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EDITORIAL

This last issue of HTB for 2010 includes reports from several Autumn conferences including the Glasgow HIV Congress, the Lipodystrophy Workshop held in London and a meeting focused on HIV and ageing held in Baltimore.

Some of the meetings already have online webcasts of key presentations and this is the best way to follow the meetings for those unable to attend in person.

We also include a report from the iPrEX study that showed tenofovir/FTC taken by HIV-negative people prior to and after sex can protect against catching HIV, though any precision on the degree of protection is less clear. However, the protection is likely to be higher in someone who is careful to adhere to PrEP/PEP than the 44% protection reported in the top-line results.

Richard Jefferys basic science reports include the published results of longer follow up on the single case of functional cure in an HIV-positive man who received stem-cell transplantation from a donor with the delta-32 deletion. We reported this case from the CROI conference in 2008. This man is cured.

The challenge for everyone else is highlighted in his report of a patient in the USA who has an HIV viral reservoir estimated at 1 HIV-infected T-cell per 1.7 billion. Viral load rebounded – albeit slightly delayed (out to 50 days) – after discontinuing HAART.

Treatment access news highlights the global crisis for global treatment funding – despite the Global Fund achieving it's highest yet 3-year funding pledge, treatment programmes are already being capped to new patients in some countries. And access to treatment globally is threatened again from proposed EU legislation seeking to reduce access to generic antiretrovirals.

We are also including a copy of a new treatment guide as a supplement to this issue.

HIV and your quality of life: a guide to side effects & complications has been updated and expanded to include other aspects of living with HIV and the online version includes over 350 references.

As with other i-Base guides, these booklets are available free and in bulk for UK individuals, clinics and organisations. Please order online in the usual way.

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

Finally, we would like to wish all our readers best wishes for the coming holidays and to welcome you back in 2011 reinvigourated for whatever path of HIV advocacy, action and healthcare that you chose to commit your energy.

CONFERENCE REPORTS

10h International Congress on Drug Therapy in HIV Infection

7–11 November 2010, Glasgow

Introduction

The 'Glasgow conference' is held every two years and attracts a broad interest from both European and US clinicians and researchers.

This year the conference abstracts are already posted online as a supplement to the Journal of the International AIDS Society (Volume 13, Supplement 4).

http://www.jiasociety.org/supplements/13/S4

In the references to our reports we include both the conference abstract numbers and the IAS publication link.

A PDF file of the abstracts is also available (direct download):

http://www.biomedcentral.com/content/files/pdf/1758-2652-13-S4-full.pdf

Approximately 200 posters are online as PDF files, categorised by general topics, and posted to the 'webcast' pages of the conference website. A few webcasts are included in this selection.

http://www.hiv10.com/webcastsearch.asp

Reports in this issue include:

- Virological findings from the SARA trial of boosted protease inhibitor monotherapy
- Nevirapine exposure was not associated with hypersensitivity in patients from Malawi
- Estimating the number of people in a country or region with HIV who are undiagnosed and in need of ART

- High preterm delivery rates associated with initiation of HAART during pregnancy at a London clinic
- Minority M184V variants detected in women after receiving 3TC/FTC and LPV/r-containing regimens in pregnancy
- The Antiretroviral Pregnancy Registry reports no increased rate of birth defects with atazanavir exposure
- Pharmacokinetics of lopinavir/ritonavir in combination with rifampicin based TB treatment in children
- Efavirenz versus nevirapine based first line treatment in a South African cohort
- GSK572: 24-week results in treatment-naïve and raltegravir-experienced patients
- Consensus guidelines recommend routine use of genotypic tropism testing for European patients prior to using maraviroc
- UK studies on bone health: increased fracture rates reported in HIV-positive people
- Muscle weakness or pain analysed as possible raltegravir side effect
- Adding maraviroc does not boost CD4s in randomised trial
- Switch to twice-daily unboosted atazanavir outdoes switch to once-daily dose
- Small but higher rates of AIDS and non-AIDS complications with uncontrolled HIV despite CD4s over 350

Virological findings from the SARA trial of boosted protease inhibitor monotherapy

Polly Clayden, HIV i-Base

There is currently an interest in using boosted protease inhibitor monotherapy as a maintenance strategy in resource rich countries.

A pilot substudy of the DART trial, Second-line Anti-Retroviral therapy in Africa (SARA), randomised 192 patients who had received 24 weeks of lopinavir/ritonavir-based (LPV/r) second-line combination therapy to either continue on this combination or to receive LPV/r maintenance monotherapy. Prior to the switch, DART patients had taken first line therapy for a median of 4.4 years.

Data were presented as a late breaker poster at IAS 2010 suggesting few differences between the two groups in CD4 increases or adverse events in the short term. [1] At week 24 the mean CD4 gain was 48 vs 42 cells/mm3 in the combination and monotherapy arms respectively. For those completing 72 weeks the gains were 159 vs 153 cells/mm3.

No real-time virology was performed in DART but plasma samples were stored from: time at switch to second line, time of SARA randomisation, 24-weeks after SARA randomisation and latest time point (35-107 weeks after SARA randomisation).

Dave Yirrel presented results at Glasgow 2010 from a retrospective analysis of viral load, measured by Roche Amplicor v1.5 on the stored samples. In addition, genotype resistance was assessed on samples with viral load >1000 copies/mL at 24 weeks. Analyses were intent to treat. [2]

The median CD4 counts overall were 86 cells/mm3 at switch to second line and 245 cells/mm3 at SARA randomisation. The majority of patients (86%) had received a triple nucleoside first line regimen and the remainder two nucleosides and an NNRTI. At SARA randomisation 22% were receiving LPV/r + 2/3 NRTIs, 15% LPV/r + NNRTI and 62% LPV/r + NNRTI + NRTI. Of those with viral load measurements 135/173 (77%) had viral load <50 copies/mL.

The investigators found a higher proportion with undetectable viral load among patients on combination therapy compared to monotherapy at week 24, p=0.007. They reported 77% (70/91) vs 60% (66/94) had viral loads <50 copies/mL and 94% vs 84% had viral load <1000 copies/mL.

Among the small number of patients for whom 96-week data were available for analysis, the proportion with rebound to ≥200 copies/mL was greater in the monotherapy than combination therapy arm: 50% vs 20% (n=7 per arm). This difference was similar among those with rebound ≥1000 copies/mL: 40% vs 10% (n=7 in the monotherapy and , n=8 in the combination therapy arms).

Genotype results from the patients with viral load ≥1000 copies/mL at 24 weeks showed 0/5 patients with major protease inhibitor mutations of those in the combination therapy arm and 4/16 (of 19 patients with rebound to 1000 copies/mL) in the monotherapy arm.

The investigators concluded that, over the relatively short period of follow up (median 60 weeks) since SARA randomisation, there was an increase in low level viraemia with monotherapy compared to combination therapy, but no evidence of systematic increase in viral load after loss of suppression.

The EARNEST trial due to start next year will provide data on the long-term effectiveness of PI maintanance monotherapy in this setting. [3]

C O M M E N T

Neither the numbers involved, nor the duration of the trial make it possible to make any definite conclusion from these data. But it does seem that boosted PI monotherapy may not be a viable option in settings without access to viral load monitoring.

References

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3. Europe - Africa Research Network for Evaluation of Second-line Therapy (EARNEST) study. http://earnest.cineca.org/index.php

Nevirapine exposure was not associated with hypersensitivity in patients from Malawi

Polly Clayden, HIV i-Base

Although there is a risk of hypersensitivity, nevirapine (NVP) is used widely in first line regimens in resource- limited settings.

The relationship between drug exposure and hypersensitivity with NVP is unknown. It is possible that it is influenced by the effect of polymorphisms in CYP2B6 and CYP3A5 on drug metabolism.

Laura Dickenson and colleagues from Malawi and Liverpool showed findings from a study designed to develop a population pharmacokinetic (PK) model for NVP serum concentrations, and, in turn, to determine the impact of patient demographics, hypersensitivity and genetics on the PK of the drug.

The population PK model included 180 drug-naïve HIV-positive patients (of which 101 were women), starting NVP-based treatment at Queen Elizabeth Central Hospital, Malawi between March 2007 and September 2008. At the time of PK sampling, they were a median age of 34 years old, with a median CD4 cell count of 156 cells/mm3 (range 1-812). The median duration of treatment was 6 weeks (1-26). Twenty-five patients were hypersensitive and 23 coinfected with hepatitis B or C.

The investigators performed rich and sparse sampling in 40 and 140 patients respectively. PK data were available for single nucleoside polymorphisms (SNPs): CYP3A5*6, CYP3A5*3, CYP2B6 983T>C, CYP2B6 516G>T and CYP2B6 785A>G in 89/180 patients. Genotyping was performed using Sequenom iPLEX.

The investigators used non-linear mixed effects modelling (NON-MEM, VI 2.0) to investigate the effects of patient demographics, hypersensitivity, hepatitis and CYP3A5 and CYP2B6 on NVP apparent oral clearance (CL/F).

They found a one-compartment model with first order absorption best described the data. For the final model (n=89) NVP CL/F (relative standard error RSE%) was 2.67 (5%) with interindividual, interoccasion variability of 30% (29%) and 32% (26%) respectively.

The apparent volume of distribution and absorption rate constant were 141L (22%) and 0.77h-1 (31%) respectively.

They reported that none of the available patient demographics were associated with NVP CL/F. Nor did they find an association between NVP CL/F and hypersensitivity or hepatitis.

Only CYP2B6 983T>C and CYP3A5*3 had an impact on NVP CL/F; reducing it by 25% in 983C heterozygotes (allelic frequency 18%) and 40% in CYP3A5*3 homozygotes (allelic frequency 5%).

They concluded that NVP exposure was not associated with the development of hypersensitivity, "which is more likely to be an immunological phenomenon." They added that further studies are warranted to determine the mechanism of NVP hypersensitivity.

Reference

Dickenson L et al. Population pharmacokinetic and pharmacogenetic analysis of nevirapine in hypertensive and tolerant HIV-infected patients from Malawi. 10th International Congress on Drug Therapy in HIV Infection, November 7-11. Glasgow. Poster abstract P181. Published in Journal of the International AIDS Society 2010 13(Suppl 4):P181.

http://www.jiasociety.org/content/13/S4/P181

Estimating the number of people in a country or region with HIV who are undiagnosed and in need of ART

Polly Clayden, HIV i-Base

Estimating the number of people in a country or region with undiagnosed HIV in need of ART is essential for testing and treatment programmes.

Rebecca Lodwick and colleagues from the University College London showed a simple method for making this estimate, which uses data on simultaneous HIV/AIDS diagnoses at low CD4 count.

The HIV surveillance data needed for this method are the number of previously undiagnosed people presenting with AIDS

(simultaneous HIV/AIDS) in a year with CD4 count at diagnosis. The number of people with simultaneous HIV/AIDS in a CD4 stratum represents a proportion of the total undiagnosed people with CD4 count in that stratum. The proportion is equivalent to the annual incidence of AIDS in people in that stratum, which can be estimated from cohort studies.

For each stratum the number of people with undiagnosed HIV is estimated by dividing the number of people with simultaneous HIV/AIDS diagnoses (with CD4 count in the stratum) by the CD4 specific AIDS rate.

The investigators obtained an uncertainty range associated with this estimate by assuming the AIDS rate varies according to a normal distribution and the observed number of diagnoses according to a Poisson distribution. They accounted for these two sources of uncertainty simultaneously over 10,000 runs.

They illustrated this method for people with undiagnosed HIV and CD4 count below 200 cells/mm3. Using data from CASCADE the incidence of AIDS in this CD4 stratum among ART naïve patients has been estimated to be 0.25 per year (95% CI, 0.21-0.28). They used an example that supposed during the past year there were 50 simultaneous HIV/AIDS diagnoses with CD4 counts below 200 cells/mm3. Then the estimated number of undiagnosed people in this CD4 stratum would be 50/0.25=200. The estimated 95% uncertainty range would be 144-268.

They acknowledged that a potential source of bias is the possible under-diagnosis and under-reporting of simultaneous HIV/AIDS diagnoses.

They also note that the method depends on high levels of ascertainment of people presenting with simultaneous HIV/AIDS and on availability of CD4 count at diagnosis.

The investigators intend to make a SAS programme available that will perform this calculation.

References

Lodwick RK et al. A method to estimate the number of people in a country or region with HIV who are undiagnosed and in need of ART. 10th International Congress on Drug Therapy in HIV Infection, November 7-11. Glasgow. Poster abstract P165. Published in Journal of the International AIDS Society 2010 13(Suppl 4):P165.

http://www.jiasociety.org/content/13/S4/P165

High preterm delivery rates associated with initiation of HAART during pregnancy at a London clinic

Polly Clayden, HIV i-Base

HAART use in pregnancy has been associated with preterm delivery (PTD) in some studies but not others.

Graham Taylor and colleagues performed an analysis of pregnancies prospectively recorded at a London clinic between 1995 and 2010.

This review included data for 331 deliveries. The majority of women were black African (78%) and infected through heterosexual intercourse (94%). Their median age was 32 years and median CD4 count 380 cells/mm3. They attended their first antenatal appointment at a median of 13 weeks gestation. Of the group, only eight women took no antiretrovirals prior to delivery and seven took dual NNRTIs.

The remaining women received HAART or prophylaxis, and are described in Table 1.

The investigators reported 45/331 PTD (13.6%) before 37 weeks gestation. Of these, 60% of deliveries were before 34 weeks. They observed no significant difference between women starting new continuous HAART (17.2%) and those already receiving HAART pre-conception (12.6%).

They found a lower rate of PTD among women receiving nevirapine-based HAART to those receiving protease inhibitor-based HAART, which occurred in 16/143 (11.2%) and 23/103 (22.3%) respectively, p=0.02.

