

may–june 2017

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HIV TREATMENT BULLETIN

HTB is published in electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered using the form on the back page or directly from the i-Base website:

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

or by sending an email to: subscriptions@i-Base.org.uk

Editor: Simon Collins

Contributing Editor: Polly Clayden

Medical consultants:

Dr Tristan Barber, Chelsea & Westminster Hosp, London.

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

Dr Graeme Moyle, Chelsea & Westminster Hosp, London.

Dr Stefan Mauss, Düsseldorf.

Prof. Caroline Sabin, UCL Medical School, London.

Dr Graham P Taylor, Imperial College, London.

Dr Stephen Taylor, Birmingham Heartlands Hospital.

Dr Gareth Tudor-Williams, Imperial College, London.

Dr Edmund Wilkins, Manchester General Hospital, Manchester.

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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

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

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EDITORIAL

Welcome to the May/June edition of HTB.

As usual, this is a very diverse issue, covering treatment news and advances for both high and low income countries.

Although we lead with anecdotal reports of side effects linked to generic abacavir, this is mainly for unexplained recent symptoms where this might be important to consider.

Conference news comes from three meetings and includes a review of the Option B+ programme in Malawi plus a pipeline from CROI on new ARVs.

ARV news includes new drug submissions and labelling safety updates, continued in journal reviews relating to HIV complications and pathogenesis.

This is the second issue of HTB that is only being distributed in electronic format.

This means that if you used to receive HTB by post, please register for electronic subscriptions to continue to receive HTB and other i-Base publications.

<http://i-base.info/htb/about/subscribe>

Please also consider helping with our funding appeal to support i-Base for the next year.

New resources

- ART in pictures (June 2017)

A new 32-page A4 publication that uses pictures and non-technical text to explain HIV treatment.

- Guide to hepatitis C for people living with HIV coinfection (April 2017)

Revised throughout to include latest information about DAA treatment, including access.

All publications are free to UK clinics.

Please order online or using the form on the back cover of this issue of HTB.



i-Base 2017 appeal: we need your help....

This year, the i-Base 2017 was launched to respond to larger changes in our funding.

Your regular support can make a big difference.

We could reach our £100,000 target if:

- 500 people support i-Base with £9.00 a month

and...

- 1000 people support with £4.50 a month.

Please become one of our subscribers that help.

- i-Base continues to provide all services free, including free community publications for all UK clinics.
- The i-Base website gets more than 400,000 users every month. And last year the i-Base Q&A service answered almost 6,000 individual questions from HIV positive people.
- HIV services are being dramatically cut across the UK, and much of the voluntary sector is vulnerable, including i-Base.

If you can support our work, all contributions are appreciated and make a difference.

Moving to electronic distribution of HTB will help, but by itself will not be enough.

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

This link includes the option to securely donate online or offline.

If you would like to help i-Base in other ways, or would like more information about this i-Base appeal, please contact Suzanne Thompson or Simon Collins at HIV i-Base on 020 8616 2210.

Thank you for your help.



TREATMENT ALERT

Unexpected side effects with generic abacavir – and potential for rare reactions to other generic ARVs

Simon Collins, HIV i-Base

Several anecdotal reports of mouth ulcers have recently been reported in people switching to generic abacavir in the UK. [1]

This should highlight awareness of the potential of likely-rare new side effects, even when both formulations have been approved as bioequivalent.

These are likely to be very uncommon reactions, but given they are currently unexpected, it is important to consider new symptoms following a switch to generic formulations. It is also important during the early months of using generics that such symptoms are reported to the UK yellow card scheme. [2]

Background

As many widely used HIV medicines reach the end of patents, the move to generic formulations will save the NHS millions of pounds each year.

Generic medicines used in the UK are just as carefully monitored as original formulations. Generics have proven to have the same pharmacokinetic properties as original formulations with comparable drug levels of the active ingredients. However, some generic medicines are manufactured slightly differently, using different non-active ingredients in medicines – called excipients – and also sometimes using a slightly different base compound. [3]

Both abacavir and tenofovir are now available as generics in the UK, using slightly different base compounds. This is partly to overcome restrictions linked to the original patents. Other generic ARVs including lamivudine, nevirapine and efavirenz use the same base formulations as the original drugs.

Abacavir/lamivudine

Three manufacturers now provide generic versions of Kivexa, the dual nucleoside single pill containing abacavir and lamivudine manufactured by ViiV Healthcare. Although a patent extension still exists for Kivexa, ViiV Healthcare are not challenging or enforcing this.

The two generic formulations manufactured by Lupin and Mylan, both use a base salt of abacavir hydrochloride, compared to an abacavir sulphate base in Kivexa. The generic formulation manufactured by Teva is present as a free base. All three formulations have proven to be similar in terms of active ingredients.

Although the generic formulations have different packaging, all three formulations are similar size, shape and orange to Kivexa.

Tenofovir DF/emtricitabine

Although generic versions of Gilead's Truvada (tenofovir DF/emtricitabine) are not currently available in the UK, this is expected to change in the summer 2017, with several generic manufacturers

likely to launch so-called “at-risk” generic formulations (as they might be challenged by Gilead).

Many of the generic formulations used outside the UK use a different tenofovir base tenofovir disoproxil maleate (TDM) rather than tenofovir disoproxil fumerate (TDF) used in the originator drug. The active drug is the same from all formulations.

Nevirapine

The UK generic version of Boehringer Ingelheim’s version of nevirapine (Viramune) is currently manufactured by Teva.

Both versions are once-daily extended release formulations, with similar shape, size and are off-white.

C O M M E N T

Whether there is an association between these events and the switch to generics is not clear.

Even if they are related, this is likely to be a rare event since switching to generics is standard practice with all medicines provided by the NHS when patents have expired and cheaper alternatives exist. These reports should not deter people from switching to generics.

However, anybody who develops similar symptoms that do not resolve swiftly should contact their healthcare provider taking note of the brand of generic as well as the batch number.

The suspected reactions to generic abacavir were first reported at a meeting of the NHS CRG drugs group. They included one case of persistent and worsening mouth ulcers that developed for several weeks after switching from Kivexa. The symptoms in this case improved within one day of switching back to originator formulation.

Case details are currently being collected, including the generic brand and batch number, for a detailed report. Other cases should be reported to the yellow card scheme. [2]

The Drugs Subgroup of the HIV CRG “are aware of this potential issue and advise that patients should discuss any concerns related to their clinical care, including potential side effects with their clinical teams in the first instance. This group will continue to monitor the situation and respond to any alerts raised from the Medicines and Healthcare products Regulatory Agency who are responsible for monitoring any reports of adverse events linked to all licenced treatments.” [4]

The vast majority of the 17 million HIV positive people globally are effectively treated with generic medicines with no currently reported differences compared to the originator product.

However, single cases of reactions to different excipients for other medicines have occasionally been reported.

- **An allergic reaction to croscarmellose sodium used as excipient in a generic furosemide preparation in a patient who had previously been taking branded furosemide. [5]**

- **GI disturbance in lactose-intolerant patient with an arrhythmia who was switched from one formulation of antiarrhythmic drug (e.g., Isoptin 120 mg or Rytmonorm 300 mg) to another that contains a lactose-based excipient (e.g., Verapamil or Propafenone Sandoz).**

The originator versions of HIV drugs will still be available for rare cases of reactions to generic formulations.

References

1. CRG Drug Group, (11 May 2017).
2. MHRA yellow card scheme. <https://yellowcard.mhra.gov.uk>
3. NHS Specialist Pharmacy Service. New generics antiretroviral product (2016). <https://www.sps.nhs.uk/articles/new-generic-antiretrovirals-products-2016>
4. CRG Drug group can be contacted by emailing the HIV CRG lead commissioner. <janette.harper@nhs.net>
5. Mumoli N et al. An allergic reaction to croscarmellose sodium used as excipient in a generic drug, QJM. 2011;104:709–10.

CONFERENCE REPORTS

18th International Workshop on Clinical Pharmacology of Antiviral Therapy

14-16 June 2017, Chicago

Introduction

The annual pharmacology workshop focuses mainly on treatments for HIV and viral hepatitis.

But this year include a few presentations on other antivirals, hence its name change: International Workshop on Clinical Pharmacology of Antiviral Therapy (a workshop formally known as the International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy).

The abstract book and slides from most oral presentations are online at the conference website.

<http://www.infectiousdiseasesonline.com/event/workshop/antiviralpk-2017>

Articles in this issue are:

- Dolutegravir pharmacokinetics in pregnancy
- High rates of undocumented efavirenz side effects in Uganda

Dolutegravir pharmacokinetics in pregnancy

Polly Clayden, HIV i-Base

Dolutegravir exposure and trough concentrations in third trimester of pregnancy appear to be similar to postpartum, according to data from the PANNA Network presented at the 18th International Workshop on Clinical Pharmacology of Antiviral Therapy.

PANNA is a European clinical pharmacology network to investigate the pharmacokinetics (PK) of new antiretrovirals in HIV positive pregnant women receiving them as part of routine care.

The study objectives were to describe dolutegravir: PK in the third trimester and postpartum; safety and efficacy for mothers and infants; and placental transfer.

It enrolled nine women receiving dolutegravir 50mg once daily at four European hospitals (June 2015 to June 2017). Of these three women had only third trimester PK results and one woman was excluded from the PK analysis

At delivery women were a median age of 30 years old (range 21–42) and 38 weeks (range 34–40) gestation. Infant birth weight was a median of 3180 grams. Maternal ART regimens were dolutegravir plus: 4 (44%) tenofovir DF/emtricitabine; 4 (44%) abacavir/lamivudine; and 1 (12%) darunavir/ritonavir + tenofovir DF.

The investigators performed PK sampling in the third trimester at approximately 33 weeks and postpartum 4–6 weeks after delivery (reference). Blood samples were taken: predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post dose. Cord blood was also taken at delivery to determine cord blood/maternal blood (CB/MB) ratio.

The resulting PK parameters for dolutegravir in third trimester and postpartum are described in Table 1.

Table 1: PK parameters dolutegravir third trimester and postpartum

Parameter	Third trimester (n=8)	Postpartum (n=5)	GM ratio (90% CI)
AUC 0-24h (h*mg/L)	42.9 (39)	44.8 (56)	0.95 (0.60 to 1.48)
Cmax (mg/L)	3.4 (33)	3.0 (41)	1.07 (0.78 to 1.47)
C24h (mg/L)	0.7 (109)	1.1 (71)	0.66 (0.32 to 1.36)
Tmax (h)	3.0 (1.0–4.5)	3.8 (0.5–8.0)	-
CL/F (L/h)	1.2 (39)	1.1 (56)	1.06 (0.67 to 1.66)
T1/2 (h)	9.9 (50)	14.9 (27)	0.75 (0.58 to 0.98)

Values are geometric mean (CV%); except for Tmax, median (range).

When the investigators looked at individual exposure and Ctrough in some women they observed a decrease in pregnancy but in others exposures were higher.

They also noted that levels at the end of the dosing interval remained above the IC90 for dolutegravir.

CB/MB ratio (n=5) was 1.4 (0.35–1.6) suggesting efficient placental transfer but limited by the small number of maternal infant pairs.

All women had a viral load <50 copies/mL approaching delivery. At the time of analysis seven infants were uninfected and one infant's status was unknown.

There was one intrauterine foetal death at 34 weeks gestation due to cholestasis pregnancy syndrome. No further birth defects were reported.

There were two serious adverse events, not related to study drug that required hospital admissions to rule out pre-eclampsia.

C O M M E N T

The PK parameters in third trimester are comparable with those from the IMPAACT P1026s reported at CROI last year. But the postpartum exposure is higher in the IMPAACT study. The reason for that difference is not clear.

Further data on dolutegravir in pregnancy will be presented at IAS 2017.

Reference

Bollen P et al. A comparison of the pharmacokinetics of dolutegravir in pregnancy and postpartum. 18th International Workshop on Clinical Pharmacology of Antiviral Therapy. 14-16 June 2017, Chicago. Oral abstract 0_7.

High rates of of undocumented efavirenz-related side effects in Uganda

Simon Collins, HIV i-Base

Although CNS side effects associated with efavirenz have led to newer drugs being recommended in high income countries, WHO guidelines for low and middle income countries still recommend efavirenz for first-line therapy.

This difference in care between rich and poor countries is exaggerated by a genetic polymorphism (G516T in CYP P450 2B6) that significantly increases drug levels of efavirenz (by reducing clearance rates) being more common in African compared to Caucasian populations.

Kay Seden from University of Liverpool and colleagues from Makerere University, Uganda, presented results from a prospective, longitudinal observational study to report all side effects in a cohort of 246 Ugandan patients on antiretroviral therapy (ART).

Baseline demographics included mean age 35 years (IQR: 34 to 38), 62% women, median CD4 520 cells/mm³ (329 to 716).

Overall, 134/246 patients were taking an efavirenz-based combination. Of these, 58/134 (43%; 95%CI: 35 to 52%) reported CNS-associated side effects (nervous system and/or psychiatric disorders). Severity was self-graded >5/10 by 45 (61%): with 47 (64%), 25 (34%) and 2 (3%) reported as minor, moderate and severe, respectively.

The median duration of side effects was 28 months (IQR 19-42) and only 7% had been reported in medical notes.

In multivariate analysis, risk of side effects was not associated with patient factors such as age, sex, weight or clinical stage.

C O M M E N T

The researchers included a comment that many of these patients might benefit from using the lower 400 mg dose of efavirenz.

Similar side effects in the UK should routinely result in a switch to an alternative combination.

