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CONFERENCE REPORTS

50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

12–15 September 2010, Boston

Introduction

ICAAC is a large antimicrobial conference and HIV studies often are not a sufficiently large part of the programme for i-Base to be able to attend this annual US meeting.

Many of the oral presentations were similar to the main studies reported from the International AIDS Conference held in July in Vienna.

The limited studies here were largely reported from abstracts online, or are included thanks to reports from NATAP.

- Raltegravir pharmacokinetics in pregnancy
- Low birth weight associated with HAART in pregnancy in Zambia
- Bilirubin levels in infants following in utero atazanavir exposure compared to exposure to other antiretrovirals
- Four-drug single-pill antiretroviral equivalent to Atripla at 48 weeks
- High rates of bone loss and progression with HIV in longitudinal study
- Novel mutations and shifting susceptibility to darunavir and tipranavir

ICAAC remains one of the most backward conferences in terms of democratising access to medical studies. There are no web cast session, online poster access requires conference registration and login and abstracts are not archieved for free access.

For a limited period, abstracts from the conference are published on the conference website. Access is via the 'conference planner' resource.

http://www.icaac.org

Raltegravir pharmacokinetics in pregnancy

Polly Clayden, HIV i-Base

Raltegravir shows variability in absorption and disposition in non-pregnant adults. Additionally the physiological changes associated with pregnancy may have an effect on drug disposition and decreased plasma concentrations have been observed with some protease inhibitors.

Edmund Capparelli and colleagues showed results from a study to determine the pharmacokinetics (PK) of raltegravir in the third trimester of pregnancy and compare these to postpartum PK data in the same women and to historical controls.

Women were enrolled in IMPAACT P1025 and its PK substudy and receiving 400 mg raltegravir twice daily in combination regimens. At the time of the evaluation all women had been on two weeks or more of stable therapy.

The investigators performed PK evaluations during the third trimester and 6-12 weeks post partum. Samples were collected pre-dose and 1, 2, 4, 6, 8 and 12 hours post dose. Cord blood and maternal samples were collected at delivery.

The target trough concentration was 35ng/mL (this is the target trough concentration in non-pregnant adults).

Ten pregnant women completed the third trimester evaluation and six the postpartum PK. Women were a median of 20.9 years (range 20.0–35.4) and weighed a median of 79.6 kg (range 61.4–120.7) in the third trimester.

The investigators reported highly variable PK but these were not significantly different between pregnancy and post partum. The cord blood and maternal plasma concentrations were similar indicating that raltegravir crosses the placenta.

Raltegravir pharmacokinetics in pregnancy are shown in Table 1 and plasma concentrations at delivery shown in Table 2.

Table1: Raltegravir pharmacokinetics in pregnancy and postpartum, median (range)

Parameter	Third trimester (n=10)	Postpartum (n=6)
AUC (mcg*hr/mL)	8.3 (3.0–17.5)	7.5 (2.0–25.5)
Cpre-dose (ng/mL)	85 (14–455)	498 (<10–772)
C12h (ng/mL)	107 (37–579)	77 (33–93)
Cmax (ng/mL)	1775 (685–6320)	2760 (352–8860)
CL/F (L/hr)	50 (23–133)	54 (16–200)
Met C12h target	10/10	5/6

Table 2: Delivery plasma concentrations, median (range)

Parameter	n=7
Cord blood raltegravir (ng/mL)	125 (22–939)
Maternal delivery plasma raltegravir (ng/mL)	145 (28–626)
Cord blood/maternal plasma ratio	1.20 (0.09–2.26)

The investigators concluded: "Raltegravir exposure was not consistently altered during third trimester compared to postpartum and historical data and the standard dose appears appropriate during pregnancy."

C O M M E N T

These data are reassuring.

Ref: Capparelli EV et al. Raltegravir pharmacokinetics during pregnancy. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 12–15 September 2010, Boston. Poster abstract H-1668a.

Low birth weight associated with HAART in pregnancy in Zambia

Polly Clayden, HIV i-Base

Investigations of the risk of preterm delivery (PTD) and low birth weight <2.5kg (LBW) associated with antiretroviral use (particularly protease inhibitors) in pregnancy have yielded conflicting results both in resource limited and well-resourced settings.

Results were presented from a Zambian study authored by Michael Silverman and colleagues looking at the association with lopinavir/r (LPV/r). [1] Its name, The Aluvia study, perhaps reveals, that it was conducted in association with Abbott, the innovator manufacturer of the drug.

This was a prospective study of LPV/r plus AZT and 3TC taken twice daily at the standard dose started between 14 and 30 weeks of gestation in 280 Zambian women who planned to breastfeed.

The investigators compared these results with historical data from the Zambia Exclusive Breastfeeding Study (ZEBS), conducted at the same location but at a time when HAART was unavailable. Almost all (99.3%) the women in ZEBS received single dose nevirapine (NVP) prophylaxis.

At the time of the analysis, 200 women had delivered 206 live infants and six week HIV DNA PCR results were available for 158 infants, out of which two (1.3%) were diagnosed with HIV.

The combined rate of HIV-infection at six weeks and mortality at three months post partum was 8/153 (5.2%) compared to 144/958 (5.2%) in ZEBS, p<0.001.

They reported a mean birth weight for the Aluvia cohort of 2.9kg (SD 0.5) with a LBW incidence of 35/206 (16.9%) compared to 105/937 (11.2%) in ZEBS, p=0.02.

There were no significant differences in maternal risk factors for LBW (CD4 <350 cells/mm3, anaemia, multiple birth, febrile illness).

When they compared the women with LBW and non-LBW infants in the Aluvia group the investigators reported no differences in potential risk factors (maternal CD4 count, hypertension, other infections, anaemia, diabetes, malaria) apart from a higher incidence of multiple births in the LBW group (4/33 vs 1/167, p<0.01).

They concluded that the LPV/r regimen does appear to be associated with LBW in this cohort, but that (unsurprisingly) the transmission rate is lower than that with single dose NVP.

Note: this article is only a summary of the abstract.

C O M M E N T

These data are consistent with observations in Europe and Botswana.

Ref: Silverman MS et al. Low birthweight (LBW) associated with antepartum HAART in Zambia. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 12–15 September 2010, Boston. Poster abstract H-1662.

Bilirubin levels in infants following in utero atazanavir exposure compared to exposure to other antiretrovirals

Polly Clayden, HIV i-Base

Chee and colleagues showed results from a small retrospective cohort study looking at infant billirubin levels in infants of mothers enrolled from a pregnancy registry at Inova Fairfax Hospital, Richmond, Virginia.

The primary outcome in this study was mean billirubin level within 72 hours after birth among three groups: atazanavir (ATV), another PI or NNRTI exposure. The secondary outcome was the proportion of infants with billirubin levels greater than 5mg/dL within 24 hours and reported clinical jaundice.

The investigators reported that, out of 52 infants born between 1999 to 2009 to mothers receiving ATV (n=12), another PI (n=21) or a NNRTI (n=19), 22 had billirubin levels measured to secondary to jaundice risk factors or clinical jaundice.

They found mean billirubin levels of: 6.7mg/dL (95% CI, 4.9-8.5), 5.5mg/dL (95% CI, 2.9-8.1) and 4.8 mg/dL (95% CI, 0-11.2, p=0.36), in the ATV, other PI and NNRTI groups respectively. Among the 16 infants with levels measured within 24 hours 7/8 (88%), 3/6 (50%) and 0/2 had concentrations greater than 5mg/dL, in the same groups respectively, p=0.03.

They noted that all preterm infants <37 weeks infants or those with a history of jaundiced sibling had billirubin greater than 5mg/dL at 24 hours. Clinical jaundice was recorded in 3/12 (25%), 4/21 (19%) and 1/19 (5%) in the ATZ, other PI and NNRTI respectively.

They concluded that at 72 hours billirubin levels were not significantly different among the three groups but the difference at 24 hours in the proportion of infants with concentrations greater than 5mg/dL was significant. They suggested that, although ATV exposed infants could be at increased risk for elevated billirubin levels, these levels may not lead to clinically significant jaundice.

Note: this article is only a summary of the abstract.

Ref: Chee JE et al. Comparison of neonatal bilirubin levels following in utero exposure to atazanavir versus exposure to other antiretroviral agents. 50th ICAAC Boston, 12-15 September 2010. Poster abstract H1664.

Four-drug single-pill antiretroviral equivalent to Atripla at 48 weeks

Mark Mascolini for NATAP.org

Quad–the coformulated antiretroviral combining the integrase inhibitor elvitegravir, the booster cobicistat, tenofovir, and emtricitabine–proved virologically equivalent to efavirenz plus tenofovir/emtricitabine (coformulated as Atripla) after 48 weeks in previously untreated people. [1]

In a separate 48-week analysis, atazanavir/cobicistat yielded virologic response rates similar to atazanavir/ritonavir.

These two phase 2 studies enrolled antiretroviral-naive people with a viral load at or above 5000 copies, a CD4 count above 50, and no resistance to NRTIs, NNRTIs, or PIs. Both trials were double-blind and active controlled, the first comparing Quad with Atripla, the second comparing atazanavir/cobicistat with atazanavir/ritonavir in people also taking tenofovir/FTC.

Researchers randomised 48 people to Quad, 23 to Atripla, 56 to atazanavir/cobicistat, and 29 to atazanavir/ritonavir. Ages averaged about 35, and about 90% of study participants were men. Median pretreatment viral loads were 4.6 or 4.7 log in all four treatment groups (about 40,000 to 50,000 copies). Median pretreatment CD4 counts were 354 in the Quad group, 436 in the Atripla group, 341 in the atazanavir/cobicistat group, and 367 in the atazanavir/ritonavir group. AIDS rates were 16% or lower in all treatment arms. Six people in the atazanavir/cobicistat group never received an antiretroviral dose and were not included in the analysis.

Three people (13%) discontinued Quad, none because of adverse events; 3 people quit Atripla, 1 because of an adverse event (suicidal ideation); 5 people (10%) quit the cobicistat group, 2 because of side events (vomiting and rash); and 3 people (10%) quit the ritonavir group, 1 because of an adverse effect (ocular icterus). Rates of drug-related grade 1 to 4 adverse events were 46% with Quad, 57% with Atripla, 36% with atazanavir/cobicistat, and 48% with atazanavir/ritonavir. Rates of grade 3 or 4 adverse events were 4% with Quad, 9% with Atripla, 4% with cobicistat, and 0% with ritonavir.

In a missing-data-equal-failure analysis, proportions with a week-48 viral load below 50 copies were 90% with Quad versus 83% with Atripla, and 82% with atazanavir/cobicistat versus and 86% with atazanavir/ritonavir. The first result meant Quad was noninferior to Atripla in 48-week efficacy. In a missing-data-excluded analysis, 48-week sub-50-copy rates were 96% with Quad versus 95% with Atripla, and 91% with cobicistat versus 96% with ritonavir. CD4 count gains through 48 weeks averaged 240 with Quad, 162 with Atripla, 230 with atazanavir/cobicistat, and 206 with atazanavir/ritonavir.

Mean percent changes in glomerular filtration rate estimated by the Cockroft-Gault method (eGFR) were -14% with Quad versus -4% with Atripla and -12% with atazanavir/cobicistat versus -11% with atazanavir/ritonavir. Changes in eGFR appeared early in the trial and remained stable through 48 weeks. Concerns over renal toxicity with cobicistat arose at week 24 in this trial, when eGFR and serum creatinine were worse with Quad than with Atripla. [2]

In the cobicistat-ritonavir comparison, rates of jaundice were low (3% to 4%) and similar in the two treatment arms. Rates of ocular icterus were higher but equivalent in the two arms–12% in the cobicistat group and 14% in the ritonavir group.

C O M M E N T

The change in eGFR is reported as a calculation error rather than evidence of toxicity but is clearly a difficulty that will require a new management algorithm.

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1. Elion R et al. The single tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (QUAD) maintains a high rate of virologic suppression, and cobicistat is an effective pharmacoenhancer through 48 weeks. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 12–15 September 2010, Boston. Abstract H-938b.
2. Cohen C et al. Single-tablet, fixed-dose regimen of elvitegravir/emtricitabine/tenofovir disoproxil fumarate/GS-9350 achieves a high rate of virologic suppression and GS-9350 is an effective booster. 17th Conference on Retroviruses and Opportunistic Infections. February 16-19, 2010. San Francisco. Abstract 58LB.
http://www.retroconference.org/2010/Abstracts/39864.htm

High rates of bone loss and progression with HIV in longitudinal study

Mark Mascolini for NATAP.org

Bone mineral density measurements in a 391-person Barcelona study showed progression to osteopenia or osteoporosis in more than one quarter of these HIV-infected people over a median follow-up of 2.5 years. [1]

Longer time taking a protease inhibitor (PI) or tenofovir raised the risk of worsening bone loss. This retrospective analysis focused on 391 HIV clinic patients who had at least two DEXA bone scans between 2000 and 2009. Each person had a median of 3 scans (interquartile range [IQR] 2 to 5), and the median time between scans was 2.5 years (IQR 1.2 to 5.3). Time between scans stretched beyond 5 years in 105 people (27%). Median age of the study group stood at 42.7 years (IQR 38 to 48), and median time on antiretroviral therapy was 8 years (IQR 4.4 to 12). Three quarters of these people were men.

The first DEXA scans in study participants showed osteopenia in 49% and osteoporosis in 22%. Bone loss prevalence is probably higher in this study group than in a general HIV population, since everyone in the study had two or more scans and physicians are more likely to order scans when they suspect a high risk of bone loss.

From one DEXA scan to the next, 12.5% of study participants progressed from normal bone mineral density to osteopenia and 15.6% progressed from osteopenia to osteoporosis. Among the 105 people with more than 5 years between DEXA scans, 18% progressed from normal bone density to osteopenia and 29% progressed from osteopenia to osteoporosis.

Multivariate analysis identified three traditional risk factors as independent predictors of progression to osteopenia or osteoporosis. Each year of age raised the risk 7% (odds ratio [OR] 1.07, 95% confidence interval [CI] 1.05 to 1.08, p<0.001), while male gender more than doubled the risk (OR 2.23, 95% CI 1.77 to 2.8, $P < 0.0001$). Low body mass index also made progression more likely.

Two antiretroviral-related factors raised the risk of progression. Each year of PI therapy raised the risk 18% (OR 1.18, 95% CI 1.12 to 1.24, p<0.001), and each year of tenofovir upped the risk 8% (OR 1.08, 95% CI 1.03 to 1.14, p<0.0019). However, taking a PI when the DEXA was performed lowered the risk of progression (OR 0.61, 95% CI 0.49 to 0.74, p<0.0001).

Ref: Bonjoch A, Figueras M, Puig J, et al. Bone mineral density in a large cohort of HIV infected patients. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 12–15 September 2010, Boston. Abstract H-226.

Novel mutations and shifting susceptibility to darunavir and tipranavir

Mark Mascolini for NATAP.org

Prevalence of mutations conferring resistance to the protease inhibitors (PIs) darunavir and tipranavir has dropped in recent years, according to an analysis of Monogram Sciences' resistance database [1].

The study also identified novel darunavir and tipranavir mutations and correlated declining susceptibility to darunavir with rising prevalence of mutations that make virus *more* susceptible to tipranavir.

Monogram researchers plumbed their database for viral samples with matched genotypic and phenotypic data, then used univariate and multivariate analyses to pinpoint mutations strongly associated with susceptibility to darunavir or tipranavir (measured as fold-change in 50% inhibitory concentration).

The investigators further assessed the potential impact of each mutation with *in silico* site-directed mutagenesis, a technique that identifies paired viral samples with matched amino acids at relevant resistance positions but with a single mutation at a specified position. For the 2141 darunavir-resistant samples, the Monogram team evaluated temporal trends in resistance from 2006 through 2009.

Three novel mutations were strongly associated with resistance to both darunavir and tipranavir: E35N, I47A, and V82L. Three other mutations--L10F, G48M, and V82F--were linked to resistance to darunavir only. And three other mutations--I54S, I84A, and I84C--were tied to resistance to tipranavir only. Overall prevalence of mutations associated with resistance to darunavir and tipranavir dropped from 2006 through 2009.

Among darunavir-resistant viral samples, average resistance to darunavir climbed from 38-fold to 50-fold over the study period. This jump in fold change correlated closely with a decrease in average tipranavir fold change from 7.6 to 4.3; the r(2) value for this inverse correlation was 0.99.

During the study period, prevalence of three darunavir-related mutations in the Monogram database rose--I50V from 11% to 15%, I54L from 17% to 33%, and L76V from 5% to 9%. Earlier studies found that these mutations make HIV more susceptible to tipranavir. The Monogram genotypic-phenotypic analysis confirmed the impact of these mutations on susceptibility to tipranavir.

The Monogram investigators suggested that increasing resistance to darunavir (measured as fold-change in susceptibility) "appears to be strongly associated with selection of mutations associated with darunavir resistance that have [a] sensitising effect on tipranavir." The researchers proposed that continued scrutiny of resistance databases "is essential to detect emerging trends in drug resistance and to identify novel mutations that improve the accuracy of genotypic interpretation algorithms."

