

HIV treatment bulletin

S O U T H

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htb south

HIV Treatment Bulletin South

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EDITORIAL

Welcome to the first issue of 2010. Which includes our first few reports from CROI and from several other conferences.

We welcome that the WHO guidelines now recommend treatment at 350 cells/mm³ and that they place a strong emphasis on using alternative nucleosides to d4T. That they place a high value on maternal health and they can now recommend breastfeeding with antiretroviral interventions are also good news.

Our next issue will include further reports from CROI including TB, maternal health and paediatrics.

Southern African HIV Clinician's Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinician's Society has grown to a membership of over 15 000 in the Sub Saharan region and internationally - a clear recognition of the services and support provided.

The Southern African HIV Clinician's Society is the largest special interest group within the South African Medical Association (SAMA). It is also the largest HIV interest group in the world.

The Society is thrilled to be part of the HIV Treatment Bulletin South initiative. This is a valuable publication for all Health Care Practitioners. This publication has essential, current and scientific information about research and HIV treatment updates with particular implications for clinical practice.

For more information about the Society or on how to become a member please visit:

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CONFERENCE REPORTS

17th Conference on Retroviruses and Opportunistic Infections (CROI)

16-19 February, 2010, San Francisco

Introduction

As we go to press we have just returned from the 17th annual CROI held in San Francisco. For the first time, poster discussions are included in the conference webcasts and with most of the posters now posted, this means the whole conference can now be accessed online at the following link:

<http://retroconference.org/2010>

We include a few reports in this issue and will continue our coverage in the June HTB South.

- No significant difference in virological failure found between once-yearly versus twice-yearly viral load monitoring in Thai study
- Model predicts rate of transmitted drug resistant virus in resource limited settings
- More concerning research on the Free State ART programme
- Vitamin D deficiencies in people with HIV

No significant difference in virological failure found between once-yearly versus twice-yearly viral load monitoring in Thai study

Nathan Geffen, TAC and Polly Clayden, HIV i-Base

A poster by Chalwarith and colleagues at CROI presented the results from a retrospective comparison of two Thai cohorts to determine if there were differences in virological failure and resistance mutation rates in once-yearly versus twice-yearly viral load monitoring. [1]

The study compared 424 patients who received a viral load test annually via the Universal Health Coverage Programme to 154 patients who received two viral loads a year via the Social Security Health Programme. All patients were on stable HAART at the Chiang Mai University Hospital. There were no significant differences in measured baseline characteristics. Men comprised 46% of the sample. The mean age was 40 years. Nearly 98% of patients were on two NRTIs plus an NNRTI. Median CD4 count was 60 cells/mm³ (IQR: 30-138 cells/mm³).

The investigators found no significant differences in incidence of virological failure (defined as viral load >1000 copies/mL) between the two cohorts. The rate in the twice-yearly group was 5.3% (8 patients; 3.08 per 100,000 person days) versus 8% (34 patients; 4.32/100,000 patient days) in the once-yearly group. The hazard ratio for the once-yearly group was 1.37 (95%CI: 0.63-2.95; p=0.428). Neither did sex, age or baseline CD4 count predict virological failure. However, adherence, measured as total doses taken over total prescribed, was predictive (HR: 0.01; 95%CI: 0.01-0.03; p<0.001).

Patterns of NRTI mutations also did not differ between the two groups. Table 1 shows the mutations that were detected in a subset of patients.

COMMENTS

The authors conclude that once-yearly viral load monitoring in resource-limited settings is justified. This is an observational comparison and there may be other differences between the cohorts that could easily confound the comparison. Also, numbers are small so the lack of difference could be due to a type II error. So the conclusion the authors draw may be too strong based on those data. However, following the findings of DART, this study may add to the argument that (as a number of experts suggest) once-yearly viral loads are a good compromise, where feasible, between the need for minimising patient risk and maximising the number of people on treatment.

Ideally large studies are needed before we can be comfortable that we know what the differences in outcome from different monitoring strategies are.

Ref: Chalwarith R et al. Frequency of plasma HIV RNA monitoring: Impact on outcome of antiretroviral therapy. 17th CROI. 16-19 February 2010. Poster abstract 500.

<http://www.retroconference.org/2010/Abstracts/37132.htm>

Table 1: Mutations in a group of patients in the two cohorts. From Chalwarith et al.

Mutations	Total (n=37) (%)	Once-yearly VL (%)	Twice-yearly VL (%)	p-value
M184V	33 (89.2)	27 (87.1)	6 (100)	0.351
≥3 TAMs	8 (21.6)	6 (19.4)	2 (33.3)	0.446
K65R	3 (8.1)	2 (6.5)	1 (16.7)	0.401
Q151M	2 (5.4)	2 (6.5)	0 (0)	0.522
T69 insertion	12 (32.4)	10 (32.3)	2 (33.3)	0.945
K103N	8 (21.6)	7 (22.6)	1 (16.7)	0.747
V106A	1 (2.7)	1 (3.2)	0 (0)	0.656
V108M//I/A	8 (21.6)	7 (22.6)	1 (16.7)	0.747
Y181C//I/V	21 (56.8)	16 (51.6)	5 (83.3)	0.151
Y188C/L/H	3 (8.1)	3 (9.7)	0 (0)	0.427
G190A/S	10 (27.0)	8 (25.8)	2 (33.3)	0.704

Model predicts rate of transmitted drug resistant virus in resource-limited settings

Polly Clayden, HIV i-Base

Making switching decisions based on clinical monitoring, as happens in many resource-limited settings, has led to concern about the potential widespread transmission of drug resistant virus in populations where antiretroviral options are limited.

A poster at CROI, authored by Andrew Phillips and colleagues showed results from a computer simulation model designed to predict transmission of drug resistance according to the monitoring strategy used as the basis for guiding switches to second line treatment.

The investigators modelled a scenario using a stochastic simulation model of a high prevalence heterosexual epidemic beginning in 1985 and introducing treatment in 2003 for people with WHO stage 4/ <200 cells/mm³ CD4. The first line regimen used in the model was d4T+3TC+NVP and second line AZT+ddI+LPV/r.

This was used to predict the proportion of new infections with transmitted drug resistant virus from 2010 to 2020 according to the timing of introduction of 6 monthly viral load monitoring (based on threshold of 500 copies/mL) to guide switching from first to second line.

In 2010, it was assumed that 20% people with HIV were diagnosed and 12% on ART (44% coverage). The authors made an optimistic assumption that the diagnosis rate would increase after 2010 and treatment started at CD4 <350 cells/mm³.

The model predicted that the levels of transmitted resistance from introducing viral load in 2010 or 2015 would be similar after 2015. The predicted proportion of newly infected people with transmitted drug resistance in 2020 was 5.4% if viral load monitoring were introduced in 2010, 6.1% if introduced in 2015, and 12.4% if clinical WHO Stage 4 monitoring were used throughout.

When a viral load threshold of 5000 copies/mL, instead of 500 copies/mL, for six monthly monitoring was used, the predicted proportion increased to 6.0% in 2020.

Using viral load monitoring only once every 3 years, with the first at year 1, predicted a value of 7.2%, while use of a single viral load measurement at 1 year (and no subsequent measures) a value of 8.5%.

Looking at the death rate in the HIV-positive population the values predicted were: 2.7 (2.4 for people on treatment) 2.8 (2.7) and 3.1 (3.3) per 100 person years, with use of viral load monitoring from 2010, 2015 and use of WHO 4 clinical monitoring throughout the period, respectively. (2.9 [2.7] per 100 person years with WHO 3 or 4 clinical monitoring).

But, if the assumed increase in diagnosis and coverage since 2010 did not take place, the death rate was predicted to be 4.7 per 100 person years, even with use of viral load.

The authors wrote: "There is a long term need for introduction of some form of cheap, practical, and sustainable viral load monitoring in resource limited settings which can be used in rural as well as urban settings. These tests do not need to be able to do more than distinguish those with viral load levels of above and below some low threshold such as 500 copies/mL."

They added, "Our results also indicate that even very infrequent (eg 3 yearly) testing, is likely to provide significant benefit in reducing resistance transmission".

Ref: Phillips A et al. Predicted effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first- to second-line antiretroviral regimens in resource-limited settings. 17th CROI. 16-19 February 2010. Poster abstract 596.

<http://www.retroconference.org/2010/Abstracts/38818.htm>

More concerning research on the Free State ART programme

Nathan Geffen, TAC

We have previously reported studies showing the high mortality on waiting lists in the Free State programme due to the long median time it took to initiate patients on HAART. Suzanne Ingle of Bristol University and colleagues have analysed this data further. Ingle presented it at CROI. [1]

The investigators analysed over 22,000 patients enrolled from May 2004 to December 2007 in the province's ART programme. At baseline, the median age was 36 years, 65% of patients were female, 14.5% had CD4 counts <25 cells/mm³, 12.2% had 25 to 50 cells/mm³, 23.1% had 50-100 cells/mm³ and 50% had 100 to 200 cells/mm³. The number of patients enrolled increased from almost 4,000 in 2004 to over 6,500 in 2007.

By 2 years, 28% of patients had died pre-treatment and 68% had started HAART. CD4 count was strongly associated with risk of death:

- For patients with CD4 counts below 25 cells/mm³, 46% had died pre-treatment and only 51% started HAART.
- For people with a CD4 count of 25-50 cells/mm³, 35% died and pre-HAART and 61% started HAART.
- For those with a CD4 count of 100 to 200/mm³, 17% died pre-HAART and 75% initiated HAART.

Patients with less than 25 cells/mm³ were 3.5 times as likely to die pre-treatment as patients with CD4 counts from 100 to 200 cells/mm³ (95%CI: 3.26-3.78).

Men were 1.3 times more likely to die pre-treatment than woman (95%CI:1.22-1.36). There was also evidence that age was associated with mortality pre-treatment: people older than 50 were 1.17 times more likely to die than 30 to 39 year olds (95%CI: 1.06-1.29). The probability of initiating HAART improved from 2004 to 2007 (HR: 1.56: 1.5-1.63).

Nearly 3,000 patients had CD4 counts >200 cells/mm³ and were not eligible for treatment on the basis of CD4 count (it is unclear how many of them were clinically indicated for treatment, see comments) at baseline. They had a median CD4 count of 260 cells/mm³ (IQR: 227-318). The median time to their next CD4 measurement was 183 days and the median CD4 decline was 113 (IQR: 70-183). Yet the median CD4 count at eligibility for treatment for these patients was a mere 101 cells/mm³.

COMMENT

The previous studies on the Free State programme reviewed in HTB, showed that the waiting period is too long and causes substantial mortality. Besides emphasising these findings, this study appears to indicate that patients with lower CD4 counts are not being prioritised sufficiently. Furthermore, even patients who are in care before meeting treatment eligibility criteria end up initiating treatment at very low CD4 counts.

It is unclear whether all of the 3,000 patients with CD4 counts > 200 cells/mm³ were not considered eligible for treatment by their health facilities. Surely some of these patients would have met the South African treatment guidelines clinical criteria for initiating HAART. There needs to be research to determine if the clinical criteria guidelines for initiation are being ignored.

Last year the former Minister of Health, Barbara Hogan, commissioned independent reports into the state of the health departments in the nine provinces. These reports have not been made public, but the Budget and Expenditure Monitoring Forum has obtained the Free State one and placed it on its webpage. Here is the URL:

<http://www.tac.org.za/community/files/bemf/FreeStateIST.pdf>

The report's priority findings were:

1. There are material unfunded mandates at provincial level contributing to overspending.
2. There is a lack of cohesion between policy formulation, budgets and resources to implement policies and planning.
3. The current model for the scale up of ART is unsustainable from a health systems perspective and unaffordable from a budgeting perspective.
4. There is a dearth of national guidelines, norms, standards and targets.
5. Human resource recruitment processes need to be overhauled to make them fit for purpose.
6. Monitoring and evaluation (M&E) is inadequate and managers at all levels pay lip service to M&E.
7. Much time and effort goes into planning, but the process is formulaic and based on compliance rather than being utilised as an effective management tool.
8. Senior management are preoccupied with bureaucratic functions, especially financial, and are not focused on service delivery.
9. Drug budgets have not been prioritised and the Free State Department of Health has had a shortage of medicines from November 2008 through to March 2009, affecting many aspects of service delivery.

These factors surely explain the problems with the Free State ART programme and rectifying them is urgent. Moreover, they are problems unlikely to be confined to the Free State. The National Department of Health, with the assistance of other national organs of state, therefore has to take urgent action to address these challenges.

As Francesca Conradie who chaired the session at which this research was presented said, "We need to find patients earlier and start them earlier."

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. 16-19 February 2010, San Francisco. All oral abstracts are available as webcasts.

<http://www.retroconference.org/2009/data/files/webcast.htm>

1. Geffen N. ARV Programme results: reports at IAS. HTB South 2(4) October-December 2009.
<http://i-base.info/htb-south/files/2010/02/htbsoct-dec09.pdf>
2. Ingle S. Pre-treatment Mortality and Probability of Starting ART in Patients Enrolled in the Free State ARV Program, South Africa: Implications for Treatment Guidelines. Oral abstract 108.
<http://www.retroconference.org/2010/Abstracts/37166.htm>

Vitamin D deficiencies in HIV management

Nathan Geffen, TAC

HTB has run several articles on vitamin D deficiencies in previous issues in relation to bone problems, tenofovir and efavirenz. There is increasing concern and research about vitamin D deficiency in people with HIV, especially with regard to African immigrants and people of African descent living in the cold climates of North America and Europe. There were several posters on this topic at CROI 2010 and so a themed discussion on it was held, chaired by discussants Peter Reiss of the University of Amsterdam and Michael Yin of Columbia University. Reiss started the session by giving a clear explanation of the basic science of vitamin D. [1-3]

Background

Vitamin D is a group of fat soluble prohormones that mainly originate in the skin where ultraviolet radiation interacts with 7-dehydrocholesterol to form pre-vitamin D₃ and then vitamin D₃. This process is harder in people with darker skins. Some vitamin D₃ is also consumed from diet and supplements. The main purpose of vitamin D is to increase the flow of calcium in the bloodstream.

Vitamin D₃ is hydroxylated by the enzyme 25-hydroxylase into hydroxylated vitamin D, 25(OH)D, in the liver. An alternative pathway to hydroxylated vitamin D is via vitamin D₂ acquired from diet, but this is considered a less important source.

The hydroxylated vitamin D, 25(OH)D is then further hydroxylated in the kidneys to one-alpha-hydroxylated-vitamin D (1 α -25(OH)₂D) which is the active metabolite. The enzymes involved in this process belong to the cytochrome p450 family, which is a catalyst for some antiretrovirals. There is also speculation that HIV itself affects the production of vitamin D (discussed further below).

Even though one-alpha-hydroxylated-vitamin D is the active metabolite, for diagnostic purposes the amount of its precursor, 25(OH)D is measured. This is because if there is a deficiency in 25(OH)D, an auto-regulatory mechanism upregulates the manufacture of one-alpha-hydroxylated-vitamin D. So a person can have sufficient amount of the active metabolite, but still have a deficiency of vitamin D, which is why the precursor is measured.

Clinical consequences of vitamin D deficiency

Widely accepted criteria for clinically sufficient, insufficient and deficient levels of vitamin D are given in Table 1. However, as Reiss pointed out, by this definition, 40 to 100% of elderly people are deficient in vitamin D and the criteria do not account for ethnic differences. Moreover optimum levels of vitamin D for skeletal and extra-skeletal health have not been established neither in the general population nor for specific ethnic groups. As is clear from the presentations described below, these criteria are not standardised.

Table 1: Criteria for clinical definitions of 25(OH)D3 in blood (Reiss [3])

	European (SI) measurement	US measurement
Sufficient	≥ 75 nmol/L	≥ 30 ng/mL
Insufficient	50-75 nmol/L	20-30 ng/mL
Deficient	<50 nmol/L	<20 ng/mL

Julian Falutz of McGill University has compiled a table of studies examining vitamin D levels in people with HIV (Table 2). They cover a wide range of countries, seasons, CD4 count ranges and levels of ARV uptake, giving a diverse range of proportions of people categorised as sufficient, insufficient or deficient.

The role of HIV and its treatment in vitamin D regulation is speculative and complex. HIV might affect dietary intake in sick people which in turn might affect levels of vitamin D. HIV might also affect the 1-alpha hydroxylation step and thereby inhibit synthesis of the active metabolite. Vitamin D might also be used by maturing and proliferating T-cells. With their increased production during HIV infection, there might be greater utilisation of vitamin D. The utilisation of cytochrome p450 enzymes by NNRTIs and protease inhibitors might also affect levels of vitamin D. The hydroxylation step in the kidney takes place in the proximal tubular cells, which are also affected by tenofovir, and this might impact on vitamin D levels. On the other hand ritonavir inhibits 1α-hydroxylase and consequently this might lead to an accumulation of unconverted 25(OH)D in the kidneys.

Vitamin D receptors are found on nearly all cells and deficiency of it is associated with many diseases such as osteomalacia (softening of bones), inflammatory conditions, hypertension, cardiovascular disease, insulin resistance, renal disease, prostate and colon cancer, greater risk of bacterial infection, cognitive dysfunction and frailty.

