

## january–february 2013

### CONTENTS

<b>EDITORIAL</b>	<b>2</b>	
<b>HTB SUPPLEMENT</b>	<b>2</b>	
• i-Base guide to changing treatment		
<b>TREATMENT ALERT</b>	<b>2</b>	
WHO statement: generic antiretroviral therapy is safe and effective		
<b>CONFERENCE REPORTS</b>	<b>4</b>	
3rd International Workshop on HIV and Women, 14 - 15 January 2013, Toronto, Canada		
• Introduction		
• Nevirapine-containing ART does not reduce combined oral contraceptive effectiveness		
• Minimal risk of sexual HIV transmission for heterosexual couples when the HIV positive partner has an undetectable viral load		
• Differences by age for women in response to initial ART: meta-analysis from clinical studies submitted to the FDA		
• Lopinavir/ritonavir in pregnancy: results from a systematic review		
• Possible mechanisms for adverse pregnancy outcomes in HIV positive women		
<b>CONFERENCE REPORTS</b>	<b>8</b>	
43rd Union World Conference on Lung Health, 13 - 17 November 2012, Kuala Lumpur, Malaysia.		
• Introduction		
• Paediatric TB: glimpses of PK data and a potential new approach to drug development		
<b>ANTIRETROVIRALS</b>	<b>10</b>	
• Dolutegravir submitted to EU, US and Canadian regulatory agencies		
• Darunavir: new oral suspension and 800 mg formulations approved in EU		
• US label changes for rilpivirine and Eviplera follows EU caution on high baseline viral load: new summary on drug resistance		
<b>TREATMENT ACCESS</b>	<b>12</b>	
• New UNITAID grants focus on paediatric HIV, TB and malaria		
• Global Fund results continue upward trend		
• Germany extends €200million annual support to Global Fund until 2016		
• New analysis of country pledges and contributions to the Global Fund		
• Renewal of Indian Global Fund Grant made conditional on government funding for ART		
• MSF and DNDi report highlights importance of research into neglected diseases		
<b>SIDE EFFECTS &amp; COMPLICATIONS</b>	<b>15</b>	
• Smoking is largest contributor to reduced life expectancy in Danish HIV cohort		
• Low bone mineral density in MSM irrespective of HIV status		
<b>PAEDIATRIC CARE</b>	<b>18</b>	
• The American Academy of Pediatrics recommends that HIV positive mothers not breastfeed their infants, regardless of maternal viral load and ART		
• US paediatric guidelines updated		
<b>TREATMENT GUIDELINES</b>	<b>20</b>	
• Implications of WHO guidelines increases CD4 threshold for starting treatment to 500 cells/mm <sup>3</sup>		
<b>TUBERCULOSIS COINFECTION</b>	<b>22</b>	
• FDA approves bedaquiline for MDR TB: first new tuberculosis drug in half a century		
• US fund additional \$11million for Xpert TB diagnostics in 14 countries		
<b>BASIC SCIENCE</b>	<b>23</b>	
• Attack of the killer helpers (part two)		
• Lymph node fibrosis, CD4 T cells and immune reconstitution		
• New research on gut CD4 T-cell depletion and HIV pathogenesis		
<b>TRANSMISSION &amp; PREVENTION</b>	<b>26</b>	
• UK group describe risk of HIV transmission for people on effective ART as "extremely low"		
• CDC issues brief on the prevention benefits of HIV treatment		
• WHO recommendations for prevention and treatment of HIV for sex workers and their clients		
<b>OTHER NEWS</b>	<b>27</b>	
• "AllTrials" campaign for publication of research results		
<b>ON THE WEB</b>	<b>27</b>	
<b>FUTURE MEETINGS</b>	<b>29</b>	
<b>PUBLICATIONS AND SERVICES FROM i-BASE</b>	<b>30</b>	
<b>DONATION FORM</b>	<b>33</b>	
<b>ORDER FORM</b>	<b>34</b>	

## EDITORIAL

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### Welcome to the first HTB issue of 2013.

We kick off with a World Health Organisation (WHO) statement emphasising that generic antiretroviral therapy is safe and effective. This was issued in response to a widely distributed article from the BBC perhaps implying otherwise, and explains its prominence as a treatment alert. As the NHS in the UK is on the brink of making significant savings using generic ARVs, clarity on their efficacy will be increasingly essential to maintain confidence in HIV care.

Our conference coverage starts with the 3rd International Workshop on HIV and Women. Now in its third year, this meeting is gaining in importance and gives an opportunity for in depth discussion on topics that are often lost or marginalised at larger meetings. One focus of the meeting was hormonal contraception. Why did it take so long to clarify that the 30 percent decrease in contraceptive hormone levels when they are taken with nevirapine does not appear to reduce the effectiveness of combined oral contraceptives?

A systematic review revealed minimum risk of heterosexual transmission, when the HIV positive partner has an undetectable viral load on ART. A recent joint statement from The British HIV Association (BHIVA) and the Expert Advisory Group on AIDS (EAGA) as well as one from the US Centers for Disease Control (CDC) on the prevention benefits of ART - both summarised in this issue - reinforce the earlier Swiss statement.

The 43rd Union World Conference on Lung Health included news on paediatric TB, including early pharmacokinetic data on second line drugs and plans for more rapid assessment of investigational ones for children. Other important TB news covered later in the issue is the FDA approval of bedaquiline for MDR TB: the first new tuberculosis drug in half a century; US funding for Xpert TB diagnostics and new UNITAID grants focus of paediatric TB.

The integrase inhibitor dolutegravir has been submitted to regulatory agencies and review articles on the complications of ART include an important study highlighting that mortality is driven more from smoking than HIV and that reduced bone mineral density may be prevalent prior to HIV infection.

Nathan Geffen takes a look at the implications of changing WHO antiretroviral guidelines to 500 threshold for starting treatment. And Richard Jeffery's provides fascinating Basic Science updates.

Finally please consider supporting the AllTrials campaign (alltrials.net), reported in Other News. This demands publication of all research results to help regulators, doctors and patients to make informed decisions about treatments.

### HTB supplements

Two i-Base guides have been updated and reprinted in February 2013:

- Changing treatment and drug resistance
- HIV testing and the risks of sexual transmission

Both are already online and are available free, including in bulk to UK clinics. Please order online in the regular way.

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

## TREATMENT ALERT

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### WHO statement: generic antiretroviral therapy is safe and effective

**A recent BBC report that inaccurately commented on safety issues in relation to generic HIV treatment was sufficiently erroneous and widely distributed to prompt the unusual response of this public statement from the WHO.**

#### WHO Department of HIV/AIDS and Department of Essential Medicines and Health Products

On 16 January 2013, an article entitled "Study questions generic HIV drug use" appeared on BBC News Health (note this article has since been modified) [1]. The article was based on original research by Rochelle Walensky et al that was published in the Annals of Internal Medicine on 15 January 2013, and describes a mathematical simulation of HIV disease. [2]

Unfortunately, the BBC News Health article presented the findings of the modelling study as indicative of the need to make an ethical trade-off between cost savings and efficacy. The response below from WHO's Department of HIV/AIDS and Department of Essential Medicines and Health Products points out that such an interpretation is misleading and not supported by the extensive global evidence of the efficacy of quality-assured generic antiretroviral therapy. [3]

## Generic antiretroviral therapy is safe and effective

Rochelle Walensky and colleagues provide important estimates of the potential cost savings associated with the introduction of generic-based antiretroviral therapy (ART) in the United States. Using conservative assumptions, they estimate first-year savings of up to US\$ 920 million and lifetime average savings of US\$ 42,500 per eligible patient. However, the authors of the study caution that this may require a tradeoff between drug efficacy and cost savings, as the regimens proposed in the model are not available fixed-dose combinations and may have inferior efficacy and could lead to poor adherence.

We would like to highlight three points related to this analysis.

First, the assumption of inferior efficacy is based on the suggesting that lamivudine (3TC) has poorer efficacy than emtricitabine (FTC). This assumption is in contrast to a recent systematic review that found no evidence of any difference between the two drugs in terms of efficacy and safety [4].

Second, the assumption of poorer adherence is based on the fact that generic formulations are not available as fixed-dose combinations. This may be the case in the United States, but quality-assured generic fixed-dose combinations of tenofovir, emtricitabine and efavirenz (TDF+FTC+EFV) do exist and are used in other parts of the world. [5].

Third, each of the scenarios includes the originator TDF product because TDF is patented in the US, and the estimated cost of this regimen is US\$ 9,200 per patient/year. However, a fixed-dose combination of TDF+FTC+EFV including generic TDF is currently available internationally and costs less than US\$ 200 per patient/year [6]. Taken together, these points suggest that potential cost savings in the United States of using generic regimens could be even greater than concluded by this analysis, with no negative consequences in terms of efficacy or adherence. It is important to also highlight that in this analysis, presumed differences between generic and originator regimens are associated with the use of different drugs (3TC versus FTC), and formulations (separate tablets rather than fixed-dose combinations), and not the use of generic drugs per se:

Walensky et al rightly consider quality-assured generic and originator drugs to be equivalent in terms of safety and efficacy. Despite ongoing doubts and controversies about the use of generic antiretrovirals over the last decade [7], comparative studies have found no differences in safety or efficacy between originator and quality-assured generic antiretrovirals [5]. Ensuring access to affordable antiretroviral therapy has been an essential precondition of the global scale up of antiretroviral therapy, and both generic and originator companies have an important role to play in ensuring that current and future antiretroviral regimens are accessible and affordable for all who need them.

The study by Walensky et al opens an important discussion about the extent to which patients in the United States are able to access more affordable, fixed-dose antiretroviral regimens that are already available in many other countries. Unfortunately, the findings of the modeling study are being portrayed as indicative of the need to make an ethical trade-off between cost savings and efficacy. Such an interpretation is misleading and is not supported by the extensive global evidence of the efficacy of quality-assured generic ART.

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## C O M M E N T

**Generic, off-patent medicines account for 65-85% of all NHS prescriptions.**

**Maintaining clarity on these issues will become increasingly important for confidence in HIV care in the UK, as patents are due to end for several of the most widely prescribed ARVs.**

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## CONFERENCE REPORTS

### 3rd International Workshop on HIV and Women

14 - 15 January 2013, Toronto, Canada

#### Introduction

**The International Workshop on HIV and women is held annually in January and is now in its third year.**

This years meeting included several useful overviews notably on contraception and the risk of transmission and acquisition, drug interactions with contraception, women and hepatitis C, and ageing in women with HIV.

Workshop materials - the abstract book and slide presentations - are online.

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

<http://preview.tinyurl.com/a5n9mfn>

Reports in this issue include:

- Nevirapine-containing ART does not reduce combined oral contraceptive effectiveness
- Minimal risk of sexual HIV transmission for heterosexual couples when the HIV positive partner has an undetectable viral load
- Differences by age for women in response to initial ART: meta-analysis from clinical studies submitted to the FDA
- Lopinavir/ritonavir in pregnancy: results from a systematic review
- Possible mechanisms for adverse pregnancy outcomes in HIV positive women

### **Nevirapine-containing ART does not reduce combined oral contraceptive effectiveness**

**Polly Clayden, HIV i-Base**

**Nevirapine is associated with a 30% decrease in contraceptive hormone levels in pharmacokinetic (PK) studies. Adequately powered studies have not previously been conducted to assess clinical outcomes, such as ovulation, in women receiving concomitant oral contraception and nevirapine.**

At the 3rd International Workshop on HIV and Women, Kavita Nanda from FHI 360 presented findings from a study comparing ovulation rates in women receiving combined oral contraceptives (COCs) with nevirapine-containing ART and COCs alone.

This was a non-randomised clinical trial of HIV positive women aged 18 – 35 years who had regular menstruation, were sexually active, and had no medical contraindications to COC use. It was conducted in South Africa and Uganda between June 2009 and May 2011.

The study enrolled 196 women receiving nevirapine-containing ART and 207 women currently ineligible ( $\geq 350$  cells/mm<sup>3</sup>) as a COC-only control group. All women received COCs containing 30 mg of ethinyl estradiol and 300 mg of norgestrel. The investigators estimated ovulation weekly serum progesterone ( $>10$  nmol/L was considered presumptive evidence of ovulation) in the first two treatment cycles. Participants took COCs for at least one cycle before their ovulation assessment. They were tested for pregnancy monthly for 24 weeks.

Women were a median of 29 years of age; most women were in the normal range for BMI and had been pregnant before.

