pipeline will describe these studies in detail. [8]

### References

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<http://www.medicinespatentpool.org/medicines-patent-pool-viiv-healthcare-signlicence-for-the-most-recent-hiv-medicine-to-have-received-regulatory-approval/> CHECK LINK
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4. UNAIDS. Press release. Three new agreements announced with the potential to expand access to innovative HIV treatment in low- and middle-income countries. 30 November 2015.  
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8. Clayden P. Fit for purpose: antiretroviral treatment optimisation. 17 July 2015.  
<http://i-base.info/htb/28509>

## **Botswana “Treat All” programme will move to universal treatment with dolutegravir as first-line ART**

**Simon Collins, HIV i-Base**

**On 3 June 2016, a press release from ViiV Healthcare announced an agreement with the Botswana Ministry of Health for dolutegravir to be commissioned as first-line therapy. [1]**

This will be part of a national “Treat All” public health programme to provide universal access to HIV treatment in Botswana.

Botswana is the first country in sub-Saharan Africa to move to using dolutegravir as first-line therapy - bringing the country in line with guidelines high-income countries that moved to recommend integrase inhibitor combinations rather than starting treatment with efavirenz.

Dolutegravir brings viral load down quicker and more effectively than efavirenz. It is associated with fewer side effects and a lower risk of drug resistance.

The low milligram dose needed for dolutegravir (50 mg vs 600 mg for efavirenz) helped the Clinton Health Access Initiative (CHAI) negotiate for the price of generic dolutegravir to be comparable to generic efavirenz. [2]

WHO recommended dolutegravir as part of alternative first-line ART in late 2015.

### Reference

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2. Collins S. Better generic ART for low and middle income countries: dolutegravir at US \$44 a year. HTB January/February 2016. <http://i-base.info/htb/29508>

## **South Africa takes bold step to provide HIV treatment for all**

### **UNAIDS press statement**

*Antiretroviral therapy to be offered to all people living with HIV as soon as possible after HIV-positive diagnosis.*

The Government of South Africa has announced a major policy shift that will move the world faster towards the global 90–90–90 treatment target.

On 10 May 2016, the South African Minister of Health, Aaron Motsoaledi, announced in his Health Budget Vote Speech to the Parliament of South Africa that the country will implement a new evidence-based policy of offering HIV treatment to all people living with HIV by September 2016.

This groundbreaking announcement brings South Africa, which already has the world’s largest HIV treatment programme, in line with the latest World Health Organization guidelines on HIV treatment. South Africa is among the first countries in Africa to formally adopt this policy.

South Africa already encourages everyone who is HIV negative or who does not know their HIV status to be tested for HIV at least once a year. However, instead of having to undergo an additional test of the immune system (the CD4 cell count) to determine eligibility for treatment, people who are diagnosed HIV-positive will be offered HIV treatment as soon as possible after diagnosis.

“South Africa takes another bold step towards ending its AIDS epidemic by 2030, once again demonstrating that scientific evidence, paired with political will, saves lives,” said UNAIDS Executive Director Michel Sidibé.

This major advance comes only months after the government announced that it will provide pre-exposure prophylaxis (PrEP) to sex workers in 10 sex worker programmes from June this year. South Africa is also considering whether to expand the offer of PrEP to prevent HIV in vulnerable young women, based on the lessons learned from demonstration projects.

These combined efforts demonstrate the South African Government’s commitment to maximizing the benefits of antiretroviral medicines for both the prevention and treatment of HIV. This approach has proved to be highly effective in reducing new HIV infections and AIDS-related deaths in high-prevalence settings, such as South Africa.

Provision of HIV treatment for all is estimated to cost an additional US\$ 66 million per year and will be paid for by South Africa from domestic resources in this year’s budget.

While much success has been achieved by the country’s HIV treatment programme, with approximately 3.5 million people on HIV treatment today, the number of new HIV infections is unacceptably high, with an estimated 340 000 new



HIV infections in 2014.