Reference

1. Stawiski E, Paquet A, Napolitano C, et al. Identification of novel mutations strongly associated with darunavir and tipranavir resistance and their trends in a commercial database. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 12–15 September 2010, Boston. Abstract H-912.

CONFERENCE REPORTS

XVIII International AIDS Conference

18–23 July 2010, Vienna

Introduction

We continue our coverage of this important conference. For earlier rpeorts including details of online conference access, please see the July/August edition of HIV Treatment Bulletin.

Reports in this issue include:

- Spray-dried nanoparticle formulation of efavirenz
- Switching boosted-PIs to raltegravir
- Scaling up: what to do first?
- A new point-of care CD4 test
- Efavirenz-based regimens among women of reproductive age receiving ART in Johannesburg
- Male circumcision retains effectiveness at reducing risk of HIV infection: 54 month results

Abstracts from the conference are published on the conference website:

http://www.aids2010.org

Spray-dried nanoparticle formulation of efavirenz

Simon Collins,HIV i-Base

On the first day of the conference, researchers from the Council for Scientific and Industrial Research (CSIR) in South Africa (a scientific research institute primarily funded by the South African government), presented tentative results for the development of a nanoparticle formulation of the NNRTI efavirenz. [1, 2]

Nanotechnology has the potential to overturn many of the limitations to universal acces:

- The quantity of active drug is greatly reduced – perhaps by greater than 100-fold.
- Manufacturing cost have the potential to fall as dramatically, Most of the costs for generic drugs prices are due to raw materials: perhaps >90% compared to <1% of a Western drug price.
- Longer acting and delayed delivery formulations reduce the dosing period for daily to every 1, 2, 3 or 4 weeks etc. This should improve supply chain issues (fewer deliveries etc) and improve combination effectiveness and quality of life relating to adherence.

- Reducing the quantity of active drugs potentially reduces the risk of side effects, many of which are dose-related. Compounds whose development has been stopped due to toxicity concerns, may become feasible at nanoparticle doses. For example, another research group is even looking at transdermal indinavir. [3]

The group encapsulated efavirenz in polycaprolactone nanoparticles by a double emulsion spray drying technique using two organic solvents. The nanoparticles had an average size of 220.6 ± 0.950 nm when using ethyl acetate and 372.1 ± 19.96 nm using dichloromethane. This formulation overcomes the hydrophobic nature of efavirenz to improve bioavailability and met other manufacturing standards including encapsulation efficiency and a smooth particle surface.

C O M M E N T

If this research proves effective this has the potential to have as great an impact on global treatment as the first availability of generic antiretrovirals.

Human studies are needed before any idea of the dosing period can be determined. These are oral formulations and the group has already used the same technique for AZT and d4T. They plan to produced fixed dose combination formulations. Results from in vivo studies (not yet started) are hoped to be available by June 2011.

Although the reduced dosing is expected to reduce side effects, until this is determined, oral dosing with existing formulations prior to using a long-lasting version (in order to rule out hypersensitivity reactions) may be an important safety consideration, unless a rapid acting antidote to each drug is also available.

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Switching boosted-PIs to raltegravir

Simon Collins, HIV i-Base

Two studies, both from Spain, looked at switching a boosted protease inhibitor to raltegravir in people on stable, virally suppressed treatment.

The first study (called ODIS) included 222 people on stable treatment (<50 copies/mL for at least 24 weeks) who switched the boosted PI (48% on atazanavir, 28% on lopinavir and 13% on fosamprenavir) to raltegravir. [1]

The study randomised patients 2:1 to raltegravir once-daily (n=149) or twice daily (n=73). At three months, patients on the twice-daily arm with undetectable viral load were randomised 1:1 to either once-daily raltegravir or to continue BID dosing (n=35). The primary endpoint was viral suppression 24-weeks after the initial randomisation, with secondary endpoints that included metabolic changes.

Although median time on prior antiretrovirals was over 8 years, 40% people had previously used sub-optimal HAART, with just under 70% having prior recorded virological failure and 33% having documented NRTI resistance. Approximately half the patients had HCV coinfection.

By 24 weeks, more people had viral load rebound in the once-daily group (6.4% vs 2.9%, NS p=0.18). More importantly, a much bigger difference in failure rates was seen in people who had a previous history of resistance to nukes: 16.2% (12/74) vs less than 0.7% (1/148), p<0.001. This was associated with previous virological failure, especially if previous NRTI-resistance was documented.

Median total cholesterol, HDL and LDL reduced by –10 mg/dL, –3 mg/dL and –6 mg/dL respectively (p<0.05) but TC:HDL and TG changes were not significant. In a multivariate analysis, only prior NRTI resistance predicted risk of virological failure OR 28.45 (95% CI: 3.62-223.56), p=0.001.

In the second study (called SPIRAL) 273 people on stable treatment with similar treatment experience to the ODIS study were randomised 1:1 to either continue on their boosted-PI or switch the PI to raltegravir. [2]

The main difference in baseline factor compared to ODIS was a higher use of lopinavir/r (over 40%) as the baseline PI. The primary endpoint was viral suppression at week 48. After a year, 90% of people in each group remained on the assigned treatment.

Reasons for discontinuations were similar between groups. By ITT analysis 89% vs 87% remained free from virological failure respectively, (difference NS 2.6%; 95%CI: –5.2%, 10.6%), meeting the predefined criteria for non-inferiority (lower limit of 95%CI –12.5%). Virological failure occurred in four (raltegravir) vs six (PI) patients, with prior resistance history impacting slight more in the PI group, although these are small numbers. Tolerability was good with only 2% patients in each group discontinuing due to side effects; and grade 4 events occurred in 4% patients in each group.

Mean changes in baseline lipids reduced significantly in the raltegravir group: TC –11% vs +2%; LDL –6% vs –3%; HDL –3 vs +6%; TC:HDL –5% vs –1%; TG –22% vs –5%.

This significantly reduced the percentage of people in the raltegravir group who needed lipid-lowering treatment based on guidelines (NCEP).

These results were compared to the pooled results from the SWITCHMRK I and II studies which were stopped prematurely based on poorer virological responses in the raltegravir switch groups compared to the maintained lopinavir/r arms (approximately 88% vs 95% maintaining virological suppression at 24 weeks). [3] The publication of these results detailed a similar relationship between prior treatment failure and risk of virological failure after switching to raltegravir. [4]

C O M M E N T

A previous history of virological failure, as seen in the SWITCHMRK studies clearly increases the risk of virological failure when changing a boosted-PI to raltegravir.

If resistance, especially to NRTIs is not a concern, the lipid improvements may warrant the use of raltegravir, though these are less significant when switching from PIs that affect lipids to a lesser extent than lopinavir/r. The current cost of raltegravir in the UK limits the use of raltegravir as a switch option based on better tolerability.

Other studies looking at once-daily raltegravir dosing are ongoing.

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Scaling up: what to do first?

Polly Clayden, HIV i-Base

The revised 2009 WHO guidelines have four major changes since the 2006 edition:

- Routine CD4 counts
- Earlier ART initiation – CD4 threshold of 350 cells/mm3 from 200 cells/mm3
- Changing d4T to tenofovir in first-line regimens
- Increased number of sequential lines of treatment

In an oral session, Rochelle Walensky from Harvard presented findings from a study using a mathematical model simulated to project the clinical and economic outcomes from implementing each of these changes and combinations of these changes.

This study was designed to assist policy makers with their prioritisation process in recognition that implementing all of the guideline changes immediately poses major challenges in most resource limited settings.

The study used input data from a South African cohort with a mean age 32 years and a mean CD4 count of 375 cells/mm3 (ie healthier patients with the potential to benefit from starting earlier). Other input parameters included 24-week ART suppression rates of 75% and 78% rate of suppression at 24-weeks for first and second line ART respectively; annual costs of $36 and $135 for d4T and tenofovir respectively and 1.7-2.6% and 0.4-1.6% incidence of d4T and tenofovir related toxicity were also used.

The investigators ranked, in terms of survival and cost effectiveness, all 13 possible combinations of: (1) ART initiation at CD4

<200 cells/mL or CD4 <350 cells/mm3; (2) Replacing d4T with tenofovir; and (3) Number of available treatment regimens (1 or 2).

They examined 5-year survival, projected life expectancy and incremental cost effectiveness of different treatment scenarios. They used the WHO definition of less than 1x per capita GDP as the threshold for "very cost effective". For South Africa this is <$5,400 per year of life saved.

The baseline assumption was that patients received a single, d4T-based ART regimen, initiated at WHO Stage III/IV.

Dr Walensky reported that the projected baseline survival was 99 months, with a 65% 5-year survival rate. Switching from d4T to tenofovir gave a modest improvement, with a 110-month life expectancy and 67% 5-year survival. Adding ART at <200 cells/mm3 to baseline gave a 116 month life expectancy and 80% 5-year survival. Adding a second line regimen increased life expectancy to 121 months but added little to 5-year survival (66%) compared to baseline. Adding ART started at <350 cells/mm3 increased life expectancy to 124 months and 5-year survival to 87%.

Stepwise additions of switching to tenofovir or adding a second-line regimen to a one line d4T-containing regimen initiated at 350cells/mm3, gave increased life expectancy of 140 and 178 months and 91% five year survival (for both changes) respectively.

Switching to tenofovir from d4T in addition to initiating at 350 cells/mm3 and adding a second-line, ie following the complete WHO revisions, increased life expectancy to 192 months with 91% 5-year survival.

Dr Walensky summarised the above results noting that the incremental life expectancy gains are maximised with the following stepwise programmatic additions: first – the expansion of ART eligibility to CD4 <350 cells/mm3 one-line (124 months); followed by the addition of second line therapy (178 months); finally followed by the replacement of d4T with and tenofovir (192 months).

When examining the incremental cost-effectiveness of alternative programmes, three were found to be economically effective: d4T 350 cells/mm3/one-line (cost-effectiveness ratio $610/year of life saved [YLS]), tenofovir/< 350 cells/mm3/one-line ($1,410/YLS), and tenofovir/<350 cells/mm3/two-lines ($2,230/YLS). The investigators noted that these results persisted despite plausible variation in efficacy and cost assumptions.

The results of this study are extremely sensitive to the price of tenofovir. A sensitivity analysis revealed a decrease in the price of tenofovir from $135 to $51 per person year would make tenofovir more effective and less costly than d4T.

Dr Walensky suggested that the limitations to this study were that it only shows results for people initiating ART and did not address people in ongoing care. Also that while the analysis looks at value for money it does not project the implications of each component of the WHO recommendations on programme budgets.

To the question "What to do first" she concluded that the decision is dependent on a country's current policy and capacity. In countries without laboratory capacity, CD4 monitoring and ART at <350 cells/mm3 is the most crucial priority to start with. Where this is already available, replacing d4T with tenofovir are both cost effective and give survival benefits. The addition of second-line ART offers greater survival benefit but with substantial increases in total costs.

Ref: Walensky R et al. Scaling up WHO recommendations for HIV therapy in resource-limited settings: what to do first? Oral abstract WEAE0205.

A new point of care CD4 test

Polly Clayden, HIV i-Base

One of the most exciting sessions at the conference – Point of care CD4 testing in resource-poor settings - was hidden away in a mini room at 7 am on Wednesday morning. [1]

This satellite session presented the work to date on the development of a CD4 point of care test, appropriate for use in resource-limited settings. This programme is funded and led by the CD4 Initiative, Imperial College London, managed by Dr Hans-Georg Batz and Dr Steven Reid, and Zyomyx Inc. in San Francisco is developing the assay.

This initiative, established in 2005, set out with the ambitious target to develop a point of care test in four years (from January 2007) to a set of predetermined specifications. Three prototypes were assessed against flow cytometry and the Zyomyx test compared favourably so the initiative is proceeding with its development.

We describe the CD4 Initiative in the TAG Pipeline Report 2010. [2]

Peter Wagner from Zyomyx presented a project review from the company. Besides the specifications necessary for the health system and operator of a point of care test – simple to use and maintain, low cost, not dependent on electricity etc – he outlined the technical challenges and solutions in terms of point-of-care cell counting.

He explained that cells are not soluble markers. They are large, sticky, prone to lysis and gravitate to the bottom of any flow cell. This makes them difficult to process, mix and capture within integrated devices and machines. Additionally, in order to count CD4 cells and meet the specifications for simplicity, it is necessary to remove monocytes with no reagents or extra steps for the operator.

The assay needs to allow full capture of CD4 cells without loss due to lysis, entrapment or non-specific binding in order to make a complete cell count.

Dr Wagner noted that in general, reacting cells with reagents or beads in solution works better technically than approaches that

require cells to find a cartridge surface for sorting. He also said, “gravity is your enemy”(e.g. for proper sample mixing) unless you can use it to your advantage for the test principle which this device does.

The assay utilises a proprietary cell stacking approach to CD4 counting. A finger prick blood sample is taken. This is introduced into a one-piece, injection-molded, closed system cartridge, at the blood inlet port, which closes with a cap. The cartridge is placed in the mixer/spinner device. This is hand powered with no batteries required or does not need to be kept cool. It performs two functions, mix and spin.

In the cartridge, CD4 beads bind to CD4 cells to selectively transfer them to a volumetric measurement compartment forming a compact stack. Monocytes are removed through binding of magnetic CD14 beads for magnetic separation within the flow path. The height of the stack gives the CD4 count readout by eye as a dark line similar to a mercury thermometer.

The assay is fully quantitative, which surpassed the original specifications for a cut-off test. Therefore it can be used for treatment decisions and monitoring. No external reagents are required and it can give a result in less than 10 minutes.

Dr Wagner reported similar performance to flow cytometry in collaboration with Steven Deeks UCSF group with 100% sensitivity, 94.34% specificity, 92.31% positive predictive value and 100% negative predictive value.

The group will begin field-testing the device in Malawi in early 2010.

C O M M E N T

A CD4 test that is not reliant on electricity, that is easy to use, fast, disposable, that requires no cold chain or maintenance and is point of care, offers enormous possibilities for decentralisation of treatment delivery.

For a health worker, the skills required are performing a finger stick, twisting a lid, using a mechanism not unlike a lettuce spinner and reading off a gauge like a thermometer. Less than two hours of training is required. So use in the community seems completely feasible.

The fast turnaround would mean no return visit by patients for results, which has the potential to reduce loss to follow up that happens frequently at this stage. Although DART demonstrated that ART can be delivered safely without routine monitoring, a test is still required to start treatment. That this test is quantitative means it is useful beyond the decision of when to start treatment, and DART investigators also suggested that there is a role for CD4 testing from the second year on ART to guide the switch to a second line regimen. This will become more important as programmes mature.

The CD4 Initiative came about through a generous grant from the Gates Foundation. Additional funds are needed to finalise the work and bring the project to commercial production. It is absolutely critical that this funding is found.

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Further information

CD4 Initiative:
http://www1.ic.ac.uk/departmentofmedicine/divisions/infectiousdiseases/infectious_diseases/cd4_initiative/

Zyomyz:
http://www.zyomyx.com/index.php

TAG:
http://www.treatmentactiongroup.org

Early infant diagnosis

Polly Clayden, HIV i-Base

The new WHO paediatric guidelines now recommend immediate antiretroviral therapy for children with confirmed HIV infection aged <24 months. However identifying HIV-infected infants and linking them to treatment programmes, particularly fast, is easier said than done.

DNA-PCR testing is generally used for early infant diagnosis (EID), but it is expensive and requires sophisticated, centralised laboratories and trained technicians. Although DNA-PCR has been used in resource-limited settings, its long turnaround time contributes to infant loss-to-follow-up and loss of benefit of immediate initiation of treatment. Currently, no point-of-care (POC) HIV tests are available for infants.

In a special session at IAS 2010, Susan Fiscus presented an excellent overview of the current tools available and the prospects of POC technology for early EID. [1,2]

She began with a list of desirable qualities for a POC diagnostic test:

- Rapid (≤ one hour)
- Sensitive (≥ 95%)
- Specific (≥ 98%)
- Inexpensive (<$5 per test)
- Simple (equipment: battery operated, few moving parts, small footprint/technique: minimum training required)
- Robust – no cold chain required
- Commercially available
- CE marked/FDA cleared

But she quoted Bill Rodriguez's remark on the subject: "Cheap, fast or accurate. Pick two."

The current tests used for EID are HIV DNA and total nucleic acid assays. The gold standard is the Roche AMPLICOR HIV DNA assay, version 1.5. This test is used in many countries and can use whole blood pellets or dried blood spots (DBS).

The Roche Qualitative Total Nucleic Acid Assay has also been introduced. This test works on whole blood and DBS. In one study it was shown to be 100% sensitive and 99.7% specific.

Abbott is also developing a DNA assay.

These tests need large, expensive equipment and are probably only suitable for sophisticated, centralised laboratories.

For resource limited settings, HIV DNA assays need to be POC. Dr Fiscus described three tests in development.

Researchers at the Centre for Innovation in Global Health Technologies (CIGHT) at Northwestern University are working on a POC DNA-PCR. At CROI in February, they reported a lower limit of detection of 5 copies/reaction and good sensitivity and specificity. [3] This assay uses a small, portable, battery-operated analyser, which can assemble the reaction and perform fluorescence detection and thermal cycling. The analyser card integrates DNA extraction, PCR reagent storage without refrigeration and PCR amplification.