Reference

Seden K et al. High prevalence and long duration of nervous system and psychiatric adverse drug reactions in Ugandan patients taking efavirenz 600mg daily. 18th International Workshop on Clinical Pharmacology of Antiviral Therapy. 14-16 June 2017, Chicago. Poster abstract P_55.

CONFERENCE REPORTS

11th INTEREST Workshop

16–19 May 2017, Lilongwe, Malawi.

Introduction

The INTEREST Workshop, shows findings from African HIV treatment and prevention research and is largely attended by delegates from the continent.

This year, the workshop was held in Lilongwe, Malawi.

Reports in this issue include:

- Increased risk of ART failure after low-level viraemia in a large South African cohort
- Option B+ Malawi

Increased risk of ART failure after low-level viraemia in a large South African cohort

Polly Clayden, HIV i-Base

Viral load cut-off as defined by WHO guidelines fails to identify a significant number of HIV positive people at risk for virological failure, according to findings from South Africa presented at the 11th INTEREST workshop.

Current WHO ART recommendations define failure as viraemia above 1000 copies/mL during treatment. In high-income countries, with stricter viral load cut-off (50 copies/mL), detectable viral load below 1000 copies/mL during ART (low-level viraemia) has been linked to treatment failure.

The currently recommended preferred first-line ART regimen has a low genetic barrier to resistance: NNRTI + 2NRTI.

Lucas Hermans presented findings from an evaluation of low-level viraemia and its impact on ART failure in a large South African cohort managed according to WHO guidelines.

The study was conducted across 19 urban and 38 rural HIV treatment sites. Adult participants were included if they had received ART for 20 weeks or more and had viral load monitoring.

Low level viraemia was defined as 50–1000 copies/mL and stratified by level: 51–199, 200–399 and 400–999 copies/mL, and duration. Outcomes were ART failure above 1000 copies/mL and switch to second-line. The investigators used Cox proportional hazard models corrected for sex, age and baseline CD4, to estimate the association between low-level viraemia and subsequent viral failure in the subset of participants with 52 weeks or more of first-line ART without failure.

Overall 71,056 participants met inclusion criteria: 67,380 treated with first-line ART; 1,602 second-line ART and 2,074 with both. Virological

failure on ART occurred in 21.6% of people on first-line ART; 35% of these resuppressed <1000 copies/mL on the same regimen.

Low level viraemia occurred in 12% per year; 23.1% of participants had low-level viraemia at any time during follow up and this was persistent in 21.3% of cases.

Low-level viraemia between 51–199 copies/mL was common (59%). It was associated with increased hazard of failure of first-line ART, HR 3.0 (95% CI 2.8 to 3.3); ART failure without resuppression on same regimen, HR 3.2 (95% CI 3.0 to 3.5); and switching to second line, HR 2.9 (95% CI 2.4 to 3.4), compared to <50 copies/mL. The investigators saw a further increase in risk of failure with higher ranges and duration of low-level viraemia. And lower baseline CD4 was independently associated with low-level viraemia.

Dr Hermans noted that despite these risks, WHO guidelines do not recommend clinical intervention in cases of repeated low-level viraemia below the cut-off of 1000 copies/mL. "This poses concerns for long term virological suppression in WHO-guided treatment programmes", he suggested.

References

Hermans LE et al. Increased risk of treatment failure after low-level viraemia in a large cohort of South African HIV positive patients treated according to under WHO guidelines. 11th INTEREST, 16–19 May 2017, Lilongwe, Malawi. Oral abstract 7.

A similar earlier analysis from this study was presented at CROI 2017:

Hermans LE et al. Increased risk of cART failure after low-level viremia under WHO guidelines. CROI 2017. 13–16 February 2017. Seattle, Washington. Oral abstract 113.

<http://www.croiconference.org/sessions/increased-risk-cart-failure-after-low-level-viremia-under-who-guidelines> (abstract)

<http://www.croiwebcasts.org/console/player/33589> (webcast)

Option B+ Malawi

Polly Clayden, HIV i-Base

Malawi began Option B+ (universal lifelong ART for pregnant and breastfeeding women) in 2011, which led to a rapid scale up of women accessing ART irrespective of CD4 count.

Since then the Malawi programme has matured and Treat All has been adopted for all populations including pregnant women – both nationally and in WHO guidelines. As with non-pregnant adults, pregnant women receive a first-line ART regimen of efavirenz/tenofovir DF/lamivudine (EFV/TDF/3TC).

The 11th INTEREST Workshop – also conducted in Malawi – included a number of posters from studies designed to monitor and evaluate various aspects of the programme including: ART uptake, retention in care, long-term safety, treatment failure, and maternal and infant adverse events and outcomes.

These are: The National Evaluation of Malawi's PMTCT programme (NEMAPP), PROBE (PMTCT Retention of Option B+ Evaluation) study and The Option B+: ART Safety and Durability during First and Subsequent Pregnancies research study at Bwaila District Hospital in Lilongwe.

ART in pregnancy and partner's HIV disclosure protective against early infant transmission

NEMAPP reported good ART coverage and generally low vertical transmission. [1] Starting ART during pregnancy and partner's HIV status disclosure to the mother were protective against early infant transmission. [2]

NEMAPP is a two-year longitudinal cohort study across 54 health facilities, started in November 2014, using two-stage cluster sampling to evaluate infants at 4–12 weeks of age. Mothers attending an under-5 clinic were tested for HIV and HIV-exposed infants received DNA testing at baseline, 12 and 24 months.

Of 2125 HIV positive mothers, 2082 (96.1%) knew their status before or during pregnancy and 1865 (88.5% but varying widely between 54.9% and 100% across sites) were diagnosed and started ART in pregnancy. The vertical transmission rate was 4.2% (95% CI 2.9 to 6.1) overall: women receiving ART 2.5% (95% CI 1.6 to 3.9) and 17.9% (95% CI 13.0 to 21.2) for those not receiving ART. The rate of transmission varied from 1.4% (95% CI 0.5 to 3.9) in women who started ART before pregnancy to 20.2% (95% CI 5.8 to 50.7) in those starting ART postpartum.

Early infant transmission was lower if a woman started ART before compared with during their pregnancy: 2.3 vs 3.5%, $p=0.014$. It was also lower for those that disclosed their status to their partners: 2.0 vs 5.8%, $p=0.008$.

In multivariate analysis for the subgroup of women receiving ART during pregnancy, the likelihood of early infant transmission almost doubled if a woman started ART during compared with before pregnancy: aOR 1.9, $p=0.032$. Partner's HIV status disclosure to the mother was also significantly protective against early infant transmission, aOR 0.39, $p=0.011$.

Maternal health status or missed ART, exclusive breastfeeding and infant nevirapine prophylaxis were not associated with early transmission among mothers receiving ART.

Low maternal mortality and morbidity postpartum

Mothers had low mortality and morbidity at 4–26 weeks postpartum associated with increased ART uptake in asymptomatic women in an analysis of maternal health in NEMAPP. [3]

Of 1307 women evaluated, 67.3% ($n=879$) were 6–12 weeks postpartum and 1151 ($n=88.1\%$) receiving ART.

At ART initiation 171 (13.1%) women had minor illness and 51 (3.9%) major illness according to self-reported health status. Of these 155/171 (90.6%) and 47 (90.4%) respectively reported improved health status.

In a nested cohort study including 580 women, their health status at enrollment was: 94% normal, 3.6% minor illness not affecting normal activities and 0.7% major illness needing daily assistance. Of the 580 women 56.2% had CD4 >500 cells/mm³ and 71.9% undetectable viral load.

More women receiving ART reported normal health than those who stopped ART (95.6 vs 87.5%) $p<0.001$, as did more women with CD4 >500 cells/mm³ (97.2 vs 92.8), $p=0.02$. In multivariate analysis adjusted for ART status and duration of known HIV status poor functional health was associated with CD4 <500 cells/mm³, aOR 2.6, $p=0.03$.

No difference in ART use or vertical transmission rates in adolescent mothers compared with older ones

Limited evidence suggests that vertical transmission prevention outcomes in young and adolescent women are worse than for adult women. [4]

A national evaluation comparing the use of services (uptake of antenatal testing and ART) and vertical transmission rates between young or adolescent mothers and adult mothers found adolescents less likely to be newly identified HIV positive. But among the known HIV positive women, there was no difference between age groups in ART use or vertical transmission rates.

The study included 33,744 mother-infant-pairs: 53.8% were defined as young (12–24 years) and 20.5% were adolescent (12–19 years) mothers. Overall 97.8% reported having an HIV test before or during last pregnancy.

Young mothers had more likely missed antenatal HIV testing than adult mothers: OR 1.8 (95% CI 1.2 to 2.7). Of all the mothers 11.3% were diagnosed with HIV before or during pregnancy; this was lower in young (4.6%) and adolescent (2.8%) mothers.

Adolescents were less likely newly identified HIV positive (previously negative) than young and adult mothers: OR 0.5 (95% CI 0.2 to 0.9). But newly identified HIV positive (previous unknown) young mothers might have missed earlier diagnoses more frequently than adult mothers: OR 3.5 (95% CI 0.9 to 14.4).

Among the known HIV positive women, 94.7% reported receiving ART, with no difference between young or adolescent and adult mothers. Overall vertical transmission rate at 4–26 weeks was 4.7%, with no difference between young or adolescent and adult mothers.

Asymptomatic women and those with better treatment literacy more likely to access ART

Accessing ART in health centres, being asymptomatic and treatment literacy were associated with high ART uptake. [5] But after starting treatment, neither of these predictors were associated with default or transferring to another health facility, according to a national assessment of Option B+ outcomes.

This was a secondary data analysis of the PROBE study. PROBE was a retrospective cohort of women attending antenatal clinics. The main variables in the study were: women coming for a second routine visit (uptake) and default and transfer out (outcomes).

The analysis revealed, of 2739 women with 17,769 observations and complete information, 410 defaulted, 39 transferred out, 14 died and 4 stopped.

In Cox proportional hazards model the risk of defaulting was 30% lower in the Ministry of Health compared with Christian Health Association of Malawi facilities: HR 0.7 (95% CI 0.56 to 0.87). Pregnant women had a 64% higher risk of defaulting than breast feeding women: HR 1.64 (95% CI 1.29 to 2.07). Default rate was 21% lower among adults compared with adolescents: HR 0.79 (95% CI 0.62 to 0.99); 40% lower in women with ART education compared with those without: HR 0.6 (95% CI 0.47 to 0.77); and 61% higher in symptomatic women compared with asymptomatic: HR 1.61 (95% CI 1.05 to 2.48).

In multistate model (using sub-hazards) women accessing services in health centres had 65% probability of ART uptake: SHR 0.35

(95% CI 0.30 to 0.41); 182% in women with ART education: SHR 2.82 (95% CI 2.43 to 3.26); and 19% lower among symptomatic women: SHR 0.81 (95% CI 0.70 to 0.94).

The investigators noted that after starting ART the risk of either defaulting or transferring to another facility was not significantly associated with any predictor.

Unmarried women and those in new relationships more likely to be lost to follow up

Of 299 newly diagnosed, ART naive pregnant women enrolled in the prospective observational study from May 2015 to November 2016 at Bwaila Hospital, 35 (12%) were lost to follow up, including 9/35 before delivery. [6] Being unmarried and in a newer relationship were associated with loss to follow up.

The study defined loss to follow up as missing after 90 days from last documented visit, excluding those that died. A trained community liaison was informed of all missed visits and traced the participants physically or by phone until they either found them or had made three attempts to do so.

At enrollment participants were a median age of 26 years (IQR 26–30) and the majority were married (89%) and/or had been in the relationship for one year or more (77%). The median follow up was 11 months (IQR 8–14). Three died during the study. Of the participants lost to follow up 6/35 (17%) were brought back into care after they were traced.

The overall incidence of loss to follow up per month was 1% (95% CI 0.8 to 1.5). Being married and staying longer in a relationship were associated with lower risk of loss to follow up, respectively: HR 0.4 (95% CI 0.18 to 0.88), $p=0.023$, and HR 0.43 (95% CI 0.22 and 0.84), $p=0.01$.

Although being unmarried and in a newer relationship were associated with loss to follow up the investigators added that this is not exhaustive. It is important to identify women undergoing socio-economic as well as treatment related risk factors to ensure that women are maintained in care and ART during pregnancy and beyond.

High rates of unintended pregnancy and low rates of contraception

Like many African countries that adopted Option B+ by 2015, Malawi has high fertility rates and infrequent use of contraception. An analysis of pregnancy intentions of women enrolled in the programme revealed extremely high rates of unintended pregnancies and low rates of contraceptive use. [7]

This prospective study included the 299 newly diagnosed, ART naive pregnant women in the cohort described above and 427 who had been receiving ART for six months or more.

The newly diagnosed women were: younger than those already receiving ART (26 vs 31 years); had been in a relationship for shorter time (5 vs 7.6 years); were less likely to have an HIV positive partner (11 vs 59%); and had fewer living children (1.8 vs 2.3), all $p<0.05$. Newly diagnosed women also had shorter travel time to the clinic. Similar proportions were married (88 vs 92%) and reported physical or verbal abuse (17 vs 15%).

The majority of participants reported having and unintended pregnancy: 55 vs 76%, newly diagnosed and receiving ART

respectively. Only 6 vs 14% in the respective groups reported using contraception. Of those with an unintended pregnancy 7 vs 18% (12/164 vs 59/325) reported using contraception.

Multivariate analysis showed no significant difference between newly diagnosed women and those receiving ART in the rates of: mistimed pregnancy (OR 1.32); unwanted pregnancy (OR 2.27); contraceptive use (OR 1.44); and unintended pregnancy with contraceptive use (OR 1.76).