“The United Nations has a vision to transform the world through the 2030 Agenda for Sustainable Development,” said Mr Motsoaledi. “Ending the AIDS epidemic as a public health threat by 2030 is among the Sustainable Development Goals. The South African Department of Health is committed to this goal and achieving a long and healthy life for all South Africans.”

Source:

UNAIDS press statement. South Africa takes bold step to provide HIV treatment for all. (13 May 2016).

[http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2016/may/20160513\\_UTT](http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2016/may/20160513_UTT)

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## SIDE EFFECTS AND COMPLICATIONS

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### **Persistent HPV infection may be related to tissue type in HIV positive people**

**Gareth Hardy, i-Base**

**Rhonda Meys and colleagues at Chelsea and Westminster Hospital have conducted the first study to examine the relationship between persistent warts, HPV infection and tissue type in HIV positive people [1].**

The investigators found that in HIV positive people specific HLA class I tissue types are associated with persistent HPV infection and there are particular HPV genotypes that are more commonly seen.

The study looked at individuals who have a history of persistent cutaneous or genital warts and examined the HPV serotypes found in wart biopsies as well as their class I and class II HLA types. The study recruited patients of northern European descent in three groups: 1) HIV positive people with HPV disease (>6 months history of persistent warts); 2) HIV positive people with no history of HPV disease; 3) HIV negative individuals with HPV disease (>6 months history of persistent warts).

All HIV positive people in the study were male, had been on ART for more than 1 year and had viral loads below 50 copies/mL for more than 6 months. In contrast 29% of the HIV negative individuals with HPV disease were female.

In total 137 individuals were recruited to the study of which 49 were HIV+/HPV+ cases, 46 were HIV+/HPV- cases and 42 were HIV-/HPV+ cases. All individuals were HLA typed and their HPV genotypes were determined by PCR from biopsies of wart tissue. HPV has 120 genotypes that are divided up amongst five different genera: alpha-papillomavirus; mu-papillomavirus; nu-papillomavirus; gamma-papillomavirus; and beta-papillomavirus. Different genera of HPV tend to infect either cutaneous dry skin or genitalia. Therefore primers were designed to detect cutaneous wart-associated HPV or genital wart-associated HPV.

Primers for cutaneous HPV included the following 23 genotypes 1, 2, 3, 4, 7, 10, 27, 28, 29, 40, 41, 43, 48, 50, 57, 60, 63, 65, 77, 88, 91, 94 and 95. Primers for genital HPV included 25 genotypes 6, 11, 16, 18, 31, 33, 34, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 66, 68, 70 and 74. Furthermore the following 25 beta-papillomaviruses were detected with a separate set of primers 5, 8, 9, 12, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 36, 37, 38, 47, 49, 75, 76, 80, 92, 93, and 96.

Of all the individuals with HPV infection, 86% of HIV positive individuals and 69% of HIV negative individuals had a history of cutaneous warts, 39% of HIV positive individuals and 45% of HIV negative individuals had a history of genital warts and 24% of HIV positive individuals and 14% of HIV negative individuals had a history of both. Three individuals in each group also had a history of penis or anal cancer.

HLA-B\*44 was the main tissue type allele of significant difference in this study. HLA-B\*44 is present in approximately 32% or a comparable blood donor population, but was found to be present in the genotypes of 47% of HIV+/HPV+ cases and only 17% of the HIV+/HPV- control cases ( $p=0.004$ ,  $p$ -corrected=0.54). In the HIV-/HPV+ group HLA-B\*44 was found at a frequency of 33%, similar to the general population. Subtype analysis revealed that HLA-B\*44:02 was the predominant allele in this group and was present in 38% of HIV+/HPV+ cases and only 7% of HIV+/HPV- control cases ( $p=0.0006$ ,  $p$ -corrected=0.04), while it is present in the genotypes of 19% of a comparable blood donor population ( $p=0.0006$ ,  $p$ -corrected=0.43).