They noted that 32 women receiving a short-course of HAART (START) during pregnancy to prevent mother- to-child HIV transmission would have been eligible, if they were willing to deliver by pre-labour caesarean section (PLCS), to receive AZT monotherapy, according to the 2008 BHIVA guidelines. Of these, 23 received PI based START and 39% (9/23) had PTD events compared to 6.2% receiving AZT monotherapy, p=0.0005.

The investigators acknowledged, “The role of HAART and PI-based HAART in PTD has been controversial” and even in this single centre study “confounders abound”, despite all women being managed by one team in accordance with BHIVA guidelines.

There was significant variation in CD4 counts and viral loads between women starting HAART in pregnancy and those taking AZT monotherapy or already receiving HAART at conception.

They concluded that their data suggest that PI-based HAART initiated during pregnancy is associated with a significantly increased rate of PTD and that this is influenced by maternal immune status.

They added that further investigation of the mechanism and impact of timing of antiretrovirals to optimise the safe use of this important intervention is overdue.

Table 1. Rates of preterm delivery by treatment/prophylaxis strategy

Treatment / prophylaxis	N	Median CD4 (Baseline ANC)	Median viral load c/mL	PTD Number (%, 95% CI)
AZT monotherapy	65	460	2648	4 (6.2; 2.4-14.8)
START	64	360	8930	15 (23.4; 14.7-35.1)
New continuous HAART	58	150	23430	11 (19.6; 11.3-31.8)
Pre-conception HAART	127	385	49	13 (9.6; 5.9-16.2)

C O M M E N T

The association between HAART and PTD continues to be demonstrated, particularly in European cohorts.

The investigators rightly stress that "confounders abound" and that further investigation into the mechanism and how best to optimise strategies is long overdue.

Reference

Taylor G et al. High preterm delivery rates associated with initiation of HAART during pregnancy. 10th International Congress on Drug Therapy in HIV Infection, November 7-11. Glasgow. Poster 158. Published in Journal of the International AIDS Society 2010 13(Suppl 4):P158.

http://www.jiasociety.org/content/13/S4/P158

Minority M184V variants detected in women after receiving 3TC/FTC and LPV/r-containing regimens in pregnancy

Polly Clayden, HIV i-Base

Short-term antiretroviral therapy (START) of two NRTIs and a ritonavir boosted PI is used frequently to prevent mother to child transmission in the UK. Resistance is rarely detected using standard genotyping following this strategy.

Sabrina Surah and colleagues conducted a multicentre study to determine whether minority M184V variants emerge with 3TC/FTC and LPV/r containing START regimens in pregnancy, and, if so, whether this has an impact on future treatment success.

The investigators used an allele-specific real time PCR (ASPCR), optimised for subtypes B, C and AG, to detect minority M184V variants. This assay has a lower limit of detection of 0.5%.

Plasma samples were tested pre and post treatment and routine population based sequencing (Viroseq) was also performed.

Samples from 38 women were tested and ASPCR failed in 15 (39%). Of the remaining 23 women, 16 (42%) had wild type (WT) virus and 7 (18%) had minority M184V sequences with a range of detection between 0.5% and 14%. The investigators noted that all samples were WT with population-based sequencing.

ASPCR failed to amplify from pre- treatment samples in 4/7 women with minority M184V and was WT in 3. Therapeutic drug monitoring of lopinavir was performed in a subset of women.

The investigators found no difference in prior ART, duration of START, drug concentration of LPV/r or virological suppression with subsequent ART in women with or without mutations. There were more women with subtype C among those with M184V mutations, 5/7 (62%) than those with WT, 1/16 (6%).

The investigators suggested that the possible association with HIV-1 subtype C requires further evaluation and a clade effect on acquisition of resistance has been reported following nevirapine use in pregnancy.

C O M M E N T

That there was no difference in subsequent virological suppression between women with minority M184V mutations after START regimens is reassuring.

Reference

Surah S et al.: Minority M184V variants in women exposed to 3TC/FTC-containing lopinavir-ritonavir (LPVr) regimens in pregnancy. 10th International Congress on Drug Therapy in HIV Infection, November 7-11. Glasgow. Poster 159. Published in Journal of the International AIDS Society 2010 13(Suppl 4):P159.

http://www.jiasociety.org/content/13/S4/P159

The Antiretroviral Pregnancy Registry reports no increased rate of birth defects with atazanavir exposure

Polly Clayden, HIV i-Base

Data showing outcomes after atazanavir (ATV) exposure, from the Antiretroviral Pregnancy Registry (APR), were presented as a poster.

Pregnant women receiving ATV were enrolled from June 2003 (when the drug received FDA approval) and the analysis presented was performed to January 31 2010. Atazanavir is FDA pregnancy category B.

There were a total of 698 women with ATV-exposed pregnancies enrolled during this period and 588 were eligible for analysis. Their mean age was 29 years; 12.9% were white, 63.9% black and 16.7% Hispanic. The majority (87.9%) was American.

Most women (82.5%) had a baseline CD4 count greater than 200 cells/mm3.

Of the 588 pregnancies, 18 were multiple gestations; 604 outcomes were recorded, including 567 live births. There were 12 live births with defects and one in an induced abortion. Of a total of 13 infants with birth defects, 8/368 were first trimester exposures giving a rate of 2.2% (95% CI, 0.9-4.2%) and 5/199 were second/third trimester exposures, with a rate of 2.5% (95% CI, 0.8-5.8%). The relative risk of defects of first trimester exposures to second/ third trimester exposures was 0.87 (95% CI, 0.29-2.61).

The overall prevalence of birth defects among ATV-exposed infants was 2.3% (95% CI, 0.29-2.61), which the investigators noted compared favourably to the CDC MACDP general population rate for birth effects of 2.7% (95% CI, 2.68-2.76).

The organ systems affected included: heart/circulatory system, renal/urinary system, central nervous system, chromosome abnormal/anomaly, cleft hip/palate, other muscular/skeletal defects and specified syndromes.

The investigators did not observe a pattern of birth defects in this group.

Reference

Esker et al. Assessing the risk of birth defects associated with atazanavir exposure in pregnancy. 10th International Congress on Drug Therapy in HIV Infection, November 7-11. Glasgow. Poster 113. Published in Journal of the International AIDS Society 2010 13(Suppl 4):P113.

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Pharmacokinetics of lopinavir/ritonavir in combination with rifampicin based TB treatment in children

Polly Clayden, HIV i-Base

Lopinavir/ritonavir (LPV/RTV) is first line treatment for young children in South Africa. Concomitant treatment for TB is common in children with HIV. There is a complicated interaction between this boosted protease inhibitor and the first line TB drug, rifampicin (RIF), which reduces the bioavailabilty and Cmin of LPV by approximately 75% and 99% respectively.

Two strategies are possible to increase the LPV levels when it is dosed with RIF - either increasing the dose of RTV to a LPV:RTV 4:4 ratio or doubling the dose to a LPV:RTV ratio 8:2.

Chao Zhang and colleagues from the University of Cape Town showed a population pharmacokinetic (PK) model developed to describe the interactions between LPV, RTV and RIF in children. They used this to look at the effect of various factors (age, BSA, weight, gender, haemaglobin, albumin, ALT) on LPV and RTV PK, and make dosing recommendations for HIV/TB coinfected children receiving these drugs concurrently. [1]

In this study, 39 children with HIV only received the standard dose of LPV/RTV, 4:1, (control group); 15 coinfected children received the super-boosted dose, 4:4; and 20 the double dose, 8:2. Then 11 coinfected children received the standard dose following RIF-based treatment. Repeated sampling was performed (4-6 from each child) up to 12 hours post dose.

The children were a median age of 21 months (range 6 months to 4.5 years) and a medium weight of 10.2kg (range 5-17kg).

Using a one-compartment model with first order absorption for LPV and a one-compartment model with transit absorption for RTV, the investigators modelled the effect of RTV concentration on LPV clearance as direct inhibition with an Emax model.

The investigators found that, during concomitant treatment with RIF, the relative oral bioavailability of LPV was reduced by 79% in children receiving the twice the standard dose of LPV/RTV. RTV clearance was 18 L/h with RIF and 13L/h without.

The estimated baseline clearance of LPV, when there was no detectable RTV was 4.34 L/h. As the concentrations of RTV increased, the clearance of LPV decreased in a sigmoid relationship (EC 50, 0.051 mg/L). They found volume of distribution for LPV and RTV were 11.7 and 102 L respectively.

When the investigators performed simulations for dose optimisation during RIF-based TB treatment with a target of LPV concentrations with Cmin >1mg/L in 95% of children, they predicted doses of LPV/RTV as described in Table 1. They noted that smaller children required higher mg/kg doses of LPV/RTV, in both 4:1 and 1:1 ratios, than larger children.

Table 1: Simulation for dose optimistion of LPV/RTV during RIF-based TB treatment

Body weight	LPV:RTV 4:1		LPV:RTV 1:1
	12 hourly LPV dose (mg/kg)	8 hourly LPV dose (mg/kg)	12 hourly LPV dose (mg/kg)
4-6 kg	50	25	20
6-8 kg	42	22	17
8-12 kg	37	21	15
12-18 kg	30	18	12

C O M M E N T

The same group previously presented data to show that the double dose LPV/r is not sufficient for children when coadministration with rifamipicin. [2]

The current median LPV dose using double dose strategy in this study is 23 mg/kg,

The investigators suggestion for dose adjustment in this study is much higher than double dose. Or they suggest switching to an 8 hourly dose strategy considering the adverse effect slinked to higher doses. [3]

References

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http://www.retroconference.org/2009/Abstracts/34615.htm
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Efavirenz versus nevirapine based first line treatment in a South African cohort

Polly Clayden, HIV i-Base

A poster authored by Peter Block and colleagues compared the effectiveness of efavirenz and nevirapine in a multisite cohort of South African adults attending public health facilities.

This was a retrospective analysis of routine data from 27,350 adults initiated on ART between March 2004 and March 2007 in public health facilities. Participants were a median age of 34.4 (IQR 29.4-40.8) with a median CD4 count of 113 cells/mm3 (IQR 57-165).

The investigators found, over a median follow up of 9.3 months (IQR 4.6-17.7), in multivariate analysis, participants receiving efavirenz-based combinations were more likely to achieve undetectable viral load at six months, OR 1.31 (95% CI, 1.1--1.54) and at any time between six and 36 months, OR 1.28 (95% CI, 1.16-1.41). They were also more likely to die, AHR1.24 (95% CI, 1.07-1.45) and less likely to change regimen OR 0.53 (95% CI, 0.48-0.59).

Additionally, a subset analysis of 18,527 participants for whom pregnancy and TB status were known revealed no difference in mortality risk between those receiving efavirenz and nevirapine based regimens AHR 1.17 (95% CI, 0.99-1.37).

C O M M E N T

This study adds to a body of evidence showing superior results with EFV for first line ART when compared to NVP. Given the resource constraints in developing countries EFV should therefore be the preferred NNRTI for first line use. Protease inhibitors are not suitable for first line in developing countries due to increased cost. However; the possible link between EFV use in the first trimester and teratogenicity complicates its use with many women receiving EFV or initiating ART presenting only in the second trimester of pregnancy.

In the absence of suitable alternative NNRTIs or protease inhibitors, recommendations against the use of EFV in pregnancy need to be reviewed. In addition more work needs to be done to advocate for the reduction in price of suitable alternatives.

Reference

Bock P et al. Comparing the effectiveness of efavirenz and nevirapine for first-line antiretroviral treatment amongst an adult treatment cohort from South Africa. 10th International Congress on Drug Therapy in HIV Infection, 7–11 November 2010, Glasgow. Poster abstract P10. Published in Journal of the International AIDS Society 2010 13(Suppl 4). P10.
http://www.jiasociety.org/content/13/S4/P10

GSK572: 24-week results in treatment-naïve and raltegravir-experienced patients

Simon Collins, HIV i-Base

Oral presentations in Glasgow presented 24-week data on the pipeline integrase compound S/GSK1349572 (GSK572) in naïve and experienced patients. [1, 2]

In general, the promising early results were sustained: 16-week data were presented at the IAS conference in Vienna in July (see HTB August 2010).

The SPRING-1 dose-finding phase 2 study (approximately 50 people in each of 4 arms) in treatment naïve patients reported over 90% patients achieving viral suppression <50 copies/mL by 24 weeks compared to 78% in the efavirenz control group. Although this presentation noted that 26% of participants had a baseline viral load >100,000 copies/mL viral load in the remaining 74% patients must have been significantly lower given that median baseline viral load for the whole study was only approximately 25-40,000 copies/mL (4.4–4.6 logs).

Three people had confirmed virological failure (2 rebounds at week 2 and 24 with 572, one failure to achieve >1 log decline at week 4 with efavirenz who later suppressed), with no resistance detected.

No new tolerability concerns were raised, with GSK572 continuing to show a lipid advantage (mean change from baseline in LDL cholesterol was +0.023 vs +0.468 mmol/L in the combined 572 vs efavirenz arms).

CD4 increases were significantly higher in the combined GSK572 arms (median change +172 vs + 110, p=0.008).

The VIKING study reported results from 17/27 raltegravir-experienced patients who continued treatment out to 24 weeks. Baseline median fold change in raltegravir susceptibility for the whole study was 161, range: 0.57- >166. The study design added GSK572 (50 mg once-daily) to the failing combination for 10 days before optimising the combination on day 11 based on phenotypic sensitivity.

Virological responses correlated with phenotypic susceptibility score (PSS): 2/12 (17%) subjects with PSS =0, 4/7 (57%) with PSS=1 and 8/8 (100%) with PSS ≥2 achieved <400 copies/mL at Week 24. This highlights the imperative to only use integrase inhibitors in combinations in which they are supported by preferably at least two other drugs to which the virus is sensitive.

Importantly, a second cohort following the VIKING protocol is investigating using GSK572 50 mg twice-daily to attempt to overcome the phenotypic resistance at the 50mg dose, supported by PK/PD modeling. [4]

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Unless stated otherwise, references are to the Programme and Abstracts of the 10th International Congress on Drug Therapy in HIV Infection, 7–11 November 2010, Glasgow, published in Journal of the International AIDS Society 2010, 13(Suppl 4).

