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CONTENTS

EDITORIAL	2	PREGNANCY	15
CONFERENCE REPORTS	2	<ul style="list-style-type: none"> Raltegravir pharmacokinetics in pregnancy and neonates Efavirenz pharmacokinetics among pregnant women with and without tuberculosis coinfection 	
54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 5-9 September 2014, Washington, DC		OPPORTUNISTIC INFECTIONS	20
<ul style="list-style-type: none"> Introduction Summary of antiretroviral studies at ICAAC: darunavir-based FDC with TAF, cobicistat, doravirine, Stribild and gel formulation PrEP Switch from efavirenz to rilpivirine quells CNS toxicity, improves sleep HIV persists in lung macrophages of people on suppressive ART Only 10% of veterans with HCV or HCV/HIV in the US treated for HCV 		<ul style="list-style-type: none"> Immunotherapy for PML: two case reports using IL-7 and experimental recombinant JCV VP1 protein therapeutic vaccination 	
CONFERENCE REPORTS	7	SIDE EFFECTS AND COMPLICATIONS	21
20th International AIDS Conference, 20-25 July 2014, Melbourne		<ul style="list-style-type: none"> Kidney signal trouble worsens over 5 years in Japanese on tenofovir 	
<ul style="list-style-type: none"> Introduction Update on baseline STIs in UK oral PrEP study (PROUD) High prevalence of COPD at baseline in START study sub-study Risk of CVD or type-2 diabetes according to change in BMI after starting ART Rosuvastatin may be partially effective in moderating residual immune activation on ART Reasons for loss to follow up in the Malawi Option B+ programme 		HIV REINFECTION & TRANSMISSION	22
ANTIRETROVIRALS	13	<ul style="list-style-type: none"> HIV reinfection has limited impact on disease progression 	
<ul style="list-style-type: none"> Single-pill dolutegravir/abacavir/3TC (Triumeq) approved in EU and US Cobicistat and elvitegravir approved in the US as single pills Positive opinion to approve darunavir/cobicistat in Europe 		BASIC SCIENCE AND CURE RESEARCH	23
GUIDELINES	14	<ul style="list-style-type: none"> Case report: Stem cell transplantation from CCR5 delta-32 homozygous donor selects for X4-tropic HIV Stemming the flow from HIV reservoirs with neutralising antibodies 	
<ul style="list-style-type: none"> UK updates PEP guidelines: raltegravir replaces PIs and no indication if positive partner has an undetectable viral load BHIVA pregnancy guidelines: 2014 interim update US HIV guidelines for management of chronic kidney disease (IDSA, 2014) 		HEPATITIS C	24
		<ul style="list-style-type: none"> Daclatasvir approved in EU for HCV genotypes 1-4 CHMP gives positive opinion to approve coformulated sofosbuvir/ledipasvir in Europe European activists protest at meeting of European Health Ministers for access to new HCV drugs 	
		OTHER NEWS	26
		<ul style="list-style-type: none"> DSMB open report strongly supports importance of START study 	
		FUTURE MEETINGS	26
		PUBLICATIONS AND SERVICES FROM i-BASE	27
		DONATION FORM	29
		ORDER FORM	30

EDITORIAL

This edition of HTB includes conference reports from the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and a few final ones from the 20th International AIDS Conference (IAS 2014).

Updates from ICAAC include: news on tenofovir alafenamide, suggesting potential bone and renal benefits with this compared to the current formulation of tenofovir; non-inferiority of cobicistat for boosting atazanavir compared to ritonavir; an update on the pipeline NNRTI doravirine; a post-hoc analysis of Stribild in black participants; and tenofovir gel for prevention.

We are grateful to NATAP and include their ICAAC reports on switching from Atripla to Eviplera, which significantly reduced central nervous system toxicity; on the detection of HIV in lung alveolar macrophages; and low US uptake of HCV treatment in a 2008-2013 analysis of the VA cohort in Washington.

Reports from AIDS 2014 cover the PROUD study of oral PrEP – with discussion about access to Truvada for PrEP in the UK and Europe; high baseline rates of COPD in a substudy of the START trial ; the risk of cardiovascular disease or type-2 diabetes according to change in BMI after starting ART; and loss to follow up in the Malawi Option B+ programme – which needs some improvement.

Recent new ARV approvals are: the new FDC of dolutegravir plus abacavir and 3TC; cobicistat and elvitegravir as single agents in the US and a positive opinion for co-formulated darunavir/cobicistat in Europe. For hepatitis C treatment, daclatasvir was approved in Europe for genotypes 1-4 and the CHMP gave a positive opinion to approve co-formulated sofosbuvir/ledipasvir.

Other antiretroviral news includes data on raltegravir in pregnancy and for infants; efavirenz PK in pregnancy and in the presence of rifampicin for TB treatment and a report showing kidney signal trouble worsens over 5 years in a Japanese cohort receiving tenofovir.

Gareth Hardy reviews two important journal papers: one reporting little clinical impact from HIV reinfection (so long as drug resistance is not an issue) and a second reporting an experimental approach to treating PML that may be applicable for HIV positive people.

And Richard Jefferys once again updates us on basic science and cure research.

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CONFERENCE REPORTS

54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

5-9 September 2014, Washington, DC

Introduction

Although this large North American conference always includes a separate section in the programme on HIV, this is a conference that we are rarely able to attend.

A summary of highlights from ICAAC 2014 is included in this issue thanks to coverage on natap.org of about 60 studies. This includes hyperlinks to both longer articles and slides from oral presentations that are not otherwise available on the conference website.

<http://www.natap.org/2014/ICAAC/ICAAC.htm>

The final programme is available in PDF format from the ICAAC website.

<http://www.icaac.org/images/2014/ICAAC2014-FinalProgram.pdf> (PDF)

Abstracts are available using the search facility in the online programme planner, but links to individual abstracts involve long URLs that for some previous conferences are not maintained permanently.

<http://www.abstractsonline.com/Plan/AdvancedSearch.aspx>

<http://www.abstractsonline.com/plan/start.aspx?mkey=%7B5D6B1802%2DE453%2D486B%2DBCBB%2DB11D1182D8BB%7D>

Reports in this issue are:

- Summary of antiretroviral studies at ICAAC: darunavir-based FDC with TAF, cobicistat, doravirine, Stribild and gel formulation PrEP
- HIV persists in lung macrophages of people on suppressive ART
- Switch from efavirenz to rilpivirine quells CNS toxicity, improves sleep
- Only 10% of veterans with HCV or HCV/HIV in the US treated for HCV

Antiretroviral studies at ICAAC 2014: darunavir-based FDC with TAF, cobicistat, doravirine, Stribild and gel formulation PrEP

Simon Collins, HIV i-Base

The following summaries provide a brief overview of some of the antiretroviral studies presented at ICAAC 2014. For full details please see reports on NATAP.org, many of which include presentations slides.

Single pill PI-based FDC using tenofovir alafenamide fumerate (TAF)

Week 48 results were presented comparing a single-pill fixed dose combination (FDC) that includes darunavir, cobicistat and FTC with tenofovir alafenamide (D/C/F+TAF; n=100), compared to separately dosed darunavir and cobicistat plus FTC/tenofovir DF (DRV+COB+TDF/FTC; n=50). [1]

This was a phase II, randomised, placebo controlled study. The primary endpoint was virological suppression to <50 copies/mL at week 24, which was reported for 75% vs 74% in the TAF vs TDF arms [weighted difference: 3.3% (95%CI: -11.4%, +18.1%)]. At week 48, these rates were 77% vs 84% [weighted difference: -6.2 (95%CI: -19.9, +7.4), p=0.35].

Bone and renal markers suggested potential benefits for TAF. At 48 weeks, reductions in bone mineral density in both spine (-1.57% versus -3.62%, p=0.003) and hip (-0.84% vs -3.82, p<0.001) were significantly less with TAF than with TDF. Median reduction in eGFR was also less (-2.9% vs -10.6%, p=0.017). Median change in proximal tubular proteinuria rose significantly less with TAF than with TDF (+9% vs +54%, p=0.003).

As expected from earlier studies, plasma concentrations of tenofovir were significantly lower and intracellular concentrations approximately 6-fold higher using TAF compared to TDF.

Cobicistat vs ritonavir to boost atazanavir

Extended follow-up continued to support non-inferiority for boosting atazanavir with cobicistat compared to ritonavir. Results were presented from a randomised, blinded, active-controlled phase III study in 700 treatment-naïve patients. [2]

At 144 weeks, suppression to <50 copies/mL was 72% vs 74% [difference -2.1% (95%CI: -8.7% to 4.5%)] in the cobicistat vs ritonavir groups respectively. This compared to 85% vs 87% [difference -2.2 (95%CI: -7.4% to 3.0%)] at week 48.

A single-arm study looked at switching ritonavir to cobicistat as the booster for either atazanavir or darunavir in 73 people who were on stable ART but who had a reduced renal function, defined as creatinine clearance (CrCl) 50 to 89 mL min. [3]

Almost half of study participants, 47%, had CrCl below 70 mL/min (median 71; range 42 to 98), and one third had proteinuria, 38% had hypertension, 18% had diabetes, and 3% had HIV-associated nephropathy.

Although 26% of people discontinued cobicistat (10% relating to side effects) there were no cases of proximal renal toxicity and no renal safety signal. The researchers concluded that cobicistat could be an option for this patient group. It was not clear from the presentation whether TDF was also used in this study.

Doravirine: 100 mg dose selected for new NNRTI

A phase II dose-ranging study of the NNRTI doravirine (MK-1439) in development at Merck, reported that once-daily dosing at 100 mg achieved target concentrations for both wild-type virus and against common NNRTI-associated mutations (including K103N, Y181C and G190A). [4]

No correlation was seen between dose (at 25, 50, 100, and 200 mg) and either side effects or viral suppression at week 24 and the 100 mg dose will go forward for further development.

Stribild response in black patients

A higher virological response rate was reported for black participants using Stribild compared to Atripla in a post-hoc analysis of the Gilead 102 study. Approximately 25-30% of participants in this phase III treatment-naïve registrational study were black. [5]

At week 144, the percentage of black participants with viral suppression to <50 copies/mL was 78% vs 66% [difference, 12.4%; (95%CI: -0.1% to 25%), p=0.052] in the Stribild vs Atripla arms respectively, a finding which fell short of statistical significance. The result was not explained by differences in baseline characteristics between the two combinations. However, differences in adherence (defined as taking >90% doses) was significant: 89% versus 76% in the Stribild vs Atripla arms respectively (p=0.023). Serious adverse event rates were similar (19% vs 18%), but grade 2 to 4 events (13% vs 35%), and side-effect related discontinuations (2% vs 11%, p=0.014) were both higher in the Atripla group.

By comparison, in non-black participants, rates of viral suppression <50 copies/mL were 81% vs 79% in the Stribild vs Atripla arms respectively. These results are perhaps important for highlighting difficulties associated with Atripla, as CNS side effects were reported at higher rates compared to Stribild, but it is also important to note that this was a post-hoc analysis.

TDF/FTC vaginal ring protects 6 of 6 monkeys from weekly SHIV exposure

Intravaginal rings containing tenofovir and emtricitabine (TDF/FTC) in six pods protected 6 of 6 macaques from weekly exposure (for 16 weeks) to simian hybrid HIV (SHIV), while all animals not wearing a ring became infected.

It was estimated that a comparable ring for women would be able to provide a similar level of protection for a least one month. [6]

Tenofovir suspension in vaginal gel protects 10 of 10 mice from HIV

A new TDF intravaginal gel protected 10 of 10 humanised mice from a single HIV challenge (4 hours after the gel) and they remained negative for four weeks. This new formulation uses a nanoparticle suspension of TDF that is liquid at room temperature but that becomes viscous at body temperature.