The SUN study

Christine Dao of the CDC presented results of the SUN study. This study assessed levels of vitamin D (measured by 25(OH)D, as with all other studies presented here) from 2004 to 2006 in the United States in 672 adults with HIV. Insufficiency was defined as less than 30ng/mL. The study found 71.6% of participants were vitamin D insufficient. Black race, Hispanic ethnicity, lower ultraviolet exposure, hypertension, lack of exercise and efavirenz exposure were independently associated with insufficiency. On the other hand renal insufficiency (GFR<90) and ritonavir exposure were independently associated with lower odds of insufficiency. In question time, Dao stated that 9% of participants were deficient, defined in this study as a 25(OH)D less than 10ng/mL (which is different from the definition of deficiency given above). [4]

Italian cohort

Antonella d' Arminio Monforte of the University of Milan presented the results of an observational cohort with retrospective analysis in vitamin D in stored plasma samples of 852 patients contributing 1,498 measurements. Of these, 262 measurements were taken before and 1,236 after ART initiation. Insufficiency was defined the same way as the European measurement in Table 1, but deficiency was defined as less than 30nmol/L. [5]

Insufficiency was found in 804 (54%) of measurements, while deficiency was found in 98 (7%). In 116 patients measured pre- and post-ART initiation in the same season, there was a non-significant drop of vitamin D levels (average of 7.57 nmol/L per year; p=0.11).

Table 2: Vitamin D studies in people with HIV (Falutz)

Study	N	Sex/race	Age	CD4	ARV (%)	Season	25(OH)D Low (%)	25(OH)D Insufficient (%)	25(OH)D Normal (%)
Stephensen (US) 2000	238(+) 121(-)	72%F 75%B	20	?	?	Spring-summer in 86%	?	87	?
Seminari (Italy) 2002	68	80%M, all white	41	150	100	Nov-Jun	?	81	?
Bang (Sweden) 2004	115	M, all white	44	480	62	Autumn-Winter	23	36	40
Rubin (NYC) 2005	62	M, 34% white	48	540	92	Autumn-Winter	42	34	24
Rodriguez (Boston) 2005	57	77% M, 60% white	46	430	81	Winter-Spring	48	?	?
Van der Ven (Holland) 2006	254	75% M, 73% white	41	420	79	Jan-Aug	29	?	71
Wetz (London) 2008	47	60% M, 60% black	41	455	88	1/3 tested in Autumn-Winter	74	17	9
Garcia-Aperico (Spain) 2008	30	100% M and white	38	550	56	Oct-Jun	86	?	?
Falutz	41	83% M	54	549	100	Autumn	5	55	40

The following were significantly associated with deficiency versus normal values (adjusted odds ratios):

- Age (per 10 years older) (OR: 1.53; 95%CI: 1.11-2.09; p=0.009)
- Non-Caucasian origin (OR: Caucasians were 0.17 times as likely to have deficiency; 95%CI: 0.07-0.42; p=0.0001)
- Lower CD4 count (per 100 cells/mm³) (OR: Higher CD4 count was 0.9 times as likely to have deficiency; 95%CI: 0.82-0.99; p=0.04)
- Lower BMI (OR: for each unit higher, 0.9 times as likely to have deficiency; 95%CI: 0.83-0.98; p=0.01)
- NNRTI versus PI use (OR: participants on PI regimens were 0.47 times as likely to have deficiency; 95%CI: 0.27-0.84; p=0.01)
- Season: (with summer as reference: OR of autumn: 1.24; 95%CI 0.51-3.05; p=0.64; winter: 4.84; 95%CI: 2.07-11.33; p=0.0003; spring: 8.3; 95%CI 3.61-19.09; p=0.0001)

During questions, d'Arminio Monforte stated that they had found that deficiency was associated with clinical events, in particular cardiovascular ones, but the direction of any causal effect, if any, was unclear. She also pointed out that in the HIV-negative population obesity is associated with deficiency, while in this cohort the opposite occurred: lower BMI was associated with deficiency.

Swiss cohort

Christoph Fux of University Hospital, Bern presented data on vitamin D deficiency in 211 patients in the Swiss HIV cohort, half of whom were measured in spring and half in autumn. As with the Italian cohort, insufficiency was defined the same way as the European measurement in Table 1, but deficiency was defined as less than 30nmol/L. [6]

At baseline before ART initiation, there was 14% deficiency in autumn and 42% deficiency in spring. After 12 months of ART – at which point all patients were virologically suppressed - this was virtually unchanged (47% in spring, but not significant). White race people had significantly higher vitamin D levels than Asian, Hispanic and black race people.

Interestingly, measurements of one-alpha-hydroxylated-vitamin D were also taken and it was found that there was some compensation, ie when 25(OH)D levels were lower, there was a higher ratio of the active metabolite to 25(OH)D.

In multivariate analysis, white race (14.1 umol/L higher; p=0.001) and, surprisingly, duration of HIV by 10 years (6.4; p=0.02) were associated with higher 25(OH)D levels. While BMI (-0.7; p=0.05), active IDU (-11.2; p=0.02), spring (-17.7; p<0.001) and NNRTI use (-8.2; p=0.002) were associated with lower levels. Sex, age, HCV positivity, cGFR<60mL/min, previous AIDS, CD4 count and tenofovir use were not significantly related to lower levels.

Interestingly, for one-alpha-hydroxylated-vitamin D levels, the results were different. Neither race nor season were significant. BMI was now positively associated with vitamin D levels (1.7; p<0.001), as was tenofovir use (7.8; p=0.02). HCV positivity was negatively associated (-9.1; p=0.04) as was previous AIDS (-11.6; p=0.007) and CD4 count by 100 cells (-2.6; p=0.003).

Tanzanian cohort

Saurabh Mehta of Harvard Medical School presented data from Tanzania on the association between vitamin D levels and wasting, acute respiratory infections and thrush. They defined low vitamin D level as less than 32 ng/mL. Vitamin D levels were measured in 884 pregnant Tanzanian women who were followed up for a median of 70 months. In January, this research group published an article in PLoS One showing that low vitamin D levels are associated with increased HIV disease progression (RR: 1.25; 95%CI: 1.05-1.5) and anaemia (RR: 1.46; 95%CI: 1.09-1.96). Women in the highest vitamin D quartile had a 42% lower risk of all-cause mortality (RR:0.58; 95%CI: 0.4-0.84). This group has also previously published a widely cited study showing that a vitamin supplement delayed disease progression and mortality in this cohort, but the supplement did not contain vitamin D [7-9].

In this study, low vitamin D was associated with a 45% higher risk of wasting (BMI<18kg/m²; p=0.03), a higher incidence of acute respiratory infections (RR: 1.28; 95%CI: 1.05-1.55) and a much higher incidence of thrush (RR:2.92; 95%CI: 1.43-5.96). They also found a linear relationship between any vitamin D level and wasting.

In question time, Mehta pointed out that no association was found with seasonal factors (Tanzania is near the equator). He also said that they found no association between vitamin D and TB, but did find an association between children born to mothers with deficiency and TB. When asked to comment on which way the association between wasting and vitamin D went, Mehta explained that the vitamin D level was measured at baseline when women with wasting were excluded from analysis and that the wasting in this cohort came subsequent to the vitamin D measure.

WIHS cohort

Audrey French of Rush University Medical Centre presented data from a cross-sectional sub-study of the Womens' Interagency HIV Study (WIHS), whose objective was to see if there was an association between vitamin D deficiency and bacterial vaginosis. WIHS is a longitudinal multi-site study of about 3,000 women with and without HIV. The substudy is from Chicago and New York City and includes 480 HIV-positive and 122 HIV-negative participants.

Bacterial vaginosis was diagnosed using the Amsel criteria. Vitamin D insufficiency was defined as 20-30ng/mL and deficiency as less than 20ng/mL. Prevalence of deficiency was 60% and insufficiency was 24%. Black race was the only predictor of deficiency in an analysis using demographics, socioeconomic status and HIV associated variables including HIV status. Factors associated with bacterial vaginosis in multivariate analysis were black race (OR: 6.08; 95%CI: 2.66-13.9), number of recent sexual partners (OR: 2.3; 95%CI: 1.12-5.06) and vitamin D deficiency (OR: 2.3; 95%CI: 1.02-5.19). The correlation co-efficient between vitamin D and bacterial vaginosis was -0.14 (p<0.001).

During question time, it was stated that vitamin D status was not associated with bone mineral density. Two researchers indicated that in their US cohorts of HIV-positive and HIV-negative people, they had not found an association between HIV status and vitamin D status. But another researcher indicated that a Swiss study had found a difference.

The need for a clinical trial

Michael Yin summarised the session, emphasising the many unanswered questions, lack of data and need for clinical trials of vitamin D. Study participants to consider include people initiating ART especially efavirenz, people who are aging and people in resource limited high TB prevalence areas. Study endpoints to consider are bone density, muscle mass, fall risk, insulin resistance, cardiovascular disease, CD4 count, HIV progression, opportunistic infections and other measures of innate and adaptive immunity. He suggested a vitamin D supplement dose of 1000 to 2000IU per day was a reasonable dose. [10]

He also described unanswered questions about screening. He asked if there should be universal screening (adopted by European AIDS Clinical Society) or targeted screening aimed at older people, black race people, people with previous fractures or low bone mass density, people who are frail or have sarcopenia and patients on efavirenz. He suggested that a target in patients of 40-60ng/mL or 100-150nmol/L should be aimed for.

During question time Yin was asked about the risk of high dosages. He described a study that looked at vitamin D and its correlation with calcium levels. Hypercalcaemia was only seen at levels of 200-240 nmol/L, which was far higher than could be reached with the doses he was proposing. Another questioner asked whether clinical or surrogate end point markers should be the endpoint of a vitamin D trial. Reiss responded that a trial looking at clinical endpoints would have to be too large and consequently surrogate endpoints would have to be used.

COMMENTS

These studies contribute to our understanding of vitamin D deficiency in people with HIV. However, there remain many unanswered questions relating to the clinical implications of vitamin D deficiency, how and what to measure and appropriate target levels in different populations, if supplementation is indicated.

In the absence of data from clinical trials, most HIV guidelines defer to national protocols for management of bone disease, recommending supplementation for patients with deficient levels. Supplementation for bone disease is very unusual though in a Southern African setting due to so much exposure to sunlight.

While a Cochrane review found statistically significant evidence for prescribing vitamin D to patients taking systemic corticosteroids, other reviews found insufficient evidence to show supplementation prevents fractures in older people, or during pregnancy or to treat chronic kidney diseases or children with cystic fibrosis.

Peter Reiss noted that the size and cost of an adequately powered randomised trial probably makes this unlikely. Management should therefore also lifestyle changes, including greater exposure to sun and improved diet, when this is likely to be sufficient for some patients.

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Unless stated otherwise, all references are to the Programme and Abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. 16-19 February 2010, San Francisco. All oral abstracts are available as webcasts.

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12th European AIDS Society Conference (EACS)

11-14 November 2009, Cologne

Introduction

In this issue we continue reports from this European conference that is held every two years.

This year a comprehensive programme of lectures and sessions available as webcasts and podcasts and include many of the slide sets:

<http://www.europeanaidsclinicalsociety.org>

<http://www.multiwebcast.com/eacs/2009/12th>

Access requires a free one-time registration using the invitation code: EACS2009

The abstracts from the meeting do not appear to be available online, but are published in HIV Medicine (2009, volume 10, issue S2).

The following reports are included in this issue.

- Screening for anal cancer recommended for HIV-positive men
- Once-daily darunavir/r monotherapy is suboptimal as initial regimen in treatment-naïve people
- Central fat accumulation remains a significant problem in patients starting HAART after 2005 with higher incidence in women compared to men
- Gender-based differences in patients receiving antiretroviral therapy
- Pilot PK study of two generic paediatric formulations of lopinavir/ritonavir vs originator products
- TMC278 does not show teratogenic potential in animal models
- No clinically relevant interactions between TMC278 and oral contraceptives (norethindrone plus ethinylestradiol)
- Etravirine pregnancy data from five cases: no dose adjustment required

Screening for anal cancer recommended for HIV-positive men

Simon Collins, HIV i-Base

A plenary session at EACS reported that new evidence supports screening for anal cancer in HIV-positive men. [1]

This is important, because the increased risk of anal cancer in gay men, and particularly in HIV-positive gay men, has been highlighted for many years. Screening is safe and treatment is effective, especially when diagnosed early and the importance of establishing a screening programme has been repeatedly raised by community-based advocates for many years. Controversially, NHS guidelines do not recommend screening for anal cancer in the two largest risk groups: HIV-positive people and gay men.

The presentation, by Professor Mark Bower from the Chelsea and Westminster Hospital, London, who also chaired the panel for the BHIVA malignancy guidelines [2], clearly supported a review of the NICE decision. He also highlighted that current healthcare resources could not cope adequately with any significant increase in demand for screening.

The lecture started by highlighting the difficulties that are inherent in proving the clinical benefit for any screening programme, including for those that are now an integrated part of NHS care (such as cervical and breast cancer). Interpreting data is dependent on the choice of endpoints, control groups and inherent biases that generally will always support the benefits from screening, even if reduced mortality cannot be inferred.

For example, the incidence of a cancer, or advanced cancer, or even using reductions in cancer specific mortality as an endpoint, does not necessarily provide the data to prove the benefit of screening due to three important inherent biases in evaluating any screening programme are just as relevant in the context of anal cancer and HIV.

Firstly, lead time bias refers to greater survival time after diagnosis. This may be driven by the earlier diagnosis commonly resulting from any availability of broader screening and so survival time since diagnosis does not necessarily have any impact on final mortality. Awareness of a diagnosis for longer is dependent on effective treatment to translate into better prognosis and longer survival.

Secondly, lag time bias refers to the tendency for a greater proportion of cancers picked up in a screening programme to be more slowly progressing and less aggressive compared to symptomatic cancers picked up in any control group. In this case, slow growing cancers have a longer screening time in which to be detected and this will translate to an apparent improvement in survival.

Finally, over-diagnosis bias relates to picking up cancers in screening programmes which are never going to progress, or in patients who will die from unrelated or natural causes. This translates to a higher incidence of diagnosis in a screening population but a lower incidence of cancer-related mortality.

Despite the scientific difficulties associated with proving the effectiveness of a screening programme, the presentation outlined why anal cancers screening is now appropriate, based on proven incidence in this population and the effectiveness of treatment.

Although anal cancer was not included as an AIDS-defining malignancy in the US CDC 1993 definitions, unlike cervical cancer that has a similar incidence and etiology, a meta-analysis of major cohort studies has suggested that anal cancer is 20-50 times more common in HIV-positive people than age and gender matched general population. [3] This is an enormous relative risk: by comparison, tobacco smoking is associated with an approximate 17-fold increased risk for lung cancer.

The HIV effect is also more than a direct result of a weakened immune system: transplant patients who have artificially reduced immunosuppression, only have a 4-5 fold increased risk of anal cancer.

Part, or much, or this increased incidence in HIV-positive gay men, may be related to the increased risk that was reported in MSM in pre-HIV data. [4]

Results from 11 linked HIV and cancer registries estimated a relative risk of 59 for HIV-positive MSM, but the same study also highlighted a 6-fold increased relative risk in HIV-positive compared to HIV-negative IDU's. [5]

Population studies now estimate the incidence of anal cancer at 1.5 per 100,000 in the general population, but at 35 and 70 per 100,000 in the general population, gay men and HIV-positive gay men respectively. One cohort, in San Diego, reported an even higher rate of 224 in HIV-positive MSM. [6] This compares to an incidence of cervical cancer before the introduction of screening or 15 per 100,000.

Anal cancer does not appear related to CD4 count, and some studies have suggested that the incidence post-HAART may be increasing. [8] This can be balanced by evidence that suggests that, due to effective treatment, survival rates in the HAART era now approximate to that in HIV-negative cohorts (of around 75% at two years). [8]

A limited number of studies support a similar etiology between cervical and anal cancer, with 5% patients diagnosed with AIN2/3 and a similar proportion of patient after surgery for anal warts, progressing to anal cancer. A UCSF study published in 1997 in HIV-positive MSM suggested a progression rate of 20% from normal cytology to HSIL and a 60% progression rate for men diagnosed with LSIL to HSIL (with 5% reverting to normal). In 21 patients with invasive anal cancer (from the same UCSF cohort of 1700 men), the median time to progression from a diagnosis of HSIL was 47 months (range 4-139 months). [9].

However, natural history studies should now be considered unethical, as they would for cervical cancer, given the clear link between AIN2/3 and risk of progression to anal cancer and the availability of effective treatment.

Anal cytological screening is easy, well tolerated and acceptable to patients. Results show either normal cytology or one of three diagnosis: ASCUS, LSIL or HSIL (Abnormal Squamous Cells of Undetermined Significance; Low-grade Squamous Intraepithelial Lesions; or High-grade Squamous Intraepithelial Lesions).

In the screening algorithm developed by Joel Palefsky in the US, normal results should lead to repeat annual screening as routine follow-up. ASCUS, LSIL and HSIL should prompt high-resolution anoscopy, with repeat annual anoscopy for AIN1 and treatment for AIN2/3. [10] This is supported by several studies reporting acceptable rates of 34-83% sensitivity and 38-72% specificity for anal cytology compared to histology.