The investigators found no statistically significant differences in ovulation rates between the two groups: 26% of the ART and 16% of COC-only groups ovulated in the first cycle; 18% of ART and 19% of COC-only ovulated in the second and 11% of ART and 12% of COC-only ovulated in both cycles. The unadjusted odds ratio (OR) for ovulation in the ART group compared with the COC-only group was 1.4 (95% CI 0.85 - 2.18),  $p=0.2$ .

Women receiving COCs at baseline were 62% less likely to ovulate during follow up, OR 0.38 (0.2 – 0.7),  $p=0.002$ . Older age (29 – 32 years) halved the likelihood of ovulation, OR 0.51 (0.27 – 0.98),  $p=0.04$ .

There were nine pregnancies in each group, giving pregnancy rates of 10 per 100 woman years (95% CI 5-19) for each group. Women who missed three or more pills in a row were 17 times more likely to get pregnant; OR 16.76 (3.15 – 89.24),  $p=0.001$ . Self reported adherence and condom use did not differ between the two groups.

Adverse events were no different between the groups; three were serious but unrelated to the study medication (**malaria, cellulitis and fracture**), all in COC-only group.

C O M M E N T

**Dr Nanda also gave a good overview of what is important with drug interactions with contraceptives at this meeting.**

Ref: Nanda K et al. Nevirapine-containing ART does not reduce combined oral contraceptive effectiveness: results from South Africa and Uganda. 3rd International Workshop on HIV & Women, 14 - 15 January 2013, Toronto, Canada. Oral abstract O\_03.

[http://regist2.virology-education.com/2013/3HW/docs/07\\_Nanda.pdf](http://regist2.virology-education.com/2013/3HW/docs/07_Nanda.pdf)

## **Minimal risk of sexual HIV transmission for heterosexual couples when the HIV positive partner has an undetectable viral load**

**Polly Clayden, HIV i-Base**

**A systematic review of publications reporting on rates of HIV transmission between heterosexual couples, where the HIV positive partner has an undetectable viral load on ART, revealed minimum risk of transmission.**

Michelle Letchumanan, on behalf of researchers from Canada and Uganda, presented results at the 3rd International Workshop on Women and HIV.

The investigators searched electronic databases for all relevant observational studies and randomised controlled trials (RCTs) from 1950 to January 2012. To increase sensitivity, they reviewed the reference lists of identified studies and review articles, and conducted a hand search of selected journals to identify recently published articles that may have been missed by the literature search.

They included studies reporting HIV transmission rates, ART history and viral load of the HIV positive partner. Only three studies met all the eligibility criteria with confirmed full virologic suppression in the HIV positive partner. A further two cohort studies, and one RCT (HPTN 052) had ART and viral load data but viral suppression was unconfirmed and these were included in a secondary analysis.

The three studies with confirmed undetectable virus reported on 991 heterosexual couples with 2,064 person-years of follow up available. The limit of detection was 50 copies/mL in one study, 500 and 50 copies/mL for another in earlier and later study periods respectively and 400 copies/mL in the third study included in this analysis.

The other three studies with unconfirmed viral suppression gave 8,170 person years of follow-up from the two observational studies reporting on 3,470 couples and the RCT reporting on 1,763 couples.

The investigators reported a transmission rate of 0 per 100-person years (95% CI: 0-0.5) for ART-treated patients when viral suppression was confirmed. The combined transmission rate when viral load was confirmed and unconfirmed was 0.14 per 100-person years (95% CI: 0.4-0.31).

Four transmissions occurred within 6 months of starting ART when viral suppression was unconfirmed. Removing these transmissions for a sensitivity analysis in compliance with the Swiss Statement criteria further reduced the upper limit of the 95%CI and yielded a transmission rate of 0 per 100-person years (95% CI: 0-0.1).

Dr Letchumanan noted that the study limitations included lack of data on: same-sex couples, type of sexual intercourse (vaginal or anal), frequency of sexual exposure, direction of transmission, viral load at the time of transmission, sexually transmitted infections rates and the extent of condom use.

But the implications for heterosexual couples are that there is a dramatically reduced minimum risk when the HIV positive partner has full viral suppression on ART, with caveats with regards to information on sexual intercourse type, STIs, and condom use.

C O M M E N T

**This study has been accepted for publication PLOS One and it gives extra reassurance to couples opting for this approach and health workers providing their care.**

Ref: Letchumanan M et al. Systematic review of HIV transmission between heterosexual serodiscordant couples where the HIV positive partner is fully suppressed on ART. 3rd International Workshop on HIV & Women, 14 - 15 January 2013, Toronto, Canada. Oral abstract O\_04.

[http://regist2.virology-education.com/2013/3HW/docs/08\\_Letchumanan.pdf](http://regist2.virology-education.com/2013/3HW/docs/08_Letchumanan.pdf)

## **Differences by age for women in response to initial ART: meta-analysis from clinical studies submitted to the FDA**

**Polly Clayden, HIV i-Base**

**Data on the effect of age and/or menopause in response to ART in women are scant.**

Preliminary analyses of the FDA database suggest a benefit of older age (50 years and above) for virological response, but no clinically or statistically significant gender differences in immunological responses overall (although some effect with NNRTI/NRTI).

US data has suggested that HIV positive women may undergo menopause earlier (46.5 years) than the general population (49 for African American and 51 years for white women). As menopause data was not collected in the trials included, J Yan, who presented findings from the FDA meta-analysis at the 3rd International Workshop on Women and HIV, explained that 50 years of age was used as a surrogate for this comparison.

Datasets of all treatment naïve women, enrolled in registrational ART trials submitted to the FDA between 2000-2010, were evaluated in this meta-analysis looking at age group differences at Week 24 and 48 in viral load < 400 copies/mL and CD4 change from baseline.

The database included 4,414 HIV positive treatment naïve women enrolled in 32 RCTs. Women were stratified into three groups: ≤35 years old, 36 - 49 years old and ≥50 years old, with the group difference between the youngest and oldest age groups being the major focus. Analyses were also performed looking at types of antiretroviral regimens. The majority of the women received either 2 NRTI/NNRTI (45.6%) or 2 NRTI/PI (46.19%) regimens.

The investigators reported a statistically significant lower virological suppression rate in women aged < 35 than those in ≥50 age group at both weeks 24 and 48 (estimated 95% CI of the log odds ratio difference at week 24 and 48 were respectively: -0.94, -0.24, and - 0.78, -0.17).

There were no clinically or statistically significant differences in CD4 increase (week 24 and 48 respectively: 95% CI -8.21, 25.25 and 95% CI -16, 22.76). However the younger group receiving NRTI/NNRTI regimens showed better responses at both time points albeit with huge confidence intervals (week 24 and 48 respectively: 95% CI 6.43, 52.59 and 95% CI 0.48, 53.88).

Ref: Yan J et al. Differences by age for women in the response to initial HAARTs: Meta-analysis from clinical studies submitted to the FDA (2000 – 2010). 3rd International Workshop on HIV & Women. 14 - 15 January 2013, Toronto, Canada. Oral abstract O\_011.

[http://regist2.virology-education.com/2013/3hw/docs/19\\_Yan.pdf](http://regist2.virology-education.com/2013/3hw/docs/19_Yan.pdf)

## Lopinavir/ritonavir in pregnancy: results from a systematic review

**Polly Clayden, HIV i-Base**

**Pharmacokinetic studies suggesting that pregnant women experience declines in lopinavir/r levels in the third trimester have led to differing dosing guidelines.**

BHIVA do not recommend increasing the standard 400/100 mg twice daily dosing in the third trimester, whereas US DHHS guidelines recommend a dose increase.

Marisol Martinez from Abbvie (the pharmaceutical company formerly know as Abbott) showed findings from a systematic review undertaken by the company to assess maternal and infant clinical and safety outcomes in pregnant women treated with lopinavir/r containing regimens. The investigators searched PubMed, EMBASE, and HIV conferences for studies published through May 31, 2012. Studies were selected if they included HIV positive pregnant women receiving regimens containing this boosted protease inhibitor (regardless of dose) and reported maternal and infant outcomes as a primary objective.

They identified 13 publications/presentations describing nine studies. The studies included 2675 women treated with lopinavir/r: 1618 were dosed at 400/100 mg twice daily, 70 received >800/200 mg/day with dosing interval not specified and 987 received an unknown lopinavir/r dose.

Overall >80% of women (64 – 97%) achieved viral suppression according to the threshold in the study in which they enrolled (200 – 1000 copies/mL). There was no significant difference in the proportion of women with viral load ≥1000 copies/mL in the one study that looked at both standard and high doses of lopinavir/r.

There were increases in maternal CD4 counts in four studies that reported this at enrollment and at or near delivery.

Vertical transmission rates ranged from 0 - 2.8%. The rate was respectively 0.6% (1/164) and 0.0% (0/70) in the one trial that compared standard to higher-dose.

Rates of preterm delivery <37 weeks ranged from 8.7 – 22.6%, low birth weight from 11.5 – 20.3%, still births from 0.3 – 3% and infant mortality from 0 – 5.8%.

No maternal deaths were attributed to lopinavir/r. Maternal SAEs including obstetrical and post-partum complications were reported in 4 studies (n=1011) and occurred in 0 - 36.1% of women.

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### C O M M E N T

**Of note with this analysis is the large variation in study settings. The analysis does not appear to support routine dose increase of lopinavir/r in the third trimester of pregnancy.**

Ref: Pasley M et al. Systematic review of the safety and efficacy of Lopinavir/ritonavir-based antiretroviral therapy in pregnant women. 3rd International Workshop on HIV & Women, 14 - 15 January 2013, Toronto, Canada. Oral abstract O\_15.

[http://regist2.virology-education.com/2013/3hw/docs/24\\_Martinez.pdf](http://regist2.virology-education.com/2013/3hw/docs/24_Martinez.pdf)

## Possible mechanisms for adverse pregnancy outcomes in HIV positive women

Polly Clayden, HIV i-Base

HIV positive women experience higher levels of adverse pregnancy outcomes than the general population. The mechanisms responsible for this remain unknown.

Two studies by researchers in Toronto exploring possible hypotheses to explain these adverse events were presented at the 3rd International Workshop on Women and HIV. [1, 2]

Proper angiogenesis (the formation of blood vessels) is needed for the optimal formation of the placenta. A balance between pro- and anti-angiogenic factors is needed. An anti-angiogenic state has been associated with low birth weight, preterm delivery, and preeclampsia. HIV and antiretrovirals - protease inhibitors in particular - have been associated with altered levels of some angiogenic factors. However, this phenomenon has not been studied in HIV positive pregnant women.

Lena Serghides, on behalf of the Angiogenesis and Adverse Pregnancy Outcomes in Women with HIV (AAPH) study group, described their ongoing study. The overall study hypothesis is infection with HIV and/or ART disrupt the angiogenic balance required for a successful pregnancy and so contribute to adverse outcomes in HIV positive women.

The study is currently enrolling 100 HIV positive pregnant women at five sites in Toronto. Women are recruited in their first trimester or early in their second and 4-9 blood samples are collected throughout pregnancy. A control group of 100 HIV negative pregnant women matched for gravidity, age, ethnicity, and educational levels are being enrolled as controls.

Maternal, placental, and cord blood, and placenta tissue are collected at delivery. Women are divided into three groups: those with full-term pregnancies and no complications, those delivering a small for gestational age neonate, and those that delivering preterm.

So far, 50 HIV positive women have been enrolled and 36 women have completed the study. A further 11 controls have been enrolled of whom three have completed the study. About 70% of women are black with a median age of 31.5 years undergoing their first second or third pregnancy. Over a third have experienced a previous miscarriage.

The majority of the HIV positive women received a boosted protease inhibitor-containing regimen.

Of the 36 HIV positive women who have completed the study, 6 delivered preterm (28, 32, 33, 2x34 and 36 weeks), this gave a rate of 16.7% compared to background rate of 8.1% in Ontario. A further 7 infants were small for gestational age (<10th percentile), 19.4% compared to background rate of 9.3%. There was one foetal death at 12 weeks.

The investigators found, compared to the 50th percentile for gestational age, HIV positive women had significantly lower birth weight (approximately 400g less,  $p=0.01$ ), and placental weight (approximately 40g less,  $p=0.036$ ). They observed a significant correlation between placental and foetal weight ( $R^2=0.37$ ,  $p=0.0005$ ).