Overall 76% of women in the programme reported an unintended pregnancy and only 18% used any contraceptive method. "This highlights the missed opportunity to engage these women in family planning and suggests shortfalls in the integration of ART and family planning under Option B+ in Malawi", the investigators wrote.

Lower viral load suppression at delivery with longer duration of ART

Unsurprisingly women in the cohort with longer duration of ART during pregnancy had lower risk of unsuppressed viral load at delivery. [8]

Women are frequently diagnosed with HIV and start ART late in pregnancy but it is unclear whether they achieve viral suppression and how this varies with time on ART in Malawi. Investigators from the Bwaila district hospital study also looked prospectively at the association between time on ART and viral load (≥ 1000 and ≥ 40 copies/mL) at delivery in the newly diagnosed women.

For the 299 participants enrolled, the median gestation age at first antenatal visit was 22.1 weeks (IQR 18.1–26.3). The median duration of ART before delivery was 17 weeks (IQR 13–21). Of 253 (84.3%) with viral load measurements at delivery, 40 (15.9%) and 78 (31%) had ≥ 1000 and ≥ 40 copies/mL respectively.

Compared with women who had received ART for 12 weeks or less at the time of delivery, women who received ART for 13–20 weeks, RR 0.52 (95% CI 0.36 to 0.74), or 21–35 weeks, RR 0.26 (95% CI 0.14–0.48) were less likely to have viral load ≥ 40 copies/mL.

Hepatotoxicity rate does not support routine laboratory monitoring

An analysis of hepatotoxicity risk does not support routine laboratory monitoring pregnant women receiving EFV-based ART. [9]

Pregnant women start ART with TDF/3TC/EFV without routine liver enzyme monitoring. Previous studies have shown conflicting results risk for hepatotoxicity in pregnant women on EFV-based regimens.

This study was also conducted at Bwaila Hospital, in the cohort of 299 women.

The investigators evaluated laboratory values from the first 6 months on ART (enrollment, months 3 and 6) for DAIDS Grade 1 or higher alanine aminotransferase (ALT, ≥ 50 IU/L) (Fisher's exact tests)

Prevalence of elevated ALT at baseline was 0.3%, 0.4% at month 3, and 7.2% at month 6. The 6-month incidence of elevated ALT was 7.9%. Only 3 women (1.1%) had DAIDS Grade 3 or 4 ALT levels. All 3 women were postpartum and not taking other hepatotoxic medications. Of these women, one remained on TDF/3TC/EFV with resolved ALT levels, one switched to a non-EFV regimen, and one died of fulminant hepatitis despite ART discontinuation.

This analysis found no significant association with low CD4 count ($p=0.62$) or WHO stages ≥ 2 ($p=0.28$, although twice as many women

developed elevated ALT compared with stage 1: 13.3 vs 6.7%) with the development of hepatotoxicity. Data on viral hepatitis co-infection status were not available.

The investigators suggested that symptom monitoring is likely reasonable under a public health approach.

High prevalence of syphilis

Another analysis from Bwaila Hospital reported worrying prevalence of syphilis among HIV positive pregnant women. [10]

This cross-sectional study aimed to estimate the prevalence of syphilis and describe risk factors in this population.

Women were screened for syphilis using point-of-care rapid Alere determine TP tests. All women who tested positive were treated on the same day with a single dose of benzathine penicillin by intramuscular injection. Women testing positive were also encouraged to send their partners for treatment.

Of 350 pregnant women enrolled, the mean age was 28.3 years and mean gestational age was 22 weeks; 89% were married; and 88% lived with the partner.

The prevalence of syphilis in these women was 6% (95% CI 3.9% to 9.0%). Relationship duration was shorter in women testing positive for syphilis but this was not statistically significant. No factors (level of education, parity, marital status, WHO staging, and partner characteristics for current pregnancy) were significantly associated with the prevalence of syphilis.

"Aggressive measures are urgently needed to strengthen universal syphilis screening and testing efforts at antenatal clinics to prevent mother to child transmission of syphilis" the investigators wrote.

High rate of antenatal depression

Nearly half of the women in an antenatal depression study self-reported a history of anxiety or depression. [11]

Women included in this baseline analysis ($n=729$) were starting ART for the first time or had been on ART for 6 months or more.

The investigators assessed depressive symptoms using the Edinburgh Postnatal Depression Scale (EPDS). In Malawi, a score of ≥ 6 has been shown to indicate probable major depression, and was considered a positive result.

The majority of women were currently married (90%), unemployed (62%), and had not intended their pregnancy (68%). Nine percent ($n=68$) of women screened positive for depression, and 46% ($n=328$) self-reported a history of depression or anxiety.

Women were more likely to screen positive for depression: who self-reported a history of depression or anxiety aOR 2.83 (95% CI 1.63 to 4.92); had ever experienced verbal intimate partner violence aOR 2.01 (95% CI 1.12 to 3.60); had not intended their current pregnancy aOR 1.97 (95% CI 1.02 to 3.80), or were unmarried aOR 2.14 (95% CI 1.07- 4.27).

Depressive symptoms affect a notable proportion of HIV positive women in antenatal care on ART in Malawi (9.5%), and nearly half of the women self-reported a history of depression or anxiety. Clinicians in clinics without routine depression screening should be watchful for antenatal depression among women with a history of depression or anxiety, intimate partner violence, unintended pregnancy, or are unmarried.

Education and having an HIV positive partner protective against ART failure

An analysis of treatment failure among women already receiving ART at first antenatal visit found an overall prevalence of 7%. [12] Having more education and having an HIV positive partner were protective against ART failure.

This study, again at Bwaila Hospital, included 434 women. The median age of the women was 30.8 years (IQR 26.9–34.2); 93% were married and 82% attended antenatal clinic in the second trimester.

The overall prevalence of ART failure was 7.1% (95% CI 5.1 to 10.0). Women with secondary or tertiary education had reduced odds of ART failure compared with women with none or primary education: OR 0.67 (95% CI 0.27 to 1.70). For women who knew their partners' HIV status, those with HIV positive partners also had reduced odds of ART failure compared with those with negative partners: OR 0.45 (95% CI 0.10 to 2.03).

The investigators suggested countries with limited resources for viral load screening at first antenatal clinic visit should develop mechanisms to identify women at risk of having developed ART failure to prompt switch to an alternative and effective regimen during pregnancy.

Saturday clinic feasible to improve retention in study

The addition of a Saturday clinic is a feasible way to reduce visit duration and accommodate retention in care. [13]

The Bwaila Hospital study enrollment did not meet its targets in the first year due to constraints including a shortage of clinic space and clinic overcrowding. The investigators hypothesised that adding a Saturday clinic would reduce overcrowding and visit duration during the week and would improve retention and enrollment.

This was an observational study of participant visit duration before and after Saturday clinic introduction and an anonymous Likert-type scale acceptability survey.

The investigators observed a total of 77 visits: 28 before and 49 after adding the Saturday clinic. They found the average time spent with a nurse during a follow-up visit went down from 78 minutes before to 57 minutes after the addition of the Saturday clinic, $p=0.0337$. But the average time spent with a clinician was not significantly affected, $p=0.270$.

The majority of women surveyed on both weekdays and Saturdays reported that time spent in clinic was acceptable. Six out of the 46 women surveyed said that Saturday was their preferred day. The effect of adding the Saturday clinic on retention is yet to be determined.

The addition of a Saturday clinic is a feasible way to reduce visit duration and accommodate retention. Subject surveys indicate this is an acceptable way to decrease crowding and improve subject satisfaction.

C O M M E N T

The 11th INTEREST Workshop included an abundance of data from the Malawi Option B+ programme. But some of these summaries are a bit sketchy as unfortunately not all the posters materialised at the meeting.

The observation that women with partners who have not disclosed their HIV status are more likely to transmit to their infants is

important. This is the first time that HIV status disclosure between partners has been documented to affect vertical transmission at national level.

The study looking at contraception also noted that in Malawi 33% of pregnancies are mistimed and 11% unwanted. And 39% discontinue their modern contraceptive within 12 months due to method-related concerns/side effects (26%) or desire to become pregnant (26%). It would be interesting to know if any of the women with unintended pregnancies on ART and using contraception were using hormonal implant methods and this could be linked to EFV. This study highlights a missed opportunity to engage women in ART programmes with family planning.

The study linking longer duration of ART with viral suppression at delivery came as no surprise. That under a third of women had viral load <40 copies/mL is likely to be improved with the introduction of dolutegravir and swifter viral decline.

References

All references are to the programme and abstracts of the 11th International workshop on treatment, pathogenesis and prevention work in resource-limited settings (INTEREST), 16–19 May 2017, Lilongwe, Malawi (published in *Reviews in Antiviral Therapy & Infectious Diseases* 2017_02).

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11. Harrington B et al. Prevalence and factors associated with antenatal depression among women enrolled in Option B+ PMTCT in Malawi. Poster abstract 33.
12. Chagomerana et al. Prevalence of antiretroviral therapy (ART) treatment failure among HIV-infected pregnant women at first antenatal care: PMTCT Option B+ in Malawi. Poster abstract 148.
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CONFERENCE REPORTS

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

13-16 February 2017, Seattle

Introduction

This year CROI was held in Seattle where more than 4000 researchers and health workers and a small number of community activists meet to work through more than 1000 studies will be presented at the meeting.

Conference materials are all posted online, including comprehensive webcasts of all oral presentations.

Abstracts are available in a searchable database and most posters are available in PDF format from the abstract page.

<http://www.croiconference.org>

The following final report from CROI 2017 is included in this issue.

- Impressive HIV pipeline at CROI 2017

Impressive HIV pipeline at CROI 2017

Simon Collins, HIV i-Base

CROI 2017 was notable for perhaps presenting the strongest collection of studies on the HIV treatment pipeline for years. And while current ART is safe and effective these studies showed ways it could become better still.

There are plenty of good aims for better drugs. Treatment could involve smaller pills, less frequent dosing, long-acting formulations (weekly, monthly, yearly), with lower doses, fewer side effects and drug interactions, stronger resistance profiles and they could be cheaper and more accessible.

CROI included research into new drugs in current classes: nukes, NNRTIs, PIs and integrase inhibitors – and compounds with new targets and mechanisms of action – including a capsid inhibitor and a range of different monoclonal antibodies. See Table 1.

The following brief summaries link to the abstracts, posters and webcasts from the meeting.

NRTIs/NtRTIs

NRTIs are the oldest class of drugs but are still the backbone of most ART combinations. Two new compounds in the pipeline are of particular interest.

EFdA (MK-8591)

EFdA is an NRTI now in development by Merck (development name MK-8591) that is notable for high potency (10 mg oral dose), long plasma half-life that allows once-weekly oral dosing, a slow-release removable implant that might only require annual dosing and ongoing studies looking at use for both treatment and prevention.

A poster at CROI 2017 reported that MK-8591 also had even better activity in vitro against HIV-2 compared to six HIV-1 isolates (including HIV-1 subtypes A, B, C and D and group O). This includes being fully active against NRTI mutations K65R and Q151M (although the M184V variant conferred 10-fold resistance). [1]

Another poster reported that EFdA reaches good drug levels in vaginal and rectal tissue - supporting further PrEP studies. [2]

GS-9131 - NRTI with activity against NRTI resistance

GS-9131 is a prodrug of GS-9148 about which early animal and in vitro drug resistance studies presented at CROI 2006. [3]

Other published studies highlight the potential for low risk of toxicity in animal studies and retains in vitro phenotypic sensitivity to broad NRTI resistance including mutations at K65R, L74V and M184V and multiple TAMs. [4]

The poster at CROI 2017 confirmed results from previously published studies into the activity against common NRTI mutations. [5]

The compound has good potency (EC₅₀ = 25-200 nM) with activity against HIV-1 subtypes A, B, C, D, E, F, group O and N (EC₅₀ 0.29-113 nM), also against HIV-2. Synergistic activity was reported for GS-9131 in combination with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TFV and TAF.

Currently, GS-9131 is not easy to synthesise and it will need to overcome manufacturing challenges to become easier and cheaper to make.

NNRTIs

Doravirine

Doravirine is a once-daily NNRTI from Merck that can be taken with or without food and few drug-interactions and that retains activity against common first generation NNRTI mutations (K103N, Y181C, G190A and E138K).

In a late breaker oral presentation at CROI 2017, doravirine was non-inferior to boosted darunavir in a phase 3 study, showing similar viral suppression and low rates of side effects at the 48-week primary endpoint. [6]

Last year at CROI, results from a phase 2b study reported non-inferiority compared to efavirenz. [7] A fixed dose combination of doravirine/TDF/3TC (using generic NRTIs) is already in phase 3 studies and a long-acting formulation is in development. [8, 9]

Two posters were also presented this year on (i) increased doravirine levels from a drug interaction with ritonavir [10] and (ii) on the ability to use doravirine in severe renal impairment (eGFR < 30 mL/min/1.73 m²) without dose adjustment [11].

Elsulfavirine, prodrug of VM-1500A

Elsulfavirine is an NNRTI being developed by Viriom for registration in low-income countries.