The three mice that were given an inactive gel all became infected. [7]

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Switch from efavirenz to rilpivirine quells CNS toxicity, improves sleep

Mark Mascolini, NATAP.org

Switching from Atripla (efavirenz plus tenofovir/emtricitabine [TDF/FTC]) to Eviplera (rilpivirine plus TDF/FTC) significantly relieved central nervous system (CNS) toxicity and improved sleep in people with those problems while taking Atripla.

All but 1 of 40 study participants who switched in this London/Brighton study maintained virologic control through 24 weeks.

The once-daily single-tablet combination pill Atripla remains a recommended and popular first-line antiretroviral regimen. People who start efavirenz in Atripla or other regimens often suffer short-term neurologic side effects, but sometimes those problems persist. Eviplera (Complera in the US) is a once-daily single-tablet combination of TDF/FTC with another NNRTI, rilpivirine.

UK researchers conducted this single-arm study to track changes in CNS toxicity and sleep patterns after people who had those problems with Atripla switched to Eviplera.

To gauge changes in side effects, the investigators used the AIDS Clinical Trials Group CNS toxicity questionnaire, including 10 items such as dizziness, depression, anxiety, and somnolence. The sleep questionnaire included 19 items.

The analysis included 40 people with Atripla-related CNS toxicity, 36 of them men. Age averaged 47 (range 24 to 73), and people had taken efavirenz for a median of 42 months (range 24 to 100).

Median CD4 count at the switch measured 610 (interquartile range 436 to 884). One person had a detectable viral load at 60 copies 12 weeks after switching to Eviplera. After that, this person stopped keeping study visits. All other study participants maintained a viral load below 50 copies through 24 weeks.

CD4 counts did not change substantially through 24 weeks of follow-up. Median total CNS score fell from 40 at the switch to Eviplera to 12 after 4 weeks, 20 after 12 weeks, and 13 after 24 weeks ($p < 0.001$ for all comparisons). Proportions of people reporting grade 2 to 4 adverse events improved significantly from baseline to week 24 for abnormal dreams, anxiety, confusion, depression, dizziness, insomnia, impaired concentration, and somnolence.

Median total sleep questionnaire score improved from 30 at the switch to 14 at week 24 ($p 0.001$). Twenty-four weeks after the switch to Eviplera, study participants had significant improvements in total cholesterol (-0.9 mmol/L), low-density lipoprotein cholesterol (-0.57 mmol/L), and triglycerides (-0.35 mmol/L) ($p < 0.001$ for all changes from baseline).

A single serious adverse event, thrombocytopenia, emerged in 1 person. The researchers proposed that identifying people with efavirenz toxicity "is essential as use of alternate agents leads to improvement in tolerability and toxicity."

Reference: Rowlands J, Higgs C, De Esteban N, et al. Multicenter open-label study of switching from Atripla to Eviplera for CNS toxicity. ICAAC 2014. September 5-9, 2014. Washington, DC. Abstract H-1005.

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HIV persists in lung macrophages of people on suppressive ART

Mark Mascolini, NATAP.org

HIV could be detected in lung alveolar macrophages of antiretroviral-naive people as well as people taking partially or completely suppressive antiretroviral therapy. HIV frequency in macrophages did not correlate with plasma viral load. [1]

HIV persistence in cellular and tissue reservoirs despite suppression in plasma with combination antiretroviral therapy is a well-appreciated phenomenon.

Because HIV-infected alveolar macrophages can be detected in bronchoalveolar lavage samples from antiretroviral-naive people with HIV, researchers in Malawi, the UK, and the US conducted a three-way comparison study, postulating that lung macrophages could be an HIV reservoir.

The researchers recruited HIV positive and negative people at the Queen Elizabeth Central Hospital in Blantyre, Malawi. The study involved 5 HIV negative adults, 12 HIV positive antiretroviral-naive adults, and 37 adults taking combination antiretroviral therapy.

Twenty-seven treated people were taking a first-line regimen of nevirapine, stavudine, and lamivudine, and 10 were taking first-line efavirenz, tenofovir, and lamivudine.

The researchers collected bronchoalveolar lavage and blood samples from all participants. They used flow cytometry, immunophenotyping, and fluorescence in situ hybridization (FISH) to identify HIV-infected alveolar macrophages in lavage samples. The investigators divided study participants into HIV negative (2 men and 3 women), antiretroviral-naive (3 men and 9 women), antiretroviral experienced for under 4 years (6 men and 16 women), and antiretroviral experienced for 4 years or more (6 men and 9 women).

Ages in those four groups averaged 29.6, 28.5, 31.5, and 37.0, and CD4 counts averaged 657, 336, 459, and 428. The group with fewer than 4 years experience had taken antiretrovirals for an average 1.4 years (range 0.3 to 3.9), and the group with 4 or more years experience had been treated for an average 6.1 years (range 4.0 to 8.9).

All antiretroviral-naive people had a detectable viral load. Among people with treatment experience, 6 (27%) with fewer than 4 years experience, and 4 (27%) with 4 or more years experience had a detectable viral load. Viral loads averaged 216,852 copies in the naive group, 14,939 copies in the group with under 4 years of treatment, and 4812 copies in the group with 4 or more years of therapy.

HIV-infected alveolar macrophages could be detected in everyone with HIV infection at the following frequencies:

- Antiretroviral-naive: 2.3% (95% confidence interval [CI] 0.3% to 4.2%)
- On antiretrovirals under 4 years: 1.4% (95% CI 0.4% to 2.5%)
- On antiretrovirals 4 or more years: 1.1% (95% CI 0.3% to 2.0%)

HIV-infected macrophage frequency did not correlate with HIV RNA in plasma ($r = 0.005$, $p = 0.67$).

The researchers concluded that “HIV persists in alveolar macrophages during potent ART,” a finding “implying that the lung may be an important reservoir of HIV.” They suggested that “understanding the formation and maintenance of this viral reservoir could provide important clues for the development of strategies to clear HIV from latently infected host cells.”

C O M M E N T

It is unclear from this report why the results were not presented separately for people who had undetectable viral load on ART. This information would have the most important significance.

Average results when both treatment groups included people with ongoing replication appear to miss the main area of interest, namely the degree to which optimal ART may impact on this site.

Reference : Mwandumba HC, Jambo KC, Banda DH, et al. Persistence of HIV in alveolar macrophages during antiretroviral therapy. ICAAC 2014. September 5-9, 2014. Washington, DC. Abstract H-1636.

Only 10% of veterans with HCV or HCV/HIV in the US treated for HCV

Mark Mascolini, NATAP.org

Only 1 in 10 veterans diagnosed with HCV or HCV and HIV in the Washington, DC Veterans Administration (VA) Medical Center got treated for HCV in a 2008-2013 analysis. [1]

The HCV/HIV group had significantly worse fibrosis by FIB-4 score than the HCV-only group, but otherwise the groups did not differ much in HCV progression markers, liver cancer, or mortality.

More than 225,000 veterans in the national VA system have HCV infection, according to researchers who conducted this study. They noted that about 40% of HIV-positive people in the Veterans Aging Cohort Study have HCV infection. In some populations, HIV coinfection raises the risk of progression to cirrhosis and death in people with HCV [2-5], and coinfecting people get HCV therapy less often than people infected only with HCV. Because research comparing HCV-monoinfected people and HCV/HIV-coinfecting people remains scant, the VA team conducted this comparison.

This retrospective analysis involved veterans in the Washington HCV Clinical Case Registry from January 2008 through December 2013. The investigators measured fibrosis both by APRI and FIB-4.

The analysis included 4327 veterans infected only with HCV and 402 coinfecting with HCV/HIV. Age averaged 59 in the HCV group and 56 in the HCV/HIV group, and more than 96% in both groups were men. A lower proportion of HCV-only vets was black (71% versus 81%) and a higher proportion white (14% versus 8%). Proportions in the HCV group and the HCV/HIV group who were underweight were 4% and 7%, normal weight 32% and 42%, overweight 36% and 35%, and obese 28.5% and 16%.

Among veterans with HCV/HIV, median CD4 count stood at 472 (interquartile range [IQR] 295 to 667), and 69% had an undetectable viral load.

Alcoholic liver disease was significantly more frequent in the HCV-only group than in coinfecting veterans (4.6% versus 1.5%, $p=0.0019$), as was diabetes (31% versus 25.4%, $p=0.0202$). But compared with HCV-only veterans, coinfecting veterans had a higher frequency of any renal disease (13.3% versus 17.2%, $p=0.0335$) and end-stage renal disease (5.4% versus 8.2%, $p=0.0312$).

A significantly higher proportion of coinfecting veterans had a FIB-4 above 3.25 (31% versus 26%, $p<0.0061$). But the groups did not differ in proportions with an APRI above 1.5 (18% and 16%) or in median FIB-4 (2.39 and 2.06) or median APRI (0.6 and 0.52).

Among veterans genotyped, more than 90% in both groups had HCV genotype 1. Among genotyped people, only 272 HCV-only veterans (10%) and 22 HCV/HIV-infected veterans (8%) had received treatment for HCV infection, a nonsignificant difference. Only 10% in each group attained HCV suppression. Proportions of participants with a diagnosis of hepatocellular cancer (4% with HCV, 3% with HCV/HIV) and proportions who died of any cause (14% and 15%) did not differ significantly between groups.

The VA team noted that their findings of similar HCV progression indicators in HCV-monoinfected and HCV/HIV-coinfecting veterans are at odds with previous studies showing worse HCV infection in coinfecting people [2-5]. This difference, they surmised, could reflect better HIV control in the VA population. Because all US military personnel get tested for HIV regularly, their infection is typically diagnosed earlier than in the general population, and they all have ready access to free treatment.

Low HCV treatment rates in this cohort, the researchers stressed, “should be improved given the availability of more effective and less toxic direct-acting agents.”

C O M M E N T

The low take-up of HCV treatment in this cohort with medical coverage indicates the low acceptability of combinations that are based on pegylated-interferon plus ribavirin.

An affordable price for direct acting antivirals, including sofosbuvir, could cure most of these people within months.

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CONFERENCE REPORTS

20th International AIDS Conference

20-25 July 2014, Melbourne

Introduction

We continue our coverage of reports from the AIDS 2014 Conference held in Melbourne in July.

The abstracts, Powerpoint slides, posters and webcasts from the meeting are accessible online using the programme at a glance link from the conference website.

<http://www.aids2014.org>

<http://pag.aids2014.org>

Articles in this issue of HTB are:

- Update on baseline STIs in UK oral PrEP study (PROUD)
- High prevalence of COPD at baseline in START study sub-study
- Risk of CVD or type-2 diabetes according to change in BMI on ART
- Reasons for loss to follow up in the Malawi Option B+ programme

AIDS 2014: PREVENTION

Update on baseline STIs in UK oral PrEP study (PROUD)

Simon Collins, HIV i-Base

The cost-effectiveness of pre-exposure prophylaxis (PrEP) can only be considered in association with the background risk of HIV in the people who use it. Baseline data from the UK PROUD are important for showing that this study has accurately enrolled a suitably high-risk group.

PROUD is an ongoing randomised two-year pilot study of oral PrEP (using daily Truvada) that compares immediate PrEP to a standard-of-care control group that gets PrEP after 12 months. It has been fully enrolled since April 2014.

Baseline data including HIV risk and recent STI history for 511 of the 545 participants were presented in a poster at AIDS 2014. [1]

The study recruited largely white, educated, employed gay men in their thirties. Baseline demographics include median age 36 (IQR 30-43), ethnicity: white (79%), other (5%), mixed (4%), Asian (4%), black (3%), Chinese (2%) and Irish (2%); education level: 60% at university degree level or above, 17% to A-level. Most men were in full-time (72%) or part-time (9%) employment and 8% were unemployed (11% other or no answer). Almost half (46%) were in an ongoing relationship and 30% were living with a partner.