Data from Micronics Real Time PCR was also presented at CROI 2010. [4] This assay uses a credit card sized device and microfluidic principles for both nucleic acids extraction and amplification. The investigators reported good sensitivity and specificity in this study.

The Biohelix Isolamp is another simple HIV DNA test under development. This assay couples helicase-dependent isothermal amplification (HDA) with amplicon detection using a disposable cassette. Early data were presented at the 2010 HIV Diagnostics Conference. [5]

She explained that the CIGHT test is not yet ready for field-testing and is on hold while the group focuses on a POC p24 test. Both the Micronics and BioHelix tests appear to be in the proof of concept stage and are not ready for field testing yet either.

It is possible to use qualitative HIV RNA assays as an alternative to HIV DNA. The qualitative Gen-Probe Aptima is the only HIV RNA test approved by the FDA for diagnosis. Although the FDA approval is for plasma or serum, this system works well with DBS. It is very sensitive and specific and is being used by the State of New York for EID.

She mentioned that it is unclear whether HIV RNA assays will be as sensitive when infants are being prophylaxed or if mothers are receiving antiretrovirals and breastfeeding the child.

Several other HIV viral load assays are currently commercially available, but are not POC, require large expensive equipment, and are suitable for centralised laboratories.

Dr Fiscus described three POC RNA assays that are in development. The SAMBA (simple amplification based assay) is currently being developed by the University of Cambridge and Diagnostics for the Real World. Data were recently published in JID. [6] This test uses isothermal amplification and visual detection by dipstick. It has a limit of detection of 75 copies/mL using 250 mL of plasma, and 400 copies/mL using 100 mL whole blood. No cold chain is required and it can be battery operated. It is simple to operate and little training is needed. There will be a clinical trail for regulatory approval in 2011.

Dr Fiscus showed recent unpublished data from her own research group. The IQuum LIAT quantative POC HIV assay is a real time PCR, which can be battery operated, is easy to use and requires little training. It gave 92% correlation with Abbott m2000 with 75 plasma samples. It has not yet been tested with whole blood. The assay takes 60 minutes to perform but does need a cold chain.

Inverness Medical Innovation's CLONDIAG, uses a microarray, real time detection method. It can use fingerstick, whole blood or plasma. The sample is applied directly onto the test cartridge, which is processed by a compact, battery driven instrument. Preliminary data provided by the manufacturer are promising.

Finally p24 antigen tests, which have limited use in adult diagnostics, can be used for EID. The ultrasensitive, heat dissociated p24 antigen assay has been shown to work well with both plasma and DBS.

As far as POC is concerned, Dr Fiscus showed results from the CIGHT p24 antigen rapid test that were recently published ahead of print in JAIDS. [7] This assay is performed, by adding 25mL of plasma to 75mL buffer. This mixture is heated in a water bath at 90 degrees for four minutes. A test strip is then inserted and gives a read out after 20 minutes. Trials in Cape Town showed 95% sensitivity and 99% specificity.

She also described an improved CIGHT POC p24 antigen rapid test under development. This assay uses whole blood and heat shock to increase sensitivity. It consists of a plasma separator, reaction tube, reaction buffer and rapid test strip. It is battery operated and each test should cost $1-2.

In keeping with Bill Rodriguez's remark she presented the most likely future tests in a table. See Table 1.

Table 1: 'Cheap, fast or accurate. Pick two" Susan Fiscus

	Cheap: ≤ $5 USD	Fast: ≤ 60 min	Accurate: Sensitivity ≥95% Specificity ≥ 98%	Whole blood	Robust (battery operated and no cold chain)
IQuum LIAT	?	Yes	Yes	In development	Needs cold chain
CLONDIAG	?	Yes	?	Yes	Yes
SAMBA	$10-20?	≤ 90 min	Yes	Yes	Yes
CIGHT p24	Yes	Yes	Yes	Yes	Yes

She concluded that promising POC assays for EID today include: IQuum's LIAT, SAMBA, CIGHT p24 and possibly CLONDIG's viral load assay.

C O M M E N T

This was an incredibly useful overview and it looks like we can be optimistic about having a POC test for EID in the next couple of years.

Other presentations at the conference dealt with the challenges of access to EID. In the same session, Shaffiq Essajee noted that EID access has improved and in some countries more than 50% of exposed infants are tested. [1] But infant testing is usually linked to PMTCT and if coverage is low, so is infant testing coverage. Globally only 15% of exposed infants get a test. Even when there is access to EID, infected infants do not necessarily get ART.

Laura Guay showed that there are similar coverage cascades with EID to that of PMTCT. [8] Losses occur at each step of the cascade. She showed data from a programme of the Elizabeth Glaser Pediatric AIDS Foundation in which there were 4226 infants with known exposure. Of these 4099 (97%) had EID drawn, 895 (70%) had results returned from the lab with 449 (15%) positive results. Then only, 230, (51%) received results, 200 (87%) enrolled in care and 178 (89%) infants initiated treatment. Overall, she explained, there were 633 infected children, of which 71% were identified and 28% treated. "And this" she said "is a good programme".

A related poster showed Ministry of Health data from 84 sites in Cambodia, Namibia, Senegal and Uganda with >21,000 infants tested. [9] Although the study was called "Increasing uptake of HIV early infant diagnosis services in four countries" and showed steady increases in sample volume, in 2008, it was still low in three of the countries reviewed: Cambodia 14%, Senegal 9% and Uganda 21%. Namibia however achieved 86-100% EID coverage. Less than half these infants ever tested via EID were tested in their first two months of life. Coverage of optimal service (early testing) is consequently even lower. And of those infants tested HIV positive via EID, attrition is significant 72%, 67% and 67% were not alive and on ART in Uganda, Cambodia and Senegal respectively.

The investigators concluded: "Significant strides to establish and increase access to and uptake of EID testing have been made across all countries reviewed. When decentralising, it is important for programming to focus on early identification and access to the full package of exposed infant services including EID."

So as well as a POC test for EID, which will take care of some of the obstacles to successful diagnosis and treatment, programmes need to ensure good systems for patient management and links between services to ensure that they can take full advantages of the promise of these new technologies.

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Efavirenz-based regimens among women of reproductive age receiving ART in Johannesburg

Polly Clayden, HIV i-Base

South African guidelines recommend efavirenz-based regimens as the preferred first line.

Out of concern about efavirenz use in pregnancy the 2004 guidelines only recommend its use in women of reproductive age when they are using injectable contraception plus condoms; the 2010 revision amended this to “reliable contraception”. Nevirapine is recommended for the remainder, who are “unable to guarantee reliable contraception”.

Three posters authored by researchers from the Reproductive Health Unit, University of the Witwatersrand and Johns Hopkins Bloomberg School of Public Health, showed findings from investigations into how well these guidelines were being followed, the fertility intentions of women receiving efavirenz based and other antiretroviral regimens, and whether providers discuss these issues with women of reproductive age receiving ART. [1, 2, 3]

Colleen Hanrahan and colleagues looked at the application of guidelines. This prospective cohort study enrolled non-pregnant women on ART aged 18-35 years in September 2009-January 2010 in four Johannesburg clinics. The investigators conducted baseline interviews to determine demographics, contraceptive use and the fertility intentions of the women. A record review was used to confirm ART regimens.

They classified women correctly assigned to first line regimens at baseline according to the 2004 guidelines, which were in use at the time of the evaluation, and two interpretations of the 2010 guidance, “reliable contraception”. They used logistic regression to determine predictors of “inappropriate assignment”.

The investigators reported, out of a cohort of 805 women on first line ART, 44.6% (95% CI, 41.2–48.0%) were receiving efavirenz-based regimens at baseline. Overall 26.5% (95%CI: 23.4–29.5%) of women were receiving hormonal contraception.

Of those receiving efavirenz, 90% (95% CI, 86–93%) were incorrectly assigned according to 2004 guidance, but only 11% (95% CI 9–15%) were wrongly assigned to nevirapine. These proportions reduced to 77% for efavirenz and 27% for nevirapine and 24% for efavirenz and 73% for nevirapine interpreting the 2010 guidance as using hormonal contraception and hormonal contraception or consistent condom use respectively.

In a multivariate analysis including: age, time on ART, CD4 count, number of living children, relationship and employment status and enrollment site, none were significant predictors of incorrect assignment to efavirenz. For nevirapine, each additional child gave a two-fold increase in the odds of incorrect assignment, AOR 1.95 (95% CI 1.34–2.84), $p<0.001$.

In a related study Sheree Schwatz and colleagues presented data from a cross-sectional analysis of the same baseline interviews to compare differences in current and future fertility intentions. This analysis included a total of 851 women; the 805 on first line regimens described above plus a small proportion (5.4%, n=46) receiving second line regimens with a boosted PI.

Multivariate analysis revealed women on efavirenz-based regimens were older and had more living children, both $p<0.001$. Of these 39% were either currently trying to conceive or planned to do so in the next year. Women receiving nevirapine were more likely to be currently trying to conceive than those receiving efavirenz, $p=0.025$, but were no more likely to plan to in the next year, $p=0.17$.

In the third study describing communication between providers and HIV-positive women receiving ART about fertility and reproduction, less than half (40.7%) of the 851 women enrolled reported that providers had talked to them about future pregnancy options.

Older women and those with higher income were more likely to have fertility discussions with providers in multivariate analysis whereas parity, CD4 count, time on ART, regimen, marital status or fertility intentions were not associated with the likelihood of these discussions.

The investigators also found that PMTCT knowledge was significantly higher if their providers has discussed this with them $p<0.001$. Only about a third (35.4%) understood that efavirenz is contraindicated if trying to conceive and this was not associated with efavirenz use, $p=0.774$. A small proportion (6.4%) said a provider had told then not to have more children and 36% were unsure whether their provider approved of them having children. Discussion about contraception varied by type: 93.5% of women reported that their providers had discussed male condoms, 71.6% female condoms, 45.2% injectable contraceptives, 41.6% oral contraceptives and 18.8% sterilisation.

C O M M E N T

These data make the important point that no matter what labeling or guidelines recommend concerning use of efavirenz in pregnancy there is a strong likelihood that it will happen.

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Male circumcision retains effectiveness at reducing risk of HIV infection: 54 month results

Nathan Geffen, TAC

A late breaker by Bailey and Colleagues presented at the International AIDS Conference reported on the follow-up to the randomized male medical circumcision trial conducted in Kisumu, Kenya, involving 2874 men aged 18 to 24 years at enrollment. [1]

The authors had previously reported a 60% protective effect of male circumcision against HIV acquisition at 24 months after enrollment, and 64% at 42 months. This poster indicates that this protective effect extends to at least 54 months after enrollment.

As of March 2010, 1552/1740 men (89%) consented to extended follow-up: 767 in the circumcision group and 785 in the control group. The age and number of sexual partners at baseline were the same in both groups. 49% (387/795) of those in the control group have been circumcised since December 2006.

The number of HIV seroconversions by 54 months of follow-up was 39 in the circumcised group and 79 in the uncircumcised group (RR = 0.34; 95%CI: 0.23-0.51). The estimated cumulative incidence [95% CI] at 54 months was 4.0% [95%CI: 2.8-5.7] in the circumcised group and 10.6% [95%CI: 8.2-13.6] in the uncircumcised group ($p<0.0002$, RR=0.36; 95%CI: 0.24-0.55). The annualised incidence in the circumcised group was 0.91 per 100 person-years and 2.45 per 100 person-years in the uncircumcised group (p=0.0007).

The authors conclude that they found that the 60% protective effect of circumcision against HIV acquisition over 24 months is sustainable, and possibly strengthened, over 54 months of study. They write that these results provide support for policy makers, donors and implementers to scale up comprehensive, safe, voluntary medical male circumcision in appropriate regions as rapidly as possible.

C O M M E N T

This important finding demonstrates the lasting preventative effect of voluntary male medical circumcision. On 14 July the Bophelo Pele Male Circumcision Project in Orange Farm, one of the sites for the other two randomised controlled trials that showed the efficacy of circumcision, announced that they had reached the milestone of 20,000 safe circumcisions.

This intervention has long-term efficacy and has been proven that it can be conducted at scale and safely. It is therefore sensible to roll it out in areas with large heterosexual epidemics. It needs to be scaled up across sub-Saharan Africa.

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CONFERENCE REPORTS

Towards a cure: HIV reservoirs and strategies to control them

16–17 July 2010, Vienna

Rapporteur summaries

Immediately prior to the main IAS conference there was a two-day meeting with an excellent programme focusing on the growing body of research looking at targeting the HIV viral reservoirs, both tissue compartments and latently infected cells. The reports below are rappporteur summaries from the IAS website. Unfortunately this meeting was not webcast, however, many of the powerpoint presentations are posted online.

http://www.iasociety.org/Default.aspx?pageId=349

Where the posters from the meeting were also presented to the main conference, these abstracts are also online.

http://www.iasociety.org/Default.aspx?pageId=417

Opening session

Steve Deeks from the University of California San Francisco addressed two major questions: the clinical implication of residual viraemia on the pathogenesis of non-related AIDS diseases and how inflammatory mechanisms and T-cell activation can contribute to viral persistence.

Despite the strong impact of ART on survival and quality of life of HIV-infected patients, a gap in expectancy of life between non HIV-infected people and ART-treated patients still remains. Actually although HAART improves vascular function it does not completely restore vascular health (Hsue et al. CROI 2010). How could we explain this picture?

Two consequences of HIV infection persists in treated patients: residual viraemia and inflammation markers. The question to answer is whether both events are related to each other, and more importantly, if this impacts on mortality due to non-AIDS events, in particular cardiovascular diseases, in ART-treated patients.

Little evidence supports a direct role for residual replication as a factor involved in both inflammation and non-AIDS related diseases. Cohort studies and most intensification treatment trials have failed to show a relationship between residual viraemia and inflammatory parameters (Dinoso et al. PNAS 2009, Hatano et al. CROI 2010).

An inflammatory state represents a risk factor for the development of cardiovascular disease. In this context, numerous studies have shown persistent T-cell activation and increased inflammatory markers in chronic HIV infection but also in ART-treated patients. Increased immune activation parallels a lack of recovery of vascular health (Kaplan et al. CROI 2010). A best knowledge of the real impact of different factors causing chronic inflammation such as continuous bacterial translocation, CMV viremia, increased levels of cytokines and D-dimer (Volderbing and Deeks, Lancet 2010) represents a central issue of research.

Regarding the mechanisms of viral persistence in reservoirs and in particular the potential role of the immune system in the maintenance of such reservoirs different authors have shown a close relationship between immune activation levels and the size of the reservoir. Particularly relevant is the size of the reservoir in the gut that increases the number of infected cells tenfold in comparison with classical estimates (Yuki et al JID 2010). Strong activation of the GALT system undoubtedly contributes to higher susceptibility to infection of lymphoid cells in this compartment. Together with these mechanisms, homeostatic proliferation of particular subsets of memory T cells further contributes to expansion and persistence of the latent reservoir (Chomon et al, Nat Med 2009).

As a general conclusion, in the ART era we face a new scenario in which the wild destruction of the immune system and lethal opportunistic infections have been replaced by new mechanisms of immune dysfunction and new causes of morbidity in HIV-positive patients. These non-AIDS events probably are not related with persistent residual viraemia but with chronic activation and premature senescence of the immune system. To understand the pathogenic mechanisms of this new scenario represents a major challenge in order to improve the health of patients and to reduce the survival gap still remaining in comparison with HIV-negative people.

Session 1: Where and what are viral reservoirs? HIV reservoirs and sanctuary sites

Satya Dandekar opened the session pointing to the major questions to be addressed in the field of viral reservoirs. Two levels in assessing viral reservoirs are usually considered, cell types and anatomic tissues. A spectrum of viral reservoirs must be considered because cellular types differ in their capacity to sustain productive or latent infection and their susceptibility to viral cytopathic effect. Regarding anatomical reservoirs, gut and brain are probably the main tissues hosting HIV reservoirs during ART and interestingly both sites share two characteristics: the presence of activated cells and a microenvironment that can make drug accessibility difficult.

Among others, the following questions were raised: the potential role of early treatment to reduce both the size of the reservoirs and to allow better immune reconstitution of the GALT system; the impact of ART intensification to reduce reservoir size; and, the role of natural immunity to control HIV reservoirs. Finally the relevance of SIV models to answer these questions was also emphasised.

Three presentations addressed the role of gut as reservoir in ART treated patients and two communications focused on the origin of viral reservoirs in CNS.

Data assessing CD4 and lymphocyte activation in different gut regions were discussed by Steven Yukl from the Plus study group. Previous work presented at CROI 2010 by this team showed that levels of HIV DNA in CD4 T-cells varies across gut sites and suggested that the terminal ileum could represent an important reservoir site and a source of ongoing replication despite ART. To get better insight into the role of the ileum in HIV infection, sample biopsies from 10 HIV-positive people on ART and 8 HIV-negative controls were compared. CD4 levels were lower in ileum from HIV-positive people despite ART, but approached to normal recovery in rectum. Interestingly, a different distribution of memory subsets between blood and gut and among gut sites was found. A decreased proportion of effector and transitional memory cells was found in ileum and these differences could account for the higher HIV DNA content in CD4 T cells in gut. Although these data should be confirmed in a large number of patients they suggest the existence of different compartments in the gut regarding cellular distribution, response to ART and reservoir size.