HLA-C\*05 was also present in the genotypes of HIV+/HPV+ individuals at a significantly increased frequency of 33% compared to 9% of HIV+/HPV- controls ( $p=0.009$ ,  $p$ -corrected=0.59). 37% of HIV+/HPV+ individuals carried both HLA-B\*44 and HLA-C\*05 compared to 7% of HIV+/HPV- controls ( $p=0.001$ ,  $p$ -corrected=0.07). No differences were

found between the groups in the proportion of subject who were homozygous for one or more HLA alleles.

Analysis of HPV genotype was conducted on wart biopsies from 30 HIV+/HPV- individuals and 36 HIV-/HPV+ individuals. In 29% of biopsied warts, more than one HPV genotype was identified, showing that mixed in HPV infection was common. Multiple beta-papillomavirus HPVs were detected in wart biopsies from 60% of HIV positive individuals compared with 38% in warts from HIV negative individuals ( $p=0.03$ ).

The number of different types of beta-papillomavirus HPVs was also greater in HIV positive people who had a median of 3 (IQR 0.3-8) compared with HIV negative people who had a median of 1 (IQR 0-2), ( $p=0.002$ ). HPV 7 was present in cutaneous warts from 8% of HIV positive individuals, but not present at all in HIV negative individuals ( $p=0.04$ ).

In contrast HPV 2 was more frequent in cutaneous warts of HIV negative people, where it was identified in 30 % of the group, compared to 3% of HIV positive people ( $p=0.002$ ). There was no difference between HIV positive and negative people in the frequency of HPV genotypes associated with genital warts, though the number of warts examined was small.

The authors suggest that the differences in HLA-type between groups suggest an effect of HLA class I on predisposition to HPV, while evidence in the literature suggests more of a role for HLA class II [2]. This is one of few reports that identify HLA class I as potentially important in susceptibility to HPV. This is the first study to examine HLA-associations with HPV infection in HIV positive patients. The authors also note that the effect of HLA class I maybe indirect, as it is known to play a significant role in HIV infection.

Importantly, this study highlights the possibility that the relatively rare HPV 7 may be an important pathogen in HIV positive people.

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## ON THE WEB

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### Community reports

#### RITA: HIV and smoking

**The most recent issue of RITA from the Center for AIDS in Houston is on HIV and smoking.**

<http://centerforaids.org/pdfs/rita0116.pdf> (PDF)

This issue includes three main articles.

- An interview with Jonathan Shuter on motivating and helping HIV positive smokers to quit, including discussion of his innovative online quitting program, PositivelySmokeFreeMe.
- A review article analyzing smoke-ending strategies in people with HIV.
- A review article summarising the impact of smoking on health of HIV positive people and how that impact differs from smoking's effect in the general population.

The issue also includes two 2-page summaries: "Ten things every HIV positive smoker should know" and "Ten things every HIV clinician should know about smoking."

#### HIV criminalisation

**A new report "Advancing HIV Justice 2" shows that HIV criminalisation is a growing, global phenomenon.**

However, advocates around the world are working hard to ensure that the criminal law's approach to people living with HIV fits with up-to-date science, as well as key legal and human rights principles.

<http://www.hivjustice.net/news/new-report-shows-hiv-criminalisation-is-growing-global-problem-but-advocates-are-fighting-back>

[http://www.hivjustice.net/wp-content/uploads/2016/05/AHJ2.final2\\_10May2016.pdf](http://www.hivjustice.net/wp-content/uploads/2016/05/AHJ2.final2_10May2016.pdf) (PDF)

## ChemSex forum

**As recent meeting in London on HIV and ChemSex has posted workshop materials online.**

Presentations:

<http://www.slideshare.net/Checkpoints14/presentations>

Posters:

[https://drive.google.com/folderview?id=0B9E\\_UBugz0VWZXloSFdqekRxS2M&usp=sharing](https://drive.google.com/folderview?id=0B9E_UBugz0VWZXloSFdqekRxS2M&usp=sharing)

Audio files with slides presentations:

<https://www.youtube.com/playlist?list=PLF-szL8WntiUXDHITYLwpFYNLOUr-lyXd>

## FUTURE MEETINGS

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### Conference listing 2016

The following listing covers some of the most important upcoming HIV-related meetings and workshops. Registration details, including for community and community press are included on the relevant websites.

