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CONTENTS

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EDITORIAL

This issue of HTB leads with reviews from the 14th Pharmacology Workshop that was held in Amsterdam in April.

We also continue our reports from CROI 2013, with coverage of pregnancy and PMTCT, cardiavascular complications, new treatments for hepatitis C and basic science and cure studies.

While US regulatory decisions are delayed for the separate formulations of elvitegravir and cobicistat, this does not affect the fixed dose combination Stribild (Quad) that received EU approval on May 28th as HTB went to press.

Paediatric formulations of raltegravir and efavirenz have been approved by the European Commission and US FDA respectively.

Global access news reports the final decision by the Indian Supreme Court to find against Novartis in their protracted claim to extend patent rights for the chemotherapy drug imatinib mesylate.

We have reported on this case in HTB for over seven years. The results are a significant victory for common sense and global health and have implications for HIV and other treatments in resource-limited countries.

We include the press release from MSF in full with links to further information.

Other treatment access news includes that WHO will increase the CD4 threshold for ARV treatment to 500 cells/mm^3, in the updated treatment guidelines due for release next month.

Also looking forward, next month the annual i-Base/TAG Pipeline Report for 2013 will be distributed in electronic format as a July supplement to HTB.

The publication will be formally launched at the 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Kuala Lumpar from 30 June to 3 July 2013.

This is the fourth year that i-Base has been able to collaborate with the Treatment Action Group in New York to produce this comprehensive review of pipeline research into treatments and vaccines for HIV, hepatitis and tuberculosis. The collaboration include a new searchable "pipeline website" with archives from the last ten years.

http://www.PipelineReport.org

HTB print distribution to BHIVA members

Please note that BHIVA members who are reading HTB electronically and who want to continue or return to reading the print edition, need to resubscribe online:

http://i-base.info/forms/postsub.php

Or email your full contact details, including full postal address details to:

subscriptions@i-Base.org.uk

Although the British HIV Association will continue to distribute HTB to BHIVA members, this will now only be in electronic fromat.

The print edition continues to be available free.

CONFERENCE REPORTS

14th International Workshop on Clinical Pharmacology

22-24 April 2013, Amsterdam

Introduction

The annual pharmacology workshop usually highlights interesting studies with relevance to both clinical practice and pipeline drug development.

Although we were unable to attend the workshop this year, the following summaries should be considered preliminary as they are based on the conference abstracts.

These reports include:

- Population pharmacokinetics of efavirenz to inform dosing in children three months of age and above
- Bilirubin as a surrogate marker for atazanavir in children
- Transplacental transfer of atazanavir and neonatal hyperbilirubinaemia
- Tenofovir population pharmacokinetics in pregnancy

- Effect of rifampicin on BMS-663068 in healthy volunteers
- Coformulated darunavir/cobicistat: an alternative to separate ritonavir boosting
- Continuous infusion of T-20 in multidrug resistant patient with intolerance of s.c. injections

The presentations from the 2013 workshop are due to be posted as slides. The abstract book has not yet been posted to the conference web site.

http://www.virology-education.com

Population pharmacokinetics of efavirenz to inform dosing in children three months of age and above

Polly Clayden, HIV i-Base

The US FDA recently expanded the indication for efavirenz (EFV) to include children at least three months old based on a population pharmacokinetic (PK) model to assess dosing for this age group. [1] These data were presented at the 14th International Pharmacokinetics Workshop. [2]

The recommended dose of efavirenz (EFV) for children and adolescents three years and above is based on body weight and ranges from 200 mg once daily for those weighing 10 to <15 kg, to 600 mg for those ≥40 kg. Prior to the FDA update, EFV was not recommended for children <3 years or <10 kg (this is still the case in the EU).

The population PK model was based on 3289 concentration values from 168 babies, children and adolescents, aged 3 months to 21 years (57 < 3 years), weighing 3.3 to 117 kg (from studies PACTG382, PACTG1021 and A1266922). The model also incorporated 1232 values from 24 healthy adults (A1266059). Paediatric trials contributed 88% of participants and 73% of observations for analysis. The model included pre-specified covariates: age, weight, gender and race.

Simulations of steady state EFV exposures (n=1000 PK parameter sets, 100 paediatric participants per weight category) were performed for various doses of EFV capsule-sprinkle and capsule formulations, in order to identify those that gave comparable exposure between participants weighing <10 kg and ≥10 kg. The criteria used for this were target steady state AUC 190-380 uM*h and Cmax and Cmin of 5.2 – 8.2 and 1.9-2.9 ug/mL, respectively (80-125% of the reference Cmax and Cmin values from children weighing 10 – 15 kg).

The investigators found the steady state PK were well described by a linear two-compartment model with first-order absorption. Weight was a clinically meaningful covariate on EFV clearance, central volume and rate of absorption. Age was not significant in the presence of weight.

Simulation results suggested that the doses in table 1 produce comparable exposure to that of children ≥10 kg who received the current approved dose. These doses produced a median AUC within the target range; simulation results for Cmax and Cmin also supported them.

Table 1: EFV doses according to weight bands

Weight band	Dose (once daily)
≥ 2.5 to <5 kg	100 mg
≥ 5 to <7.5 kg	150 mg
≥ 7.5 to 10 kg	200 mg

The simulation results also confirm the current once daily dosing recommendation for children weighing ≥10 kg (≥3 years).

References

1. Food and Drug Administration (U.S.). Sustiva (efavirenz) pediatric patients labeling update. 2 May 2013. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm350744.htm
2. Bertz R et al. Population pharmacokinetics of efavirenz in pediatric patients to inform dosing in children ≥ 3 months of age. 14th International Workshop on Clinical Pharmacology. 22-24 April 2013. Amsterdam. Poster abstract P_18.

Bilirubin as a surrogate marker for atazanavir in children

Polly Clayden, HIV i-Base

Findings for a study looking at paediatric atazanavir dosing and plasma bilirubin as a possible surrogate for atazanavir therapeutic drug monitoring (TDM) were presented at the 14th International Workshop on Clinical Pharmacology.

Although atazanavir dose is not predictive of Cmin, bilirubin might be a surrogate marker for atazanavir Cmin in this population.

TDM data of atazananvir from children and adolescents ≤18 years from a Canadian cohort were analysed. Atazanavir Cmin were estimated using a half-life of 10.10 and 5.58 hours with and without ritonavir boosting respectively, for levels taken more than 4 hours post-dose. Cmin below 0.15 was considered subtherapeutic. The investigators evaluated associations between dose Cmin and bilirubin Cmin.

Data from 15 participants and 35 TDMs were included in the analysis; the majority (93%) was black and 67% were girls. Their median age was 15 years (range 8-18), weight 49 kg (range 29-74) and body surface area 1.47 m2 (range 1.00 -1.88). The median atazanavir dose was

4.42 mg/kg (range 3.40 – 10.49) and 150 mg/m2 (range 125-299); most (74%) doses were boosted with ritonavir.

The median Cmin for TDMs for participants receiving unboosted atazanavir (n=5) was 0.05 mg/L (range 0-0.25); 60% of these were in the subtherapeutic range. For those receiving boosted atazanavir (n=19), median Cmin was 0.79 mg/L (range 0-1.85), 11% subtherapeutic. Cmin could not be evaluated in 11 TDMs.

The investigators found no association between Cmin and dose: mg/kg, p=0.81 and mg/m2, p=0.75; this remained similar after adjustment for ritonavir use. They found bilirubin concentrations of 18 ug/L to be predictive of Cmin $\geq$ 0.15 mg/L with 95% sensitivity and 80% specificity, AUC 0.91 (95% CI 0.76 – 1.00). They noted that the results need to be confirmed in prospective studies.

Ref: Wong A et al. Biliruben as a surrogate marker for atazanavir concentrations in a pediatric population. 14th International Workshop on Clinical Pharmacology. 22-24 April 2013. Amsterdam. Poster abstract P_14.

Transplacental transfer of atazanavir and neonatal hyperbilirubinaemia

Polly Clayden, HIV i-Base

Results from a study evaluating the transplacental transfer of atazanavir (ATV) and the incidence of hyperbilirubinaemia in ATV exposed neonates were presented at the 14th International Workshop on Clinical Pharmacology.

In this analysis, foetal cord blood of 16 (15 pregnancies with one set of twins) in utero exposed infants were evaluated for ATV and bilirubin concentrations. The investigators then compared these to maternal levels at time of delivery. Neonatal bilirubin levels in the first 24 hours of life were also collected.

Of the mothers, six were receiving ATV before conception and nine started treatment between 19 and 33 weeks gestation. Most (13/15) women were virologically suppressed <50 copies/mL at delivery. The infants weighed a mean of 3.3 kg (range 2.0-4.7) at birth. The twins were born pre-term at 35 weeks and the remainder of infants were born at >37 gestation.

The investigators noted considerable variability in maternal ATV concentrations at delivery but suggested this was most likely to be due to the differences in time of sampling since last dose. Median ATV concentration was 1250 ng/mL (range <48 – 34441); 13/15 were above than the MEC of 150 ng/mL. Detectable ATV levels were observed in 12/15 cord blood samples, median 223 ng/mL (range <48 – 531), 8 were above the MEC and three were borderline.

Linear regression analysis revealed a significant association between maternal and cord blood ATV concentrations, R2 = 0.632, p<0.001. The mean ratio of maternal to cord blood concentration was 0.14 (95% CI 0.08-0.20).

Median maternal serum total bilirubin concentration at delivery was 23.5 mmoL/mL (range 6 – 102); median cord blood total bilirubin concentration was 34mmoL/mL (range 15- 89) and median neonatal total bilirubin concentration was 60 mmoL/mL (range 19 – 146).

One infant with an indirect bilirubin level of 146mmoL/mL at 27 hours of age was excluded from the analysis. Among the remaining infants, investigators reported a significant correlation between neonatal unconjugated bilirubin concentration and both maternal serum unconjugated bilirubin and cord unconjugated bilirubin concentrations, respectively R2=0.693, p=0.02 and R2=0.759, p=<0.001. They observed no correlation between ATV level and bilirubin concentrations. There were no cases of hyperbilirubinaemia.

They noted that transplacental transfer of ATV might offer additional protection to the neonate from vertical transmission of HIV, with therapeutic levels observed in most of the cord blood samples in this study.

Ref: Lambert J et al. Transplacental passage of atazanavir and neonatal hyperbilirubinaemia. 14th International Workshop on Clinical Pharmacology. 22-24 April 2013. Amsterdam. Poster abstract P_16.

Tenofovir population pharmacokinetics in pregnancy

Polly Clayden, HIV i-Base

Changes in tenofovir pharmacokinetics (PK) during pregnancy are associated with weight gain and reduction in serum creatinine with enhanced glomerular filtration, according to an analysis presented at the 14th International Pharmacology Workshop.

Physiological changes that occur during pregnancy, including altered gastrointestinal function and increased glomerular filtration rate, have the potential to alter drug disposition. An approximate reduction of one third in tenofovir exposure during pregnancy has previously been observed in other studies.

IMPAACT P1026 is an ongoing, prospective, non-blinded study of PK in pregnant women receiving routine antiretroviral treatment (ART). This analysis included data from women receiving 300 mg tenofovir disoproxil fumarate (135.6 mg tenofovir), either as a standalone in an ART regimen or as a component of a fixed dose combination.

The investigators collected steady state tenofovir PK profiles in the third trimester – at 30 to 36 weeks gestation – and two to 12 weeks post partum. There was also optional sampling in the second trimester – between 20 and 26 weeks gestation.

Samples were taken pre-dose and 1, 2, 4, 6, 8, 12 and 24 hours post-dose. Tenofovir plasma concentrations were determined by LC-MS-MS.

Pregnancy stage, serum creatinine, concomitant antiretrovirals (ritonavir boosted PIs), albumin and age were assessed as potential covariates in univariate and multivariate models.

The 86 steady-state PK profiles collected included 650 plasma tenofovir concentrations from 46 women during the second trimester (n=7), third trimester (n=41) and postpartum (n=38); 54 (63%) women received a boosted PI.

The investigators found age, pregnancy state, serum creatinine and age to be associated with CL/F in univariate analysis but only serum creatinine remained significant in the multivariate model.

Post-hoc AUC estimates were significantly lower during the third trimester vs postpartum: GM 2.38 vs 2.90 mcg*h/mL, p=0.009 with a third trimester ratio of 0.83 (90% CI 0.75 – 0.91).

Ref: Powell MB et al. Changes in tenofovir population pharmacokinetics during pregnancy. 14th International Workshop on Clinical Pharmacology. 22-24 April 2013. Amsterdam. Poster abstract PP_03.

Effect of rifampicin on BMS-663068 in healthy volunteers

Polly Clayden, HIV i-Base

A study presented at the 14th International Workshop on Clinical Pharmacology showed the effects of P-glycoprotein (P-gp) and Cytochrome P450 3A4 (CYP3A4) on BMS-626529 AUC and Cmax, with clinically significant reductions.