Gabriella d'Ettorre from University of Rome analysed intestinal biopsies from sigmoid colon in either 14 ART-treated or treatment-naive patients, to correlate HIV-DNA levels, immune activation and microbial translocation. They found a 50% reduction in proviral HIV DNA levels in treated compared to naïve patients, but very incomplete reduction of microbial translocation and T cell activation (<20%) was found between both groups. HIV-DNA level in the GALT correlated directly with the levels of LPS suggesting that mucosal damage and the size of the reservoir directly contribute to chronic immune activation in ART-treated patients.

Finally, John Zaunders from St Vincent's Hospital at Sydney, analysed HIV-1 DNA levels in different lymphocytic subsets from eight HIV-positive patients with high CD4 counts. This analysis focused on memory CD4 displaying the integrin pattern a4+ß7+ that define gut-homing CD4 T cells, that can migrate from blood into GALT and back into blood via draining lymphatics and thoracic duct. The authors proposed the hypothesis that these gut-homing cells should be preferentially infected but their results clearly show that the majority of HIV DNA was found in CD4+ T cells that were not gut-homing (ß7-). Therefore, these provocative data suggests that the majority of infected CD4+ T cells in PBMC were unlikely to have been activated and infected in GALT. The question remaining is where they become infected?

Two presentations addressed the role of viral replication in CNS. Melissa Churchill from Burnet Institute in Melbourne studied the infection of astrocytes in the brain of 14 patients with different degrees of HIV-associated encephalitis (HIVE) and HIV-associated dementia (HAD). Combining laser capture and single-cell microdisecction with sensitive Alu-PCR, integrated HIV-DNA was found in astrocytes. Two aspects are remarkable in the work: first that the magnitude of astrocyte infection that varies between 0 and 20% correlates with HAD and severity of HIVE. Second, that astrocyte infection frequency correlates with proximity to macrophages and is maximal at the perivascular regions of the deep white matter suggesting the transmission by trans-migrating cells. Further studies analysed the activity of the HIV-LTR isolated from infected astrocytes that displayed lower activity than LTR from PBLs in the same patient but transcriptional activity was triggered by HDAC.

Finally, Ronald Swanstrom from University of Carolina at Chapel Hill, through in depth sequence comparison between blood plasma and CSF, showed a compartmentalisation that was associated with neurological status. Whereas in asymptomatic subjects similar sequences were found in blood and CSF, in HIV-associated dementia (HAD) specific sequences were exclusively found in CSF, strongly suggesting active viral replication in the CNS compartment. Based on the decay rate of the virus in CSF in patients with viral encephalitis, either T cells or macrophages were proposed as sources of viral replication. In patients with viral compartmentalisation and fast decay following ART, HIV would replicate in brain T cells whereas in those patients with slow viral decay in CSF the source of virus would be macrophages or microglial cells. Phenotypic data trying to correlate this different kinetics with infection of different cell lines were discussed in support of this hypothesis.

Overall, both presentations showed consistent and provocative data that highlights the role of the CNS as a viral reservoir that needs to be considered when designing strategies aimed at a cure of HIV-1 infected individuals.

In summary, this session addressed particularly relevant issues and probably more questions than answers were generated. Particularly relevant was in many presentations the use of new technologies to analyse and quantify the reservoir size in gut and CNS in a precise manner. However, the extreme difficulty to get material from gut and CNS represent a major limitation in the study of such still hidden reservoirs in vivo.

Session 2: What are the mechanisms of persistence?

This session was dedicated to discuss the molecular mechanisms involved in the establishment and the maintenance of latent HIV reservoirs and its dynamic nature.

First, Dr Eric Verdin in his overview talk focused on HIV transcriptional silencing leading to the establishment and maintenance of latency. Work from different laboratories suggests that transcriptional silencing of HIV is a multifactorial process that involves: lack of key transcription factors (e.g. NF-kB, NF-AT, STAT5, P-TEFb); recruitment of chromatin modifiers (e.g. HDACs, Suv39H1); and DNA methylation. All of which lead to the formation of a repressive chromatin environment. Three talks mainly dedicated to the molecular mechanisms of transcriptional latency followed.

First, Dr Alessandro Marcello explored the possible correlation between nuclear localisation and HIV transcriptional status. In the latency model used HIV was found in the nuclear periphery. Activation of the provirus did not change its localisation. Reports from different laboratories show that in its transcriptionally repressed state, the viral promoter is stalled due to the action of negative transcription elongation factors. Positive transcription elongation factor b (P-TEFb) is a critical cofactor for the viral protein Tat

which is required for efficient elongation of HIV mRNA. In his effort to understand the molecular mechanism involved in CTIP2-mediated repression of HIV promoter, Dr Rohr found that CTIP2 exists in 2 repressive complexes. One containing HDAC2 and the methyltransferase SUV39H1 while the other is composed of CTIP2 and inactive PTEFb. Thus, CTIP2-mediated repression of P-TEFb activity contributes to HIV latency.

Dr Bijan Sobhian then characterised the composition of Tat/P-TEFb complexes. He found that Tat exists in two biochemically distinct complexes. The active complex, Tatcom1 is composed of core PTEFb and additional new factors known to play a role in transcription elongation. This multifunctional complex contains proteins important for optimal PTEFb activity. Tatcom1 subunits are recruited to the viral promoter in Tat dependent manner. Knockdown of this subunit reduced Tat transcriptional activity. Thus, active P-TEFb should be stimulated to reactivate HIV from latency. An important challenge for the future is to find a way to target active PTEFb to silence HIV promoter.

Dr Tae-Wook Chun emphasised on the dynamic nature of the latent reservoir. Low-level viraemia exists in a majority of HAART-treated patients and is not well understood. Ongoing viral replication may account for this viraemia in some patients. Understanding where this virus comes from will be essential to purge the latent reservoir.

Finally, Dr Gero Hütter led a discussion about the recent case in which a delta CCR5 bone marrow transplant allowed a patient in Berlin to stop HAART without any rebound in viremia. HIV RNA and DNA were undetectable in patient samples. These results suggest that reconstitution of the immune system by CCR5 negative bone marrow also eradicates the latent reservoir. [Editorial note: or that the reservoir persists but new virus is unable to reestablish infection in CD4 compartment due inability to enter these cells].

In conclusion, this session highlighted the multifactorial nature of HIV latency and the long way we still have to go to understand it fully. Combinatorial therapies or identification of common mechanism will then probably be required to reduce the latent reservoir in HAART treated patients. Given the paucity of latently infected cells available (1/106 lymphocytes), it is also difficult to work on primary cells from patients. Since the different models of latency have many shortfalls, isolating or at least enriching the population of latently infected cells obtained from patients is a key issue.

Session 3. What is the role of the immune system in HIV persistence?

Brigitte Autran provided an overview for the session, highlighting the good and bad roles of the immune response to HIV-1 infection. Also highlighted was the potential of exhausting the HIV-1 reservoir through a combination of therapy intensification and immune interventions such as IL-7 or HDAC inhibitors.

Central memory CD4+ T-cells (T_{CM}) and transitional memory CD4+ T-cells (T_{TM}) represent the major reservoir of viral DNA. It is possible that through IL-7 triggered homeostatic proliferation (the ability of T-cells to divide in the absence of activation), the latent reservoir could be expanded. Vicente Planelles and colleagues described a system where T_{CM} cells were generated *ex vivo*. When infected, these cells were shown to have a high proportion of integrated virus but a low proportion of productive infection. IL-7 was shown to be a poor reactivator (1/8 efficiency of μCD3/μCD28) of latent virus. IL-7 could however, cause vigorous proliferation of T_{CM} cells. The authors concluded that IL-7 induced cell division could occur with minimal viral reactivation, suggesting that homeostatic proliferation could be expanding the latent reservoir.

The depletion of CD4+ T-cells in the gastrointestinal associated lymphoid tissue (GALT) leads to increased microbial translocation, which is proposed to contribute to systemic immune activation. David Asmuth and colleagues sought to determine whether CD4+ T-cell depletion in the GALT and systemic immune activation correlated with the presence of pro-inflammatory "gram-negative" bacteria orders in the gut. Presenting a pilot study of individuals pre- and post-initiation of therapy, higher proportions of pro-inflammatory gram-negative bacterial orders were associated with duodenal CD4+ T-cell depletion and systemic immune activation. This suggests an immunopathogenic role of bacteria in the duodenal tissue of HIV-1 infected individuals.

Resting CD4+ T-cells are a reservoir of latent infection. Vanessa Evans et al. investigated whether dendritic cells (DCs) played a role in the establishment of a latent infection in resting CD4+ T-cells. Using an *in vitro* model of HIV-1 latency in resting CD4+ T-cells, co-culture with myeloid dendritic cells (mDCs) induced a latent infection. This promotion of latency required both cell-cell contact and soluble factors. The authors suggest a possible pathway for the establishment of latency in vivo in lymphoid tissues.

The HLA-B27 and HLA-B57 alleles are over-represented in Long Term Non Progressors (LTNPs). Benjamin Descours and colleagues sought to investigate the impact on HIV-1 reservoirs by the strong immune control mediated by these protective alleles. Using a cohort of LTNPs, the –B27/–B57 alleles were associated with lower infection levels in T_{CM} cells. Anti-gag CD8 T-cells were associated with increased T_{CM} pool size. Thus the authors concluded that strong HIV-specific immunity in HLA-B27/57 patients results in maintenance of a larger and healthier T_{CM} pool.

HIV-1 elite controllers (ECs) are a small proportion of HIV-1 infected individuals who have undetectable viraemia in the absence of therapy. The role of immune protection in these individuals is not well defined. In this light, Mathias Lichterfeld and colleagues assessed the role of p21, a host protein shown to inhibit HIV-1 replication, in elite controllers. CD4+ T-cells from ECs were less susceptible to HIV-1 infection and these cells had significantly higher expression of p21. p21 acted by reducing both HIV-1 reverse transcription and mRNA transcription. This study demonstrated that p21 up-regulation in ECs is part of the immune control of HIV-1.

Session 4: What host factors are at a play?

Host factors influencing HIV-1 infection and/or pathogenicity offer an attractive opportunity for therapeutical intervention. However, only a handful of such factors have been shown to be clearly relevant so far. Paul de Bakker overviewed recent Genome Wide

Association Studies (GWAS) that aimed to identify host genetic differences influencing HIV viral load (VL) or disease progression. All GWAS clearly showed that variants in CCR5/CCR2 and in the Major Histocompatibility Complex (MHC) influence both parameters. However, this has been known for a few years, and although some new candidates outside the MHC have been proposed to modulate VL, the associations with VL are lost when larger samples of datasets are analyzed. Thus, Paul de Bakker assumes that GWAS have pretty much failed so far in providing robust associations of new gene variants influencing HIV-1. Larger cohorts of individuals or alternative approaches, such as whole genome sequencing or the integration of more clinical parameters may be needed to obtain more significant information, especially in the case of rare variants.

In the meantime, significant advances have been achieved in the understanding of the mechanisms of action of "classical" host factors which impact different steps in the replication cycle of HIV-1. RhTrim5-alpha blocks HIV-1 replication by interacting with the capsid after viral entry hindering completion of reverse transcription. The inhibition of the cellular proteasome rescues reverse transcription while maintaining the block of infection, suggesting a role of the proteasome in the blockage. Cindy Danielson showed that HIV-1 infection induces the relocalisation of the proteasome from the nucleus to rhTRIM5-alpha-containing cytoplasmic bodies. Danielson was able to visualise long term associations of the proteasome with flurorescent viruses moving dynamically through the cell, which often resulted in a decrease in the virus signal. Although it has been clearly demonstrated that the cellular factor LEDGF/p75 has a deep impact in HIV-1 replication by interacting with integrase and targeting viral integration towards active transcription units, it remained controversial whether LEDGF/p75 is essential or not for HIV-1 replication.

Rik Luk Guy Schrijvers reported the analysis of the first LEDGF/p75 integrase binding domain knockout human cell line. LEDGF/p75 knockout does not avoid HIV-1 replication although it results in the inhibition of single round infections and much delayed replication of productive virus. The number of integrated copies is reduced in LEDGF/p75 knockout, and integration in these cells occurs away of genes and preferentially in CpG islands. Once the virus integrated, some host micro RNA (miRNA) can modulate HIV-1 expression contributing to virus latency.

By performing miRNA qPCR array analyses of CD4+ T cells from HIV-1 exposed uninfected individuals (EU), elite long term non progressors with undetectable viral load (eLTNP), viremic patients and healthy donors, Claudio Casoli showed that the first three groups of individuals shared an altered expression of 8 miRNA, when compared to healthy donors, which may be interpreted as a signature of exposition to the virus. Furthermore, another pattern of expression allows distinguishing infected individuals (both eLTNP or viremics) from EU, which happen to have significantly lower levels of DICER and DROSHA, enzymes involved in the processing of miRNA. Exposition of CD4+ T cell to recombinant gp120 induces the same alterations in the patters of miRNA expression observed in vivo, which suggests that gp120-CD4 interactions may be responsible of the modulation of miRNAs. For leaving the infected cell, HIV-1 needs to overcome, via the viral protein Vpu, the effect of the restriction factor tetherin, which tethers virus to the cell surface inhibiting virus release.

Because, theterin localises into lipid rafts in the cell membrane and rafts are involved in the establishment of the viral synapse and HIV-1 cell-to-cell transmission, Björn Kuhl hypothesised that tetherin might affect this mechanism. Using transduced cells lines expressing or not tetherin, Kuhl observed that when tetherin is present in the cell surface it inhibits cell-to-cell transmission of HIV-1 devoid of Vpu, confirming recent observations by other groups. However, this effect of tetherin is also counteracted by Vpu. Interestingly, in the absence of tetherin, the transmission of the Vpu mutant was better than that of the wild-type virus, suggesting that Vpu may present a fitness cost in cell-to-cell transmission that is outweighed by the advantage of anti-tetherin action.

Session 5: What are the potential therapeutic interventions and how to evaluate them?

The session was started by co-chairperson, Christine Katlama, who said that the thought of a cure for HIV should be freed from the realm of science fiction in light of novel results.

Frank Maldarelli then addressed the need of precise quantitative measures for ongoing viral replication during antiretroviral therapy (ART). In his view, residual viraemia during ART does not depend on the potency of antiretroviral drugs, and intensification of ART with NNRTIs or protease inhibitors does not contribute to abatement of residual viremia. He however quoted a recently published study (*Buzón et al., Nat Med* 2010), in which some patients with undetectable viraemia did show evidence for further antiretroviral effects upon ART intensification with integrase inhibitor raltegravir.

In this regard, Una O'Doherthy, used a novel assay for the measurement of residual viral replication, and showed that two thirds of patients on ART sporadically had an excess of non-integrated proviral DNA, strongly suggesting that viral replication cycles sometimes occur despite ART.

The presentation by Carolina Garrido showed that switching an ART regimen to a raltegravir-containing regimen conferred additional immunological benefits such as increases in CD4 counts, which might be caused by an increased thymopoiesis.

Dr. Carolina Gutierrez presented results from ART intensification using the CCR5 inhibitor maraviroc. She obtained a decrease in the numbers of cells infected with replication-competent HIV-1 in peripheral blood and a decrease in the activation levels of CD4+ and CD8+ T cells at the long term. Novel strategies aimed at curing HIV-1 were also presented in this session.

As pointed by co-chair Alain Lafeuillade, these can be distinguished in strategies reverting HIV-1 latency and in the so-called viral "sabotage" strategies, reducing the capacity of the viral reservoir to expand.

Among the former strategies, Sandrina Da Fonseca presented *in-vitro* data showing that CD4+ T cells expressing high levels of the surface antigen PD1 from HIV-1 infected patients are enriched in integrated and total HIV-1 DNA and expression of PD-1 correlated with the size of the viral reservoir. She showed that this may be due to the fact that PD-1, by interacting with its ligand PD-L1, maintains proviral DNA in a latent status. Disruption of this protein-protein interaction through drugs or antibodies induced

viral replication of integrated provirus, which might represent a novel therapeutic avenue.

As a sabotage strategy, Dr. Andrea Savarino presented his latest in-vivo data using the gold-based compound auranofin (Gar1041). This drug induces down regulation of the cell survival-associated antigen CD27 in central memory T-cells, likely decreasing the half-life of this reservoir for the latent provirus. When administered to monkeys infected with SIVmac251 and treated with intensified ART, a significant decay in proviral DNA was observed, as well as a delay in the rebound of viraemia following therapy suspension. Moreover, following this treatment, monkeys acquired an ability to maintain low-level viraemia and high CD4 counts in the absence of ART, thus opening new avenues for obtaining a drug-free remission of the infection.