Results from 48-week were presented at CROI 2017 from a randomised, double-blind phase 2b study conducted in Russia in 120 treatment naive participants. Elsulfavirine 20 mg was compared to efavirenz 600 mg, each with tenofovir-DF/FTC background NRTIs. [12]

The elsulfavirine arm reported similar viral suppression to <50 copies/mL (81% vs 73%), including those with baseline viral load >100,000

Table 1: HIV pipeline from CROI 2017

Compound	Comment	Phase	CROI 2017 Refs
NRTIs			
EFdA (MK-8591)	Highly potent, low dose, active against NRTI resistance. Long half-life, potential as oral (weekly dose) and implant (annual implant for PrEP).	Phase 1	CROI 2017: Abs 435 and 440.
GS-9131 prodrug of GS-9141	Active against NRTI resistance. Synergy reported with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TFV and TAF. Will be coformulated with other Gilead drugs. Currently difficult to synthesise in bulk.	Pre-clinical	CROI 2017: Abs 436.
NNRTIs			
doravirine	Active against first generation NNRTI resistance. Non-inferior to efavirenz. Generic FDC with TDF/3TC in phase 3 studies.	Phase 3	CROI 2017: Abs 45LB. CROI 2016: Abs 470.
Elsulfavirine, prodrug of VM-1500A	Only being developed for use in low and middle income countries. Similar activity to efavirenz in phase 2 Russian study,	Phase 2	CROI 2017: Abs 452LB.
Integrase inhibitors			
dolutegravir	Already approved integrase inhibitor but now in a new two-drug coformulation with the NRTI rilpivirine.	FDC with RPV now submitted.	CROI 2017: Abs 44LB.
cabotegravir	Oral formulation integrase inhibitor.	Phase 2.	CROI 2017: Abs 442.
cabotegravir LA	Injection with very long half-life – detectable after more than one year following single injection. Research as both treatment and prevention.	Phase 3 (for both ART and PrEP)	CROI 2017: Abs 84 and 439.
bictegravir	Once-daily, unboosted, low-dose with completed phase 3 studies and coformulation as part of an FDC with FTC/TAF.	Submitted to FDA.	CROI 2017: Abs 41.
GS-9695 and GS-9822	Non-catalytic integrase inhibitors no longer being studied due to renal toxicity.	Stopped.	CROI 2017: Abs 434.
Protease inhibitors			
GS-PI1	New QD unboosted PI, high potency, long half-life, potential in FDC single table regimen (Gilead).	Pre-clinical	CROI 2017: Abs 433.
Capsid inhibitors			
GC-CA1	Early stage for new class with activity at multiple stages of viral lifecycle. Sub-cutaneous injection with monthly or less frequent dosing.	Pre-clinical	CROI 2017: Abs 38.
Monoclonal antibodies (mAbs)			
PRO 140 (CCR5 target)	Once-weekly (350 mg) sub-cutaneous injection with potential to maintain viral suppression for more than two years after stopping ART. Also, with ART against multiclass resistance.	Phase 3	CROI 2017: Abs 437.
ibalizumab (CD4 binding site)	Intravenous infusion (800 mg every two weeks) being studied in addition to optimised ART in single arm study in people with multiclass HIV drug resistance. Previously called TNX-355.	Phase 3	CROI 2017: Abs 438 and 449 LB.
VRC01 (CD4 binding site)	Intravenous infusion (40 mg/kg) being studied with ART for effect on reservoir and in cure research and as PrEP (2 large phase 3 studies are ongoing). Sub-cutaneous dosing of infants to prevent transmission at birth or from breastfeeding.	Ph 1 (infants), ph 2 (cure-related and adult PrEP)	CROI 2017: Abs 330 LB and 760.
UB-421	Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption.	Phase 2	CROI 2017: Abs 450LB.

copies/mL (78% vs 62%), with fewer CNS side effects (32% vs 62%).

A long-acting injectable formulation is being used in ongoing studies for treatment and PrEP and results will be presented at IAS 2017 in Paris this summer.

Protease inhibitors

GS-PI1

GS-PI1 is a once-daily unboosted protease inhibitor with high potency and a long half-life, and in vitro sensitivity against some second-generation PI resistance, in pre-clinical development by Gilead.

An oral presentation at CROI 2017 reported a high barrier to resistance both after in vitro passaging and against multiple resistance complexes from multiple PI-resistant clinical isolates, and pharmacokinetic data from rat and dog studies. [13]

Integrase inhibitors

Dolutegravir/rilpivirine dual therapy

Although already approved as an oral integrase inhibitor, results from the SWORD 1 and 2 studies were presented at CROI 2017 for use with oral rilpivirine as two-drug maintenance therapy. [14]

Based on these results coformulated fixed dose combination with the NNRTI rilpivirine has already been submitted to the US FDA for approval as a two-drug maintenance therapy. [15]

Cabotegravir

The original oral formulation of this integrase inhibitor was initially used for run-in phase for studies using long-acting injections. Similar to the dolutegravir study above, results were presented at CROI 2017 using oral cabotegravir together with oral rilpivirine as a two-drug maintenance therapy. [16]

This phase 2b study presented 144 week results on 243 patients who started therapy with triple therapy (dose ranging CAB or efavirenz, plus background TDF/FTC NRTIs, and who switched to oral CAB plus rilpivirine maintenance therapy at week 24 if viral load was undetectable.

Of 181 participants randomised to CAB, 160 began the dual maintenance phase and 138 entered a further open label phase at week 96.

Although virologic suppression was generally good and tolerability included no cabotegravir-related discontinuations for side effects, five patients developed resistance to one or both drug during the study.

During the maintenance and OL phases, 7 (4%) reported drug-related AEs \geq Grade 2. SAEs occurred in 15 (9%) CAB Pts (none drug related) and 4 (3%) withdrew due to AEs.

Cabotegravir-LA

Cabotegravir LA is a long-acting integrase inhibitor in late-stage phase 3 studies using two-monthly dose intramuscular injections both for HIV treatment and PrEP prevention.

The extremely long half-life (detectable pharmacokinetic tail more than year after a single injection) brings new concerns linked to stopping treatment both for use in ART and as PrEP

With ART, substituting a new drug is easy given treatment interruptions are now rare, but the risk of drug resistance developing in case of PrEP failure is more than a theoretical concern as this has been

reported with current oral PrEP when started in very early infection (ie before HIV can even be detected).

An animal study at CROI showed similar concerns are important for cabotegravir. Six monkeys were given cabotegravir shortly after being infected with SIV and 4/6 developed integrase resistance. The concern from integrase resistance is that it might limit the option of integrase inhibitor treatment in people who become positive. [17]

Although the current cabotegravir formulation is well tolerated in studies, it requires a relatively large volume (two injections) into muscle. Research into easier formulations that has absorption and HIV activity at lower doses was presented in a poster. [18]

Bictegravir

Bictegravir (formerly GS-9883) is a once-daily integrase inhibitor with a plasma half-life of 18 hours that has *in vitro* activity against many integrase-associated mutations. Bictegravir has high protein binding (99%) limiting penetration to CSF but does not require boosting or need to be taken with food.

Two oral presentations were presented at CROI 2017, most importantly results from a phase 2 study (also published in the Lancet) which showed non-inferior efficacy and tolerability compared to dolutegravir. [19, 20]

Drug interaction studies at the conference reported increased bictegravir AUC (61-74%) by CYP3A4 inhibitors (voriconazole and darunavir/c), with a greater increase (~4-fold) by potent dual inhibitors of UGT1A1 and CYP3A4 (atazanavir and atazanavir/c). Bictegravir AUC is reduced by 75% by rifampin, a potent CYP3A4/UGT1A1/P-gp inducer and by 38% with rifabutin. [21]

Phase 3 studies are completed using a fixed dose combination coformulated with FTC/TAF, with comparator drugs that include dolutegravir and darunavir in treatment-naïve studies and plus various switch studies for people already on treatment. This FDC uses an improved formulation of bictegravir that only requires a 50 mg dose.

On 12 June 2017, the FDC of BIC/FTC/TAF was submitted to the US FDA for approval. [22]

GS-9695 and GS-9822

GS-9695 is a non-catalytic integrase inhibitor (NCINI) that binds to a conserved pocket on the enzyme that is also targeted by LEDGF. The compound (previously developed by Boehringer Ingelheim as BI-224436) has potential for low dose, once-daily dosing, unboosted, with high barrier to drug resistance. A follow-on compound GS-9822 strengthened the resistance profile.

However, a poster at CROI 2017 reporting unpredictable kidney/urothelial toxicity in monkeys has led to discontinuation of development of this compound. [23]

Capsid inhibitors

GS-CA1

First data was presented on GS-CA1, the first compound in a new class of HIV capsid inhibitors, with a formulation that can be used for slow-release injections. [24]

Capsid is the cone-shaped structural core within the virion that protects HIV RNA and related enzymes. As part of a dynamic process, the capsid protein (p24) first breaks down to release viral contents into the CD4 cell to enable reverse transcription and also

needs to reassemble inside new virions as part of the maturation process the end of the lifecycle.

GS-CA1 acts both the early and late stages by binding at a site that blocks both disassembly and assembly leading to defective new virions that are non-infectious.

The compounds is potent with EC50 in target cells of 60 to 140 pM (compared to 1000 to 19000 for efavirenz, dolutegravir and atazanavir) with activity against drug resistance to current HIV classes. Although population sequencing showed the binding site to be highly conserved, capsid resistance can be generated from in vitro serial passaging.

The investigational compound is currently developed as a subcutaneous injection that in rat studies maintained plasma concentrations nine times above the protein adjusted EC95 ten weeks after a single injection. This suggests that monthly or longer dosing intervals in humans.

Monoclonal antibodies (mAb)

CROI 2017 included important new results for several broadly neutralising monoclonal antibodies (mAbs) given by infusion or injection, some of which have been the focus of research for many years. These compounds have potential to be used in very different settings, with use as treatment, as a cure strategy and as prevention.

This is a rapidly developing new class with multiple target sites and numerous compounds, with the expectation that combination mAb therapy will be required to prevent viral escape. [25]

PRO 140

PRO 140 is a humanised IgG4 antibody that blocks HIV entry by binding to CCR5 but which is active against maraviroc-resistant virus. PRO 140 has been in development for more than ten years, that paradoxically has designated “fast-track” status, with potential for activity against multiclass HIV drug resistance.

The current study used weekly dosing of 350 mg self-administered sub-cutaneous injections of PRO 140 monotherapy as a switch strategy in participants on stable oral ART with undetectable viral load, who interrupted ART. This was initially a 12-week study with a three-year extension follow-up for people who maintain viral suppression. [26]

Of 41 participants from the first phase, 16 joined the extension phase. Of these, 1/16 withdrew consent, 5/16 had subsequent viral rebound (two consecutive results >400 copies/mL) and 10/16 have maintained viral suppression with follow-up for longer than two years. Of these, 7/10 had undetectable viral load <1 copy/mL, with others at 4, 10 and 19 copies/mL.

No serious side effects or related discontinuations were reported, including low inject site reactions.

Ongoing phase 3 studies include (i) monotherapy switch study in 300 participants with viral suppression >48 weeks on ART, and (ii) in addition to ART as part of salvage combination in 30 participants with multidrug resistance to other classes.

Ibalizumab

Ibalizumab is another humanised IgG4 antibody in phase 3 studies that blocks HIV entry and that has been a potential HIV pipeline

compound for well-over ten years. Ibalizumab blocks the CD4 receptor and is active against both CCR5- and CXCR4-tropic HIV.

Two studies were presented at CROI 2017. One was a single-arm, 24-week, open label study in 40 extensively treatment-experienced participants adding ibalizumab (800 mg IV every two weeks) to background ART (optimised from day 14). [27, 28]

Mean baseline viral load was 5.0 log copies/mL with 18% > 5 log copies/mL. Mean CD4 was 150 cells/mm³ with 17 people <50 cells/mm³ and 10 people with CD4 between 50 to 200 cells/mm³. More than half the participants had resistance to three classes, one-third to four classes and 40% used another investigational drug (the gp-120 attachment inhibitor fostemsavir).

One week (at day 7) after the initial loading dose (2000 mg IV) added to current failing therapy, viral load dropped by > 0.5 log copies/mL in 83% of participants and > 1.0 log in 60%.

At week 24, mean viral load decrease from baseline was -1.6 log copies/mL, with 55% and 48% having reductions >1 log and >2 log respectively. Viral load was undetectable (<50 copies/mL) in 43% of participants. Baseline CD4 > 50 cells/mm³ was associated with greater viral load reductions.

There were 9/40 discontinuations, mostly (8/9) in patents with lowest CD4 (<50 cells/mm³). This included 4 deaths (liver failure, KS, end-stage AIDS and lymphoma), all in the low CD4 group. Three people withdrew consent and two were lost to follow-up.

Side effects (n=17) were mostly mild or moderate, but included one case of IRIS.

The second study was a phase 1/2 pharmacokinetic study using an 800 mg intramuscular formulation of ibalizumab in eight HIV positive people not on ART.

Mean viral load and CD4 count at baseline was 55,000 copies/mL and 314 cells/mm³ respectively.

After the initial 3-day peak, drug levels were comparable to historical data using the IV formulation.

However, maximum viral load reductions (~1.2 log copies/mL) occurred by day 7, subsequently returning to baseline (likely due to resistance) compared to reductions of ~2 log/copies/mL at day 14 with the 2000 mg loading dose with the infusion formulation that was sustained for 24 weeks.

Tolerability was improved using the IM formulation.

VRC01

VRC01 is another broadly neutralising mAb that targets the CD4 binding site that can be given by infusion or sub-cutaneous injection and that is being studied for multiple potential uses.

One study at CROI reported no additional impact on reducing the latently infected viral reservoir from adding VRC01 to ART. [29] Other roles in cure research is ongoing [30].