The median number of partners (for anal sex) in the previous three months was 10 (IQR 4-20) with median of 2 (IQR 1-5) and 3 (IQR 1-7) times for receptive and insertive anal sex respectively.

Participants already highly aware of HIV: they had a median of three HIV tests in the previous year and 36% had used post exposure prophylaxis (PEP). Of 446/511 answering the questions on STI history during the previous year, this included rectal gonorrhoea (27%), rectal chlamydia (22%) and syphilis (11%). Of 279 participants tested at baseline, 12 (5%) had rectal gonorrhoea, 10 (4%) had chlamydia and 12 (5%) had syphilis.

An earlier analysis of this data was previously presented at the BHIVA 2014 spring conference. [2]

Early data on STI rates during the study included five cases of sexually transmitted HCV, also presented at BHIVA. [3]

C O M M E N T

The PROUD study is due to announce results within a year after the last enrolled participant reaches the end of the two-year follow-up. Gilead has agreed to provide TDF/FTC to all participants until the end of this study.

The HIV Clinical Reference Group (CRG) have set up a group to look at drawing up a policy for PrEP on behalf of NHS England that includes broad membership including clinicians, PHE, NHS England, patient reps, BHIVA, BASHH, as well as modellers and economists. This group is currently finalising search criteria for an evidence review that will cover predicted uptake, number of infections averted, cost effectiveness, cost and affordability.

These draft guidelines are likely to be available for stakeholder and public comment in 2015.

It is currently unclear whether the bottleneck for an EU review of Truvada for PrEP use is due to lack of a clear regulatory pathway from the European Medicines Agency (EMA), given phase III randomised data was sufficient for the FDA approval and subsequent data is now available, or due to the Gilead not following through with an application regardless.

The lack of an indication should not be used to further block access given the wide use of ARVs as PEP for which no indication has been granted.

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AIDS 2014: SIDE EFFECTS & COMPLICATIONS

High prevalence of COPD at baseline in START study sub-study

Gareth Hardy, HIV i-Base

Chronic obstructive pulmonary disease (COPD) has been a leading cause of death globally (currently third highest) for at least the last 25 years. The main risk factor for COPD is cigarette smoking.

Although observational studies have reported that HIV infection is an independent risk factor for COPD, these have generally been in small European or North American cohorts.

At AIDS 2014, Ken Kunisaki and colleagues at Minneapolis Veterans Administration Health Care System, Minnesota, presented baseline lung-function results from the pulmonary substudy of the ongoing international START study, reporting prevalence of COPD by region, age and smoking status. [1]

COPD is characterised by destruction of lung tissue (emphysema), airway inflammation and airway fibrosis. Airways become collapsible and narrowed, trapping air in the lung, hyperinflating the chest and leading to shortness of breath with exertion.

The substudy recruited 1027 treatment-naïve adults from 20 countries. Enrolment by regions included United States (91), Asia (103), Latin America (191), Europe, Israel, Australia (313), and Africa (328). Other baseline characteristics included 29% women, 38% black and 34% white.

Due to the nature of the main study, median CD4 count was high (648 cells/mm³; IQR 582, 767) and people were in relatively early infection (HIV diagnosed for median 1.2 years (IQR 0.4, 3.5).

Approximately a third were current smokers (29%) and 11% were former smokers. Median age was 36 (IQR 30, 44) with entry criteria for the substudy being older than 25.

Lung function was assessed using standardised spirometry with COPD defined as FEV1/FVC ratio (forced expiratory volume in 1 second/forced vital capacity) below the predicted 5th percentile.

Overall, COPD was present in 6.8% of the cohort (95% CI: 5.3% - 8.5%), varying by region, with a strong association with current smoking and age. Prevalence was 12% in current smokers compared to 5% in former and 6% in never smoked.

However, almost half of those with COPD (47%) reported never smoked. COPD prevalence was 92% in those aged >44 compared to 4% in those under 30. Prevalence was 9.1% in Europe, Israel and Australia, 8.2% in the USA, 7.8% in Africa, 3.3% in Latin America and 2% in Asia.

In multivariate analysis with FEV1/FVC ratio as the dependent variable, COPD was more strongly associated with older age ($p < 0.0001$) and increased smoking pack-years ($p < 0.0001$), and more weakly with region ($p = 0.01$). Gender had no effect.

The researchers speculated that the variation in COPD according to region may result from non-smoking factors such as environmental exposure to biomass fuel use, or occupational exposure to dust and smoke. However, no data on these parameters was collected.

In conclusion, COPD was found to be common in this cross-sectional analysis of HIV positive adults in early HIV infection, especially among smokers and older adults.

The researchers stressed the importance of smoking cessation interventions in adults with HIV as COPD is likely to emerge as a major co-morbidity in this population. However, the observation that nearly half of those with COPD reported never smoking, suggests the need for further investigation of COPD incidence.

The main START study has randomised 4685 HIV positive people with CD4 counts >500 cells/mm³ to either immediate or deferred ART (when CD4 is 350) with a primary endpoint of serious events of death. Top-line results are expected by the end of 2016, the predicted time for reaching 213 endpoints. [2]

C O M M E N T

This substudy from START will produce the largest longitudinal dataset for incidence of COPD in HIV positive people and with randomised data on the role of ART.

A second cross-sectional study was also just presented at ICAAC 2014, reporting 9% prevalence of COPD in 623 patients attending a single site in France. In this study, age and smoking history increased the risk of COPD (OR 1.61 [95%CI: 1.14-2.28] and 1.28 (95%CI: 1.09-1.50), respectively). Notably, COPD was previously undiagnosed in 77% of cases. [3, 4]

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Risk of CVD or type-2 diabetes according to change in BMI after starting ART

Gareth Hardy, HIV i-Base

Initiation of ART usually leads to increased weight and body mass index [BMI] that might be associated with an increased risk of cardiovascular disease [CVD] and type II diabetes.

Amit Achhra at the Kirby Institute for Infection and Immunity in Society, in Sydney, investigated the relationship between short term increases in BMI following ART and risk of CVD or type II diabetes in over 9000 people enrolled in the international, prospective, multi-cohort D:A:D study. They reported that for each unit of BMI increase within the first year following initiation of ART, the risk of CVD and diabetes significantly increased. However, the implications of these results depended on baseline BMI.

Selection criteria included being treatment naive when initiating ART and having BMI measurements within the previous year and after one year [+/- 6 months] following ART initiation. The outcomes for the study were new CVD [myocardial infarction, invasive cardiovascular procedures or stroke] and diabetes events. Exclusion criteria included pre-existing CVD or diabetes. The study comprised 9,321 people, who were stratified according to their pre-ART BMI as under weight (< 18.5 kg/m²), normal (18.5 - 25), over weight (25 - 30) or obese (> 30). Poisson regression models were used to determine the risk of CVD or diabetes according to one-year change in BMI, stratified by pre-ART BMI category, cohort and established CVD and diabetes risk factors and calendar year.

Most people fell into the two middle BMI stratifications: normal weight [64%], and overweight [23%]. While only small numbers fell into the two extreme BMI groups: initially underweight [6%] and obese [6%]. Three quarters of the cohort were male and half were men who have sex with men [MSM]. Smoking inversely correlated with baseline BMI.

After one year of ART, the mean increase in BMI was +0.67 kg/m². Baseline BMI was strongly related to response with mean changes of +1.82, +0.77, +0.30 and -0.01 in the underweight, normal, overweight and obese groups respectively. This trend continued with mean changes at 5 years of +2.5, +1.38, +0.73 and +0.14 in the same groups respectively. The underweight group gained the most BMI and the obese group remaining stable or losing weight. Overall, the percentage of overweight or obese cohort subjects increased from 29.6% before ART to 35.5% during ART.

A total of 97 [1.0%] CVD events were reported during 43,982 person years (PY) with an incidence of 2.21/1000 PY [95% CI: 1.76 - 2.68]. Pre-ART BMI was positively related to CVD event rate (95%CI) per 1000 PY: 1.73 (0.56 - 4.03), 2.13 (1.63 - 2.73), 2.41 (1.55 - 3.59) and 2.78 (1.12 - 5.74) in the under, normal, over and obese groups respectively.

However, when the risk of CVD was assessed according to the increase in BMI units, the normal weight group had the highest risk [incidence risk ratio (IRR) 1.18 (CI: 1.04 - 1.32), p=0.01]. This translates to an 18% increased risk of CVD per unit of BMI gained for the normal group. In

contrast, there was no effect on the risk of CVD from increased BMI for the obese group [IRR: 1.08 (0.71 – 1.64), $p=0.714$], the overweight group [IRR 0.80 (0.62 – 1.02), $p=0.070$] or the underweight group [IRR 0.92 (0.54 – 1.56), $p=0.792$].

Analysis by pre-ART BMI (to work with even distribution) only showed higher CVD rate for the middle two quartiles [20.9 - 23.0 and 23.0 - 25.5] when adjusted for both demographics and all time-updated variables.

Type-2 diabetes developed in 125 patients (1.4%) during 43,278 PY, with a rate of 2.89 per 1000 PY. Similar to CVD, when stratified according to pre-ART BMI group, the rate of diabetes also appeared to be related to higher BMI, with the highest rates in the obese group [IRR 9.97 (CI: 6.32 – 14.96)] and the overweight group [IRR 4.05 (CI: 2.88 – 5.54)], and the lowest rates in the underweight group [IRR 2.04 (CI: 0.76 – 4.53)] and the normal group [IRR 2.01 (1.51 – 2.59)]. When the risk of diabetes was assessed according to the increase in BMI units after one year of ART, there was an approximately 20% elevated risk of diabetes per unit gain in BMI for those with normal BMI before ART [IRR 1.19 (CI: 1.06 – 1.33)] and those overweight [IRR 1.22 (CI: 1.06 – 1.40)]. There was not a significant increase in diabetes risk per unit of BMI gained in the underweight or obese groups. In all groups taken together, there was a 10-11% increase in risk for diabetes associated with each unit gain in BMI. This result did not change by categorising pre-ART BMI groups according to quartiles.

The researchers conclude that short-term gains in BMI after ART could be associated with increased risk of CVD, mostly in people with normal/intermediate levels of BMI before ART and that increases in BMI are associated with higher risk of diabetes in all groups. They urge caution in the interpretation of the result that there was no change of CVD risk with gain in BMI for the high BMI pre-ART group, as the sample size was low and BMI may not be the best predictor of CVD.

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Rosuvastatin may be partially effective in moderating residual immune activation on ART

Gareth Hardy, HIV i-Base

Many HIV positive people never achieve a CD4 recovery to >500 cells/mm³ on ART even after many years on treatment. The role of residual immune activation in this response is unknown and as statins have anti-inflammatory effects their potential to modify immune activation may be important.

At AIDS 2014, Laurence Weiss, of the Université Paris Descartes, Paris, presented a poster from the CESAR-IMEA trial investigating whether rosuvastatin can decrease cellular and soluble markers of immune activation in patients receiving ART. [1]

In this open label, phase II trial, patients were enrolled who had >2 years ART, with CD4 counts <500 cells/mm³ and viral loads <40 copies/mL. C-reactive protein had to be <10 mg/mL with no indication for statin use. Rosuvastatin (20 mg, once-daily) was administered for 3 months, followed by 3 months follow up. The primary outcome was change in the proportion of CD38+ HLA-DR+CD8+ T lymphocytes after 12 weeks. Mean CD4 count at baseline was 319 cells/mm³ [IQR 284-442].

Of 50 patients who enrolled in the study, 43 reached study endpoints.

There was no significant change in the proportion of CD38+HLA-DR+CD8+ T cells throughout the follow-up. Despite this, the investigators reported a significant decline in the proportion of CD38+CD8+ T cells between baseline and week 12 ($p=0.001$) that was sustained until week 24. There were significant decreases in the percentage of Ki67+CD4+ T cells at week 12 ($p=0.048$), in HLA-DR+CD4+ T cells ($p=0.044$) and soluble CRP levels ($p=0.047$). No changes were observed in the other soluble activation markers: IL-6, sCD14 and D-dimer.