Closing session

Sharon Lewin highlighted social issues linked to the importance of research into a cure for HIV. Full life expectancy is not restored by ART, according to data derived from the Danish HIV cohort and showing that HIV-positive individuals may to date expect to live a life 70% shorter than the healthy. Even this reduced life expectancy is not accessible to each of the people living with HIV in the world: for every two people starting ART, there are five new HIV infections, and the total projected economic resources required to control the disease are increasing.

As shown by the important results obtained from the beginning of the epidemic (diagnostic tools, ART), community engagement will be important for reaching the ambitious goal of eradicating HIV. Basic science should indeed meet the requirements of people living with HIV (PLWH). One example is that methods for quantifying HIV reservoirs, such as lymph node and gut biopsies are highly invasive. Moreover, clinical trials for strategies aimed at HIV eradication are currently needed by the PLWH community. Finally, a higher level of involvement of politicians and media would be important for addressing resources to this ambitious goal.

Daria Hazuda highlighted the difficulties in the drug discovery process. From 5,000–10,000 compounds (but these numbers may be higher) that are synthesised for in-vitro evaluations, approximately 250 are selected for further preclinical investigations in cellular and animal models. Among these, an average of five compounds is addressed to clinical trials and only one of them obtains FDA-approval. In this context, the research for drugs aimed at curing HIV/AIDS offers special difficulties. In the case of antilatency compounds, there are several cellular models available (LTR-reporter constructs, chronically infected, inducible cell lines, retroviral vectors, and primary cell models), and the results obtained in these different models may not be comparable. Merck has put major effort in the development of histone deacetylase (HDAC) inhibitors as antilatency drugs. HDAC inhibitors could be used in combinatorial approaches, as they act downstream from the "sparking signal" required for activation of HIV-1 transcription (provided by nuclear factors). In this regard, protein kinase C (PKC) activators may play a major role in providing the "sparking signal", and some of them are synergistic in combination with HDAC inhibitors in inducing HIV-1 escape from latency in vitro. When HDAC inbibitor, vorinostat and a PKC activator were administered to a monkey model for lentiviral (SHIV-RT) persistence during ART, it was possible to show decreases in tissue viral DNA levels but no delay in viral load rebounds when therapy was suspended. This result may however be improved by combining this approach with other strategies.

The session was closed by Paula Munderi, highlighting the need of controlling HIV spread in serodiscordant couples, and Christine Rouzioux, who addressed the need of studying those rare patients showing a remission of the disease after therapy suspension.

Source: IAS

Rapporteurs: José Alcamí (opening and S1), Xavier Contreras (S2), Michael Roche (S3), Asier Sáez-Cirión (S4), Andrea Savarino (S5 and closing).

ANTIRETROVIRALS

START study given green light for full study

On 27 August 2010 investigators involved in the international START trial learnt that the US Division of AIDS has committed to expanding the number of sites in order to enroll 4,000 participants by the end of 2012.

The decision was based on success of enrollment in the initial phase of the study.

START is looking at the risks and benefits of early treatment (starting above CD4 500 or waiting until 350).

It is the only ongoing randomised study that has looked at starting treatment at CD4 counts above 500.

C O M M E N T

Recruitment into the pilot phase needs to continue at UK sites as important sub-studies are connected to the phase 1 enrollment. The roll over into the main study is continuous, so the goal is also now for 4000 participants by 2012.

The commitment to new funding will now enable new sites to join the study. This study has the potential to generate some of the most important data on the impact of HIV, treatment, an ageing from both the main and sub-studies.

Further information: START@ctu.mrc.ac.uk

http://www.insight-trials.org

Saquinavir prolongation of QT interval: Roche issue Dear Doctor letter

On 5 July 2010 Roche issued the following letter to health care providers. These results followed an FDA mandated phase 4 in HIV-negative volunteers.

Association of saquinavir (Invirase) with arrhythmogenic risk due to prolongation of the QT and PR intervals

Dear Healthcare Professional

Roche, in coordination with the European Medicines Agency, would like to notify you of the risk of QT prolongation associated with saquinavir (Invirase), and the subsequent important safety-related addition to the Summary of Product Characteristics (SmPC) for Invirase.

Summary

Healthcare professionals should note that:

- Saquinavir is contraindicated in patients with congenital or acquired QT prolongation or other predisposing conditions for cardiac arrhythmias, including concurrent therapy with other drugs that prolong the QT and/or PR interval.
- The combination of saquinavir with drugs known to increase the plasma level of saquinavir is not recommended and should be avoided when alternative treatment options are available.
- Saquinavir should be discontinued in case of arrhythmias, QT or PR prolongation.

Recommendations

- The recommended dose of saquinavir should not be exceeded since the magnitude of QT and PR prolongation may increase with increased plasma levels of saquinavir.
- Baseline and follow-up electrocardiogram recording should be considered (e.g. in patients taking concomitant medication known to increase the plasma level of saquinavir).
- Patients should be warned of the arrhythmogenic risk and told to report any signs of cardiac arrhythmias (e.g. chest palpitations, syncope, presyncope) to their physician.

For detailed information on the administration and use of saquinavir, please refer to the Summary of Product Characteristics.

Further information on the safety concern

Saquinavir is indicated for the treatment of HIV-1 infected adult patients. Saquinavir should only be given in combination with ritonavir and other antiretroviral medicinal products.

The effects of therapeutic (1000/100 mg twice daily) and supra-therapeutic (1500/100 mg twice daily) doses of saquinavir/ritonavir on the QT interval were evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg) study in healthy male and female volunteers:

In the therapeutic and the supra-therapeutic arm 11% and 18% of subjects, respectively, had a QTcS[1*] between 450 and 480 msec. In the moxifloxacin active control group, none of the subjects had a QTcS over 450 msec. No study subjects experienced QT prolongation > 500 msec or torsade de pointes in the study.

PR interval prolongation of > 200 msec was observed in 40% and 47% of subjects receiving saquinavir/ritonavir 1000/100 mg twice daily and 1500/100 mg twice daily, respectively, and in 3% and 5% of subjects in the moxifloxacin active control group and the placebo arm, respectively.

Events of syncope/presyncope occurred at a higher than expected rate and were seen more frequently under treatment with saquinavir/ritonavir.

Communication information

The Patient Information Leaflet will be revised in accordance with the updated Summary of Product Characteristics.

TREATMENT ACCESS

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
d4T/3TC/nevirapine FDC tablets 30 mg/150 mg/200 mg	Hetero, India	10 September 2010
d4T/3TC/nevirapine FDC tablets 30 mg/150 mg/200 mg	Macleods, India	30 August 2010

"Tentative Approval" means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, but because of existing patents and/or exclusivity rights, it cannot yet be marketed in the United States. Tentative approval does, however make the product eligible for consideration for purchase under the PEPFAR program for use outside the United States.

Fixed Dose Combinations are reviewed for PEPFAR under the FDA guidance titled "Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously approved Antiretrovirals for the Treatment of HIV". This document was developed to clarify what regulatory requirements apply to such applications, what issues might be of concern, and how these issues should be addressed. The guidance is intended to encourage sponsors to submit applications for combination and co-packaged products, and to facilitate submission of such applications to FDA.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079742.pdf

Effective patent dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 116 since the programme started. An updated list of generic tentative approvals is available on the FDA website:

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

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

IAS highlight funding shortfall crisis for Global Fund

IAS Press Release

The Global Fund to fight AIDS, Tuberculosis and Malaria is a demand-driven public private partnership established in 2002 to mobilise and intensify the international response to the three diseases. The Global Fund is the largest multilateral funder of public health in developing countries and is making a significant contribution to achieving the Millennium Development Goals (MDGs).

The 3rd Voluntary Replenishment of the Global Fund will be taking place on the 4-5th October in New York. The Global Fund has developed three resource scenarios in preparation for the replenishment meeting:

- **Scenario 1 – US$ 13 Billion** - Would allow for the continuation of funding of existing programmes. New programmes could only be funded at a significantly lower level than in recent years.
- **Scenario 2 – US$ 17 Billion** - Would allow for the continuation of funding of existing programmes. In addition, funding for new programmes would come close to that of recent years.
- **Scenario 3 – US$ 20 Billion** - Would allow for the continuation of funding of existing programmes. In addition, well performing programmes could be scaled up significantly, allowing for more rapid progress towards the achievement of the health-related Millennium Development Goals.

Through the Universal Access Now Campaign, IAS Secretariat has been actively advocating for the full replenishment of the Global Fund as an effective means to bring us closer to reaching universal access to HIV prevention, treatment, care and support services and also to the health related MDGs. In a final push before the Replenishment meeting the IAS has taken a decision to target Germany and Sweden, two key donor countries to the Global Fund. Both countries have not yet stipulated whether they will increase their contributions to the Global Fund. We believe there is a window of opportunity to lobby these two countries and to call on them to increase their contribution and commitment to the Global Fund. If Germany and Sweden increase their contributions it

may in turn encourage other European donors to follow suit. We urge all IAS members to write to the governments of both Germany and Sweden, please make your voices heard!

In addition there are a number of advocacy activities that are currently underway:

- The Millennium Development Summit will be taking place from the 20–22 September in New York. The primary objective of the Summit is to accelerate progress towards all the Millennium Development Goals (MDGs) by 2015, taking into account the progress made towards the internationally agreed development goals. The summit is expected to undertake a comprehensive review of successes, best practices and lessons learned, obstacles and gaps, challenges and opportunities, leading to concrete strategies for action. The IAS will provide an update on the outcomes of the MDG Summit via the Stronger Together Blog:

  http://www.iasociety.org/

- A Global Week of Action running from the 20–28 September to the support the 3rd Voluntary Replenishment of the Global Fund has been launched. A number of CSOs have planned media and outreach activities taking place during this week.

  http://www.globalfundreplenishment.org/global-week-of-action/

- An International sign-on letter calling on governments to fully finance the Global Fund to Fight AIDS, TB and Malaria has been launched. This petition will be delivered to world leaders at the 3rd Voluntary Replenishment Meeting.

  http://www.globalfundreplenishment.org/

Without a successful Global Fund Replenishment, the world will not meet the health related MDGs – the Global Fund that provides over 50% of AIDS treatment in resource poor countries and two thirds of international funding for TB and malaria is crucial to this effort. Make your voices heard, we must continue to hold governments accountable to ensure that universal access targets and the health related MDGs are achieved.

C O M M E N T

In the UK the STOP AIDS Campaign is doing work on lobbying government to increase support to the Global Fund. The 'Here I Am' campaign joins with advocates in developing countries as well as within the UK. Here is a link to more information about it:

http://domain2323665.sites.fasthosts.com/HERE_I_AM.asp

http://www.hereiamcampaign.org/

Individuals in the UK need to make this a political priority.

Source: Letter from IAS President, Elly Katabira

The need for expanded access to experimental medicines for drug-resistant TB

Nathan Geffen, TAC

Currently treatment outcomes for multi-drug-resistant (MDR) and extensively drug-resistant (XDR) TB are poor. Neel Gandhi presented data at IAS2009 showing 69% one-year mortality for MDR TB and 82% mortality for XDR TB in Tugela Ferry. Over time, mortality for MDR TB had declined from 87% to 45% but there was no significant decline in mortality for XDR TB. At the same conference, Max O'Donnell presented data showing that of 72 patients treated for XDR TB in a Durban hospital, less than half were alive and in care at six months. [1, 2, 3]

Several new drugs are being developed for TB. [4]

The furthest along in the pipeline for the treatment of drug-resistant TB is Tibotec's TMC207. A small phase IIa trial (n=43) published in the New England Journal of Medicine last year showed quicker time to sputum-negative conversion with TMC207. [5, 6] Further data is expected to be presented at the World Lung Conference in Berlin later this year.

OPC-67683 produced by Otsuka is also in a phase II drug trial. No human trial data has yet been published for this compound, but it has been reported at a conference to have succeeded in phase I safety, tolerability and pharmacokinetic testing as well as a 7-day early bactericidal study. [7]

Both these compounds are novel in their class. TMC207 is a diarylquinoline and OPC-67683 is a nitroimidazole. They are both therefore expected to be active against current strains of drug-resistant TB.

The need for expanded access to new TB drugs has been the subject of discussions at two meetings, at a satellite conference organised by the Treatment Action Group during the World Lung Conference in Mexico in December 2009 and more recently at Open Forum 4, hosted by TB Alliance in Ethiopia. At the latter there was a panel discussion on expanded access. One of the panel speakers, Brian Woodfall of Tibotec, indicated that the company is prepared to expand access to TMC207. [8]

There are compelling reasons to expand access to TMC207 and even OPC-67683 before they receive regulatory approval:

- Patients with MDR-TB or XDR-TB might reasonably believe that the risk of not taking these drugs outweighs the risk of taking them, given the extremely high mortality and prolonged treatment periods for these conditions. It is arguably unethical to deny patients access to these drugs when they are at high risk of death or need to get back to work or their life's activities.
- Health workers are at especially high risk of contracting MDR and XDR TB. O'Donnell presented data at IAS2009 showing that in the general Kwazulu-Natal population: the rate of MDR TB was 11/100,000. But in health workers it was 59 per 100,000 people (OR: 5.5; 95%CI; 4.7–6.5). For XDR TB the rate was 1/100,000 in the general population versus 4/100,000 in health workers (OR: 3.89 95%CI: 2.0-7–1). [2] People who risk contracting a fatal illness by doing their essential work should surely be entitled to extraordinary measures to save their lives if they become ill. Also, health systems are overstretched. Saving the lives of nurses with drug-resistant TB will help reduce the loss of skills as well as the loss of confidence of other health workers.
- There is a precedent for expanded access. In the late 1980s and throughout most of the 1990s, community pressure led to expanded access programmes (EAPs) to new antiretrovirals for HIV-positive people who required urgent access to treatment. Over 100,000 people in the US are estimated to have benefited from EAPs. More than 35,000 people (22,000 in the US) accessed ddI from 1989 to 1991 prior to registration. People with drug-resistant TB today have just an urgent need. [9]

The cautions for EAPs are well known:

- The limited data both for efficacy and safety. Although EAPs are usually only launched when approval is guaranteed, there are exceptions (for example the adefovir EAP enrolled 9,000 people for whom toxicity overweight efficacy and adefovir was never approved as an antiretroviral.
- Maintaining consistent drug supplies is another legitimate concern. With TB medication, non-adherence has a greater potential public health impact than with HIV.
- Resistance if the new compound is not sufficiently supported by other active drugs. Adding a single drug to failing regimens essentially puts patients on functional monotherapy.
- Unknown interactions between the new compound and other TB of HIV drugs.
- A potential impact on ongoing registrational trials (for people who may be maintained on a placebo when the EAP would provide definite access. For ARV EAPs the research concerns we met by careful definition of entry criteria and trial design.

None of these concerns are greater than the need for expanded access in this example. Given the high fatality rate with TB, we will know with greater confidence by the end of 2010 whether the risks associated with TMC207 outweigh the benefits. Adherence is as big an issue post-registration as it is pre-registration. The risk of monotherapy can be reduced in time once the pipeline becomes more robust and people with XDR TB can be given regimens with multiple experimental drugs (eg both TMC207 and OPC-67683).

Even people with XDR TB are not necessarily resistant to every drug in their regimen and so will not necessarily be placed on monotherapy with the addition of a new drug. As for interactions, trials are underway for TMC207 in patients taking ARVs. Also, therapeutic drug monitoring could aid the administration of drugs in some expanded access sites. Placebo patients can be recruited from the healthier end of the MDR TB spectrum and should expect to be placed on the intervention drug immediately after the placebo period if the drug performs well.

EAPs can provide additional safety and operational data on the new drugs – while ensuring that they are not used as a cheaper replacement for randomised clinical data. Only sites with capacity to ensure a reliable drug supply, adequate resistance testing and high probability of patient adherence should be able to participate. Sites run by organisations like Médecins Sans Frontières and Partners in Health should qualify.

Drug trials are unfortunately not an adequate way to expand access, at least not in their current form. Including healthy subjects for phase I trials and placebo patients, a search on clinicaltrials.gov in August 2010 reveals that there are just over 900 places presently being recruited for OPC-67683 and TMC207. But there were already nearly 30,000 notified cases of MDR-TB in 2007. [10]

Instead, either the drug companies responsible for the drugs or a respectable international NGO, such as TB Alliance, needs to administer expanded access. This will involve negotiating with regulatory authorities in multiple countries. These regulatory authorities also need to be flexible and co-operate with expanded access programmes. This mechanism should be set up by January 2011 ideally with published site and patient qualification criteria and a procedure for applying for the drugs.

Expanded access is necessary but not ideal. There would be fewer people needing expanded access if drugs moved through the pipeline quicker. The new TB drugs are taking extraordinarily long to reach the point where regulatory authorities can approve them. TMC207 was discovered in 2003. It is not expected to receive regulatory approval anywhere before 2012. Compare this with HIV drugs such as AZT. It's anti-AIDS effect was discovered in 1984 and it was registered three years later. [11]

Also compare current development times with the development times of the original TB drugs. The very first TB drug, streptomycin, moved from discovery in 1943 to successful completion of controlled clinical trial in 1947, so that many patients, including George Orwell, were using the drug by 1948. [12, 13] As the above mortality rates show, patients in the 1940s with TB were probably no worse off than current patients with drug-resistant TB.