Finally, the recent availability of reasonable and established treatments for AIN2/3 (infrared coagulation with clearance rates 50-60% at one year; topical trichloroacetic acid; imiquimod with 40% resolution vs 8% control; and surgical anal mucosectomy), that argue for the reevaluation of anal cytological screening.

While cost-effectiveness is always a factor in screening programmes the presentation made the following points:

- The first cost effectiveness study reported that cervical screening (3-yearly) in HIV-negative women was estimated at costing USD\$180,000 per life year saved. This compared to approximately USD\$11,000 for anal cytology screening in HIV-positive men. [11]
- A more detailed and recent analysis from the same group estimated costs of USD \$16,600 and \$13,000 per Quality Adjusted Life Year saved (QALY) for annual or two-yearly screening in HIV-positive MSM. For HIV-negative MSM these costs were \$34,800 and \$15,100 respectively. [12]
- A recent UK study determined screening in HIV-positive men is estimated to cost UKP £39,400, and that this is apparently not cost-effective. [13]

While the BHIVA/BAASH guidelines have stated that the benefit of screening is 'not yet proven', a more positive set of guidelines from New York State has recommended screening in HIV-positive MSM, HIV-positive CIN/VIN, and HIV-positive people with a history of genital warts, although these recommendations are unlikely to be running in practice due to the demand this would place on anoscopy services.

For any screening to be effective it will be dependent on providing timely anoscopy follow-up for patient with abnormal cytology results.

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Once-daily darunavir/r monotherapy is suboptimal as initial regimen in treatment-naïve people

Simon Collins, HIV i-Base

A tiny pilot for a Phase 2 study in treatment naïve patients was stopped prematurely, concluding that once-daily darunavir/r was not sufficiently potent as initial treatment in treatment naïve patients for the study to continue.

Seven patients (with baseline viral load <100,000 copies/mL and CD4 counts > 100 cells/mm³ and no evidence of drug resistance) were started on open-label darunavir/r monotherapy. At week 4, all patients had >1log drop in viral load and by week 8, viral load was <400 copies/mL in 4/7. However, the trial was stopped as 5/7 patients had inadequate viral responses (together with the high level of screening failures - 38/45 screened - which would limit enrollment for the larger planned study).

All seven patients achieved viral loads <50 copies/mL following intensification with nucleosides. CD4 responses at week 12 were +167 cells/mm³. No grade 3-4 clinical or laboratory events were reported. No darunavir-associated mutations were seen in the two patients with genotype results.

COMMENT

Although these results were disappointing as initial therapy, an analysis of the MONET study that randomised people with undetectable viral load (<50 copies/mL) on any HAART regimen

to either darunavir/r as monotherapy or plus dual RTIs, reported non-inferiority (difference = -1.6; 95%CI -10.1 to +6.8%) in terms of the percentage of people in each group with <50 copies/mL at week 48 (86.2% vs 87.8% respectively). [2]

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Central fat accumulation remains a significant problem in patients starting HAART after 2005 with higher incidence in women compared to men

Simon Collins, HIV i-Base

A cross-sectional study from two large French hospitals presented at EACS was important for confirming that central fat accumulation (CFA), one of the symptoms associated with HIV-related lipodystrophy, remains a significant side effect, even for patients who have started treatment recently.

Isabelle Poizot-Martin and colleagues used waist circumference as a surrogate marker of CFA in 838 HIV-positive patients (71% male, 29% female) who started combination antiretroviral therapy (cART) before (Group 1, n=723) or after January 2005 (Group 2, n=115).

CFA was defined as >102/88 cms (using NCEPATPIII guidelines) or >94/80 cms (using IDF classification), for men/women respectively.

Median age (years) was 46 in Group 1 and 44 in Group 2 (p=0.004). Median CD4 count was 523 and 472 cells/mm³, respectively (p=0.06) and viral load was < 40 copies/mL in 84% of patients in each group. Exposure to cART was 11.6 vs 2.1 years for Group 1 and 2 respectively.

CFA was reported in significantly higher rates for women compared to men in both groups, but also at higher rates in women who started treatment after 2005 compared to women who started treatment earlier, as detailed in Table 1.

Table 1: Percentages of patients with CFA diagnosed by waist circumference

	Group 1		Group 2	
	NCEP	IDF	NCEP	IDF
Men	12.7%	29.2%	11.8%	37.6 %
Women	24.4%*	52.6%**	43.3%*	76.7%**

* p=0.028 ** p=0.013 (between group comparisons)

While there were significant differences in use of different drugs in Group 1 compared to Groups 2 (mainly a higher use of triple-nucleoside regimens: by 11 vs 2% of patients), there were no significant differences by sex, particularly for Group 2.

COMMENT

While further associations are limited in a single cross-sectional dataset, the conclusion that CFA remains highly prevalent in patients who started treatment recently, is important.

The different rates of CFA in women compared to men had been previously reported and clearly warrant further study.

The results support the importance for every new antiretroviral to include prospective monitoring of body fat changes within Phase 3 studies. It is difficult to understand how any new drug could be approved without data on the impact it has on lipodystrophy and body fat changes.

Ref: Poizot-Martin I et al. Abdominal adiposity remains highly prevalent in French HIV-infected patients having initiated antiretroviral therapy after 2005. 12th EACS. 11-14 November 2009, Cologne. Abstract PS11/1.

Gender-based differences in patients receiving antiretroviral therapy

Polly Clayden, HIV i-Base

Several studies looked at the impact of gender on different aspects of antiretroviral treatment.

UK CHIC Study

The UK Collaborative HIV Cohort (CHIC) Study analysed the impact of starting HAART among heterosexuals initiating treatment between 1 January 1998 and 1 January 2007 at <350 CD4cells/mm³ and viral load (VL) >500copies/mL. [1]

The analyses used logistic and Cox regression models adjusted for age, ethnicity, calendar year, initial ART, previous AIDS and pre-ART CD4/VL. Sensitivity analyses were performed in which women who initiated HAART for the first time during pregnancy or became pregnant in their first year of HAART were excluded.

Of 3666 eligible patients for this study, 1487 (40.6%) were male and 2179 (59.4%) female. The investigators reported that men who started therapy in this group were significantly older than women, median 38 vs 33 years; had lower CD4 counts, 122 vs 160 cells/mm³ and higher viral load, 5.0 vs 4.7 log copies/mL, both p=0.0001.

Men were less likely than women to start with a nevirapine-based regimen (18.4 vs 34.7%).

They found no significant differences in initial viral load response, adjOR men vs women 0.95 (95% CI 0.87-1.03), p=0.19; or time to rebound, adjRH, 1.17 (0.93-1.47), p=0.19. However, men were less likely to stop a drug in their regimen, for reasons other than viral failure. (In this analysis, 79.4% of the group experienced initial viral load response (defined as <50 copies/mL) and 19.2% experienced viral rebound (two consecutive viral load >500 copies/mL).

CD4 counts increased across the cohort by a mean of 112 and 156 cells/mm³ at 6 and 12 months respectively. Men had significantly lower increases than women at both time points by 14.6 (p=0.005) and 12.1 (p=0.05) cells/mm³ respectively.

The overall findings remained unchanged when the investigators excluded pregnant women from the analysis. Of 2179 women included, 273 (12.5%) started HAART in pregnancy and 40 (1.8%) became pregnant within a year of starting.

The investigators noted that some gender differences became more pronounced and statistically significant in this sensitivity analysis.

Men were more likely to have viral rebound than women, RH 1.33 (1.04-1.71), p=0.02, but they continued to be less likely to discontinue treatment for reasons other than virological failure, RH 0.76 (0.65-0.88), p=0.0002. CD4 increases remained lower in men by 11.1 cells/mm³, p=0.03; and 10.9 cells/mm³, p=0.07, at 6 and 12 months respectively.

The investigators concluded that virological outcome was similar between men and women in this cohort. They suggested that the higher CD4 increase on treatment may be explained by their higher nadir and baseline CD4 count.

They also suggested that the finding that women were more likely to discontinue their treatment for reasons other than viral failure may be associated with a higher incidence of adverse events such as CNS toxicities associated with efavirenz. They wrote: "Further investigation into the reasons for discontinuation may shed light on the different CD4 responses and improve ART sequencing options for men and women."

STAR and STELLA cohorts

STAR and STELLA are two German prospective, multicentre cohort studies for antiretroviral naïve patients starting a lopinavir/r-based regimens.

A 48-week analysis comparing treatment outcomes, adverse events and self reported symptom distress, between men and women, was performed. [2]

Of a study population including 1136 patients, 984 were men and 172 were women. Men were older (median 41 vs 38 years, p=0.001), had higher median viral load (5.1 vs 4.9 log copies/mL, p<0.001), a lower CD4 percentage (12% vs 14%) and similar absolute CD4 counts (194 vs 214 cells/mm³).

At 48 weeks in ITT analysis, 308/467 (66%) men and 50/74 (68%) women had viral load <50 copies/mL. Median increases in CD4 count were 218 vs 198 cells/mm³ in men and women respectively.

Using the ASDM self-reported questionnaire to look at symptom distress revealed similar scores in men and women, 11.0 vs 12.5 respectively at baseline. Scores in both groups decreased significantly at week 48, by 3 and 2 in men and women respectively, both p<0.01.

Baseline symptoms of adverse events of any grade were documented in 16% men and 10% women, p=0.05. At 48 weeks 26% men and 15% women reported adverse events, p=0.04.

A similar proportion of men (7%) and women (5%) discontinued lopinavir/r for toxicities and 1% and 2% due to virological failure.

In Kaplan Meier analysis the investigators found the probability of remaining on treatment was similar, (76% vs 78%) in men vs women.

They reported no differences in virological and immunological outcomes and similar rates of discontinuation due to adverse

events between men and women initiating lopinavir/r based regimens.

CASTLE study

The CASTLE study was a multinational noninferiority study comparing atazanavir/r- to lopinavir/r- based regimens both with background tenofovir and emtricitabine in 883 patients.

An analysis was performed at 96 weeks to look at virological, immunological and safety profiles by gender. [3]

Overall 277/883 (31%) patients in this study were women. Baseline characteristics were similar in men and women in this study.

As previously reported, once-daily treatment with atazanavir/r was noninferior to twice-daily lopinavir/r, 74% of patients receiving atazanavir/r and 68% of patients receiving lopinavir/r achieved VL <50 copies/mL at week 96; difference estimate 6.1% (95% CI, 0.3-12%, p<0.05).

Discontinuation rates were higher for women than men in both treatment groups: 21% vs 14% and 29% vs 18%, women vs men, in patients receiving atazanavir/r and lopinavir/r, respectively.

In ITT analysis, more men than women had VL <50 copies/mL at 96 weeks: 77% vs 67% and 71% vs 63%, men vs women, in patients receiving atazanavir/r and lopinavir/r respectively. These differences were not observed in on treatment analysis.

Mean CD4 cell increases from baseline, rates of adverse events and lipid profiles were similar between genders. GI adverse events and lipid profiles were lower in both men and women receiving atazanavir/r than lopinavir/r.

The investigators wrote: "Consistent with other ARV clinical trials, gender differences in treatment efficacy were primarily due to higher discontinuation rates in women."

GRACE

GRACE (Gender, Race and Clinical Experience) was a multicentre open label phase 2b study to assess the safety and efficacy of duranavir/r plus optimised background regimen.

A post hoc analysis was conducted to investigate factors correlated with adherence in GRACE. [4]

In this study the mean age of patients was 42.9 years, 66.9% patients were women, and 61.5% and 22.4% of the total population were black and Hispanic respectively. At baseline women were younger on average and tended to have less advance disease and be less treatment experienced than men.

The virologic response (VL<50 copies/mL) at week 48 was 53.4% in ITT analysis. See Table 1 for response rates by sex and race.

Table 1: Virologic response <50 c/mL at week 48 by sex and race, n (%)

	Black	Hispanic	Caucasian
Women	89/191 (46.6)	35/60 (58.3)	21/34 (61.8)
Men	39/73 (53.4)	24/36 (66.7)	18/31 (58.1)

The response rate in patients with ≥95% adherence was 63.1% compared to only 34.7% in those with <95% adherence.

In multivariate analysis the investigators found no significant differences between sexes or across race in GRACE. More

IAS/USA major protease resistance associated mutations, participation at a non-academic site, fewer NRTIs in the OBR, being a non-smoker and having a CV medical history were predictive of ≥95% adherence.

References

All references are abstracts from the 12th European AIDS Conference (EACS), 11-14 November 2009, Cologne.

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2. Koegl C et al. No subjective or objective gender differences in ART-naïve patients initiating a lopinavir/ritonavir-based regimen. 48 week data from the German STAR and STELLA cohorts. Abstract PE 7.9/19.
3. Johnson M et al. Gender based differences in antiretroviral-naïve patients treated with ritonavir-boosted protease inhibitors: results from the CASTLE study through 96 weeks. Abstract PE7.3/8
4. Squires K et al. Rates and predictors of adherence in treatment experienced women and men in GRACE (Gender, Race And Clinical Experience). Abstract PE10.1/2.

Pilot PK study of two generic paediatric formulations of lopinavir/ritonavir vs originator products

Polly Clayden, HIV i-Base

Affordable protease inhibitors in suitable formulations for children are urgently needed.

De Kanter and colleagues from the University Nijmegen, the Netherlands, showed pharmacokinetic (PK) data from a phase I, open-label crossover study to evaluate two generic paediatric formulations of lopinavir/ritonavir developed by Cipla Pharmaceuticals (Lopimune tablets and granules 100/25mg). This was a pilot study designed to exclude large (>40%) differences in the exposure to lopinavir achieved using the generic formulations compared to the originator product (Kaletra).

Twelve HIV-negative adult volunteers were randomised to receive the following sequences of regimen ABC, ACB, BCA, BAC, CAB, CBA: A=Kaletra tablets, B=Lopimune granules and C=Lopimune paediatric tablets. They were given single doses of medication (400mg lopinavir) on an empty stomach at one-week intervals and a 32-hour PK curve was recorded. A 32-hour PK curve was also recorded for 5/12 volunteers after receiving lopinavir granules and Kaletra oral formulation both with food.

The volunteers were a median age 24 (range 21-55) years, height 1.79 (range 1.63-1.95) meters and weight 72 (range 51-87) kg. One third of the group were women.

The investigators found the median lopinavir AUC_{0-t} was 71.8 h.mg/L (IQR 48.7-93.5) with Kaletra tablets (A), and 38.7 h.mg/L (IQR 28.7-52.2) and 58.7 h.mg/L (IQR 42.5-79.4) with Lopimune granules (B) and Lopimune tablets (C) respectively. With Kaletra tablets as a reference these differences were statically significant, B vs A, p=0.003 and C vs A, 0.015.

C_{max} median values were 7.2 mg/L (IQR 5.8-8.3), 4.6 mg/L (IQR 4.1-5.2) and 6.5mg/L (IQR 5.0-7.1); B vs A, p=0.003 and C vs A, p= 0.012.

The investigators also noted lower ritonavir concentrations with the Lopimune formulations compared to Kaletra.

A sub-group of volunteers received Lopimune granules (n=5) and Kaletra oral solution (n=4) with food. In this comparison, the median lopinavir AUC_{0-t} was 62.1 h.mg/L (IQR 43.8-126.3) with Kaletra tablets, and 58.5 (IQR 55.4-77.6) and 49.6 h.mg/L (IQR 39.1-58.1).

C_{max} median values were 7.2 mg/L (IQR 4.6-9.1), 6.4 mg/L (IQR 5.5-7.6) and 5.2mg/L (IQR 4.3-5.7).

The investigators concluded that it is possible to exclude large differences in PK parameters for the Lopimune paediatric tablets, compared to Kaletra, when received on an empty stomach. Large differences can also be excluded for the Lopimune granules when these are received with food.

They added that, based on these results, it was acceptable to start PK and dose finding trials of the Lopimune paediatric tablets and granules even though the Cipla bioequivalence study was not yet complete.

COMMENT

This study did not test the effect of different compositions of meals on the absorption of LPV/r. They used a standardised "normal" European/Dutch breakfast, to see if the absorption would be better with food than without, as this is the case with the absorption of lopinavir from Kaletra oral solution. The absorption from the granules might be dependent on the amount of fat in the meal as is stated in the Summary of Product Characteristics.

Since this small study, the Cipla formulation has changed and has been slightly refined, so there is an ongoing bioequivalence study. CHAPAS 2, which will look at these products in children, is waiting on these results before it begins (probably around March). CHAPAS 2 will be able to investigate absorption among breastfeeding children and also those who are malnourished.

Ref: de Kanter et al. The pharmacokinetics of two generic co-formulations of lopinavir/ritonavir for HIV-infected children: a pilot study of pediatric lopimune formulations vs the branded product in healthy volunteers. 12th EACS, Cologne, November 11-14, 2009. Abstract PE15.2/1.

TMC278 did not show teratogenic potential in animal models

Polly Clayden, HIV i-Base

TMC278 (ripivirine) is a novel NNRTI currently under investigation. The embryo-foetal toxicity was evaluated in rats and rabbits.