C O M M E N T

The researchers concluded that rosuvastatin added to ART could result in sustained decreases in CD8 T cell activation. However, the lack of any decrease in the main marker of T cell activation, expression of CD38 and HLA-DR on CD8 T cells, is a major concern with this conclusion.

Although CD38 expression decreased on all CD8 T cells, this has questionable significance in terms of reducing T cell activation. CD38 can be constitutively expressed by various T cells in the absence of activation, for example naive T cells. Therefore it is not, on its own, a reliable marker of T cell activation and must be paired with other activation markers such as HLA-DR or markers of memory phenotype.

The reduction in the percentage of CD8 T cells expressing CD38, in the absence of a reduction in the percentage of CD8 T cells expressing both CD38 and HLA-DR together, calls into question the ability of rosuvastatin to reduce T cell activation in this study.

Despite this, the observed reduction in Ki67 in CD4 T cells is slightly more encouraging.

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AIDS 2014: PREGNANCY & PMTCT

Reasons for loss to follow up in the Malawi Option B+ programme

Polly Clayden, HIV i-Base

The Option B+ programme in Malawi has reported considerable loss to follow up. Two presentations at AIDS2014 explored some of the reasons for this and offered some recommendations. [1, 2]

Malawi began Option B+ (universal lifelong ART for pregnant and breastfeeding women) in 2011. The programme's introduction led to a 7-fold increase in women starting ART for PMTCT in just over a year. But loss to follow up is considerable: 27% reported by 12 months from starting ART and 24% by 6 months in facilities with high volume of patients.

Hannock Tweyla presented findings from a study that looked at outcomes and reasons for loss to follow up of women from the Malawi Option B+ programme.

This retrospective cohort study, conducted at Bwaila Hospital, Lilongwe, used data from electronic medical records (EMR) and a patient-tracing programme. The hospital has the largest antenatal clinic (ANC) and maternity wing in the country with over 14,000 registrations annually. The Lilongwe District Health Office and partners provide the PMTCT service, which starts approximately 110 pregnant and breastfeeding women on ART every month.

Pregnant women with unknown HIV status accessing the service are offered a group counselling service and opt out HIV testing. Expert mothers provide support to the women for the first and all follow up visits. All HIV positive women are registered in the EMR system and started on ART on the day of diagnosis.

The tracing programme staff list women who miss an appointment by three weeks or more and women who consent (during registration) are traced up to three times by phone or visit. Tracing outcomes are categorised as: dead, uninterrupted treatment, treatment interruptions, self transfer out, stopped ART, never started ART and not traced.

Between September 2011 and September 2013, the investigators identified 2930 HIV positive women who started ART for PMTCT Option B+; of these 2,458 (84%) were pregnant (the remainder were breastfeeding). The women's median age at ART initiation was 26 years (IQR 22-30) and follow up was 8.2 months (IQR 3.1-16.7).

Out of 2,930 women, 577 (20%) missed a scheduled appointment for at least three weeks; 272 only collected their antiretrovirals at the start of treatment and did not return. The overall incidence of loss to follow up was 23.5 % per year. Retention was 85%, 82% and 79% at three, six and 12 months respectively.

In multivariate analysis, factors associated with loss to follow up were: younger age, 13 to 24 vs 25+, adjusted rate ratio (ARR) 1.29 (95% CI 1.09-1.52); breastfeeding vs pregnant, ARR 0.63 (95% CI 0.49-0.89); and earlier year of Option B+ implementation, 2011 vs 2012 ARR 1.25 (95% CI 1.06-1.49), all $p < 0.001$. Of note more recent data showed further decline in loss to follow up, 2013 vs 2012 ARR 0.41 (95% CI 0.29-0.58) – likely due to stabilisation of the programme.

Of 577 women, the investigators successfully traced 228 (40%) and established that 9 (4%) had died. Of the 219 women found alive: 67 (30%) had self-transferred to another ART clinic, 118 (77%) had stopped taking ART, 13 (9%) were on ART uninterrupted, 9 (6%) had treatment interruptions, 7 (5%) had not started ART and 5 (3%) declined to be interviewed.

Reasons given by women ($n=111$) for stopping ART were: travelled away (38%), transport costs (16%), limited understanding of ART (10%), suspected side effects (10%), very weak/sick (10%), non disclosure to husband (8%), religious belief (5%), forgotten (5%) and other reasons 44%.

The investigators noted that at 23.5% per year the loss to follow up rate among women started on ART in this Option B+ programme is greater than that reported in the general HIV population accessing ART for their own health of 9.3% per year. Almost half (47%) of women who were lost to follow-up received ART once and never returned for their appointment, leaving them at risk of vertical transmission. A considerable proportion of women could not be traced due to incorrect addresses documented in their clinic files – the investigators suggested that women could give false physical addresses because of fear of stigma and discrimination. A third of the women self-transferred to another clinic, which suggests national retention in PMTCT programme is underestimated.

The investigators concluded with a number of recommendations:

- ANC/ART clinics should further enhance post-test counselling by engaging HIV testing counsellors and expert mothers for ongoing counselling and psychosocial support.
- Targeted programmes for young women need to be established.
- ART clinics need to establish data linkages so information on patients that transfer can be shared.
- Further decentralisation of PMTCT services with good ANC/maternity services is needed.

A related presentation by Joep van Oosterhout showed results from a survey conducted across all health facilities providing PMTCT/ART services in the South East Health Zone of Malawi. The survey was undertaken to identify approaches to Option B+ service delivery (models of care) adopted in the national programme, in which great variation between retention rates has been reported (42-100%).

The investigators explored associations of the diverse models of care with programme performance indicators: uptake of HIV testing in ANC, uptake of ART, and retention on ART.

The South East Health Zone comprises 6 of 28 districts with 3.5 million inhabitants. There are approximately 154,000 pregnancies in the South East Zone per year and 22,500 (14.6%) of these are among HIV positive women. By June 2013 (when the investigators conducted the study), the South East Zone had 153 health facilities with integrated HIV care services.

The investigators used a structured questionnaire with questions covering: the availability of services, staff involved in PMTCT/ART service provision, the location where newly infected pregnant women are started on ART, the timing of adherence counselling for ART initiation, and the timing of transfer to ART or mother-infant clinic.

They used routinely collected health facility reports to determine uptake of HIV testing and counselling, and ART initiation for newly identified HIV positive pregnant women. They then evaluated 6-month outcomes for women registered as having started ART under Option B+ between July 2012 and December 2012. High HIV testing uptake was defined as greater than 85% in this evaluation and high retention on ART as greater than 92%.

Of 153 health facilities, 141 were included in the study of which the investigators identified four models of care:

1. Facilities where women are started and followed on ART at ANC clinic until birth (n=75).
2. Facilities where women receive only the first dose of ART at ANC clinic with follow up at ART clinic (n=38).
3. Facilities where women are referred from ANC to the ART clinic for ART initiation and follow-up (n=18).
4. Facilities serving as ART referral sites and that do not provide ANC (n=9).

They found that the proportion of women tested for HIV during ANC was highest in model A facilities 82% (95%CI 78-85) and lowest in model B facilities 68% (95% CI 61-74). The proportion of women starting ART was 81% (95% CI 78-85), across all four models. The highest 6-month retention rates were found in models C and D, 90% (95% CI 86-94) and lowest in model B facilities, 78% (95% CI 74-84).

In multivariate analysis, factors significantly associated with ART retention were district location, volume of patients (lower retention with higher volume) and the model of care. Model C facilities were 5 times more likely than model B to have high 6-month retention rates. Facilities with fewer than 31 women in the 6-month cohort were 5 times more likely to have high retention rates than facilities with the most women.

Dr van Oosterhout noted that approximately a quarter of pregnant women (18-32%) were not tested for HIV at ANC. HIV testing uptake was associated with ratio of women to testing staff, test kit stock outs and model of care.

In the survey 7-20% of women had defaulted Option B+ by 6 months and retention was associated with district location, patient volume and model of care.

The investigators concluded that overall the worse programme indicators were in model B facilities, where women only receive the first dose of ART at ANC.

C O M M E N T

An article in JAIDS earlier this year illustrated the “complex personal, societal, and structural barriers to continued HIV care facing postpartum women receiving ART through Option B+” revealed in a South African study. [3] The authors noted that although some of these barriers are true of all non-pregnant adults in the same setting, postpartum HIV positive women need targeted support and adapted programmes.

The study also highlighted the need for increased treatment literacy, stressing the importance of a return to HIV care for the mother’s own health after delivery.

“As countries seek to expand ART access and eligibility through Option B+, they must ensure that the unique needs of HIV positive postpartum women are addressed to retain them in care and facilitate adherence to ART”, the authors wrote.

James McIntyre gave an excellent update of Option B+ successes and challenges at the 2014 paediatric workshop. [4]

It is worth noting that most data so far is not looking at the plus part of Option B+ and refers to pregnancy, breastfeeding and immediately postpartum.

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ANTIRETROVIRALS

Single-pill dolutegravir/abacavir/3TC (Triumeq) approved in EU and US

Simon Collins, HIV i-Base

The fixed dose combination (FDC) of dolutegravir (50 mg) plus abacavir (600 mg) plus 3TC (300 mg) was approved on 22 August 2014 in the US and on 3rd September 2014 in the EU. [1, 2]

This integrase inhibitor-based combination - brand name Triumeq - is not recommended for anyone with documented or suspected integrase inhibitor associated mutations, as this would require a higher dose of dolutegravir.

As with any combination including abacavir, Triumeq is contraindicated in people with HLA-B*5701 and should never be restarted in anyone with a suspected hypersensitivity reaction, irrespective of HLA-B*5701 status.

EU approval is based primarily upon data from the phase III SINGLE study in treatment-naïve adults (using dolutegravir and abacavir/3TC as separate pills), plus a bioequivalence study of the FDC single pill compared to dolutegravir and abacavir/lamivudine as separate pills. A pharmacovigilance plan for Triumeq will be implemented as part of the EU marketing authorisation.

The recommended adult dose is one tablet once daily orally with or without food. For further details, see the product information. [3, 4]

C O M M E N T

NHS England is still finalising recommendations for dolutegravir as a single medication, even though EU approval for this was in January 2014. This decision is expected in October 2014.

It is unclear whether access to the FDC will require a separate set of commissioned guidelines. Presumably, as long as the price for the FDC is comparable to that of the separate components, another 9-month evaluation should not be needed.

In Scotland, dolutegravir has been available since May 2014, with advice on Triumeq from the Scottish Medicines Consortium due on 8th December. [5]

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Cobicistat and elvitegravir approved in the US as single pills

Simon Collins, HIV i-Base

On 24 September 2014, the FDA approved separate formulations of cobicistat (Tybost) 150 mg tablets and elvitegravir (Vitekta) 85 mg and 150 mg tablets. [1, 2]

Cobicistat is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other ARVs as part of an HIV combination. Cobicistat is **not** interchangeable with ritonavir to increase systemic exposure of darunavir 600 mg twice daily, fosamprenavir, saquinavir, or tipranavir due to lack of exposure data and is not recommended with these drugs.

Cobicistat and elvitegravir were approved in the EU last year - in September 2013 and November 2013, respectively.

C O M M E N T

Since EU approval, UK access to separate evitegravir has been restricted to getting this directly from Gilead.

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Positive opinion to approve of darunavir/cobicistat in Europe

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On 25 September 2014, the Committee for Medicinal Products for Human Use (CHMP) recommended granting market authorisation for a coformulated version of darunavir (800 mg) plus the pharmacokinetic booster cobicistat (150 mg). [1]

The indication is for use in treatment-naïve and treatment-experienced adults with no darunavir-associated mutations.