BMS-663068 is a pro-drug of BMS-626529. BMS-626529 is a substrate of the P-gp transporter and primarily metabolized by an esterase-mediated hydrolysis pathway and, to a minor extent, CYP3A4. The study evaluated the effects of rifampicin on the pharmacokinetics (PK) of BMS-626529 after a single dose of BMS-663068 in healthy male volunteers.

This was an open-label, one sequence, one-way interaction study conducted in 15 participants. Day 1: all participants received a single dose of BMS-663068 1200 mg in the morning with a standard meal (Treatment A). Days 6 - 12: participants were given rifampicin 600 mg once daily in the evening. Day 11: all participants received a single dose of BMS-663068 1200 mg in the morning with a standard meal (Treatment B).

Samples for BMS-626529 were taken pre-dose and up to 48 hours post-dose on days 1 and 11. All participants were monitored for adverse events.

Following administration of BMS-663068, the investigators found the ratios of geometric means for BMS-626529 AUCinf and Cmax with and without rifampicin were,0.181 (90% CI 0.163 – 0.200) and 0.241 (90% CI 0.208 – 0.279), respectively. Median Tmax, mean T1/2 and mean CTL/F values were: 5 and 4 hours, 6.29 and 6.84 hours and 686 mL/hr and 3841 L/hr, respectively.

The investigators noted that the similar size of reduction in both AUC and Cmax in conjunction with a similar elimination rate suggested that the interaction is likely to be primarily mediated by P-gp induction but a contribution of CYP3A4 could not be ruled out.

They concluded that this study demonstrates the effects of the P-gp and CYP3A4 inducer rifampicin on BMS AUC and Cmax, with a clinically significant reduction by 82 and 76% respectively.

Ref: Hruska M et al. The effect of rifampin on the phamacokinetics of the HIV-1 attachment inhibitor pro-drug BMS-663068 in healthy subjects. 14th International Workshop on Clinical Pharmacology. 22-24 April 2013. Amsterdam. Poster abstract P_05.

Coformulated darunavir/cobicistat: an alternative to separate ritonavir boosting

Simon Collins, HIV i-Base

Results from a phase I cross-over study in HIV negative volunteers reported bioequivilence for a new fixed-dose formulation of darunavir/cobicistat compared to the two compounds dosed separately.

Earlier studies have reported that 800 mg darunavir achieved similar PK whether boosted by 150 mg cobicistat or 100 mg.

Least square mean (LSM) ratio values were close to 100% for both darunavir and cobicistat under both fed (high fat breakfast) and fasted conditions, with tight 90% CI values that were well within the 80%-125% range allowed for bioequivlence.

Food increased darunavir and cobicistat Tmax similarly (approximately 4 hr fed vs 3 hr fasted) with combined and single formulations. Food significantly increased (LSM ratio) darunavir Cmax by 227% and AUC by 70% compared to fasted state, with little impact of food on cobicistat levels.

The collaboration between Janssen and Gilead (who manufacture cobicistat) to enable a coformulated boosted-PI will also be used in single-tablet fixed-dose combinations that include Gilead's NRTIs.

Ref: Kakuda TN et al. Bioequivalence of darunavir/cobicistat fixed-dose combination (FDC) versus single agents in healthy volunteers. 14th International Workshop on Clinical Pharmacology. 22-24 April 2013. Amsterdam. Poster abstract P_10.

Continuous infusion of T-20 in multidrug resistant patient with intolerance of s.c. injections

Simon Collins, HIV i-Base

A poster from NW Neijzen and colleagues from UMC Utrecht reported on using continuous infusion of enfuvirtide (T-20) using a tunnelled central venous catheter in a 70 year old patient with multidrug HIV resistance and intolerance to subcutaneous injections.

T-20 was prepared in an elastomeric pump (5 mL.hr, 275 mL, 180 mg T-20 over 24 hours). Before and after switching formulations multiple plasma samples were used to determine individual pharmacokinetics.

The formulation was stable at 2-8° for seven days and for 24 hours at room temperature, and continuous infusion resulted in therapeutic plasma concentrations that were approximately four times higher that previous Ctrough using s.c. administration (3529 vs 755 ng/mL; the proposed MEC for T-20 is 2100 ng/mL).

During two months of follow-up the patient remained clinically stable, with an undetectable viral load and increasing CD4 count.

Ref: Neijzen RW et al. Continuous intravenous infusion of enfuvirtide in an out-patient clinic with a multiresistant HIV strain and severe injections site reactions. 14th International Workshop on Clinical Pharmacology. 22-24 April 2013. Amsterdam. Poster abstract P_09.

CONFERENCE REPORTS

20th Conference on Retroviruses and Opportunistic Infections (CROI)

3-6 March 2013, Atlanta

Introduction

The annual CROI continues to be the most important scientific meeting covering the diversity of basic and clinical science and both the main conference and a pre-meeting programme of lectures for new investigators are promptly posted online as open access web casts.

http://www.retroconference.org

Our second collection of reports from this meeting, continue with coverage of comorbid complications and basic science, extending the coverage is the previous issue of HTB.

Reports in this issue include:

- Small increase in birth defects in the French Perinatal Cohort
- Uptake and retention in Malawi's Option B+ programme
- Optimising ART initiation in pregnancy through linkage of services vs integration of ART into antenatal care
- Cardiovascular disease and other non-AIDS defining events
- Dramatic advances at CROI for HCV treatment
- Basic research highlights from CROI 2013
- Probiotic/prebiotic supplement combination shows benefits in SIV-infected pigtailed macaques

Unless stated otherwise, references are to the Programme and Abstracts of the 20th Conference on Retroviruses and Opportunistic Infections (CROI), 3-6 March 2013, Atlanta.

http://www.retroconference.org

Small increase in birth defects in the French Perinatal Cohort

Polly Clayden, HIV i-Base

Data presented at CROI 2013 showed a small increased risk of some birth defects with first trimester exposure to some antiretrovirals in the French Perinatal Cohort (EPF). [1]

In an oral presentation, Jeanne Sibiude from INSERM showed findings from the ANRS funded French Perinatal Cohort (EPF) - a national multicentre cohort started in 1986. EPF prospectively enrols HIV positive pregnant women delivering in 90 participating centres. Children are followed for two years.

The aim of the study was to estimate the prevalence of birth defects in children born to women receiving antiretroviral drugs during pregnancy, compared to unexposed children. The study also investigated associations with specific drugs. There was no comparison to background population.

Live births, exposed to antiretrovirals in utero, between 1994 and 2010, were included (n=13,124). Birth defects were evaluated using both the EUROCAT (Europe) and the MACDP (US) classifications. Univariate and multivariate logistic regression were used to investigate associations with antiretrovirals.

EUROCAT classification identified 575 birth defects, giving a prevalence of 4.4% (95% CI 4.0-4.7); with MACDP classification, which included minor defects, 914 were identified, giving a prevalence of 7.0% (95% CI 6.5-7.4).

There was no association between efavirenz exposure (n=372) and overall birth defects. According to MACDP classification there was an association between efavirenz exposure in the first trimester and neurological defects, AOR 3.2 (95% CI 1.1 - 9.1), p=0.03. The four defects were: pachygyria, agenisis of corpus colossum, hydrocephaly and cerebral cyst.

First trimester exposure to AZT (n=3,267) was associated with overall birth defects, AOR 1.4 (95% CI 1.1-1.8), p=0.002. There was an organ system specific association with heart defects, AOR 2.5 (95% CI 1.6-4.2), p=0.001, according to both classification systems.

ddI exposure (n=927) was associated with head and neck birth defects, AOR 1.93 (95% CI 1.11-3.34), p<0.05.

3TC exposure (n=3,772) was associated with muscoskeletal, AOR 1.4 (95% CI 1.05-1.87), p=0.04, and head and neck defects AOR 1.96 (95% CI 1.2-3.21), p=0.03. Dr Sibiude noted that these were only by MACDP classification and mostly minor.

In conclusion Dr Sibiude suggested that in countries where this is possible recommendations to avoid efavirenz in pregnancy should be maintained, stressing the need for surveillance where it is used routinely. The association between AZT and heart defects needs further detailed investigation to clarify the mechanism, she added.

Overall she concluded: "However, the potential risk of birth defects has to be balanced with the major success of current PMTCT strategies."

C O M M E N T

EFV in pregnancy has courted controversy since neural tube defects were reported in three of twenty in utero exposed monkeys during preclinical studies. [2] Subsequent human data have been reassuring including that from a meta-analysis, which found no association between EFV exposure and birth defects. [3, 4]

Upcoming WHO 2013 guidelines recommend EFV-based regimens as the preferred first line ART (including for pregnant women). Many national guidelines, including BHIVA, also recommend its use in pregnancy.

Although the EPF is the largest prospective cohort to date, when these data on neurological events are considered in the context of all available data, the estimated prevalence of birth defects overall (<3%) and neural tube defects (<0.01%) remains unchanged. [5]

It is notable that none of the events reported were neural tube defects and the findings were only significant using one classification system.

Elevated risk of heart defects associated with AZT exposure was reported previously in a retrospective analysis – which also found higher prevalence of EFV associated defects than other cohorts – but not in the Antiretroviral Pregnancy Registry (APR). [6, 7, 8]

APR data to July 2012 on 6388 live births with first trimester exposure shows 18/702 defects for EFV, prevalence 2.6 (95% CI 1.5-4.0) and 127/3864 for AZT, prevalence 3.3 (2.7 to 3.9). EFV defects include a single case of myelomeningocele and a single case of anophthalmia with severe facial clefts and amniotic binding. It is unfortunate that these data were not submitted to the APR.

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Uptake and retention in Malawi's Option B+ programme

Polly Clayden, HIV i-Base

Malawi's Option B+ programme for has led to a 763% increase in HIV positive pregnant women receiving antiretroviral treatment (ART), according to data shown at CROI 2013.

Beth Tippet Barr presented findings from the first 18 months since the introduction of Option B+ by the Malawi Ministry of Health.

The 2010 WHO guidelines made CD4 count testing a prerequisite for PMTCT, which was unfeasible in Malawi. Instead the Department of Health expanded their ART public health programme to test-and-treat for pregnant and breastfeeding women, who are now all eligible for lifelong treatment, whatever their CD4 count or clinical stage. After a positive HIV test, women receive efavirenz/tenofovir/3TC – this regimen will also become the standard adult first line regimen in Malazi later in 2013.

Implementation began in July 2011, which required the decentralisation of ART into all antenatal care (ANC) facilities, resulting in rapid expansion from 350 to over 650 sites. It also required training of nearly 5000 health-care workers. Prior to starting Option B+ many pregnant women still received only single dose nevirapine prophylaxis at smaller ANC sites.

A strong M&E framework underpins the programme: routine ANC and ART data is collected during quarterly supportive supervision visits, which include validation of reports from primary patient records. A 2011 independent data quality audit, commissioned by the Global Fund, showed 99.2% data accuracy.

Dr Tippett Barr presented data up to the end of 2012. Before Option B+ was introduced the initiation of ART had flat-lined in Malawi for almost two years to about 18,500 people starting per quarter. There was a rapid increase in new patients starting treatment in the first few months of the programme to almost 35,000 in the fourth quarter of 2011.

In the third and fourth quarters of 2012, the total number of women receiving any antiretrovirals during pregnancy increased to 20,687 from 13,910 in quarters one and two of 2011 – the period preceding the implementation of Option B+. This was a 49% increase in total antiretroviral coverage of known HIV positive pregnant women.

Such rapid scale up represents a 763% increase in the use of ART in pregnant women and the elimination of single dose nevirapine and dual prophylaxis regimens in Malawi.

An unexpected finding was the large numbers of women initiating ART during the breastfeeding period at the start of the programme – 41% in the fourth quarter of 2011. The Department of Health had not anticipated the backlog of women who heard about Option B+ and came forward. The number of women initiating during breastfeeding was sustained at about 25% over the last two quarters of 2012.

Data on women who were already receiving ART in pregnancy were not disaggregated until the last three quarters shown in the data set, when this was about 25%. This proportion of women is expected to increase as the programme matures.

Retention in care at 12 months showed 78% of women were alive and on treatment, which was similar to 81% of all other adults. Only 4% of the Option B+ patients not retained had died, compared to 31% of other adult patients.

Several key recommendations came out of this analysis:

- Reduce the number of women who do not start ART during pregnancy.
- Continue to monitor and support PMTCT coverage and retention on ART, including reasons for lack of uptake and loss to follow up.
- Examine family and community influence on the sustained high ART initiation during the breast feeding period
- Document maternal and infant outcomes.
- Document the public health impact of Option B+.

C O M M E N T

These data are impressive and it is amazing what programmes can achieve with political will and allocation of resources.

As pointed out in the discussion after the presentation, the retention figures are from pregnant or breastfeeding women, so there are no data yet for the plus part of Option B+. There is a strong "ART for life" message associated with the programme and It will be important to see whether women elect to remain on ART after the breastfeeding period.