Another study reported tentatively positive safety results from using a single injection in infants after birth to limit risk of mother-to-child transmission with a potential role of additional injections when breastfeeding is a risk. [31]

Two other large international dose-finding, placebo-controlled phase 2 VRC01 PrEP studies are already ongoing that allow the option for participants to also use open-label oral TDF/FTC PrEP. [32, 33]

UB-421

UB-421 is a third mAb that targets CD4 binding that had data presented at CROI 2017 from a phase 2 study in 29 virally suppressed participants on ART who used UB-421 monotherapy during an 8-week treatment interruption. [34]

UB-421 was given by infusion either 10 mg/kg weekly or 25 mg/kg every two-weeks. Although there were no cases of viral rebound during the monotherapy phase, viral load did rebound at 35 to 62 days after the last UB-421 dose in five participants who delayed restarting ART.

All five later restarted ART and viral load became undetectable.

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Paediatric HIV: CROI 2017

Polly Clayden, HIV i-Base

A number of presentations at CROI 2017 showed data on early HIV treatment and diagnostics in young children.

Treatment of acute infection in neonates

Just over 30% of infants achieved undetectable viral load and 10% became PCR negative after very early initiation of treatment in South African study. [1]

ART in primary infection may reduce the size of the viral reservoir and allow viral control off treatment. Infants can be identified soon after infection.

The LEOPARD study tracks the response to ART in neonates started on ART in early infection at Rahima Moosa Mother and Child Hospital in Johannesburg.

Of 30 neonates who started ART within 48 hours of birth with six months or to one year follow up, over half (57%) were male and mean birth weight was 3015 grams. All infants received nevirapine (NVP), lamivudine (3TC) and zidovudine (AZT) with substitution of lopinavir/ritonavir (LPV/r) for nevirapine at median of 27 days (IQR 18 to 32) later.

Approximately 25% of mothers had received no treatment before delivery and 25% <12 weeks of ART; the remainder were already

on ART or had received >12 weeks of treatment. Median infant viral load before ART was 30,000 copies/mL (range 60 to >2 million).

Viral load was measured at frequent intervals lower detection limit of 20 copies/mL and qualitative HIV diagnostic PCR tests were repeated.

Three of the 30 infants died at 43, 61 and 89 days respectively; all were male. Only one was low birth weight but all three had high baseline viral load.

There was wide variability in virological response among the remaining infants – from those who did not achieve undetectable viral load to three who became PCR negative. More than a third achieved and sustained undetectable viral load. The children remain in follow up.

Rapid decline of HIV DNA in infants starting very early ART

Infants receiving early ART experience very rapid early phase HIV and DNA decay according to a related study conducted at Stellenbosch University, South Africa. [2]

The study was designed to investigate total HIV DNA kinetics in infants who started ART as soon as possible after birth.

Eleven infants diagnosed through a public health sector birth diagnosis programme started ART 0 and 8 days after birth (median 3 days). Infants started ART with AZT/3TC/NVP, with NVP replaced by LPV/r after two weeks of age and AZT replaced by abacavir at three months of age.

Peripheral blood mononuclear cells (PBMCs) and plasma were processed at three monthly visits. Total DNA was measured with a sensitive quantitative PCR assay and RNA was also quantified.

Median baseline viral load was 4.0 (range 2.4 to 4.7) log₁₀ copies/mL. Five infants were included in the kinetic study.

In three infants RNA declined to <100 copies/mL within 3.3 months. In the other two this occurred within 6.3 and 6.7 months. DNA decay was in two phases, very fast in the first two weeks, then relatively slow but progressive.

DNA decay in three infants with <100 copies/mL before 3.3 months, phase 1: conditional R² 0.97 (95% CI: 0.90 to 1.00); median decay -2.3 log₁₀ copies/month (range -2.1 to -2.7); 200 fold/month (range 122 to 545). Half-life 4 days (range 3.4 to 4.4).

Phase 2 in five infants: conditional R² 0.97 (95% CI: 0.90 to 1.00); median decay -0.15 log₁₀ copies/month (range -0.13 to -0.2); 65 fold/year (range 33 to 222). Half-life 60.7 days (range 46.9 to 72.4).

The first phase was much faster than that reported in adults. The investigators noted that it was a conservative estimate as baseline DNA could be even higher as they divided by total cells in dried blood spots and only about 50% were lymphocytes. Second phase decay is much faster than in infants starting ART at two months.

Very rapid early phase HIV RNA and DNA decay poses a diagnostic challenge in infants receiving ARV prophylaxis or presumptive ART before definitive diagnosis.

Lack of evidence of ongoing HIV replication after eight years on ART

Children started on continuous ART in the CHER trial showed no sign of viral evolution after 7 to 8 years of treatment. [3]

In this study the investigators performed single-genome sequencing of the p6-PR-RT region of the HIV genome on plasma RNA before ART or PBMC DNA shortly after starting ART and on PBMC DNA approximately eight years after starting treatment. They compared HIV populations phylogenetically to look for emerging new variants. They also tested for panmixia to see if populations shifted over time. And they measured diversity of populations to see if there is accumulation over time.

Ten children were included: eight who started ART at less than 12 months and were fully suppressed on ART for 7 to 8 years and two replication controls who had viraemia for 1 to 3 years before or during ART.

The two controls showed clear evidence of HIV evolution. Data on one control with 1.3 years with detectable viral load out of 6.9 years on ART showed increased viral diversity (baseline 0.1%, long term 0.6%), a significant virus population shift by panmixia ($p < 10^{-4}$), and longer branches in ML trees.

The eight children with fully suppressed virus did diverge from founder virus. Data on one case who started ART at 1.8 years and remained on treatment for 8.1 years showed populations that were virtually identical, no panmixia shift ($p = 0.3$) and no significant increase in viral diversity (baseline 0.04%, long term 0.1%). Results were similar among the eight children with suppressed virus.

"These data from early ART-treated children strongly refute the concepts that ongoing HIV replication is common on current ART regimens and that it replenishes the HIV reservoir", the investigators wrote.

Nevirapine dosing regimen achieved target concentrations in HIV-exposed low birth weight infants

Data from IMPAACT P1106 showed nevirapine (NVP) dosed at 2 mg/kg once daily (birth to 14 days old) followed by 4 mg/kg daily achieved trough concentrations above the 0.1 ug/mL prophylaxis target in low birth weight infants <2500 g. [4]

IMPAACT P1106 is a Phase 4 study on PK and safety in low birth weight infants receiving antiretroviral and tuberculosis medicines as part of their clinical care in two South African sites.

Arm 1 looked at NVP HIV prophylaxis. Infants were stratified by birth weight: <1400 g (n=12), 1400 to <1800 g (n=12), and 1800 to <2500 g (n=16). PK samples and safety data were collected at study entry (day 7 to 14) and at 4, 6, 10, 16 and 24 weeks of age.

The study enrolled 40 low birth weight infants with mean birth weight of 1675 g (range 950 to 2460 g) and mean gestational age of 33 weeks (range 28 to 40).

There were 94 NVP trough concentrations available from 27 infants with mean weight of 2147 g (range 965 to 6050 g) and mean postmenstrual age of 37 weeks (range 29 to 56 weeks) at time of sampling.

The mean NVP trough concentration was: 1.87 ug/mL (range < 0.02 to 10.69); 6/94 (6%) < 0.1 ug/mL. Below target samples were all from later visits (median postmenstrual age 44 weeks; median weight of 3903 grams) when at home receiving NVP from caregiver.

At first visit, lower gestational age was associated with higher NVP concentration normalised for dose: $r = -0.47$, $p = 0.02$. Across all visits, NVP trough concentrations were inversely related to infant

postnatal age: $r = -0.45$, $p < 0.001$).

Three infants died: two from sudden unexpected death and one from confirmed sepsis. Nine infants had Grade 3/4 expected AEs (common in premature infants), most frequent presumed or confirmed sepsis (n=6). Ten infants had Grade 3/4 unexpected AEs, most common being pneumonia (n=4). All AEs were unrelated to nevirapine.

Lopinavir/ritonavir super-boosting overcomes rifampicin interactions in children

Super-boosting LPV/r for a 1:1 ratio was safe and effective and overcomes rifampicin interaction for TB/HIV co-treated children in a South African study. [5]

This was an open-label, prospective, non-inferiority study evaluating super-boosted LPV/r (1:1) during rifampicin co-treatment compared with LPV/r (4:1) after stopping TB treatment in children weighing 3 to 15 kg.

Eighty of 96 enrolled children completed the study; 30% were <12 months at enrolment and seven completed the study before 12 months of age. TB treatment was started before ART in 73% children.

The percentage of modelled C_{min} levels below target (<1 mg/L) was 7.6% (95% CI 0.4% to 16.2%) for super-boosting during rifampicin co-treatment, vs 8.8% (95%CI: 0.6% to 19.8%) without rifampicin. The median difference was -1.1% (95%CI: -6.9% to 3.2%), confirming the non-inferiority (10% threshold) of LPV exposure during super-boosting with rifampicin to standard LPV/r without rifampicin.

Lopinavir/ritonavir started at seven days of life impairs infant growth

The ANRS 12174 trial comparing LPV/r vs 3TC in HIV exposed uninfected children showed LPV/r started at seven days was associated with lower weight gain. [6]

In the trial, conducted in Burkina Faso, South Africa, Uganda and Zambia, 1273 HIV uninfected, breastfed children born to HIV positive mothers were randomised at seven days to either 3TC or LPV/r until the end of breastfeeding (maximum 50 weeks) as pre-exposure prophylaxis.

Infants were weighed and measured monthly and their z-scores calculated and compared. The analysis included 1266 children, with 14537 visits.

There was no difference in the height for age z-score between arms. But the weight for age score was lower in the LPV/r arm than in the 3TC arm: difference of means -0.22 (95% CI -0.34 to -0.09) $p < 0.01$, at 26 weeks, and of -0.25 (95% CI -0.46 to -0.03), $p = 0.02$, at 50 weeks.

The impact of LPV/r was greater for girls and, and in Burkina Faso and Uganda than in Zambia and South Africa.

The investigators will continue to follow up the children and look at whether or not this effect persists at five years old.

Targeted HIV screening at birth can identify most in utero transmissions

In utero transmission only occurred among infants identified as high risk in Botswana – using information available from the mother or her obstetric record at the time of delivery. [7] Targeting high risk infants will identify the large majority of in utero HIV transmissions

Botswana tests for in utero and intrapartum vertical transmission by infant HIV PCR at six weeks. The Early Infant Treatment Study was conducted to identify HIV infected infants at birth and offer immediate ART. Abstract eBook

Mothers were assessed for risk factors, which included: <8 weeks ART in pregnancy, last CD4 known <250 cells/mm³, last viral load >400 copies/mL, poor ART adherence in pregnancy, lack of maternal AZT in labour, and lack of infant post-exposure prophylaxis. Infants received heel stick and dried blood spots were collected for testing by PCR.

In the first year of the study, 4086 HIV exposed infants were delivered, 3541 (87%) had not been discharged, 2580 (63%) were eligible, and 2303 (56%) agreed to be screened for HIV.

Of those screened, 369 (16%) were identified as high risk for HIV. Twelve (0.5%) of the 2303 infants were identified as HIV positive at birth.

All 12 positive infants were identified as high risk at the time of screening, and all were identifiable as high risk by either: <8 weeks of maternal ART in pregnancy (9/157) or lack of maternal HIV suppression at last viral load test (3/6).

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TREATMENT ACCESS

WHO adds dolutegravir and PrEP to updated Essential Medicine List

Polly Clayden, HIV i-Base

Dolutegravir for treatment of HIV and PrEP with tenofovir alone, or in combination with FTC or 3TC are among the additions to the updated version of the World Health Organisation (WHO) Model list of essential medicines – according to a press release 6 June 2017.

The WHO Essential Medicines List (EML) is used by many countries to help increase access to medicines and guide decisions on which ones should be made available to their populations. Launched in 1977, the EML is updated every two years.

The updated EML has added 30 drugs for adults and 25 for children, giving a total of 433 considered essential to public health.

This version includes “the biggest revision of the antibiotics section in the EML’s 40-year history”, in which WHO experts have grouped antibiotics into three categories: access, watch and reserve.

As well as dolutegravir and PrEP for HIV, other new additions include drugs for hepatitis C and TB. Co-formulated sofosbuvir + velpatasvir is included, which is the first combination therapy to treat all six types of hepatitis C. And newly added TB medicines are: delamanid for children and adolescents with MDR-TB; clofazimine for children and adults with MDR-TB; and paediatric fixed-dose combination formulations of isoniazid, rifampicin, ethambutol and pyrazinamide.

C O M M E N T

Andrew Hill and his group have now estimated the real costs of the entire EML using the same methodology they first applied to HIV drugs and then extended to hepatitis, TB and cancer.

These costings will be released in the near future and there are many lessons to be learned from HIV access and pricing campaigns that could be applied to other essential medicines for low- and middle-income countries.

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WHO press release. WHO updates Essential Medicines List with new advice on use of antibiotics, and adds medicines for hepatitis C, HIV, tuberculosis and cancer. 6 June 2017. Geneva.

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ANTIRETROVIRALS

Dolutegravir/rilpivirine submitted to EMA and FDA as oral two-drug maintenance combination

Simon Collins, HIV i-Base

On 1 June 2017, ViiV Healthcare submitted a new drug application to the US FDA for the two-drug oral combination of cabotegravir and rilpivirine.

This is unusual in several respects: for combining only two drugs (rather than three or more) with an indication of maintenance treatment (ie as a switch rather than first-line combination)

The submissions are based on the SWORD 1 and 2 studies that were presented at the 2017 Conference on Retroviruses and Opportunistic Infections in February.

The US submission uses a priority review voucher to get an expedited review, usually within six months. Vouchers are commercially traded between companies with this one costing US\$130 million.