Several placental abnormalities were seen in the HIV positive women, including fibrotic lesions, intervillous thrombi, villous immaturity, inflammation, as well as higher than expected rates of succenturiate lobes (12%, normal rate 1-5%), and velamentous insertions (20%, normal rate 1-2%).

Although the study is incomplete the findings to date are an indication that adverse outcomes are high in this cohort of HIV positive women, including a high incidence of low birth weight and placental abnormalities. Dr Serghides asked whether angiogenic factors might be useful as biomarkers of pregnancy outcome and whether they are potential therapeutic targets. This research is ongoing.

A related presentation by Eszter Papp from the same research group showed findings from a study which looked in vitro and vivo at whether protease inhibitor-containing ART could influence progesterone production in placental cells, and how ART exposure influences progesterone levels and birth outcomes in a mouse model.

It is known that protease inhibitors inhibit enzymes involved in the synthesis of steroid hormones (contraceptive drugs) including progesterone. Progesterone is needed to maintain pregnancy and decreased levels have been linked to low birth weight and preterm delivery in humans. The investigators exposed placental cytotrophoblast (BeWo) cells to human plasma equivalent concentrations of NRTIs AZT and 3TC and protease inhibitors atazanavir, darunavir, lopinavir, and ritonavir either individually or in clinically relevant combinations with hypoxia control. Progesterone levels were measured by immunoassay.

In addition, pregnant mice were exposed to human-equivalent doses of ART, AZT/3TC plus boosted lopinavir or water as control throughout gestation (day 0-18). Pregnancy failure, number of implantations or foetuses, viability and foetal weight were recorded. Placental weight was also collected and progesterone levels were quantified from maternal plasma. The investigators found BeWo cells exposed to protease inhibitors had significantly lower progesterone production, while NRTIs had no effect on progesterone expression. Exposure to boosted protease inhibitor plus two NRTI combinations yielded lower progesterone levels in all cases.

Pregnant mice exposed to lopinavir/r and two NRTIs showed similar patterns. Mice exposed throughout gestation had more foetal loss (approximately 30% increase), less viable offspring per litter as well as significantly lower foetal and placental weights. There were significantly lower progesterone levels after ART exposure, which positively correlated with foetal weight ( $R^2$ , 0.4595,  $p<0.05$ ). Early (pre-implantation) exposure appeared to have more severe effect on birth outcomes than delayed (post implantation) exposure but even with sustained progesterone levels, foetal viability decreased.

The group plans further investigations into the fate of implants exposed pre-implantation only, the benefits of progesterone supplementation and comparing different antiretroviral combinations. They will also investigate correlations between progesterone levels and birth outcomes in humans (AAPH study participants).

#### References

1. Papp E et al. Angiogenesis and Adverse Pregnancy Outcomes in Women with HIV: the AAPH study. 3rd International Workshop on HIV & Women. 14 - 15 January 2013, Toronto, Canada. Oral abstract O\_012.  
[http://regist2.virology-education.com/2013/3hw/docs/21\\_Serghides.pdf](http://regist2.virology-education.com/2013/3hw/docs/21_Serghides.pdf)
2. Papp E et al. Progesterone level changes after cART exposure **in vitro** and **in vivo** are possibly linked to adverse birth outcomes. 3rd International Workshop on HIV & Women. 14 - 15 January 2013, Toronto, Canada. Oral abstract O\_013.  
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## CONFERENCE REPORTS

### 43rd Union World Conference on Lung Health

13 - 17 November 2012, Kuala Lumpur, Malaysia.

#### Introduction

**The long running International Union Against Tuberculosis and Lung Disease Conference was held in Kuala Lumpur this year. The sessions on paediatrics were excellent and it was good to see them in the "big room".**

Webcasts are online at:

<http://uwclh.conference2web.com/content/all>

### Paediatric TB: glimpses of PK data and a potential new approach to drug development

Polly Clayden, HIV i-Base

**There are scant data for second-line TB drugs in children and there is very little to guide use of even first-line ones in neonates and infants with low birth weight.**

There is also a need to ensure that any new developments for adults are speedily tested for paediatric use. Three presentations at the 43rd Union World Conference presented findings from pharmacokinetic (PK) evaluations of TB drugs in children and a novel approach to paediatric drug development. [1, 2, 3]

#### PK of second line TB treatment in children

There is virtually no data on second-line TB drug dosing in children. Child friendly formulations are not usually available and the doses using divided and/or crushed tablets are uncertain. PK data on which to base optimal dosing is lacking. Also, second-line drugs are more toxic than those used in first line treatment and adverse events are hard to monitor in children. TB drugs are also frequently used with antiretrovirals in TB/HIV coinfecting children.

Annekke Hessling from the Department of Paediatrics and Child Health, University of Stellenbosch, Cape Town, described a large ongoing study to characterise PK and toxicity of second-line TB drugs for treatment and prevention of drug resistant TB in HIV positive and negative children, by age and HIV status. She presented preliminary data for three second-line TB drugs: ethionamide, amikacin and ofloxacin.

This ambitious study will be running over the next five years with an enrollment target of 276 children. Age matched HIV positive children not on TB treatment will be enrolled as controls (42 receiving efavirenz and 22 lopinavir/r). The drugs under evaluation are: ethionamide, terizidone, ofloxacin, levofloxacin, moxifloxacin, amikacin, high dose isoniazid (INH), PAS, linezolid and capreomycin. The study includes intensive PK sampling, clinical follow up until treatment completion for children with active TB, cross sectional PK data from children receiving prophylaxis and toxicity monitoring.

Dr Hessling presented data from HIV positive and negative children, receiving routine treatment or prophylaxis for MDR TB, from December 2011 to September 2011. Children with severe anaemia (Hb <8g/dL) and/or weighing <5 kg were excluded.

Directly observed, exact doses were administered using the upper limit of the recommended doses following a standard breakfast: ethionamide 20 mg/kg (recommended dose 15 – 20 mg/kg/day), amikacin 20 mg/kg (15 – 22.5 or 30 mg/kg/day) and ofloxacin (15 – 20 mg/kg/day). Intensive sampling was performed at 0, 1, 2, 4, 6 and 8 hours post dose and C-max, T-max, AUC0-8 and t1/2 were compared to adult targets.

Seventy children (46 with TB disease and 24 receiving prophylaxis) were in the study group. Respectively, 12, 15 and 19 children in the disease group were age <2, 2 - 5 and 6 - 15 years. Only children < 5 years are prophylaxed for TB, of these 6 were <2 and 18 were 2 – 5 years old. Overall, 12 (26.7%) children in the TB disease group were HIV positive and receiving ART. About 70% of the children with TB disease had pulmonary TB and the remainder had extra pulmonary TB or both.

The PK evaluation for ethionamide, revealed HIV negative children with higher C-max in the 0 – 2 years age group than the other two groups (median 7.66 vs approximately 5 ug/mL) but this was not significant; T-max peaked sooner and achieved higher target levels earlier (mean



1.80 hours vs 3.15 in the oldest age group,  $p=0.001$ ), although overall exposure (AUC) was similar across age groups. HIV positive children had lower levels than HIV negative ones (median 4.86 vs 6.37  $\mu\text{g}\cdot\text{h}/\text{mL}$ ,  $p=0.051$ ). Dr Hessling noted that a larger sample size would probably show lower AUC as well. She described the finding that younger children peaked higher and earlier as “quite surprising” as the only other study that has looked at ethionamide PK in children by age group showed the opposite, she suggested that this might be due to crushing the tablets. The lower levels seen with HIV positive children compared to negative is consistent with that observed previously. Although adult targets are unclear, the MIC achieved in children was similar or above that of adults.

For amakacin,  $C_{\text{max}}$  was lower in the youngest group than the other two (median 43.65 vs approximately 49  $\mu\text{g}/\text{mL}$ ),  $T_{\text{max}}$  was lower (mean 1.00 vs approximately 1.13 hours) and AUC lower (median 103.85 vs 159.25  $\mu\text{g}\cdot\text{h}/\text{mL}$  in the oldest group,  $p=0.016$ ). Levels did not differ by HIV status. At a dose of 20 mg/kg per day all children exceeded the adult target ( $C_{\text{max}}$  35 – 40  $\mu\text{g}/\text{mL}$ ). Dr Hessling suggested that perhaps 15 mg/kg, less frequent dosing and TDM should be evaluated particularly with relation to toxicities (amakacin can cause irreversible deafness). Interim data at a median of just over five months follow up showed hearing loss in 3/28 children, all with levels exceeding the adult target  $C_{\text{max}}$ . She also noted its low early bacterial activity, although it is given for MDR-TB, this compounded with its high toxicity, make it, “not such a wonderful drug”.

Giving ofloxacin achieved higher  $C_{\text{max}}$  in the youngest versus oldest groups (median 9.4 vs 7.16  $\mu\text{g}/\text{mL}$ ), higher and earlier mean peak in  $T_{\text{max}}$  (1.42 vs 2.60 hours,  $p=0.39$ ) and similar overall exposure. This drug is given routinely as prophylaxis for MDR-TB and levels were higher in this group but this might be an age effect as it is given only to younger children. There was no difference by HIV status and adult targets were achieved.

This study is ongoing and will result in a very large and important data set.

### **Isoniazid PK in neonates and infants**

In a related presentation, Adrie Bekke from the Stellenbosch group presented data from a study conducted to determine INH PK parameters at a dose of 10 mg/kg/day in low birth weight infants (<2500 g), and to define the PK of INH in relation to the N-acetyltransferase-2 (NAT2)-genotype. INH is recommended as prophylaxis for TB-exposed infants. There are limited data to guide dosing in neonates and no PK data for low birth weight infants. In 2009, WHO recommended higher doses of TB drugs for children (INH 10-15 mg/kg/day) but there is uncertainty about the correct dose for this very young population.

The study was prospective, with longitudinal intensive PK sampling, measuring INH serum concentrations at 2, 3, 4 and 5 hours post-dose and conducted at Tygerberg Hospital, Stellenbosch.

Twenty low birth weight infants were included in the evaluation, of which 14 (70%) were male, 16 (80%) were HIV-exposed and 13 (65%) were preterm. The infants were a median gestational age of 35 weeks (IQR 34–38) and weight of 1874 grams (IQR 1366–2105).

Of the 20 infants, 5 were homozygous slow, 11 heterozygous fast/slow, and 4 homozygous fast NAT2-genotype. There was a median elimination constant rate,  $C_{\text{max}}$ ,  $T_{\text{max}}$ , AUC<sub>2-5</sub> and half-life of 0.13  $\text{h}^{-1}$ , 5.64  $\mu\text{g}/\text{mL}$ , 2.02 hours, 13.62  $\mu\text{g}\cdot\text{h}/\text{mL}$  and 5.55 hours, respectively.

All of the infants achieved adult target INH values, which range between 3 and 5  $\mu\text{g}/\text{mL}$ , 2 hours post dose. Measured alanine aminotransferase (ALT) values were generally normal apart from one grade 1 and one grade 2 elevated result, which returned to normal at 6 months.

Dr Bekke noted that as the low birth weight infants achieved adult, if not higher, targets the upper range of the WHO recommended dose (15 mg/kg/day) of INH might be too high for this population. The NAT2 expression on the clearance of INH appears to be delayed, supporting immature enzyme maturation and cautions the administration of higher dosing. The limited safety data was reassuring. More work is urgently needed looking at TB drug dosing in infants.

### **A novel approach for the evaluation of new TB drugs in children**

Researchers from the TB Alliance and the Stellenbosch group have been looking at a novel approach for speeding access to new TB drugs and regimens in infants and young children. Carl Mendel presented the proposed framework for this evaluation.

TB Alliance are a not for profit product development partnership. It will soon be appropriate to begin trials in children for at least one of the drugs that are currently being studied in adults.

Dr Mendel first summarised what is known about developing TB drugs for children. He explained that trials with efficacy as the primary endpoint are not required for children as power would be prohibitive and at least similar efficacy to adults is assumed. Matching PK to that in adults has proven to be safe and effective. But trials in children cannot begin until the adult dose has been established and safety and efficacy demonstrated in this population – what is controversial is when this is.

The researchers currently have several open questions including whether DS and DR TB patients should be distinguished and how closely should PK in children match that of adults particularly with paediatric formulations that are not always bioequivalent.

When to begin paediatric trials needs to balance the risk with beginning early: the drug might fail in adults or toxicities could be first seen in children, to that with starting late: a drug already on the market might be used in children without adequate information or a drug might be delayed in this population. He suggested that for a drug without particular safety concerns, the group consider as soon as two months safety and efficacy data are available in adults to be appropriate.