The large number of women initiating ART during the breastfeeding period are concerning. This was particularly notable at the start of the programme but remained high throughout the study period. Dr Tippet Barr explained that this was community initiated – women came in and asked for treatment - she speculated that it was possible women had tested HIV positive previously in pregnancy but had taken time to process their diagnosis. The programme started with immediate initiation of treatment following diagnosis but now women come back to start ART after about seven days.

Monitoring the programme will include birth defect surveillance.

Ref: Barr BT et al. Uptake and retention in Malawi's Option B+ PMTCT program: lifelong ART for all HIV+ pregnant or lactating women. 14th CROI. Atlanta, GA. 3-6 March 2013. Oral abstract 82.

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Optimising ART initiation in pregnancy through linkage of services vs integration of ART into antenatal care

Polly Clayden, HIV i-Base

The separation of antenatal care (ANC) and ART services can be an obstacle to starting ART in pregnancy. Interventions to improve antenatal ART services can maximise the proportion of eligible women starting ART in pregnancy and minimise delays in ART initiation. [1]

Landon Myer from the University of Cape Town showed findings at CROI 2013 from a study evaluating two interventions that could potentially improve ART in pregnancy: enhanced linkage (EL) - using lay counsellors as navigators to guide pregnant women from ANC to ART services - vs integration (IN) of ART into ANC services - with screening and initiation performed by midwives without referral as part of routine ANC care.

The study was conducted at s single large ART programme with an adjacent ANC clinic in the township of Gugulethu, Cape Town, South Africa. It used a sequential before/after design to compare outcomes associated with standard of care (SOC) compared to the two interventions: SOC – January to June 2011; EL - July to December 2011; IN – January to June 2012.

Routine public health sector staff implemented the services with weekly monitoring and support from the research team. Eligibility for ART was according to South African guidelines, initiation at CD4 $\leq$ 350 cells/mm3 and/or WHO stage 3 or 4. Women received efavirenz/tenofovir/3TC. Data were collected describing the proportions of women completing each step in the PMTCT and ART "cascades," and delays between these.

During the study period 8752 women sought ANC care with 95% uptake of testing, 26% testing HIV positive with 90% CD4 results available. The proportion of eligible women screened for and initiating ART increased significantly from baseline. SOC 26% and 21%; EL 53% and 49% and IN 93% and 86% women were screened and initiated ART respectively, $p<0.001$ for both comparisons (differences persisted after adjustment for maternal age, gestation, education and CD4 count).

The delay from a positive HIV test in ANC to identification as eligible for ART did not vary, median, 18 days (IQR 16 – 36). But the delays from identification to ART initiation decreased significantly. Median delay: SOC 29 days (IQR 14 – 46); EL -15 days (IQR 9 - 24) and IN 7 days (IQR 5 – 14), $p=0.003$ for both comparisons.

These operational interventions to strengthen antenatal ART initiation lead to significant increases in the proportion of women starting ART as well as decreases in the delays to ART initiation, Dr Mayer concluded. But, extra interventions are needed to address the delays between HIV testing, identification as ART-eligible, and referral for ART.

C O M M E N T

The persistent delay from the day of HIV diagnosis, reported in this study and many others, remains an issue. Dr Myer described this phenomenon as "sobering", remarking, "we want as close to instantaneous initiation and excellent retention."

A related poster showing cost effectiveness modelling of point of care (POC) testing in ANC found this to be cost effective in South Africa. [2] The investigators reported that compared to "low access" laboratory, POC was cost saving unless the test cost $305 or more, or the proportion of women tested and receiving results was less than 14%. With "high-access" laboratory, POC remained cost saving unless the test cost more than $45 or the proportion of women tested and receiving results was less than 84%. When POC also improved time to ART initiation, there were also clinical benefits. The group intends to look at using POC in the programme to help to shrink the delay.

There were no increased costs with additional staffing in this programme. The EL intervention used lay counsellors, already working in the ANC, and the IN intervention an extra public sector midwife - reduced staffing at the adult ART clinic would offset this cost.

The of numbers of women accessing ART in ANC is likely to increase in South Africa and programmes also have concerns about retention in care post partum.

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CROI 2013: COMPLICATIONS

Cardiovascular disease and other non-AIDS defining events

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Several studies at CROI 2013 looked at the pathogenesis and treatment of myocardial infarction and the outcomes of the treatment of cardiovascular disease (CVD) in HIV patients including an important oral presentation session. [1]

No evidence of premature ageing effect in HIV positive patients

Similar to some other conditions including diabetes, hyperlipidaemia and rheumatoid arthritis, HIV positive people are at higher risk of developing serious age-related co-morbidities including myocardial infarction and kidney and liver disease. It is still unclear whether HIV positive patients experience these conditions at similar or younger ages compared to HIV negative individuals and this is often discussed under the contentious concept of accelerated and premature ageing.

Keri Althoff and colleagues from the Veterans Ageing Cohort Study (VACS) compared mean age at diagnosis for myocardial infarction (MI), end stage renal disease (ESRD) and non AIDS defining cancers, and also compared their incidence by HIV status. [2]

Premature ageing was defined as differences in mean age at MI, ESRD and cancer diagnosis. All analysis were adjusted for race, sex and body mass index (BMI), alcohol use, cigarette smoking, hepatitis C infection, anaemia and diabetes. Myocardial infarction and end stage renal disease analysis only were adjusted for hyperlipidaemia, lipid lowering medication, hypertension, anti hypertensive medications and statin use.

The analysis was based on data collected from 2003 to 2008 on >100,000 patients with HIV positive cases matched by age, race and ethnicity 1:2 to HIV negative controls from the same cohort. HCV was more common in HIV positive people (35% vs 15%) but diabetes (17% vs 25%), hypertension (25% vs 38%) and dyslipidaemia (36% vs 44%) was more common in HIV negative people.

In the HIV positive group, 19% had a CD4 count <200 cells/mm^3, 61% had undetectable viral load (<500 copies/mL) and 25% had an AIDS diagnosis. PI-based and NNRTI-based were each used by about 45% of people on ART. Mean age was 55 (+/- 8) years.

Mean age for each of the primary endpoints are detailed in Table 1 and although incidence rates remained higher for HIV positive vs. negative people, there were no differences in the adjusted analyses for age at diagnoses for MI and ESRD with the marginally lower age for cancers (0.7 years) unlikely to have clinical significance.

In conclusion HIV positive individuals had a greater rate of MI, ESRD and HIV associated cancers compared to HIV negative individuals.

There was no difference in mean age or adjusted mean age at MI and ESRD by HIV status. There was a modest difference at the age of non AIDS defining cancers in HIV patients (about 6 months younger in HIV positive groups). There was higher incidence of Hodgkin's disease but over all no difference in the incidences of other HIV associated or non-AIDS defining cancer rates in HIV patients.

Table 1: Mean age at diagnosis and adjusted rates by HIV status

	HIV pos (yrs)	HIV neg (yrs)	adj. mean difference, years (95% CI)	aIRR vs HIV neg (95% CI)
MI	55.3	55.3	-0.04 (-0.62, +0.64)	1.81 (1.49, 2.20)
ESRD	55.3	58.5	-0.23 (-0.69, +0.23)	1.43 (1.22, 1.66)
HIV related cancer **	54.9	57.8	-0.57 (-0.93, -0.21)	1.84 (1.62, 2.09)
Other cancers	58.5	58.7	-0.45 (-0.78, -0.12)	0.95 (0.85, 1.06)

** HIV-associated cancers were defined as anal, lung, liver and oral/pharynx cancers and Hodgkin lymphoma.

Even when a small age difference was found, the different risk factors and pathogenesis in HIV positive people are likely to explain this which is very different to the less scientific concept of premature ageing.

An analysis by Kathy Petoumenos from DAD group also found limited evidence of accelerated risk of cardiovascular disease (CVD) in HIV positive patients. [3]

The study hypothesised that accelerated ageing in HIV positive patients would mean an accelerating risk of CVD with older age, and that the increased risk per year older would be higher in D:A:D relative to the results from risk equations developed for the general population (Framingham, CUORE, ASSIGN). The researchers included 24,323 men (man age 41 years) prospectively followed in the D:A:D study (approximately 139,000 patient years of follow up) who had data collected on conventional CVD risk factors but who had no prior CVD events.

Primary events included 474 MIs, 683 cases of coronary heart disease and 884 cases of cardiovascular disease events. Crude event rates for each of these endpoints was 2.29, 3.11 and 3.65 per 1000 PYFU at age 40-45 and 6.53, 11.91 and 15.89 at age 60-65 years. They showed that there was a slowly accelerating risk of cardiovascular disease for year older and which was somewhat raised compared to the general population based on the equations for cardiovascular disease. The relative risk with MI was not different between D:A:D and the general population. The researchers did not find evidence of accelerating risk of cardiovascular disease with age in their study population.

C O M M E N T

Adjustment for younger age of HIV cohorts compared to HIV negative general population controls appears to explain much of the difference seen in studies that previously reported younger age at diagnosis of non-AIDS events in HIV positive people.

Use of coronary CT angiography to detect early noncalcified plaque in asymptomatic patients

Two oral presentations reported on the incidence of coronary artery calcification in HIV patients.

Wendy Post and colleagues from the Multicenter AIDS Cohort Study (MACS) investigated the association of age with subclinical coronary atherosclerosis (Noncalcified Coronary artery Plaque (NCP) in a cross sectional observational study in 873 MSM (n=571 HIV positive and 302 HIV negative) enrolled in four US urban cohorts. [4]

NCP is an early stage of atherosclerosis but is more serious than established calcified plaque as it may be more prone to thrombus formation and plaque rupture. Gradual expansion of sub-clinical plaque are less associated with myocardial infarctions (MI) and sudden coronary deaths (SCD) than cute plaque rupture accounts for 75% of MI and 50% of SCD.

All men received non-contrast cardiac computed tomography (CT) scans with 660 eligible patients also receiving coronary CT angiography to detect NCP and mixed plaque, and stenosis. Plaques were graded and scored by degree of stenosis, size and composition. Participants were aged 40 to 70 years, without prior cardiac or coronary surgery and weighed less than 300 pounds (a limitation for CT scans). HIV positive patients were mostly (88.6%) on ART, 80% of whom had undetectable viral load, were younger (by about 30 months), with a lower BMI (26.1 vs 27.4). They were more likely to be current smokers (32% vs 21%), and have dyslipidaemia (lower LDL and HDL and higher trigylcerides).

Coronary plaque of any type was present in 77% of HIV positive vs 62% of negative men. This difference in this rate was significant after adjusting for CVD risk factors (OR 1.80; p=0.009). There was a similar association with NCP (p=0.002), and a trend for mixed plaque (p=0.053), but no association for either calcified plaque or stenosis >50%.

In both groups, any plaque was associated with older age [OR (95%CI) per year: 1.13 (1.09-1.17) vs 1.06 (1.03-1.09), respectively; both p<0.0001] but with NCP this was only significantly associated with age in HIV positive group (p=0.002). By contrast, associations between age and the presence of any type of plaque did not defer by HIV status.

These analysis however adjusted for age and race but not CVD risk factors. There was no association between the presence of plaque or NCP with traditional HIV risk factors including nadir CD4 count, viral load, a history of AIDS and duration of HAART exposure. Nadir CD4, detectable viral load, duration of ART were independently associated with stenosis >50%.

Although the degree of coronary calcium burden in the general population is predictive of CVD events, these people tend to also have high rates of non-calcified plaque. However, in the Q&A session, it was pointed out that while the prevalence of coronary calcium was higher in HIV positive patients, both groups in this study had similar rates of coronary calcium burden.

A second study, presented by Steven Grinspoon from Massachusetts General Hospital also used CTA to investigate morphologic features of coronary plaques in 102 HIV positive to 41 HIV negative controls, prospectively enrolled and matched for traditional CVD risk factors (but all asymptomatic for CVD disease), looking at the relationship with markers of immune dysregulation. [5]

Similar to the previous study, this group have also reported higher rates of subclinical plaque, mostly non-calcified, in HIV positive compared to HIV negative patients and that additionally this is associated with higher levels of circulating sCD163 (a marker of activated macrophages).

The study analysed more than 2500 coronary segments with previous identified plaque (out of a maximum 18 per patient). Duration of HIV infection was 13 years (+/- 6.5) and 95% were on antiretroviral therapy (80% undetectable), with a mean duration of 7 years (3-11) on ART.

The prevalence of high-risk attenuated or positively remodeled plaque was significantly higher for in the HIV positive group (7.9% vs zero for the highest risk three feature analysis, p=0.02), with HIV patients having higher numbers of plaques (0-4 plaques, p=0.01), with a significant association with HIV status in the adjusted analysis (p=0.02).

Several inflammatory and immune markers were higher in the HIV positive group including IL-6 (p=0.01), LPS (p=0.0004) and sCD163 (p=0.0007) but not d-dimer (p=0.93), CRP (p=0.49) or MCP-1 (p=0.13), with a trend for sCD14 (p=0.08) but in the multivariate model, only sCD163 retained a strong association with risk of vulnerable plaque (p=0.009).