In this study, pregnant Sprague-Dawley rats (by oral gavage) and New Zealand white rabbits (by oral dosing) received doses of TMC278 during the period of organogenesis (days 6-17 and 6-19 in rats and rabbits respectively).

Doses observed were: 400, 120 and 40 mg/kg/day in rats; and 20, 10 and 5 mg/kg/day in rabbits. Both animal models had a control group.

The investigators reported moderate maternal toxicity (reduced food consumption, and body weight gain, and increased thyroid weight) in rats at the two higher doses. In rabbits they did not observe any maternal toxicity.

They reported no teratogenic effect in either animal and there was no effect of treatment on pregnancy parameters.

In rats in the two higher dose groups they observed an increase in incidence of dilated renal pelvis (visceral variant) 120 mg/kg/day, p<0.05 and 400 mg/kg/day, p<0.01 compared to the control group. This was the only finding on embryo-foetal development in rats.

The maternal and embryo-foetal development no observable adverse effect level (NOAEL), was 40 mg/kg/day, associated with a maternal AUC_{0-24h} of 37 ug.h/mL.

With rabbits, the only finding was a slight increase in the incidence of minor variations of the left subclavian artery, p<0.05 and hypoplastic interparietal bone, p<0.05 compared to the controls in the group receiving 20 mg/kg/day.

The maternal toxicity and embryo/foetal NOAELs were 20 mg/kg/day and 10 mg/kg/day, respectively, which were associated with maternal AUC_{0-24h} of 232 ug.h/mL and 170 ug.h/mL.

The investigators concluded that TMC278 did not show teratogenic potential in rat and rabbit models at drug exposures 13-80 times higher than those in HIV-positive patients receiving 25 mg/qd at steady state (TMC278-C204 Study AUC_{0-24h} was 2.8 ug.h/mL).

Based on this data they suggest that further studies in women of child bearing potential are warranted.

Ref: Desmidt M et al. Absence of a teratogenic potential from a novel next-generation NNRTI, TMC278. 12th EACS. 11-14 November, 2009. Cologne. Abstract PE7.1/4.

No clinically relevant interactions between TMC278 and oral contraceptives (norethindrone plus ethinylestradiol)

Polly Clayden, HIV i-Base

An open label trial conducted by Crauwels and colleagues evaluated the pharmacokinetic (PK) interaction between TMC278 and norethindrone plus ethinylestradiol.

In this analysis, 18 HIV-negative volunteers received 1mg norethindrone plus ethinylestradiol 35ug (combined oral contraceptive pill, Ovysmen) once a day for three sequential 21-day cycles spaced with 7-day intervals. TMC278 was co-administered for the first 15 days of the third cycle at a once daily dose of 25 mg. TMC278 and Ovysmen were taken within 10 minutes after breakfast.

At day 15 of the second and third cycles 24 PK profiles of norethindrone, ethinylestradiol and TMC278 were obtained. Plasma samples were analysed using validated LC-MS/MS methods, with a lower limit of quantification of 1.0 ng/mL for TMC278, 50.0 pg/mL for norethindrone and 2.0 pg/mL for ethinylestradiol. Serum levels of progesterone luteinising hormone (LH) and follicle-stimulating hormone (FSH) were determined on days 1 and 14 of the second and third cycles.

PK parameters were calculated using non-compartmental analysis. Statistical analysis compared the test treatment, Ovysmen+TMC278 to the reference, Ovysmen alone.

The women in the study were a median age of 26 years, weight 69.5kg and BMI 24.6. The majority (67%) were white.

The investigators reported no effect on norethindrone PK when co-administered with TMC278. With ethinylestriol, neither the C_{min}, nor the AUC_{24h} were affected and C_{max} increased by 17% in the presence of TMC278. This increase is not expected to have a clinically relevant effect. See Table 1 for results of PK parameter ratios for norethindrone and ethinylestriol in the presence of TMC278.

Table 1: PK parameter ratios for norethindrone and ethinylestriol in the presence of TMC278

Parameter	n/n	Norethindrone (90% CI)	Ethinylestriol (90% CI)
AUC _{24h} pg.h/mL	14/15	0.89 (0.84-0.94)	1.14 (1.10-1.19)
C _{max} pg.h/mL	15/17	0.94 (0.83-1.06)	1.17 (1.06-1.30)
C _{min} pg.h/mL	15/17	0.99 (0.90-1.08)	1.09 (1.03-1.16)

Steady state PK parameters of TMC278 25mg/QD in the presence of noretindrone and ethinylestriol were comparable to values observed in previous trials of TMC278 alone. TMC278 25mg/QD had no clinically relevant effect on FSH, LH or progesterone serum levels in the presence of noretindrone and ethinylestriol.

The investigators concluded that the contraceptive efficacy of 1mg norethindrone plus ethinylestriol 35ug is expected to be maintained in the presence of TMC278 25mg/qd without dose modifications.

Ref: Crauwels et al. Pharmacokinetic interaction study between TMC278 an NNRTI, and the contraceptives northindrone plus ethinylesradiol. Abstract PE4.3/3

Etravirine pregnancy data from five cases: no dose adjustment required

Polly Clayden, HIV i-Base

A pharmacokinetic (PK) and safety study of etravirine (ETR) was conducted in five pregnant women receiving this next generation NNRTI through compassionate use during the clinical development programme.

PK assessments were performed in the third trimester and/or time of delivery. Samples were collected 1, 3, 6 and 12 hours post dose. Cord blood samples were obtained where possible. Plasma concentrations were determined using high performance LC-MS/MS (LLOQ 2ng/mL).

A non-compartmental model was used for the PK analysis and compared with population PK data from earlier trials. The investigators noted that in these trials (DUET-1 and DUET-2) PK parameters did not differ significantly between men and women.

In this study three women received ETR throughout pregnancy and two only in the third trimester.

The investigators reported comparable values in all five women to historical controls. See Table 1.

Three of the women had caesarean sections (one preterm due to twins) and the remainder vaginal deliveries.

The babies were all healthy. One was born with a polyotia but was otherwise normal. No other abnormalities were reported.

The investigators concluded that ETR PK in five pregnant women is comparable to that in non-pregnant adults, which suggests that no dose adjustment is needed. In this small study ETR did not have an effect on foetal toxicity.

ETR in pregnant women will be evaluated further in an ongoing trial investigating PK parameters of darunavir/r and ETR during the second and third trimesters and up to 12 weeks postpartum. [2]

Table 1: PK parameters of ETR in third trimester

Case	T _{max} (h)	C _{max} (ng/mL)	AUC _{12h} (ng.h/mL)	C _{0h} (ng/mL)
1	3	896	4,277*	387
2	6	1,210	6,448*	521
3	3	474	4,788	149
4	3	1150	8,870	898
5	3	445	3,041	434
Mean	-	835	5,485	478
SD	-	363	2,253	272
DUET population PK n=575				
Mean	-	-	5,506	393
SD	-	-	4,710	391

AUC=Area under the curve; C=concentration; T=time

* AUC 6h

COMMENT

The importance of conducting these studies and reporting even no effect must be stressed as guidance in this area is vague for many antiretrovirals.

References

1. Izurieta P et al. Safety and pharmacokinetics of etravirine in pregnant HIV-infected women. 12th EACS. Cologne. 11-14 November 2009. Abstract PE4.1/6.
2. A study to assess the pharmacokinetics (blood levels) of TMC114 (darunavir) taken with TMC114r (ritonavir), and TMC125 (etravirine) in HIV-1 infected pregnant women
<http://clinicaltrials.gov/ct2/show/NCT00855335>

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
3TC/AZT/nevirapine 150/300/200mg. Fixed Dose Combination	Strides Arcolab, India	22 December 2009
Efavirenz, 200mg tablets	Strides Arcolab, India	12 February 2010
Nevirapine 50mg tablet for oral suspension	Aurobindo, India	24 February 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.

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>

COMMENT

This brings the total of FDA approved generic drugs and formulations to 107 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/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm122951.htm>

PEPFAR launches five-year strategy

On 1 December 2009, the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) launched a five-year strategy outlining the direction of the program for its next phase.

The goals included, to:

- transition from an emergency response to promotion of sustainable country programs;
- strengthen partner government capacity to lead the response to this epidemic and other health demands;
- expand prevention, care, and treatment in both concentrated and generalised epidemics;

- integrate and coordinate HIV/AIDS programs with broader global health and development programs to maximise impact on health systems; and
- invest in innovation and operations research to evaluate impact, improve service delivery and maximise outcomes.

In addition, it announced new targets for the program around prevention, care and support, treatment, and sustainability. As a component of the Global Health Initiative, PEPFAR will be carefully and purposefully integrated with other health and development programs.

COMMENT

This announcement was seen as a disappointing by many people who expected a stronger commitment to the potential role for the US in global health.

This level of funding will result in reducing the numbers of HIV-positive people who will be able access the PEPFAR funded treatment programmes as new patients each year.

However, the US still donates far more to treatment programmes than other western countries, and activists outside the US also need to focus on increasing the levels of funding for treatment access by their governments.

Source: PEPFAR press release. (01 Dec 2009).

The PEPFAR strategy is published online:

<http://www.PEPFAR.gov/strategy>

Global Fund approves US\$2.4 billion in new grants

TheGlobalFund.org

In its ninth round of funding the Global Fund to Fight AIDS, Tuberculosis and Malaria has made an overall approval of grants with a two-year commitment of US\$2.4 billion.

This is the second largest ever approved by the Global Fund, following a US\$2.75 billion round in 2008. The Global Fund has now approved a total funding of US\$18.4 billion for 144 countries since it was created in 2002.

The Global Fund also approved the roll-out of the pilot phase of a facility to reduce prices for effective malaria medicines (AMFm). The Pilot phase will take place in nine African countries and Cambodia and be funded through US\$216 million in funding from UNITAID, the United Kingdom government and the Bill and Melinda Gates Foundation. It aims to provide access for everybody to effective artemisinin combination treatments for malaria and save lives by reducing the use of old, ineffective medicines.

The Global Fund Board decided to launch its next round of grants in May 2010. This round of funding will be considered for approval at a Board meeting to be held some time between November 2010 and January 2011.

Source: GFFATM Press release. Global Fund approves US\$2.4 billion in new grants. (12 Nov 2009).

http://www.theglobalfund.org/en/pressreleases/?pr=pr_091112

UNITAID decision to fund 'patent pool' to boost access to new medicines

UNITAID and MSF press releases

On 15 December 2009, UNITAID, an international health financing agency, agreed to fund a licensing agency that will be able to administer a patent pool for AIDS medicines.

This will offer licenses to generic manufacturers, and has the potential to reduce prices and facilitate the combination of drugs from different makers into fixed-dose combinations. This first step will mean that formal negotiations with drug companies can hopefully now begin.

UNITAID has identified 19 products from nine companies for potential inclusion into the pool. Companies that UNITAID has already consulted include Gilead, Tibotec, Merck and Sequoia.

This programme is supported by the Médecins Sans Frontières' Campaign for Access to Essential Medicines. "This is an important decision, but the pool will be judged on its outcome for patients," said Michelle Childs, Director of Policy & Advocacy at MSF. "We've been encouraged by the positive responses from a number of companies to our campaign in support of the pool. Now that the pool has been given a green light, patent holders need to move from expressions of general support to firm and formal license commitments. We urge them to do so. This needs to happen fast, as the clock is ticking for millions of patients."

"The Board has confirmed that this pool is for all developing countries, but as this is a voluntary mechanism, the ultimate outcome will depend on the decisions of patent holders. Countries can still use the legal mechanisms at their disposal such as compulsory licensing and pro-health patent laws to ensure people have access to the life-saving medicines they need."

Source: MSF and UNITAID press releases, (14/15 Dec 2009).

UNITAID Executive board approves breakthrough plan to make AIDS treatment more widely available at lower cost: patent pool could save over one billion dollars a year.

<http://www.unitaid.eu/en/The-Medicines-Patent-Pool-Initiative.html>

Factors affecting cost of ART: Data from Aid for AIDS

Nathan Geffen, TAC

Two recent articles, published in PLoS Medicine and the Annals of Internal Medicine, clarify factors affecting the cost of ART programmes. They were both published by researchers analysing the Aid for AIDS, a company that manages HIV-related care for medical insurance funds and companies in the private sector in Southern Africa. The studies find that poor adherence as well as the period just preceding and succeeding ART initiation are associated with highest costs. [1,2]

Immediate pre- and post-ART period is most costly: PLoS Medicine article

The PLoS article found that higher costs for patients joining the managed care programme were associated with low baseline

CD4 cell count, high baseline HIV viral load, and shorter duration in HIV care prior to starting ART. Higher costs in the long term were associated with lower adherence, switching to a protease inhibitor and starting ART at an older age.

In this analysis, patients on two medical schemes, with large numbers of patients enrolled in the Aid for AIDS programme, were selected. Patients on these two medical schemes do not have to make co-payments for their ART. Patients included in the analysis were ART-naïve at programme entry, older than 19 and commenced treatment at some point from November 1998 to November 2007. Women who received prevention of mother-to-child transmission prophylaxis but were otherwise ART-naïve were also included. Criteria for starting ART on the programme are similar to the South African and WHO treatment guidelines, with the major differences being that patients have greater choice in which regimens they use and the CD4 initiation threshold is 350 cells/mm³ not 200 cells/mm³ as in the South African public health system. To make the results more generalisable, only patients who initiated with two NRTIs and one NNRTI were included.

The Aid for AIDS database includes demographic data, CD4 cell counts, viral loads, previous ART history and patient health-care claims. The authors considered direct costs incurred by the providers, ie the medical schemes. For the cost of medical goods and services, the amount agreed to annually following negotiations between private healthcare providers and funders was used and not the amount charged by the provider or reimbursed to the patient. Prices were deflated from 1998 onwards (in the case of ARVs) and inflated (all other) to 2007 prices.

The database has 49,517 unique claim categories but 4,000 account for over 95% of costs. These latter categories were grouped as follows: ART, other medication, maternity-related care (antenatal services, delivery, caesarean section, and post-delivery paediatric care), general practitioner care, specialist care, hospital accommodation and procedures, CD4+ cell count and viral load monitoring and other investigations (eg laboratory tests and radiology).

The most common first line regimen was zidovudine, lamivudine, and efavirenz. The most common second line antiretroviral regimen was lopinavir/ritonavir, zidovudine, and didanosine. CD4 and viral load monitoring were done 1.5 times per annum on average. Hospitalisation rates were 441 days per 100 patient years in the first 6 months of ART and 179 days per 100 patient years subsequently. Hospitalisation incidence was highest in patients with the lowest CD4 counts. 31% left the programme, 24% of them by two years. There were no statistically significant differences in the baseline data between patients who stayed on the scheme and those who left. Interestingly, BMI at baseline was available for over 4,400 patients. Of these, 13% were <18.5kg/m², 52% were ≥18.5kg/m² and <25kg/m² and 35% were ≥25 kg/m².

Over 10,700 patients comprising over 600,000 patient months, about half of which were on ART, were included in the analysis. Median follow-up on ART was 26 months. Patients with missing CD4 and viral load data at baseline were eliminated from the dataset, leaving just over 7,400 for the main costing analysis.

The cost data was skewed, with 10% of patients accounting for 90% of costs. The mean total cost of the programme was highest from the four months preceding ART initiation to the eight months after. Over eight month periods the mean monthly total costs in US dollars were:

- 377 (95%CI: 337-418) for 4 months prior to 4 months post ART
- 183 (95%CI: 160-206) for 5 to 12 months post ART
- 161 (95%CI: 138-183) for 13 to 24 months post ART
- 115 (95%CI: 98-131) for >24 months post ART

Lower baseline CD4 count and higher baseline viral load were significantly associated with higher costs in the 4 months prior to 4 months post ART initiation. At 5-12 months post ART initiation, a baseline CD4 count < 50 cells/mm³ remained a significant predictor of higher cost (1.35 times more than a CD4 count >200 cells/mm³ and ≤350 cells/mm³; 95%CI: 1.07-1.63). Interestingly patients who initiated with CD4 counts >350 cells/mm³ had a 1.57 (95%CI: 1.21-1.92) times higher mean total monthly cost than patients with CD4 counts from 200 to 350 cells/mm³, presumably because many of them were being initiated following a stage 4 opportunistic infection as opposed to crossing the CD4 initiation threshold. Since nevirapine is cheaper than efavirenz, it also predicted lower cost. So did being on first-line versus second-line treatment. Better adherence also predicted lower cost, but this is discussed in greater detail in the summary of the Annals of Internal Medicine article.

Poor adherence increases cost: Annals of Internal Medicine article

The Annals of Internal Medicine focused on the effect of adherence on cost. For many patients using Aid for AIDS, medicines are dispensed monthly to patients at a pharmacy. This allowed Aid for AIDS to measure adherence in such patients, as opposed to patients receiving monthly home deliveries (the former have to pro-actively obtain their medicines as opposed to the latter who simply receive). Patients have to submit claims to an Aid for AIDS managed medical scheme for reimbursement for the cost of the medicines. The researchers measured adherence for a patient as the number of months for which claims were made divided by the number of months from ART initiation to death, withdrawal from the programme or study end. This result was then multiplied by 100. The study found that greater ART adherence was associated with lower direct health care costs.