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Consensus guidelines recommend routine use of genotypic tropism testing: new focus on maraviroc as a switching option

Simon Collins, HIV i-Base

New consensus guidelines on tropism testing, produced by a panel of European virologists with expertise in HIV drug resistance produced from a literature review of 57 journal papers and 42 conference abstracts were presented by Annemarie Wensing.

Currently the use of maraviroc is technically restricted to people who are shown to have R5-tropic HIV determined by phenotypic tropism testing (Trofile ES). However, genotypic population sequencing of the V3 loop of env has shown quantifiable differences between X4 and R5 tropic virus and using a genotypic predictive algorithm has similar accuracy at predicting R5 tropism. While phenotypic tropism testing requires viral load >1000 copies/mL, genotype testing can be used for patients who are currently virologically suppressed on treatment, increasing the confidence in identifying people who might benefit from maraviroc as a switch option.

Key recommendations include tropism testing for ARV-naïve patients (who have limited drug choices, perhaps due to toxicity of their first treatment, drug resistance or drug interactions) and treatment experienced patients prior to a change of treatment (noting

the importance of repeat testing over time due to shifting tropism).

The panel recommended both the phenotypic Enhanced Sensitivity Trofile Assay (ESTA) and genotypic population sequencing, but recognise that for patients not based in the US, genotypic testing will be preferred due to greater accessibility, lower cost and shorter turnaround time. The list price of ESTA is close to $2000 (although ViiV can subsidise this cost) compared to €150-250 for genotype tests. [3]

The panel also provides guidance on technical aspects and interpretation issues.

For genotype testing triplicate PCR amplification and sequencing is advised using the online geno2pheno interpretation (coreceptor) tool [2] with a false positive rate (FPR) of 10%. If the viral load is below the level of amplification, proviral DNA can be used, and the panel recommends performing triplicate testing and use of an FPR of 10%. If genotypic DNA testing is not performed in triplicate the FPR should be increased to 20%.

C O M M E N T

Although prospective data on the use of genotypic tropism testing are generally from small observational studies, the ability to set the FPR depending on patient circumstances is important. For patients with very limited treatment options or with a strong background regimen, using a lower cut-off may be acceptable to improve the chance of using maraviroc when the presence of low-level X4 may be acceptable. Increasing the precision for excluding X4 by setting a higher FPR may be more important in less experienced patients to avoid the loss of other drugs in the combination. [2]

The geno2pheno includes adjustment for CD4 nadir, relevant given that HIV progression correlates positively with the risk of shifting from R5 to X4 virus.

BHIVA guidelines recommend routine use of triplicate testing but not routine tropism testing for all naïve patients (unless maraviroc is being considered as a treatment option. [4]

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UK studies on bone health: increased fracture rates reported in HIV-positive people

Simon Collins, HIV i-Base

Several studies reported on various aspects of HIV and bone health.

Barry Peters and colleagues from Kings College London reported results from a cross-sectional case-control study looking at fracture risk, bone mineral density (in lumbar spine and hip) and a wide panel of bone-related investigations.

Cases were 223 randomly selected HIV-positive patients stratified by age with age and gender matched controls. Investigations included serum calcium, phosphate, 25OH vitamin D, alkaline phosphatase, parathyroid hormone, albumin, sex hormone binding globulin (SHBG), testosterone, CD4, HIV RNA. Fracture risks (fracture history, smoking, alcohol, BMI, activity level etc) were included to calculate FRAX score and remaining lifetime fracture probability (RLFP).

The study included patients with broad demographics: 133(60%) were male, 106(48%) were Caucasian, 71(33%) had AIDS at diagnosis.

Osteoporosis/osteopenia were present in 13%/39% of males and 11%/29% females, and was approximately 2.4/3.0 fold greater than age-matched controls. The overall mean 10-year fracture risk was 3.16%. RLFP exceeded 1.0 in 76% HIV patients, and <20% controls.

Factors associated with low BMD after multivariate analysis included having started antiretroviral therapy (adjusted OR 3.61; 1.38,9.42, p 0.01); BMI (aOR 0.90; 95%CI 0.83,0.96, p<0.001); alkaline phosphatase (aOR 1.01; 1.00,1.02, p<0.05) and testosterone (aOR 1.04; 1.01,1.07, p<0.01).

No association was found between fracture risk and age, gender, ethnicity CD4 count or vitamin D levels.

A second UK cross-sectional study reported fracture risks from 859/1050 HIV-positive patients attending the Lawson HIV clinic at Brighton Hospital who returned detailed questionnaires (that included demographics, lifestyle and fracture and HIV history and risk). This cohort was less diverse: 775 were men and 84 women; 87% Caucasian, with mean age was 43 years (range 19-77 years) and mean duration of HIV infection of 8 years (range 0–23 years).

Overall, 125 (15%) subjects reported 200 fractures: 119 (15%) men and 6 (7%) women. Common fracture sites were forearm (n=65), tibia/fibula (n=29), hand/foot (n=22) and digit (n=19). Hip fractures occurred in 6 subjects and 2 had clinical vertebral fractures.

Fractures significantly grouped in either younger (75% less than 25 years, median 7-12) or older (17% were 40–60 years). In the older group, typical osteoporotic fractures sites included forearm (n=6, mean age 48 years) and tibia/fibula (n=4, mean age 49 years); there was 1 hip fracture (age 46 years).

Both studies commented on management and monitoring with the first suggesting the higher fracture risk supports screening at an earlier age compared to HIV-negative populations and the Brighton study suggesting that screening may be important in younger patients.

C O M M E N T

Significantly higher rates of osteopenia and osteoporosis in HIV-positive compared to age- and sex-matched HIV-negative people have been well documented for at least 12 years, and this is now supported by more recent studies reporting increased fracture rates. [3]

Paediatric and adolescent HIV infection will compound these risks by reducing bone development (which peaks at around 30 years, subsequently declining). Additionally, reduced bone mineral density is one of the few negative associations with HIV treatment. [4]

Some clinics already recommend baseline DEXA scans for people older than 50 years. Paediatric guidelines have yet to directly address the long-term impact of both HIV and antiretroviral treatment on bone health, other than in the context of tenofovir treatment. Longer duration of both HIV infection and use of HIV treatment during the period of bone growth (up to age 30) would support a caution for optimising bone health and monitoring in younger people.

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Muscle weakness or pain analysed as possible raltegravir side effect

Mark Mascolini, natap.org

Muscle symptoms, especially weakness, emerged as a possible side effect of raltegravir in a database comparison of people taking this integrase inhibitor or the protease inhibitors darunavir/ritonavir. [1]

Although the symptoms compelled no one to stop raltegravir, researchers from Milan suggested that muscle weakness and pain be monitored in people taking raltegravir.

The study involved people starting raltegravir or darunavir and followed in the database of the Italian Coordination Group for Allergies and HIV Infection (CISAI), which aims to identify side effects of new antiretrovirals. [2] The investigators recorded muscle symptoms and classified them according to American Heart Association guidelines. They also ranked creatine phosphokinase (CPK) elevations according to the DAIDS table.

The analysis involved 391 people, 258 of them (66%) men, and 152 (39%) with AIDS. Age averaged 44.5 years (+/- 9.0), CD4 count 348 (+/- 260), and viral load 3.26 log (+/- 1.54) (about 2000 copies). While 135 people (35%) had HCV antibodies, 155 (40%) had a diagnosis of lipodystrophy. Only 16 people (4%) had never taken antiretrovirals before starting raltegravir or darunavir. The 293 people taking raltegravir did not differ significantly in demographic or clinical characteristics from the 98 taking darunavir.

When beginning raltegravir or darunavir, 13 people starting raltegravir versus 1 starting darunavir reported muscle pain (4.4% versus 1.0%, p=0.20), while 12 starting raltegravir and none starting darunavir reported muscle weakness (4.1% versus 0%, p=0.04). Muscle pain or weakness developed in 17 people during raltegravir therapy and in 1 while taking darunavir (5.8% versus 1%, p=0.05).

Among people with normal CPK when starting these drugs, CPK rose above 200 U/L in 26 taking raltegravir and 11 taking darunavir, a nonsignificant difference (8.9% versus 11.2%). CPK elevations were not associated with muscle pain or weakness.

No one stopped raltegravir because of CPK elevations or worsening muscle symptoms, and no cases of rhabdomyolysis were reported.

The CISAI investigators believe their findings suggest clinicians monitor patients starting raltegravir for muscle symptoms, including pain and weakness, and to pursue further diagnostic evaluation if these symptoms persist.

Researchers at St. Thomas' Hospital in London reported what appears to be the first case of DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), a severe dermatologic reaction, in a 55-year-old man switching from a protease inhibitor to raltegravir. [3]

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Adding maraviroc does not boost CD4s in randomised trial

Mark Mascolini, natap.org

Adding maraviroc to a suppressive regimen taken by people with a meager CD4 response did not boost CD4 count or CD4 percentage over 12 weeks in a small randomised trial. [1]

Maraviroc-induced improvement of certain T-cell subsets suggested this intensification strategy may have some immunologic advantage. But whether such an advantage yields clinical benefits that outweigh maraviroc-related risks and cost remains to be seen.

This multicenter Italian study recruited people with a prompt sub-50 virologic response to antiretroviral therapy who had sluggish CD4 gains. Stefano Rusconi (Universiti degli Studi di Milano) and colleagues randomised 50 people to add maraviroc and 50 to continue their current regimen. This planned 12-week analysis involved 37 people adding maraviroc and 27 in the control arm who reached that point. Follow-up will continue for 12 months.

Median CD4 count rose from 190 (range 144 to 237) to 211 (184.5 to 285.5) at week 12 in the maraviroc group, and from 170 (131.5 to 218) to 174 (126 to 247) in the control arm, a nonsignificant difference (p=0.241). Median CD4 percentage remained stable in the maraviroc group (14.8% at baseline to 14.4% at week 12) and in the control arm (12.7% at baseline and 12.9% at week 12).

Median CD8 count fell from 775.5 to 661.5 in the control arm, while climbing from 603 to 759 in the maraviroc arm, a significant difference (p=0.004). Pfizer investigator Hernan Valdez has proposed that this seemingly inauspicious jump in CD8 cells represents early redistribution of CD8 cells from cellular compartments, which stops after about 24 weeks. [2]

Ninety-six-week follow-up of antiretroviral-naive people randomized to maraviroc in two trials found little overall CD8-cell change in that span, but antiretroviral-experienced people who took maraviroc in the MOTIVATE studies had a big CD8 gain through 96 weeks. [3]

Rusconi compared week-12 T-cell subset changes in 12 people who added maraviroc and 12 who did not. The maraviroc group tended to gain more memory CD4 and CD8 cells than the control group, with no significant loss in naive T cells. Rusconi and colleagues proposed these shifts suggest "a role of maraviroc in reducing peripheral antigen-driven T-cell death, possibly preserving new T-cell production." Levels of activated (HLA-DR+ CD38+) T cells declined similarly in people adding or not adding maraviroc. CD8-cell expression of Ki67, a proliferation marker, fell in the maraviroc group (p=0.06) but not in the control group.

Except for five blips between 50 and 125 copies, everyone in the trial maintained virologic suppression during the first 12 weeks, and the researchers saw no clinical setbacks. There were 12 adverse events in the maraviroc arm (32%), but only one was judged related to maraviroc. Nonetheless, 3 people stopped maraviroc because of adverse events. Eight adverse events were recorded in the control arm (30%).

Adding maraviroc to a suppressive regimen also failed to hoist CD4 cells in an earlier pilot study. [4]

Two meta-analyses of CD4 responses in clinical trials yielded conflicting conclusions on whether CCR5 antagonists hold an edge over other antiretroviral classes [5, 6], though these meta-analyses could not adjust for factors predicting CD4 cell restoration.

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Switch to twice-daily unboosted atazanavir outdoes switch to once-daily dose

Mark Mascolini, natap.org

Retrospective analysis of French patients who switched from a suppressive regimen to once- or twice-daily unboosted atazanavir found higher atazanavir concentrations and better virologic responses in the twice-daily group.

The analysis involved 69 people with an undetectable viral load who switched to once- or twice-daily unboosted atazanavir from 2004 through 2009. Everyone had atazanavir concentrations measured at least 2 weeks after the switch and relevant clinical and virologic data. The investigators considered a trough concentration below 0.150 mg/L inadequate. Twenty-seven people took the protease inhibitor (PI) at a dose of 400 mg once daily and 42 took a twice-daily dose of 200 mg.

The once-daily and twice-daily groups did not differ significantly in age (average 48 and 50), proportion of men (63% and 79%), proportion with European origin (78% and 81%), time since HIV diagnosis (average 11 years in both groups), time on antiretroviral therapy (average 8 and 9 years), proportion starting a new two-nucleoside backbone (93% and 100%), number of previous PIs (average 2 in both groups), proportion switching from boosted atazanavir (44% and 31%), proportion taking tenofovir (52% and 31%, p=0.083), or baseline CD4 count (average 527 and 589).

Treatment duration averaged 18 months in the once-daily group and 14 months in the twice-daily group. Time to atazanavir level measurement was statistically equivalent in the two groups (average 7.8 weeks and 3.1 weeks, p=0.226). People who switched to a once-a-day dose gained more CD4 cells on average than the twice-a-day group, but this difference lacked statistical significance (41 versus 8, p=0.627).

Six out of 27 people (22%) who switched to once-daily atazanavir had a virologic failure during follow-up, compared with 1 of 42 (2%) in the twice-daily group, a significant difference (p=0.012). Seventeen people (63%) in the once-daily group versus 4 (9%) in the twice-daily group had an atazanavir trough below 0.150 mg/L (p<0.001). Average trough concentration was significantly lower with once-daily dosing (0.19 versus 0.36 mg/L, p=0.012). And significantly more people stopped once-daily atazanavir because of virologic failure or a low trough (10 [37%] versus 4 [9%], p=0.006). Three people in both groups (11% and 7%) changed drugs because of intolerance (p=0.437). The only person with virologic failure while taking twice-daily atazanavir had a trough above 0.15 mg/L.