In the question session, the non-prediction of age and smoking was explained by these traditional factors having a close association with calcified but not non-calcified plaque and that these are relatively young patients (mean age 44) who have had little time to build up coronary calcium.

This group also studied a small group of elite controllers, compared to HIV positive suppressed patients and HIV negative controls, but reported few differences, perhaps to low numbers under-powering comparisons. [6]

It is also notable that a late breaker poster from the same group reported similarly higher plaque (34.7 vs 12.0%, p = 0.04) and correlation to increased sCD163 (p=0.006) in 60 HIV positive women (median age 47, HIV duration 15 years, 84% undetectable), compared to 30 HIV negative controls. [7]

C O M M E N T

These studies were important for their focus on patients with sub-clinical atherosclerosis. The highlight specific potential risks for HIV positive patients related to immune activation that are additional to traditional risks seen in general population studies and which occur even with suppressed viral load.

Coranry calcium burden, which may be the most predictive for future events was not different by HIV status in the MACS cohort.

While coronary artery calcification score is important in the general population non-calcified plaques have been found to be important as well.

Non-calcified plaques appear to be more vulnerable for getting dislodged from the arterial wall and get thrombus in the distal places. These finding may have implications for the risk of myocardial infarctions and optimal timing for CVD screening for ageing in HIV positive patients.

Post-MI survival in HIV positive patients

Several posters also looked at clinical responses in HIV positive people who experienced MI.

The D:A:D study reported dramatic improvements in short-term mortality outcomes post-MI over time in this important HIV cardiovascular study, that appeared to be related to a higher use of invasive CVD procedures (ICP). [8]

The study included 844 people with an MI, 84% of who were on ART and 61% had viral load <50 copies/mL. This group was 91% male, median age 50, median CD4 count 444 cells/mm3 (IQR 297, 666) and 66 (8%) had had a prior MI.

Over a median follow-up of 33 months, 88 (10%) patients experienced a further MI, and 281 (33%) patients died. There were 172 deaths during the first month after the MI (short-term mortality rate: 20.4%). At least one ICP in the first month was used by 419 patients (60% of those surviving >1 day) (31 bypass, 402 angioplasty, 1 carotid endarterectomy).

Over time, mortality rates in the first month dropped from 26.4% in 1999-2002 to 8.2% in 2009-2011 with use of early ICP increasing from 43% to 73% in the earlier vs later periods respectively.

A US study concerned that HIV positive people might have poorer access to the emergency services that are essential in ensuring rapid responses to MIs reported similarly positive outcomes irrespective of HIV status, though the numbers of HV positive patients was relatively low. [9]

In this registry 30/646 patients (4.5%) were HIV positive, with HIV positive patients being younger (50 vs. 62 years, p <0.01), significantly more likely to use illegal drugs (43% vs 13%, p <0.01) and with a trend towards fewer traditional cardiovascular risk factors (hypertension, 34% vs 53%, p = 0.06 and dyslipidaemia, 14% vs. 30%, p = 0.09).

There were no differences in the rates of angioplasty, stent placement or in-hospital mortality between the two groups and after multivariate adjustment, HIV positive patients were significantly more likely to use emergency services (OR 3.03, 95% CI: 1.16 – 7.88).

A second multivariate analysis from the VACS study reported that HIV positive people had higher rates of heart failure compared to HIV negative patients, and that this resulted in significantly higher hazard ratios, there was no difference in outcomes related to whether ejection fraction was preserved or reduced. [10]

C O M M E N T

The improved immediate survival over time after MI in HIV patients is helpful and encouraging for both health workers and HIV positive patients.

Aspirin use in HIV positive patients

While there is increased risk of CVD in HIV positive patients, aspirin use has not been studied in this group. Sujit Suchindran and colleagues from Massachusetts General Hospital presented results from a retrospective a cohort analysis of around 3,700 HIV positive patients and 33,000 HIV negative controls without known baseline coronary heart disease, followed from 2000 to 2009 in a US healthcare cohort. [11]

They investigated use of aspirin whether it reduced incidence of cardiovascular disease. They found that aspirin use was lower in HIV patients, particularly men and those with highest cardiovascular disease risk. However, aspirin use had no obvious effect in reducing myocardial infarction in HIV positive patients compared to the HIV negative individuals.

Aspirin use was recorded as being slightly but significantly lower among HIV positive people compared to HIV negative controls (12.4% vs 15.3%, p <0.001) although the difference was driven by lower use by HIV positive men rather than women. It was more almost 50% lower amongst higher risk patients with two or more coronary heart disease risk factors (22.1% vs 42.4%, p <0.001), with similarly reduced use byt both HIV positive men and women.

In multivariate analyses, aspirin use was only associated with reduced risk of myocardial infarction amongst HIV negative patients with no association of protection in overall HIV group or any subgroup.

C O M M E N T

Aspirin use was lower amongst HIV positive patients compared to HIV negative patients with a greater relative difference amongst those with significant cardiovascular risk. Although benefit was not demonstrated in HIV positive patients, this was an observational study with potential for selection bias especially with data dependent on hospital inpatient and outpatient prescription registries.

In the absence of evidence from randomised studies, aspirin use should probably be considered in HIV positive patients for similar indications as the general population.

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CROI 2013: HEPATITIS C COINFECTION

Dramatic advances at CROI for HCV treatment: telaprevir, boceprevir, faldaprevir, sofosbuvir, ABT-450, ABT-267, ABT-333 and ledipasvir

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The wealth of hepatitis C studies at CROI 2013 included two oral abstract sessions, a symposium, a young investigator session and numerous poster sessions.

These featured new drugs in co-infected patients and interferon-free combinations in mono-infected patients highlighting the clinical decisions for optimal management and timing of treatment. Several studies were also presented on drug-drug interactions.

New and pipeline treatments

The three new groups of drugs with direct activity against hepatitis C are NS3/4 protease inhibitors (first generation of which, telaprevir and boceprevir are already approved), nucleoside/tide and non-nucleoside NS5B polymerase inhibitors (generally furthest along in pipeline development) and NS5A inhibitors. Although the study design differs between studies the top line results in this report highlights the vibrant optimism for approaching therapies.

NS3/4 protease inhibitors

There were several studies using NS3/4 protease inhibitors with pegylated interferon plus ribavirin (pegIFN/RBV) in coinfected patients with HCV genotype 1 infection.

Results from two ANRS studies using telaprevir and boceprevir in HCV treatment-experienced patients were included as oral presentations. These two recently approved drugs that are already standard of care but require dosing three times a day. Approximately 30-35% of patients in both studies had F3/4 cirrhosis although, as with most of the studies at CROI, decompensated cirrhosis was an exclusion criteria. Treatment duration was 48 weeks although this was extended to 72 weeks for patients without early treatment responses.

An interim analysis at 16 weeks reported approximately 90% of patients using telaprevir and 50-70% using boceprevir had early treatment responses (ETR) defined as undetectable HCV RNA. This has a strong correlation to sustained virological response (SVR), irrespective of previous non-response to pegIFN/RBV. This included 70% patients with F4 cirrhosis in the telaprevir study.

However, side effects were significant. Approximately 10% patients on telaprevir discontinued before week 16, about 30% of participants had grade 3/4 side effects and 58% required erythropoietin. There were 67 grade 3/4 side effects reported by the 39 patients in the boceprevir study, including 21 serious adverse events.

Once-daily NS3/4 PIs: faldaprevir and simeprevir

Interim 12-week data in 308 HIV/HCV coinfected patients (239 naïve, 69 previous relapsers) was also presented for faldaprevir. This is a once-daily NS3/4 protease inhibitor in development with Boehringer Ingelheim. All patients also used pegIFN plus ribavirin and the majority were also on ART. [3]

This late-breaker oral presentation reported greater than 90% ETR in HCV treatment-experienced patients and 85% in those using HCV treatment for the first time. These results were equivalent to those seen in HCV monoinfection. Approximately 10% of patients reported serious side effects with 6% of patients discontinuing the study early due to tolerability.

Another two oral late-breakers presented interim 24-week results with simeprevir (TMC435). This is a once-daily NS3/4 protease inhibitor in development with Tibotec/Janssen. [4, 5]

One study included 50 HCV treatment-naïve patients and 14 prior non-responders. All patients used pegIFN plus ribavirin. Rapid viral response (RVR) rates were approximately 90% at week 4 but was lower in previous null responders. Overall, 15% of patients experienced HCV treatment failure (approximate breakdown: naïve 9%, previous relapsers 0%, previous partial responders 10%, previous null responders 36%). Approximately 30% of patients reported grade 3/4 with serious adverse events in 5% of patients and 4 discontinuations.

Interim results from a second study, combined simeprevir with the investigational nucleotide NS5B polymerase inhibitor sofosbuvir which is being developed by Gilead. This study was in prior non-responders, with some patients randomised to additional ribavirin but without using pegIFN. In the very small numbers of patients with longer follow-up data, sustained viral response (SVR) rates at week 4 and 24 were greater than 85%. The suggestion from this dataset was that when two effective DAAS are combined, even for previous IFN null-responders, ribavirin may not be required.

Shorter treatment duration: 12 weeks in acute HCV

Telaprevir with pegIFN plus ribavirin was also associated with higher response rates from shorter duration of treatment (compared to historical results using only pegIFN plus ribavirin) in a US study of acute HCV genotype-1 infection. The results were from a small single-arm open-label study in 18 men with HCV genotype 1 and health insurance that would cover telaprevir treatment. [6]

Patients with RVR at week-4 stopped treatment at week 12, with an additional 12 weeks of pegIFN plus ribavirin for two patents without RVR.

The SVR rate at 4 weeks after end of treatment was 83% (15/18 patients). Over 75% of these men had IL28B CC genotypes. Interpretation of these results is thus complicated by the difficulty of knowing whether some of these people may have spontaneously cleared HCV without treatment and whether the shorter duration of therapy may only be applicable to sub-set of patients with IL28B CC genotypes, as is already becoming apparent in chronic genotype 1 HCV monoinfection.

Drug interactions

The complexity of drug interactions with new HCV treatments was highlighted in several studies.

An interaction between telaprevir and ribavirin (RBV) in monoinfected patients appears to increase plasma levels of ribavirin by 1.5 fold and intracellular levels of RBV mono-, di- and tri-phosphates (by 2-3 fold). The mechanism for this is not yet unexplained, but this could explain the high rates of anaemia seen in the ANRS studies reported above. [7]

A poster reported that boceprevir increased plasma levels of the HIV NNRTI rilpivirine [GMR (90%CI) for AUC, Cmax and C24h levels was 1.39 (1.27, 1.52), 1.15 (1.04, 1.28), and 1.51(1.36, 1.68) respectively] but that this was not considered clinically significant and that no dose adjustment was necessary. [8]

CYP-mediated interactions between faldaprevir (FDV) and some ARVs in a study in uninfected volunteers reported that FDV exposure increased by 130% with darunavir/ritonavir (requiring an FDV dose reduction) and decreased with tenofovir, and efavirenz (by 22% and 35% respectively, both requiring FDV dose increase). FDV has no clinically significant affect on levels of darunavir or tenofovir [9]

The best source for this growing complex field is the HCV drug interaction website developed by Liverpool University. [10]

Interferon-free treatment in HCV monoinfection

Several studies in HCV monoinfected patients provided early results from other exciting pipeline HCV drugs often in interferon-free oral combinations.

A US NIH-sponsored phase II study in difficult to treat (mostly African-American patients with genotype 1, non-CC monoinfection) using sofosbuvir (NS5B nucleotide) plus high/low dose ribavirin, reported high week 4 and week 12 early response rates (>95% and 90%) but that significantly lower SVR rates 24-weeks post-treatment (48-70%) suggesting that full weight-base ribavirin dosing is still required. [11] This is different to the sofosbuvir/simeprevir combination (Cosmos study reported above).

An interferon free combination from Abbott used three new compounds: ABT450/ritonavir (PI), ABT 267 (NS5A inhibitor) and ABT-333 (non-nuceloside polymerase inhibitor), with and without ribavirin, reported SVR rates of around 90% or higher at 12 week post-treatment in treatment naïve patients and around 90% in prior null responders. They also reported very low rates of relapse in the 4-drug arm in prior null responders after 8 and 12 weeks of treatment (~12% and 1% respectively, with little or no association with high HCV viral load or IL28B HCV genotype. In a logistic regression analysis of the quadruple therapy arms, length of therapy less than 12 weeks was the only statistically significant factor associated with risk of relapse, but note that this study excluded cirrhotic patients. [12]

Simeprevir (TMC-435) plus sobosfuvir (GS-7977), with and without ribavirin, with both 12 week and 24 week treatment arms in genotype 1 prior null responders showed significantly reduced rates of rapid virologial responses (RVR week 4) in the two-drug arms, suggesting that ribavirin may affect viral kinetics.. However, early results (SVR4) showed little difference between the 12 and 24 week treatment groups, suggesting that 12 weeks may be possible even fro prior null responders. [13]

Final results from another interferon-free combination using two Gilead compounds: sofosbuvir (NS5B nucleotide) plus ledipasvir (GS-5885; NS5A inhibitor), plus ribavirin, in patients with genotype1 monoinfection (25 treatment-naive and 9 previous non-reponders) reported 100% end of treatment responses and 100% 4-week post-treatment responses. [14]

The challenge in the current management of HCV/HIV coinfected patients is assessing who should use currently available, more difficult, but still successful treatments, and who may be able to wait for the treatment in development that are likely to be easier to tolerate.