This formulation be the first single-pill, once-daily, boosted protease inhibitor for rich countries (as there is a generic atazanavir/ritonavir).

The same meeting also extended the indication for darunavir to include boosting with either ritonavir or cobicistat. [1]

Recommendations from the CHMP are usually followed with full approval, expected within three months.

The formulation is manufactured by Janssen-Cilag and will be marketed in Europe with the brand name Rezolsta. It is already available in Canada under the trade name Prezcobix. [2]

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GUIDELINES

UK updates PEP guidelines: raltegravir replaces PIs and no indication if positive partner has an undetectable viral load

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The UK Chief Medical Officers' Expert Advisory Group on AIDS (EAGA) has issued new guidance for Post Exposure Prophylaxis (PEP) that includes using raltegravir rather than a boosted protease inhibitor. [1]

The switch to raltegravir as the third active drug in PEP should improve tolerability. Fewer side effects may increase the number of people who come forward to use PEP. It could also increase the number of people who complete the monthly course of PEP as drop out rates are generally high.

Raltegravir is more rapidly absorbed, compared to PIs, and this may improve the chance that PEP is effective at stopping potential HIV infections.

Prescribing guidelines are also being updated to say the PEP is no longer indicated if the HIV positive partner has an undetectable viral load (<200 copies/mL) although also, somewhat unhelpfully, that "PEP should be offered to those who are anxious about the risk".

This new guidance reflects the dramatic impact HIV treatment has on reducing the risk of transmission. Results from the PARTNER study reported no linked transmissions between sero-different partners after more than 44,500 times when sex occurred without using condoms. [2]

Although some clinics have already switched to the new combination a few centres may continue with existing stocks (using Kaletra). This should only be for a short period.

The BHIVA website reports that the guidelines for PEP after sexual exposure (PEPSE) produced by BASHH with input from BHIVA are currently being updated according to NICE-accredited guideline development processes and should be available in late 2014/early 2015.

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BHIVA pregnancy guidelines: 2014 interim update

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The British HIV Association guidelines for the management of HIV infection in pregnant women 2012 have been reviewed and updated May 2014.

The purpose of the 2014 interim review was to look at developments that led to either a change in recommendation or a change in the strength of the existing recommendation. The changes and the supporting evidence are highlighted in yellow.

There have been no major changes in recommendations and the updates are summarised as follows:

- The prevalence data from the UK have been updated.
- Safety: new data on efavirenz and raltegravir.
- Prescribing: darunavir updated.
- Resistance: data on mutations associated with the use of AZT monotherapy added; 21 days' antiretroviral cover is recommended to prevent mutations following single-dose nevirapine.
- IV AZT: guidance refined to include all viral loads >1000 rather than 10 000 copies/mL.
- Hepatitis: information added on telaprevir and boceprevir.
- Mode of delivery: new data on transmission rates by mode of delivery at low viral load (50-399 copies/mL) added, strengthening the evidence for the existing recommendation to consider planned Caesarean section at these levels.
- Infant diagnostic section has been updated. No other change to paediatric section including infant feeding advice.

The guidelines will be fully updated and revised in 2017. The writing group will continue to look at new information from high-quality studies and amendments made to the current recommendations before this date where they consider this be clinically important.

Reference

British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review)
<http://www.bhiva.org/documents/Guidelines/Pregnancy/2012/BHIVA-Pregnancy-guidelines-update-2014.pdf> (PDF)

US HIV guidelines for management of chronic kidney disease (IDSA, 2014)

HIV guidelines for management of chronic kidney disease were published in the 17 September edition of Clinical Infectious Diseases. [1]

The HIV Medicine Association of the Infectious Diseases Society of America (IDSA) produced the guidelines.

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PREGNANCY

Raltegravir pharmacokinetics in pregnancy and neonates

Polly Clayden, HIV i-Base

Two articles published ahead of print online in JAIDS describe raltegravir pharmacokinetics (PK) during pregnancy and in neonates following maternal dosing. [1,2] The data reported support previous smaller studies suggesting: a dose adjustment is not necessary in pregnancy; raltegravir could be a good option to provide pre-exposure prophylaxis to the foetus before and during delivery.

Raltegravir data from IMPAACT 1026 – an ongoing prospective study of antiretroviral PK during pregnancy and postpartum [3] – were first presented at the 50th ICAAC, 2010. [4,5]

The study compared the PK of raltegravir in the second and third trimesters of pregnancy with that postpartum among eligible women receiving standard dose (400 mg twice daily) in antiretroviral regimens before week 35 of gestation. Women who enrolled during the second trimester also had intensive raltegravir PK performed between 20 and 26 weeks gestation (repeated between 30 and 36 weeks). Women who enrolled in the third trimester had PK sampling between 30 and 36 weeks. All women had PK sampling between 6 and 12 weeks post partum.

The study enrolled 42 women. The majority was of African origin from the USA, with a median age of 30 years. Duration of raltegravir use was respectively 88 and 56 weeks for women who enrolled in the second and third trimesters. Half the women received raltegravir with two NRTIs – mainly as their first antiretroviral regimen. The other half received multiclass antiretroviral regimens (at least three classes), and these women were mostly drug-experienced with raltegravir added as an additional agent to prevent vertical transmission. Two women were receiving concomitant ritonavir-boosted atazanavir, which can increase raltegravir exposure.

The majority (>90%) of women had viral load <400 copies/mL by the third trimester. The infants had a median gestational age of 38.4 weeks (range 36.6-42.4) at delivery; at the time of reporting 34 were HIV negative and eight results were pending.

The PK parameters for raltegravir are shown in Table 1.

Table 1: Raltegravir median (range) PK parameters

Parameter	2nd trimester (2T) (n=16)	2T vs PP p-value	3rd trimester (3T) (n=41)	3T vs PP p-value	Postpartum (PP) (n=38)
AUC0-12 (ug*hr/mL)	6.6 (2.1-18.5)	0.03	5.4 (1.4-35.6)	0.001	11.6 (1.6-39.9)
C12h (ug/mL)	0.06 (0.01-0.4)	0.02	0.06 (0.01-0.61)	0.3	0.08 (0.02-1.34)
Cmin (ug/mL)	0.05 (<0.01-0.16)	0.03	0.57 (<0.01-0.61)	0.66	0.05 (<0.01-0.9)
Cmax (ug/mL)	2.25 (0.37-5.96)	0.09	1.77 (0.32-7.82)	0.003	3.04 (0.31-12.6)
Tmin (hr)	12.0 (0-12.0)	0.91	12.0 (0-12.0)	0.67	12.0 (0-12.0)
Tmax (hr)	4.0 (1.0-8.0)	ND	2.0 (0-12.0)	ND	2.0 (0.8.0)
CL/F (L/hr)	60.6 (21.6-190.5)	0.36	74.8 (11.2-285.7)	0.21	34.8 (10.0-250.0)
Vd/F (hr)	264.1 (36.4-11228.5)	0.08	329.4 (71.8-10183.2)	0.61	238.8 (42.9-3032.4)
T1/2 (hr)	2.9 (1.2-85.6)	0.26	3.7 (1.1-211.7)	0.57	3.6 (1.1-30.5)
n (%) above C12h 10th percentile non-pregnant	11/16 (69%)	0.49	33/41 (80%)	1.0	30/38 (79%)

The investigators found that pregnancy reduced raltegravir exposure with median AUC of approximately 50% lower in both trimesters than postpartum. They noted that the C12h was below the target level in more than 10% of women at each sampling time (including post partum). During pregnancy, in about a third of the women, the raltegravir concentration continued to decline after dose, compared to about 10% in the post partum period. The investigators suggested this phenomenon indicated a lag in absorption. Overall the C12h was quite variable.

As the women in this study had high rate of virologic suppression, a large variability of plasma concentrations is also seen in non-pregnant adults, and there does not appear to be a clear association between raltegravir concentrations and virologic effect, the investigators do not recommend a change in dosing from 400 mg twice daily.

The second article described raltegravir PK in neonates following the maternal dose from IMPAACT 1097 – early data from this evaluation were shown at the 13th PK workshop, 2012 and 20th CROI, 2013. [6,7,8,9]

IMPAACT 1097 looked at the washout PK and safety of in utero/intrapartum exposure to raltegravir in full-term neonates. [10] Mothers receiving raltegravir and their infants were enrolled in the study prior to delivery.

Neonatal plasma samples were collected at 1-5, 8-14 and 30-36 hours after birth in infants with birth weight >2 kg, gestational age >37 weeks who had not received medications that could induce UGT1A1. Dried blood spots were taken from infants to look at UGT1A1 polymorphisms.

Infants' blood samples were also taken for total and direct bilirubin, liver transaminases and creatinine at 8-14, 30-36 hours and 1-2 weeks after birth and for complete blood counts at 8-14 hours and 1-2 weeks after birth. The infants were monitored until 20 weeks of age for raltegravir toxicity.

The study enrolled 22 mother/infant pairs, all of which were included in the safety analysis and 19 infants had complete evaluable data. Of 22 infants, 6 (27%) were girls, 13 (59%) were African American and 8 (36%) Hispanic. The median gestational age at delivery was 38 weeks (range 37-40) and birth weight was 3080 grams (range 2200-4100).

At delivery the median maternal raltegravir concentration was 540 ng/mL (range 12-5809), at a median of 4.6 hours after dosing (range 1.1-21.0). Median cord blood raltegravir concentration was 957 ng/mL (range 24-3974) and median cord blood to maternal delivery concentration was 1.48 (range 32-4.33).

Median infant concentrations and the time of collection after birth were: 671 ng/mL (range 13-2672) at 1.9 hours (0.9-4.4), 507 ng/mL (range <10-2280) at 9.3 hours (7.9-13.3), 481 ng/mL (range <10-2106) at 20.5 hours, and 291 ng/mL (<10 – 1402) at 33.8 (range 30.3-35.8).

Raltegravir concentrations increased in 9/19 (47%) of infants over the initial 12-24 hours after birth before declining. The investigators noted that raltegravir concentrations were above the IC95 (14ng/mL) through the last time point for all but one infant. Elimination T1/2 could not be determined for another. For the remaining 17 infants, median T1/2 elimination was 28.6 hours (range 9.3-184; IQR 22.0-69.2).

UGT1A1 genotyping was obtained for 17 infants, of whom 16 also had PK evaluations. Eight infants were (TA)6/(TA)6 homozygotes, 7 were (TA)6/(TA)7 heterozygotes, 1 was a (TA)5/(TA)6 heterozygote and 1 (TA)7/(TA)7 homozygote. The investigators found no differences in median raltegravir concentrations at any time point or in elimination when they compared the (TA)6/(TA)6 infants to the other three UGT1A1 genotypes. The investigators suggested that it is more likely the immaturity of neonatal UGT1A1 enzyme activity accounts for the variability in raltegravir PK than the infant genotype.

Five infants (22.7%) had grade 3 or 4 laboratory events (total bilirubin, creatinine, haemoglobin, neutrophil count and glucose), 2 had grade 3 or 4 signs or symptoms (fever and respiratory discomfort) and 1 grade 3 or 4 diagnosis (metabolic/endocrine disorder).

One infant was low birth weight (2200 grams) and there were no reported deaths or stillbirths. The investigators did not consider any of the adverse events to be related to maternal raltegravir. One infant received phototherapy for hyperbilirubinaemia. The infant was heterozygous (TA)6/(TA)7 with a raltegravir T12 of 75.4 hours. None of the infants received exchange transfusion therapy.

C O M M E N T

The BHIVA guidelines recommend raltegravir containing regimens for late presenting women and if viral load is unknown or >100,000 copies/mL.

The authors of the pregnancy study above also suggest that raltegravir might be an option for women receiving co-treatment for TB with a rifampicin-containing regimen.