The investigators concluded that switching to twice-daily unboosted atazanavir “may be more appropriate” than switching to once-daily unboosted atazanavir in people with an undetectable viral load. They called for a randomised trial to validate their findings.

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Small but higher rates of AIDS and non-AIDS complications with uncontrolled HIV despite CD4s over 350

Mark Mascolini, natap.org

EuroSIDA cohort members with a CD4 count above 350 and uncontrolled viral replication ran a higher risk of fatal and nonfatal AIDS than people with controlled viremia.

This 10,000-person analysis found less marked correlations between uncontrolled viremia at a 350-plus CD4 count and fatal or nonfatal non-AIDS complications – usually heart disease, non-AIDS cancers, or liver disease.

The AIDS analysis involved 10,998 EuroSIDA cohort members, while the non-AIDS analysis involved 10,278. Everyone had a CD4 count above 350 and a viral load measured in one of three brackets: under 500, 500 to 10,000, or over 10,000. Inclusion began on 1 January 1997 for AIDS diagnoses and 1 January 2001 for non-AIDS diseases. The investigators halted follow-up if the CD4 count or viral load had not been measured in the preceding 6 months, if the CD4 count fell below 350, or at a person's last EuroSIDA visit or death.

During follow-up, the EuroSIDA team recorded 379 new AIDS diagnoses and 476 non-AIDS diagnoses. The most frequent non-AIDS problems were cardiovascular disease in 176, non-AIDS cancers in 163, and liver problems in 32. About 75% of cohort members were men, about 87% white, and about 45% infected through sex between men. More than 90% with a viral load under 500 copies/mL were taking antiretrovirals, compared with about 63% in the 500-to-10,000-copy bracket about 35% with a viral load above 10,000 copies/mL.

Incidence of new AIDS diagnoses was 2.38 per 100 person-years in people with a viral load above 10,000 copies/mL versus 0.69 per 100 person-years in those with a viral load under 500 copies/mL. This increased rate involved AIDS diagnoses of any severity. Incidence of non-AIDS diagnoses was similar in people with a viral load below 500 copies/mL (1.40 per 100 person-years), people with 500 to 10,000 copies/mL (1.56 per 100 person-years), and people with a load above 10,000 copies/mL (1.39 per 100 person-years). Rates of cardiovascular and non-AIDS cancer diagnoses were similar in the three viral load strata.

Multivariate analyses for AIDS diagnoses factored in viral load bracket, gender, HIV exposure group, region of European, HBV and HCV status, smoking status, hypertension, antiretroviral status, year of follow-up on antiretroviral therapy, and prior AIDS. This analysis determined that people with a viral load above 10,000 had a three times higher risk of a new AIDS diagnosis than those with a load under 500–even though everyone had a CD4 count above 350.

The multivariate models for non-AIDS diagnoses adjusted for age, peak viral load, HIV exposure group, region of Europe, HBV and HCV status, diabetes, hypertension, smoking, prior AIDS, and antiretroviral status. Compared with cohort members who had a sub-500 viral load, those with 500 to 10,000 copies had a 48% higher rate of new non-AIDS diagnoses, while those with a load above 10,000 copies had a 54% higher rate. The impact of viral load on incidence of non-AIDS events was independent of CD4 count and similar in different CD4 strata.

The EuroSIDA investigators noted that they need a larger database "to fully investigate the relationship between viral replication and specific non-AIDS events in patients who are not immune compromised."

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CONFERENCE REPORTS

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

4–6 November 2010, London

Introduction

This annual workshop continues to be an important forum for its focus on the potential mechanisms behind lipodystrophy and metabolic complications.

The meeting programme includes plenary lectures on HIV related comorbidities by international speakers from outside the HIV field.

This year these included:

- Vitamin D insufficiency and its immune and metabolic consequences – John Adams
- Intestinal microflora and low grade metabolic inflammation – Remy Burcelin

- The effect of inflammation on lipid and lipoprotein metabolism – Kenneth Feingold
- Neuroimaging: HIV-related neurocognitive impairment and HIV-related disorders – Rolf Jäger
- Body composition, fat and bone: What's the connection to drugs and HIV – Clifford Rosen
- Adverse Drug Reactions in the Treatment of HBV-monoinfection – Heiner Wedemeyer

Meeting abstracts, published as a supplement to Antiviral Therapy are available to download from a direct link on the conference website

http://www.intmedpress.com/lipodystrophy/default.cfm?itemtypeid=18&title=Programme

Webcasts are available at:

http://www.intmedpress.com

Bio-Alcamid associated with unacceptable complication risks: no longer recommended as a treatment for facial lipoatrophy

Simon Collins, HIV i-Base

The final oral presentation at the 12th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV included important information for clinical management for facial lipoatrophy, reporting a 10% complication from Bio-Alcamid gel implants. This should result in the product no longer being used in the UK.

Jeya Nadarajah from University of Toronto presented results from a retrospective review to determine the incidence of complications in 263 HIV-positive people (during 375 person years of follow up) who were treated with Bio-Alcamid in Toronto. [1]

Bio-Alcamid polyalkylimide gel is marketed as a biochemically inert, non-reabsorbing polymer that can be injected subcutaneously under aseptic conditions in up to 25 mL volume. The use of larger volumes made this an option for patients with more severe lipoatrophy, when lower volume resorbable fillers like poly-L-lactic acid (New-Fill) require many more treatments. After injection, the material encapsulates within a 0.2 mm collagen membrane as an 'endoprosthesis'. Although promoted as semi-permanent and extractable, this becomes an increasingly difficult procedure the longer the implant has been in place.

Previous complications have been reported in case studies [2,3,4,5] and a retrospective analysis published in 2009 (including 270 HIV-positive patients) reported a 4.8% complication rate that given "the severity of the complications, and the difficulty in treating them [polyalkylimide presents] too high a risk for a cosmetic treatment". [6]

Of the 263 people in the Toronto group, most had their first treatment in 2005 (~ n=100) or 2006 (~n=85). Demographic and treatment data available for 240 people included median age was 49 (IQR 44–54), 96% were male, 95% of treatments were to the cheeks and temples, with a median of four injections injections using a median of 11 mL (10-15 mL).

Antibiotic prophylaxis using Cephalexin for five days was provided for all treatments including the 145 patients (60%) who required subsequent touch-up treatment.

At least one infectious complication was reported for 51/263 patients (19%) with 13 definite (5%) and 38 probable. This was calculated as an incidence rate of 0.14 infections per person year of follow-up and a definite incidence rate of 0.034 per PYFU. Time to complication from last injection indicated that most were late complications (after 1-4 years). Secondary touch-up treatment was most significant risk factor for complications: 86% of people with complications had had subsequent touch-up treatment compared to 54% of people without complications ($p<0.0001$).

In 30 patients with more detailed notes, the recent manipulation of the face prior to infection was related to dental work (n=10), cosmetic surgery (n=2), partial removal of Bio-Alcamid (n=2), trauma (n=1) and oral ulcers (n=1). Of the 17 patients who had cultures sent for microbiological confirmation, 13 were positive (5 staphylococcus aureus including 1 MRSA; 3 viridans group streptococcus; 1 gram positive coccus; 1 gram positive anaerobic coccus; 1 propionibacterium acnes, 1 gram negative bacillus; and 1 enterobacter.

Medical management with antibiotics for an average 4 weeks (range 7 days to 19 months), with two patients remaining on chronic therapy. Surgical procedures including incision and drainage, aspiration or debridement were performed in 22 people and included 7 full and 15 partial removals of Bio-Alcamid. Approximately two-thirds of the infections (n=35; 68%) resolved and one-third relapsed (n=16, 31%).

The study limitations included that this was retrospective observational data and that the researchers only identified centers with large volumes – both potentially underestimating incidence. Also, data were extracted from surgical charts that often missed important variables and this limited clinical diagnosis in absence of microbiologic confirmation.

C O M M E N T

This study highlights the difficulty in recording the safety of treatments that are provided in private clinics, often for products for which there are little safety and efficacy data from clinical trials.

The private clinic in the UK that has treated several hundred men in the UK has since discontinued its use [7], as have clinics in Spain, Canada and Mexico. UK complications from private practice have usually been picked up and managed by NHS clinics with expertise on treating HIV-related lipoatrophy.

Because Bio-Alcamid removal becomes more difficult and traumatic the longer the implants have been in place, patients who received treatment need to be advised of the importance of minimising the risk of future complications. This includes avoiding non-sterile needle puncture from dental treatment or supplementary treatment for facial lipoatrophy, and reducing risk of facial trauma.

n the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) are assessing the safety of Bio-Alcamid. UK cases should be notified by heathcare professional or patients using the MHRA Yellow Card scheme (yellowcard.mhra.gov.uk).

An estimated 30 products (classed as medical devices rather than medicines) are being used in Europe but, unlike New-fill, few have been studied in controlled trials for HIV-related lipoatrophy.

Higher volume treatment using PMMA (polymethylacrylate) has been reported (including at the Lipodystrophy workshop [8]) in HIV-related lipoatrophy (including both facial and buttock restoration). [9]

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CONFERENCE REPORTS

First International Workshop on HIV and Ageing

4–5 October 2010, Baltimore

Introduction

The following reports from this first workshop on HIV and ageing are included thanks to natap.org.

- T-cell senescence linked to KS in people with good HIV c**ontrol**
- Higher risk of potential drug-drug interactions in HIV patients over 60
- **Age raises fracture risk more in HIV-people**

Conference abstracts can be viewed and downloaded as a PDF file from the workshop material link on the conference website.

http://www.virology-education.com/index.cfm/t/Workshop_Material/vid/A4CBF039-CC45-D34A-CB82F8E1F0D16BA3

Several of the presentations are also available online:

http://regist2.virology-education.com/1stAging/4_October.html

T-cell senescence linked to KS in people with good HIV control

Mark Mascolini, natap.org

HIV-positive people with Kaposi sarcoma (KS) despite tight control of HIV replication had higher levels of immunosenescent (immunologically feeble) CD4 and CD8 cells than HIV-positive people without KS, according to results of a comparative study at the University of California, San Francisco (UCSF). [1] People with KS also had lower levels of naive CD4 and CD8 cells.

Accelerated senescence of critical immune system cells, including CD4s and CD8s, has been documented in people with HIV infection, despite good response to antiretroviral therapy. Researchers postulate that ongoing immune cell activation and turnover account for this immune-cell exhaustion. Until this study, however, T-cell senescence had not been compared in HIV-infected people with versus without an AIDS malignancy, in this case KS.

Researchers at the University of California, San Francisco (UCSF) reported earlier on a group of HIV-infected men with KS despite high CD4 counts and low viral loads. [2]

When KS first emerged as an AIDS-defining condition, it appeared mostly in people with low CD4 counts. Because the men in this study were responding well to antiretroviral therapy, the UCSF team wondered whether KS may be a marker of immunosenescence in the current antiretroviral era.

To find out, the researchers compared immune-cell marker levels in 19 people with unremitting KS despite good control of HIV replication and 47 HIV-positive people without KS. The investigators considered T cells with CD57 receptors (CD57+) or without CD28 receptors (CD28-) as immunosenescent cells. They defined naive T cells as those bearing CD27, CD28, and CD45RA receptors (CD27+CD28+CD45RA+).

The 19 people with biopsy-proved KS were older than the no-KS group (median 54 versus 43 years, $p<0.001$). Compared with the no-KS group, people with KS had lower CD8 counts (median 933 versus 1200) but higher CD4 counts (median 701 versus 523), though these differences lacked statistical significance. Everyone in both groups had a CD4 count above 300 and a viral load below 75 for at least 24 months. The study excluded people taking interferon for hepatitis C virus, current malignancy (other than KS), or a history of immunomodulatory therapy. There were no women in either group.

People with KS had a significantly higher proportion of CD57+ CD8 cells (median 41.5% versus 27.7% in controls without KS, $p=0.005$ in an age-adjusted analysis). The researchers also saw a trend toward higher frequency of CD57+ CD4 cells in patients with KS (median 7.4% versus 3.7%, age-adjusted $p=0.07$).

KS patients had a higher proportion of CD28- CD4 cells than people without KS (median 9.1% versus 4.8%, age-adjusted $p=0.03$). And people with KS had a higher proportion of CD28- CD8 cells (median 60.5% versus 51.3%, age-adjusted $p=0.044$).

Naive (CD27+CD28+CD45RA+) CD8-cell proportions were lower in people with KS than in those without KS (median 11.3% versus 20.7%, age-adjusted $p=0.022$). And there was a trend toward lower frequency of naive CD4 cells in the KS group (median 23.0% versus 32.2%, age-adjusted $p=0.11$).

Telomere length did not differ between the people with versus without KS. (Telomeres are the end regions of human DNA that protect the chromosome from deterioration. Telomere shortening in humans can induce replicative senescence and block cell division.)

The UCSF team suggested that elevated populations of immunosenescent T cells and a shallow naive T-cell pool provide "strong evidence that immunosenescence is associated with presence of KS in these individuals, in spite of their undetectable viral loads and relatively high CD4 counts." What the study does not explain, workshop cochair Charles Flexner observed, is how much HIV versus KSHV (the herpesvirus that causes KS) may be driving immunosenescence.

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Higher risk of potential drug-drug interactions in HIV patients over 60

Mark Mascolini, for natap.org

HIV-positive people over 60 years old had HIV longer, used antiretrovirals longer, took more total drugs, and had a higher rate of potential drug-drug interactions than HIV patients 60 or younger seen at the same clinic.

Older people had a doubled rate of potential interactions between protease inhibitors (PIs) or nonnucleosides (NNRTIs) and cardiovascular drugs.