While increasingly complex regulatory requirements are part of the problem, the main cause of the long time taken to bring new TB drugs to market is political will. Patients with MDR-TB today are for the most part poor and politically marginalised in contrast

to TB patients of the 1940s in Europe and people with HIV in the 1980s in the United States. Pharmaceutical companies, including Tibotec and Otsuka, public entities such as the NIH and the governments of high drug-resistant TB burden countries like South Africa, China, India and Russia need to put up more R&D money for TB drugs and diagnostics. We cannot simply depend on the Gates Foundation, which is by far the biggest contributor to the approximately $500m spent on TB R&D in 2008. [14]

Just as we have a Global Fund to Fight AIDS, TB and Malaria, perhaps we need an international fund to drive TB drugs and diagnostics research.

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Indian activists challenge proposed EU trade agreements: Global access to Indian generic ARVs threatened

Delhi Network of Positive People

In the coming weeks India and European Commission are negotiating on the provisions of a free trade agreement between India and the EU. Chief negotiators met on 23 September, but key negotiations on Intellectual Property (IP) will be held in New Delhi in the first week of October.

The European Commission is putting pressure on India to adopt new IP provisions that are even more restricted than TRIPS, plus provisions such as data exclusivity, patent term extensions and IP-enforcement provisions (injunctions, third party liability, criminal remedies, damages, border measures).

These provisions, if accepted by India, will further undermine generic production and supply of essential medicines to developing countries.

We request organisations and individuals across the world to join Delhi Network of Positive People in a sign on letter to issue an appeal to the Indian government to agree to any IP provisions in the FTA negotiations.

DO NOT TRADE AWAY OUR LIVES!

If you want to join the sign on letter, send your name, organisation and country to:

Vikas Ahuja, DNP+:

vikas2contact@gmail.com.

LETTER TO INDIAN PRIME MINISTER Dr. Manmohan Singh

Hon'ble Prime Minister of IndiaThe Prime Minister's Office

South Block, Raisina Hill

New Delhi, India-110 011

Telephone: 91-11-23012312.Fax: 91-11-23019545 / 91-11-23016857New Delhi, October 1, 2010

Re: India's central role in medicines supply is under threat

Don't sign on to intellectual property provisions in the India-EU FTA

Dear Prime Minister,

We are writing on behalf of patient groups, of people living with HIV (PLHIV) networks, HIV & public health organisations, medical organisations, public interest NGOs and concerned individuals to express our concerns before the next round of negotiations between India and the European Union (EU) in the name of a bilateral free trade and investment agreement (FTA) to be signed before the end of 2010.

India plays a key role in producing, registering and supplying essential medicines, not only for Indian patients, but to all developing countries. A study published recently in the International AIDS Society journal "A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries" highlights the central role that India's generic production plays in AIDS treatment. It concludes that Indian generic manufacturers have supplied more than 80% of donor-funded AIDS medicines to developing countries in the last seven years.

We are alarmed that the Indian government may accept intellectual property (IP) provisions that will undermine the production, registration and worldwide availability of essential generic medicines. This is not the first time. India through a series of legal amendments in the last decade has already enforced the requirements for intellectual property protection under international law.

The TRIPS agreement, which bound India to introduce a product patent regime in 2005, has already begun to curtail the country's ability to produce low-cost generic versions of newer HIV, hepatitis and cancer medicines. Because India signed the TRIPS Agreement, some new essential medicines have already been patented in India and cannot be domestically produced, leaving patients in India and across the developing world without access to affordable versions of these medicines.

Trade agreements being currently discussed–particularly the one with the European Commission–will further restrict this access. If India signs up to the IP clauses therein which go significantly beyond TRIPS standards, it will further reduce the country's vital role as provider of essential medicines. As you know, the EU is trying hard in every forum to increase IP standards that will benefit European pharmaceutical companies but will have a grave impact on generic production and supply of medicines and ultimately access to medicines for patients in the developing world.

Issues of Concern in EU-India Free Trade Agreement that could affect access to medicines

The EC is using these bilateral trade and investment agreement negotiations with India to pursue IP provisions that goes significantly beyond the TRIPS standards ("TRIPS-plus").

Patent term extension known as Supplementary Protection Certificates in the negotiations would extend a pharmaceutical company's monopoly by increasing the life patent on a medicine beyond 20 years. These extra years enable the patent holder to maintain a monopoly position and continue to charge artificially high prices for the drug, free from generic competition.

Exclusive rights over pharmaceutical test data (so called "data exclusivity") figures prominently in the negotiations. The current text of the IP chapter on pharmaceutical test data as proposed by the EU to India essentially requires that India amend its drug regulatory legislation in a manner that will not permit the placing of a generic pharmaceutical product on the market if the originator has submitted any clinical trial data relating to the medicine to the Indian DRA (Drug Controller General of India).

If India accepts this clause, the Drug Controller General of India (DCGI) will be legally prohibited from registering a generic medicine as long as the exclusivity lasts over the trial data (usually several years). Generic producers will have to submit their own safety and efficacy data to register the generic. This will oblige generic companies to repeat clinical and pre-clinical trials.

The repetition of trials raises grave ethical issues, as it would require withholding safe and effective medicines from some patients (the control group), solely for the purpose of proving something that is already known. This will not pass the scrutiny of ethical committees, making it impossible for generic companies to repeat the clinical trials. In addition, repetition of clinical trials will take time and involve costs that the generic producers usually cannot afford.

Intellectual property enforcement provisions include a number of different measures (border measures, criminal sanctions for IPR infringement etc.) and attempt to govern the way the disputes around patents and civil trademark infringements will be managed by Indian courts. If India signs up to these clauses, the Indian judiciary will have its hands tied and will no longer be able to balance IP rights with the right to health of patients.

The investment chapter extends the definition of investment to include intellectual property. If accepted by India, multinational drug companies would then have the standing to sue the Indian government potentially in a bid to block sovereign actions like compulsory licensing, price control and regulation. It is critical to remove IP from the definition of investment so that both the use

of compulsory licensing, price regulation, as well as refusal to provide exclusive rights over test data (data exclusivity) cannot be linked to either the definition of investment or factored in the consequences of expropriation.

Accepting the IP provisions will benefit European pharmaceutical companies - but they will have a grave impact on generic production of medicines and ultimately access to medicines for patients in the developing world.

The Indian government will be trading away our lives by agreeing to the EU's demands on intellectual property and enforcement in FTA negotiations.

We request India to not TRADE AWAY OUR LIVES and right to health in the name of another trade agreement to be signed before the end of 2010.

As the Prime Minister of India, we urge you to refuse the IP provisions outlined above.

We request you to ensure that generic competition remains possible in India. So many lives depend on it worldwide.

Signed by:

Delhi Network of Positive People (DNP+), India
LOCOST (Low Cost Standard Therapeutics), India
Medico Friends Circle (MFC), India
Drug Action Forum – Karnataka, India
India All India Drug Action Network (AIDAN), India
Nikhil Gurung, AAVASH SAMUHA, Nepal
Bijay Pandey, Youth Vision, Nepal
Syaiful Brasila, PKNK (South Kalimantan of PUD), Indonesia
Paul Cawthorne, MSF Access Campaign, Thailand

Russian HIV activists arrested in Red Square for protesting drug stock-outs

On 15 September 2010, a demonstration in Moscow called for the end of interruptions of treatment for people living with HIV. Treatment interruptions started in April this year and have affected at least one quarter of Russia's regions.

The activists came to Red Square to protest against a bureaucracy that will not guarantee uninterrupted supply of medicines for people living with HIV. As part of the protest, three women in white coats were walking a leashed man in a bear suit. They explained that this symbolised the official chaos and negligence. The leash on the bear represents the need to curb lawlessness. The protesters attracted the attention of Muscovites and tourists.

Many activists came from regions affected by the treatment stockouts. Soon after the demonstration started, the Federal Security Service arrived and detained the protestors.

The community press release stated "We, people living with HIV, are tired of inhumane treatment by bureaucrats. They cannot or do not want to ensure timely supply of essential medicines that determine whether we live or die. We cannot afford to be hostages of laziness, incompetence and negligence - it is our right to live! Today we face a choice between dying quietly at home and drawing the attention of media and government. Silence for us means death!".

All the detainees have been released unharmed and will reportedly face administrative fines.

According to the Russia's Federal AIDS Center, more than half a million people are diagnosed with HIV. Less than 50% of the 120,000 people who need treatment currently receive it.

For the last four years, they face interruptions of essential antiretroviral therapy for HIV infection. Those interruptions have irreversible consequences to our health and threaten our lives. Three lawsuits have been brought to court in Kazan, Moscow and Tula.

A website has been launched specifically to record absence of medicines in 2010, and includes reports stockouts of antiretroviral medicines in Ulyanovsk, Samara, Arkhangelsk, the Moscow Oblast, Vladimir, Kaliningrad, Saratov and other regions. Interruptions in prisons are recorded almost in all regions of Russia.

http://www.pereboi.ru/stockouts/

C O M M E N T

The demonstration in Moscow achieved good media coverage including several central information agencies, like Russian Informational Agency NEWS (RIAN).

The evening press department of the Ministry of Health replied to the media with the press-release where it was stated in particular that there are currently no treatment interruptions in Russia.

This automatically means that activists in Russia will continue their fight for the rights to treatment.

This action was not held by one or two organisations, but by activists and NGOs from across Russia. People came to Moscow from all over the country to join the protest. In my opinion is very positive aspect of the action. Activists were united over the message and demands, highlighting that such widespread support and involvement demonstrates stock-outs are routinely reported in all those regions.

Chinese HIV positive activist Tian Xi to go on trial on trumped up charges

Press Release, Treatment Action Campaign

On September 21st 2010 Chinese activist Tian Xi will go on trial in Henan Province charged with "suspicion of intentional destruction to property." Tian Xi is 23 years old. He is HIV positive and was infected with HIV as a child as a result of a blood transfusion at the time when thousands of people in Henan and other provinces were infected with HIV through state-sponsored blood selling programmes in the 1990s. In an unprecedented action, activists from across China will attend Tian Xi's trial to express solidarity with him.

For the last five years Tian Xi has been campaigning for compensation for himself and others, as well as for the Chinese government to admit its culpability in the blood scandal and hold those directly responsible to account. Tian Xi's crusade has drawn the ire of the Chinese authorities and he has been frequently harassed and detained. However, he has never been charged before and we fear that his trial will be used to put him out of sight for a number of years as has happened with other outspoken human rights activists such as Hu Jia, currently still in prison after nearly three years.

The charge of "suspicion of intentional destruction to property" arises because Tian Xi appears to have been lured back to Henan with an official offer of trying to resolve his complaints. However when he got there he was refused meetings and in a fit of anger broke several minor objects in a hospital office where he had gone to meet the hospital director and collect his ARV medicine.

Tian Xi and other activists' frustration arises from the fact that Henan provincial courts refuse to accept any lawsuits relating to HIV, leaving victims of the disaster with no recourse except petitioning. In Chinese tradition, in a case of no other recourse, citizens may bring complaints against local officials to higher-ranking government offices. However, only a tiny percentage of these petitions ever receive a favorable response, and many petitioners, including Tian Xi, have been detained and tortured in what are known as "black jails".

Although the Chinese authorities say that he is being charged on ordinary criminal grounds - "suspicion of intentional destruction of property" – it is obvious from the circumstances surrounding this case, Tian Xi's communications with various organisations, and the documents he obtained from township officials ordering his detention, that he was arrested because of his ongoing and persistent HIV petitioning, not because of the hospital incident.

The Treatment Action Campaign calls on UNAIDS and civil society organisations worldwide to monitor the trial of Tian Xi and to issue statements calling for his immediate release. We call for UNAIDS executive director, Michel Sidibe, to urgently intervene to secure Tian Xi's release.

We call on civil society organisations to write letters of protest to the Chinese Ambassador, Zhong Jianhua at:

PLEASE SEND APPEALS BEFORE 13 OCTOBER 2010 TO:

Head of Xincai County Government

Wang Jingfeng Xianzhang, Xincaixian Renmin Zhengfu

1 Zhengfujie, Xincaixian, 463500, Henansheng

Director of the Xincai County Department of Public Security

Bian Fenglu Juzhang

Xincaixian Gong'anju, Shenglijie, Guluzhen

463500 Henansheng, People's Republic of China.

And copies to:

Premier WEN Jiabao Guojia Zongli

The State Council General Office, 2 Fuyoujie, Xichengqu, Beijingshi 100017, People's Republic of China.

Further information:

http://www.amnesty.org/en/library/asset/ASA17/036/2010/en/1beb620d-11d0-466d-b213-6719fc276659/asa170362010en.html

US waiting lists increase by over 300% in five months

In a new perspective on treatment access, in April 2010 we reported that almost 900 people were on waiting lists in the US for access to treatment on the ADAP public assistance programme.

Within five months this figure has more than tripled, and in September it reached 3,214 people in 9 states.

Cost-containment strategies instituted over the last years included reducing formularies, lowering the level of financial eligibility, using a CD4 threshold of <350 cells/mm3, initiating waiting lists, capping enrollment and capping use of T-20.

For an update on the states with waiting lists and other cost containment measures go to the ADAP Watch update at:

http://www.nastad.org

WOMEN'S HEALTH

Genital tract viral load in women with below detectable plasma viral load

Polly Clayden, HIV i-Base

Plasma viral load levels are frequently used as surrogate markers for genital tract viral loads when quantifying transmission risk - both sexual and mother to child - in HIV-positive women.

A paper, authored by Susan Cu-Uvin and published ahead of print in AIDS showed findings from an investigation to determine patterns of genital tract shedding in women receiving HAART with viral loads below detection in plasma.

The study enrolled women who had undetectable plasma viral load (≤ 80 copies/mL) for 6 months and were receiving care at the Miriam Hospital Immunology Centre, Providence, Rhode Island, USA.

The investigators measured paired plasma and genital tract viral loads every four weeks. Women were classified as persistent (at least two consecutive monthly visits with detectable genital tract viral load), intermittent (detectable genital viral load on visits preceded and followed with undetectable) or non-shedders (undetectable genital viral load). They used longitudinal analysis to investigate rates of genital tract shedding and the association with plasma viral load, CD4 count and genital tract infections. Markov transition models were used to describe the temporal dynamics of viral load in the plasma and genital tract.

Out of 62 women who completed screening, 59 women contributed 582 study visits. Of these 95% and 98% had undetectable plasma and genital tract viral load respectively. Their median baseline CD4 was 458 cells/mm3 (range 120-1346). About half (49%) were receiving NNRTI-based regimens and the majority of the remainder (42%) protease inhibitor-based HAART.

Thirty-two of the 59 women (54%) had at least one detectable genital tract viral load measurement during the study period and 22/59 (37%) had detectable genital viral load when plasma viral load was undetectable. Four women (6.8%) were classified as persistent shedders, 18 (31%) as intermittent shedders and 27 (46%) as nonshedders.

When the investigators sampled three subcompartments, genital viral load detection increased compared to a single compartment. It was more likely (72% of visits) for just one subcompartment to have HIV shedding than more than one subcompartment, p=0.05. They found the maximum viral load measurement in the genital tract when viral load was undetectable was 456,000 copies/mL in the endocervix, 648,000 copies/mL in the ectocervix and 480,000 copies/mL in the vagina.

Overall the estimated probabilities of genital tract shedding were between 6 and 8% of visits in each of the three subcompartments. Genital shedding in at least one subcompartment was estimated to occur at 13% of visits (95% CI 9-18%). This occurred in 9% (95% CI 6-14%) of visits when plasma viral load was undetectable. Genital tract viral load was significantly more likely to be detectable when plasma viral load was detectable at the previous visit OR 2.15 (95% CI 1.1-4.3) but plasma viral load was not significantly more likely to be detectable when genital tract viral load was detectable at the previous visit OR 0.91 (95% CI 0.27-3.1).

The investigators wrote: "The findings of the present study add to the growing evidence that in the HAART era, women with below detection plasma viral load may have less risk of HIV sexual transmission on a population level, but may continue to be possibly infectious on an individual level."

Ref: Susan Cu-Uvin et al. Genital tract HIV-1 RNA shedding among women with below detectable plasma viral load. AIDS 2010, Vol 24. Published ahead of print 25 August 2010.

HPV-based screen-and-treat is effective for cervical cancer prevention in HIV-positive women

Polly Clayden, HIV i-Base

Louise Khun and colleagues report results from a trial of a simple cervical cancer prevention strategy using non-cytological screening methods - ie HPV DNA testing or visual inspection with acetic acid (VIA) - with immediate treatment where indicated for HIV-positive South African women, in a paper published ahead of print in AIDS.

The study authors note that it has been hard to establish conventional cytology based screening programmes in resource-limited settings. Yet, it is well known that HIV-positive women have high rates of human papillomavirus (HPV) and are at increased risk for developing cervical cancer. Furthermore as HIV-positive women are living longer on HAART, it is likely that more of these women will develop cervical cancer unless effective prevention strategies are put in place.

This was a randomised controlled trial of two screen-and-treat strategies of over 7000 non-pregnant women age 35-65 recruited from three clinics in Khayelitsha between January 2000 and December 2002.