The researchers identified about 16,500 patients over 18 years old from 2000 to 2006 in South Africa. About 10,000 were excluded from analysis because they received home deliveries of their medicines, did not initiate treatment using an NNRTI, had no baseline CD4 count, were not treatment-naïve or had less than 6 months follow-up. The final cohort consisted of over 6,800 patients.

For determining costs, claims were categorised as relating to ART, hospitalizations, physician consultations, testing to determine CD4 cell counts and viral loads, investigations (laboratory

tests for toxicity monitoring, radiography, ultrasonography, and computed tomography), non-ART medications, and other costs (physical therapy, audiology, and other paramedical specialties).

Patients were divided into adherence quartiles, with quartile 1 having the lowest and quartile 4 having the highest adherence. Table 1 lists some outcomes per quartile.

The mean monthly cost for all patients was \$370, of which ART was \$32, hospitalisations \$151, consultations \$76, investigations \$37 and non-ART medications \$53. Interestingly, the median monthly cost of treatment increased with adherence, from \$211 in quartile 4 (most adherent, IQR: \$153-\$315) to \$177 in quartile 1 (least adherent, IQR:\$106-\$331). Yet the mean cost decreased from \$376 in quartile 1 to \$313 in quartile 4 (a p-value cannot be calculated for this using standard statistical techniques because the distribution is not normal). This is because some non-adherent patients account for a disproportionate amount of monthly hospitalisation expenditure (\$190 in quartile 1 to \$92 in quartile 4; cf ARV costs which rise from \$11 per month in quartile 1 to \$47 in quartile 4). Also, many patients in quartile 1 have no costs at all. Increasing adherence across the quartiles decreased monthly costs for patients with non-zero costs by \$70, \$133, and \$192, respectively (p < 0.001).

COMMENT

Aid for AIDS has a large patient database and regularly publishes important findings such as these. While this study is very useful, as pointed out by the PLoS editor, it is not clear how generalisable these results are to public health systems. Also, using pharmacy refill claims does not necessarily correlate precisely with adherence. But this is a limitation of all surrogate measurements of adherence. Particularly interesting is that hospitalisation costs and not ARVs account for most of the monthly cost of the programme.

Ideally research such as this also needs to be published by the South African Department of Health on the public health system. However, the quality of its data is poor owing to the failure to implement an adequate monitoring and evaluation system.

The higher cost of treatment in the period just before and after HAART initiation, particularly for people with low CD4 counts, highlights the need to get patients into care earlier, and, just as important, to keep them in care. A scaled up public messaging campaign linking testing to earlier treatment might increase the mean CD4 count at ART initiation. But for the public health system, this also means addressing a host of systemic problems that delay care.

The positive association between adherence and cost-effectiveness

Table 1: Outcomes by adherence quartile

Description	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-value
Number of patients	1,701	1,753	1,647	1,732	
Person years	3,641	4,209	3,794	3,902	
Alive at end of study	675	969	1153	1,350	
Dead	224	122	80	52	<0.001
Withdrew	801	662	411	330	<0.001
Switched to courier pharmacy	145	232	328	351	<0.001
Women	925	1,064	1,042	1,150	<0.001

and treatment outcomes support the authors' conclusion that ART programs should "invest in systems to monitor adherence and then initiate proactive rather than reactive interventions to improve adherence." These findings should be an impetus to the Department of Health to improve adherence by introducing standardised high-quality adherence counselling, phasing stavudine out of the public health system, introducing once-daily tenofovir based combination pills, co-packaging pills that cannot be co-formulated, packaging pills in ways that patients can easily see when they are supposed to take their next pill and giving simple but accurate treatment literacy pamphlets written in an appropriate language to patients when they collect their pills. In this regard, see the letter reproduced below from several HIV clinicians and treatment activists to the Department of Health and generic manufacturers.

References

1. Leisegang R et al. Early and Late Direct Costs in a Southern African Antiretroviral Treatment Programme: A Retrospective Cohort Analysis. PLoS Med December 2009 6(12).
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2. Nachega JB et al. Association of Antiretroviral Therapy Adherence and Health Care Costs. Annals of Internal Medicine 5 January 2010 152(1).
<http://www.ncbi.nlm.nih.gov/pubmed/20048268>

Letter to SA Department of Health and generic drug manufacturers

5 March 2010

Dear Colleagues

PACKAGING OF ANTIRETROVIRAL PRODUCTS IN NEXT TENDER

Over 800,000 patients receive antiretroviral treatment in the South African public health system. Hundreds of thousands of HIV-positive women have been through the prevention of mother-to-child transmission programme. These programmes have saved and will continue to save many lives. Consequently, the public sector antiretroviral tender is large. The current tender is estimated to be worth R4.1 billion over two years. The tender expires in May and a new tender is being planned.

Given the importance of this programme, its size, its cost, and the increasing complexity of administering ART to patients on multiple regimens, the state should be able to make demands on how suppliers package the drugs in ways that will ease the running of the programme for health workers and patients, promote adherence and reduce prescription errors. The new tender presents an excellent opportunity to achieve this.

In particular:

1. Preference should be given to fixed dose combination medicines. The next tender should include once-daily tenofovir/FTC or 3TC/efavirenz pills. Regimens that cannot be co-formulated (e.g. tenofovir/FTC or 3TC/nevirapine and AZT/3TC/lopinavir/ritonavir) should ideally be co-packaged.
2. The tender specification should include the requirements that the most commonly prescribed first-line regimen be packaged as part of an adherence promoting calendar package, as is done for oral contraceptives. This should include 28 days with

the days of the week, and optionally an extra pill, for use in emergencies when appointments are unavoidably missed.

3. Packaging should be designed so that it is easy for health workers, particularly pharmacists and nurses, to match a patient's needs according to the treatment guidelines with the appropriate medicines.

These requirements may have substantial implications for companies tendering to provide these drugs, but the scale of the intervention requires that everything be done to reduce the burden on the health services of prescribing and adherence promotion. Already some years ago Malawi was able to provide the standard national ART regimens in specially designed packaging for the national ART programme. South Africa has the resources and leverage with this tender to go one step further. This could dramatically improve the quality of the programme, likely improve patient outcomes, ease the burden on health-workers and make the programme more cost-effective.

Yours sincerely

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GUIDELINES

As we go to press the South African National Antiretroviral Treatment guidelines 2010 are being finalised. We will review these in the next issue of HTB South.

WHO publish major revisions to HIV management guidelines

Polly Clayden, HIV i-Base

At the end of November 2009 the WHO released three Rapid Advice documents to guide HIV treatment and prevention strategies. [1]

The documents were:

- Antiretroviral therapy (ART) for adults and adolescents [2]
- Treatment for pregnant women and prevention of infant infection [3]
- Infant feeding [4]

Rapid advice: antiretroviral therapy for adults and adolescents

Since the last guideline revision in 2006, new evidence has become available, particularly concerning the earlier initiation of therapy. This document makes key recommendations in eight areas.

1. When to start?

Antiretroviral therapy should be started in all patients with ≤ 350 CD4 cells/mm³ and with WHO clinical stage 3 and 4. (CD4 testing is required to identify patients with WHO clinical stage 1 and 2 who need to start treatment).

2. What to start?

The recommended first line regimens are:

- AZT+3TC+efavirenz (EFV)
- AZT+3TC+nevirapine (NVP)
- TDF+3TC or FTC+NVP
- TDF+3TC or FTC+NVP

3. ART for HIV/TB co-infection

ART should be started in all HIV-positive people with active TB. TB treatment should be commenced first and followed by ART as soon as possible. EFV is the preferred NNRTI.

4. ART for HIV/HBV co-infection

ART should be started in all HIV-positive people needing treatment for their HBV. Regimens should contain dual-HBV therapy including tenofovir (TDF) plus 3TC or FTC.

5. ART for pregnant women

Recommendations for when to start and what to start with are as for a non-pregnant adult except that they do not recommend using efavirenz during the first trimester of pregnancy.

6. When to switch?

Where available they recommend viral load to confirm treatment failure (defined as persistently above 5000 copies/mL) and if this is available routinely, 6 month monitoring. Where viral load is not available they recommend use of immunological criteria to confirm treatment failure.

7. Second-line ART

Atazanavir/r (ATV/r) or lopinavir/r (LPV/r) are the recommended boosted PIs for second-line regimens. If d4T or AZT was used first-line, tenofovir plus either 3TC or FTC are recommended. If TDF was used first-line, then AZT+3TC or FTC.

8. Third-line regimens

This recommendation is not specific. New drugs such as integrase inhibitors and second generation NNRTIs and PIs are suggested. People on failing second line regimen with no available options are recommended to continue with that regimen.

COMMENT

These guidelines are produced to inform national providers of the best standard of clinical care. In aspects that are currently aspirational, guidance is included on how to change from existing practice, for example in moving from using d4T to alternative drugs.

Two clinical questions not addressed are:

i) **Whether lopinavir/r (Kaletra/Aluvia) monotherapy may have an important role in second-line regimens, given the supportive data from several studies? This would reduce cost and RTI-associated toxicity from drugs that may only provide limited antiretroviral activity, especially if nucleoside resistance developed on first-line treatment. This could provide some support for future third-line treatment, when CCR5 and integrase inhibitors become available.**

ii) **Whether the recommendation to select a high cut-off for virological switching (>5000 copies/mL) might result in an unnecessarily high risk of accumulating resistance to first-line drugs. As viral load monitoring is sometime only 6-monthly, this could delay a more protective earlier switch. Viral load blips have been reported up to 2000 copies/mL, though are usually lower, so deciding a true virological rebound at 2000 copies/mL may be worth considering in order to protect future options.**

Rapid advice: treatment for pregnant women and prevention of infant infection

Again, this Rapid Advice was informed by new data particularly showing the benefit of starting ARV prophylaxis earlier in pregnancy and extended prophylaxis to mothers or infants is effective in reducing transmission during breastfeeding. They noted, "For the first time there is enough evidence for WHO to recommend ARVs while breastfeeding."

The document addresses women who were both eligible and ineligible for ART for their own health and makes seven key recommendations.

1. As described in 5 above.
2. Eligible pregnant women should start ART irrespective of gestational age and continue throughout pregnancy, delivery and then indefinitely.

3. The preferred regimens for women eligible for treatment are:
- AZT+3TC+NVP
 - AZT+3TC+EFV

Alternative regimens are:

- TDF+3TC(or FTC)+NVP
- TDF+3TC (or FTC)+EFV

4. Infants of mothers receiving ART for their own health should receive:

- Daily NVP from birth until 6 weeks of age if breastfed.
- Daily AZT or NVP from birth until 6 weeks of age if not breastfed.

5. Women not eligible for ART for their own health should receive an ARV prophylaxis strategy. This should be started from as early as 14 weeks gestation or as soon as possible for women presenting later.

6. ARV maternal prophylaxis option A:

- Antepartum daily AZT
- Single dose NVP from onset of labour
- AZT+3TC during labour and delivery
- AZT+3TC 7 days postpartum

Breastfed infants should receive daily NVP throughout the period and one week after breastfeeding. Non –breastfeeding infants should receive daily AZT +NVP from birth to 6 weeks of age.

7. ARV maternal prophylaxis option B:

- AZT+3TC+lopinavir/r (LPV/r)
- AZT+3TC+abacavir (ABC)
- AZT+3TC+efavirenz (EFV)
- TDF+FTC+efavirenz (EFV)

Breastfed infants should receive daily NVP from birth until 6 weeks of age. Non –breastfeeding infants should receive daily AZT +NVP from birth to 6 weeks of age.

Options A and B are summarised in Table1.

COMMENT

The recommendations regarding the use of nevirapine and efavirenz are important in the new guidance for pregnant women. That the recommendations give high value to maternal health and the benefit that this has on transmission to her infant is most welcome. In the remarks in the guidelines it is noted that this also places relatively low value on the potential toxicity risks for the mother and unborn infant.

The adult ART guidance document highlights the low quality, conflicting evidence on the risks of efavirenz causing neural tube defects and that the overall rates of birth defects reported for efavirenz, nevirapine, lopinavir/r or tenofovir appear to be similar and also similar to rates reported for the general population. Initiation of efavirenz is not recommended in the first trimester and they remark that since the neural tube closes in the first 28 days and very few pregnancies are recognised by this time, the actual risks of starting efavirenz in the first trimester are hard to estimate.

Their review of nevirapine safety in pregnant women with CD4 counts 250-350 cells/mm3 did not confirm an elevated risk of serious

Table 1. ARV prophylaxis options recommended for HIV-infected pregnant women who do not need treatment for their own health

Option A: Maternal AZT	Option B: Maternal triple ARV prophylaxis
Mother	Mother
AZT from 14 weeks gestation sdNVP at onset of labour* AZT+3TC during labour and delivery AZT + 3TC 7 days post partum *sd NVP can be omitted if mother receives >4 weeks of AZT post partum	Triple ARV from 14 weeks until one week after all exposure to breast milk has ended AZT+3TC+LPV/r AZT+3TC+ABC AZT+3TC+EFV TDF+FTC+EFV
Infant	Infant
Breastfeeding: Daily NVP from birth until one week after exposure to breast milk has ended Non-breastfeeding AZT or NVP for 6 weeks	Breastfeeding Daily NVP from birth to 6 weeks Non-breastfeeding AZT or NVP for 6 weeks

side effects so the WHO panel concluded the benefits of using nevirapine in this situation outweigh the risks of not initiating ART.

This panel was unable to conclude whether it was better to use efavirenz or nevirapine in pregnant women after the first trimester and with higher or unknown CD4 cell counts and they added that over half the panel preferred efavirenz in these situations.

These recommendations will make things a lot easier from a programmatic point of view, whether national guidelines will follow suit remains to be seen.

Rapid advice: infant feeding in the context of HIV

This is a set of revised principles and recommendations intended for policy makers, academics and health workers in resource limited settings to assist national infant feeding strategies and implementation, in the context of HIV.

They draw on and further elaborate the revised WHO recommendations for ARVs to prevent mother to child transmission and in particular to prevent postnatal transmission through breastfeeding, which they describe as a major breakthrough that should contribute to improved child survival.

Key principles include:

1. Balancing HIV prevention with protection from other causes of child mortality. This principle recognises the association between maternal health and child survival.
2. Integrating HIV interventions into maternal and child health services. This should include CD4 testing and appropriate antiretroviral therapy or prophylaxis for the mothers' health and/or to prevent MTCT.

3. Setting national recommendations for infant feeding in the context of HIV. Either breastfeeding with antiretroviral interventions or avoid all breastfeeding.
4. Informing mothers, known to be HIV positive about infant feeding alternatives.
5. Providing services to support mothers to feed their infants appropriately.
6. Avoiding harm to infant feeding practices in the general population.
7. Advising mothers who are HIV-negative to breastfeed on ways to remain HIV-negative: and mothers of unknown status should be offered HIV testing.
8. Investing in improvements in infant feeding practices in the context of HIV.

Key recommendations:

1. Making sure HIV-positive mothers receive the treatment and care they need to reduce transmission through breastfeeding in accordance with the WHO guidelines.
2. Mothers should exclusively breastfeed for the first six months and introduce appropriate complimentary foods thereafter and continue breastfeeding for the first 12 months of the infant's life.
3. Stopping breastfeeding should occur gradually over one month and abrupt stopping is not recommended. Mothers who have been receiving prophylaxis should continue for one week after breastfeeding stops.
4. If mothers stop breastfeeding at any time formula or expressed, heat treated-breastmilk.
5. Conditions must be AFASS – affordable, feasible, acceptable, sustainable and safe to safely formula feed.
6. Heat treated expressed milk may be considered as an interim strategy in some circumstances such as an infant with low birthweight who cannot breastfeed, if the mother is unwell or antiretroviral drugs are not available.
7. Mothers are strongly encouraged to breastfeed infants known to be infected, exclusively for the first 6 months and then continue as recommended for the general population

2. World Health Organization. Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents. November 2009. <http://www.who.int/hiv/pub/mtct/advice/en>
3. World Health Organization. Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. November 2009. <http://www.who.int/hiv/pub/mtct/advice/en>
4. World Health Organization. Rapid advice: infant feeding in the context of HIV. <http://www.who.int/hiv/pub/paediatric/advice>

US guideline update: treat when CD4 is <500 cells/mm³

On 1 December 2009, the US Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were updated.

Changes are highlighted in yellow on the PDF file and include:

New section

Based on interests and requests from HIV practitioners, a new section entitled “Considerations in Managing Patients with HIV-2 Infection” has been added to the guidelines. This new section briefly reviews the current knowledge on the epidemiology and diagnosis of HIV-2 infection and the role of antiretroviral therapy in the management of patients with HIV-2 mono-infection and HIV-1/HIV-2 coinfection.

Key updates

Drug resistance testing In this revision, the Panel provides more specific recommendations on when to use genotypic versus phenotypic testing to guide therapy in treatment-experienced patients with viremia while on treatment.

- Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens (AIII).
- Addition of phenotypic testing to genotypic testing is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors (BIII).

Initiation of antiretroviral therapy In this updated version of the guidelines, the Panel recommends earlier initiation of antiretroviral therapy with the following specific recommendations:

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness or with CD4 count < 350 cells/mm³ (AI).
- Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy (AI), HIV-associated nephropathy (AII), and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).
- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm³. The Panel was divided on the strength of this recommendation: 55% of Panel members for strong recommendation (A) and 45% for moderate recommendation (B) (A/B-II).