As separate drugs, dolutegravir is marketed as Tivicay by ViiV Healthcare and rilpivirine is marketed as Edurant by Janssen Sciences.

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ViiV Healthcare press statement. ViiV Healthcare submits regulatory applications for the first HIV maintenance regimen comprising only two medicines. (01 June 2017).

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Bictegravir/FTC/TAF: new once-daily integrase-based FDC submitted to US FDA

Simon Collins, HIV i-Base

On 12 June 2017, Gilead Sciences submitted a new drug application to the US FDA for a single tablet fixed-dose combination (FDC) of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF).

Bictegravir (formerly GS-9883) is a potent once-daily integrase inhibitor, with mean plasma concentration more than 20 x above the IC95 at 24 hours and low inpatient differences. It is used at low milligram dose (50 mg) leading to a small pill with TAF. Bictegravir has a plasma half-life of 18 hours, doesn't need PK boosting and can be taken with or without food.

Potential drug interactions that affect bictegravir are likely to be dependent of inhibition or induction of both CYP3A4 and UGT1-A1 with little expected effect of bictegravir on other drugs.

The application is based on non-inferiority results from four phase 3 studies. These include a treatment naive study compared to dolutegravir and several switch studies in people with viral suppression on current treatment.

A similar submission to the European Medicines Agency (EMA) is planned for 3Q 2017.

Source: Gilead press statement. Gilead submits new drug application to U.S. food and drug administration for fixed-dose combination of bictegravir, emtricitabine and tenofovir alafenamide for HIV treatment. (12 June 2017).

<http://www.gilead.com/news/press-releases>

FDA updates cobicistat and Stribild labels: interactions with systemic, inhaled, nasal and ophthalmic corticosteroids

Simon Collins, HIV i-Base

On 5 May 2017, the FDA updated labels for cobicistat and Stribild with information about interactions with most (but not all) corticosteroids.

The direction of the interactions is for ARV levels to be reduced for cobicistat, elvitegravir, atazanavir and darunavir. At the same time, corticosteroid levels have the potential to be increased.

The corticosteroids with this potential for interactions include betamethasone, budesonide, ciclesonide, dexamethasone, fluticasone, methylprednisolone, mometasone, prednisone and triamcinolone.

However, no clinically significant interactions have been observed with either beclomethasone or prednisolone.

The labels note:

- Coadministration with oral dexamethasone or other systemic corticosteroids that induce CYP3A may result in loss of therapeutic effect and development of resistance to elvitegravir, atazanavir or darunavir. Consider alternative corticosteroids.
- Coadministration with corticosteroids whose exposures are significantly increased by strong CYP3A inhibitors can increase the risk for Cushing's syndrome and adrenal suppression.
- Alternative corticosteroids including beclomethasone and prednisolone (whose PK and/or PD are less affected by strong CYP3A inhibitors relative to other studied steroids) should be considered, particularly for long-term use.

Source

FDA HIV email update. TRIBILD and TYBOST labels have been updated. (5 May 2017)

The US labels will be updated labels will soon be available drugs@fda or DailyMed.

<https://www.accessdata.fda.gov/scripts/cder/daf>

<https://dailymed.nlm.nih.gov/dailymed/index.cfm>

COMPLICATIONS & SIDE EFFECTS

Increased prevalence of diabetes in HIV positive people

Gareth Hardy, HIV i-Base

Diabetes Mellitus (DM) occurs at an increased frequency in people with HIV infection and may develop at earlier stages than it does in the general population.

As antiretroviral therapy (ART) enables people with HIV to live longer, there has remained some controversy about whether or not the risk of diabetes is increased in HIV infection. [1]

Alfonso Hernandez-Romieu and colleagues at Emory University, Atlanta, Georgia, compared the frequency of diabetes mellitus in two large nationally representative health surveys, one for people with HIV and the other for the general population. They then examined the relationships between DM and other factors within and between these two groups. [2]

The Medical Monitoring Project contains data on 8,610 HIV positive people collected between 2009 and 2010. The National Health and Nutrition Examination Survey contains data on 5,604 adults in the general population. Logistic regression models were fitted to the data to determine the weighted prevalence of DM.

Using these models the researchers aimed to:

1. Estimate the frequency of DM in this representative sample of HIV positive people;
2. Compare the frequency of DM between HIV positive people and HIV uninfected people;
3. Determine other factors that are associated with DM in HIV positive people.

Data was collected on socio-economic variables: age, sex, race/ethnicity, education, poverty level, as well as clinical variables: body mass index (BMI), time since HIV diagnosis, CD4 count, viral load, use of ART and HCV infection. The analysis did not include pregnant women and was restricted to adults over 20 years old and participants diagnosed with DM, defined as:

- Being told by a doctor that they had diabetes.
- Taking insulin.
- Taking diabetic medication to lower blood sugar (patients taking metformin monotherapy, who were not diagnosed with diabetes were excluded, as metformin can be used to treat pre-diabetes and other conditions).

The weighted prevalence of DM was calculated for HIV positive people and for each of the additional socio-economic and clinical factors. Multivariate logistic regression models were used to determine the relationships between DM and these additional factors.

The unadjusted frequency of DM in HIV positive people was 10.3% (CI 9.1-11.5%). This is higher than the US general population in which the frequency of DM was 8.3% (CI 7.2% - 9.4%). Among the HIV positive participants with DM, 3.9% (CI 2.9% - 5.2%) had type-1 diabetes, 52.3% (CI 46.7% - 57.8%) had type-2 diabetes and 43.9% (CI 38.1% - 49.8%) had unspecified diabetes.

Following an adjustment of the data for differences in the socio-economic variables, obesity and HCV infection, the adjusted prevalence difference in DM between HIV positive people and the general population was 3.8%. The largest difference in the frequency of DM in HIV positive people compared to the general population was in those with HCV infection (6.3%), those with high school or equivalent education (5.1%), women (5%), non-Hispanic whites (4.9%), those at or below the poverty line (4.6%), those with obesity (4.4%), and those aged 20-44 years (4.1%).

For people with HIV, the increase in adjusted prevalence of DM was lowest (6.7%) in younger people aged 20-44 years, whereas it was highest for those aged over 60 years (19.6%) and for those with obesity (18.9%). In HIV positive people without obesity the adjusted prevalence of DM was still increased at 7.9%. In addition, time since HIV diagnosis and geometric mean CD4 count were independently associated with DM in people with HIV. Interestingly, nadir CD4 count was not associated with increased prevalence of DM, in contrast to other studies. [3]

In conclusion, in this nationally representative US sample of HIV positive people, the frequency of diabetes was higher than the general population, and was independently associated with increasing age, obesity, longer time since HIV infection and CD4 count. After adjusting for other factors DM was 3.8% higher than in the general population. The data in this study suggests that HIV positive adults are at a higher risk of diabetes at a younger age and in the absence of obesity.

The researchers suggested that their results have important implications for care providers:

- Existing DM screening guidelines should be followed before and after starting ART.
- An examination of data from other prospective studies should be conducted to determine if screening guidelines need to be modified, as DM occurs at increased frequency in younger and non-obese HIV positive people.
- Improved tests for DM diagnosis and monitoring should be investigated in HIV positive people.
- Further research is required to establish optimal DM management approaches in HIV positive people.

COMMENT

There might be some different factors for US compared to European studies, but the conclusion to increase awareness of risk and to follow diabetes guidelines is important in all countries.

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Poppers and cancer risk in HIV negative and HIV positive gay men

Gareth Hardy, HIV i-Base

Previous research has shown that use of poppers may be associated with transient immunosuppression in animal models and may facilitate infection with cancer-causing viruses such as human herpes virus-8 (HHV-8), which causes Kaposi's Sarcoma (KS).

A new report from the prospective observational Multicentre AIDS Cohort Study (MACS) suggests that heavy use of poppers might be associated with increased risk of individual virus-associated cancers. This link was observed in HIV negative men but not in men who were HIV positive. Heavy use was defined as daily or weekly for at least a year. The study was reported by Anupriya Dutta and colleagues from the Dana-Farber Cancer Institute in Boston, Massachusetts. [1]

Increasing numbers of HIV positive people live into older age, with increased risk of many cancers, especially those associated with viruses such as HHV-8, human papilloma virus (HPV), Epstein Barr Virus (EBV), and hepatitis B and C viruses (HBV and HCV).

Previous studies of cancer risk in HIV positive MSM have tended to examine cohorts of mixed sexual orientation, which means that risk factors specific to MSM may be overlooked, such as sexual transmission of cancer-associated viruses like HHV-8 or HPV. There is a higher frequency of cancers in HIV positive MSM that are caused by sexually transmitted viruses [2] and it is not known whether recreational drug use contributes to this by increasing rates of high risk sex [3] or for other reasons.

One concern is that unlike most recreational drugs, poppers are thought to cause transient immuno-suppression [4] and so they may facilitate sexual transmission of cancer-associated viruses. Dutta and colleagues investigated the association between popper use and cancer risk in HIV positive and negative MSM.

Participants from MACS attended semi-annual clinic visits at which behavioral, clinical and laboratory data were obtained. Out of a total 6972 participants, 3223 were eligible (1660 HIV negative and 1563 HIV positive). Popper use was self-reported and usage level was defined as:

- Heavy (daily or weekly use for at least 1 year).
- Light (monthly or less).
- Non-use, comprising the control group.

Data was also collected on cancer occurrence per 100,000 person years, viral load, CD4 count, CD4/CD8 ratio and ART use, which was stratified according to whether participants started ART early (1996 to 2000) or late (2001 to 2010). Poisson regression models were generated and adjusted for age, race, and ART calendar period and models restricted to HIV positive MSM were also adjusted for CD4 count and viral load.

Heavy popper users (20.3% HIV negative and 33% HIV positive) reported more sexual partners, more sexually transmitted infections (syphilis and genital warts) and more poly-drug use compared to non-popper use controls. There were no differences in CD4 count, CD4:CD8 ratio or viral load between heavy popper users and non-use controls.

Within the 3223 participants, there were 327 incidents of cancer among 296 participants. Single cancers occurred in 269 participants, two different cancers occurred in 24 participants and three cancers occurred in three participants.

The crude incidence of many cancers was higher in heavy popper users than controls, in both HIV positive and HIV negative MSM. These cancers included Non-Hodgkins Lymphoma (NHL), squamous cell carcinoma of the skin, prostate cancer and others. The incidence rate of anal cancer was higher among heavy popper users only in the HIV negative participants. Conversely, melanoma was higher among heavy poppers users only in the HIV positive participants. As expected there was a much higher incidence of cancers in HIV positive participants, independently of popper use.

Importantly, the significant association between heavy popper use and risk (incidence rate ratio/IRR) of NHL (IRR 1.98%; 95% CI: 1.1 to 3.57) or squamous cell carcinoma of the skin (IRR 1.54; 95%CI: 0.9 to 2.63), was only apparent in unadjusted models. In adjusted models, heavy popper use was not associated with risk of any cancers.

When the researchers looked at just HIV positive MSM in adjusted models, there was no association between heavy popper use and incidence of virus-associated cancers, including KS, anal cancer or squamous cell carcinoma of the skin.

An association between heavy popper use and cancer risk in HIV negative MSM alone was harder to determine as the incidence of cancers in this group was much lower. In order to gain sufficient numbers to power this assessment the researchers created a composite group of individual cancers, which consisted of KS, NHL, Hodgkin's lymphoma and anal cancer. In HIV negative MSM, heavy popper use was significantly associated with risk of composite virus associated cancers among older men aged 50 to 70 years old in adjusted models (IRR 3.04; 95%CI: 1.01 to 9.12).

Furthermore, using a continuous variable of cumulative popper exposure in adjusted models, increasing cumulative exposure to poppers was significantly associated with increased risk of virus associated cancers among older HIV negative MSM (IRR 1.012 [1.003 – 1.022]) per day of use, per year over the first five years of study enrollment.

This research provides evidence that heavy use of poppers (daily or weekly for at least 1 year), is significantly associated with the risk of virus-related cancers in MSM who are HIV negative and this risk becomes greater over the age of 50.

The researchers speculate that the most likely reason why there was no apparent effect of popper use on cancer risk in HIV positive MSM is because the immunodeficiency induced by HIV is far more profound than any immunosuppressive effect of poppers.

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Case report of capsulitis with elvitegravir and cobicistat (EVG/c)

Roy Trevelion, HIV i-Base

Although capsulitis was associated with early protease inhibitors (predominantly indinavir) a recent case report now links this to the integrase inhibitor elvitegravir/c (EVG/c).

Capsulitis is a painful joint condition that is marked by increasing limitation of joint movement. It affects large joints such as the shoulders and hips. If the shoulder is affected it is called frozen shoulder.

The 56-year-old man was initially admitted to hospital in May 2015 for pain in the right hip that had worsened over the previous six weeks. Although diagnosed with HIV in 1998, the report refers to starting first-line ART with amprenavir/r + TDF/FTC which must have been several years later. He switched to single tablet EVG/c/TDF/FTC in November 2014 to reduce pill count.

In April 2015 the pain worsened steadily, resulting in significant loss of mobility. Flexion movement was limited to 80% and internal rotation was 15% and MRI imaging confirmed the clinical diagnosis of capsulitis of the right hip. The patient was treated with three infusions of pamidronate 60mg (days 1, 2 and 30) and paracetamol with opioid analgesics. He was transferred to rehabilitation, made steady progress, and was able to walk unaided in November 2015.

However, from August, bilateral shoulder pain developed, with limited of movement (0% internal rotation and 70% abduction) consistent with MRI confirming worsening bilateral shoulder capsulitis.