The traditional approach to collecting PK and then safety data in children is sequentially in de-escalated weight bands. This approach is conservative and experience in older children might not mitigate the risk in younger groups as differences are caused by changes in metabolism at different ages. Drugs to be used mainly by children are not developed in this way.

The TB Alliance plan proposes hospitalised TB patients in all age groups receive single dose for initial PK (based on adult dose and modeling) on top of background therapy, which is a small and manageable risk. Next step would be 14 day multiple dose PK also in hospitalised TB patients.

This approach means that approval for the youngest children would not be delayed – 0-2 is a critical age for TB and has a huge and unmet need for treatments. It is important though that studying the older group is not delayed if paediatric formulations are not available for the younger ones.

Dr Mendel concluded that this approach could provide faster information for registration and he noted that both the FDA and EMA have indicated that they are open to considering it.

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## ANTIRETROVIRALS

### **Dolutegravir submitted to EU, US and Canadian regulatory agencies**

**On 17 December 2012, ViiV Healthcare issued a press release announcing the submission of regulatory applications in the European Union (EU), United States (US) and Canada for the investigational integrase inhibitor dolutegravir (S/GSK1349572).**

These submissions are for the treatment of HIV infection in adults and adolescents (children aged 12 years and older).

Ref: ViiV press release. ViiV Healthcare announces regulatory submissions for dolutegravir in the EU, US and Canada. 17 December 2012.  
<http://www.viivhealthcare.com/media-room/press-releases/2012-12-17>

### **Darunavir: new oral suspension and 800 mg formulations approved in EU**

**Two new formulations of darunavir were recently granted EU approval.**

On 25 October 2012, the EU approved a 100 mg/ml oral suspension of darunavir (Prezista), and the use of darunavir co-administered with low dose ritonavir, in combination with other ARVS, for the treatment of HIV-1 in treatment-experienced paediatric patients age 3 years and above, weighing at least 15 kg body weight. [1]

The approval is based on a 48-week analysis of ARIEL, a Phase II, open-label trial to evaluate pharmacokinetics, safety, tolerability and antiviral activity of darunavir in combination with low dose ritonavir in treatment-experienced HIV-1 infected children from 3 to < 6 years of age.

The EU also recommended approval of the darunavir 100 mg/ml oral suspension for use in patients who are unable to swallow tablets, providing an additional way to receive treatment.

The EU approval for the oral suspension was also based on TMC114-C169: a Phase I open label randomised crossover trial in healthy participants to compare the oral bioavailability to that of the 300 mg tablet formulation with 100 mg ritonavir under fasted and fed conditions.

The second formulation, is an 800 mg darunavir tablet that reduces the pill count for standard daily adult dose from 2 x 400 mg to 1 x 800 mg tablet. Both formulations require boosting by 100 mg ritonavir.

Both are now available in the UK.

#### References

1. Janssen-Cilag press release. Darunavir (Prezista) oral suspension receives EU approval for young children with HIV-1 infection. 25 October 2012.
2. Janssen-Cilag press release. FDA Approves New 800mg PREZISTA (darunavir) tablet. (9 November 2012).  
<http://www.jnj.com/connect/news/all/fda-approves-new-800mg-prezista-darunavir-tablet>

### **US label changes for rilpivirine and Eviplera follows EU caution on high baseline viral load: new summary on drug resistance**

**Simon Collins, HIV i-Base**

**On 7 December 2012, the US FDA approved changes to the rilpivirine (Edurant) package insert that included restricting the indication to treatment-naïve adult patients with HIV viral load less than 100,000 copies/mL.**

Previously, the FDA had only highlighted the poorer responses in patients with baseline viral load >100,000 copies/mL. This brings the US indication in line with the label indication originally granted by the EU. On 25 January, a similar change occurred for the Fixed Dose Combination of Eviplera that contains rilpivirine/tenofovir/FTC.

Of note, the FDA review included a different summary of data relating to the risk of resistance based on baseline viral load and CD4 count, that appears to be different analysis of the 96 week pooled phase 3 data in the EU Summary of Product Characteristics, see Table 1 and 2.

This showed that in people failing virologically, there were disproportionately higher rates of resistance when stratified by both baseline viral load (above vs below 100,000 copies/mL) and baseline CD4 count (above vs below 200 cells/mm<sup>3</sup>).

**Table 1: Rilpivirine resistance by baseline viral load**

	VL <100,000 copies/mL	VL >100,000 copies/mL
NNRTI	26% (14/54)	74% (40/54)
NRTI	22% (11/50)	78% (39/50)
M184V	23% (11/50)	77% (36/47)
K65N/R	0 (0/8)	100% (8/8)

**Table 2: Rilpivirine resistance by baseline CD4 count**

	CD4 >200 cells/mm <sup>3</sup>	CD4 <200 cells/mm <sup>3</sup>
NNRTI	37% (20/54)	63% (34/54)
NRTI	28% (14/50)	72% (36/50)

The virologic outcome of randomised treatment of the two phase 3 registrational studies TMC278-C209 and TMC278-C215 at Week 96 is summarised in Table 10 in the full US SPC (not reproduced here).

### Side effects

Several changes were made in the label changes relating to side effects including the importance of hepatic monitoring, especially in patients with HBV or HCV coinfection. Nephrolithiasis was added as a “Less common” side effect and nephrotic syndrome was added to the post marketing experience subsection.

### Drug interactions

Troleandomycin was removed from the table of drug interactions and telithromycin was added with the clinical comment that telithromycin may cause an increase in the plasma concentrations of rilpivirine (inhibition of CYP3A enzymes). Where possible, alternatives such as azithromycin should be considered.

## C O M M E N T

**These results highlight the lower response rates for people with the most advanced HIV disease, defined by baseline viral load, due to the higher potential for clinically important drug resistance.**

**A recent meta-analysis of over 12,000 patients from 21 studies originally presented at the IAS2012 conference and recently published in HIV Medicine (albeit Janssen sponsored) suggested that lower responses at high viral appears to be an underlying trend across all ARV studies in all classes. [3, 4]**

**The focus on CD4 count, while plausible, is not supported by statistical values, and appears to be based on low patient numbers and wide confidence intervals. Non-inferiority conclusions from sub-group analyses similarly need to be interpreted cautiously as these studies are under-powered for such comparisons.**

**What appears different with rilpivirine is that these response rates were also significantly lower compared to the efavirenz-based control group, and that this was independent of the choice of background nukes.**

**For full details see the new product label. [1]**

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1. FDA list serve. Labeling updates for Edurant (rilpivirine). (7 December 2012).  
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<http://onlinelibrary.wiley.com/doi/10.1111/hiv.12004/abstract>

## TREATMENT ACCESS

### New UNITAID grants focus on paediatric HIV, TB and malaria

**On 7 December 2012, UNITAID announced several new grants to enable the production of adapted treatments for children in resource limited settings. Among these grants (in USD) are:**

Up to \$17.3 million to the Drugs for Neglected Diseases initiative (DNDi) to make child-adapted paediatric HIV treatments available. This project will help save the lives of some of the 72% of children that require life-saving HIV treatment but don't have access.

Up to \$16.7 million to the TB Alliance to support the production of appropriate paediatric TB medicine formulations. Currently, a lack of child-adapted TB medicines contributes to high morbidity among children.

Up to \$34 million to the Medicines for Malaria Venture (MMV) to accelerate the global adoption of injectable artesunate, the best treatment for the 8 million annual cases of severe malaria, occurring mostly in under-five-year-olds in Sub-Saharan Africa.

In addition to these principle grants, the UNITAID Executive Board approved four market entry grants to manufacturers of point-of-care HIV diagnostic tests in the final stages of development.

A positive decision regarding the request from the Global Fund for an extension of funding of the Affordable Medicines Facility – malaria (AMFm) is expected in January. Finally, the Executive Board also confirmed its commitment to supporting the WHO Prequalification of Medicines Programme on a multi-year basis.

Source UNITAID press release

<http://www.unitaid.eu/resources/press-centre/releases/1053-eb17-project-release>

<http://www.dndi.org/media-centre/press-releases>

## Global Fund results continue upward trend

### Global Fund Observer

**The key results numbers for programmes supported by the Global Fund continue to rise. On 30 November, the Global Fund announced 2012 year-end estimates for the outcome and output numbers it tracks. [1]**

The number of people receiving antiretrovirals (ARVs) is estimated at 4.2 million, an increase of 27% over the 3.3 million estimated for 2011. The year-over-year increase from 2011 to 2012 for some of the other numbers is even greater: 35% for the number of insecticide-treated nets (ITNs) distributed for malaria; 46% for the number of HIV care and support services provided; and 88% for the number of HIV behavioural change communications. See Table 1 below for details.

**Table: Cumulative results for programmes supported by the Global Fund to end 2012 compared with 2011**

Category	Results to December 2012	Results to December 2011	Year to year change
No. of people receiving ARVs	4.2 million	3.3 million	+ 27%
TB smear-positive cases detected and treated	9.7 million	8.6 million	+ 12%
No. of condoms distributed	4.2 billion	3.5 billion	+ 20%
No. of HIV counselling and testing sessions	250 million	190 million	+ 32%
No. of malaria ITNs distributed	310 million	230 million	+ 35%
HIV behavioural change communications	300 million	160 million	+ 88%
No. of women receiving PMTCT treatment	1.7 million	1.3 million	+ 30%
Services to most-at-risk populations	30 million	23 million	+ 30%
HIV care and support services provided	19 million	13 million	+46%

The announcement from the Global Fund did not include an estimate of lives saved through Fund-supported programmes. In July, the Fund estimated that the programmes it supports had saved 8.7 million lives through the end of June 2012.

The results numbers have been rising steadily and rapidly for several years. Given that fewer new grants have been awarded in the last couple of years (compared to previous years), one might expect that the large increases in the year-over-year results would start to diminish. That they have not yet started to go down is probably due to the fact that there are a large number of active grants, many of which have only recently entered their second phases.

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1. Global Fund press release. Global Fund support extends antiretroviral treatment to 4.2 million people. (29 November 2012). <http://www.theglobalfund.org/en/mediacenter/newsreleases>
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## Germany extends €200million annual support to Global Fund until 2016

### Global Fund press release

**On 24 January 2013, Germany announced that it will contribute €1 billion to the Global Fund to Fight AIDS, Tuberculosis and Malaria, enabling health workers to continue efforts to prevent and treat these three highly infectious diseases.**

The commitment represents a continuation of Germany's pledge for annual contributions of EUR 200 million for a total of five years, through 2016.

However, the demand for funding is likely to outstrip the impressive commitment. The Global Fund will continue to seek additional sources of funding, and to explain the need for more contributions from wealthy donor nations and the private sector.

For the period 2011–2013, Germany was the fourth largest contributor to the Global Fund, behind the US, France and the UK.

Reference:

Global Fund, Germany makes EUR 1 billion contribution to the Global Fund. (24 January 2013).

<http://www.theglobalfund.org/en/mediacenter/newsreleases/>

## New analysis of country pledges and contributions to the Global Fund

### Aidspan.org

**A new report from by the Global Fund-focused NGO watchdog Aidspan, available online, includes an analysis of donor pledges to the Global Fund in relation to gross national income. [1]**

They calculated the Global Fund donor score for each of the 30 countries that have the largest economies and that are defined by the World Bank as "high income." (The definition of "high income" is based on standard of living, not size of economy.) In this analysis, the five highest donors were Sweden, Norway, France, the United Kingdom and Canada. See Tables 1 and 2.

The Global Fund donor scores shown in Tables 1 and 2 are based only on direct pledges to the Global Fund. Some of the countries listed also contribute indirectly, via the European Commission (pledges from the European Commission make up 4% of total pledges to the Fund), UNITAID or Debt2Health. Some countries also donate considerable amounts of money for non-Global Fund programmes to fight AIDS, TB and malaria (such as through bilateral aid). Others don't give much money for the three diseases, but may give to other charitable or development causes.

Three of the countries shown in Table 2 as having a Global Fund donor score of F – Italy, Spain and Ireland – pledged substantially to the Global Fund prior to 2011. Because of their domestic economic difficulties, none of these countries pledged anything for 2011–2013, and each of them failed to fully cover its pledge for at least one year before 2011. However, during 2011–2012, Ireland did make some contributions to cover part of the unpaid portion of its 2010 pledge; and there are signs that Spain may again become a donor to the Global Fund.