COMMENT

The most interesting recommendation is mixed feeding for infants 6-12 months of age. The panel remarked that transmission risk previously considered to be associated with this strategy should diminish with antiretroviral interventions. They also suggest that this may avoid many of the complexities associated with stopping breastfeeding and providing a safe and adequate diet to the infant during this period. This was considered a major advantage.

References

1. World Health Organization HIV Treatment Recommendations. New HIV recommendations to improve health, reduce infections and save lives. (1 Dec 2009) http://www.who.int/mediacentre/news/releases/2009/world_aids_20091130/en

- For patients with CD4 counts >500 cells/mm³, 50% of Panel members favor starting antiretroviral therapy (B); the other 50% of members view treatment as optional (C) in this setting (B/C-III).

Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers may elect to defer therapy, based on clinical and/or psychosocial factors on a case-by-case basis.

What to start in antiretroviral-naïve patients

Increasing clinical trial data in the past few years have allowed for better distinction between the virological efficacy and safety of different combination regimens. Instead of providing recommendations for individual antiretroviral components to use to make up a combination, the Panel now defines what regimens are recommended in treatment naïve patients.

Regimens are classified as “Preferred,” “Alternative,” “Acceptable,” “Regimens that may be acceptable but more definitive data are needed,” and “Regimens to be used with caution.

The following changes were made in the recommendations:

- Raltegravir + tenofovir/emtricitabine” has been added as a “Preferred” regimen based on the results of a Phase III randomised controlled trial (AI).
- Four regimens are now listed as “Preferred” regimens for treatment-naïve patients:
 - i) efavirenz/tenofovir/emtricitabine;
 - ii) ritonavir-boosted atazanavir + tenofovir/emtricitabine;
 - iii) ritonavir-boosted darunavir + tenofovir/emtricitabine; and
 - iv) raltegravir + tenofovir/emtricitabine.
- Lopinavir/ritonavir-based regimens are now listed as “Alternative” (BI) instead of “Preferred” regimens, except in pregnant women, where twice-daily lopinavir/ritonavir + zidovudine/lamivudine remains a “Preferred” regimen (AI).

Additional updates The following sections and their relevant tables have been substantially updated:

- What not to use
- Management of treatment-experienced patients
- Treatment simplification
- Hepatitis C coinfection
- Antiretroviral-associated adverse effects
- Antiretroviral drug interactions
- Preventing secondary transmission of HIV

These and other DHHS guidelines are available on the NIH aidsinfo website

<http://www.aidsinfo.nih.gov>

Direct download (PDF):

<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>

COMMENT

The main concern in these guidelines is the strength of the statement for new recommendations for starting treatment.

Currently the document states that the whole panel recommends starting treatment for people with a CD4 count 350-500. This leaves no indication of support for the view that there is insufficient data to balance the risks against the benefits.

Although this is discussed in the main document in more detail, the summary of the guidelines does not accurately reflect the later discussion. The summary is far more widely read than the entire document, and it would therefore be helpful for this wording to be reconsidered.

This years recommendations are especially important as they coincide with the enrollment of the NIH-funded START study which may be the only opportunity to look at both the risks and benefits from a randomised study.

So while there is data supporting short-term safety, there is no data based on long-term risk.

An example of risk comes from the trials of the preferred regimens referenced with the latest data (STARTMRK, ARTEMIS etc). Viral suppression to <50 copies/mL (the primary goal of treatment) was not achieved by around 15% patients at 48 weeks and 20% by week 96. In the context of lifelong treatment, low levels of resistance currently reported, may become more serious if second-line treatment also fails. Population-based uptake of treatment in Western countries is also frequently associated with higher rates of failure.

A second example is that no combination has been shown not to cause fat accumulation, itself associated with additional longer-term health complications, as well as reduced quality of life. This complication may also be related to race and gender.

These potential risks from earlier treatment are not addressed in the main guidelines.

In addition, while the summary states that ‘some people may defer treatment’, this is suggested for ‘clinical or psychosocial factors’ and is tied to an earlier sentence about people who might have difficulty with adherence.

While the document is only produced as guidance, the DHHS guidelines are widely interpreted as indicating the minimum recommended standard of care, based on the best available evidence. Clinical trials, especially NIH funded trials, become unethical if they recommend less than the current standard of care for any participant.

While many clinicians, researchers and advocates believe that there is still equipoise on the use of treatment by people with counts 350-500, the current summary brings them into conflict with what are otherwise, one of the most useful documents for the management of HIV infection.

Given the summary has already been widely distributed and publicised, it would help if any subsequent update addresses whether a randomised trial in people with CD4 counts lower than 500

cells/mm³ remains ethical. Currently the guideline summary states that expert opinion believes that further research is unnecessary.

This is important in the context of the START trial which is just enrolling patients and which will be the most important study to inform on this and many other questions.

The history of previous recommendations from the DHHS panel on the when treatment should be started shows the importance of collecting evidence from a randomised study. Earlier recommendations to start at 500 and 350 have probably resulted in widespread complications from side effects and resistance.

Other changes in the guidelines are positive, especially the inclusion of a new section on HIV-2.

Updated paediatric HIV treatment guidelines (PENTA, 2009)

Polly Clayden, HIV i-Base

The updated PENTA guidelines were published in the November 2009 edition of HIV Medicine. These guidelines offer practical recommendations for treating children with HIV in Europe.

The main changes since the 2004 guidelines are:

When to start?

Universal treatment is recommended as soon as possible after diagnosis for all infants less than 12 months of age. The guidelines stress particular urgency for infants infected despite prevention of mother to child transmission (PMTCT).

For children 12 months or older, HAART should be started in all symptomatic cases (CDC stage B or C, WHO stage 3 or 4). Children 12 months or older with no or minor symptoms (CDC stage A or N or WHO stage 1 or 2) treatment should be started when CD4 count or percentage falls below the following thresholds:

1 to <3 years	CD4<25% or 1000 cells/mm ³
3 to <5years	CD4<20% or <500 cells/mm ³
Above 5 years	CD4 count <350 cells/mm ³

These treatment thresholds differ significantly from the 2004 guidelines, see Table 1 for comparison of PENTA guidelines 2004 and 2009. Some recommendations also differ from the WHO and US treatment thresholds, see Table 2 comparison of PENTA, WHO and US treatment thresholds.

In children aged more than 12 months with no or minor symptoms and CD4 counts or percentages above these thresholds, HAART should be considered if the viral load exceeds 100,000 copies/mL.

What to start with?

The guidelines recommend a regimen of two NRTIs and either an NNRTI or a boosted PI for ARV-naïve children with no evidence of resistance. They note that a PI may be preferred in children with anticipated poor adherence.

Abacavir and 3TC are recommended for children who are HLA-B*5701 negative and AZT and 3TC for those who are HLA-B*5701 positive.

Nevirapine is recommended for children <3 years and efavirenz for older children.

Lopinavir/ritonavir is recommended for young children. For older children alternative boosted PIs may be used, including fosamprenavir/r and duranavir/r which are licensed for children from 6 years, atazanavir/r (which is licensed in the US for children from 6 years but not in Europe) and saquinavir/r (which is not licensed for children but may be suitable for adolescents).

Other recommendations

Recommendations on the use of resistance testing, TDM and HLA testing are informed by adult data and paediatric cohorts in Europe.

The guidelines highlight the paucity of data from RCTs on which to base recommendations for children and note that available trials tend to be small, therefore "... we continue to rely on cohort studies, extrapolation from adult data and expert opinion." They recommend that wherever possible children should be enrolled in clinical trials.

Drug information will be available alongside the guideline, and will be kept updated, on the PENTA website www.pentatrials.org

COMMENT

WHO paediatric guidance is due for update imminently, and is likely to recommend earlier treatment in line with updated WHO adult guidance.

WHO and PENTA will provide different recommendations based on the same data. This reflects both the paucity of high quality evidence from randomised clinical trials, on which the guidelines are based, and that PENTA guidelines are intended for use in Europe while WHO guidelines will predominantly inform national guidelines in less well resourced countries, where the ability of treatment programmes to deliver care may also be an issue.

We intend to summarise and review new WHO paediatric guidance later in 2010 when it is published. PENTA guidelines are not likely to change when new WHO paediatric guidance is published, and remain the current recommendations for treating children with HIV in Europe.

Ref: PENTA Steering Committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric infection. HIV Medicine 2009, 10, 591-613.

Table 1: Comparison of PENTA guidelines 2004 and 2009

	PENTA 2009	PENTA 2004
	0-11 months	0-11 months
Clinical	Treat all	Treat CDC stage B or C
Immunological (CD4%/count)	-	Treat <35%
Virological	-	Consider >1,000,000 copies/mL
	12-35 months	12-47 months
Clinical	Treat CDC stage B or C/WHO stage 3or4	Treat CDC stage C
Immunological (CD4%/count)	Treat <25% or <1000 cells/mm3	Treat <20%
Virological	Consider >100,000 copies/mL	Consider >250,000 copies/mL
	36-59 months	4-12 years
Clinical	Treat CDC stage B or C/WHO stage 3or4	Treat CDC stage C
Immunological (CD4%/count)	Treat <20% or <500 cells/mm3	Treat <15%
Virological	Consider >100,000 copies/mL	Consider >250,000 copies/mL
	5 years +	13-17 years
Clinical	Treat CDC stage B or C/WHO stage 3or 4	Treat CDC stage C
Immunological (CD4%/count)	Treat <350cells/mm3	Treat <200 cells/mm3 Consider 200-350 cells/mm3
Virological	Consider >100,000 copies/mL	Consider >250,000copies/mL

Table 2: Comparison of current PENTA, WHO and US treatment thresholds

	PENTA 2009	US 2008	WHO 2008
	0-11 months		
Clinical	Treat all	Treat all	Treat all
Immunological (CD4%/count)			
Virological			
	12-35 months		
Clinical	Treat CDC stage B or C/WHO stage 3 or 4	Treat CDC stage B	Treat WHO stage 4 and severe 3
Immunological (CD4%/count)	Treat <25% or <1000 cells/mm3	Treat <25%	Treat <20% or <750 cells/mm3
Virological	Consider >100,000 copies/mL	Consider >100,000 c/mL	
	36-59 months		
Clinical	Treat CDC stage B or C/WHO stage 3 or 4	Treat CDC stage B	Treat WHO stage 4 and severe 3
Immunological (CD4%/count)	Treat <20% or <500 cells/mm3	Treat <25%	Treat <20% or <350 cells/mm3
Virological	Consider >100,000 c/mL	Consider >100,000 c/mL	-
	5years +		
Clinical	Treat CDC stage B or C/WHO stage 3 or 4	Treat CDC stage B or C	WHO stage 4 or severe 3
Immunological (CD4%/count)	Treat <350 cells/mm3	Treat <25% or <500 cells/mm3	Treat <15% or <200 cells/mm3
Virological	Consider >100,000 c/mL	Consider >100,000 c/mL	

SIDE EFFECTS

HIV disease and renal function

Simon Collins, HIV i-Base

Although earlier ARVs including AZT and indinavir were associated with renal toxicity, the focus on routine renal monitoring has increased significantly due to the widespread use of tenofovir. While there is limited data on the impact of HIV and treatment on renal function, several recent studies contributed new information in this area.

PI-initiated HAART shows eGFR improvement over seven years

Catherine Leport and colleagues from the APROCO-COPILOTE cohort published long-term results of renal function in over 1100 patients who started protease inhibitor (PI) based combinations between 1997 and 1999 in 47 French HIV centres. [1]

Changes in eGFR in this cohort, estimated by MDRD ignoring adjustment for race, increased by +0.72 mL/min/1.73m²/month (95%CI 0.40–1.03) from treatment initiation to month 16 and then remained stable +0.01/month (95% CI, –0.08 to 0.10) for up to 7 years. The proportion of patients with a GFR of <60 or 60–90 were stable over time at approximately 5% and 39%.

This rate increase was lower among men and those with low BMI, AIDS, or who had used indinavir.

The cohort was 77% male; median age was 37 years (IQR 32–43), ethnicity was 10% African/90% Caucasian; 21% had a prior history of AIDS, and median baseline GFR was 93 mL/min/1.73m² (IQR, 82–107). GFR was estimated using the abbreviated MDRD formula, ignoring adjustment for race.

After a median follow-up of 7.0 years (IQR 3.8–8.4), the median CD4 level increased from 273 cells/mm³ (IQR 126–421) to 524 (IQR 370–737).

The mortality rate was higher for patients with baseline eGFR <60: 4.1 per 100 vs 1.6% among those with baseline GFR of 60–90, and 1.8% among patients with GFR 90 (p=0.21, adjusted for baseline age, CD4 count, HIV RNA level, AIDS stage, and injection drug use).

The study also analysed the impact of individual ARVs, although noting that this requires caution in interpreting results from a cohort study.

Indinavir and nelfinavir were the first PI for 40% and 29% patients, respectively. At 7 years, only 13% patients were still receiving their initial PI. Overall, 532 patients were started on indinavir and received it for a median duration of 21 months (IQR 9–42 months), whereas from 2001 onwards, 214 patients received tenofovir for a median duration of 20 months (IQR 8–38 months).

Changes in eGFR over time did not differ between patients who initiated tenofovir, regardless of GFR (<90 vs 90), and those who never used tenofovir, and it did not differ for patients who received indinavir prior to tenofovir, compared with those who never received tenofovir (data not shown). This is a different finding to that reported in the Swiss Cohort Study. [2]

In the multivariate analysis of GFR evolution over time, male sex, AIDS stage, lower baseline BMI, and receipt of indinavir were associated with a poorer evolution of GFR during the first 16 months of treatment. Beyond 16 months, a poorer evolution of GFR was associated with African origin and baseline CD4 cell count 200 cells/mm³ but not receipt of indinavir or tenofovir.

Loss of kidney function despite successful HAART

A paper from Andy Choi and colleagues in the 23 October issue of AIDS reported risk factors associated with reduced kidney function in an HIV-positive cohort of patients both on- and off-HAART, including 7% untreated viral controllers.

They followed 615 patients for a mean of 3.4 (±2.5) years. Mean age was 45 years and 13% were women. Half the group were white, 25% were black and 10% were Hispanic. 15% of the group has risk factors for kidney disease including HCV, hypertension, hyperlipidaemia and smoking.

In this study, in contrast to Leport et al, the overall rate of kidney function calculated by changes in eGFR, declined by -2.6 mL/min/1.73m² [95%CI: -3.0 to -2.1] per year. In multivariable adjusted analyses, predictors of eGFR decline included female sex, diabetes, and hyperlipidemia, but not CD4 cell count or viral load.

The impact of HAART, was assessed in a sub group of 82 patients who started HAART during the study. GFR declined an average of -4.7 (95%CI -6.7 to -2.6) per year during the 1.2 years before HAART, and this improved to -1.9 (95% CI -3.7 to -0.1) during a mean 2.9 years of follow-up after starting treatment. In adjusted analysis, HIV treatment was associated with a +2.8 (95% CI 0.8-4.7) per year improvement in eGFR slope. Although these patients benefited from HAART, they continued to lose kidney function at a rate of -1.9 (-3.7 to -0.1) per year.

When comparing 45 untreated to 173 treated viral controllers (defined as having a viral load <500 copies/mL), patients on HAART had greater eGFR declines (adjusted difference -4.4 (-6.7 to -2.1) per year in treated versus untreated controllers).

Intermittent viral blips in the treated group were also associated with more rapid rates of eGFR loss [-6.7 (-11.1 to -2.4) per year.

Hypertension and diabetes were both strongly associated with renal decline in treated patients [-4.0 (-7.6 to -0.5) and -5.6 (-10.3 to -0.8) per year, respectively].

Unfortunately this study was underpowered to look at the impact of individual drugs, especially indinavir and tenofovir, and had limited data on other important markers of kidney health or treatment in individual patients.

The study concluded that although HIV treatment appears to help curb kidney function decline, patients who achieved durable viral suppression continue to experience substantial loss of eGFR and that loss of kidney function may be attributable to treatment-related factors, intermittent viremia, and traditional risk factors for kidney disease.

End Stage Renal Failure in HIV-positive patients in the UK

A review of the clinical epidemiology of end-stage renal failure (ESRF) in the UK (defined as starting permanent renal replacement therapy (pRRT), was undertaken by Loveleen Bansi and colleagues from the UK-CHIC study, and published in the 27 November issue of AIDS. [4]

Results were collected from almost 22,000 patients attending seven leading HIV centres between 1998-2007. ESRF occurred in 68 patients (0.31%), 44 (65%) of whom were black. The prevalence increased in black patients from 0.26% in 1998/99 to 0.92% in 2006/07 ($p=0.001$ for trend) and from 0.03% to 0.11% in non-black patients ($p=0.07$ for trend). Patients with ESRF were more likely to be female (29 vs. 21%), of black ethnicity (65 vs. 25%), and have lower nadir CD4 cell count (median: 72 vs. 179 cells/mm³).

In multivariable analysis, black ethnicity was associated with a higher risk of ESRF [HR 6.93, 95%CI: 3.56, 13.48], and higher current CD4 cell count with a reduced risk per 50 cells/mm³ higher (HR: 0.83, 95%CI: 0.76, 0.95).