Because older people tend to have more illnesses requiring pharmacotherapy, they run a higher risk of drug-drug interactions resulting from polypharmacy. To analyse prescription and nonprescription drug use in older and younger people with HIV infection, researchers at the Toronto General Hospital Immunodeficiency Clinic retrospectively compared relevant HIV- and treatment-related data in 528 people under 60 years old and 38 people who were 60 or older. All study participants tested positive for HIV between 1 January 1996 and 31 December 2009.

Compared with younger patients, the 60-plus group were diagnosed with HIV in an earlier year (2001 versus 2003, p<0.01) and started antiretroviral therapy earlier (2002 versus 2004, p=0.04). The older people were more likely to be Caucasian (65% versus 47%, p=0.06), less likely to be black (19% versus 35%), less likely to be immigrants (13% versus 30%, p=0.02), and less likely to come from an HIV-endemic area (19% versus 35%, p=0.05).

A higher proportion of older study participants had a current viral load below 50 copies/mL (89% versus 74%, p=0.03), and a slightly higher proportion of older people were taking antiretrovirals (95% versus 87%). Current CD4 count did not differ substantially between the 60-and-older group and the under-60 contingent (median 496 versus 475 cells/mm3).

Older people had taken a higher median number of total drugs than younger people (7, interquartile range [IQR] 5 to 11, versus 4, IQR 3 to 7), a highly significant difference (p<0.0001). Among people taking antiretrovirals, similar proportions of older and younger people were currently taking nucleosides (97% versus 91%), NNRTIs (39% versus 41%), and PIs (61% versus 53%).

The 60-and-over group took certain types of drugs significantly more often than younger people: drugs for gastrointestinal problems (63% versus 38%, p<0.01), drugs for cardiovascular disease (55% versus 24%, p<0.0001), anticoagulants or antiplatelets (18% versus 7%, p=0.01), systemic hormonal agents (16% versus 5%, p=0.01), musculoskeletal agents (24% versus 9%, p<0.01), and narcotics or analgesics (39% versus 17%, p<0.001). Anticonvulsant therapy was more frequent in the older group (16% versus 7%, p=0.06), but older people took psychotropic agents at virtually the same rate as younger people (34% versus 30%).

Four potential drug interactions were significantly more frequent in older people:

- PI/NNRTI plus a cardiovascular drug: 42% versus 20%, p=0.003
- PI/NNRTI plus an anticonvulsant: 16% versus 5%, p=0.02
- PI plus a cardiovascular drug: 34% versus 13%, p=0.001
- PI plus warfarin: 8% versus 1%, p=0.01

Relatively high (and statistically similar) proportions of older and younger people were taking atazanavir with an acid-reducing agent (16% versus 10%, p=0.37).

The investigators noted that their study is limited by its cross-sectional nature, by their inability to determine whether prescribing physicians had modified doses, and by the lack of data on actual consequences of potentially harmful drug-drug interactions. Still, the findings offer a look at age-related polypharmacy in people with HIV and underline the greater risk of drug-drug interactions among older patients, who generally take more drugs than their younger HIV-infected counterparts.

Reference

Tseng A, Raboud J, Walmsley S, Sterling S, Salit I. Polypharmacy in older patients: a study of medication use and potential drug interactions in an aging ambulatory HIV clinic population. 1st International Workshop on HIV and Aging. 4-5 October 2010. Baltimore. Abstract O_08.

Age raises fracture risk more in HIV-positive people

Mark Mascolini

Age had a greater impact on fracture risk in people with HIV than in matched controls without HIV, according to a retrospective cohort study involving well over 200,000 individuals. [1]

Among 30-to-59-year-olds, HIV with or without AIDS independently raised the fracture risk.

The study involved 238,336 adults continuously enrolled in the Ingenix Impact National Benchmark Database for more than 12 months from January 1997 through March 2008. Researchers studied 59,584 HIV-infected people matched 3-to-1 with HIV-negative people according to gender, month and year of enrollment in the Ingenix cohort, and duration of cohort membership. They defined fracture as a low-impact nontraumatic fracture. AIDS criteria were a CD4 count <200 cells/mm3 or AIDS-defining conditions.

Nearly three quarters of HIV-positive cases and HIV-negative controls (71.5%) were men. Prevalence of several fracture risk factors were higher in the HIV-positive group: excess alcohol use (2.5% versus 1.3% in controls), low weight (7.9% versus 1.6%), lipodystrophy (3.4% versus 0.04%), hepatitis B virus (4.1% versus 0.2%), hepatitis C virus (6.5% versus 0.6%), and excess steroid use (5.5% versus 3.6%). But prior fracture rates were similar (2.0% among people with HIV and 1.9% in controls), as was use of proton pump inhibitors (14.5% versus 10.5%). A slightly larger proportion of controls took bisphosphonates (2.0% versus 1.3% of people with HIV). Only 51% in the HIV group were taking antiretrovirals.

Through 13,757 person-years of follow-up, 9027 people (3.8%) fractured a bone, including 4.2% with HIV and 3.7% without HIV. Fracture incidence was 14% higher in the HIV group (incidence rate ratio 1.14, 95% confidence interval [CI] 1.09 to 1.20).

A statistical model considering numerous fracture risk factors identified five independent predictors of fracture in the entire cohort (HR, 95%CI):

- Prior fracture: hazard ratio (HR) 4.49 (3.89 to 5.18)
- Excess alcohol: HR 1.90 (1.65 to 2.20)
- Low physical activity: HR 1.77 (1.73 to 1.82)
- Anti-osteoporosis bisphosphonate use: HR 1.49 (1.29 to 1.72)
- Low weight: HR 1.32 (1.18 to 1.48)

The researchers then identified independent fracture risk factors in three age groups:

People under 30

- Prior fracture: HR 7.77 (3.23 to 18.67)
- Excess alcohol: HR 2.24 (1.06 to 4.74)

People 30 to 59 years old

- Prior fracture: HR 3.81 (3.14 to 4.63)
- Low physical activity: HR 2.24 (1.90 to 2.65)
- Excess alcohol: HR 1.86 (1.55 to 2.23)
- Anti-osteoporosis bisphosphonate use: HR 1.36 (1.20 to 1.68)
- Low weight: HR 1.30 (1.12 to 1.50)
- HIV without AIDS: HR 1.18 (1.09 to 1.28)
- HIV with AIDS: HR 1.15 (1.06 to 1.26)
- Vitamin D deficiency or D or calcium supplementation: HR 0.72 (0.54 to 0.98)

People older than 59

- Prior fracture: HR 2.79 (1.68 to 4.64)
- Low physical activity: HR 2.65 (1.67 to 4.21)

The researchers could not explain why vitamin D deficiency or vitamin D or calcium supplementation was protective in their analysis.

Linear trend analysis showed that, compared with HIV-negative people, fracture risk rose significantly more with advancing age among HIV-infected people without AIDS (p=0.012) or with AIDS (p=0.001). The increased fracture trend with age in HIV-infected people was higher in those with AIDS than in those without AIDS.

The investigators noted that their analysis suffered from lack of data on bone mineral density, race, and over-the-counter drugs. Only 6% of people analysed reported smoking, so the researchers did not including smoking in the analysis.

An earlier comparison of 8,525 people with HIV and 2,208,792 people without HIV in a Boston healthcare system found significantly higher fracture prevalence in both men and women with HIV than in uninfected men and women. [2]

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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
abacavir 300 mg tablets	Hetero, India	29 September 2010
AZT/3TC 300/150mg tablets	Stides Arcolab, India	18 October 2010
Abacavir 60mg dispersible paediatric tablets	Matrix, India	29 November 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

Shortfall in funding for the Global Fund

Global Fund press release

At the donors meeting in New York in October, it was announced that donors had made a US $11.7 billion commitment to the Global Fund to fight AIDS, Tuberculosis and Malaria for the years 2011-2013.

Although these contributions will form the largest ever financial pledge to date, earlier this year the Global Fund provided three scenarios possible according to the size of the donor commitment.

1. US $13 billion would support the continuation of existing programmes. Newer programmes could only be funded at a significantly lower level than last year.
2. US $17 billion would support existing programmes. It would also allow for funding of new proposals at a similar level to those of recent years.
3. US $20 billion would support and scale up existing programmes, fund new proposals. This scenario would allow for more rapid progress towards the health related Millennium Development Goals (MDG).

So the sum pledged so far has fallen short of the lowest financial scenario. "I deeply appreciate the efforts of all the public and private donors who with this replenishment have shown their continued confidence in the Global Fund," said Michel Kazatchkine, the Executive Director of the Global Fund. "However, we need to recognise that this amount is not enough to meet expected demand. It will lead to difficult decisions in the next three years that could slow down the effort to beat the three diseases. I will continue a relentless effort to seek the additional resources the Global Fund needs to fully contribute towards achieving the MDGs."

Source:

http://www.theglobalfund.org/en/pressreleases/?pr=pr_101005c

Europe! HANDS OFF OUR MEDICINE

MSF press release

Millions of people in developing countries rely on affordable generic medicines produced in countries like India to stay alive. But the European Commission is pushing aggressive policies that will severely restrict people's access to these life-saving medicines. The attack is taking a number of different forms – free trade agreements, international treaties, customs regulations. If Europe succeeds, millions of people across the developing world could see their source of affordable medicines dry up, as generic companies will no longer have the space to produce or sell them. Send letters now and demand Europe gets its HANDS OFF OUR MEDICINE.

How can you help?

Act now and send letters to European officials demanding that they get their HANDS OFF OUR MEDICINE and stop pursuing policies that will restrict millions of patients getting life-saving treatment.

Watch videos from patients and doctors around the world telling Europe "HANDS OFF" and share them with your friends, familiy, and network.

Source: MSF HANDS OFF OUR MEDICINE Campaign

http://www.msfaccess.org/main/access-patents/hands-off-our-medicine-campaign/

DNP+ president uses 5ml of blood to meet Carla Bruni-Sarkozy

DNP+ press release

Indian activist, Vikas Ahuja, President of the Dehli Network of Positive People (DNP+) took a bold step to get the message across about the consequences that the Indian-EU free trade agreements would have on the production of generic antiretrovirals. Armed with letters from his organisation to the Prime Minister of India, a HANDS OFF OUR MEDICINE postcard and wearing an HIV POSITIVE T-shirt, he set of to the ART clinic where Carla Bruni was expected to visit as UNAIDS ambassador for PMTCT.

Confronted by tough security and asked to leave, he instead headed for the nearby HIV testing centre and registered. Although he had known he was positive for 17 years, this way he was nearby when she came to talk to hospital staff. "Ms Carla Bruni, I am a person living with HIV and working for the Dehli Network of Positive People, I would be obliged if you could please give me two minutes of your valuable time." He said. "Yes sure" she replied. So he wasted no time in handing here the letters and explaining that the agreement was, "trading away our lives." She gave him her assurance that she would personally go through the documents and get back to him on the matter. "On the way back to the DNP+ office, smiling to myself, I thought, hopefully giving my precious 5ml blood was not a waste in the end." He said.

Sources
Delhi Network of Positive People (DNP+)
http://www.dnpplus.org/
DNP+ Reaction Statement to Indian Trade Minister

http://www.msfaccess.org/main/access-patents/free-trade-agreements/india/dnp-reaction-statement-to-indian-trade-minister

Medicines Patent Pool: first research funder announced

TAG press release

Earlier this year, in July, UNITAID formed an intellectual property–sharing scheme for antiretroviral drugs. This project is targeted to scaling up access to antiretrovirals drugs in the developing world.

Called the Medicines Patent Pool it aims to simplify licensing processes, and encourage the development of fixed drug combinations and paediatric formulations.

In September, the US National Institutes of Health (NIH) announced that it would be the first research funder to contribute to the scheme.

Treatment Action Group's executive director, Mark Harrington welcomed this step. "By becoming the first research funder to license medical patents to the Medicines Patent Pool, the NIH has taken a historical step towards helping facilitate equitable global access to medical innovations made with taxpayer funds to fight diseases of global concern such as HIV, tuberculosis and malaria."

Sources and further information:

TAG press release: Treatment Action Group statement on first anti-HIV drug license to Medicines Patent Pool from U.S. National Institute of Health (NIH). (September 2010).

http://www.treatmentactiongroup.org/press.aspx?id=4204

Asher Mullard interviews Ellen 't Hoen, Medicines Patent Pool's executive director in Nature Medicine.

Mullard A. Straight talk with...Ellen 't Hoen. Nature Medicine 16, 1351 (2010) doi:10.1038/nm1210-1351. Published online 6 December 2010.

ANTIRETROVIRALS

Once-daily raltegravir fails to demonstrate non-inferiority compared to twice-daily dosing in phase 3 treatment naïve study

MSD Press Release

Merck (known as MSD in the UK) has reported initial results from the Phase III study investigating the safety and efficacy of an investigational 800 mg once daily dose of raltegravir (Isentress) tablets compared to the currently approved 400 mg twice-daily dose, each given in combination with a once-daily fixed-dose combination of emtricitabine and tenofovir (Truvada), in adult treatment-naïve HIV-1-infected patients. Raltegravir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced adults.

In the study, although the treatment regimen that included raltegravir once daily enabled more than 80 percent of patients to achieve viral suppression, raltegravir 800 mg once daily did not demonstrate non-inferiority to the treatment regimen that included raltegravir 400 mg twice daily.

Within this study, 775 patients were randomised, of which 770 patients received the study drug and are included in the current analyses. After 48 weeks in the study, 83.2% (n=318/382) of patients receiving the regimen including raltegravir 800 mg once-daily achieved undetectable viral levels (HIV-1 RNA <50 copies/mL), compared to 88.9% (n=343/386) of patients receiving the twice-daily regimen. The treatment difference between the 800 mg once daily group and 400 mg twice-daily group was -5.7%, with an associated 95% confidence interval (CI) of (-10.7%, -0.83%). The difference did not meet the pre-defined statistical criteria for non-inferiority.