This issue was the focus of a retrospective Spanish study looking at the risk of liver decompensation in 102 patients (86% were men) with HCV/HIV coinfection and with F3/F4 (57/43%) fibrosis over 12 years (median 5.6 years follow-up). [15]

Baseline characteristics included median (IQR) age was 39 (37-44) years, CD4 cell count 497 cells/mm3 (331-666) and 71% had undetectable HIV viral load.

The incidence of decompensation events per 100 patient years was 0.12 (95% CI: 0.05-0.28) cases vs 0.45 (0.26-0.78) for patients with F3 vs. F4 stage respectively at baseline. The probability of remaining free of decompenstation for patients with F3 vs F4 was: at 1, 3 and 5 years was 98% (88%-100%) vs 86% (71%-93%); 94% (82%-98%) vs 75% (59%-86%) and 84% (62%-94%) vs 59% (38%-75%) respectively (p=0.007).

Although baseline fibrosis F4 vs F3 only showed a borderline association [HR 2.7; 95%CI: 0.93-7.95; p=0.067), baseline platelet count <100 x 10^3 was significant associated with the risk of decompensation (HR 3.9: 95%CI 1.4-11.2; p=0.011). Predictors for progression also included F4 stage on biopsy or liver stiffness >14.6 KPa with Fibroscan.

Although the study concluded that patients with F3 fibrosis are at significant risk of decompensation over three years – the expected time needed for need drugs to become available – monitoring may help identify patients who have the lowest risks and where waiting may be appropriate.

Note: This article is based on a BHIVA feedback lecture that is posted online as a webcast. [16]

C O M M E N T

This is a very exciting time for HCV coinfection.

While both telaprevir and boceprevir plus pegIFN and ribavirin continue to be standard of care and dramatically improve response rates in genotype 1 infection, treatment involves complex daily regimens, careful management of interactions with ARVs and other medications and side effects are difficult.

Although ribavirin is likely to continue to be needed with other oral HCV drugs that are furthest in the pipeline, treatment may be able to be shortened to 12 weeks with some combinations. These are generally once-daily drugs with fewer side effects, in all-oral combinations with very high rates of viral efficacy.

While results look impressive and encouraging these were generally interim analyses at early time points, and that patients with decompensated cirrhosis were not included.

Close monitoring is needed to determine the risks of deferring treatment for patients with the lowest risk for liver decompensation.

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CROI 2013: BASIC SCIENCE

Basic research highlights from CROI 2013

Richard Jefferys, TAG

Gene modification of virus-specific CD4 T cells

Patrick Younan from the Fred Hutchinson Cancer Research Center delivered an interesting talk about transplantation of gene-modified stem cells in pigtailed macaques). [1]

The experiment used lentiviral vectors to deliver the gene for a virus entry inhibitor, C46 (also known as M87), it has a similar mechanism of action to the approved antiretroviral Fuzeon), into stem cells along with a green fluorescent protein (GFP) marker to make the modified cells identifiable. Four macaques underwent stem cell transplantation, with two given C46-modified cells and two controls given cells with only the GFP marker. All were subsequently challenged with the dual-tropic SIV/HIV hybrid virus SHIV89.6P. T

The two controls displayed typical rapid CD4 T-cell loss, and one was euthanised at week 32 due to the onset of simian AIDS. In contrast, recipients of the modified cells recovered CD4 T-cell counts after an initial dip and showed significantly lower viral loads. Levels of gene-modified CD4 T cells peaked at around 90% during acute infection, but subsequently declined to pre-challenge levels (around 20% in one animal, 55% in the other) during follow-up.

Despite the decline in modified CD4 T cells, levels of unmodified cells improved over time, suggesting a protective effect of the intervention on the overall CD4 T-cell pool.

Further studies revealed that superior SHIV-specific CD4 T-cell and antibody responses were associated with the salutary outcome. SHIV-specific CD4 T cells were not detectable in either of the controls. Younan found that a striking 85% of the SHIV-specific CD4 T cells in treated animals were gene-modified, suggesting that protection of these cells had allowed them to better perform their role of providing help to B cells and CD8 T cells.

One potentially encouraging implication of this work is that gene therapy approaches might not have to protect all susceptible cells from HIV infection in order to offer benefit; if sufficient numbers of HIV-specific CD4 T cells can be protected, it is possible that these cells will do a better job of coordinating the immune response against HIV, leading to improved control of viral replication. This possibility is being investigated in ongoing trials of Sangamo BioSciences SB-728-T gene therapy, which aims to protect CD4 T cells by abrogating expression of the CCR5 coreceptor.

Engineering SIV to spare the CD4 T-cell help

Adrienne Swanstrom from the University of Pennsylvania described a novel approach to defining the role of infection of CD4 T cells in SIV pathogenesis, using an engineered version of the highly pathogenic SIVmac239—named iMac-delta-D385—that does not bind the CD4 molecule. [2]

In a preliminary experiment involving just two macaques, Swanstrom found that the modified virus replicated to levels comparable to the wild-type SIVmac239 during acute infection and targeted a variety of non-CD4 cell types, but was then robustly controlled by the immune response. Strong neutralising antibody responses were detected, which is unusual in pathogenic SIV infection, and ongoing work is now looking at CD8 T-cell responses. The findings, at least so far, suggest that sparing CD4 T-cell help led to more effective CD4 T cell–dependent immune responses and superior control of SIV replication.

CMV vector vaccination leads to apparent clearance of SIV infection

Louis Picker from the Vaccine and Gene Therapy Institute at Oregon Health & Science University gave an update on results obtained in macaques with a CMV-based vaccine against SIV. [3]

As Picker has shown in published work, the vaccine consistently facilitates strict control of a pathogenic SIVmac239 challenge in around 50% of immunized macaques. [4]

The remarkable news shared by Picker at CROI is that, over time, these protected animals appear to clear SIV infection. This claim is based on multiple criteria, including loss of detectable virus, waning of CD8 T-cell responses to viral antigens not included in the vaccine, and the failure to transmit infection to uninfected macaques despite transfer of over 50 million blood and/or tissue white blood cells (in contrast, similar transfers from elite controller animals or those on suppressive ART reliably transmitted infection).

Picker noted that the CD8 T-cell responses in the vaccine recipients appear to "violate all the rules" in that they target very large numbers of different SIV epitopes and, in many cases, their ability to recognise the virus involves MHC class II molecules, which normally facilitate antigen recognition by CD4 T cells rather than CD8 T cells.

Picker is now working to shed further light on these findings, as well as collaborating with the Vaccine and Gene Therapy Institute of Florida to try and develop a CMV vaccine vector that can safely be studied in humans.

Results from multidose vorinostat trial

Sharon Lewin from Monash University in Melbourne debuted data from the first multidose trial of vorinostat (also known as SAHA) as a potential anti-HIV latency drug. [5]

Consistent with results published by David Margolis from a single-dose trial, expression of HIV RNA significantly increased among the twenty participants after 14 days of vorinostat. However, there was no evidence for reduction in the size of the latent HIV reservoir, suggesting that additional approaches will be needed to facilitate the elimination of the infected cells. As expected, vorinostat side effects were more prevalent as a result of the multiple dosing, particularly fatigue and lethargy.

Curing HIV removes the scars of the past

One small but encouraging piece of news about the lone adult considered cured of HIV, Timothy Brown, was to be found in a presentation by Joyce Sanchez from the University of Minnesota. [6]

Sanchez's study focused on lymphoid structure abnormalities in people with HIV, particularly fibrotic (scarring) damage to lymph tissue resulting from persistent HIV replication and associated immune activation. The extent of lymph tissue fibrosis can be quantified by measuring collagen deposition using imaging techniques.

Sanchez showed that in gut lymph tissue, even HIV controllers (individuals with low viral loads in the absence of ART) have levels of collagen deposition that are higher than those of uninfected individuals (15.9% compared with 7%). However, samples from Timothy Brown showed levels of collagen deposition comparable to the uninfected study participants (6.8%), consistent with studies showing no HIV activity in his body (despite the occasional detection of viral genetic material that was reported last year).

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Probiotic/prebiotic supplement combination shows benefits in SIV-infected pigtailed macaques

Richard Jefferys, TAG

Over the years a number of small studies have been published suggesting that there might be benefits associated with probiotic and/or prebiotic supplementation in people with HIV infection.

Probiotics typically comprise live microbes that play a key role in maintaining gut health—commonly known as "good bacteria" —while prebiotics are food ingredients intended to stimulate the expansion and activity of these bacteria. The past decade has seen a renewed interest in gut health in HIV infection due to evidence that the virus severely depletes CD4 T cells in the GI tract, leading to diminished immune surveillance, compromised gut wall integrity and microbial translocation (the leakage of gut bacteria into the systemic circulation). Additionally, suppression of HIV replication by antiretroviral therapy (ART) does not necessarily restore gut CD4 T cell numbers and markers of microbial translocation have been associated with poor immune reconstitution despite ART.

To try and address the question of whether a combination of probiotics and prebiotics (referred to as synbiotic treatment) might serve as a useful adjunct to ART, Nichole Klatt and colleagues conducted a study in the animal model of SIV-infected pigtailed macaques and reported that, compared to ART alone, adjunctive synbiotic treatment (the specific products used were VSL#3 and Culturelle) had positive effects on gut CD4 T cells and antigen-presenting cells, and also reduced fibrosis in local lymph tissue. The results appear encouraging, and were discussed at the recent CROI by senior author Jason Brenchley. [1] The results were also published in the February 1st issue of the Journal of Clinical Investigation. [2]

Something that isn't mentioned in the JCI paper, or addressed directly in Brenchley's talk, is that previous work from this research group has shown that gut integrity in pigtailed macaques is unusually compromised even in uninfected animals; [3] in a separate new paper published in the March 15th issue of the Journal of Immunology, they show that this correlates with the faster progression to AIDS that occurs in this monkey species. [4]

On the one hand, this may make pigtailed macaques a useful worst-case scenario in terms of modelling the contribution of microbial translocation to HIV pathogenesis and studying interventions like probiotics, but on the other hand the extent to which findings from this extreme situation can be extrapolated to humans is as yet unclear.

Available published data on synbiotic treatment in people with HIV appears limited, either involving individuals not on ART or very short-term follow-up. From a PubMed search, no trials have used the specific combination of VSL#3 and Culturelle. Currently clinicaltrials.gov lists one open clinical trial of the probiotic Biola ® that is enrolling individuals both on and off ART; study sites are limited to Oslo, Norway and Stockholm, Sweden. [5]

According to US-based researchers, there are plans afoot to conduct a randomised controlled clinical trial to assess whether the promising results from the Brenchley laboratory can be translated to humans with HIV infection.

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TREATMENT ACCESS

Upcoming WHO ART guidelines

Polly Clayden, HIV i-Base

Top lines from the not yet final, revised WHO guidelines have now been presented in two public forums – a satellite before CROI 2013 in Atlanta, and at the 3rd International HIV Treatment as Prevention Workshop in Vancouver. Neither presentation is available online.

The guidelines will recommend starting ART at CD4 counts below 500 cells/mm3, with priority given to people less than 350. There will also be non-CD4 guided recommendations for people with TB or hepatitis B, pregnant women – either stopping after breastfeeding or lifelong treatment (Options B and B+) - people with negative partners and children less than five.

The guidelines will be consolidated, ie adult, pregnancy and paediatric recommendations in the same document and will include guidance on implementation.

They will be released at the IAS meeting in 2013, when we will give a more detailed review.

Fixed dose combination efavirenz/tenofovir/FTC for South Africa

Polly Clayden, HIV i-Base

After a considerable wait (and considerable campaigning), in 2012, the South African Minister of Health, announced the award of a new antiretroviral tender – worth R5.9 billion (£406,226,800).

For the first time since the ART programme began, the tender includes a triple fixed-dose combination (FDC). The FDC is efavirenz/tenofovir/FTC for first line treatment and it is anticipated that over 90% of new patients will be eligible to initiate this FDC, including pregnant women.

Source: The Southern African Clinicians Society advice document. Fixed-dose combination for adults accessing antiretroviral therapy. SAHIVMED Vol 14, No 1 (2013).

http://www.sajhivmed.org.za/index.php/sajhivmed/article/view/913/798

New UNAIDS report highlights progress in the AIDS response in Africa

UNAIDS reports more than 7 million people now on HIV treatment across Africa - with nearly 1 million added in the last year - while new HIV infections and deaths from AIDS continue to fall.