The neonatal study reported above includes careful discussion on the elimination of transplacentally-acquired raltegravir in infants, particularly those born preterm. The authors note that once raltegravir concentrations started to decline, the rate of elimination was highly variable and most infants very had slow elimination, with the longest T1/2 of 184 hours.

They stress that excessive raltegravir concentrations must be avoided in neonates as high concentrations might increase the risk of bilirubin neurotoxicity. And sub-therapeutic concentrations, which could lead to development of raltegravir resistance, also need to be considered.

They caution that giving raltegravir to preterm infants is likely to pose a higher risk of central nervous system bilirubin toxicity and should be avoided until raltegravir has been well-studied in term and preterm infants.

Two IMPAACT studies are investigating the safety of raltegravir given directly to term infants and washout raltegravir PK in low birth weight infants.

IMPAACT P1110 is a dose-finding PK study to evaluate the safety and tolerability of raltegravir granules given to high-risk, HIV-exposed infants during the first 6 weeks of life with standard antiretroviral prophylaxis. P1110 will start with an initial cohort, receiving two single doses of raltegravir approximately one week apart, followed by a second cohort receiving daily dosing.

Version 2 of P1097 looks at raltegravir washout PK in low birth weight infants, and P1110 might also be expanded to include low birth weight infants.

Together the studies should provide the data necessary to develop raltegravir-containing regimens suitable for the first month of life for prevention and treatment (and possibly cure) of HIV in infants.

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Efavirenz pharmacokinetics among pregnant women with and without tuberculosis coinfection

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Pregnancy increased the risk of low efavirenz (EFV) concentrations, but vertical transmission was rare in a South African study of HIV treatment in pregnant women with and without tuberculosis (TB) coinfection. [1]

Four other studies have shown similar limited effects of pregnancy on EFV pharmacokinetics (PK). [2] Twelve studies have shown no significant effects during long-term treatment with EFV and rifampicin. [3]

TSHEPISO

EFV is recommended for treatment of HIV positive pregnant women. Pregnancy and TB treatment or prophylaxis can affect EFV PK, a woman's own HIV treatment and risk of vertical transmission.

A paper first published ahead of print in the Journal of Infectious Diseases in July, and updated 5 September 2014, showed results from a PK substudy of TSHEPISO – a prospective cohort study looking at the effects of TB on maternal and infant outcomes in pregnant HIV positive women. We previously summarised preliminary results from this substudy – presented at AIDS 2012 – in HTB South. [2,3]

HIV positive pregnant women with active TB or matched controls, from the Chris Hari Baragwanath Hospital in Soweto, were enrolled in TSHEPISO at 13 to 34 weeks gestation between January 2011 and January 2013. Two controls were enrolled for each case – matched for maternal and gestational age, date of enrolment and site of planned delivery but not antiretroviral (ART) use or regimen. Women receiving EFV for 10 days or more at week 36 of gestation could participate in the substudy.

The EFV dose was 600 mg once daily, isoniazid 5 mg/kg (maximum 300 mg) and rifampicin 10 mg/kg (maximum 600 mg) – according to national and WHO guidelines.

In the substudy, sampling was performed at 37 weeks gestation or at delivery and then six weeks post-partum. EFV levels were also measured in cord blood at delivery and in infants at one week of age. Plasma concentrations were determined by liquid chromatography-tandem mass spectrometry. EFV trough concentrations (C_{min}) were predicted using population PK models. Women had CYP286 genotyping and were categorised as extensive, intermediate, slow or very slow metabolisers. Maternal viral load was measured at delivery and that of the infants at six weeks of age.

There were 97 participants in the substudy, 44 were coinfecting with TB and 53 had HIV only. Cases and controls were similar at enrolment with median values of approximately: 28 years of age, 30 weeks gestation and a CD4 count of 310 cells/mm³. A greater proportion of controls had a viral load less than 20 copies/mL (58% vs 28%). This difference was probably explained by the delay in starting ART among those needing treatment for TB; duration of EFV use was 12 and 21 weeks for the cases and controls respectively. The median gestational age at delivery was 39 weeks.

The distribution of women with extensive, intermediate, slow and very slow CYP2B6 metaboliser status was similar between the two groups, respectively 22%, 56%, 19% and 3%.

The investigators reported a median EFV C_{min} during pregnancy of 1.35 ug/mL (IQR 0.90–2.07) compared with 2.00 ug/mL (IQR, 1.40–3.59) postpartum; 27% compared with 13% of women had an EFV C_{min} of <1 ug/mL. The proportion of women with extensive CYP2B6 metaboliser status with C_{min} of <1 ug/mL during pregnancy was 72%.

The median EFV C_{min} for women receiving rifampicin- and isoniazid-containing TB treatment during pregnancy was 1.33 ug/mL (IQR 0.83–2.22) compared with 1.57 ug/mL (IQR 1.56–1.83) for those receiving isoniazid alone as TB prophylaxis and 1.28 ug/mL (IQR 1.04–1.92) for those receiving no TB drugs. The proportion of women with C_{min} of <1 ug/mL was 36% for those receiving rifampicin- and isoniazid, 20% for those receiving isoniazid and 23% for those receiving no TB drugs. Use of isoniazid was associated with higher C_{min} among slow CYP2B6 metabolisers.

Cord blood samples were available for 50 infants and the median EFV concentration was 1.30 ug/mL (IQR 0.75–2.33); 10% were below the limit of quantification (0.2 ug/mL). The investigators noted that cord and maternal pre-partum concentrations were highly correlated, r=0.95. EFV concentrations for one-week old infants were below the limit of quantification in 66% (44/67); quantifiable EFV correlated with higher cord blood concentrations, r=0.75.

There was one HIV infection among 91/93 live born infants. The mother enrolled in the study at 37 weeks gestation, having received EFV-based ART for 67 days and TB treatment for 51 days. The infant was exclusively breastfed and received nevirapine prophylaxis. The infant tested negative at 22 days by HIV DNA PCR and had a CD4 percentage of 38% but tested positive at 48 days and had 32% CD4. At the second test the infant's mother had an HIV viral load of 218, 672 copies/mL and reported breastfeeding.

The investigators concluded that pregnancy increased EFV clearance and the proportion of women with EFV C_{min} <1ug/mL was higher in pregnancy than after delivery. They noted that women with extensive CYP2B6 metaboliser status might be at particularly high risk of low EFV C_{min} and merit special attention if an EFV dose of 400 mg is considered.

TB treatment that includes isoniazid and rifampicin does not reduce overall TB concentrations but women with TB and HIV coinfection were more likely to have detectable viral load at delivery than those with HIV alone, probably because ART was started later. Vertical transmission was rare among participants and the investigators considered the one case that did occur likely to be related to breastfeeding and maternal adherence post partum.

Other studies show similar findings

In a related article, published as a letter in the 19 June 2014 edition of AIDS, Andrew Hill and colleagues from Liverpool University, WHO, Chelsea and Westminster Hospital and Chaing Mai University, performed a systematic review of five studies of EFV PK in pregnancy – including TSHEPISO from 2012 conference abstract – which included 235 women treated with 600 mg EFV once daily. Results from the literature review updated with published data from TSHEPISO are summarised in Table 1.

Table 1: PK studies of EFV in pregnant women

Study	TSHEPISO	IMPAACT p1026s	PROMOTE	AMATA	Cassard
No. of participants	97	25	105	13	16
Country	South Africa	Thailand/USA	Uganda	Rwanda	France
Ethnicity	100% African	21/25 Asian	100% African	100% African	No data
PK sampling	Single samples	Intensive 24 hour	Single samples	Single samples	Single samples
Effect of pregnancy on EFV PK	Modest increase in clearance	No effects on Cmax or AUC, 12% reduction in C24h	No effects on clearance	EFV in infant plasma	No change in Cmin by trimester
Viral load at delivery	<20 copies/mL 58% (no TB treatment) 28% (TB treatment)	<400 copies/mL 100%	No data	<200 copies/mL 100%	<200 copies/mL 100%
Vertical trans. rate	1/91 (with PCR results)	1/25	0/56	0/13	No data

The authors concluded that these five studies reported that EFV drug concentrations were not significantly affected and high rates of viral load suppression in the mothers at the time of delivery. “The overall results suggest that pregnancy has limited, if any clinically important effect, on efavirenz pharmacokinetics.” they wrote. The additional data from women in TSHEPISO does not appear to alter their conclusion.

No effects longer-term with EFV and rifampicin co-treatment

Andrew Hill and colleagues from Liverpool University and Chelsea and Westminster Hospital have also performed a systematic review looking at EFV PK in the presence of rifampicin (either Cmin or mid-dose concentration). This review was presented as a poster at AIDS 2014.

The authors identified studies with a sequential or cross-over design. They found six that evaluated <8 days of EFV-rifampicin treatment, with reductions in EFV concentrations of 19% to 54% compared with EFV treatment alone. One study of 2 to 6 weeks of EFV-rifampicin treatment showed mean Cmin reductions of 34%. Five longer-term studies evaluated 4 to 24 weeks of EFV-rifampicin treatment with increases in EFV concentrations of 6% to 26%. See Table 2.

Table 2: Effects of rifampicin-based treatment on EFV Cmin

Study	No. of participants	Population	Country	Duration of EFV	Effect of rifampicin on EFV	PK parameter
Short term studies						
Lee 2013	33	HIV-	UK	Single -dose	-45%	C24h
Cho 2011	10	HIV-	USA	Single -dose	-54%	AUC
Yenny 2011	8	HIV-	Indonesia	Single -dose	-39%	AUC
Lopez 2002	8	HIV+	Spain	7 days	-22%	Cmin
BMS	12	HIV-	USA	7 days	-32%	Cmin
Kwara 2011	11	HIV-	USA	8 days	-19%	C24h
Bienvenu 2014	21	HIV+	Rwanda	2-6 weeks	-34%	mid-dose conc.
Long-term studies						
Orrell 2011	34	HIV+	South Africa	4 weeks	+9%	mid-dose conc.
Semvua 2013	21	HIV+	Tanzania	8 weeks	+11%	Cmin
Luetkemeyer 2013	19	HIV+	International	24 weeks	+6%	Cmin
Freidland 2006	20	HIV+	South Africa	24 weeks	+26%	Cmin
Cohen 2009	17	HIV+	South Africa	24 weeks	+22%	mid-dose conc.

The authors also noted two additional longitudinal studies. In one the differences in EFV Cmin between rifampicin treated and untreated patients were only seen in the first 1 to 4 weeks of co-treatment, with no significant effects during longer-term treatment (Mukonzo 2013). And in the other rifampicin co-treatment only reduced EFV concentrations significantly during the first week, but not afterwards (Ngiamisi 2011).

In the systematic review, they found that rifampicin only lowered EFV concentrations in the first 1 to 4 weeks of treatment. There were no reductions in EFV after levels 4 to 24 weeks of combined treatment.

They wrote: “The reason for the lack of long-term effect of rifampicin on EFV in several large studies, despite clear reductions in short-term studies, is unclear.” They suggested that the populations might differ between the studies, or rifampicin might only lower EFV concentrations in the short time before auto-induction of EFV metabolism has occurred.

Based on these results, the authors concluded that dose modification of EFV does not appear to be justified, when co-administered with rifampicin-based treatment.

C O M M E N T

Two PK studies will look at EFV concentrations with 400 mg in the presence of rifampicin and in the third trimester of pregnancy.

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OPPORTUNISTIC INFECTIONS

Immunotherapy for PML: two case reports using IL-7 and experimental recombinant JCV VP1 protein therapeutic vaccination

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Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection in the brain that is caused by JC polyomavirus (JCV) and associated with profound immunodeficiency. At present there is no antiviral drug for use against JCV and the options to treat PML are limited to restoring protective immunity.