Five of the countries shown in Table 2 as having a Global Fund donor score of F – Austria, Czech Republic, Israel, Qatar and United Arab Emirates – have never donated to the Fund.

Based solely on the size of the pledges, and looking now at all donors to the Global Fund, not just the 30 largest economies, the largest pledges for 2011–2013 were made, in decreasing order by the US, France, the UK, Germany, Japan, Canada, the Bill and Melinda Gates Foundation, the EC, Sweden, Norway, Australia, Netherlands, Denmark, Russia and Belgium.

During the years 2001–2005, every pledge made to the Global Fund was fully paid. Since then, this has not been the case: \$645 million in pledges made to the Global Fund for the years 2006–2011 has not yet been paid.

The private sector provided only 0.3% of total pledges for 2011–2013 (about \$10 million annually). However, this does not include (Product) RED, an alliance of various private sector companies, which, without making pledges, contributes about \$20 million annually.

**Table 1: Explanation of Aidspan's Global Fund (GF) donor score**

GF donor score	Average annual pledge (2011-13) as a % of gross national income (GNI)
A	Greater than 0.010%
B	From 0.007% to 0.010%
C	From 0.003% to 0.006%
D	From 0.001% to 0.002%
E	Below 0.001%
F	Zero

**Table 2: The “Global Fund donor scores” for the 30 high-income countries with the largest economies, based on pledges for 2011–2013**

Global Fund donors	Donor	Pledge to the Global Fund	
		Average annual pledge, \$m.	As % of GNI *
A	Sweden	99.1	0.0197%
	Norway	76.5	0.0174%
	France	477.7	0.0172%
	UK	340.0	0.0144%
	Canada	179.0	0.0114%
B	USA	1,333.3	0.0088%
	Denmark	27.0	0.0080%
	Netherlands	63.5	0.0076%
	Germany	263.4	0.0073%
	Australia	72.7	0.0071%
C	Belgium	18.0	0.0035%
	Japan	200.0	0.0035%
D	Finland	5.2	0.0020%
	Switzerland	8.3	0.0014%
	Saudi Arabia	5.6	0.0011%
E	Kuwait	0.5	0.0004%
	South Korea	2.0	0.0002%
F	Austria, Czech Republic, Greece, Hungary, Ireland, Israel, Italy, Poland, Portugal, Qatar, Singapore, Spain, United Arab Emirates	0.0 each	0%

\* This column shows each country's average annual pledge to the Global Fund during 2011–2013 as a percentage of its 2011 gross national income

Source: Summary from Aidspace press information on the Aidspace report. Donors to the Global Fund: Who Gives How Much? (12 December 2012).

<http://www.aidspace.org/page/other-publications>

## Renewal of Indian Global Fund Grant made conditional on government funding for ART

**Aidspace.org**

**The Global Fund is calling on India to increase government funding for the provision of antiretroviral treatment (ART) for people living with HIV.**

The Global Fund is concerned about the sustainability of the National AIDS Control Programme (NACP) in India because the NACP is relying 100% on Global Fund resources to finance its ART budget.

The Fund would like to see India pick up the bill for a significant portion of ART expenses, which would permit Global Fund resources to be re-directed to programmes that support vulnerable and high risk groups, community systems strengthening and accelerated expansion of community based interventions in high prevalence states.

The Global Fund said that it will include a Board Condition in the grant agreement for the next implementation period of a Round 4. Specifically, requires a sustainability plan for the National AIDS Control Program.

Source: Global Fund Observer. Board Imposes Conditions on Renewal of India HIV Grant: Global Fund wants more government funding for ART. (12 December 2013).

<http://www.aidspace.org>

## MSF and DNDi report highlights importance of research into neglected diseases

**MSF and DNDi press release**

**A new report produced jointly by Médecins Sans Frontières (MSF) and the Drugs for Neglected Diseases initiative (DNDi) highlights the disparities between medical research and global disease burden in an analysis of research developments over the last decade. [1]**

Despite important progress in research and development (R&D) for global health over the past decade, only a small fraction of new medicines

developed between 2000 and 2011 were for the treatment of neglected diseases, highlighting the 'fatal imbalance' between global disease burden and drug development for some of the world's most devastating illnesses.

The report details that between 2000 and 2011, 3.8 percent of newly approved drugs (excluding vaccines) were for tropical diseases, TB, and other neglected infections, which together account for 10.5 percent of the global disease burden. Much of the progress in the treatment of neglected diseases and important patient benefit during this time came about through drug reformulations and repurposing of existing drugs against these illnesses. However, only four of the 336 new medicines (new chemical entities) developed between 2000 and 2011 were for the treatment of neglected diseases.

According to the DNDi and MSF analysis, three of the four brand-new medicines approved for neglected diseases in the past decade were for malaria, with none for the 17 neglected tropical diseases (NTDs) defined by the World Health Organization (WHO), nor TB. Furthermore, as of December 2011, only 1.4 percent of nearly 150,000 registered clinical trials were focused on neglected diseases.

Some individual successes have emerged from the proliferation of global R&D over the last decade. For example, product development partnerships (PDPs) were responsible for over 40 percent of neglected disease products registered between 2000 and 2011, including new TB diagnostics and malaria combination treatments.

Source: MSF press release. Millions of patients still waiting for medical "breakthroughs" against neglected diseases: analysis of health R&D pipeline shows important progress, but significant gaps in innovation remain. (13 December 2012).  
<http://www.dndi.org/media-centre/press-releases.html>

Ref: MSF/DNDi report. Medical innovation for neglected patients: important progress over past ten years, but "fatal imbalance" persists  
<http://www.doctorswithoutborders.org/publications/article.cfm?id=6474>

Download PDF report

<http://www.doctorswithoutborders.org/publications/reports/2012/Medical%20Innovations%20for%20Neglected%20Patients.pdf>

Links

Doctors Without Borders/Médecins Sans Frontières (MSF)  
<http://www.doctorswithoutborders.org>

About Drugs for Neglected Diseases initiative (DNDi)  
<http://www.dndi.org>

## SIDE EFFECTS & COMPLICATIONS

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### **Smoking is largest contributor to reduced life expectancy in Danish HIV cohort**

**Nathan Geffen, CSSR**

**A recent analysis from the Danish HIV Cohort Study, published as an access article in *Clinical Infectious Diseases* has reported that smoking is the biggest cause of life-years lost in Danish people with HIV, and that this is a much bigger cause of death than HIV-related illnesses. [1]**

This long-established cohort provides excellent observational data to estimate life-expectancy and mortality differences in HIV positive versus HIV negative controls. Denmark provides free ART, high-quality care, at specialist centres, with low loss to follow-up, so health systems failures are less likely to confound results. For example, participants are routinely seen every few months and (since 2004) tobacco and alcohol use is recorded annually.

This analysis included all patients receiving care from 1995 to 2010 who were older than 16 at HIV diagnosis and who had smoking data available. Time was calculated from the date of first available smoking status, age 35 years or one year after the date of HIV diagnosis, whichever came last, until death, emigration, or 1 September 2010.

Current smokers were defined at enrolment as people who smoked any type of tobacco at least once a week. Previous smokers were defined as people who were smokers but had given up before enrolment. All others were defined as never-smokers. Smoking status was not changed during the study.

Of 5,300 people with HIV in the cohort, over 2,400 were excluded because of injection drug use (567), missing data on smoking (1,497) or age less than 35 years at the end of the study period or at censoring (363). This left just under 3,000 people in the study.

Participants were then matched by sex and year of birth with over 10,600 HIV negative controls. A separate analysis that included injection drug users (IDU) was also performed. IDU were excluded from the main analysis as the extremely high smoking rates (only 7/567 didn't smoke) and lower life-expectancy than the general HIV positive population, would both confound the results.

At baseline, smoking was both more common for HIV positive people and individual cigarette use was higher. Among HIV vs controls respectively, rates were 47% vs 21% for current, 18% vs 33% for previous and 35% vs 47% for never smokers. The median number of cigarettes smoked a day by current smokers was 20 (IQR: 10-20) vs 15 (IQR: 10-20) in the positive vs negative groups.

In the HIV positive group, viral load, AIDS diagnosis at baseline, years of ART and years since diagnosis were similar across smoking categories, but hepatitis C status was 9.8%, 5.4% and 4.8% respectively. The HIV positive population was ethnically diverse while the case controls were entirely Danish. However a sensitivity analysis found that neither this, nor gender, had a marked impact on the results.

The two groups were followed for over 14,000 and 45,000 patient years, respectively. The median follow-up time was 4.2 years (IQR: 3.1–5.5) for HIV patients and 4.1 years (IQR, 2.9–5.8) for population controls.

Factors in the multivariable analysis included age, year of HIV diagnosis, excess consumption of alcohol, body mass index, CD4 cell count, and viral load at baseline. Smoking was the factor associated with the highest risk of death and did not interact with these other variables.

The excess mortality associated with smoking was much higher among HIV patients compared to the case controls but the relative risk of death associated with smoking did not differ. This is because the smoking rate was much higher in the HIV-positive cohort.

The main results of the study were:

- Life expectancy for a 35-year-old HIV positive person was calculated as 62.6 years (95% CI: 59.9-64.6) for smokers, 69.1 years (95% CI, 67.5-71.2) for previous smokers and 78.4 years (95% CI: 70.8-84.0) for never-smokers. The loss of life-years associated with smoking was twice as high as HIV-related causes.
- HIV positive smokers had higher all-cause mortality (mortality rate ratio [MRR] 4.4; 95% CI: 3.0-6.7).
- HIV positive smokers had higher non-AIDS-related mortality (MRR: 5.3; 95% CI: 3.2–8.8).
- HIV positive smokers who smoked 30 or more cigarettes a day had higher mortality than those who smoked less than 30 (MRR 4.2; 95% CI: 2.6-6.9).
- The excess mortality rate per 1,000 person-years among HIV positive current vs HIV positive never smokers was 17.6 (95%CI: 13.3-21.9). For smokers versus never smokers without HIV this was 4.8 (95% CI: 3.2-6.4).
- The population-attributable risk of death associated with smoking was 61.5% among HIV patients and 34.2% among controls.
- AIDS-related deaths were also more likely among smokers and previous smokers versus never-smokers: 5.2 (95%CI: 3.7-7.3) vs 6.0 (95%CI: 4.0-10) vs 1.4 (95%CI: 0.7-3.0), respectively.
- More than 60% of deaths in the HIV positive cohort were due to factors associated with smoking.

The MRR for cancer deaths was 5.1 (95%CI: 3.6-7.2) vs 5.1 (95%CI: 3.0-8.6) vs 1.7 (95%CI 0.8-3.3), for current vs previous vs never smokers, respectively. The corresponding rates for cardiovascular disease were 2.7 (95%CI: 1.7-4.3), 0.7 (95%CI: 0.2-2.9) and 0.8 (0.3-2.2). The authors explained that while the risk of cardiovascular disease for previous smokers diminishes quickly to be similar to non-smokers, the higher cancer risk remains. Overall mortality was halved in previous smokers compared to current smokers, emphasising the importance of successful cessation interventions.

There was a trend to higher rates of violent deaths among current and previous smokers versus never smokers, indicating that smokers and alcohol use was higher in smokers, but although this was not statistically significant, this indicates that there may be some confounding in the study's main findings (also with social-economic status). The authors also speculated that the much higher contribution to mortality by smoking in HIV positive people versus the general population might be due to nicotine causing inflammation.

## C O M M E N T

**The association of smoking to mortality was so large that it is almost certainly a significant cause of lost life-years in people with HIV, even allowing for confounding that is possible in any observational study.**

**It is unclear whether the greater association with death due to smoking in HIV positive people compared HIV negative controls is, as the authors speculate, due to HIV-related factors, or because HIV positive smokers are more likely to have other risks.**

**Nevertheless, this study is clear evidence that for well-resourced HIV care centres with cohorts that have good access to ART, finding ways to reduce smoking should be a priority. This is easier said than done. Nicotine is more addictive than alcohol, heroin, meta-amphetamines, cocaine and marijuana. [2]**

**Additional research is needed on effective smoking cessation interventions as a Cochrane review shows that while some smoking cessation interventions help, their effects are modest and they have side effects. [3]**

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## Low bone mineral density in MSM irrespective of HIV status

Simon Collins, HIV i-Base

**A recurring difficulty in interpreting the high rates of reduced bone mineral density (BMD) in HIV positive people is the lack of appropriate reference data.**

Results from a Dutch study in gay men (MSM) published in the *Journal of Infectious Diseases* provided new data reporting that BMD may be reduced in gay men, irrespective of HIV status. This is important given the many factors that relate to bone health, including weight/BMI, diet, smoking, exercise, age, testosterone (TST) levels, in addition to HIV and ARV treatment.