The overall treatment difference observed between the once-daily and twice-daily groups was primarily due to results in patients with high viral load. Among patients with more than 100,000 copies/mL of HIV-RNA, 74.3 percent (n=113/152) of those in the once-daily group achieved viral suppression compared to 84.2 percent (n=128/152) of those in the twice-daily group. The safety and tolerability profiles of the two regimens were similar in the study, and were consistent with current prescribing information for raltegravir.

Based on these initial results, and following the recommendation of an independent Data Monitoring Committee, MSD will end the study. MSD is notifying clinical investigators of this decision this week and is recommending that patients should be transitioned to approved, marketed antiretroviral therapy (ART) as per local HIV-1 treatment guidelines. If raltegravir treatment is to be continued, the approved dose of 400 mg twice daily should be prescribed.

Results from this study will be submitted for presentation at an appropriate scientific meeting in 2011.

C O M M E N T

There are insufficient data included in this press release to be able to comment much on these results, which are likely to be presented at CROI in two months.

While the results are disappointing, they may not rule out a role for once-daily dosing as a switch option (perhaps supported by drug level monitoring) in adherent patients who started treatment with a low baseline viral load and who are already suppressed on twice-daily raltegravir-based or other HAART combinations.

Although the pre-defined lower limit of the 95%CI (likely to be -10%) was lower than some similar studies (-12% is often used) these top-line results clearly do not support once-daily raltegravir as an option for treatment-naïve patients with baseline viral load >100,000 copies/mL.

The development of integrase resistance is a significant loss to future treatment options, so that when a once-daily regimen is important, using drugs with a proven once-daily efficacy should be preferred.

Source: MSD Press Release: MSD reports initial results of Phase III study of Isentress (raltegravir) investigational once-daily dosing in treatment-naïve adult patients infected with HIV-1. (29 November 2010).

http://www.merck.com/newsroom/news-release-archive/prescription-medicine-news/2010_1129.html

FDA safety updates to antiretroviral labels

The following summaries cover revisions to the US drug labels that were recently approved by the US Food and Drug Administration (FDA). Please check the full update for details.

Revised labels are posted to the FDA website:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory

Update to US saquinavir label

On 23 October the FDA approved label changes for the antiviral drug saquinavir (Invirase), describing a potential change in the electrical activity of the heart when saquinavir is used in combination with ritonavir. Changes in the electrical activity of the heart may lead to abnormal heart rhythms.

The Dear Doctor letter for this change was included in the September/October issue of HTB.

Links

Revised saquinavir label
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020628s033,021785s010lbl.pdf

Roche issue Dear Doctor letter: Saquinavir prolongation of QT interval. HIV Treatment Bulletin, September/October 2010.
http://i-base.info/htb/13984

PREVENTION

Pre-exposure prophylaxis with tenofovir/FTC reduces sexual transmission of HIV between men at high risk: results from the iPrEX study

Simon Collins, HIV i-Base

The published results and the supportive supplementary appendix from a large international study (conducted in Peru, Equador, Brazil, US, Thailand and South Africa) provide the first human evidence that daily tenofovir/FTC (Truvada) can reduce the risk of HIV sexual transmission in men who have sex with men (MSM) at a high risk of HIV exposure. [1, 2]

The results should challenge approaches to HIV prevention and they have the potential to drive improved access to tenofovir as an ARV treatment.

The iPrEX study results, together with the full protocol and supplementary information was published online in the New England Journal of Medicine, and are all available without subscription. The top-level results - reducing infection by 44% with minimal safety side effects were widely publicised but the adherence and drug level analyses suggest a far higher potential for protection.

The study randomised just under 2500 men (including 29 transgender women (male-to-female, <1%) to either daily tenofovir/FTC or placebo. As with other prevention studies, iPrEX included intensive risk-reduction counselling, free condoms (monthly), behaviour interview (quarterly) and sexual health monitoring (at least 6-monthly).

Importantly, participants were at high risk of infection due to their behaviour risk. Ten percent of the approximately 5000 people initially screened for the study were already HIV-positive and a further 10 became infected between screening and enrolment.

Participants were young (~50% aged 18-24; 20% 25-29 and 20% 30-39 years); sexually active in the previous 12 weeks (18 partners; SD $\pm$35); at high risk (~80% having had unprotected anal intercourse (UAI) in the previous 6 months with a partner of unknown HIV status); high STI incidence (13% syphilis, 35% HSV-2 at baseline). Over 40% participants had transactional sex in the previous 6 months, alcohol use was common and high (>4 drinks per drinking day in >50% participants) and HIV awareness/ disclosure was low (only 2% had knowingly have sex with an HIV-positive person in the previous 6 months). Baseline characteristics were similar between the two arms.

The primary endpoint of at least 85 HIV infections was therefore reached quickly - after a median of 1.2 years (maximum 2.8 years), and total of 3324 patient years of follow-up (PYFU). This was despite a self-reported reduction in risk behaviour (a 50% reduction in the number of partners for receptive intercourse and increasing condom use for receptive intercourse from 50% to 75% of partners) - both potentially the result of a greater focus on HIV risk form the counselling and/or awareness of risk from using a daily prophylaxis.

New infections were reported in 100 participants (36 vs 64 in the active vs placebo group) and demonstrated a crude 44% protection rate (95%CI: 15 to 63; p=0.005) for the active group. Protection was higher in people who reported highest risk sex (recent UAI); 58% protection, 95% CI, 32 to 74). There was no significant between-group difference in protection by geographical region, race or ethnic group, circumcision, level of education, alcohol use, or age.

The analysis of adherence (>95% by self report and 90-95% by pill count; both from week 8 onwards, and slightly lower during the first 8 week) reported higher protection with greater adherence. In a post hoc analyses, pill use on 90% or more of days was recorded at 49% of visits on which efficacy was 73% (95% CI, 41 to 88; p<0.001)

However, results from a small pharmacokinetic sub-study looking at drug levels (both in plasma and intracellular) suggested actual adherence rates could have been dramatically lower. Although the drug level results should be interpreted with caution due to their low number, the associations with infections and suboptimal or undetectable levels were compelling.

Drug levels (testing was sensitive to tenofovir and FTC taken within 14 days, though tested a median of 35 days (IQR 28–56) post-infection) were only detected in plasma or cells in 3/34 (9%) newly infected people in the active arm. Of the 3 people with detectable levels, none had cell-associated drug levels higher than median levels in 22 HIV-negative controls. Conversely, 91% of infections in this sub-group appeared not to be taking tenofovir/FTC on a fortnightly–let alone daily–basis). Rates in an active-arm matched control group of 43 people who were not infected, detected drug levels in approximately 50% of people. Only 8% of this HIV-positive group who were considered high adherence (>50% pills) by self-report were considered on treatment by drug level (compared to 54% of HIV-negative controls).

The odds of HIV infection in people in the active arm with detectable drug levels were 12.9-fold lower (95%CI;1.7 to 99.3; p<0.001), corresponding to a relative reduction in HIV risk of 92% (95% CI, 40 to 99; p<0.001). After adjustment for reported unprotected receptive anal intercourse, the relative risk reduction was 95% (95% CI, 70 to 99; p<0.001).

There was a reassuringly high concordance (>95%) between both plasma and their respective intracellular active moieties and between each drug (both drug were similarly detected in each compartment).

Side effects and tolerability

Although side effects were frequently reported, these were similar between active and placebo groups (70% each, p=0.50) and a similar incidence of serious adverse events (5% each group, p=0.57; NS). Moderate nausea (Grade 2 or higher) was reported more frequently in the active group during the first four weeks (p=0.04)). Unexplained weight loss (>5% weight) occurred more frequently in the active arm (34 vs 19 events, p=0.04).

Creatinine levels were raised (1.1 x ULN or 1.5 x baseline) for 26 measurements in the active arm vs 15 times in the placebo group (2% vs 1% respectively, p=0.08), with 44% remaining in the normal range and 88% of elevated levels not confirmed on the subsequent test. Seven people in the active arm and three in the placebo arm discontinued due to elevated creatinine.

Resistance

While correlation between protection and active drug levels suggests that pre- and post-exposure dosing may be more critical than daily dosing, the risk of resistance in people who become infected is more complicated. Although resistance was not detected in any of the 34 people in the active arm who became infected - potentially exposed to intermittent or continuous dual-therapy - the lack of difference between viral load in infected people in the active and placebo arms (5.15 vs 5.10 log copies/mL in the tenofovir/FTC and placebo groups respectively, p=0.72) suggests low or non-adherence.

However, in 2/10 people in the active arm who were subsequently found to be HIV-positive at baseline, were found to have M184 mutations that could have potentially developed during early exposure to dual tenofovir/FTC therapy. While this could also be explained by infection with drug-resistant HIV (a third person had broad NNRTI and RTI resistance). Further studies, supported by modelling, would help determine whether a higher risk of resistance would be likely to come from daily PrEP (exposure to dual therapy during seroconversion) or intermittent PrEP (exposure to suboptimal drug levels between drug use).

C O M M E N T

These results are overwhelmingly supportive for a potent new prevention option to reduce the risk of sexual acquisition of HIV in gay men. On an individual risk with good drug levels (PK supports this being taken 24 hours before and within 2 hours after exposure) the reduction in single exposure risk may be as significant as that conferred by an undetectable viral load (<50 copies/mL) in reducing infectiousness of an HIV-positive partner (each >90% reductions). Nevertheless, results from ongoing studies of intermittent PrEP will inform this assumption.

These data do not address the practicality of daily PrEP as a population intervention to reduce infection but they do strongly inform individual protection in the context of high adherence prior to and after exposure risk.

Concerns about the practicality of PrEP as a population-based intervention were quickly raised to challenge the optimism of these positive results: and the efficacy levels in iPrEX clearly don't support policy changes. Three of these concerns focus on i) 44% efficacy being too low to support population-based widespread use, ii) the ethics of using a lifesaving treatment that is currently accessed by less than 20% of people on treatment in resource-limited settings and iii) implementation. distribution and access.

The first issue may change significantly given positive impact that use of PrEP has now shown, especially if PrEP is combined with other risk reduction options. The second may determine that PrEP will initially be an option used more in Western countries - as with condoms, or antiretroviral treatment. If PrEP safely reduces he risk of sexual transmission then it should be an option that people can

chose, whether through private or public health care - as with condoms. If PrEP really works (with careful adherence) the global demand should theoretically drive greater demand, lower prices and more rapid access within ARV treatment programmes.

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Further information

iPrEx Study press release and fact sheets:

http://www.iprexnews.com

iPrEx study materials NIAID: Press Release:

http://www.niaid.nih.gov/news/newsreleases/2010/Pages/iPrEx.aspx

Q&A:

http://www.niaid.nih.gov/news/QA/Pages/iPrExQA.aspx

SIDE EFFECTS

FDA approves tesamorelin for reduction of central fat accumulation

Simon Collins, HIV i-Base

On November 10, 2010, the Food and Drug Administration approved tesamorelin (Egrifta) to treat HIV patients with lipodystrophy, a condition in which excess fat develops in different areas of the body, most notably around the liver, stomach, and other abdominal organs (visceral body fat). Tesamorelin was approved to induce and maintain a reduction of excess visceral abdominal fat in HIV-infected patients with lipodystrophy.

Tesamorelin is the first FDA-approved treatment for lipodystrophy, and is a synthetic growth hormone releasing factor (GRF) that is administered in a once-daily injection.

Excess visceral fat accumulation may contribute to other health problems as well as reducing quality of life. The short-term results from the tesamorelin studies did not address the risk of cardiovascular disease.

Tesamorelin was evaluated in two clinical trials involving 816 HIV-positive adult men and women with lipodystrophy and excess abdominal fat. Of these, 543 patients received tesamorelin during a 26-week, placebo-controlled period. In both studies, patients treated with tesamorelin experienced greater reductions in abdominal fat (15–17%) measured by CT scan, compared with patients receiving placebo injections.

The most commonly reported side effects in the studies included joint pain (arthralgia), skin redness and rash at the injection site (erythema and pruritis), stomach pain, swelling, and muscle pain (myalgia). Worsening blood sugar control occurred more often in patients treated with tesamorelin than with placebo.

Tesamorelin was developed by a Theratechnologies Inc and marketed in the US by EMD Serono.

C O M M E N T

Although tesamorelin is now approved in the US, is has not been submitted to the European Medicine Agency (EMA).

The regulatory study design mandated that all patients discontinued treatment at the end of the 52-week study, with most patients using tesamorelin for only 26 weeks (either in the first or second half of the cross-over study). Patients who switched to the placebo injections in the second half of the study generally saw visceral fat return within a few months.

The decision to discontinue treatment, rather than switching to study exploratory maintenance doses, means that the FDA have approved a treatment that needs to be continued, but which only has 52-week safety data.

However, approval is conditional on further safety studies to be completed by 2015 that will assess longer-term efficacy and safety data.

Finally, as we went to press, a price for tesamorelin had not been set. With marketing by Serono (who also market recombinant Human Growth Hormone) it may not be an easily affordable option for most people.

Therapeutics have still not committed to providing compassionate access to tesamorelin for European patients who participated in these approval studies and who have seen optimistic results from treatment reverse back to baseline levels.

Source: FDA list serve

Product labeling for tesamorelin will be made available soon on:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
http://www.emdserono.com/en/index.html

PAEDIATRIC CARE

Initiating nevirapine with fixed dose combination "mini-pills" in Zambia

Polly Clayden, HIV i-Base

The shortage of appropriate paediatric antiretroviral formulations has been a major barrier to scale up of treatment of children in resource-limited settings. The initiation of nevirapine is complicated by the recommendation to escalate the dose, requiring a regimen change two weeks after starting treatment.

The Children with HIV in Africa – Pharmacokinetics and Adherence of Simplified Antiretroviral Regimens (CHAPAS) Trials, are investigating new antiretroviral formulations and strategies for children. This is a joint project of the University of Zambia and University Teaching Hospital Zambia, the Medical Research Council (UK), Radboud University Nijmegen, Netherlands and the University of Padova, Italy, began in 2005. [1] We have followed this project in HTB for some time.