The patient was treated with injected corticosteroid and paracetamol and nefopam to reduce inflammation and pain. ART was switched back to the original amprenavir combination. There was a rapid reduction in pain and the patient gradually regained function and range of movement. He had no further joint problems. The timing of symptoms in relation to starting treatment and lack of other factors make this treatment the most likely cause.

The authors report this as the first case of capsulitis caused by EVG/c, FTC, TDF. HIV itself is not considered a predisposing factor.

They concluded that elvitegravir and cobicistat be considered amongst the possible causes of capsulitis. Further studies are needed, but this is supported but onset after switch and rapid improvement in symptoms after discontinuation. Previously, capsulitis has been linked to indinavir (26 patients) and nelfinavir (1 patient). This is the first case linking capsulitis and elvitegravir and/or cobicistat and the first linked to an integrase inhibitor.

Ref: Al Tabaa O et al. Right hip and bilateral shoulder capsulitis in an HIV-infected individual treated with elvitegravir and cobicistat. *AIDS*. 15 May 2017 - Volume 31 - Issue 8 - p 1195-1196 doi: 10.1097/QAD.0000000000001420.

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CURE RESEARCH

Natural history of elite controllers

Gareth Hardy, HIV i-Base

A small subset of HIV positive people, referred to as elite controllers, are able to spontaneously control HIV infection to below 50 copies/mL without ART.

Although genetic studies have identified HLA-type as a likely contributor to spontaneous control of viraemia (SCV), at least a third of cases do not carry these alleles. [1]

In a recently published study in *AIDS*, Otto Yang and colleagues at the University of California, Los Angeles, presented a review from almost 30,000 HIV positive people attending AIDS Healthcare Foundation clinics in LA and Miami to assess the frequency, demographics and outcome of SCV. [2].

To be included in the study, participants had to have at least three viral load measurements within a one-year period. SCV was defined as having at least three consecutive viral load measurements <50 copies/mL plasma over one year, in the absence of ART. Loss of SCV was defined as having three consecutive viral load measurements >50 copies/mL plasma or a single measurement >1000 copies/mL of plasma. Transient viral load measurements >50 copies/mL plasma that did not lead to loss of SCV were defined as viral blips. Follow up was cut off after loss of SCV or initiation of ART, which in itself was not considered loss of SCV. Comparisons were made between those with SCV and those without, and between those who maintained SCV and those who became viraemic.

Out of 29,811 records, 53 HIV positive people met the definition of SCV (0.18%). Twenty six (49%) were women and three were (6%) were transgender (male to female), 33 (62%) were black, 17 (32%) were white (four were latino), and one (2%) was Asian. Data on route of transmission was collected from 26 people, of which 24 (45%) were sexual and two (4%) were via I.V. drug use. The HLA allele B*5701 which is protective against HIV disease progression was only present in two people, who were both white, out of 18 who were screened. Over the observation period, nine people became viraemic after a mean of 6.1 years (SD 3.5, range: 1.5 to 11.3). Five people started ART without becoming viraemic.

SCV was significantly more likely to occur in women than men, (26/4517 [0.58%] women versus 24/24,603 [0.1%] men, $p < 0.001$). SCV was also significantly more likely to occur in blacks than whites, (33/10,089 [0.33%] blacks versus 17/16,559 [0.1%] whites, $p < 0.001$). The highest frequency of SCV was among black women (20/2841 [0.7%]) and the lowest amongst white men (11/15,064 [0.07%]).

In the nine people who lost SCV during the study period, the rate of loss was linear over the estimated duration of infection, corresponding to 1.22% per year, which equates to a half-life of 40.8 years. There were no significant differences in rate of SCV loss according to race, sex or estimated age at time of infection.

Viral blips occurred in 18 people and were significantly associated with progression compared to those without blips ($p = 0.04$). The frequency of viral blips was higher for the nine people who lost SCV (15.9% [10/63] viral load measurements) compared with the 44

people who maintained SCV (5.8% [28/484]), but were no greater in magnitude or any more frequent before loss of SCV.

This research represents the most detailed assessment of SCV frequency according to sex and race so far and finds that sex and race are significant determinants of SCV prevalence, with higher rates in women and black people. In addition, more frequent viral blips were associated with loss of SCV.

The researchers also performed a mathematical assessment of viral blip magnitude in sustained and non-sustained SCV groups and concluded that blip magnitudes are consistent with low-level viral set points (at <50 copies/mL) and reflect variation around stable means.

In the discussion section of this paper the authors concluded, perhaps controversially, that “persons with SCV are not qualitatively different, but rather represent an extreme in the continuum of log-normally distributed plasma viraemia set points across persons with untreated infection”, rather than being qualitatively distinct from other persons with HIV.

C O M M E N T

A huge variety of biological factors, some known and some not known, influence and determine the continuum of viraemia containment. SCV is therefore liable to have underlying complex biological factors that determine it.

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Evidence of smaller HIV reservoirs in a Ugandan cohort

Richard Jefferys, TAG

The size of the reservoir of replication-competent HIV that persists in individuals on ART has been described in several studies from North America, but no information has previously been presented from the African continent, where the burden of HIV infection is greatest.

A study just published in *Clinical Infectious Diseases* by Jessica Proddger and colleagues takes a first step toward filling this gap, and the results may be surprising. [1]

The researchers measured the size of the replication-competent HIV reservoir in a cohort of 70 individuals on suppressive ART in Rakai, Uganda, and compared the results to those obtained previously in a study involving 51 participants from Baltimore. On average, the reservoir was three-fold smaller: 0.36 infectious units per million cells (IUPM), compared to 1.08 IUPM. This translates into approximately one out of every 2.7 million CD4 T cells containing replication-competent HIV in the individuals in Rakai versus one out of every million cells among those in Baltimore.

In both cohorts, a higher set point viral load prior to treatment was associated with a larger HIV reservoir, while a longer duration of viral suppression due to ART was associated with a smaller reservoir. These findings indicate that key factors that influence the size of the reservoir are shared across the two settings.

The reasons for the difference in the average amount of replication-competent HIV detected remain to be elucidated, but the researchers note that there are differences between the populations in terms of “lifetime immunologic challenges, HIV-1 subtypes, and genetic background.” Previous studies have documented environmentally driven differences in levels of immune activation when comparing Ugandan and Italian individuals living in Italy to those living in Uganda, raising the speculative possibility that elevated CD4 T cell activation and turnover might lessen opportunities for HIV to establish latency in long-lived, resting memory CD4 T cells (the cell type that generally harbors the bulk of the replication-competent HIV reservoir). [2]

Further research is needed to better understand the results, since they may have significant implications for the prospects of curing HIV infection in the African setting.

A recent open access review article published in the *Journal of the International AIDS Society* by Theresa Rossouw and colleagues touches on similar themes, discussing considerations that are likely to be important for remission and cure research in low- and middle-income countries (LMIC). [3]

These include immune activation, uncontrolled HIV replication, viral subtype, co-infections, microbial translocation and nutrition. The authors argue strongly for the importance of expanding the global reach of current efforts, stating: “the inclusion of patients from high burden LMIC is essential for cure research.” The fact that these two papers appeared within weeks of each other (they were published online May 23 and June 5, respectively) is a welcome slice of kismet, as they shed timely light on an important topic.

Source

TAG basic science blog, (12 June 2017).

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HIV TRANSMISSION AND PREVENTION

HIV superinfection is associated with specific HLA types

Gareth Hardy, HIV i-Base

A study of factors associated with HIV superinfection was recently published from a prospective study of HIV positive gay men.

While superinfection has been associated with increased disease progression, specific risk factors for superinfection have not been defined. It is unclear, for example, whether superinfection results from continued high-risk sexual behavior or incomplete immune responses during early infection.

This study, from Jouni Vesa and colleagues at the University of California, San Diego prospectively followed a high-risk cohort of 96 HIV positive MSM to investigate demographic, behavioural, clinical and immunogenic determinants of superinfection. [1]

Superinfection is defined as infection with a second HIV virus after the immune response to an initial HIV infection has already developed. Superinfection most often occurs during primary infection when humoral and cell mediated immune responses have not fully matured, enabling re-infection. By contrast, co-infection with two different viruses can also occur either simultaneously or before an immune response has been mounted to the initial infection. [2]

Men were eligible for the study if they were newly diagnosed with recent HIV and had at least one longitudinal follow up visit. Viral loads and CD4 counts were measured at each follow up visit, and evidence of superinfection was determined using ultra-deep sequencing of partial coding regions in HIV *gag*, *pol* and *env*. Participants with evidence of dual infection at enrollment were excluded. Participants were also followed while antiretroviral-naïve and were censored upon initiating ART. In order to assess if immunogenic determinants influence susceptibility to superinfection, HLA types were assessed by genotyping HLA-A, HLA-B, HLA-C and HLA-DRB1 alleles. As the number of individuals with superinfection was limited, two-digit codes for HLA lineage groups were used in the analysis.

Overall, men with documented HIV mono-infection were monitored for a median of 15.6 months (range 0.7 to 73.9 months). The median time from the estimated date of infection to presentation was 70 days (range: 10 to 170 days). During follow up, ten people became superinfected, each with subtype B, at a median time from initial infection of 10.4 months (range: 3.5 to 21.1 months).

There were no associations between risk of superinfection and age, race, sex, higher viral load, lower CD4 count and high-risk sexual behavior. In contrast, a higher number of sexual partners was associated with acquisition of superinfection at $\alpha = 0.10$ (hazard ratio 4.74, 95%CI: 0.87 to 25.97; $p = 0.073$).

Specific HLA alleles have previously been associated with increased HIV disease progression, whereas others have been shown to have a protective effect. In order to determine if HLA-alleles influence susceptibility to superinfection, at a time during which immune

responses to the initial infecting strain have not yet fully matured, the researchers determined the hazard ratios for each HLA allele.

Increased superinfection risk at $\alpha = 0.10$ was observed for: HLA-A*29 (HR 4.10, 95%CI: 0.88 to 14.76, $p = 0.069$); HLA-B*35 (HR 4.64, 95%CI: 1.33 to 18.17, $p = 0.017$); HLA-C*04 (HR 5.30, 95%CI: 1.51 to 20.77, $p = 0.010$); HLA-C*16 (HR 4.05, 95% CI: 0.87 to 14.62, $p = 0.071$); HLA-DRB1*07 (HR 3.29, 95% CI: 0.94 to 12.90, $p = 0.062$); HLA-DRB1*08 (HR 15.37, 95% CI: 2.11 to 79.80, $p = 0.011$). Decreased superinfection risk was observed for HLA-DRB1*11 (HR 0.13, 95%CI: 0.00 to 1.03, $p = 0.054$).

In multivariate analysis, assessing significant HLA alleles and number of sexual partners, the following alleles retained significance regardless of the number of sexual partners: HLA-B*35 ($p = 0.020$); HLA-C*04 ($p = 0.033$); and HLA-DRB1*08. In contrast, the increased risk associated with HLA-A*29, HLA-C*16 and HLA-DRB1*07, and the decreased risk associated with HLA-DRB1*11, were not retained in the multivariate model with number of sexual partners.

HIV is known to downregulate expression of HLA alleles. It is possible that primary HIV infection may downregulate expression of protective HLA alleles, thereby reducing the efficiency of antigen presentation to cytotoxic T cells and in turn increasing the risk of superinfection. In contrast, mechanisms that upregulate protective alleles may reduce risk of superinfection.

The authors concluded that further analysis is needed in larger cohorts to fully characterise the significance of HLA alleles associated with superinfection.

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New study of combined HIV prevention and contraception ring

Simon Collins, HIV i-Base

On 3 May 2017 nonprofit International Partnership for Microbicides (IPM) announced the launch the first study using a combined HIV PrEP and contraceptive vaginal ring.

The three-monthly ring is designed to simultaneously slowly release both the antiretroviral dapivirine and the contraceptive hormone levonorgestrel.

The primary aim of the MTN-030/IPM 041 study is safety and pharmacokinetics rather than efficacy to prevent either HIV infection or pregnancy.

Although dapivirine showed efficacy compared to placebo in women who used the ring in two phase 3 studies, dapivirine has not been approved as PrEP.

Ref: IPM press statement. IPM Advances Three-month HIV Prevention and Contraception Ring to Clinical Trial (0 May 2017).

www.IPMglobal.org

HEPATITIS C

FDA approves sofosbuvir/ledipasvir and sofosbuvir for children aged 12 to 17

FDA HIV update

On 7 April 2017 the FDA approved supplemental applications for ledipasvir/sofosbuvir and sofosbuvir to treat hepatitis C virus (HCV) in children ages 12 to 17 or weighing at least 35 kilograms.

These approvals provide paediatric treatment options for six major genotypes of HCV using the standard adult dose.

Sofosbuvir/ledipasvir is indicated for the treatment of paediatric patients 12 years of age and older or weighing at least 35 kilograms with HCV genotype 1, 4, 5 or 6 infection without cirrhosis or with compensated cirrhosis.

Sofosbuvir in combination with ribavirin is indicated for the treatment of paediatric patients 12 years of age and older or weighing at least 35 kilograms with genotype 2 or 3 HCV infection without cirrhosis or with compensated cirrhosis

For full details of paediatric use including label changes please see the updated labels at drugs@fda or DailyMed.

<https://www.accessdata.fda.gov/scripts/cder/daf>

<https://dailymed.nlm.nih.gov/dailymed/index.cfm>

Both ledipasvir/sofosbuvir and sofosbuvir are manufactured and marketed by Gilead Sciences with the trade names Harvoni and Sovaldi respectively.

Source

FDA HIV email update. FDA approves two Hepatitis C drugs for paediatric patients. (7 April 2017).