Marlou Grijzen, from the Center for Infection and Immunity, Amsterdam, and colleagues compared the BMD in primary HIV infection (diagnosed within six months, of infection, n=41), with chronic HIV infection (n=106), and in HIV negative controls (gay men with comparable lifestyles, n=30). [1] The study wanted to explain a high prevalence of low BMD in MSM during primary HIV infection, and those patients contributed data to this study. [2]

This was a prospective study for all newly enrolled MSM from 2008-2011, who were treatment-naive and aged 20-55 years when presenting for care at a single centre in Amsterdam. All patients received a DEXA scan and low BMD was defined as a z-score (matched by age, sex and race) of  $\geq 2.0$  SDs below the mean at the lumbar spine or hip (using the US NHANES IV population dataset as reference). Medical conditions known to affect bone metabolism were an exclusion criteria, including IDU, renal disease and corticosteroid use. Smoking, alcohol, diet, and fracture history were also taken together with testing for a wide panel of bone-related biochemical markers including P1NP (bone formation) and CTX (bone resorption) for the participants in primary infection and the controls, but unfortunately not for those in chronic infection.

The three groups were matched for age and race: mean ( $\pm$  SD) age 38 years ( $\pm$  8), and 80% were white. However, HIV negative men were heavier (82 vs 73 kgs,  $p=0.009$ ) with higher BMI (24.4 vs 22.7,  $p=0.04$ ).

Baseline characteristics relating to BMD-associated lifestyle factors were similar in the primary vs control patients, apart from a trend towards higher smoking rates (44% vs 23%,  $p=0.07$ ). Biochemical markers were also similar, with the few statistically significant differences still broadly within reference ranges: lower phosphate 0.93 ( $\pm$  0.18) vs 1.32 ( $\pm$  0.23) mmol/L (reference range 0.7–1.45 mmol/L) and P1NP levels 42 ( $\pm$  16) vs 52 ( $\pm$  13)  $\mu$ g/L; reference range 22–87;  $p=0.009$ ) and higher CTX 288 levels ( $\pm$  196) vs 154 ( $\pm$  93) ng/L; reference range  $<584$ ;  $p=0.001$ ).

Median CD4 and viral load in the primary vs chronic HIV positive groups were 543 ( $\pm$  253) vs 438 ( $\pm$  214) cells/mm<sup>3</sup>, and 5.3 ( $\pm$  1.2) vs 4.5 ( $\pm$  0.9) log copies/ mL, respectively.

DEXA results indicated significantly lower BMD in all three patient groups, compared to NHANES reference levels, with lower SD by both t-score and z-score for all sites (lumbar spine, femoral neck and total hip; except hip in HIV negative MSM). Notably, lumbar spine z-scores were -1.0, -1.1 and -0.8 in the primary, chronic and control groups respectively, though at other sites z-scores were less marked (approximately -0.1 to -0.3). However, there were no significant differences between groups for either score at any site, either by HIV status or duration of infection.

Low BMD at one or more sites was reported in 20% (8/41), 22% (23/106) and 13% (4/30) of the primary, chronic and control groups ( $p=0.6$ , for between arm difference).

In multivariate analysis, BMI was associated with low BMD at all sites ( $p<0.001$ ) but not HIV status.

### C O M M E N T

**These results are important in suggesting that individual health and lifestyle factors may impact on bone health prior to HIV infection and that this may have not been adequately accounted for in earlier studies. Nevertheless, this is still a small cross-sectional study.**

**The low BMD in HIV negative controls is similar to rates reported in PEP studies (10% of MSM in a San Francisco PEP study and 12% of men in the iPrEX study (lumbar spine) had low BMD ( $<2$  SD), though background risk factors were also likely to be different in each study population. [3, 4]**

**The results highlight the importance of finding appropriate controls for HIV studies. The does not detract from the importance of optimal management of bone health and longitudinal data from at least two US cohort studies have reported that low BMD in HIV positive people is associated with increased fracture risk, perhaps at a younger age to HIV negative people.**

**Differences in biomarkers of bone metabolism warrant further research, especially to help understand the impact of HIV treatment, and this should be helped by the bone sub-study of the START trial.**

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## PAEDIATRIC CARE

### **The American Academy of Pediatrics recommends that HIV positive mothers not breastfeed their infants, regardless of maternal viral load and ART**

**The American Academy of Pediatrics has issued a policy statement for doctors caring for infants born to HIV positive women.**

The statement emphasises that it is critical that they are aware of the HIV transmission risk from human milk and the current recommendations for feeding HIV-exposed infants in the United States.

It states: "Because the only intervention to completely prevent HIV transmission via human milk is not to breastfeed, in the United States, where clean water and affordable replacement feeding are available, the American Academy of Pediatrics recommends that HIV-infected mothers not breastfeed their infants, regardless of maternal viral load and antiretroviral therapy".

Ref: Committee on Pediatric AIDS. Infant Feeding and Transmission of Human Immunodeficiency Virus in the United States. Published online January 28, 2013 (doi: 10.1542/peds.2012-3543)

<http://pediatrics.aappublications.org/content/early/2013/01/23/peds.2012-3543>

### **US paediatric guidelines updated**

#### **US Department of Health and Human Services (DHHS)**

**The United States Department of Health and Human Services paediatric HIV guidelines were revised in November 2012.**

Key changes made to update the August 2011 guidelines include:

#### **Diagnosis**

New section on diagnostic testing in children with perinatal HIV exposure in exceptional situations: late seroreversion up to 24 months of age, postnatal exposure in children with prior negative virologic tests for whom there are additional HIV transmission risks (eg breastfeeding, feeding pre-masticated food), and non-subtype B HIV-1 infection and HIV-2 infection.

New section on diagnostic testing in children with non-perinatal exposure.

#### **When to start**

CD4 cell count and CD4 percentage thresholds for starting treatment are now offered for children aged >12 months, but in the case of discordance between CD4 cell counts and percentages, decisions should be based on the lower value.

Although CD4 percentage had been preferentially used to monitor immunologic status in children aged <5 years, recent analyses show that CD4 cell counts provide greater prognostic value than CD4 percentage for short-term disease progression in children aged <5 years as well as in older children.

CD4 thresholds for treatment have been further subdivided into age groups 1 to <3, 3 to <5, and  $\geq 5$  years to more precisely link them to age-related changes in absolute CD4 cell count.

The panel continues to recommend treatment of all HIV-infected infants aged <12 months, regardless of clinical status, CD4 percentage, or viral load.

They discuss current adult antiretroviral guidelines and similarities and differences between children and adults. Adult guidelines have been modified to recommend treatment for all HIV positive individuals, with the strength of the recommendation based on the pre-treatment CD4 cell count.

In addition to recommending treatment for all children with AIDS or significant HIV-related symptoms, the panel also generally recommends treatment for all children aged  $\geq 1$  year with minimal or no symptoms, with the strength of recommendation based on age and CD4 cell count/percentage. However, on a case-by-case basis, the suggest paediatricians may elect to defer therapy based on clinical and/or psychosocial factors.

ART should be initiated in HIV-infected children aged  $\geq 1$  year with minimal or no symptoms with the following CD4 values:

- Aged 1 to <3 years with CD4 cell count <1000 cells/mm<sup>3</sup> or CD4 percentage <25%.
- Aged 3 to <5 years with CD4 cell count <750 cells/mm<sup>3</sup> or CD4 percentage <25%

- Aged  $\geq 5$  years with CD4 cell count  $\leq 500$  cells/mm<sup>3</sup>

ART should be considered for HIV-infected children aged  $\geq 1$  year with minimal or no symptoms with the following CD4 values:

- Aged 1 to  $< 3$  years with CD4 cell count  $\geq 1000$  cells/mm<sup>3</sup> or CD4 percentage  $\geq 25\%$
- Aged 3 to  $< 5$  years with CD4 cell count  $\geq 750$  cells/mm<sup>3</sup> or CD4 percentage  $\geq 25\%$
- Aged  $\geq 5$  years with CD4 cell count  $> 500$  cells/mm<sup>3</sup>

### What to start with

Tenofovir disoproxil fumarate (TDF) has recently been FDA-approved for children as young as age 2 years. The panel has modified its recommendations for use of TDF in children based on Tanner staging. TDF, in combination with 3TC or FTC, is part of a recommended NRTI combination for adolescents who are Tanner stage 4 or 5, an alternative choice for those who are Tanner stage 3, and reserved for special circumstances for those aged  $\geq 2$  years and Tanner stage 1 or 2.

Etravirine and rilpivirine are also FDA-approved but are not recommended as initial therapy at this time because of lack of experience and dosing information in children.

Boosted fosamprenavir is now FDA-approved for infants as young as age 4 weeks, provided that they were born at  $\geq 38$  weeks' gestation. However, because of palatability and lower drug exposure in young infants, boosted fosamprenavir, when used in combination with 2 NRTIs, is an alternative option only in infants and children aged 6 months and older.

Darunavir with low-dose ritonavir is now FDA-approved and, when used in combination with 2 NRTIs, an alternative regimen in children aged  $\geq 3$  years. Once-daily dosing of boosted darunavir in children aged  $< 12$  years is not recommended.

Raltegravir is now FDA-approved for children aged  $\geq 2$  years, but are not recommended for initial therapy at this time because of insufficient data. Elvitegravir, another integrase inhibitor, is only available as a fixed-dose combination tablet containing elvitegravir/cobicistat/FTC/TDF, and is FDA-approved for ARV treatment-naïve adults, but not children aged  $< 18$  years. Given the lack of data in individuals aged  $< 18$  years, it cannot be considered for use as initial therapy in children at this time.

Although emerging information about the use of efavirenz in pregnancy is reassuring, the panel awaits additional safety information and recommends that alternative regimens that do not include efavirenz be strongly considered in adolescent girls who are trying to conceive or who are not using effective and consistent contraception because of the potential for teratogenicity with first trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise a woman's health.

### Treatment-experienced infants, children, and adolescents

Management of treatment failure has been more clearly limited to management of virologic treatment failure. There is no consensus on how to manage immunologic or clinical treatment failure in the absence of virologic treatment failure.

Newer individual drugs and classes of ARV drugs have been incorporated into both the discussion and the table of new regimen options for children with treatment failure.

### Adolescents

Updates have been provided in the section on contraceptive and ARV drug interactions.

An update was provided regarding pregnancy outcomes in adolescent girls.

### Dosing information

Updates with new paediatric data are provided when relevant for specific drugs:

- **FTC** - Neonatal pharmacokinetic (PK) data at a dose of 3mg/kg/day, and PK data in children indicating that the oral solution has 20% lower plasma exposure than the capsule formulation. Information is provided on Complera (fixed-dose combination of TDF, FTC, and rilpivirine) for adolescents aged  $> 18$  years and adults.
- **3TC** - Information on generic tablet formulations and weight band dosing for children who weigh  $\geq 14$  kg, using 150-mg scored tablets. Discussion on switching from twice-daily to once-daily dosing at 8 to 10 mg/kg, based on review of data from the PENTA 13 and 15 and ARROW trials.
- **d4T** - Maximum dose of 30 mg of d4T is recommended.
- **TDF** - Information on the newly available paediatric oral powder and tablets of lower milligram amounts (150, 200, and 250 mg), and dosing by weight band starting at age 2 years and 10 kg, with a discussion of the recommended paediatric dose of 8 mg/kg/dose once daily and results of the studies that led to registration of the drug. Truvada (FTC/TDF) is now FDA-approved for use in adolescents aged  $\geq 12$  years and who weigh  $\geq 35$  kg; and Atripla (FTC/TDF/efavirenz) is now FDA-approved for use in adolescents aged  $\geq 12$  years and who weigh  $\geq 40$  kg.
- **AZT** - Dosing recommendations for AZT used as prophylaxis for prevention of vertical HIV transmission and in infants have been updated.
- **Efavirenz** - Additional detail has been added involving the precaution against using efavirenz in women of childbearing potential.
- **Etravirine** - Paediatric dosing recommendations have been updated to reflect FDA approval for treatment-experienced children aged 6 to  $< 18$  years.