The number of people in Africa receiving antiretroviral treatment increased from less than 1 million in 2005 to 7.1 million in 2012, with nearly 1 million added in the last year alone. AIDS-related deaths are also continuing to fall - reducing by 32% from 2005 to 2011 as are the numbers of new HIV infections which have fallen by 33% from 2001 to 2011. The report attributes this success to strong leadership and shared responsibility in Africa and among the global community. It also urges sustained commitment to ensure Africa achieves zero new HIV infections, zero discrimination and zero AIDS-related deaths.

Source: UNAIDS press release. (21 May 2013).

http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2013/may/20130521prupdateafrica/

Report:

http://www.unaids.org/en/media/unaids/contentassets/documents/document/2013/05/20130521_Update_Africa.pdf (PDF)

Indian Supreme Court delivers verdict in Novartis case: decision safeguards access to affordable medicines and prevents abusive patenting of medicines

MSF press release

The landmark decision by the Indian Supreme Court in Delhi to uphold India's Patents Act in the face of the seven-year challenge by Swiss pharmaceutical company Novartis is a major victory for patients' access to affordable medicines in developing countries.

"This is a huge relief for the millions of patients and doctors in developing countries who depend on affordable medicines from India, and for treatment providers like MSF," said Dr Unni Karunakara, MSF International President. "The Supreme Court's decision now makes patents on the medicines that we desperately need less likely. This marks the strongest possible signal to Novartis and other multinational pharmaceutical companies that they should stop seeking to attack the Indian patent law."

India began granting patents on medicines to comply with international trade rules, but designed its law with safeguards – including a clause known as Section 3(d) - that prevent companies from abusing the patent system. Section 3(d) prevents companies from gaining patents on modifications to existing drugs, in order to ever extend monopolies.

Novartis first took the Indian government to court in 2006 over its 2005 Patents Act because it wanted a more extensive granting of patent protection for its products than offered by Indian law. In a first case before the High Court in Chennai, Novartis claimed that the Act did not meet rules set down by the World Trade Organization and was in violation of the Indian constitution. Novartis lost this case in 2007, but launched a subsequent appeal before the Supreme Court in a bid to weaken the interpretation of the law and empty it of substance. All of Novartis's claims have now been rejected by the Supreme Court.

"Novartis's attacks on 3(d), one the elements of India's patent law that protect public health, have failed," said Leena Menghaney, India Manager for MSF's Access Campaign. "Patent offices in India should consider this a clear signal that the law should be strictly applied, and frivolous patent applications should be rejected."

Although Novartis's repeated legal attacks on 3(d) were aiming to ensure even more patents were granted in India including on existing medicines, the company has raised concerns about the implications of the decision on the larger question of financing of medical innovation.

"At the moment medical innovation is financed through high drug prices backed up by patent monopolies, at the expense of patients and governments in developing countries who cannot afford those prices," said Dr Karunakara. "Instead of seeking to abuse the patent system by bending the rules and claiming ever longer patent protection on older medicines, the pharmaceutical industry should focus on real innovation, and governments should develop a framework that allows for medicines to be developed in a way that also allows for affordable access. This is a dialogue that needs to happen. We invite Novartis to be a part of the solution, instead of being part of the problem."

Source:

MSF press release. Indian Supreme Court delivers verdict in Novartis case. (1 April 2013).

http://www.msfaccess.org/resources/press-releases/2029

Timeline of events

http://www.msfaccess.org/content/timeline-key-events-novartiss-attack-pharmacy-developing-world

Q&A on patents in India and the Novartis case

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What future for India's Patent Act? Novartis vs. Union of India

http://www.msfaccess.org/content/what-future-india's-patent-act-novartis-vs-union-india

FDA approval of generic ARVs

Since the last issue of HTB, the US Food and Drug Administration (FDA) has granted tentative approval for the following new generic ARV products.

Drug and formulation	Manufacturer, Country	Approval date
efavirenz/FTC/tenofovir FDC tablets, 600 mg/200 mg/300 mg	Aurobindo, India	2 April 2013

FDC: Fixed Dose Combination

Effective patent dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:

http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

An updated list of generic tentative approvals (now at 140) is available on the FDA website:

http://www.fda.gov/oia/pepfar.htm

Source: FDA list serve
http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm

ANTIRETROVIRALS

EU approves four-in-one Stribild

STOP PRESS: On 28 May 2013, Gilead announced that the European Commission has granted market authorisation for Stribild with an indication for treatment-naive patients.

This is a single tablet combination containing elvitegravir 150 mg/cobicistat 150 mg/FTC 200 mg/tenofovir DF 245 mg.

Ref: Gilead press statement. European Commission approve Stribild, a new single tablet regimen for the treatment of HIV-1 infection. (28 May 2013).

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

EU approval for raltegravir in children aged 2 years and older

On 18 April 2013, MSD announced today that the European Commission (EC) has granted marketing authorisation to raltegravir (Isentress) for use in children two years of age and older weighing at least 12 kg.

This includes a chewable formulation (25mg and 100mg).

The new paediatric indication is based on the evaluation of safety, tolerability, pharmacokinetic parameters and efficacy of raltegravir through 48 weeks in a multi-centre, open-label study in HIV-1 infected treatment-experienced children and adolescents two through 18 years of age (IMPAACT P1066).

For full details please see the updated Summary of Product Characteristics.

Source

MSD press statement. MSD receives EU approval for Isentress (raltegravir) for combination use in children two years of age and older with HIV-1: chewable tablet for treating HIV-1 for paediatric patients age 2-11 years granted authorisation by the European Commission. (18 April 2013).

http://www.msd-uk.co.uk/newsroom/

FDA delays decision for elvitegravir and cobicistat

On 29 April 2013, a press release from Gilead noted that the FDA would not be approving applications for elvitegravir and cobicistat as separate drugs in their current form.

The press release states that the FDA Complete Response Letters "stated that during recent inspections, deficiencies in documentation and validation of certain quality testing procedures and methods were observed and that Gilead is working with FDA to address the questions raised and move the applications forward."

These applications have no impact on the previous approval of the four-in-one fixed dose combination Stribild, which contains elvitegravir, cobicistat, tenofovir and FTC. Stribild was approved by the FDA in August 2012 and is expected to receive EU approval as this issue of HTB went to press.

Source

Gilead press statement. Gilead receives complete response letters from U.S. Food and Drug Administration for elvitegravir and cobicistat. (29 April 2013).

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

FDA update label for paediatric efavirenz and capsule sprinkle formulation

On 2 May 2013, the FDA expanded the indication for Sustiva (efavirenz) to include pediatric patients at least three months old and weighing at least 3.5 kg.

For pediatric patients who cannot swallow capsules, the capsule contents can be administered with a small amount of food or infant formula using the capsule sprinkle method of administration.

The updated labeling includes a table for dosing along with the corresponding number of capsules or tablets and strength to administer.

For full details please see the updated Summary of Product Characteristics.

Table 1: Weight and dose table for paediatric use of efavirenz

Patient body weight	Efavirenz daily dose	Number of capsules (i) or tablets (ii) and strength to administer
3.5 kg to <5 kg	100 mg	2 x 50 mg capsule
5 kg to <7.5 kg	150 mg	3 x 50 mg capsules
7.5 kg to <15 kg	200 mg	1 x 200 mg capsule

15 kg to <20 kg	250 mg	1 x 200 mg PLUS 1 x 50 mg capsule
20 kg to <25 kg	300 mg	1 x 200 mg PLUS 2 x 50 mg capsule
25 kg to <32.5 kg	350 mg	1 x 200 mg PLUS 3 x 50 mg capsules
32.5 kg to <40 kg	400 mg	2 x 200 mg capsules
at least 40 kg	600 mg	1 x 600 mg tablet OR 3 x 200 mg capsules

(i) Capsules can be administered intact or as sprinkles

(ii) Tablets must not be crushed

Source:

BMS press statement. Bristol-Myers Squibb receives US FDA sNDA approval for use of Sustiva (efavirenz) in HIV-1 infected pediatric patients. (3 May 3 2013).

http://www.bms.com/News/press_releases

Cobicistat compared to ritonavir to boost atazanavir in treatment naive patients

Simon Collins, HIV i-Base

Results from a recent randomised, double-blind, double placebo, phase III study comparing cobicistat to ritonavir to boost atazanavir were published in the 26 March edition of the Journal of Infectious Diseases. [1]

Cobicistat is an inhibitor of cytochrome P450 3A4 is currently approved as one component of the four-in-one fixed dose combination Stribild, where it boosts the integrase inhibitor elvitegravir.

It is a weak inhibitor of CYP2D6 but not other CYP or UGT pathways and has a similar effect to ritonavir on other drug transporters including P-gp, BCRP, and OATP1B1/3. Unlike ritonavir, cobicistat has no activity against HIV, but it is not always interchangeable with ritonavir (for example, it can't be used to boost tipranavir).

The study included 692 treatment-naive patients, and reported that cobicistat was non-inferior to ritonavir as a booster for atazanavir based on viral efficacy <50 copies/mL at 48 weeks.

Although the side effect profile appears to offer few advantages compared to ritonavir, cobicistat is being coformulated with both atazanavir and darunavir to simplify dosing. These studies provide a clearer data set for the efficacy and safety of cobicistat compared to ritonavir, as use in Stribild is complicated by the impact of elvitegravir.

Mean (+/–SD) baseline characteristics included: age 37 years (+/-9.8), CD4 350 (+/- 170) cells/mm^3 (17% <200 and 14% >500) with median viral load 4.8 log copies/mL. Approximately 17% were women with 60% white, 18% black and 28% Hispanic. As with studies as part of Stribild, baseline entry criteria included no prior renal disease, defined as eGFR levels >70 mL/min.

Tenofovir DF/FTC was used as a background NRTIs for all patients. Response rates were 85% vs 87% (difference –2.2%; 95% CI –7.4% to +3.0%, p=0.40) in the cobicistat vs ritonavir groups respectively, using FDA ITT snapshot analysis, with no difference for the approximately 40% of patients with viral load >100,000 copies/mL at baseline (86% suppressed in each arm).

Side effects were generally mild and broadly comparable, accounting for 7% of patients discontinuing in each arm. The most commonly reported side effects (in >10% patients) included jaundice (21% vs 16%), scleral icterus (yellow eyes, 18% each arm), nausea (~17%), diarrhoea (15% vs 20%), headache (11% vs 15%) and hyperbilirubinaemia (11% vs 100%); all cobicistat vs ritonavir respectively, no significant differences.

Median increases in serum creatinine were 0.13 vs 0.09 mg/dL were greater in the cobicistat group (p< 0.001) most occurring by week 8 and stable thereafter, with 6 compared to 5 patients discontinuing for renal events. This was associated with a corresponding decrease in eGFR (–12.9 vs –9.1 mL/min respectively, p<0.001. In the cobicistat group, 1/6 was due to reduced eGFR, and 5/6 with laboratory markers associated with proximal tubopathy compared to 2/5 in the ritonavir group. These resolved on discontinuation.

Increases in total cholesterol (+5 vs +9 mg/dL, + = 0.081) and triglycerides (+19 vs +32 mg/dL, p=0.063) were numerically higher with ritonavir but not statistically different.

Cobicistat inhibits tubular secretion of creatine which reduces estimated but not actual GFR and has been reported in earlier studies. [2]

For clinical management, an increase of 0.4 mg/dL or greater may be able to be used as a conservative cut-off to address concerns about potential tenofovir renal tubular toxicity. [3]

Other ongoing formulations with cobicistat include:

- elvitegravir/cobicistat/FTC/tenofavir alafenamide fumerate (TAF)
- darunavir/cobicistat/FTC/TAF
- atazanavir/cobicistat

Cobisistat was submitted to the FDA as a separate compound in June 2012 but has yet to receive FDA approval as a separate drug.

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SIDE EFFECTS & COMPLICATIONS

Osteonecrosis in HIV positive patients is associated with increased levels of CRP and D-dimer

Simon Collins, HIV i-Base

A retrospective case control study of 43 HIV positive patients with MRI-confirmed osteonecrosis of the femoral head (n=26 symptomatic, n=17 asymptomatic) found they had significantly elevated levels of the biomarkers C-reactive protein (CRP) and D-dimer compared to a control group of 50 HIV positive patients with negative MRI results.

This was a US study by Caryn Morse and colleagues from the National Institute of Health Clinical Centre and results were published as a concise communication in the 20 February 2013 edition of AIDS. [1]

All participants were already enrolled in other NIH studies, including a natural history study of osteonecrosis,

CRP (an inflammation marker commonly associated with cardiovascular disease) and D-dimer (a coagulation degradation product) have both been associated with increased risk of mortality and serious complications in HIV positive studies, independently of CD4 and viral load.

Samples were used from osteonecroisis diagnosis (+/- 2 months) and from at least 6 months prior to and post diagnosis for the active group, with the control using samples from the time of negative MRI and 6 months later. Values below the detection limit of the test were assigned a value of 0.21 mg/mL for D-dimer and of 0.16 mg/L for CRP.