Women were randomised into one of three study arms:

- HPV and treat - women with positive HPV test had cryotherapy
- VIA and treat – women with positive VIA test had cryotherapy
- Control group – evaluation or treatment was delayed for 6 months

All women were followed at 6 months after randomisation with colposcopy and biopsy.

The trail collected data on HIV status at baseline, 6, 12, 24 and 36 months. The investigators reported 956 women had an HIV-positive test at one of these visits.

This report showed findings from a comparison of the effects of screen and treat among women ever testing positive compared to women who remained negative throughout follow up.

The investigators conducted intent to treat analyses stratified by HIV status. The primary endpoint was cervical intraepithelial neoplasia grade 2 (CIN2+) or higher.

They found, out of the HIV-positive women, 148 in the HPV-and-treat group and 104 in the VIA-and-treat group had a positive test result and underwent cryotherapy. Among the HIV-negative women, 319 and 377 in the HPV and VIA groups respectively had a positive test. There were no significant differences between HIV-positive and HIV-negative women in rates of complications and side effects in those who had cryotherapy.

Using HPV DNA testing for screen-and-treat was highly effective in reducing the risk of CIN2+ by 36 months, both for HIV-positive, RR 0.20 (95% CI 0.06-0.69) and HIV-negative women, RR 0.31 (95% CI 0.20-0.50). The investigators observed less benefit for VIA-and-treat. This strategy reached statistical significance in HIV-positive women RR 0.51 (95% CI 0.29-0.89) but did not do so in HIV-negative women RR 0.76 (95% CI 0.52-1.1).

The investigators estimated, for every 100 women screened, HPV-and-treat programme could prevent 11.9 CIN2+ cases in HIV-positive women and 3.1 in HIV-negative women. VIA-and-treat programme could prevent 7.4 cases in HIV-positive women and 1.1 in HIV negative women.

Among the controls, higher rates of CIN2+ were detected by 36 months in HIV-positive than HIV-negative women, 14.9% vs 4.6%, p=0.0006.

The rates were reduced significantly in the HPV-and-treat group, 3.1% in HIV-positive women and 1.4% in HIV-negative women, p<0.0001. These reductions were less in the VIA-and-treat group, to 7.6% in HIV-positive women, p=0.002 and 3.5% in HIV-negative women, p=0.08.

The sensitivity in the control group of HPV DNA testing at enrollment to detect CIN2+ through 36 months, was 87% in HIV-negative women and 94.4% in HIV-positive women, compared to 47.8% and 63.9% respectively in the VIA group. The positive predictive value (PPV) for HPV testing was only slightly higher among HIV-positive women than HIV-negative women, 29.9% vs 22.7% HPV-positive at baseline had CIN2+ by 36 months. For VIA this was nearly three times higher in the HIV-positive than HIV-negative women. The investigators explained that this was due to 62.2% of HIV-positive women with positive VIA test also having had HPV DNA detected vs. 26.6% of HIV-negative women.

When they compared cryotherapy failure rates between HIV-positive and HIV-negative women, in the HPV-and-treat group, there was a slightly lower rate of CIN2+ after cryotherapy in HIV-positive (2.8%) vs HIV-negative (7.1%) women, p=0.05. In the VIA-and-treat group failure rates were similar in HIV-positive (4.8%) and negative (2.8%) women, p=0.43.

The investigators wrote: “Our data provide proof-of-principle that HPV-based screen-and-treat is safe and effective in HIV-positive women. A single round of screening with an HPV test followed by cryotherapy of all screen-positive women reduced high-grade cervical cancer precursors (CIN2+) by 80%, and this reduction was sustained through 36 months.”

Ref: Kuhn L et al. Efficacy of human papillomavirus-based screen and treat for cervical cancer prevention among HIV-infected women. AIDS 2010, published ahead of print 11 August 2010.

PREGNANCY AND MTCT

Test and treat for all pregnant women in low and middle income countries?

Polly Clayden, HIV i-Base

An opinion piece, published ahead of print in JAIDS by Maria Zolfo and colleagues, argues for a universal "test and treat" strategy in all HIV-positive women in high burden countries.

They cite the WHO/UNAIDS/Unicef statistics showing that in low and middle income countries, only 21% of pregnant women tested for HIV while they were pregnant, only 24% HIV-positive pregnant women had a CD4 test to determine their eligibility for ART, only 45% received antiretrovirals and only 32% of infants of positive mothers received post natal prophylaxis.

They compare this to the extremely low rates of MTCT in industrialised countries.

They note that provider initiated testing strategies have reached 60-80% amongst pregnant women in 6 out of 10 counties with the highest burden of HIV among pregnant women suggesting that the majority will access services if they are available.

They suggest that the WHO recommended option, of a two tiered antiretroviral strategy in pregnancy of treatment for women indicated for their own health (at clinical stages 3 and 4 and $\leq$ 350 cells/mm3), and antiretroviral prophylaxis (either short course AZT plus single dose nevirapine or a triple combination regimen stopped after breast feeding) for mothers not indicated for treatment, may not be feasible in settings with limited infrastructure. Not least when there is limited access to CD4 tests.

In some high burden countries, they write, "a low tech test-and-treat intervention for all HIV-positive women not yet on ART – regardless of the CD4 count and clinical stage – will be a more feasible option to reach large numbers of women." They suggest that this should be life-long and not discontinued after breastfeeding.

Based on current evidence this strategy would mean about 50% of women would be eligible for treatment for their own health and 25% would start with CD4 between 350 and 500 cells/mm3. More controversial would be the group that starts treatment with CD4 counts above 500 cells/mm3.

In their arguments they note that the SMART study showed the disadvantages of stopping and starting treatment in non-pregnant adults, even at higher CD4 counts. Additionally lack of availability of CD4 tests may increase the risk of undetected disease progression in women stopping treatment. There is also the likelihood of a subsequent pregnancy.

There are concerns, however, about the sustainability of long term adherence and this may be particularly difficult for healthy women who do not require treatment for their own health.

The IMPAACT PROMISE study is being conducted to look at these questions and others, but results will not be available until 2014 at the earliest.

In the meantime the authors advocate for a universal "test and treat" strategy to be rapidly implemented in HIV-positive women in high burden countries.

C O M M E N T

One of the authors of this article, Erik Schouten, from the Department of HIV and AIDS, Ministry of Health, Malawi gave a presentation in a satellite session at IAS 2010, explaining changes to their national programme for pregnant women. They have decided that the best option for Malawi is exactly as described above, to start all pregnant women on one universal regimen for treatment and prevention continuing for life.

In Malawi, they take a public health approach to treatment. Universal access to reliable CD4 count will not be reached within a few years. Additionally their fertility rate is high – 5.6, and breastfeeding is recommended.

Although they acknowledge the challenges, they believe the advantages to this strategy outweigh the disadvantages and this is, "The only realistic option for Malawi."

Ref: Zolfo M et al. Time for "test and treat" in prevention of mother-to-child transmission programmes in low- and middle-income countries. J Acquir Immune Defic Syndr. Published ahead of print 2010.

Retrospective analysis finds higher prevalence of birth defects associated with efavirenz than previously reported

Polly Clayden, HIV i-Base

A study of children enrolled in PACTG protocols 219 and 219C – a multisite US cohort of children born to HIV-positive women set up to study the long term effects of in utero antiretroviral exposure – reports a higher prevalence of birth defects than found in other paediatric cohorts.

Preliminary data from this paper published in August 2010 edition of The Pediatric Infectious Disease Journal authored by Susan B Brogly and colleagues was previously shown as a poster at CROI this year, which we reported in the April 2010 edition of HTB. [1, 2 , 3]

Protocol 219 followed HIV-infected and uninfected children from May 1993 to August 2000. Children were eligible if their mothers were enrolled in a PACTG trial in pregnancy. In September 2000, protocol 219C was introduced, amending 219 to remove the eligibility criterion mandating enrolment in another PACTG trial. This study evaluated children enrolled in 219 and 219C before one year of age.

Birth defect data were recorded at study visits. Protocol 219 did not include a direct question about birth defects; 219C included this question.

The primary determinant was first trimester exposure. The investigators looked at overall antiretroviral exposure, classes of antiretrovirals and specific antiretrovirals to which at least one child with a birth defect had first trimester exposure.

The reference group was children unexposed to the particular antiretroviral (or class of drug) during the first trimester, which included antiretroviral unexposed children, those only exposed in labour, those unexposed to the particular drug but exposed to other antiretrovirals and children only exposed beyond the first trimester.

Clinicians were blinded to antiretroviral exposure and the outcome was presence of a birth defect within the first year of life.

The investigators used logistic regression models to estimate the association between first trimester in utero antiretroviral exposure and the most common categories of birth defects.

They found, a total of 117 children with a least one defect out of the study population of 2202 children. This gave an overall defect prevalence of 5.3% (95% CI, 4.4-6.3) and 4.7% (95% CI, 3.8-5.6) if just the 103 cases of major defects were included.

Prevalence was 4.8% (95% CI, 3.8- 5.6) in children unexposed in the first trimester and 5.8% (95% CI, 4.2-7.8) in exposed children.

They found that the majority of defects occurred in the heart and musculoskeletal system. They observed a higher prevalence in children whose mothers had participated in a PACTG study during pregnancy and an increase as with increased maternal age. Rates were also higher in children enrolled in protocol 219 (whether or not enrolled in 219C) than in 219C alone.

They reported a higher defect rate (5/32, 15.6%) among children exposed to efavirenz in the first trimester compared to unexposed children, AOR 4.31 (95%CI, 1.56-11.86). The defects included laryngomalacia (n=1), meningomyelocele with Arnold-Chiari Malformation Type II (n=1), hypospadias (n=1), club foot (n=1), hypertonicity of extremities (n=1) and cleft palate (n=1).

They also found an association in children exposed to lopinavir/ritonavir but when they adjusted for first trimester folate antagonist exposure, year of birth and perinatal study participation this did not persist (p=0.07) whereas the association with efavirenz did.

There was a protective effect of AZT first trimester exposure on musculosketal defects AOR 0.24 (95% CI, 0.08-0.69), but an association with heart defects AOR 2.04 (95% CI 1.03-4.05).

C O M M E N T

It is difficult to know whether this study advances or confuses the field. Although based on 2202 children, only a third (763) were exposed to any antiretroviral during the first trimester compared with almost 5000 enrolled in the Antiretroviral Pregnancy Registry (APR) to date. Consequently, with the exceptions of AZT, 3TC and nelfinavir, few subjects had been exposed to individual compounds, which accounts for the wide range of odds ratios (0.39 for ddI to 3.52 for efavirenz). A similar phenomenon has been observed over the years in the APR with new compounds that is followed by a gradual movement towards the mean as the denominator increases.

The findings also generally differ from the APR, in which only ddI (4.5%, 95% CI 2.6–7.1%) has attracted attention due to a small but persistent increase in risk of birth defects, while PIs in general, and lopinavir/ritonavir (1.7%, 95%CI 0.8–3.1%) in particular, have generally been found to be associated with no increase in risk.

As might be anticipated, folate antagonist exposure during the first trimester was associated with an increased prevalence of birth defects although data were largely incomplete and the observation did not reach statistical significance. The observed confounding of this risk with lopinavir/ritonavir exposure is a timely reminder not to forget the obvious.

It is difficult to know what to make of the apparent protective effect of AZT exposure in regard to musculoskeletal abnormalities and

increased risk of cardiac defects. The authors rightly conclude that further study is needed to rule out confounding and to examine for associations between antiretroviral exposure and specific birth defects. Prospective reporting to the APR remains the best option and a significant improvement in UK reporting to this international drug safety registry (currently standing at 3.3% of all reports) is long overdue.

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PAEDIATRIC CARE

Daily cotrimoxazole preferable to intermittent preventative therapy in HIV-infected children

Polly Clayden, HIV i-Base

WHO recommends daily cotrimoxazole preventative therapy (CPT) for infants and children. US guidelines recommend either daily or three days a week. Adult studies suggest that thrice-weekly CPT is as effective as daily but with a decrease in side effects and an increase in tolerability. The optimum frequency for CPT in children has not been determined.

A paper, published in AIDS, by Heather Zar and colleagues, reported results from a South African study of children randomised to receive either daily or thrice-weekly CPT.

The study looked at mortality, bacterial infections, hospitalisation and adverse events.

A total of 339 children, attending, either Red Cross War Memorial Children's Hospital, University of Cape Town or Tygerberg Hospital at Stellenbosch University, aged eight months and above were enrolled. Of these, 10 tested negative and five were lost to follow up within a month from randomisation.

The study, which commenced in December 2002, originally had a factorial design and compared both three times weekly CPT vs daily CPT, and isoniazid (INH) vs. placebo. The placebo arm was stopped in May 2004, on the advice of the DSMB, and all children were switched to INH. INH was then discontinued in December 2007 as most children were receiving HAART. The investigators continued to study three times weekly CPT vs daily CPT. Results are from this investigation from January 2003 through December 2007.

Of the 324 children, 165 (50.9%) were randomised to receive intermittent therapy and 159 to daily therapy. They were a median age of 23 months (IQR 9.5-48.6 months). Almost one third (30.3%) were less than 12 months of age. The majority (88.6%) were symptomatic and the median CD4 percentage was 20%. At enrolment 8.6% of children were receiving HAART, and 63.9% received it during the study. Malnutrition was common. Baseline characteristics were similar in both groups.

Overall 9% of children were lost to of which 57% were in the group receiving daily CPT. An additional 24% withdrew from the study, 13% from the daily group, mostly due to logistics. Median follow up was 1.97 years (IQR 1.3-3.3 years) vs 1.92 years (IQR 0.5-3.29 years), p=0.37, in the intermittent and daily groups respectively. The investigators reported excellent adherence in both groups.

They found similar mortality rates in both groups: 24/165 (14.5%) vs 29/159 (18.2%) deaths in the intermittent and daily groups respectively, HR 0.75 (95% CI, 0.44-1.29), p=0.3. The difference in the cumulative survival proportions estimated at one year was 0.04 (90% CI -0.03- 0.10). Therefore thrice weekly was defined as non inferior to daily CPT as the CI for difference included zero and exceeded the predefined delta of -0.1 at one year of follow up. The choice of inferiority margin was based on expert opinion.

Infants had a six-fold higher incidence of death compared to children greater than one year of age (20 vs 3.6 per 100 child years), IRR 5.91 (95% CI 3.3-11.2) p<0.0001.

Causes of death were similar in both groups. Overall this was, 32% sepsis, 25% pneumonia and 15% diarrhoea.

However intermittent CPT was associated with a two increased incidence of bacteraemia, IR 9.6 vs 4.07 per 100 child years, IRR 2.36 (95% CI 1.21-4.87), p=0.006.

Additionally children receiving intermittent IPT spent significantly more days in hospital than those receiving daily, 228.5 vs 198.5 days per 100 child years, IRR 1.15 (95% CI 1.04-1.28), p=0.004. The admission rate was similar between the two groups.

Toxicity was similar in both groups, with an overall incidence of 6.8 grade 3 or 4 events per 100 child years (46 events; 25 intermittent, 21 daily).

The investigators concluded that their results support the current WHO recommendations of daily CPT for infants and children. They acknowledge that their results may not apply to settings with different burdens of bacterial disease. They wrote: "Widespread implementation of CPT is needed in areas of sub-Saharan Africa where this intervention is not available."

Ref: Zar HJ et al. A randomised controlled trial of intermittent compared to daily cotrimoxazole therapy in HIV-infected children. AIDS 2010, volume 24: 2225-2232.

SIDE EFFECTS

Development of chronic kidney disease and antiretroviral use in EuroSIDA cohort since 2004

Simon Collins, HIV i-Base

An analysis on the risk factors associated with progression to chronic kidney disease (CKD) observed in the European observational EuroSIDA cohort was reported by Mocroft and colleagues in the 17 July edition of the journal AIDS.

This analysis included data from almost 7000 (out of almost 12,000) HIV-positive patients followed from 2004 when serum creatinine measurements were routinely collected. Inclusion criteria included at least three serum creatinine measurements (median 9; IQR 6–12) plus height and weight to calculate estimated glomerular filtration rate (eGFR). CKD was defined as either confirmed eGFR of 60 mL/min per 1.73 m^2 or below (if baseline eGFR was >60) or confirmed 25% decline in eGFR (if baseline was <60). Cumulative drug and class exposure was included in the risk model together with all standard HIV and renal factors.

At baseline, eGFR was <60 in 4% (n=278) and >90 in 60% of the study participants. Median follow-up was 3.7 years (IQR 2.8–5.7). During 21,482 person-years follow-up, 225 people progressed to CKD, mostly (n=203) changing from >60 to <60 (n=150 >70). This gave an annual incidence of 1.05 per 100 PYFU (95%CI: 0.91–1.18). Only 27 patients with baseline >90 progressed to <60.