- **Nevirapine** - Data showing a three-fold increased risk of rash and hepatotoxicity in children with CD4 percentage >15% when initiating nevirapine.
- **Rilpivirine** - The availability of Complera (fixed-dose combination of TDF, FTC, and rilpivirine) for adolescents aged >18 years and adults. A paediatric trial is under way in treatment-naïve adolescents aged 12 to 18 years. Recommendation that rilpivirine should be administered with a meal that contains at least 500 calories and should not be used with proton pump inhibitors.
- **Atazanavir** - Modifications have been made in the dosing table and new dosing recommendations are discussed.
- **Darunavir** - Additional dosing down to a weight of 10 kg and PK of this dosing by weight band are described. The caveat against darunavir use in children aged <3 years was strengthened and explained more fully. Do not use darunavir in children aged <3 years because of concerns related to seizures and death in infant rats due to immaturity of the blood-brain barrier and liver metabolic pathways.
- **Fosamprenavir** - Information on FDA approval in infants as young as 4 weeks but does not recommend use in infants aged <6 months, given concerns about palatability and low drug level exposures. Details about PK have also been added and a dosing table was added for children aged 6 months to 18 years.
- **Lopinavir/ritonavir** - Discussion on a preference for dosing in children at 300 mg lopinavir/m2 twice daily rather than 230 mg/m2 twice daily, particularly for ARV-experienced patients.
- **Raltegravir** - Information has been added on the newly available paediatric chewable tablets (25 and 100 mg), dosing by weight band starting at age 2 years, and results from the trials that led to FDA approval in children are summarised.
- **Elvitegravir** - Information has been added on the newly available fixed-dose combination tablet containing the integrase inhibitor elvitegravir plus the PK booster cobicistat and the NRTIs FTC and TDF. There are no data on its use in individuals aged <18 years.

#### C O M M E N T

**That these guidelines are updated regularly (with revisions highlighted) is very useful as is the speedy introduction of information on newly approved drugs and formulations, for different age groups. US guidance takes a more cautious approach to efavirenz use in pregnancy than BHIVA or WHO.**

Ref: Panel on antiretroviral therapy and medical management of HIV-infected children. Guidelines for the use of antiretroviral agents in pediatric HIV infection.

<http://aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf>

## TREATMENT GUIDELINES

### **Implications of WHO guidelines increases CD4 threshold for starting treatment to 500 cells/mm<sup>3</sup>**

**Nathan Geffen, CSSR**

**World Health Organization (WHO) guidelines are extremely important. Treatment policies in developing countries are guided by WHO and activists in these countries use WHO guidelines in their advocacy work.**

Currently, WHO guidelines recommend that people with HIV start antiretroviral treatment (ART) when their CD4 counts fall below 350 CD4 cells/mm<sup>3</sup>.

However, several countries have changed their ART guidelines to recommend treatment irrespective of CD4 count or at treatment thresholds of 500 CD4 cells/mm<sup>3</sup>. [1, 2, 3]

This article looks at the implications if WHO also recommend that treatment start at 500 cells/mm<sup>3</sup> which is one of the changes under consideration.

To understand the impact of the WHO guidelines, consider that there are more people living with HIV in Nigeria than in the whole of North America, Western Europe and Australia combined. Even a small country like Zimbabwe has more people living with HIV than the whole of Western Europe. [4] Sub-Saharan African, Caribbean and Asian countries are strongly influenced by the WHO guidelines, much more so than the Department of Health and Human Services (DHHS) Guidelines published in the United States. This is especially the case for countries where treatment is primarily provided through funding from the Global Fund to Fight AIDS, TB and Malaria (GFATM) or the US President's Emergency Plan For AIDS Relief (PEPFAR).

#### **The evidence**

When considering changing the CD4 initiation threshold, or dispensing with a threshold entirely, we need to consider the evidence of such a change for both an individual patient's health and for HIV prevention.

#### **Prevention**

The HPTN 052 trial showed that ART greatly reduces the risk of an HIV-positive person transmitting HIV to his or her partner. This finding was

consistent with compelling observational data. [5]

The WHO subsequently published guidance on couples HIV testing and counselling and this included the recommendation to use antiretroviral therapy for treatment and prevention in serodiscordant couples. [6] Although completed and printed for distribution at the IAS meeting in 2011, this version was withdrawn and publication was subsequently delayed by until April 2012.

There is also evidence from several places including San Francisco, Vancouver and Taiwan that reducing community viral load reduces HIV incidence. [7, 8, 9] There is also evidence from mathematical models that ART is reducing HIV incidence in South Africa. [10]

Nevertheless, for many places it is not unequivocally clear that changing the CD4 initiation threshold to 500 CD4 cell/mm<sup>3</sup> would have a significant effect on HIV incidence. In contrast to where reduction in community viral load has been shown to reduce incidence, sub-Saharan African cities have primarily heterosexual epidemics that are possibly in many cases saturated. On balance it is likely that further reducing viral load will reduce incidence in sub-Saharan Africa, but this is not a given. Moreover it has to be discussed with and proven to policy makers too because there are enormous cost implications of beginning this type of expanded treatment. This is why there are studies underway in African countries that will look at whether initiating treatment earlier reduces community incidence. [11]

## Treatment

The benefit to the patient should be the salient consideration in the WHO treatment guidelines (as opposed to the couples guidelines in which prevention of infection of the HIV-negative partner is the salient consideration). Caroline Sabin and others have shown that the observational evidence for changing the threshold from 350 is poor and does not meet the increasingly widely adopted GRADE standard. [12] GRADE is a methodology for assessing the quality of evidence. There are four ratings for quality of evidence in GRADE: high, moderate, low and very low. Using the GRADE methodology, the evidence for benefit to a patient from initiating treatment above 350 CD4 cells/mm<sup>3</sup> is low.

Moreover, guidelines in some wealthy countries have changed to and fro on the issue of when to start over the last decade and a half: from 'hit hard, hit early' to postponing down to much lower thresholds, then to 350 CD4 cells/mm<sup>3</sup>. This is precisely why the INSIGHT Strategic Timing of Anti Retroviral Therapy (START) [13] and ANRS Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (TEMPRANO) [14] trials are being conducted--to answer once and for all when the best point to start ART is for patients.

One widely circulated myth that needs to be exploded is that HPTN 052 showed that starting above 350 CD4 cells/mm<sup>3</sup> reduced disease progression. But the HPTN 052 initiation threshold was 250 CD4 cells/mm<sup>3</sup>, not 350. Data from clinical trials had previously shown that a treatment threshold of 250 cells/mm<sup>3</sup> is inferior. [15, 16] But the question of whether a 350 cells/mm<sup>3</sup> threshold is optimal remains unanswered.

There are three likely outcomes of the START and TEMPRANO studies:

- Earlier treatment is better because it reduces disease progression.
- No difference between the earlier vs. later treatment arms.
- Earlier treatment is harmful because of increased side-effects or reduced adherence.

Clinicians and AIDS activists have different expectations of what the trial result will be. But our personal prejudices don't matter. The evidence is simply not available yet to form an opinion. The WHO needs to wait. [17]

If outcomes two or three turn out to be the case and the WHO has recommended earlier treatment it will undermine the organization's treatment guidelines. At best there would have been serious cost implications for developing country health budgets; at worst patients might have been harmed. If the WHO keeps its threshold recommendation unchanged, and outcome one turns out to be the case, then the organisation would have simply taken the correct action by having waited for the evidence and in accordance with the principle of first do no harm.

## The issue of cost

Cost is profoundly important when considering public health interventions. Activists should always be concerned about cost issues. To ignore them is poor activism, not only because policy makers do not take activists seriously who ignore cost, but because it is morally problematic to ignore cost. Public health policy involves making choices determined by cost. As ART becomes more nuanced, the relative cost per disability life-year saved becomes higher and the arguments for using the money elsewhere become harder to refute. As an example of how cost has informed activism in a developing country, the Treatment Action Campaign (TAC) has been cognisant of cost in its campaigns, despite demanding that the South African government implement treatment and prevention programmes. In a court case that dealt with prevention of mother-to-child transmission in 2002, the TAC included an affidavit that showed the court that the intervention would be cost-saving. Later the TAC published research showing that ART would be affordable for the South African government. By considering cost, the TAC was able to make compelling arguments for the implementation of life-saving interventions.

The current WHO ART guidelines for adults and adolescents included two important changes. [18]

It provided for treatment to be initiated at 350 CD4 cells/mm<sup>3</sup> and for stavudine (d4T) to be replaced by tenofovir. Both of these changes have profound cost implications, but they are both supported by a very strong evidence base. Because the campaigns for these changes to be adopted by poor countries have been based on sound science, they have had some success. WHO guidelines should be seen as an achievable aspiration for poorer countries. Nevertheless, even today, several sub-Saharan countries initiate ART at 200 or 250 CD4 cells/mm<sup>3</sup> with stavudine. This shows that cost is a critical factor, perhaps the most critical factor, in getting poorer countries to change their guidelines.

Changing the CD4 initiation point from 350 CD4 cells/mm<sup>3</sup> in the new WHO guidelines would in our view be premature. It would have profound cost implications on Global Fund, PEPFAR and developing country health budgets. We would be willing to campaign for such a change in guidelines in spite of cost implications if it was supported by evidence. But the evidence is still outstanding. Expecting countries to move to a new CD4 threshold or to dispense with CD4 thresholds without sufficient evidence is a mistake.

One argument that has been made is that some ART sites cannot afford to perform CD4 counts and therefore eliminating CD4 counts from

treatment guidelines makes sense. This argument is easily refuted. First, it is much more likely that such impoverished sites will in fact simply ignore guidelines and continue to initiate treatment only when patients are symptomatic. Second there are many sites in sub-Saharan Africa that do CD4 testing that should not have to change their guidelines because there are other places that do not have CD4 counts; guidelines should not be set on the basis of worst practice. Third, sites without CD4 tests almost always initiate with stavudine and it is probably harmful to initiate HIV treatment in people with high CD4 counts on stavudine.

If the WHO recommends a change that is unsupported by sufficient evidence and that has profound cost implications, it risks changing its guidelines from effective advocacy documents that developing countries can realistically aspire to into something that is unrealistic and ignored. This would be unfortunate and possibly harmful to many individuals.

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## TUBERCULOSIS COINFECTION

### **FDA approves bedaquiline for MDR TB: first new tuberculosis drug in half a century**

#### **TAG press release**

**At the end of December, bedaquiline, the first new approved drug to treat tuberculosis (TB) in over forty years, was granted accelerated approval by the US Food and Drug Administration (FDA).**

The drug has the potential to improve the treatment for multidrug-resistant (MDR) TB, a particularly deadly and hard-to-treat form of TB that affects over a million people worldwide, and from which only about half of patients who are treated recover.

"By granting accelerated approval of bedaquiline, the FDA has sent a clear signal that there is hope for people with MDR-TB, and that fighting TB is a priority," commented Mark Harrington, executive director of TAG. "Over one million people need new TB drugs this year, and the FDA's approval shows that there is a clear regulatory pathway for approving new TB treatments and regimens. In order for bedaquiline to continue

to be effective, and lives to be saved, we will need new, safer, better companion drugs. This historic occasion must mark a new beginning for TB drug development.”

Although bedaquiline appears effective at killing TB bacteria quickly in early and mid-stage clinical trials of people with MDR-TB, Nathan Geffen from activist group Treatment Action Campaign in South Africa—one of the highest TB- and MDR-TB burden countries—urges caution in regard to its safety. “The drug is necessary for urgent cases where patients have few treatment options,” said Geffen. “But it is essential that phase III trials be conducted to ensure the drug’s safety and benefit in terms of survival.”

TAG, and TB activists more broadly, called for the FDA to require appropriate phase III trials—especially those that include HIV positive TB patients taking antiretrovirals, who have not yet been studied on the drug—quickly and thoroughly. Studies of bedaquiline in children, and drug interaction studies with other new and existing drugs in the TB and HIV pipelines, are also necessary.

Bedaquiline’s sponsor, Janssen, must also commit to carrying out these studies rapidly. They also must price the drug so that it is accessible in both the low- and middle-income countries that disproportionately bear the burden of TB, and the low-incidence settings where TB programmes receive few resources.

For bedaquiline to make an impact in preventing unnecessary TB deaths and suffering, regulators in other countries must swiftly build their capacity to review and approve new drugs, and enable them to reach those in need as quickly as safety permits. Countries must also build their capacity to roll out new drugs for MDR-TB—currently, less than five percent of those with MDR-TB receive proper treatment.