CHAPAS-1 looked at treatment with Triomune Baby/Junior - fixed dose combination (FDC) scored, dispersible "mini pills" of stavudine (d4T), lamivudine (3TC) and nevirapine in the correct ratios for children, manufactured for the trial by Cipla. The doses of the tablets are: 6 and 12 mg d4T, 30 and 60 mg 3TC and 50 and 100 mg nevirapine in Triomune Baby and Junior respectively. Data from this trial contributed to the tentative approval by the FDA for these formulations, and to the WHO dosing recommendations by weight band for fixed dose combinations of these drugs, down to 3kg.

Nevirapine toxicity has been reported to be uncommon in children receiving full dose nevirapine at initiation, but there have been no randomised trials to evaluated the safety of this strategy. CHAPAS-1 compared the initiation of antiretroviral therapy (ART) with full dose nevirapine versus half dose nevirapine for the first two weeks of treatment.

An article, authored by Veronica Mulenga and colleagues and published in the November 1, 2010 issue of Clinical Infectious Diseases, showed findings from this trial.

Children aged 3 months to 14 years, indicated for treatment in accordance with WHO 2006 guidelines, were randomised 1:1 to receive either Triomune Baby or Junior twice daily for the first two weeks (full dose group, or Triomune Baby/Junior once daily plus once daily Lamivir-S, Baby or Junior - dual 3TC and d4T combination tablets (dose escalation group).

The primary end point was grade 3 or 4 adverse events (AEs) related to nevirapine.

A total of 211 children were randomised and included in the intent to treat analysis. Children in the two groups were similar. The median age at ART initiation was 5 years (IQR 2-9 years) and 35% were less than 3 years. The median CD4 percentage was 13% and 99% of children had WHO stage 3 or 4 disease. Severe wasting and/or stunting were common.

All children were seen by a nurse at 2 and 4 weeks from initiation and subsequently every 4 weeks. Children were weighed and measured, any adverse events or new WHO events were recorded and additional ART prescribed. They were also routinely seen by a doctor at weeks 2, 4, 8 and 12 and then every 12 weeks where they had a clinical examination and blood samples were obtained.

There were 60 (31 the full dose and 29 in the escalated groups), grade 3 or 4 AEs reported in 49 children (25 in the full dose and 24 in the dose escalated) that were considered definitely or probably related to nevirapine (n=8), or there was uncertainty as to their relation to nevirapine (n=52). This gave 18 vs 16.5 events per 100 child years in the full dose and dose escalated groups respectively; incidence rate ratio [IRR] 1.09 (95% CI 0.63-1.87), p=0.74.

All AEs were asymptomatic and the children continued treatment with nevirapine. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were the most common; 11 events in the full dose and 3 in the dose elevated groups), and elevated bilirubin levels (n=34).

There was no grade 3 or 4 rash, but 13 and 2 children had grade 1 (2 in the full dose group) or grade 2 (11 in the full dose and 2 in the dose elevated groups) rashes, p=0.003. One child in the full dose group developed a second grade 2 rash after reintroducing nevirapine at half dose. Rashes started at a median of 17 days (range 8-25 days) after initiation and lasted for a median of 9 days 9range 2-24 days).

Of the 15 children who developed rashes, 3 continued full dose nevirapine; 9 (8 full and 1 elevated dose) stopped nevirapine temporarily and then successfully dose escalated; 1 in whom the rash returned after changing from full dose to half dose, substituted efavirenz and 2 (1 full and 1 dose escalated) substituted efavirenz without retrying half dose nevirapine. All but 2 children in the full dose group were managed as outpatients.

In multivariate analysis, older age (per year increase), OR 1.35(95% CI, 1.10-1.64) p=0.003, and higher CD4 count for age (per unit increase), OR 1.51 (1.03-2.20) p=0.03 were associated with nevirapine rash. More rash occurred in the full dose group versus dose escalated, OR 9.79 (1.97-48.6), p=0.005.

Twenty-two children (10%) died (12 in the full dose and 10 in the dose escalated groups). More than half the deaths occurred within the first 3 months of ART, and were most frequently due to diarrheoa and pneumonia. Most children who died had advanced HIV disease and very low weight-for-age z-scores. No deaths were judged to be drug-related.

Children in both groups had similar increases in weight for age and height for age z-scores and CD4 counts or percentages (+17.3%) at 96 weeks.

The investigators concluded that rash occurred more frequently among children starting nevirapine at full dose but 88% had no clinical toxicity. Where possible they recommend using dual d4T/3TC paediatric tablets for dose escalation

If children are initiated on full dose Triomune, caregivers need to be aware of the timing of rash. For those in whom this occurs the options are to treat through under careful observation or to manage temporarily with half dose Triomune or efavirenz.

They noted that the elevated AST or ALT values were unconfirmed, transient and resolved spontaneously. They suggested that their results concur with that of the DART trial, which showed no difference in AEs requiring regimen modifications among adults receiving routine versus clinical biochemistry monitoring, including those receiving nevirapine. The results from both DART and CHAPAS-1 suggest that routine liver function tests are not necessary after nevirapine initiation in resource-limited settings.

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BHIVA NEWS

HIV: an agenda for action

NAT recently launched a new publication, HIV: An Agenda for Action, setting out both key aims to address HIV effectively in the UK, and also the practical action to be taken to achieve those aims.

http://www.nat.org.uk/Our-thinking/Parliamentary-activity/HIV-Agenda-for-action.aspx.

The aims set out in the *Agenda for Action* are:

- To ensure that there is a national strategic approach across the UK to tackling HIV
- To reduce rates of HIV transmission through effective prevention
- To significantly reduce the number of people with HIV who are diagnosed late
- To address the current failings in treatment, care and support for people living with HIV
- To make rights, equality and respect a reality for people with HIV in the UK
- To deliver effective commissioning of HIV that addresses local need.

BHIVA has worked with NAT on a number of issues in the past and we would very much appreciate your support as an organisation in taking this agenda forward. We also feel it is important to have the support of clinicians as individuals to ask them to pledge their support to the *Agenda for Action*. It is through widespread support we will gather the momentum to make these aims a reality.

Please email to sign up.

action@nat.org.uk

BASIC SCIENCE

Berlin man remains free of detectable HIV 3.5 years after CCR5-negative stem cell transplant

Richard Jefferys, TAG

At the 2008 Conference on Retroviruses & Opportunistic Infections, a piece of paper pinned to a poster board conveyed some surprising information: an HIV-infected man who had received two stem cell transplants for acute myelogenous leukemia (and the dauntingly toxic ablation regimens that go with them) had remained off antiretroviral therapy for nearly ten months since, without any evidence of the virus coming back. [1]

The finding did not rest entirely on serendipity; his doctors had intelligently sought out a stem cell donor homozygous for the CCR5 delta 32 mutation, which prevents expression of the HIV co-receptor CCR5 on the surface of cells. Most people, including me, wandered past the poster oblivious to its potential import. But Marty Delaney, the much-missed leader of Project Inform who passed away in January 2009, was more alert. He wrote an article for the PI website describing the case, which was posted February 12, 2008. It concluded: *"This is another one of the kind of "one step at a time" approaches that we hope will one day lead to an outright cure of HIV infection, a state in which people who were once actively infected can remain "HIV undetectable" without any ongoing use of therapy. We urge other researchers to replicate or build upon this impressive case study, and we salute the patient and his doctors for taking this bold approach to treating HIV disease.*" [2]

Many months later, in November 2008, the story finally broke in the mainstream media when Mark Schoofs authored an article for the Wall Street Journal entitled "A Doctor, a Mutation and a Potential Cure for AIDS;" many other outlets followed his lead. [3] The article was prompted by a September 2008 scientific workshop on the case, sponsored by amfAR, at which the man's doctor—a cheerful German hematologist named Gero Hütter—spoke. A detailed case report followed in the 12 February 2009 issue of the New England Journal of Medicine. [4]

This month, in the first edition section of the journal Blood, the latest update on the individual in question appeared. [5]

Follow-up is now out to 3.5 years and HIV remains undetectable in blood and every tissue studied, including gut and brain. CD4 T cell counts have climbed back into the normal range (the highest they have been since the original HIV diagnosis). There are some immunological deficits reported: the numbers of naïve T cells and newly-produced T cells known as recent thymic emigrants remain lower than those of healthy individuals, but are at similar levels to those seen in stem cell transplant recipients without HIV infection. Of concern to the researchers was the fact that, before his transplant procedures, the individual showed evidence of the presence of HIV capable of entering cells via the CXCR4 receptor (X4-tropic HIV).

It was initially assumed that this virus would re-emerge at some point, but that has not occurred despite the documented presence of activated, CXCR4-expressing CD4 T cells in the gut (which would be expected to be prime targets). The paper closes with this sober statement: "From these results, it is reasonable to conclude that cure of HIV infection has been achieved in this patient."

As Marty Delaney had advocated, an expanding number of projects are aiming to build on this result. The National Institutes of Health will soon be funding a multi-researcher project named after him, the Martin Delaney Collaboratory: Towards an HIV-1 Cure. [6]

Several potentially far safer approaches to abrogating CCR5 expression via genetic modification are in—or will soon enter—human trials. In April of next year, the AIDS Policy Project, amfAR, Project Inform and TAG are sponsoring a workshop to specifically address issues related to advancing cure-related clinical research. What was once written small in a cavernous Boston conference hall now looms large, providing hope that a cure for HIV infection is possible.

The individual has now gone public in Stern magazine; his name is Timothy Ray Brown, a 44 year old US citizen. [7] A rough google translation of the article, which describes the series of difficult medical challenges he faced, including a bout of leukoencephalopathy that he is still recovering from. [8]

Given the media attention that is likely to follow, it's important to stress the not-so-good news: the extremely risky procedures that Timothy Ray Brown underwent to treat his cancer carry a very high risk of mortality, and they cannot be used to try and cure HIV in people without acute myelogenous leukemia (AML). Even for people with HIV who have AML and need a stem cell transplant, the likelihood of finding an appropriate (HLA-matched) donor with the CCR5 delta 32 mutation is extremely low due to its rarity.

C O M M E N T

We also reported this case from the CROI conference when it was first presented and this continued follow-up is impressive. Given how quickly HIV rebounds when treatment is discontinued, usually to detectable levels with a weeks and to pretreatment levels within a month or two, this person appears to be cured.

Source: Source: TAG basic science blog. (06 December 2010).
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Natural immunity to HIV infection

Richard Jefferys, TAG

The 1st November 2010 supplement to the Journal of Infectious Diseases features a suite of articles about individuals who remain HIV negative despite repeated exposure to the virus. [1]

The articles represent summaries of oral presentations given at the International Symposium on Natural Immunity to HIV that was held in Winnipeg, Manitoba, Canada, in November 2009.

The potential importance of studying highly exposed but seronegative individuals was emphasised by Gregg Gonsalves in a report on HIV basic science that TAG issued in 1993 [2]; seventeen years later, a concerted effort appears to be underway to better understand the phenomenon and glean lessons for designing biomedical prevention approaches (particularly vaccines).

There has already been a follow-up to the Winnipeg meeting: in July of this year, the National Institutes of Health sponsored a workshop in Rockville to further discuss the formation of an international research consortium (the workshop agenda is available online). [3]

Unfortunately the JID supplement is not open access, the content will become freely available after 12 months. However a report from the Winnipeg symposium that describes key presentations and outlines the consortium model was prepared by the International Center for Infectious Diseases and is posted to their website. [4]

Source: TAG basic science blog. (11 October 2010).

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Scant embers of infection can reignite viral replication

Richard Jefferys, TAG

Whittling down reservoirs of HIV-infected cells in the body is thought to be an important first step in the pursuit of a cure. Whether there might be a threshold HIV reservoir size below which the body could contain the virus without additional intervention has been unclear; there have been some reports of individuals who have interrupted antiretroviral therapy (ART) and controlled viral load to undetectable levels for extended periods, most recently from a group of French researchers who described five people (out of a

total of 32) maintaining levels below 50 copies/mL for a median of around 6 years of follow up. [1] However, the magnitude of the infectious HIV reservoir in these individuals prior to ART interruption was not reported.

In a study just published online in the journal AIDS, Tae-Wook Chun and colleagues describe the case of an individual treated early in the course of HIV infection who maintained viral suppression for over a decade on ART. [2]

Detailed evaluation of the size of the replication-competent HIV reservoir revealed an average of one infected CD4 T cell out of every 1.7 billion CD4 T cells, which the authors describe as "the lowest infectious HIV burden recorded to date in our laboratory." With the individual's consent, an exploratory interruption of ART was conducted. Viral load remained below 50 copies/mL for 50 days—longer than the previously described average of nine—but then rebounded to 1,593 copies/mL before falling back below the detection threshold again for around 70 more days. At day 143 after the interruption, viral load climbed to 8,684 copies/mL and at that point ART was restarted.

The researchers conclude that even a tiny number of infected cells can spark viral load rebound upon ART interruption. They go on to state: "In order to achieve a condition under which HIV does not rebound for extended periods of time in the absence of ART, novel therapeutic strategies aimed at more specifically targeting these extremely rare infected cells maybe necessary with or without the use of therapeutic vaccination to boost immune system control of viral rebound."

Source: TAG basic science blog. (21 October 2010).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2010/10/scant-embers-of-infection-can-reignite-viral-replication.html

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Evidence for sporadic low-level HIV replication on ART

Richard Jefferys, TAG

Una O'Doherty's research group at the University of Pennsylvania has pioneered the development of tests to measure HIV DNA that is integrated into the genome of cells.

The integration of HIV DNA presents a formidable obstacle to curing HIV infection, because it leads to the formation of a stable reservoir of infected cells that antiretroviral therapies cannot eradicate. HIV DNA can also exist in cells in an unintegrated form, but evidence indicates that this form degrades rapidly and does not persist.

In a new paper in the journal Virology, O'Doherty and colleagues describe analyses designed to assess levels of unintegrated vs. integrated HIV DNA in a small group of individuals on ART with viral loads less than 75 copies for at least a year. The researchers report that three out of seven study participants showed sporadic excesses of the unintegrated form of HIV DNA compared to integrated DNA.