The most common renal diagnosis was HIVAN, (in 53% of all patients and 82% of black patients). All cases of HIVAN were in black patients.

Response to pRRT was generally good with 70% overall 5-year survival. This was significantly better for black patients compared to those of other ethnicities (85% vs. 43%, $p=0.001$).

The group used data from the HPA and Renal Registry to estimate 231 cases of ESRF occurred in HIV-positive patients in the UK over this period and that this accounted for 0.5% of the 45,500 people who received pRRT.

In summary, this analysis highlighted a prevalence of ESRF of almost 1% in HIV-positive black patients in the UK. The favourable comparison to US incidence rates that are 5-6 times higher and better response to pRRT (98% vs 30-40% 2-year survival) was accounted for by lower rates of IV drug use and HCV coinfection.

The discussion noted that prevalence rates may have been slightly underestimated and treatment responses overestimated given that a minimum of 3 months follow-up was required for this analysis, but that given the strong association with nadir CD4 count, this is another reason to aim for earlier HIV diagnoses in black patients in the UK.

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PREGNANCY & PMTCT

Pregnancy not nevirapine associated with risk of hepatotoxicity in large cohort comparison

Polly Clayden, HIV i-Base

There is some uncertainty about the association between nevirapine, pregnancy and hepatotoxicity in HIV-positive women.

In a concise communication, published in the November 27 2009 edition of *AIDS*, David Ouyang and investigators from two large American multicentre cohorts, the Women and Infants Transmission Study (WITS) and the International Maternal Paediatric Adolescent Clinical Trials (IMPAACT) protocol P1025, showed findings from a study to estimate whether this association differs by pregnancy status in HIV-positive women.

The study compared pregnant women in WITS and IMPAACT to a non-pregnant reference group from the Women Interagency HIV Study (WIHS).

Cox proportional hazard models were used to investigate the association between nevirapine use and any liver enzyme elevation (LEE, grade 1-4) and severe LEE (grade 3-4). Potential confounders included pregnancy status.

The analysis included a total of 2050 HIV-positive women receiving HAART of which 60% were pregnant.

Pregnant women in this analysis were younger than non-pregnant, mean age 27.99 vs 35.96, $p<0.001$. They had higher CD4, lower viral loads and had been HIV-positive for a shorter duration of time. They also had less chronic hepatitis and were more likely to be both ART and nevirapine naïve. A similar proportion of pregnant and non-pregnant women had been exposed to nevirapine, with a greater proportion of non-pregnant women having CD4 ≥ 250 cells/mm³. See Table 1.

Table 1. CD4 cell count of women receiving NVP by pregnancy status

	n	%	n	%	p
NVP	218	17.73	169	20.58	0.106
CD4 \leq 250c/uL	50	23.81	22	13.92	
CD4 \geq 250c/uL	160	76.19	136	86.08	0.018

Overall the investigators found pregnant women were significantly more likely than non-pregnant women to develop any LEE, 14.2 vs 9.1% respectively, $p=0.0001$. They also had a higher rate of severe LEE, 1.2 vs 0.6%, although this difference did not reach statistical significance.

Multivariate analysis found pregnancy to be significantly associated with any LEE, RR 4.7 (95% CI, 3.39-6.53, $p<0.01$ and with severe LEE, RR 3.8 (95% CI, 1.3-11.1). However, nevirapine was not significantly associated with any LEE, RR 1.17 (95% CI, 0.8-1.7) or severe LEE, RR 1.78 (95% CI 0.4-7.82) and this was regardless of pregnancy status. The investigators noted that due to concerns in the literature about nevirapine exposure at higher CD4 counts, these variables were included in the multivariate models despite not being significant in univariate analysis and they continued to demonstrate no association with LEE.

These investigators wrote: "While we support close monitoring for clinical or laboratory evidence of hepatotoxicity with any ART regimen, our results challenge the notion that NVP is uniquely associated with hepatotoxicity during pregnancy."

COMMENT

It seems likely that pregnancy does not increase the risk of nevirapine-related toxicity at CD4 counts below 250 cells/mm³ and is therefore safe to prescribe in pregnancy in accordance with current guidelines.

However, it gets more complicated with regard to safety of nevirapine in pregnant women with CD4 counts greater than 250 cells/mm³, and this study, along with others, is not showing any signal or nevirapine-associated toxicity in pregnancy.

It is also notable that expert panel reviews for new WHO guidance did not confirm an increase of serious adverse events and concluded that the benefits of using nevirapine in this situation outweigh the risks of not initiating ART (see our review of WHO guideline revisions).

Given the temporary pregnancy related immunodeficiency in addition to any HIV-related immunodeficiency it certainly seems sensible to re-run these analyses at higher CD4 counts - eg 400 cells/mm³.

Ref: Ouyang et al. Increased risk of hepatotoxicity in HIV-infected pregnant women receiving antiretroviral therapy independent of nevirapine exposure. *AIDS* 2009, 23:2425-2430.

Birth defects following efavirenz exposure in a South African Hospital

Polly Clayden, HIV i-Base

Although efavirenz is FDA pregnancy category D, the teratogenic risk is still uncertain. The Antiretroviral Pregnancy Registry has recorded birth defects in 14/477 (2.9%) live births. Data from the MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, University College London, showed birth defects occurred in 5/205 (2.4%) infants with early pregnancy exposure.

A paper in the January 2010 edition of *AIDS* authored by Ebrahim Bera and colleagues describes findings from a regional South African cohort of pregnant women exposed to efavirenz. This is the largest study to date of efavirenz based HAART exposure from the second trimester onwards.

This study evaluated data from the Efavirenz in Pregnancy Registry which was set up in January 2006. The registry is prospective and based at Frere Hospital in East London, a referral hospital for a large area of the Eastern Cape.

Women who conceived on efavirenz and presented in the first trimester were offered the choice of termination of pregnancy (to 20 weeks gestation) or switched to another drug. Women who presented at 14 weeks or later and eligible for HAART were initiated on an efavirenz-based regimen.

The investigators reported that between 1 January 2006 and 31 December 2008, 744 women were initiated on efavirenz-based regimens from the second trimester onward. Of these,

89 women were still pregnant at the time of evaluation and 32 were lost to follow up.

During the same period, 220 women conceived while receiving efavirenz based HAART and 42 nevirapine-based HAART. Of this group, 17 and seven women were still pregnant and eight and two women were lost to follow up receiving efavirenz and nevirapine respectively.

The investigators classified women who had received efavirenz-based HAART throughout the entire first trimester as "complete first trimester exposure" and those who substituted efavirenz for another drug as "partial first trimester exposure".

This analysis evaluated data from 851 women with pregnancy outcomes.

The 623 women initiated on efavirenz in pregnancy were a median age of 28 (IQR 25-32) years with median of 9 (IQR 4-13) weeks of HAART. Birth defects occurred in 16 live births, a prevalence of 2.6% (95% CI 1.5-4.2).

The 195 women who conceived while receiving efavirenz were a median age of 30 (27-34) years, with a median of 39 (37-40) weeks of HAART. Birth defects occurred in 5/184 live births and 1/4 stillbirths, a prevalence of 3.3% (95% CI 1.2-7.0). The investigators noted that 93% of this group, received efavirenz based HAART for longer than one month before conception and all pregnancies were unintended.

There were no significant differences in the prevalence of birth defects between the first and second/third trimester exposure (prevalence ratio 1.27; 95% CI 0.5-3.20, p=0.301). Neither were there differences between complete (4/131; 3.1%) and partial (2/53; 3.8%) efavirenz exposure (prevalence ratio 0.81; 95% CI 0.15-4.29, p=0.556).

The investigators also observed a birth defect in 1/33 live nevirapine exposed infants, a prevalence of 3.0% (95% CI 0.1-15.8). The prevalence ratio of birth defects following conception on efavirenz compared to nevirapine was 1.08; 95% CI 0.13-8.65, p=0.69. However the numbers of nevirapine exposures are too small to draw any conclusions.

The investigators suggested that these data provide some reassurance on second/third line trimester efavirenz use for pregnant women. There were too few first trimester exposures in this study to make any recommendations concerning the safety or teratogenicity of efavirenz during this period.

COMMENT

This data adds to, and is consistent with, the existing experience of first trimester exposure to efavirenz. This study also provides significant new data on second and third trimester only exposure that is generally reassuring.

Bera E et al. Birth defects following exposure to efavirenz-based antiretroviral therapy during pregnancy: a study at a regional South African hospital. *AIDS* 24(2):283-289, January 2010.

CANCER AND HIV

COMMENT

Outcomes from screening study for anal cancer in HIV-positive compared to HIV-negative patients

Simon Collins, HIV i-Base

A recent paper in the September 2009 issue of *Gut* reported significantly poorer diagnostic results from colonoscopy screening in HIV-positive compared to HIV-negative controls. This included higher prevalence of lesions, larger and more advanced lesions and that these were occurring at a younger age in the HIV-positive group.

Bini and colleagues from New York performed colonoscopy screening for colonic neoplasms in 136 asymptomatic HIV-positive men older than 50 years and 272 HIV-negative controls matched for age, sex and family history. All participants were patients at a single VA site, with screening performed from 2002-2004. Exclusion criteria included previous screening (5-10 years) or positive faecal occult blood test.

The median duration of infection in the HIV-positive groups was 11 years (IQR 7-14), median CD4 count was 346 cells/mm³ (IQR, 236-707) and around 90% were on HAART, 73% of who had had undetectable viral load.

The study found a significantly higher prevalence in HIV-positive patients (62.5% vs 41.2% ($p < 0.001$)). This remained highly significant after adjustment for potential confounding variables, including age, sex, race/ethnicity, current alcohol use, current smoking, use of NSAIDs and aspirin, family history of colorectal cancer and history of screening.

Compared with control subjects, HIV-positive patients had significantly increased odds of having a neoplastic lesion (OR = 2.38; 95% CI, 1.56 to 3.63). This association remained highly significant after adjustment baseline characteristics (OR = 3.00; 95% CI, 1.83 to 4.93) and after further adjustment for tobacco, alcohol, aspirin and NSAIDs (OR = 2.84; 95% CI, 1.74 to 4.62).

Compared with controls, HIV-infected patients were significantly less likely to have hyperplastic (benign) polyps and were more likely to have adenomas 6-9 mm in diameter. More HIV-infected subjects than control subjects had two or more adenomas detected (41.2% vs 30.9%, $p = 0.04$).

Among the 11 adenocarcinomas that were diagnosed, HIV-positive patients were significantly younger than those without HIV (52.4 (SD 1.3) vs 60.3 (SD 4.0) years, $p = 0.002$), a difference of 7.9 (95% CI, 3.6 to 12.2) years. Late-stage adenocarcinoma of the colon (stage III or IV) was more common in HIV-positive subjects (3/5 (60.0%)) than in controls (1/6 (16.7%)), although this difference was not statistically significant ($p = 0.24$).

The study found no association between neoplastic lesions of the colon and duration of HIV infection, CD4 count, or viral load, but a protective effect was reported in HIV-positive people on HAART (OR = 0.13; 95% CI, 0.02 to 1.02).

The authors concluded that their findings suggest that screening colonoscopy should be offered to HIV-positive patients, although the age of initiation and the optimal frequency of screening require further study.

These add to the growing evidence supporting a screening programme for HIV-positive people as a targeted high risk group. See coverage in the EACS conference report earlier in this issue of HTB. [2]

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TRANSMISSION AND PREVENTION

Male circumcision: new data supporting protective mechanism

Simon Collins, HIV i-Base

The protective mechanism for reducing heterosexual HIV transmission to circumcised men has been attributed to two factors relating to the properties of the inner foreskin: a thinner keratin layer reducing the physical barrier and a higher concentration of CD4 and Langerhans cells that are primary targets for infection. A third factor may be that the foreskin prolongs the time that fluid that contains HIV remains in contact with genital tissue. In theory, the size of the foreskin should also positively correlate to the risk from these mechanisms, and this is supported by results from a study published in the 23 October edition of the journal AIDS. [1]

HIV infection rates were collected from 965 men in Rakai, Uganda, who were recruited for two randomised circumcision studies. These men were initially HIV-negative and followed for a total of 3920 person years, prior to circumcision as part of the trial protocol. The results from these trials have already been reported. [2, 3]

After circumcision, the foreskin surface area was calculated (length x width; cm²) and infection rates prior to circumcision were calculated by quartile. Men who became infected compared to those who remained HIV-negative were found to have a significantly greater foreskin surface area (mean 43.3 (±2.1) vs 36.8 (±0.5) cm² (p<0.01).

HIV incidence/100 person years (PY) was 0.80, 0.92, 0.90 and 2.48 for men with foreskin surface areas in the lower (7.0-26.3 cm²), second (26.4-35.0 cm²), third (35.2-45.5 cm²) and upper quartiles (45.6-99.8 cm²) respectively.

The incidence rate ratio (IRR) of HIV acquisition, after adjusting for age, education, religion, number of sex partners and condom use, was significantly higher for men in the highest compared to the lowest quartiles of foreskin surface area (IRR 2.37; 95%CI 1.05-5.31).

There was, however, no significant difference in HIV incidence between the lower three quartiles. In the adjusted analysis, older age (IRR 4.16; 95%CI 1.55, 11.19, and IRR 4.00; 95%CI 1.46, 10.74; for ages 25-30 and >30 respectively, each compared to 15-24 years), lower education level (0.40; 0.18, 0.91; secondary/tertiary vs primary/none) and catholic religion (IRR 0.37; 0.16, 0.82; Catholic vs non-Catholic) were also significantly associated with risk of HIV acquisition.

The authors concluded that their findings, in addition to the observational studies and randomised trials, add plausibility to the hypothesis that the foreskin is a tissue vulnerable to HIV acquisition.

They suggested that minimising retention of residual foreskin tissue after male circumcision using dorsal slit and sleeve procedures rather than the forceps-guided procedure (which leaves 0.5-1.0 cm of mucosal skin proximal to the corona) is a theoretical concern. However, they also reported that they did not observe any increased risk of HIV acquisition among men

with smaller foreskin surface areas that were substantially larger than residual tissue retained after circumcision surgery.

COMMENT

While the study states that these findings need to be replicated in other studies, it is difficult to see how this could be supported.

Firstly, although circumcision studies have shown protection against HPV, HSV and syphilis, men primarily want to be circumcised in order to reduce their risk of HIV infection, and should be told if they are HIV-positive at the time of surgery. It is unclear whether the men in this study would have undertaken circumcision, had they been made aware that they had already caught HIV prior to the intervention.

Secondly, now that circumcision had been proven to reduce heterosexual transmission in high prevalence settings, it is difficult to see why participants would be followed for any significant period prior to surgery.

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A caution for male circumcision programmes: high complication rates highlighted outside a trial setting

Simon Collins, HIV i-Base

Important limitations to the protective benefits from circumcision, prompted by a 2008 WHO review by Robert Bailey and colleagues, of complications during male circumcision in Kenya [1], were discussed in a recent editorial article in the 2 January 2010 journal AIDS. [2]

The original study, available online without subscription, deserves reading in full by anyone rushing to roll-out circumcision programmes on a community level.

The WHO study prospectively followed approximately 1000 men (IQR ~13-15, range 5-21 years), who were circumcised in July-August 2004, who were interviewed about complications 30-89 days after surgery. Twenty-four men were directly observed during circumcision and after 3, 8, 30 and 90 days.

The participants had either a traditional circumcision performed in a village or within a household compound, or a medical circumcision performed by someone the participant considered to be a clinician in a hospital, health centre, dispensary or private office. The researchers also interviewed 21 traditional and 20 clinical people who carried out the circumcisions.

After interviewing approximately two-thirds of participants and directly following the 24 cases, the researchers found very high rates of complications and decided to directly examine and

interview the remaining 298 men, (range 45 - 89 days after circumcision).

One or more complications were reported by 35% men circumcised traditionally and by 17% men circumcised medically (OR 2.53; 1.89–3.38; $p < 0.001$). These rates were significantly higher than the approximate 1-3% observed in clinical trials, or in infants circumcised in developed countries.

Although rates for each complication were not given, the most common self-reported complications were excessive bleeding, infections and excessive pain, with bleeding the most common. Pain upon urination, incomplete circumcision requiring repeat surgery, and lacerations of the glans, the scrotum and the thighs were also reported. Many traditional circumcisions continued to bleed and needed medical support.

Infections were equally common among subjects circumcised medically and traditionally. Those circumcised traditionally were more likely to report receiving antibiotics from local practitioners, often from “travelling nurses” with few or no qualifications. These informal practitioners often sold injections to address infections and bandaged the wound after applying gravacine (a talcum powder with penicillin). Whether it prevented infections we cannot be sure, but it tended to cake in the wound, delay healing and result in thick scarring and, in a few cases, permanent discolouration.

In 24% of the traditional cases and 19% of the medical cases, the wound had still not healed after 60 days ($p=0.056$) in contrast to 96% healed by 30 days in the randomised male circumcision in Kisumu, Kenya.