Although baseline characteristics (at time of MRI) was similar for both groups, significant differences included longer duration of HIV infection (median 11.7 (range 1.6–19.5) vs 8.8 (0.4–16.4) years, p=0.003) and lower CD4 count (median 465 (range 12–1117) vs 686 (71–1705) cells/mm3, p=0.008) for the active vs control group respectively. Most participants were male (~90%) and on ART (~90%) with only 50% in each group having viral load <50 copies/mL. A high percentage of both groups had prior use of IL-2 (40% vs 60%, respectively).

Median levels of both D-dimer (0.32 vs 0.22 mg/mL; p=0.016) and CRP (2.52 vs 1.23 mg/L; p=0.003) were significantly higher in the active vs control group and remained significant after adjustment for viral load and anticardiolipin antibody status.

However, in linear regression analysis, the patterns of elevations were different for each biomarker after adjusting for viral load. D-dimer increased from the prediagnosis to diagnosis time point only in the osteonecrosis group (from 0.2 ug/L to 0.4 ug/L vs 0.2 ug/mL in controls). CRP levels remained stable (slope = zero) in each group over time. No difference was seen in D-dimer or CRP levels between the asymptomatic and symptomatic patients in the osteonecrosis group.

In the discussion section of the paper, the authors noted that elevations in D-dimer are associated with the development of osteonecrosis, but that CRP elevation predate the development of osteonecrosis, suggesting that at-risk patients have persistently higher levels of chronic inflammation; and that both markers could potentially help identify patients at higher risk of osteonecrosis.

Ref: Morse CG et al**.** Elevations in D-dimer and C-reactive protein are associated with the development of osteonecrosis of the hip in HIV-infected adults. AIDS 27(4):591–595. 20 February 2013. doi: 10.1097/QAD.0b013e32835c206a. http://journals.lww.com/aidsonline/Abstract/2013/02200/Elevations_in_D_dimer_and_C_reactive_protein_are.11.aspx

No impact of ART on progression or regression of anal squamous intraepithelial lesions

Simon Collins, HIV i-Base

Important results from a French study of 94 HIV positive gay men who were followed prospectively, prior to starting ART, reported a lack of regression of AIN precursor lesions associated with anal cancer and no beneficial association with increased CD4 counts on ART.

This study, from Christophe Piketty and colleagues was published as a concise communication in the 28 January 2013 edition of AIDS. [1] Participants were enrolled from the Hôpital Pitié-Salpetrière, Paris between March 2006 and October 2007.

Patients were evaluated for anal cytology, histology and anal HPV DNA at 3 months prior to starting cART (baseline), month 12 and month 24 of ART. Anal cytology was classified as normal, atypical squamous cell of undetermined significance (ASCUS), atypical squamous cell that cannot rule out high grade SIL (ASC-H), low grade SIL (LSIL) and high grade SIL (HSIL). A single pathologist was responsible for all histology results and the most severe results were used.

Median (IQR) baseline characteristics included age 39.4 years (IQR 33.3-43.4), time since HIV diagnosis 2.3 years (IQR 1.0 – 3.9), CD4 count 301 (IQR 242 - 339) cells/mm3 and viral load 4.9 (IQR 4.3 – 5.2) log copies/mL.

In data from a sub-set of about 70 patients, median age at first intercourse was 20 (IQR 18-24) years and 66% had had more than 40 lifetime partners. Sexual activity included similar percentages of people having insertive and receptive anal intercourse, with approximately 45% estimated 1-100 times and 45% 100-1000 times. Only 7% estimated more than 1000 sexual experiences. Approximately 31% had a prior history of anal warts. 34% were current smokers and 16% were former smokers.

At baseline, 59% (45/76) of patients had an abnormal cytology results, with LSIL in 36% (27/76) and HSIL in 9% (7/76). After follow-up, these rates were 59% (40/68), 34% (23/68) and 15% (10/68) at month 12 and 52% (36/69), 33% (23/69) and 9% (6/69) at month 24, respectively.

The prevalence of any lesion at baseline was similar in patients with HPV-16 infection vs other oncogenic HPV genotypes (63% vs 53%, p=0.469) but HSIL prevalence was significantly different (18% vs 0%, p=0.013).

There was no significant relationship between ART, baseline or change in CD4, or viral suppression and the rate of acquisition or disappearance of anal lesions at any timepoint. Among patients with no lesion at baseline, 10 patients (35.7%) exhibited a SIL at month 12 (n=7 LSIL and n=3 HSIL). At month 24 these figures were n=5 LSIL and n=1 HSIL. Regression of anal lesions was observed, without specific therapeutic intervention, in all five patients with HSIL at baseline (n=4 to LSIL and n=1 to normal) at month 12; n= 2 ASC-H, n= 2 LSIL and n=1 normal at month 24.

At month 24, regression of the severity of lesions was observed in 44% (18/41) patients with a lesion at baseline and new lesion occurrence was observed in 37% (10/27) without a lesion at baseline.

Ref: Piketty C et al. Lack of regression of anal squamous intrapathelial lesions despite immune restoration under cART. AIDS. 2013 Jan 28;27(3):401-6. doi: 10.1097/QAD.0b013e32835ad2cb.

http://journals.lww.com/aidsonline/Abstract/2013/01280/Lack_of_regression_of_anal_squamous.10.aspx

Incidence of cancers in Australian observational cohort

Asya Saati, HIV i-Base

An Australian prospective cohort study described the incidence of AIDS-defining cancers (ADC), non AIDS-defining cancers (NADC) and all cancers from 1992-2005 reporting a strong negative association with CD4 cell count. Other HIV related factors such as prior AIDS, ART and HIV viral load were closely linked to ADCs.

This study, from Kathy Petoumenous and colleagues, was published in the February 2013 edition of HIV Medicine. This was a prospective cohort study of HIV related factors and the rate of cancer incidence from the onset of HIV diagnosis. The study included 2181 patients from the Australian HIV Observational Database (AHOD).

Cancer diagnosis was established using data from the Australian Cancer database (ACD) and the Australian National HIV database (NHD) and the National AIDs Registry (NAR). The databases were matched by a two by two name code and then AHOD was matched to the NHD and NAR records. All invasive cancers were included with the exception of nonmelanoma skin cancer. [1]

ADCs were Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and cervical cancers. All other cancers were classified as NADCs. Each incident cancer was also categorised as infection-related (IR) or non-infection related (NIR). IR cancers observed in the study were Epstein-Barr virus (Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL) and nasopharynx cancer), human herpes virus 8 (HHV-8) and HPV (cervix, vagina, penis, anus, oral cavity and pharynx cavity).

Limited information on baseline characteristics were provided, although this have been published in other papers. [2]

The study identified 139 linked cancers (n=129) out of the 2181 AHOD participants. All but one of the cancers was diagnosed in male patients. The majority of all cancers were infection related (78%). Eighty-eight cancers (63%) were ADC, 61 (69%) were KS and 27 (31%) were NHL. The most common cancers among NADCs were melanoma (n=10), lung cancer (n=6), HL (n=5) and anal cancer (n=5).

The median age for cancer diagnosis was 43 years (IQR: 37-52). Median age of ADCs cancer diagnosis was lower compared to NADCs at median 41 years (IQR: 36-49) and 50 years (IQR 39-56) respectively.

Among the 2181 AHOD patients, 1793 had a recorded date of HIV diagnosis and 107 out of the 129 diagnosed with cancer had a recorded date of HIV diagnosis. Among these cancer patients there was a total of 21,021 person years (PY) of follow-up since the date of HIV diagnosis. This gave an overall crude rate of cancer incidence of 5.09/1000 PY. Cancer incidence rate for all cancers was greatest during the period of 1993-1996 (5.4/100 PY; 95% CI 3.54-8.05/1000 PY) and for KS (92.85/1000 PY; 95% CI 1.51-4.83/1000 PY). All cancers do not include KS, NHL and NADCs numbers.

At a CD4 cell count <100 cells/mm^3, the incidence rate (/1000 PY) for all cancers was at its highest 15.9 (95% CI 9.25-25.4) compared to 2.0 (95% CI 1.15-3.17) for CD4 cell count >500 cells/mm^3. A trend observed in both ADCs and NADCs.

In multivariate analysis CD4 cell count was again the strongest risk factor for the incidence of ADC and non-ADCs. At CD4 cell count <100 cells/mm^3 the incidence rate ratio (IRR /1000 PY) of ADC was 4.32 (95% CI 1.95-9.57), p<0.001. People on ART had a lower risk factor for

ADCs [IRR of 0.45 (95% CI 0.28-0.74), p=0.002]. Prior AIDS was a strong determining risk factor [IRR 3.98; (95%CI 2.39-6.62), p=0.001].

For NADCs CD4 cell count 100-199 cells/mm^3 [IRR 3.49 (CI 95% 1.48-8.22), p=0.004] and prior AIDs [IRR 2.63 (CI 95% 1.37-5.06), p=0.004] were the two biggest risk factors. Patient numbers were too low to calculate the IRR of ART as a risk factor.

Age was a risk factor for ADCs and NADCs [IRR 1.14 (CI 95% 1.01-1.21), p=0.039] and [IRR 2.63 (CI 95% 1.37-5.06), p<0.001].

From 2000 onwards the rate of cancer incidence was much greater in NADCs [2.15; 95% CI 1.37-3.31] compared to KS [1.62; 95% CI 95% 0.92-2.62].

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BASIC SCIENCE

Searching for HIV in Timothy Brown, the Berlin Patient

Richard Jefferys, TAG

Last year, Steven Yukl from UCSF presented the results of an exhaustive search for HIV genetic material in Timothy Brown (aka the Berlin Patient)—the one adult individual considered cured of the infection. [1]

The study engendered controversy, because a few of the multiple independent laboratories that participated did obtain positive readings for trace amounts of HIV RNA and DNA in some blood and tissue samples (the vast majority of the tests, including those looking for replication-competent virus in large volumes of cells, were negative). One scientist in particular, who was not involved in the research, made wild-eyed claims—via press release, no less—that the findings meant that Brown was either not really cured or potentially had been re-infected.

The results of the study were published yesterday in the open access journal PLoS Pathogens, and the authors offer a sober discussion of their implications. [2]

In particular, they highlight the difficulty of formally proving a cure using current virologic assays that are operating at the limits of their sensitivity. Rather, they suggest, the waning of immune responses to HIV in Timothy Brown (both antibodies and T cells) may represent the clearest confirmation that he is indeed cured.

In the staid language of the methods section, the published paper also offers insight into the extent of Timothy Brown's selfless commitment to contributing to HIV cure research: "The subject was enrolled in the UCSF-based SCOPE cohort and had multiple study visits over two years. Plasma, serum, and PBMC were obtained at each visit. The subject also consented to separate procedures at UCSF, including leukapheresis, lumbar puncture, and flexible sigmoidoscopy with rectal biopsies. He was also seen at the University of Minnesota, where he underwent a lymph node biopsy and a colonoscopy with ileal and rectal biopsies."

Any one of these procedures might well prompt trepidation in most people even if they were medically indicated; to volunteer to undergo them for the purposes of research is extraordinarily laudable.

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Reviewing strategies for draining HIV reservoirs

Richard Jefferys, TAG

The April issue of Human Vaccines & Immunotherapeutics features an excellent open access review by Thomas Rasmussen and colleagues describing approaches to eliminating HIV reservoirs that are advancing into clinical trials. [1]

Prominently featured are histone deacetylase (HDAC) inhibitors, which have emerged has lead candidates for liberating latent HIV from cellular lockdown. The paper offers detailed descriptions of the various HDAC inhibitors being studied—or considered for study—and notes that the authors, who are based at the University of Aarhus in Denmark, have launched a phase I trial of one such drug, panobinostat, in people with HIV. [2] Also cited is their companion study in the January issue of the same journal (now available open access) that compares the activity of several HDAC inhibitors in clinical development. [3]

Among the less-discussed aspects of HDAC inhibitors that are highlighted in the review are the potential for both pro- and anti-inflammatory effects depending on the individual compound (the latter effect could conceivably be beneficial in HIV infection).