In multivariate analysis (adjusting for traditional CKD risk factors (age, hypertension, cardiovascular disease, HCV, diabetes, use of nephrotoxic drugs and other confounding variables), increasing cumulative exposure to tenofovir [IRR 1.16, 95% CI 1.06–1.25, p<0.0001), indinavir (IRR 1.12, 95% CI 1.06–1.18, p<0.0001), atazanavir (IRR 1.21, 95% CI 1.09–1.34, p=0.0003) were associated with a significantly increased rate of CKD. A lesser association was reported with lopinavir/r (IRR 1.08, 95% CI 1.01–1.16, p=0.030), however this was not confirmed in a second analysis and it was reported as a more tenuous association. No other antiretroviral dugs were associated with increased incidence of CKD.

There was a trend for continued exposure to increase risk with atazanavir and indinavir and an initial risk with tenofovir that was stable after 2 years. Excess risks reverted after discontinuing atazanavir and lopinavir/r but remained after discontinuing tenofovir for 12 months before normalising to that of someone without tenofovir exposure. These data were based on relatively small numbers and over short-term follow up.

A significant minority of people also reported renal improvement. 157/225 patients diagnosed with CKD who had >2 subsequent eGFR measurements, 56 later reverted back to an eGFR >60.

The study noted that the generally low prevalence and incidence of CKD within EuroSIDA was consistent other reports and that traditional risk factors (older age, hypertension and diabetes) were also independently associated with CKD in EuroSIDA. Patients with pre-existing excess risk of CKD were more likely to develop progression in they were using tenofovir. No additional risk was found when tenofovir was used with boosted-PIs.

Ref: Mocroft A et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients, AIDS: 17 July 2010 - Volume 24 - Issue 11 - p 1667–1678, doi: 10.1097/QAD.0b013e328339fe53,
http://journals.lww.com/aidsonline/pages/articleviewer.aspx?year=2010&issue=07170&article=00007&type=abstract

Tesamorelin for reduction of central fat accumulation: regulatory decision delayed in the US

Simon Collins, HIV i-Base

In May 2010, the FDA advisory panel reviewing the results of studies of a growth hormone releasing factor (GHRF) called tesamorelin (formerly TH9507, tradename Egrifta) made a universal recommendation 16:0 for approval. It is unusual for the FDA not to follow panel recommendations. However, the formal decision, expected in July was not forthcoming and a press release from Theratechnologies, the company developing tesamorelin, announced that the FDA will not make their decision before October 2010.

Tesamorelin has been shown to reduce central visceral adipose tissue (VAT) in people with HIV-associated lipohypertrophy. However, the effect is largely seen during the first six months treatment and subsequently reaches a lower plateau while maintained on treatment, with VAT returning if tesamorelin is discontinued.

The study design has been criticised for several reasons.

Firstly, the cross-over design means that data for many participancts is limited to 26 weeks. Secondly, all patients were had to discontinue GHRF at week 48 having to experience earlier benefits then reverse. Thirdly, no roll-over expanded access programme was provided by the company, even when the reversal was known due to the cross-over study design.

The limited trial data conclude that lifelong treatment is needed in order to maintain benefit. However, because all participants had treatment withdrawn, there has been no research into a maintenance dose. A roll over programme after 48 weeks would have been the ideal setting to study maintenance doses, essentail for minimising both risk of toxicity and future cost of treatment.

It is unclear whether these longer-term safety questions are related to the delayed FDA decision. Community demand for any effective treatment is clearly strong. The clinical trials showed a slightly increased risk of developing diabetes over the short time for the studies, so the longer-term risk needs to be followed closely in phase 4 studies, should approval eventually be decided. Further maintenance dose studies are also clearly warranted.

Tesamorelin has not been submitted to the EMA for regulatory approval. None of the European particiapant have been offered compassionate access to the compound.

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GUIDELINES

BHIVA monitoring guidelines online for comment

www.bhiva.org

Routine investigation and monitoring of adult HIV-1 infected individuals

The aim of this guideline is to present a consensus regarding the standard assessment and investigation at diagnosis of HIV infection and to describe the appropriate monitoring of HIV-positive individuals both on and off antiretroviral therapy.

This guideline does not address the investigation and management of specific conditions related to HIV and antiretroviral treatment, which are covered in other guidelines.

Within this guideline, assessment and monitoring of HIV-positive individuals has been categorized into the following areas:

- Initial diagnosis;
- ART-naïve individuals;
- ART initiation;
- Initial assessment following commencement of ART;
- Routine monitoring on ART.

The consultation period deadline to receive all feedback is Friday 15 October 2010**.**

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

US paediatric guidelines updated: August 2010

Polly Clayden, HIV i-Base

The US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in Pediatric Infection were updated on August 16 2010. Key revisions to the 23 February 2009 version are:

Diagnosis

Viral diagnostic testing at birth is recommended for high risk infants, for instance, those born to HIV-positive mothers who received no prenatal care and or prenatal antiretroviral therapy or who had viral loads >1000 copies/mL close to the time of delivery. The recommendation for testing HIV-exposed infants 14–21 days, 1–2 months, and 4–6 months remains.

They also recommend that an HIV qualitative RNA assay (APTIMA HIV-1 RNA Qualitative Assay) can be used as an alternative test.

When to start

The guidelines still recommend universal treatment for all infants age one year or less.

Guidance for asymptomatic or mildly symptomatic children with CD4 >25% (or >350 cells/mm3 if older than five years) and viral loads >100,000 copies/mL is strengthened. The current guidelines now "recommend" therapy in this situation compared to "consider" in the previous edition.

They also recommended that therapy can be "considered or deferred" for asymptomatic or mildly symptomatic children with CD4 >25% (or >350 cells/mm3 if older than five years) and viral loads <100,000 copies/mL; previously deferral was recommended in this situation.

They make specific recommendations in the following situations:

- Starting antiretroviral treatment is "recommended" for children age one year or less with AIDS or significant symptoms (Clinical Category C or most Clinical Category B conditions), regardless of CD4 percentage/count or viral load.
- Starting treatment is also "recommended" for children one year or above who have reached the age-related CD4 threshold for initiating treatment (CD4 <25% for children age one to five years of age and <350 cells/mm3 for children above five) regardless of symptoms or viral load.
- It is also "recommended" for children one year or above who are asymptomatic or with mild symptoms (Clinical Categories N and A or with Clinical Category B conditions: single episode of serious bacterial infection or lymphoid interstitial pneumonitis) **and** have CD4 ≥25% for children age one to five or ≥350 cells/mm3 for children age five or above **and** have viral load ≥100,000 copies/mL.
- Starting may be "considered or deferred" for children one year or above who are asymptomatic or have mild symptoms and who have CD4 ≥25% for children age one to five and ≥350 cell/mm3 for children five years old or above **and** have viral loads <100,000 copies/mL.

What to start with

The guidelines discuss recent data from clinical trials of nevirapine versus lopinavir/ritonavir-based regimens in children with single-dose nevirapine exposure for prevention of mother-to-child transmission. NNRTI-based therapy is not recommended for infants or children age <3 years with single-dose nevirapine exposure.

Darunavir/ritonavir is now recommended as an alternative protease inhibitor for initial therapy in children age >6 years.

Nelfinavir has changed from an alternative protease inhibitor for initial therapy to a protease inhibitor for use in special circumstances in children age >2 years.

Key updates usefully highlighted in yellow throughout the guidelines.

The new guidelines also include a ratings system for strength and quality of evidence and have amended some of the appendices.

Ref: Guidelines for the use of antiretroviral agents in pediatric HIV infection, August 16, 2010.
http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf

BASIC SCIENCE

Signs of progress in gene therapy for HIV

Richard Jefferys, TAG

Until recently, the idea of genetically modifying a person's immune system to make it resistant to HIV was generally viewed as extremely appealing, but so dauntingly impractical that it belonged in the realm of science fiction. Over the past year or so, an accumulation of new data has offered hope that it may eventually be possible to translate the idea into science fact.

Central to these developments is the widely reported case of an HIV-positive individual in Berlin who remains off antiretroviral therapy and free of detectable HIV after receiving a bone marrow transplant from an individual lacking the CCR5 co-receptor due to the delta32 genetic mutation. [1]

The bone marrow transplant was received (twice) during a difficult and complicated course of treatment for acute myelogenous leukemia, so the case is not seen as something that can easily be replicated in other people, but rather as a "proof-of-concept" that modifying the immune system can be a means to extinguishing HIV infection.

Complementing this remarkable case report, several studies have described improvements in techniques that may facilitate genetic modification of the immune system. A company called Sangamo Biosciences has developed a technology that allows inactivation of specific genes using enzymes called zinc finger nucleases (ZFNs); the approach is described in detail in the current issue of Nature Reviews Genetics and was also the subject of a New York Times article by Nicholas Wade at the end of last year. [2] An ongoing human trial is using Sangamo's ZFNs to delete the CCR5 gene in CD4 T cells sampled from HIV positive individuals; the CCR5-negative CD4 T cells are then expanded in number and re-infused into the donor (a very preliminary report from this trial was covered in TAGline earlier this year). [3]

In the current issue of Nature Biotechnology, a research team led by Nathalia Holt describes using the Sangamo technique to successfully modify hematopoietic stem/progenitor cells (HSPC) in mice. [4] The advantage of using HSPCs is that they are the "mother of all cells" and can potentially provide a permanent source of modified immune cells, circumventing the need for altering CD4 T cells in the lab and re-infusing them. Holt's team was able to show that, in mice, the CCR5-negative HSPCs generated immune cells of multiple types, all lacking CCR5. In "humanised" mice challenged with HIV, these CCR5-negative cells expanded

in number and reduced viral load compared to untreated mice with normal CCR5 expression. In an accompanying editorial, Steve Deeks and Mike McCune from UCSF highlight the potential importance of Holt's findings and outline the implications for future research in humans. [5]

The other recent study that is part of this evolving story was published back in June in the journal Science Translational Medicine. The research group of John Zaia at City of Hope in Duarte, California described results of an experiment in which HSPCs from four individuals with HIV and AIDS-related lymphoma were modified with three anti-HIV genes and re-infused. [6, 7] The modified HSPCs were given along with the infusions of unmodified HSPCs that are a standard part of the protocol for lymphoma treatment. Although it was a small exploratory study, the researchers were encouraged to find evidence that the modified HSPCs had given rise to cells of multiple lineages (e.g. T cells, B cells, macrophages) carrying the anti-HIV genes, albeit at very low numbers.

On 21 August the LA Times published an excellent story by Rachel Bernstein that ties these various gene therapy developments together. [8] It turns out that John Zaia's group at City of Hope will be the first to use Sangamo's CCR5-deletion approach to modify human HSPCs, likely also in people with AIDS-related lymphoma initially. The ultimate hope – "reaching for blue sky," as Deeks & McCune describe it – is that a single shot of souped-up HSPCs may one day be able to equip the immune system with enough HIV-resistant cells to vanquish the virus.

Source: TAG Basics Science web log (23 Aug 2010)

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FUTURE MEETINGS

2010–11 conference listing

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.

1st International Workshop on HIV & Aging

4–5 October 2010, Baltimore

http://www.virology-education.com

3rd BHIVA Conference on HIV and Hepatitis Co-infection

6 October 2010, London

http://www.bhiva.org

BHIVA Autumn Conference

7–8 October 2010, London

http://www.bhiva.org

12th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV

4–6 November 2010, London

http://www.intmedpress.com/lipodystrophy/

10h International Congress on Drug Therapy in HIV Infection

7–11 November 2010, Glasgow

http://www.hiv10.com

41st Union World Conference on Lung Health City

11–15 November 2010, Berlin

http://www.worldlunghealth.org/confBerlin/

18th Conference on Retroviruses and Opportunistic Infections (CROI)

27 February–3 March 2011, Boston

http://www.retroconference.org

15th International Workshop on HIV Observational Databases

24–26 March 2011, Prague

http://www.hivcohorts.com

6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2011)

17–20 July 2011, Rome

http://www.ias2011.org/

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The i-Base website has been completely redesigned with new portals for healthcare professionals, HIV-positive people and community advocates.

It is even 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 i-Base, the UK Community Advisory Board (UK-CAB), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as PDF files).

The site also includes a web-based Q&A section for people to ask questions about their own treatment:

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

RSS news feed has been introduced for HIV Treatment Bulletin for web and PDA access - we welcome your feedback on this new way to provide treatment updates.

A section on Education, Advocacy and Training includes our training manual for advocates with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

An average of 100,000 pages individual ISP accounts contact i-Base.info each month, with over 6000 hits a day.

Training manual – revised, updated and now fully online

This established training resource has been revised and updated and is now online in new format.

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

The Training Manual for Advocates provides entry-level curriculum relating to HIV and treatment.

It is made up of 8 modules for learning about aspects of HIV care has been updated and published online as an interactive resource. It provides entry-level curriculum relating to HIV and treatment.

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

http://www.i-base.info/manual/en/index.html

Sections include:

1. Immune system and CD4 count
2. Virology, HIV and viral load
3. Introduction to antiretrovirals (ARVs)
4. Side effects of ARVs
5. Opportunistic infections and coinfections
6. HIV and pregnancy
7. Drug users and HIV
8. Clinical trial design and the role of advocates

Each module includes learning objectives, non-technical review material, test questions, an evaluation and a glossary.

We hope this will be useful for training advocates and other related healthcare workers as well as for HIV-positive people who want to know more about aspects of their healthcare.

The training manual was previously only available online as a PDF document and has been widely translated. Earlier editions are available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

Generic clinic forms

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

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

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

Please contact the i-Base office if you would like help adding your own hospital or Trust logo to these forms.

Report assessing the treatment information needs African people in the UK living with HIV

This report by Winnie Sseruma and i-Base includes an analysis from workshops held last year and details African use and experience of current treatment information resources.

http://i-base.info/home/africans-and-treatment-infomation

i-Base Book: “Why we must provide HIV treatment information”

Photography by Wolfgang Tillmans

i-Base has worked as a treatment literacy project for over six years. Over this time we have always produced copyright-free material and encouraged other organisations to use, translate and adapt our material. Through this work, we have been very lucky to develop links to many other advocacy projects outside the UK.

A meeting, held in Cape Town earlier focused on how to raise the profile of treatment literacy. One result from the meeting is a publication “Why we must provide HIV treatment information”.

With text provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans, this limited edition 100-page publication is being sold by i-Base to raise funds to help support our international treatment literacy projects.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting since 2002. It now includes over 300 members from over 100 organisations. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted. Membership is free,

http://www.ukcab.net

World CAB - reports on international drug pricing

Two reports from meetings between community advocates and pharmaceutical companies, that focused on pricing issues and global access to treatment, and that are now available online.

Both are available to download as a PDF file from the i-Base website.

i-Base treatment guides

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

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

- Introduction to combination therapy (June 2009)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)
- Guide to changing treatment: what to do when your treatment fails (September 2008)
- Guide to HIV, pregnancy & women's health (January 2009)
- Guide to avoiding & managing side effects (May 2008)

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.

More information about this process is available on the i-Base website.

In addition, PDF files of some of the translated publications are available on the i-Base site.

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

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

Languages currently include:

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

Treatment 'Passports'

These popular booklets are for HIV-positive people - whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published 10 times a year in a printed version, in a pdf file that we can email to you, and on our website.

The printed version is available at most HIV clinics in the UK and is available free by post.

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.

ARV4IDUs

An electronic publication, produced in English and Russian language editions, to provide an overview of research related to IV-drug use and antiretroviral treatment.

Treatment information request service - 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

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

Online Q&A service

An online 'question and answer' service that now has over 900 questions online. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

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

Recent questions include:

- How can I lose weight without it affecting my CD4 count?
- Do ARVs act on other viruses apart from HIV such as herpes?
- Does Viagra react with tenofovir, 3TC and efavirenz?
- Does stress and lack of sleep effect your CD4 count?

Order i-Base publications via the internet, post or fax

People with internet access can use our website to order and receive publications. You can access our publications online or subscribe to receive them by email or by post; and you can order single copies or bulk deliveries by using the forms at:

http://i-base.info/order

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

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h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website:
http://www.i-Base.info; by fax or post using the form on the back page by sending an email to: subscriptions@i-Base.org.uk

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http://www.i-Base.info

HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

However, any donation that your organisation can make towards our costs is greatly appreciated.

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(Our bank details for donations: NatWest, Kings Cross Branch, 266 Pentonville Road, London N1 9NA, Sort Code 60-12-14. Account Number: 28007042)

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I do not wish to make a regular donation but enclose a one-off cheque in the sum of _____ instead.

I wish to make a one of donation (minimum £12.50 inc p&p) for the Treatment Literacy Photogrpahy Book £ _____.

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If your employer operates a Give-As-You-Earn scheme please consider giving to I-Base under this scheme. Our Give-As-You-Earn registration number is **000455013**. Our Charity registration number is 1081905

Since many employers match their employees donations a donation through Give-As-You-Earn could double your contribution. For more information on Give-As-You-Earn visit www.giveasyouearn.org

REFUNDS FROM THE TAX MAN

From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

Whichever of the above schemes you might chose to donate to i-Base we would like to thank you very much for your support.

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1 Sheet ☐ **1 pad** ☐ **5 pads** ☐ **10 pads** ☐ **Other** ☐ _____ _____

Please fax this form back, post to the above address, or email a request to HIV i-Base:

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