In the interviews with 298 men, traditionally circumcision was much more likely not to have healed (21% vs 10%, AOR 0.43; 0.22–0.84, $p=0.014$), to have significant swelling (14% vs 5%, AOR 3.20; 1.27–8.07, $p=0.014$), to have a culturally unacceptable amount of foreskin remaining (12% vs 3%, AOR 5.32; 1.54–18.31, $p=0.008$); and to higher trend to have lacerations (17% vs 10%, AOR 1.91; 0.93–3.91, $p=0.077$), and keloid scarring (17% vs 10%, AOR 1.99; 0.98–4.06, $p=0.059$).

Compared to developed country settings, delayed healing, swellings and lacerations were also prevalent among those circumcised medically.

The researchers concluded that “extensive training and resources will be necessary to build the capacity of health facilities in sub-Saharan Africa before safe circumcision services can be aggressively promoted for HIV prevention” and that “the rate of serious complications from traditional circumcisions should also serve as an alarm to ministries of health and the international health community that focus cannot only be on areas where circumcision prevalence is low”.

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PRO 2000 microbicide gel does not pan out

Richard Jefferys, TAG

Earlier this year at the Conference on Retroviruses & Opportunistic Infections, Salim Abdool Karim presented data suggesting that a vaginally applied microbicide gel called PRO 2000 might offer some protection against HIV infection in high-risk women. [1]

The results were not statistically significant but represented a trend, suggesting a 30% reduction in risk of acquisition of the virus. Some commentators at the meeting noted that because this study had two separate control arms (a placebo gel and no gel), comparing the total number of control participants from both of these arms with the group that received PRO 2000 would render the result statistically significant. To his credit, Karim emphasised that such an analysis was not a pre-specified part of the protocol and was therefore inappropriate. He also pointed out that there was a larger, ongoing phase III study of PRO 2000 involving over 9,000 women that would provide a definitive answer as to the product's efficacy.

The results from this trial, called MDP-301 and run by the UK Medical Research Council in close collaboration with Imperial College in London and investigators in four African countries, were announced on 14 December. Disappointingly, the hint of efficacy seen in the smaller phase IIb was not duplicated: there were 130 HIV infections among the 3,156 women that received PRO 2000 gel, and 123 infections in the group of 3,112 women that received placebo gel.

The first news story reporting the result appeared in the Times newspaper (UK edition) the day before and broke the embargo on the MRC releases by several hours; it was subsequently taken offline before being reinstated. The article dramatically - but erroneously - characterises the PRO 2000 result as “a significant setback.” The whole purpose of large phase III efficacy trials is to definitively answer the question of whether an intervention works and, quite often, they don't. In the case of PRO 2000, the microbicide is one of the last in a pipeline of products with relatively limited direct antiretroviral activity and, over the past several years, there has been increasing recognition in the field that more specific products are needed. Several such antiretroviral microbicides, such as the gel form of the drug tenofovir (Viread) are now in trials.

Source: TAG weblog (14 Dec 2009)

Further information on the MDP-301 trial:

Background materials from the trial's sponsor, the Microbicide Development Programme of the UK Medical Research Council:

<http://www.mdp.mrc.ac.uk>

AVAC's PRO 2000 resource page:

<http://www.avac.org/ht/d/sp/i/3426/pid/3426>

Global Campaign for Microbicides:

<http://www.global-campaign.org/MDP301.htm>

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Source: TAG basic science weblog (19 Feb 2009).

BASIC SCIENCE

Recent basic science updates from Richard Jefferys excellent web log.

Bridging the neurology-immunology barrier

The Cell Press journals *Neuron* and *Immunity* have collaborated to produce a timely free-access special issue focusing on the interrelatedness of neural and immune systems. [1]

The editors of *Neuron* write: "The brain was once thought to be a largely 'immune-privileged' system. Traditionally, research has reflected this segregation, with neuroscientists focusing on the nervous system and immunologists focusing on the immune system. Yet as science in both realms has moved forward, it has become clear that the nervous and immune systems interact on many levels, in both disease states and under healthy conditions. It is also clear that molecules traditionally viewed as neural- or immune-specific play important and often distinct roles in the other system. Experimental evidence of interactions between the neural and immune systems continues to accumulate, and the two research communities are beginning to communicate more as well. In this same spirit, *Neuron* and *Immunity* have coordinated to bring together a compilation of articles on selected topics related to the interface between the nervous and immune systems."

The issue includes articles addressing "Immune Activation in Brain Aging and Neurodegeneration" and "Neuroimmune Crosstalk in HIV Infection." [2, 3]

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Early predictors of disease progression

Richard Jefferys, TAG

Recent research involving SIV-infected macaques has suggested that the early loss of a particular type of memory CD4 T cell (known as a "central memory" T cell or Tcm) may be a key predictor of the subsequent pace of disease progression. Tcm are a long-lived subset of memory T cells that can proliferate robustly in response to antigen. Tcm proliferation generates a fleet of T cells belonging to a shorter-lived subset called "effector memory" (Tem) cells. Tem are generally viewed as first-responders that can rapidly execute anti-pathogen functions, while Tcm provide a stem-cell like renewal source for new Tem if their numbers need to be bolstered. Studies in HIV-infected people have consistently shown a loss of Tcm and increase in Tem (which equates to a decrease in long-lived resting T cells and an increase in short-lived activated T cells), but whether changes in the numbers of different T cell subsets during early infection can predict disease

progression has not been thoroughly evaluated.

A new study published in the *Journal of Infectious Diseases* set out to answer the question of whether quantifying Tcm in early infection provides prognostic information. To provide sufficient statistical power to ensure confidence in the findings, a total of 466 individuals were studied, among whom 101 progression events occurred.

It turned out that the proportion or absolute number of Tcm did not correlate with subsequent disease progression (defined as the time to AIDS or death), but several other parameters did. These included the proportion of naïve CD8 T cells, with a greater proportion being strongly associated with slower disease progression ($p < 0.001$); this correlation remained significant after adjustment for CD4 T cell count. The numbers of CD8 T cells expressing the IL-7 receptor (CD127) were also linked to the rate of progression; having fewer of these cells correlated with a faster disease course.

Immune activation was assessed by measuring the proportion of CD4 and CD8 T cells expressing the proliferation marker Ki67. In both subsets, higher proportions of Ki67-expressing cells equated to faster progression, and for CD8 T cells this relationship held up after adjustment for baseline CD4 T cell count, age, and viral load. The median time to AIDS or death among subjects with the highest levels of Ki67-expressing CD8 T cells (based on dividing participants into quartiles) was 4 years for those in the top quartile compared to 10 years for those in the lowest.

Finally, measures of cell-associated viral load (CAVL: the proportion of CD4 T cells containing HIV DNA) were correlated significantly with progression in those participants sampled within 225 days of their estimated date of seroconversion (225 days was the median time after the estimated date of seroconversion that samples were obtained). Among participants sampled later, CAVL was not significantly correlated with rate of progression, suggesting an important impact of the early spread of HIV among CD4 T cells on subsequent disease course. The researchers also evaluated CAVL in different CD4 T cell subsets: naïve, central memory, transitional memory and effector memory. To their surprise, naïve CD4 T cells showed relatively high rates of infection, albeit around 10-fold lower than the memory subsets. Because resting naïve CD4 T cells are known to be very resistant to HIV, the researchers speculate that the infected naïve cells may have been rendered susceptible by immune activation (naïve CD4 T cells have been shown to become susceptible to R5-using HIV after they receive activation signals).

The authors conclude by stating: "we find that quantification of Tcm cells in early infection does not provide predictive power for progression. However, measures of homeostasis and activation, including CD127 expression and Ki-67, do provide such information and should be studied further to determine their role in clinical monitoring of HIV-1 progression...Future efforts to identify markers of subsequent progression should focus on measures of activation and homeostasis during the earliest stages of infection."

Source: TAG Basic Science Weblog (13 Jan 2010).

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OTHER NEWS

African civil society campaign against Uganda's anti-homosexuality bill

Following the tabling of the Anti-Homosexuality Bill before the Ugandan Parliament which provides for imprisonment and the death penalty for infringements of the Bill, civil society organisations in Africa are mobilising to persuade Ugandan Parliamentarians to block this pernicious Bill. The Bill has already gone through the first reading in Parliament. We are very concerned that it may become law this year. If it is passed, even in diluted form, it would constitute a massive setback for human rights in Africa.

AIDS Law Project in South Africa have produced statement which your organisation is invited to endorse. Please also endeavour to secure the endorsements of prominent individuals, such as religious leaders, influential professional persons, heads of organisations and others with a respected public profile. The statement is self-explanatory. Kindly submit your endorsement on or before 12h00, Monday, 29 March (SA time). Please supply the full name of your organisation together with your full name, office address, telephone contact details and organisational website. Please also indicate in your email that you have been authorised by your organisation to endorse the statement.

Please send your endorsement to Ms Adila Hassim of the AIDS Law Project at:

hassima@alp.org.za

Please copy your email to Ms Phumi Mtetwa of the Lesbian and Gay Equality Project at:

phumi@equality.org.za

STATEMENT BY AFRICAN CIVIL SOCIETY

We, the individuals and organisations from African countries listed hereunder, recognise the universality of the human rights of all persons.

We affirm that the right of men and women to have same sex relationships is a fundamental human right.

We are further guided in the knowledge that all forms of discrimination, in particular against vulnerable groups, undermine the human dignity of all in Africa.

We are therefore profoundly disturbed by the nature, content and potential impact of the Anti-Homosexuality Bill ("the Bill") that was recently tabled in and is currently being considered by the Parliament of Uganda.

We believe that the Bill, if enacted, will cut deeply into the fabric of Ugandan society by:

- Violating the rights of an already vulnerable and severely stigmatised group of persons by attacking their dignity, privacy and other constitutionally protected rights;
- Disrupting family and community life by compelling everyone, by the threat of criminal sanction, to report those suspected of engaging in same-sex sexual activity;

- Seeking to withdraw Uganda from the family of nations by renegeing on the country's international law obligations;
- Undermining public health interventions such as HIV prevention, treatment, care and support;
- Promoting prejudice and hate and encouraging harmful and violent action to be taken against those engaging in same sex relations.

We respectfully call on the Parliament of Uganda to reject the Bill in its entirety.

We also call on African governments and the African Union to call on the President and Government of Uganda to withdraw the Bill and to respect the human rights of all in Uganda, without exception.

International AIDS Conference to be held in the US after over 20-year ban

The International AIDS Society has announced that the 2012 International AIDS Conference will be held in Washington, D.C. This will mark the first time the meeting has been held in the United States since 1990, when it was held in San Francisco.

The decision came largely as a result of the lifting of restrictions for people with HIV entering the United States, which was announced by President Obama in October.

The US HIV travel ban was consistently opposed by HIV activists and the decision taken by the IAS to refuse to hold meetings in the US was widely supported.

The 2012 meeting, held from 22-27 July, is expected to attract more than 25,000 delegates from nearly 200 countries, including more than 2,500 journalists.

Source: Press release, International AIDS Society. The IAS announces Washington, DC, as site of the 19th International AIDS Conference in July 2012: removal of entry restrictions on People Living with HIV by the U.S. allows for return of conference after 22-year absence. (30 Nov 2009).

The IAS maintains a detailed global database on HIV-related travel restrictions:

<http://www.hivtravel.org>

ON THE WEB

Conference reports and online abstracts:

Webcasts from 11th Lipodystrophy Workshop

11th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV

26-28 October 2009, Philadelphia, USA

It is an incredibly useful feature of this small specialised meeting that the organisers arrange for nearly all oral presentations to be available as free access webcasts.

The oral plenary lectures at the meeting are of a consistently high standard, often inviting experts from outside the HIV field to provide an overview on newly emerging issues relating to long-term HIV management.

<https://lipo09.events-register.com/lipodystrophy/default.cfm?itemtypeid=15&title=Webcasts%20and%20videos>

Webcasts from 12th EACS

11-14 November, Cologne

Presentations from this conference are now available online.

This year a comprehensive programme of lectures and sessions available as webcasts and podcasts and include many of the slide sets:

<http://www.europeanaidscinicalsociety.org>

<http://www.multiwebcast.com/eacs/2009/12th>

Access requires a free one-time registration using the invitation code: EACS2009

The abstracts from the meeting are currently only available in a subscription issue of HIV Medicine (2009, volume 10, issue S2).

How to access the webcast?

- 1) Go to: www.europeanaidscinicalsociety.org/
- 2) Click on the Webcast link to the left
- 3) Click on the webcast banner
- 4) Click Sign In and enter your username and password

How to access a single presentation?

- 1) Click on the presentation you would like to access below
- 2) Enter your username and password when prompted

Reports and journals:

PLoS Medicine

Volume 6(11) November 2009

Effects of genital ulcer disease and HSV-2 on the efficacy of male circumcision for HIV prevention: analyses from the Rakai trials. Gray RH et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000187>

Ron Gray and colleagues analyse data from two circumcision trials in Uganda to assess how HSV-2 status and genital ulcer disease affect the procedure's ability to reduce HIV infection.

Free journal on immunology and cardiovascular disease

The January 2010 issue of the journal *Clinical Immunology* is offering free access to a series of articles addressing the immunology of cardiovascular disease. Among a range of related subjects, the reviews address data on the roles of innate and adaptive immunity in the development of atherosclerosis and the status of experimental immunotherapeutic approaches to treating the disease.

Ref: *Clinical Immunology*. Volume 134, Issue 1, Pages 1-96 (January 2010). *Immunology and Cardiovascular Disease*.

<http://www.sciencedirect.com/science/journal/15216616>

Community resources and publications:

Clinical management of the HIV-positive woman

TheBody.com

A podcast discussion with Kimberly Smith and Valerie Stone

<http://broadcaster.thebody.com/t?ctl=179F25:B33203735488890861B00D26D4C955E3&>

Recent years have brought HIV health care providers a deeper understanding of the unique challenges involved in providing care to HIV-infected women. Although there remains a dearth of information regarding the impact of HIV and antiretroviral therapy on women, there is much that we do know. For instance, research has shown us that HIV-infected women can have a high rate of cervical cytological abnormalities and certain gynecologic complications. We are well aware that reproductive counseling is an essential part of care for HIV-infected women. In addition, the burdens of child and family care often create obstacles to adherence and continuation of care. These and other issues make it more important than ever that today's HIV health care providers have as complete an understanding as possible of the ideal manner in which to treat their HIV-infected female patients.

Medical resources:

HIV inSite resources

Health care of the HIV-positive transgender person

Barry Zevin, MD. September 2009. [RealAudio with slides]

<http://hivinsite.ucsf.edu/InSite?page=cfphp-zevin>

Dosing of antiretroviral drugs in adults with renal insufficiency and haemodialysis

UCSF Center for HIV Information

<http://hivinsite.ucsf.edu/InSite?page=md-rr-18>

FUTURE MEETINGS

2010 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.

7-9 April: 11th International Workshop on Clinical Pharmacology
<http://www.virology-education.com>

25-29 April: 21st Harm Reduction Conference, Liverpool.
<http://www.ihra.net>

31 May-2 June: 6th Intl HIV /HCV coinfection Workshop, Israel.
<http://www.virology-education.com>

24-25 June: 5th International Workshop on Hepatitis C - Resistance and New Compounds, Boston.

23-24 June: 5th International Workshop on Clinical Pharmacology of Hepatitis Therapy, Boston.
<http://www.virology-education.com>

15-16 July: 5th International Workshop on HIV Transmission - Principles of Intervention, Vienna.
<http://www.virology-education.com>

16-17 July: 2nd Intl Workshop on HIV Pediatrics, Vienna.
<http://www.virology-education.com>

18-23 July: XVIII International AIDS Conference (AIDS 2010), Vienna.
<http://www.aids2010.org>

12-15 September: 50th ICAAC, Boston.
<http://www.icaac.org>

11 September: 3rd International Workshop on Clinical PK of TB Drugs
<http://www.virology-education.com>

7-11 November: 10th HIV International Congress on Drug Therapy in HIV Infection, Glasgow
<http://www.hiv10.com>

HIV i-BASE

HIV i-Base is an HIV-positive led treatment information service. We produce information both for clinicians and other health workers and for people with HIV.

Our publications are used and have been adapted in many countries and settings.

Our fully searchable website is designed to be fast to access, easy to use, and simple to navigate.

All i-Base publications are available online.
<http://www.i-base.info>

i-Base produce five non-technical treatment guides, which are available online as web pages and PDF files.

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

- Introduction to combination therapy
- A guide to changing treatment
- Avoiding & managing side effects
- HIV, pregnancy & women's health
- Hepatitis C for People living with HIV

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

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

Recent questions include:

- Doubts when I'm told that my life expectancy is good...
- What is the prognosis if diagnosed with these symptoms?
- What is the risk of infecting my girlfriend with HIV?
- News reports of research that 'could' be a cure
- Does treatment work if you start with a low CD4 count?
- Can hepatitis B reactivate?
- Does yohimbe interact with HIV meds?
- Pregnancy without viral load results
- Should I start treatment at CD4 320?
- How do I time my meds when travelling?
- Is a viral load result of 50 really a blip?
- Does skipping a dose have an immediate effect?
- Does masturbation have any effect on HIV-positive people?
- Personal results from a recent diagnosis...

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.

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



HIV i-Base
www.i-Base.info



Southern African HIV Clinician's Society
www.sahivsoc.org