In light of this Maria Sospedra and colleagues at the Institute for Neuroimmunology and Clinical MS Research, University Medical Center Hamburg-Eppendorf, detail two case reports where they attempted experimental treatment of PML with a novel immunotherapeutic approach combining vaccination and IL-7, in the September issue of *Clinical Infectious Diseases*. [1]

Both PML patients were HIV negative and suffered from either an acquired or a hereditary immunodeficiency. In both cases, significant clinical deterioration during the 12 months between diagnosis and experimental treatment was reported, and during this period JCV DNA remained positive in cerebrospinal fluid (CSF).

The experimental treatment consisted of: three subcutaneous injections of recombinant human IL-7, 10 ug/kg body weight, with approximately 7 day intervals between each; three subcutaneous injections of a therapeutic vaccine, recombinant JCV VP1 protein, 1 mg, administered two days after the first dose of IL-7 and then approximately two weeks later and finally after another four weeks; imiquimod cream [a TLR7/8 agonist] was administered topically as adjuvant, at the subcutaneous injection site at the time of vaccination.

The treatment was well tolerated by both patients. Substantial reductions in CSF JCV DNA viral load occurred following treatment in both patients. While no new T2 brain lesions were observed following the treatment when assessed by MRI, the researchers noted a subtle gadolinium-enhancing MRI lesion in patient 1, and an enhancement in patient 2, indicative of an immune response to the PML lesions. Both patients experienced significant clinical improvement of neurological symptoms following treatment. Scripps neurological rating scale [SNRS] score for patient 1 improved from 71 one month before treatment, to 80 12 months afterwards. Patient 2 improved from 49 one month before treatment to 53 by 14 months after treatment and had signs of mild neuropsychological improvement regarding alertness.

JCV VP1 antigen-specific CD4 T cell proliferative responses were determined with both thymidine incorporation assays and CFSE dye-dilution assays by flow cytometry. Prior to therapy, no VP1-specific T cell responses were observed. After 84 days, both patients exhibited robust positive proliferative T cell responses to VP1, largely attributed to memory CD4 T cells by CFSE flow cytometry assays, although there were some CD8 T cell responses also. Tetanus toxoid antigen proliferative responses also improved in both patients, probably because of the immune-restorative effects of IL-7.

The authors conclude that this treatment was well tolerated, and appeared to have long-lasting efficacy by eliminating JCV viral load in CSF, inducing MRI-proven inflammation at sites of PML lesions without causing immune restoration inflammatory syndrome [IRIS] and by causing clinical stabilisation and slight improvement. Importantly, the authors suggest in their discussion that this approach is NOT suitable for people with HIV. This is most likely because rapid immune reconstitution with ART has been shown to paradoxically worsen PML or induce its onset [2].

Therefore the anticipated risk of IRIS-aggravated PML in HIV positive patients may be much greater than in people with other forms of immunodeficiency. Despite this, the authors suggest prophylactic vaccination with VP1 may be of benefit to HIV positive people, before starting ART. Further studies would need to investigate this.

C O M M E N T

We sought clarification from the corresponding author of this paper, as to why they deemed the approach inappropriate for persons with HIV infection.

They confirmed that while the approach should in principle be applicable to all PML cases, they urge caution in respect to people with HIV because immune restoration with ART should be attempted first in order to try and avoid fulminant IRIS. There is a chance that this immunotherapy in patients with IRIS-PML could further inflame immune-reconstitution mediated damage.

Dr Nicholas Davies, Consultant Neurologist at Chelsea and Westminster Hospital, London, adds that the approach may however prove useful in patients with poor immune reconstitution and little or no IRIS. In addition, the authors' suggestion of a JCV therapeutic vaccine may prove very useful for patients potentially facing immunosuppression.

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SIDE EFFECTS AND COMPLICATIONS

Kidney signal trouble worsens over 5 years in Japanese on tenofovir

Mark Mascolini, IAS newsletter

Estimated glomerular filtration rate (eGFR), a signal of kidney function, declined steadily over 5 years in HIV positive Japanese taking tenofovir (TDF) compared with those taking abacavir. The TDF group did worse than the abacavir group by three eGFR measures.

The risk TDF poses to kidney function is well appreciated. But the long-term renal impact of TDF in people who continue taking this antiretroviral is not well understood. Typically, providers switch patients from TDF to another drug if their kidney function worsens.

To assess the long-term effects of TDF on kidney function in HIV-positive people, especially those with low body weight, Japanese researchers conducted this 5-year study of 422 antiretroviral-naïve people who started a TDF regimen and 370 who started an abacavir regimen. All patients received care at a single center in Tokyo. People with lower weight are more vulnerable to TDF kidney toxicity.

The research team used logistic regression analysis to assess three renal endpoints: (1) decline in eGFR greater than 10 mL/min relative to the baseline measure, (2) more than 25% decline in eGFR, and (3) eGFR lower than 60 mL/min in two measures at least 3 months apart.

The study group had a median weight of 63 kg. Taking TDF rather than abacavir at least doubled chances of reaching all three endpoints, at the following adjusted odds ratios (aOR) and 95% confidence intervals (CI):

- More than 10 mL/min drop in eGFR: aOR 2.1, 95% CI 1.45 to 3.14, p<0.001
- More than 25% eGFR drop: aOR 2.1, 95% CI 1.50 to 2.90, p<0.001
- Two eGFRs below 60mL/min: aOR 3.9, 95% CI 1.62 to 9.36, p=0.002

Compared with the abacavir group, the average decline in eGFR grew larger as years taking TDF increased: -3.8 mL/min at 1 year, -3.6 mL/min at 2 years, -5.5 mL/min at 3 years, -6.6 mL/min at 4 years, and -10.3 mL/min at 5 years. "

In this cohort of patients with low body weight," the authors conclude, "TDF exposure increased the risk of renal dysfunction" and "loss in eGFR relative to the control increased continuously up to 5 years."

These findings should be interpreted cautiously because patients were not randomised to TDF or abacavir. As a result, factors not adjusted for when calculating odds ratios may have affected outcomes.

Source: Mascolini M. Kidney signal trouble worsens over 5 years in Japanese on tenofovir. International AIDS Society online news report. (02 September 2014). <http://www.iasociety.org/Default.aspx?pagelid=5&elementid=15988>

Reference: Nishijima T et al. Long-term exposure to tenofovir continuously decreases renal function in HIV-1-infected patients with low body weight: results from 10 years of follow-up. AIDS. 2014; 28: 1903-1910.

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HIV REINFECTION & TRANSMISSION

HIV reinfection has limited impact on disease progression

Gareth Hardy, HIV i-Base

Superinfection with a second viral variant after initial HIV infection has been described in various cohorts. However, it is currently unclear whether superinfection is associated with a clinically significant impact on disease progression or management.

In this study, Keshet Ronen from the Fred Hutchinson Cancer Research Center, University of Seattle, examined a well-characterised, prospective cohort of HIV negative women sex workers in Mombasa, Kenya, for cases of superinfection. [1]

From a total of 146 women screened, Ronen and colleagues identified and specified the timing of 21 cases of superinfection. This is currently the largest superinfection cohort and previous analysis have reported an incidence of superinfection that was approximately half the rate of initial infection.

HIV infection in this cohort occurred with clades A, C and D. Superinfections occurred with both intrasubtype and intersubtype variations and were timed from 63 to 1895 days after initial infection. The researchers investigated frequent viral load and CD4 count measurements to determine the impact of superinfection on markers of disease progression, as well as time to clinical events, in this longitudinal analysis. Of the 146 women screened for superinfection, 144 were selected based on estimation of initial infection being timed to within a one-year window. Timing of superinfection was determined as the midpoint between the last singly infected and first dual infected time points.

In order to exclude changes in viral load that occurred prior to establishment of the viral set point, viral load data was only included from after the first six months of initial infection. Viral load [\log_{10} transformed] and CD4 count [square root (sqrt) transformed] data were analysed using R. Linear mixed effect (LME) models to determine intercepts and rates of change. Cox proportional hazards regression was used to determine time to disease progression (CD4 T cell count <200 cell/mm³, initiation of ART or death).

Within the 144 women included in the screening analysis, there were 21 cases of superinfection. Of these, 133 women were included in the longitudinal data analysis as they had one or more viral load and CD4 T cell count measurements between 6 months post-initial infection and initiation of ART [median 10 measurements each]. Within this slightly smaller data set, there were 18 cases of superinfection. Comparing results of women who remained singly infected with women who ultimately acquired superinfection, the researchers found that there was a 0.009 \log_{10} viral load/mL/month faster rate of viral load increase ($p=0.0008$), but no significant faster decline in CD4 T cell count, at 0.047 sqrt cells/mm³/month ($p=0.06$). Presence of genital ulcers at HIV acquisition, initial viral subtype and HLA-B alleles had no effect on the model parameters.

The researchers also sought to determine if there were differences in any of the measured parameters between women that remained singly infected and those that became superinfected, prior to the superinfection occurring. The association between superinfection and lower pre-superinfection viral load intercept was also short of statistical significance ($-0.44 \log_{10}$ copies/mL, $p=0.06$). When this data was adjusted for initial viral subtype, genital ulcers at initial infection and possession of HLAB*57, HLAB27 and HLAB*35 this association just became significant ($-0.45 \log_{10}$ copies/mL, $p=0.05$). No such relationship was found for CD4 T cell counts.

Within the superinfection cases, there was no significant association to higher viral load intercept following superinfection, compared with before ($+0.21 \log_{10}$ copies/mL, $p=0.09$) with no relationship for CD4 T cell counts.

During study follow up, 91 of 144 individuals experienced a clinical event (defined as CD4 T cell count <200 cells/mm³, initiation of ART or death). There was no relationship between superinfection and incidence of clinical events (hazard ratio 1.07, 95%CI: 0.60 – 1.89; $p = 0.76$). The model predicted that there would be a 0.23 \log_{10} higher viral load/mL and that CD4 T cell counts would be 27 cells/mm³ lower after 5 years.

The researchers concluded that their data demonstrates a statistically significant acceleration in viral load increase and CD4 T cell count decline following superinfection, suggesting that the lower viral loads observed among individuals who subsequently acquired superinfection, compared with those who remained singly infected, may suggest that lower replication by the initial virus may predispose to superinfection.

However, and importantly, the differences in viral load were only just significant and are limited by small sample size. Lastly, the researchers suggest that the lack of an association between superinfection and clinical progression may result from the fact that the marginal differences in viral load and CD4 count were insufficient to cause differences in clinical outcome after 5 years.

C O M M E N T

This study is important for highlighting the difficulty in finding any clear signal for a clinically significant impact of superinfection.

The modeled prediction over five years of having a CD4 count that was 27 cells/mm³ lower or a viral load 0.23 \log_{10} copies/mL higher has no clinical significance, especially in the context of access to ART.

These results should provide doctors with an accurate reference for the likely safety for HIV positive people to not use condoms with other positive partners, in a situation where neither STIs nor pregnancy are a concern.

The concern about drug resistance is important if either partner is not on ART and the resistance profile is likely to be different. The transmission risk data from the PARTNER study and others, suggests that the caution about drug resistance may not be important in the context of undetectable viral load on ART.

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BASIC SCIENCE & CURE RESEARCH

Case report: Stem cell transplantation from CCR5 delta-32 homozygous donor selects for X4-tropic HIV

Richard Jefferys, TAG

A letter published yesterday in the New England Journal of Medicine describes the outcome of a recent attempt to repeat the HIV cure achieved in Timothy Brown. [1]

An HIV positive individual requiring stem cell transplantation for the treatment of cancer (anaplastic large-cell lymphoma) was matched with a donor homozygous for the CCR5 delta-32 mutation, which renders cells resistant to CCR5-tropic HIV. Pre-transplant analyses indicated that the majority of HIV in the individual was CCR5-tropic, but there was also evidence of HIV strains capable of entering cells via the CXCR4 (X4) receptor.