Since the review was published, additional relevant data has emerged from CROI: results from Sharon Lewin's trial of vorinostat were presented, [4] and George Wei from Gilead Sciences gave a glimpse at the first in vitro data on romidepsin, reporting that it is 500 times more potent at reactivating latent HIV than vorinostat (the ACTG is now planning a phase I trial). [5]

Not all the news was positive, however: as discussed in an April 4th Nature Medicine news article by Elie Dolgin, [6] Antony Cillo described study results indicating that HDAC inhibitors may only induce a small fraction of latently infected cells to produce viral proteins, possibly meaning that combinations of anti-latency approaches will be needed to comprehensively target HIV reservoirs. [7]

Potentially supplementing the armamentarium are immune-based strategies such as those targeting toll-like receptors (TLRs). TLRs are involved in the recognition of pathogenic organisms and, as the review by Rasmussen and colleagues explains, there is evidence that compounds that stimulate TLRs (TLR agonists) can induce HIV expression by latently infected cells. They reference their own study of a TLR9 agonist named CPG 7909 as a pneumococcal vaccine adjuvant in people with HIV, that—in an example of scientific kismet—allowed them the opportunity to go back and investigate its effect on the latent HIV reservoir. The results were reported at CROI and, while exploratory, showed a significant mean reduction in HIV DNA levels of 12.6% after each immunisation. The decline in HIV DNA correlated with an increase in HIV-specific CD8 T cells expressing CD107a (a marker for their release of cell-killing substances) and the chemokine MIP1-beta. [8]

Other research groups are also looking at the anti-latency properties of TLR agonists. At CROI, Camille Novis from the laboratory of Alberto Bosque presented a poster showing that Pam3CSK4, which targets TLR2/1, was able to reactivate HIV from latently infected CD4 T cells without causing T cell activation. [9]

Romas Geleziunas has cited plans to study GS-9620, a TLR7 agonist, in several presentations describing the Gilead Sciences HIV eradication programme (further details are included in his slides from the 2012 International Symposium HIV & Emerging Infectious Diseases). [10]

The review by Rasmussen et al mentions the cytokine IL-7 as a possible immunotherapy to reduce HIV reservoirs, under evaluation in a trial named Eramune 01 at the time the paper was written. Results debuted at CROI in a poster and, disappointingly, IL-7 added to intensified antiretroviral therapy (ART) was not successful in reducing HIV DNA levels (there was some evidence it may have slightly increased levels due to causing transient proliferation of latently infected CD4 T cells). Despite this outcome, IL-7 had a beneficial impact on CD4 and CD8 T cell counts, as seen in prior studies, and remains the lead candidate for enhancing immune reconstitution in individuals with poor CD4 recovery despite HIV suppression by ART (in this population, the increased risk of morbidity and mortality is a far greater concern than small changes in HIV DNA levels). [11]

The topic of targeting HIV reservoirs is the subject of another recent review, by Christine Katlama and colleagues in The Lancet. Sadly, however, this paper is not open access and requires a subscription (although it may eventually appear in PubMed's full text archive). [12]

Source: TAG basic science blog (12 Apr 2013).

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Can a route to broadly neutralising antibodies be traced?

Richard Jefferys, TAG

In recent years, new technologies have facilitated the discovery of an expanding number of antibodies capable of neutralising a broad array of primary HIV isolates from different clades.

As covered previously on the blog, these broadly neutralising antibodies (BnAbs) have been fished from the plasma of individuals with chronic HIV infection and, in most cases, do not seem to be present at titers sufficient to control viral load or retard disease progression; however, there are reasons to hope that if similar antibodies could be induced by vaccination, they could rebuff the relatively small amount of HIV that enters the body during a typical exposure.

A common feature of the BnAbs is that the B cells that produce them have gone through many more rounds of somatic hypermutation than is typically seen in other infections. Somatic hypermutation is the process by which the B-cell's antibody-producing genetic code is progressively revised, potentially leading to an increase in the affinity of the antibody for its target. The genetic code that the B-cell starts out with is known as the germline sequence (or unmutated common ancestor or UCA), and it is typically altered by around 5-15% to produce antibodies against common infections, whereas the range is 19-46% for the BnAbs against HIV. This requirement for extensive mutation appears to be connected to the unusual shapes the BnAbs must form to access the hard-to-reach conserved areas of the HIV envelope (Env) protein, which are cloaked by highly variable decoy targets.

In a paper published in the journal Nature, researchers report tracking the development of a BnAb response in an HIV-positive person, in parallel with documenting the evolution of the infecting virus. The study shows that the Env protein of the virus at the time of acute infection was able to activate B cells with a germline sequence that then underwent progressive somatic hypermation, leading to the appearance of antibodies with increasing breadth of activity against a panel of HIV isolates during weeks 41-92 of follow-up. [1]

Driving the B-cell somatic hypermutation process was stimulation of the cells by the ever-mutating Env protein of the infecting virus, which evolved and became more diverse over time (as is typical in untreated HIV infection). The researchers were able to demonstrate that the diversification of the Env protein preceded the appearance of BnAb response.

This brief description greatly simplifies a complicated study, but the implication for HIV vaccines is that it may be possible to try and mimic the process observed in this individual using sequential immunisation with vaccines containing similar Env proteins of increasing diversity. The hope would be to initially activate the right B cell, and then push it along a somatic hyermutation pathway that would lead to the eventual generation of BnAbs.

Whether this is actually feasible, however, remains to be seen. Because there is a degree of randomness involved, it may be that the relatively rare individuals who develop BnAbs represent instances of B-cells essentially hitting the somatic hypermutation jackpot as a result of repeated stimulation. But, given the implications for HIV vaccines if BnAbs could be successfully induced with some reliability, it will be essential to fully pursue the idea. In addition to the Nature paper, several other recently published studies report data relevant to this pursuit. [2]

Source: TAG basic science blog (04 Apr 2013).

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OTHER NEWS

Life insurance for HIV positive people on stable treatment

Simon Collins, HIV i-Base

An analysis from the Antiretroviral Cohort Collaboration (ART-CC) related to life expectancy from the perspective of access life insurance has been published ahead of print in the journal AIDS.

The analysis used the ART-CC database, which included more than 300,000 patient years and more than 1,000 deaths to identify HIV positive people with low risk factors for HIV progression. They then compared these outcomes with risks associated with the insured population in each country. This included selecting people who were not infected by injecting drug use, were not coinfected with hepatitis C and who started triple therapy ART from 1996-2008.

Although the methodology is complex, the paper includes important modeling results showing that successful treatment produced sufficient confidence in projections for life expectancy to be able to cover a standard 20 year mortgage for >50% of HIV positive people who have access to treatment.

The researchers hope that their data will help normalise access to these services for people who are currently excluded on the basis of HIV status alone.

Ref: Kaulich-Bartz J et al. Insurability of HIV positive people treated with antiretroviral therapy in Europe: collaborative analysis of HIV cohort studies. Published ahead of print, AIDS 2013, 27:000–00025. February 2013. doi: 10.1097/QAD.0b013e3283601199.

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ON THE WEB

Conference abstracts

19th Annual Conference of the British HIV Association

16–19 April 2013, Manchester

As with all recent BHIVA conferences, this meeting has a large amount of content available online, including free access to the conference abstracts and webcasts for the keynote and plenary lectures and oral presentations.

http://www.bhiva.org/AnnualConference2013.aspx

Free full text online articles:

PLoS Medicine

Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies - Johnson LF et al.

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001418#abstract2

This study estimates 80% of normal life expectancy for HIV positive South African adults who start ARVS while their CD4 count is still 200 or higher by using information from 6 programmes between 2001 and 2010.

The cost and impact of scaling up pre-exposure prophylaxis for HIV prevention: a systematic review of cost-effectiveness modelling studies - Gomez GB et al.

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001401

Preventing antiretroviral treatment interruptions among HIV/AIDS patients in Africa - Mills EJ and Nabiryo C.

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001370

Norma Ware and colleagues conducted a large qualitative study among patients in HIV treatment programs in sub-Saharan Africa to investigate reasons for missed visits and provide an explanation for disengagement from care.

FUTURE MEETINGS

Conference listing 2013/14

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.

Intl Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies

4 – 8 June 2013, Toronto

http://www.informedhorizons.com/resistance2013

5th International workshop on HIV paediatrics

28 - 29 June 2013, Kuala Lumpur, Malaysia

http://www.virology-education.com

Towards an HIV Cure Symposium

29 - 30 June 2013, Kuala Lumpur, Malaysia

http://event.ias2013.org/pagae/default.aspx?s=750

7th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2013)

30 June – 3 July 2013, Kuala Lumpur, Malaysia.

http://www.ias2013.org

53rd ICAAC

10 – 13 September 2013, Denver, USA.

http://www.icaac.org

14th European AIDS Conference (EACS)

16 – 19 October 2013, Brussels, Belgium.

http://www.europeanaidsclinicalsociety.org

20th IAS World AIDS Conference

20-25 July 2014, Melbourne, Australia

http://www.aids2014.org

12th International Congress on Drug Therapy in HIV Infection

2-6 November 2014, Glasgow

http://www.hiv11.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: 2012 update for PDA access

The i-Base website has been recently redesigned to meet access standards for PDA, iPad, tablet, Windows 8 and touch screen access.

It is now faster and easier to access, use and navigate.

http://www.i-Base.info

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

RSS news feed is available for HIV Treatment Bulletin for web and PDA.

The advocacy resources include an online training manual with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

An average of 200,000 pages from individual ISP accounts contact the website each month, with over 6000 hits a day.

Non-technical treatment guides

i-Base treatment guides

i-Base produce six booklets that comprehensively cover five 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 combination therapy (April 2013)
- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (March 2013)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009) - ***currently only online.***

Publications and reports

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published every two months in print, PDF and online editions.

HTB South

A quarterly bulletin based on HTB but with additional articles relevant to Southern Africa. HTB South is distributed in print format by the Southern African HIV Clinicians Society (www.sahivsoc.org) to over 20,000 doctors and healthcare workers. It is also available as a PDF file and is posted online to the i-Base website.

HTB Turkey

HIV Tedavi Bülteni Türkiye (HTB Turkey) is a Turkish-language publication based on HTB and produced three times a years by an independent group of Turkish doctors, activists and health care workers.

HTB West Balkans

HIV Bilten is an edition of HTB in Bosnian, Monteragrin, Croatian and Serbian, for the West Balkans, produced by Q Club.

Why we must provide HIV treatment information

Text from activists from 25 countries and 50 colour photographs by Wolfgang Tillmans.

Translations of i-Base publications

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 35 languages. Information to support this is available on the i-Base website.

In addition, PDF files of some of the translated publications are available online.

Please be aware that some of these translations are from earlier editions of the treatment guides, and check the publication date before relying on these editions.

http://i-base.info/category/translations

Languages include: Bosnian, Bulgarian, Chinese, Czech/Slovak, Croatian, French, Greek, Hindi, Indonesian, Italian, Kosovo, Macedonian, Nepali, Polish, Portuguese, Romanian, Russian, Serbian, Spanish and Turkish.

Advocacy resources

Online treatment training for advocates

http://i-base.info/ttfa

Entry-level curriculum relating to HIV and treatment. Eight modules include: immune system and CD4 count; virology, HIV and viral load; an introduction to antiretrovirals (ARVs); side effects of ARVs; opportunistic infections and coinfections: HIV and pregnancy; drug users and HIV; and clinical trial design and the role of advocates

Additional support material is included on how to understand aspects of science that might be new to a lay reader.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community advocates from across the UK that has been meeting since 2002. It now includes over 480 members from over 120 organisations. The CAB has a separate website, where reading material, reports and presentations from all meetings are posted. Membership is free.

http://www.ukcab.net

Phoneline and information services

Treatment information request service - 0808 800 6013

i-Base runs a specialised treatment information service.

We can provide information by phone, email and online based on the latest research.

For further details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK.

Online Q&A service

An online question and answer service that now has over 3000 questions and comments online. Questions can be answered privately, or with permission, can be answered online.

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

Other resources

Treatment 'Passports'

Booklets for HIV-positive people - whether newly diagnosed or positive for a long time - to record health and treatment history. Like other publications, they are available free as single copies, or in bulk.

Generic clinic forms

A set of generic clinic forms, developed with the Royal Free Centre for HIV Medicine, which may be a useful resource for other hospitals.

These PDF files include record sheets to track CD4 and viral load results, cardiovascular risk, hepatitis, first patient visit, patient update, day case and summary notes.

http://i-base.info/category/publications/clinic-forms

i-Base can add your hospital or Trust logo to these forms.

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

Copies of publications can also be ordered by post or fax using the form on the back page of HTB. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), HTB South, Treatment 'Passports' and all our guides to managing HIV and additional reports.

htb(e)

HIV TREATMENT BULLETIN (e)

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:
http://www.i-Base.info
by sending an email to: subscriptions@i-Base.org.uk
Editor: Simon Collins
Contributing Editor: Polly Clayden

HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies.All editorial policies are strictly independent of funding sources.

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http://www.i-Base.info

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- **HIV Treatment Bulletin (HTB) every two months** ☐ **by e-mail (PDF file)** ☐ **by post**
- **HIV Treatment 'Passports' - Booklets for patients to record their own medical history**
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide To HIV Testing and Risks of Sexual Transmission** *(February 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide To HIV, Pregnancy and Women's Health** *(March 2013)*
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- **Introduction to Combination Therapy** *(April 2013)*
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- **Guide to Changing Treatment and Drug Resistance** *(February 2013)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **HIV and your Quality of Life: Side Effects and other Complications** *(July 2012)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide To HIV and hepatitis C coinfection** *(Out of print, new edition due 2013)*
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- **Clinical Trials: a community guide to HIV research** *(March 2009)*
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____

Treatment guides in other languages are available as PDF files on the website

- **Phoneline support material** *(please specify quantity of each)*

  A3 posters _____ ***A5 leaflets*** _____ ***A6 postcards*** _____ ***Small cards*** _____

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020 7407 8489 (fax) subscriptions@i-Base.org.uk