#### **18th Annual Conference of the National HIV Nurses Association**

29 June–1 July 2016, Manchester

<http://www.nhivna.org>

#### **Global HIV Clinical Forum: Integrase Inhibitors**

16 July 2016, Durban

<http://hiv-forum.com>

#### **3rd International HIV/Viral Hepatitis Co-Infection Meeting**

17 July 2016, Durban

<http://www.iasociety.org/co-infections/hepatitis>

#### **21st International AIDS Conference (IAS 2016)**

17-22 July 2016, Durban

<http://www.aids2016.org>

#### **18th International Workshop on Comorbidities**

12 – 13 September, New York

<http://www.intmedpress.com/comorbidities>

#### **20th Annual UK Resistance and Antiviral Therapy Meeting**

15 September 2016, London

<http://www.mediscript.ltd.uk>

#### **7th International Workshop on HIV & Aging**

26 - 27 September 2016, Washington DC, USA

<http://www.virology-education.com>

#### **7th BHIVA Conference for the Management of HIV/Hepatitis Co-infection**

12 October 2016, London

<http://www.bhiva.org>

**BHIVA Autumn Conference 2016**

13–14 October 2016, London

<http://www.bhiva.org>

**HIV Research for Prevention Conference (HIVR4P) 2016**

17-20 October 2016, Chicago

<http://www.hivr4p.org>

**European HIV Clinical Forum: Integrase Inhibitors**

22 October 2016, Glasgow

<http://hiv-forum.com>

**Congress on HIV Therapy (Glasgow 2016)**

23-26 October 2016

<http://hivglasgow.org>

**24th Conference on Retroviruses and Opportunistic Infections (CROI 2017)**

13-16 February 2017

<http://www.croiconference.org>

## PUBLICATIONS & SERVICES FROM i-BASE

### i-Base website

**All i-Base publications are available online, including editions of the treatment guides.**

<http://www.i-Base.info>

The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

The Q&A web pages enable people to ask questions about their own treatment:

<http://www.i-base.info/qa>

### Three new pocket guides: ART, pregnancy and side effects

A new series of pocket-size concertina folding leaflets that is designed to be a very simple and direct introduction to HIV treatment.



The first three pocket leaflets are:

- Side effects and Quality of Life
- HIV and pregnancy
- ART (included with the Sept/Oct HTB)

We hope this is especially useful as a low literacy resource.

The leaflet uses simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

### i-Base treatment guides

i-Base produces six booklets that comprehensively cover important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

<http://www.i-base.info/guides>

- NEW: Guide to PrEP in the UK (June 2016)
- Introduction to ART (January 2016)
- HIV testing and risks of sexual transmission (June 2016)
- HIV and quality of life: side effects & complications (June 2016)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)

### Order publications and subscribe by post, fax or online

All publications can be ordered online for individual or bulk copies. All publications are free. Unfortunately bulk orders are only available free in the UK.

<http://i-base.info/order>

## **htb(e)**

### **HIV TREATMENT BULLETIN (e)**

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:

<http://www.i-Base.info>

by sending an email to: [subscriptions@i-Base.org.uk](mailto:subscriptions@i-Base.org.uk)

Editor: Simon Collins

Contributing Editor: Polly Clayden

#### Medical Consultants:

Dr Karen Beckerman, Albert Einstein College of Medicine, NYC.

Dr Sanjay Bhagani, Royal Free Hospital, London.

Prof. Diana Gibb, Medical Research Council, London.

Dr Gareth Hardy, PhD.

Prof. Saye Khoo, University of Liverpool Hospital.

Prof. Clive Loveday, International Laboratory Virology Centre.

Prof. James McIntyre, Chris Hani Baragwanath Hosp. South Africa

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**HIV i-Base, 107 The Maltings, 169 Tower Bridge Road,  
London, SE1 3LJ.**

**T: +44 (0) 20 8616 2210. F: +44 (0) 20 8616 1250**

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