Antiretroviral therapy (ART) was interrupted during the transplantation procedure, but restarted afterward due to a viral load rebound to 93,390 copies. Analysis of the rebounding virus revealed the selection of mutations associated with X4-tropism, consistent with this virus gaining a selective advantage after the transplantation of cells resistant to CCR5-tropic HIV. Viral load was successfully re-suppressed by ART for nearly a year until the individual experienced a relapse of the lymphoma.

The relapse necessitated a second ART interruption, leading to a viral load increase to 7,582,496 copies, and the individual died from the cancer shortly afterward. The researchers note the case illustrates that the presence of X4-tropic has the potential to undermine strategies that aim to cure HIV infection by knocking out the CCR5 receptor.

The case report also underscores the importance of monitoring HIV tropism in other research studies looking to provide stem cells from CCR5 delta-32 homozygous donors to HIV positive people requiring transplants for the treatment of cancers.

Two such studies are ongoing in the US: BMT CTN 0903 and IMPAACT P1107.

Source:

TAG basic science blog (28 Aug 2014).

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<http://clinicaltrials.gov/ct2/show/NCT02140944>

Stemming the flow from HIV reservoirs with neutralising antibodies

Richard Jefferys, TAG

Two recent papers address the potential of broadly neutralising antibodies (bNAbs) to decrease HIV rebound from persistent reservoirs.

In the journal *Cell*, Ariel Halper-Stromberg and colleagues report the results of experiments conducted in the humanised mouse model with a “tri-mix” of three monoclonal bNAbs: 3BNC117, 10-1074, and PG16. [1]

When administered as post-exposure prophylaxis four days after the mice were challenged with HIV, the bNAb tri-mix did not prevent infection, but there was a significant delay in viral load rebound after the treatment was stopped (compared to a control group of mice given combination antiretroviral therapy on the same schedule).

The researchers conclude that the bNAbs were more effective than ART at preventing the formation of the latent HIV reservoir in the mice, likely due to antibody-mediated effector mechanisms facilitating the clearance of infected cells (similar to recent findings in the macaque model). [2]

Subsequent experiments investigated the effects of combining the bNAb tri-mix with potential latency-reversing agents including vorinostat (an HDAC inhibitor), I-BET151 (a BET protein inhibitor) and CTLA (a T cell inhibitory pathway blocker). In humanised mice with established HIV infection, the combination of the bNAb tri-mix and all three latency-reversing agents significantly reduced the number of mice experiencing viral load rebound after therapy cessation compared to bNAbs alone (10 of 23 mice rebounded in the combination group versus 22 of 25 in the bNAbs group). In contrast, bNAbs plus any single latency-reversing agent did not show significant effects.

The second paper—published in *PNAS* by Tae-Wook Chun and colleagues—explores the effects of bNAb combinations on HIV isolated from the latently infected CD4 T cells of individuals on ART. [3]

To try and model the spread of HIV from the latent reservoir that occurs when ART is interrupted, laboratory experiments were conducted in which CD4 T cells sampled from HIV negative individuals were exposed to HIV from the latent reservoir in the presence or absence of various bNAbs. Results showed that the most potent suppression of the reservoir-derived HIV was achieved by the bNAbs PGT121 (mean 2.4 log), VRC01 (2.1 log), and VRC03 (1.8 log). The authors also note: “viral isolates from 72%, 52%, and 44% of HIV positive individuals we studied were neutralised (>2 log suppression) by PGT121, VRC01, and VRC03, respectively;” this finding underscores that not all circulating HIV is susceptible to every bNAb.

In discussing their results, the researchers suggest: “a combination of HIV-neutralising monoclonal antibodies, particularly PGT121, VRC01, and VRC03, may provide sustained virologic remission in infected individuals following the discontinuation of ART.” Because bNAbs may have the potential to be administered infrequently, they argue this could represent an alternative to continuous ART.

The paper concludes by recommending that, due to the variation in HIV susceptibility to bNAbs, “clinical trials involving passive immunisation should include prescreening of HIV isolates from the persistent viral reservoirs of infected individuals with a panel of HIV-specific antibodies, to identify those that manifest the most potent suppressive activity against the patient viral isolates.”

Currently there are two ongoing phase I, first-in-human clinical trials of the monoclonal bNAbs 3BNC117 and VRC01. [4, 5]

A study of PGT121 is also in the works. At the recent Forum for Collaborative HIV Research workshop in Washington DC, plans for a trial involving passive immunisation with VRC01 in people with acute HIV infection were presented by Jintanat Ananworanich (the presentation is available on the Forum’s website). [6]

The administration of bNAbs in these studies is via injection, but there may be alternative possibilities. As covered previously on the blog, two research groups are testing adeno-associated virus (AAV) as a possible means to generate a permanent supply of circulating bNAbs after a single injection; although the original impetus for this work was the goal of preventing HIV acquisition, there is also interest in exploring the therapeutic potential. A phase I study of the approach in HIV negative individuals, sponsored by IAVI, is currently underway in the UK. [7]

Source: TAG basic science blog (03 Sep 2014).

<http://tagbasicscienceproject.typepad.com>

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HEPATITIS C

Daclatasvir approved in EU for HCV genotypes 1-4

On 27 August 2014, the EU approved the NS5A inhibitor daclatasvir for treatment of chronic hepatitis C genotypes 1, 2, 3 and 4. [1]

Approval was based on cure rates of up to 100% when combined with Gilead’s sofosbuvir, in an all oral, interferon-free combination.

Treatment duration is 12 or 24 weeks compared to 48 weeks of treatment with interferon- and ribavirin-based regimens.

Approval was based on multiple studies. This included an open-label, randomised study of daclatasvir with sofosbuvir in genotypes 1, 2, and 3, including patients with no response to prior therapy with telaprevir or boceprevir and patients with fibrosis.

SVR12 results were 99% in treatment-naive patients with HCV genotype 1, 100% of patients with genotype 1 who had failed treatment with either telaprevir or boceprevir, 96% of those with genotype 2 and 89% of those with genotype 3. Less than 1% of patients discontinued treatment and serious adverse events were reported by 4.7% of participants.

Ongoing and completed studies include more than 5,500 patients in a variety of all-oral regimens and with the current interferon-based standard of care.

The brand name for daclatasvir is Daklinza.

For further details see the full prescribing information. [2]

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CHMP gives positive opinion to approve coformulated sofosbuvir/ledipasvir

Simon Collins, HIV i-Base

On 25 September 2014, the Committee for Medicinal Products for Human Use (CHMP) recommended granting market authorisation for a coformulated version of sofosbuvir (400 mg) plus ledipasvir (90 mg).

This will be the first single-pill, once-daily, oral combination to treat hepatitis C.

Recommendations from the CHMP are usually followed, with full approval expected within three months.

The formulation is manufactured by Gilead and will be marketed in Europe with the brand name Harvoni.

C O M M E N T

Even without knowing the price that Gilead will charge, based on the experience with sofosbuvir alone, any enthusiasm for this significant medical advice should become dramatically muted.

Reference: Meeting highlights from the Committee for Medicinal Products for Human Use (CHMP) 22-25 September 2014. (26 September 2014).
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European activists protest at meeting of European Health Ministers for access to new HCV drugs

Community press statement

On 22nd September, a coalition of leading European community health organisations protested against the limited access to new oral drugs to treat hepatitis C.

This involved a non-violent "sit-in" of people living with hepatitis C and their allies at the Mico Conference Center, Milan, to advocate for, and demand, a clear political and public health commitment and leadership from the twenty eight member states of the European Union and from the European Commission itself.

Activist demands included:

- To ensure, that all patients in serious clinical situations have immediate access to more effective therapeutic combinations of DAAs without interferon in compassionate, free use when there is no Market Introduction Authorisation (MIA) and no current adequate alternatives;
- To commit publicly to provide treatment over the next fifteen years to all, with the best available combination therapies for the elimination of hepatitis C in a sustainable and affordable way in all European health care systems;
- To allocate financial and technical resources to prevent, diagnose and treat hepatitis C, with a view to its elimination;
- To invest in the diagnosis and referral to health care of all people living with hepatitis C;
- To promote evidence and human rights based drug policies that ensure the access of people who use drugs, the group most affected group by hepatitis C, to treatment;
- To engage in meaningful conversations with the pharmaceutical companies and involve community leaders, including representatives of organisations of people who use drugs, in the process of finding fast and sustainable solutions to providing universal access to hepatitis C treatment.

Organisations involved included: EpaC, ELPA, LILA, Nadir, European Civil Society Forum on HIV/AIDS, EATG, Aids Action Europe, ELPA, World Hepatitis Alliance, INPUD, Correlation Network, Eurasian and European Harm Reduction Networks and International Harm Reduction Association (IHRA).

<http://www.aidsactioneurope.org/news/announcements/hepatitis-c-sit-european-patients-request-access-new>

OTHER NEWS

DSMB open report strongly supports importance of START study

The ninth open report from the independent Data and Safety Monitoring Board (DSMB) for the international randomised START study is available online and “enthusiastically endorses continuation, of this pivotal randomised trial that will provide the highest level of evidence about when to start ART”.

The START study looks at the risks and benefits of immediate treatment (at any CD4 count above 500 cells/mm³) compared to waiting until the CD4 count reaches around 350 cells/mm³. START enrolled the first patient in December 2009 and is now fully enrolled with 4685 participants.

This 58-page report is an important summary of the baseline characteristics in the study, including for the important sub-studies. It also includes a review of ongoing retainment and details of individual reasons for study withdrawal and loss to follow-up.

The study is driven by serious clinical events, with the primary endpoint being the time to a serious AIDS event or death from any cause. Follow-up will continue until there have been 213 events, which is estimated to be at the end of 2016.

The DSMB strongly supports the safety of continuing the study and affirms the importance of obtaining randomised data to inform this essential study question on the timing of ART.

INSIGHT website:

<http://insight.cabr.umn.edu>

Direct link to PDF file of May 2014 report:

http://insight.cabr.umn.edu/official_documents/START/open_DSMB/START_OpenDSMB_30May2014.pdf (PDF)

FUTURE MEETINGS

Conference listing 2014/2015

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.

5th International Workshop on HIV & Aging

20-21 October 2014, Baltimore, USA

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

9th International Workshop on HIV Transmission Principles of Intervention

25-26 October 2014, Cape Town, South Africa

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

12th International Congress on Drug Therapy in HIV Infection

2-6 November 2014, Glasgow

<http://www.hiv11.com>

Five Nations Conference on HIV and Hepatitis

8-9 December 2014, London

<http://www.bhiva.org>

7th International Workshop on HIV Persistence during Therapy

8-11 December 2015, Miami

<http://www.hiv-persistence.com>

XXIV International HIV Drug Resistance Workshop

21-22 February 2015, Seattle, Washington USA

<http://www.informedhorizons.com/resistance2015>

5th International Workshop on HIV & Women, from Adolescence through Menopause

21-22 February 2015, Seattle

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

22nd Conference on Retroviruses and Opportunistic Infections (CROI 2015)

23-26 February 2015, Seattle

<http://www.croi2014.org>

21st BHIVA Spring Conference

21 - 24 April 2015, Brighton, UK

<http://www.bhiva.org/AnnualConference2015.aspx>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: updates for PDA access

The i-Base website is designed 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.

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>

- NEW: Introduction to combination therapy (July 2014)
- 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 (November 2013)

Publications and reports

HIV Treatment Bulletin (HTB)

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

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.

HTB West Balkans

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

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.

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

Advocacy resources

Online treatment training for advocates

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

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

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 580 members from over 120 organisations.

<http://www.ukcab.net>

Phoneline and information services

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>

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

htb(e)

HIV TREATMENT BULLETIN (e)

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

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

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