They note that this result may indicate that a subset of individuals on ART experience sporadic low-level viral replication, which could contribute to the replenishment of their HIV reservoir. If confirmed, the findings will need to be taken into account by scientists working on approaches to curing HIV infection.

Source: TAG basic science blog. (15 November 2010).

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Plumbing HIV pathogenesis in the gut

Richard Jefferys, TAG

A trio of recent papers delve into the gut as an important site of HIV pathogenesis. Two are from the research group of Joseph Wong at UCSF, and they involve the same small cohort individuals analysed before (in the JID paper) and after (in the journal AIDS) they started a clinical trial involving intensification of their antiretroviral therapy. [1, 2]

The third paper, led by Shari Gordon from Guido Silvestri's laboratory, studies a larger group of 28 people with HIV (15 untreated and 13 on antiretroviral therapy) and 11 healthy controls. [3]

One unifying theme of the results is that not all gut sites are equal; both the levels of HIV infection and the proportions of CD4 vs. CD8 T cells vary when samples from the duodenum, terminal ileum, right colon and rectum are compared in Steven Yukl's JID paper. HIV DNA levels show a trend toward a stepwise increase as the sample sites descend, with lowest levels in the terminal ileum and highest in the rectum. Conversely, unspliced HIV RNA – a potential indicator of active viral replication - shows the opposite trend, with levels highest in the terminal ileum. Shari Gordon's study samples a slightly different array of gut sites – terminal ileum, right colon, left colon, and sigmoid colon – but also finds variation in representation of CD4 T cell subsets; naïve CD4 T cell levels are highest in the terminal ileum but decrease progressively as the sample sites get lower down the GI tract.

The Yukl paper also reports some major differences between blood and gut samples. HIV DNA levels are consistently higher in all gut sites compared to peripheral blood mononuclear cells (PBMC) and the differences are highly statistically significant with the exception of the duodenum. And while there is a positive correlation between HIV DNA levels and markers of immune activation in PBMC, there is an inverse correlation in the gut, a novel finding that the researchers suggest may be due to infected cells in the gut being tolerant or anergic (the gut is known to be a site where T cell tolerance against commensal bacteria and food antigens is induced and maintained).

Shari Gordon's study identifies several parallels between blood and gut. The levels of CD4 T cell depletion in blood correlated directly with the level of depletion measured in all gut sites. Levels of memory CD4 T cell proliferation (measured the Ki67 marker) were also directly correlate in both compartments. Gordon also finds that the magnitude of CD4 and CD8 T cell proliferation in the blood correlates with the severity of CD4 T cell depletion in the gut. This latter finding indicates that the loss of gut CD4 T cells impacts the normal balance (or "homeostasis") of the immune system in a way that contributes to systemic immune activation. Encouragingly, the study reveals substantial repopulation of gut CCR5-expressing CD4 T cells in the cohort of individuals on ART and notes that: "in our hands the extent of depletion of intestinal CD4+CCR5+ T cells appeared to be less severe than what has been reported by others during HIV infection."

The Steven Yukl paper in AIDS describes the impact of intensifying ART with either raltegravir alone or raltegravir plus efavirenz or darunavir for 12 weeks in seven of the eight individuals whose baseline values are reported in JID (one dropped out shortly after starting the trial for personal reasons). CD4 T cell counts and HIV DNA levels remained unchanged, but a significant drop in levels of unspliced HIV RNA was seen in the terminal ileum of 5/7 participants. There was also a slight decline in levels of activated CD4 and CD8 T cells in blood and gut, with the greatest change seen in the terminal ileum. The researchers conclude that the findings may be suggestive of some ongoing viral replication occurring in the terminal ileum that was impacted by ART intensification, but they stress that this interpretation needs to be confirmed by larger studies.

These papers add to the evidence that the gut plays an important role in the pathogenesis of HIV infection, but also highlight the need to better understand gut immunology in health as well as disease (an area of research that remains relatively obscure and under-supported). The suggestion that HIV may be establishing latency in tolerant CD4 T cells also has implications for cure research, because targeting this population may require different strategies than those being considered for other HIV reservoirs.

Source: TAG basic science blog. (17 November 2010).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2010/11/plumbing-hiv-pathogenesis-in-the-gut.html

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Genetic analyses reveal key mechanism of HIV control

Richard Jefferys, TAG

A new study published online in Science Express last week reports a breakthrough in understanding the association between particular immune response genes and the ability of some individuals to control HIV replication without treatment. [1]

The research was conducted through the International HIV Controllers Study, a huge collaborative effort initiated by Bruce Walker from the Ragon Institute of Massachusetts General Hospital in Boston. [2] The study collects samples from individuals who control viral load without treatment, either to less than 50 copies (elite controllers) or less than 2,000 copies (viremic controllers). A team led by Harvard geneticist Paul De Bakker conducted the analyses that led to the latest findings.

The findings relate to immunological alarms called class I HLA receptors, which display protein fragments (called peptides) from pathogens on the outside of infected cells in order to flag the cell for destruction by CD8 T cells (aka "killer" T cells). All cells in the human body except red blood cells are adorned with thousands of class I HLA receptors, and they are continually shuttling from the inside to the outside of the cell carrying peptides for passing CD8 T cells to inspect. Most of the time these peptides are from our own body's proteins--essentially cellular trash--and CD8 T cells allow the cell to go about its business. But if a class I HLA receptor emerges with peptide from a pathogen, CD8 T cells will typically respond by destroying it.

There are a wide variety of different genes that make (or in genetics language "encode") class I HLA receptors, all located in the MHC region of the human genome on chromosome six. The specific HLA genes an individual possesses are inherited from their parents. Different HLA genes make class I HLA receptors with slightly different structures, which determines the types of peptide structures the receptor can present, which in turn can influence the ability of CD8 T cells to recognize the presented peptide.

It has been known for more than a decade that certain HLA genes make receptors that seem particularly adept at presenting HIV peptides to CD8 T cells, and that possessing these HLA genes greatly increases the chances of becoming an elite controller. Conversely, some other HLA genes are associated with high HIV viral loads and rapid disease progression. However the detailed mechanisms underlying these associations had not been figured out.

The new study in Science drills down to specific structural features that are shared by class I HLA receptors encoded by the HLA genes associated with elite control. The paper includes a visual representation of a class I HLA receptor showing the locations of these features, which consist of different amino acids (the building blocks out of which proteins are made). The image is reproduced the receptor looks a little like a pair of jaws; the mouthpart is referred to as a "binding pocket" that peptides slot into.

The crux of the new finding is that the type of amino acid located at the numbered positions has a huge impact on the likelihood of an HIV-infected person controlling their viral load without treatment. Exactly why this is has yet to be fully explained, but some previous evidence that suggests these class I HLA receptors are able to present parts of HIV that cannot mutate without compromising the ability of the virus to replicate. There are also studies showing that the functionality of CD8 T cells can be influenced by the specific viral epitope they recognise; in other words, CD8 T cells that recognise viral epitopes presented by these class I HLA receptors may simply work better than others. Gaining a better understanding of exactly how these specific amino acids confer benefit is now a priority for the research team.

Another important aspect of the study is that it provides a unifying explanation for the associations between several different HLA genes and HIV control that have been reported previously. What the genes all have in common is that they encode class I HLA receptors with one or more of the structural features De Bakker and colleagues identified.

The publication of the paper last week garnered a great deal of well-deserved coverage in the mainstream media. However, as is always the case, some stories are more accurate than others. One aspect that may not have come through clearly is that while possessing these class I HLA receptor variants massively increases the chances of becoming an elite controller, it does not mean that it is certain; some individuals who have them do not control viral load, and conversely they are absent in some elite controllers. This is not really surprising, as CD8 T cells work in concert with other components of the immune system such as CD4 T cells, and these other immune responses can also impact how well HIV is controlled. Another recent paper by Hendrick Streeck from Bruce Walker's group–just published online in the Journal of Virology–provides an example by showing that HIV-specific CD4 T cells that produce IL-21 influence the function of HIV-specific CD8 T cell responses and are associated with lower viral loads.

What can be stated with certainty is that the International HIV Controllers Study is providing crucial insights into the mechanisms that underlie immune control of HIV. Close to four pages of the Science Express paper are taken up by the names of individuals and institutions that have referred people to the study, indicating the broad support for this research. Although they can't be named in the paper, the many altruistic study participants who donated samples must be saluted also.

Source: TAG basic science blog. (12 November 2010).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2010/11/genetic-analyses-reveal-key-mechanism-of-hiv-control.html

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   http://www.sciencemag.org/cgi/content/abstract/science.1195271
2. International HIV Controllers Study.
   http://www.hivcontrollers.org

ON THE WEB

Conference reports and online abstracts:

4th International Workshop on HIV Persistence during Therapy

8–11 December 2009

Every other year since 2003, researcher Alain Lafeuillade has chaired a workshop on HIV persistence during therapy. The goal of the meeting is to work toward strategies for curing HIV infection, either by eradicating the virus or inducing long-term control of viral replication in the absence of ongoing treatment. The fourth meeting was held in December of 2009, and abstracts and selected slide presentations are now available online

Final Program and Abstract Book
http://www.ihlpress.com/pdf files/AbstractBook_PW2009_111009.pdf

Selected Slide Presentations
http://www.ihlpress.com/gaj_persistence2009.html

Emerging Issues in clinical trials for new ARV development

Forum for Collaborative HIV Research (FCHR)

Details and presentations from the Forum's roundtable on 30 September 30, 2010.

OBJECTIVES:

- To discuss general developments with non-inferiority margins and adaptive design in clinical trials and regulatory experience.
- To provide perspectives on recent clinical trial experiences with investigational HIV agents.
- To propose new models to study investigational HIV agents in clinical trials and discuss possible solutions to commonly encountered issues in clinical trials.
- To discuss the need for trials in treatment naïve patients, dose-finding and identification of biomarkers for longer term safety evaluations.

http://hivforum.us1.list-manage.com/track/click?u=57bb4a7a73d2cce9128afb09b&id=259573778e&e=ffb9e298b4

Online journal access:

Feature in immunity: vaccine immunology

The new issue of the journal Immunity features a series of state-of-the-art reviews on the intersection of vaccine and human immunology research. All articles are free to access.

http://www.cell.com/immunity/current

Immunity Special feature: Vaccine Immunology

A perspective on vaccine and human immunology by Germain.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00357-2

Vaccine-focused reviews on:

- Memory T and B cells by Sallusto, Lanzavecchia, and Ahmed.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00368-7

- Dendritic cell subsets by Palucka, Banchereau, and Mellman.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00367-5

- Mucosal immunity by Chen and Cerutti.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00356-0

- Adjuvants by Coffman, Sher, and Seder.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00362-6

- Vectors by Liu.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00364-X

- Systems vaccinology by Pulendran, Li, and Nakaya.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00366-3

- Reverse vaccinology by Sette and Rappuoli.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00360-2

- HIV-AIDS by McElrath and Haynes.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00354-7

- Malaria by Good and Doolan.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00365-1

- Tuberculosis by Kaufmann.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00358-4

- Overview by D'Argenio and Wilson.

http://www.cell.com/immunity/fulltext/S1074-7613(10)00371-7

Source: TAG basic science blog. (28 October 2010).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2010/10/special-open-access-feature-in-immunity-vaccine-immunology.html

Community resources and publications:

Psychological support for people living with HIV

NAT report

http://www.nat.org.uk/Media%20library/Files/Policy/2010/Psychological%20support%20July%202010%20updated.pdf

One of the recommendations from the report is that standards for psychological support for people living with HIV should be developed. The British Psychological Society's Faculty of Sexual Health and HIV is taking the lead on this process, and BHIVA is one of the stakeholders on the working group.

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 & Women

10–11 January 2011, Washington DC

http://www.virology-education.com

18th Conference on Retroviruses and Opportunistic Infections (CROI)

27 February–3 March 2011, Boston

http://www.retroconference.org

9th European Workshop on Treatment Strategies & Antiviral Drug Resistance

23-25 March 2011, Paphos, Cyprus

http://www.virology-education.com

15th International Workshop on HIV Observational Databases

24–26 March 2011, Prague

http://www.hivcohorts.com

17th Annual BHIVA

6–8 April 2011, Brighton

http://www.bhiva.org

12th International Workshop on Clinical Pharmacology of HIV Therapy

13–15 April 2011, Miami, Florida

http://www.virology-education.com

6th International Workshop on HIV Transmission - Principles of Intervention

14–15 July, Rome, Italy

http://www.virology-education.com

3rd International Workshop on HIV Paediatrics

15–16 July, Rome, Italy

http://www.virology-education.com

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

17–20 July 2011, Rome

http://www.ias2011.org/

2nd International Workshop on HIV & Ageing

October 2011, Baltimore, USA

http://www.virology-education.com

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 for advocates

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

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.

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 370 members from over 110 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

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)
- HIV and your quality of life: a guide to side effects and other complications (December 2010)
- 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)

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 1400 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:

- What is the risk from this presciption error and taking half-dose 3TC?
- I am 54, will starting treatment protect my CD4 count?
- I am confused about my CD4 count and CD4%
- Does receiving oral sex (being sucked) possess zero risk for HIV?
- Why do the GUM clinics say to come back after 3 months if the 28 day test is negative?
- Does my partner need to use a condom if I am on efavirenz and want to become pregnant?
- I am an HIV-positive nurse. Which countries can I move to?

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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:

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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.

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

Editor: Simon Collins

Contributing Editor: Polly Clayden

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

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

HIV i-Base
4th Floor East
57 Great Suffolk Street
London
SE1 0BB
T: +44 (0) 20 7407 8488
F: +44 (0) 20 7407 8489

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Translations of earlier treatment guides into other languages are available as PDF files on our website

Phoneline support material *(pls specify required number of each)*

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

Adherence planners and side effect diary sheets - In pads of 50 sheets for adherence support

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

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