Cochrane review of HCV treatment misses real issues of access to care

Simon Collins, HIV i-Base

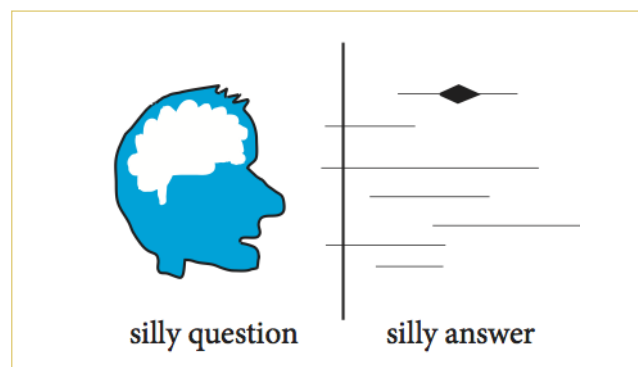
Although the Cochrane review process is designed to minimise subjective assessments and bias from studies, setting the initial questions is highly subjective.

And if the review asks a question that is not appropriately matched, the results are likely to be nonsense.

A recent Cochrane review of new hepatitis C (HCV) drugs has discredited what can be a useful process for combining results from multiple studies. Of more concern, irresponsible reporting of the review by mainstream media risks limiting access to effective treatment.

The original review was published online on 6 June 2017. [1]

It asked what appears to be a reasonable question: whether new HCV drugs prevent liver-related serious health complications including



mortality. It then reviewed 168 research studies of multiple new HCV drugs – called direct acting antivirals (DAAs) – and reported a lack of evidence showing benefits.

Importantly, the lack of evidence is very different from a lack of effect.

DAAs are in fact so effective that they cure nearly everyone within 8 to 24 weeks. This means HCV studies are short-term even if extended follow-up continues for longer. But the serious liver-related complications used as endpoints in the review are generally long-term events, with risk accumulating over years and sometimes decades.

DAA studies are much too short-term to see these endpoints, so there is not enough evidence to prove benefit on these criteria. DAA studies are usually either:

1. In people who are generally healthy, so very few events will happen in either arm over a short study; or
2. In people with very advanced liver disease when both groups are similarly likely to have higher rates of complications because long-term damage is already significant and difficult to reverse.

In either of these situations, there are likely to be few differences between active vs control groups.

Further reporting by mainstream media of the top-level results without critically reviewing the study, included an article by the health editor in the Guardian, that is even more unhelpful than the original review. [2]

In the spirit of irresponsible and alarmist journalism that is unfortunately common when looking to make headlines rather than explain science, the story in the Guardian is instead likely to cause harm:

- It could destabilise access to highly effective treatment that is already controversial because of the unnecessarily high price charged for these medicines.
- It could dissuade people from testing for HCV and accessing treatment.
- It could be used by the NHS and other health providers to block or delay commissioning of this effective treatment.

C O M M E N T

Using the Cochrane review to manipulate essential issues over access to highly effective medicines is dangerous and irresponsible. It also questions whether a peer-review process should pick up methodological weaknesses for these reviews.

News media – including community press – needs to critically access scientific studies before treating health stories as news that can be spun for a headline.

Instead, the mainstream media could have found ways to explain how scientific approaches were being distorted. A similar Cochrane approach to smoking cessation programmes would find a similar lack of evidence for health: these short programmes wouldn't see different rates of lung cancer in each group, but no-one would be stupid enough now to question the clear benefits from quitting.

HCV drugs are currently shockingly over-priced and cost is limiting access to many people who need them - both in the UK and globally. This challenges their cost-effectiveness in different settings but not their effectiveness.

Access to DAAs for people with HIV/HCV coinfection is becoming steadily easier. This is covered in detail in a new i-Base guide to coinfection – available in print and online. As with all i-Base resources, this comprehensive easy-to-read guide is available free, including in bulk for UK clinics. [3]

References

1. Jakobsen JC et al. Direct-acting antivirals for chronic hepatitis C. Cochrane review (6 June 2017). DOI: 10.1002/14651858.CD012143.pub2 <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012143.pub2/full>
2. Bosley S. 'Miracle' hepatitis C drugs costing £30k per patient 'may have no clinical effect'. The Guardian. (13 June 2017). <https://www.theguardian.com/society/2017/jun/08/miracle-hepatitis-c-drugs-costing-30k-per-patient-may-have-no-clinical-effect>
3. HIV i-Base. Hepatitis C for people living with HIV. (June 2017) <http://i-base.info/guides/hepc>

OTHER NEWS

King's Fund report on HIV services in England

Simon Collins, HIV i-Base

A new report sponsored by the King's Fund reviews the current and future network of HIV services in England.

The report explores the challenges and opportunities facing HIV services in four areas in England, and makes recommendations on future development to those in national and local leadership roles.

It explains the complex structure for commissioning separate but related aspects of HIV care and included input from all stakeholders, including people living with HIV.

The purpose of our research was to make recommendations to those in national and local leadership roles on how HIV services should develop over the next 5–10 years.

The researchers investigated the current situation for HIV services in urban and rural, low and high prevalence areas, undertaking focus groups with people living with HIV and interviewing around 100 people in local and national HIV services.

References

<https://www.kingsfund.org.uk/publications/future-hiv-services-england>

https://www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/Future_HIV_services_England_Kings_Fund_April_2017.pdf (PDF)



Toolkit to support doctors against immigration interventions in the NHS

Simon Collins, HIV i-Base

The medical charity Doctors of the World has produced a toolkit for healthcare professionals who want their GP practices to be safe places for refugees, migrants and asylum seekers.

The resource is based on six steps.

1. Make sure patients know they don't need to give a personal address
2. Display a poster declaring your surgery a safe space
3. Never ask to see a passport, visa or identity document
4. Don't ask for proof of address documents
5. Make sure frontline staff know the rules
6. Check your registration policy

The "Safe Surgeries" toolkit, is part of a campaign to give GPs and other health workers practical methods to keep their patients' addresses off NHS records.

The UK government and NHS Digital, the NHS body that stores patient information, made a deal in January to give the Home Office easier access to patient information. This allows immigration officials to use NHS patients' personal details, such as their addresses, to track down, arrest and deport undocumented migrants.

According to the Department of Health, the Home Office made 8,127 requests for data in the first 11 months of 2016. This led to 5,854 people being traced by immigration enforcement teams.

Medical professionals were not consulted about the deal and many oppose it.

The toolkit will empower medical professional to be able to make their clinics places where everyone, whatever their social or immigration status, feels able to seek the healthcare they need. It includes:

- Ways to register patients by using the address of the practice or a local organisation, instead of their home address.
- A poster for surgery reception areas that informs patients that they do not have to give their home address.
- Instructions to frontline staff to not ask for a passport or proof of ID when registering patients.

People in urgent need of care, including people living with HIV, pregnant women and people with serious cancer, can become too scared to see a doctor for fear that their details will be passed on.

UK clinics (including the London Doctors of the World clinic in Bethnal Green) see people who have been trafficked, victims of torture and parents with children who are too afraid to get healthcare they desperately need.

The charity recently helped a woman who came to their clinic whilst in labour after not having any antenatal care because she was too afraid to access it.

Dr Miriam Beeks, a GP in Lower Clapton Group Practice in east London said: Most doctors have no idea about the data sharing agreement. It's extraordinary that doctors have not been asked

about this – there has just been some sort of ministerial dictum. How could they think that doctors would not object to this? Doctors should feel confident about standing against this. We are backed up by both NHS and GMC confidentiality rules - our interactions with our patients are confidential. That's one of the basic human rights of the patient."

C O M M E N T

Many doctors hate the idea that they are being used as immigration officers and see healthcare as a basic human right.

HIV i-Base has had referrals from HIV positive people who have been too scared to engage with HIV clinics even though the NHS provides free testing, monitoring and HIV treatment irrespective of UK residency status.

This commonly leads to very late engagement with care.

References and links

1. Doctors of the World. Take action against the home office accessing NHS data!
<https://www.doctorsoftheworld.org.uk/news/medics-mobilise-against-nhs-patient-data-sharing>
2. Download the toolkit.
<https://www.doctorsoftheworld.org.uk/Handlers/Download.ashx?IDMF=06897b0f-6a03-493f-a288-f9ddce44cbcc>

For further information contact:

Nick Harvey (0203 5357956) and nharvey@doctorsoftheworld.org.uk

ON THE WEB

Online resources

Hepatology - a clinical textbook (8th edition, 2017)

Stefan Mauss, Thomas Berg, Juergen Rockstroh, Christoph Sarrazin and Heiner Wedemeyer.

<http://www.hepatologytextbook.com>

Hepatology – A clinical textbook is an up-to-date source of information for doctors and other health workers who want a broad and up to date understanding of liver disease.

The 2017 edition deals in particular with advances in treatment of HCV, hepatocellular carcinoma and primary biliary cholangitis (PBC) together with new insights in the disease mechanism in particular of NASH.

In addition, all other chapters have been thoroughly updated.

The textbook is available as a free download in PDF format and a print version can also be ordered online.

Online video: PrEP 17 – The coming of age of PrEP

A new 35 minute community video updating the way PrEP is being used in the UK is available online.

Produced by Nicholas Feustel with Prepster.info, the film continues an earlier film on the PROUD study, interviewing some of the same researchers, activists and study participants - together with new PrEP users.

The film will also be shown in various community settings - so far with dates planned in Leeds and London. Please see the website for more details.

<http://prepster.info/prep17>



HIV.gov - AIDS.gov relaunched

One of the websites that hosts the US government response to HIV has recently changed its website URL from AIDS.gov to HIV.gov.

The change is hoped to reflect the recent advances in HIV care and reduce the stigma associated with historical use of AIDS.

<https://www.hiv.gov/blog/more-than-a-name-change-aidsgov-becomes-hivgov>

FUTURE MEETINGS

Conference listing 2017

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.

International Workshop on HIV Pediatrics 2017

21-22 July 2017, Paris

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

12th International Workshop on HIV Transmissions

21-23 July 2017, Paris

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

12th International Workshop on HIV Transmissions

23-26 July 2017, Paris, France

www.virology-education.com

9th IAS Conference on HIV Science

23-26 July 2017, Paris, France

www.ias2017.org

21st Annual Antiviral Therapy & Drug Resistance Meeting

21 September 2017, London

www.mediscript.ltd.uk

8th International Workshop on HIV & Ageing

2-3 October 2017, New York, USA

www.virology-education.com

cliniQ's 4th international Trans Health Matters conference

17 October 2017, venue tbc, London

<https://www.eventbrite.co.uk/e/cliniq-trans-health-matters-2017-tickets-34763486524>

19th International Workshop on Comorbidities and Adverse Drug Reactions in HIV

23-25 October 2017, Milan, Italy

www.intmedpress.com

6th European AIDS Conference

25-27 October 2017, Milan, Italy

www.eacsociety.org

International Workshop on HIV Drug Resistance and Treatment Strategies (IWHDR)

6–8 November 2017, Johannesburg

www.HIVresistance2017.co.za

Hepatology Highlights for the Healthcare Specialist in collaboration with BVHG

15 November 2017, London

<http://www.bhiva.org>

BHIVA Autumn Conference

16-17 November 2017, London

<http://www.bhiva.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>

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>

- Introduction to ART (September 2016)
- HIV & quality of life: side effects & better health (Sept 2016)
- Guide to PrEP in the UK (November 2016)
- HIV testing and risks of sexual transmission (June 2016)
- Guide to changing treatment and drug resistance (February 2015)
- Guide to HIV, pregnancy & women's health (December 2015)

New pocket guides

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 five pocket leaflets are: Introduction to ART, HIV and pregnancy, ART and quality of life, UK guide to PrEP and HCV/HIV coinfection.

We hope these are especially useful as low literacy resources.

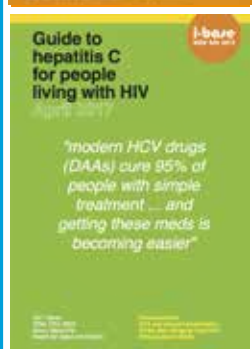
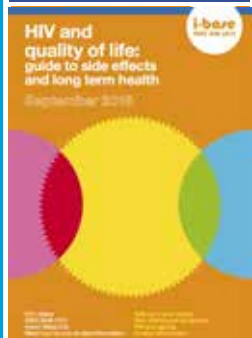
The leaflets use simple statements and quotes about ART, with short URL links to web pages that have additional information in a similar easy format.

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>

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Pocket ART quantity _____ **Pocket pregnancy** quantity _____

Pocket side effects quantity _____

• **NEW: Guide to hepatitis C coinfection (April 2017): 52-page A5 booklet**

1 5 10 25 50 Other _____

• **UK Guide To PrEP (November 2016): 24-page A5 booklet**

1 5 10 25 50 Other _____

• **Introduction to ART (September 2016): 48-page A5 booklet**

1 5 10 25 50 Other _____

• **HIV and your quality of life: guide to side effects and long-term health (September 2016): 96-page A5 booklet**

1 5 10 25 50 Other _____

• **Guide To HIV testing and risks of sexual transmission (July 2016): 52-page A5 booklet**

1 5 10 25 50 Other _____

• **Guide to HIV, pregnancy and women's health (November 2015): 52-page A5 booklet**

1 5 10 25 50 Other _____

• **Guide to changing treatment: what to do if viral load rebounds (February 2015): 24-page A5 booklet**

1 5 10 25 50 Other _____

• **HIV Treatment 'Passports' - Booklets for patients to record their own medical history**

1 5 10 25 50 Other _____

• **Phoneline A4 posters** _____

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