More information about bedaquiline

TAG press release. Treatment Action Group lauds FDA approval of first new tuberculosis drug in half a century. (31 December 2012).

<http://www.treatmentactiongroup.org/press>

FDA press release

<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm>

TB online: The case for pre-approval access to bedaquiline

<http://www.tbonline.info/posts/2012/11/24/case-pre-approval-access-bedaquiline/>

## US fund additional \$11million for Xpert TB diagnostics in 14 countries

**On 4 December 2012, the United States President’s Emergency Plan for AIDS Relief (PEPFAR) announced an additional \$11 million to provide up to 150 Xpert MTB/RIF instruments and 450,000 test cartridges in 14 high-burden countries across sub-Saharan Africa and in Burma.**

The Cepheid Xpert MTB/RIF assay is a new fully automated molecular diagnostic test for tuberculosis disease (TB). It can detect Mycobacterium tuberculosis DNA and mutations associated with rifampicin resistance directly from sputum specimens in less than 2 hours. The assay is more sensitive for detecting TB than sputum-smear microscopy with similar accuracy as culture on solid media. The ability of the Xpert assay to detect smear-negative TB provides a significant advantage over smear microscopy, especially for persons with TB who are also HIV-infected.

These additional resources bring PEPFAR’s investments to-date in Xpert MTB/RIF to more than 275 instruments in high-burden countries. Additionally, in August 2012, PEPFAR and USAID partnered with UNITAID and the Bill & Melinda Gates Foundation in an innovative public-private partnership to reduce the cost of Xpert MTB/RIF cartridges by 40% (from \$16.86 to \$9.98). This partnership also significantly accelerates access to this cutting-edge technology.

Source

PEPFAR press release. United States Government Announces \$11 Million in Additional Support for Rapid TB Test in 14 Countries. 4 December 2012.

<http://www.pepfar.gov/press/releases/2012/201507.htm>

## BASIC SCIENCE

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### Attack of the killer helpers (part two)

**Richard Jefferys, TAG**

**Among the many tasks of the immune system, the responsibility for recognising and killing virus-infected cells largely falls to the subset of CD8 T cells designated cytotoxic T-lymphocytes (CTL).**

The question of whether CD4 T cells (traditionally called just “helper” cells) can exert cytotoxic functions has historically been controversial, but over the past decade, studies have convincingly documented the existence of cytotoxic CD4 T cell responses in a variety of different settings, including HIV and SIV infection (as previously covered on this blog). [1]

A new paper in the open-access journal *Retrovirology* from Jonah Sacha's research group at Oregon Health and Science University now reports that not only are cytotoxic CD4 T cell responses detectable in macaques controlling a pathogenic SIV isolate, but they can drive the selection of immune escape mutations. As the authors note, this represents compelling evidence that CD4 T cells can directly suppress viral replication. [2]

Although it was not highlighted on the blog at the time of publication, a human study from the laboratory of Hendrick Streeck also argues for a key role of cytotoxic CD4 T cell responses in controlling HIV. [3]

Published in *Science Translational Medicine* back in February of this year, the study showed that HIV-specific cytotoxic CD4 T cell activity predicted superior control of viral load and slower disease progression (as assessed by time to CD4 T cell count <350, time to ART initiation or time to viral load >100,000 copies) in a cohort of acutely HIV-infected individuals.

Taken together, these results further underscore the importance of considering virus-specific CD4 T cell responses, both in studies of natural control of HIV replication and in attempts to design effective immune-based therapies.

Source

TAG Basic Science Blog. Attack of the killer helpers (part two). (27 November 2012).

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## Lymph node fibrosis, CD4 T cells and immune reconstitution

Richard Jefferys, TAG

**One of the less well-publicised consequences of the persistent immune activation caused by HIV infection is a type of scarring damage to lymph tissues described as fibrosis.**

Some early studies of lymph nodes from HIV-infected individuals reported evidence of this problem, but it wasn't until the publication of a study by the research group of Ashley Haase in 2002 that a connection was made between the extent of fibrosis (as measured by deposition of collagen) and maintenance of CD4 T cell numbers. [1]

Haase and colleagues showed that there was an inverse correlation between lymph node fibrosis and the number of CD4 T cells measurable in the same node. Importantly, they also found that the degree of fibrosis was significantly associated with the magnitude of CD4 T cell increases after initiation of antiretroviral therapy, with greater fibrosis linked to poorer CD4 T cell recovery.

In the subsequent years, Haase's group has delved further into the mechanisms underlying these findings. In 2011 they reported that fibrosis disrupts the fibroblastic reticular cell (FRC) network, which forms pathways along which T cells travel on their journey through lymph tissue. [2]

The FRC network provides fuel for maintaining T cell health in the form of the cytokine IL-7, and fibrotic damage to FRCs was found to inhibit the ability of T cells to access IL-7, leading to cell death. The study also identified the cytokine lymphotoxin-beta as critical for maintaining FRCs, and suggested that loss of CD4 T cells was linked to a decline in lymphotoxin-beta production, further exacerbating the problem created by the fibrosis.

In an important paper published last summer that I neglected to write about at the time, the researchers confirm that CD4 T cells are the major source of lymphotoxin-beta, thus demonstrating that fibrosis creates a vicious cycle by depleting factors needed for CD4 T cell survival, leading to CD4 T cell loss, which in turn removes a critical source of factors needed to maintain the FRC network that provides sustenance to CD4 T cells. [3] The study offers evidence that this problem is relevant to not just HIV infection but also CD4 depletion after chemotherapy and irradiation in individuals with cancer.

In an accompanying editorial, Steve Deeks from UCSF notes that the research suggests possible interventions that could be evaluated in the context of HIV-induced persistent immune activation and CD4 T cell depletion: "These experimental interventions include drugs that remove pro-inflammatory pathogens and microbial products (eg, valganciclovir for CMV, rifaximin for gut microbes, sevelamer for lipopolysaccharide), drugs that directly prevent fibrosis (eg, angiotensin II receptor antagonists\* and ACE inhibitors), and drugs that have more broad effects in reducing inflammation (eg, statins, nonsteroidal antiinflammatory drugs, methotrexate, and mesalamine)." Deeks also points out that the best way of avoiding fibrotic damage to the lymph nodes is to suppress HIV replication as soon as possible after infection. [4]

A more recent study, published in the *Journal of Infectious Diseases* this past October, offers further support for the conclusions of Haase et al. [5]

Researchers led by Brian Tabb from the laboratory of Jacob Estes at NCI-Frederick report that blocking the inflammatory cytokine TNF alpha in early SIV infection reduced lymphoid tissue fibrosis and was associated with better preservation of CD4 T cell numbers in macaques (without affecting SIV viral load). The authors conclude: "This initial study highlights the importance of early inflammatory responses to lentiviral infections and underscores the need for additional studies to ascertain the potential clinical benefits of adjunctive therapies to attenuate these responses and to improve patient outcomes."



\*TAG's new HIV Project Director Tim Horn has recently led an effort to support AIDS Clinical Trial Group investigators seeking to obtain the angiotensin II receptor antagonist telmisartan (trade name Micardis) from the manufacturer, Boehringer Ingelheim, for a study in people with HIV. Unfortunately the company remains unwilling to provide drug for the planned trial, citing regulatory concerns. This situation highlights issues that will likely arise again in the future as investigators attempt to conduct exploratory studies of these types of potential adjunctive treatments in HIV infection: many of the candidate interventions are already indicated for other uses and are off-patent or toward the end of their patent life; additionally, the research is at such an early stage that it is probing questions of disease pathogenesis rather than carving a clear path toward an FDA-approved HIV indication. Activists are continuing to discuss possible approaches to addressing these issues in order to ensure that needed research can proceed.

#### Source

TAG Basic Science Blog, Lymph node fibrosis, CD4 T cells and immune reconstitution. (07 January 2013).  
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## **New research on gut CD4 T-cell depletion and HIV pathogenesis**

**Richard Jefferys, TAG**

**In both HIV and SIV infections, it has been shown that the most rapid and extensive loss of CD4 T cells occurs in the gut.**

As a consequence, a theory has emerged positing that gut CD4 T-cell depletion plays a central causative role in driving HIV pathogenesis; the proposed mechanism is that gut wall integrity becomes compromised, leading to the leakage of normally friendly bacteria from the digestive tract and into systemic circulation, which in turn contributes to persistent immune activation and, ultimately, progression to AIDS.

However, some scientists have remained skeptical of this theory, suggesting instead that gut CD4 T-cell depletion is an effect of HIV infection, but not necessarily the primary cause of disease progression. The skeptics have gained some support from studies showing that severe gut CD4 T-cell depletion occurs during acute SIV infection in monkey species that experience no apparent ill effects from the virus (sooty mangabeys and African green monkeys). [1]

A paper published recently in the *Journal of Virology* now shows that the opposite phenomenon is also possible: a modified SIV that does not cause loss of gut CD4 T cells nevertheless causes persistent immune activation and progression to simian AIDS in rhesus macaques. [2]

#### Source

TAG Basic Science Blog, New research on gut CD4 T-cell depletion and HIV pathogenesis. (31 December 2013).  
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## TRANSMISSION & PREVENTION

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### **UK group describe risk of HIV transmission for people on effective ART as “extremely low”**

**The British HIV Association (BHIVA) and the Expert Advisory Group on AIDS (EAGA) recently issued a position statement on the use of antiretroviral therapy (ART) by HIV positive individuals to reduce HIV transmission.**

The statement cites the HPTN 052 trial - that showed 96% reduction in transmission of HIV through vaginal sex – and notes that successful ART use by the HIV positive person is as effective as consistent condom use in limiting transmission.

It stresses that this is provided the following conditions are fulfilled: absence of other STIs in both partners; the HIV positive person has sustained viral suppression below 50 copies/mL for over 6 months and regular viral load testing (3-4 monthly) is performed).

Published data are largely from heterosexual couples and there is insufficient evidence to conclude that ART offers similar levels of protection with other sexual practices – including unprotected anal intercourse (whether heterosexual or gay/MSM). The statement gives expert opinion that an “extremely low risk” of transmission can be anticipated where the conditions described above are met.

Health care professionals are recommended to discuss the impact of ART on transmission with HIV positive people as well as the possibility of starting ART for this purpose.

Ref: Fidler S et al. Position statement on the use of antiretroviral therapy to reduce HIV transmission January 2013. The British HIV Association (BHIVA) and the Expert Advisory Group on AIDS (EAGA).

<https://www.wp.dh.gov.uk/publications/files/2013/01/BHIVA-EAGA-Position-statement-on-the-use-of-antiretroviral-therapy-to-reduce-HIV-transmission-final.pdf>

### **CDC issues brief on the prevention benefits of HIV treatment**

The US CDC has issued a somewhat wordy brief on the benefits of HIV treatment, which is summarised with:

HIV testing is the foundation for both prevention and care efforts.

Early identification of infection empowers individuals to take action that benefits both their own health and the public health.

Early treatment of infected persons substantially reduces the risk of transmitting HIV to others.

The prevention benefit of treatment can only be realised with effective treatment, which requires linkage to and retention in care, and adherence to antiretroviral therapy.

Ref: Centers for Disease Control and Prevention (CDC). Issue brief: the prevention benefits of HIV treatment.

<http://www.cdc.gov/hiv/topics/treatment/resources/factsheets/tap.htm>

### **WHO recommendations for prevention and treatment of HIV for sex workers and their clients**

#### **WHO Department of HIV/AIDS**

WHO has published recommendations for prevention and treatment of HIV among sex workers in low- and middle-income countries and their clients. The objective of this document is to provide technical recommendations on effective interventions for the prevention and treatment of HIV and other sexually transmitted infections (STIs) among sex workers and their clients. These include evidence-based recommendations following the GRADE methodology as well as recommendations for good practice.

Good practice recommendations are overarching principles derived not from scientific evidence but from common sense, ethics and human rights principles. These recommendations did not go through a formal GRADE process but should be strongly promoted in all interventions with sex workers.

The technical recommendations are supported not only by scientific evidence but also the lived experience of sex workers around the world as expressed in the results of a community values and preferences survey and at the guideline consensus meeting.

Ref: WHO Department of HIV/AIDS. Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries. December 2012.

[http://www.who.int/hiv/pub/guidelines/sex\\_worker/en/index.html](http://www.who.int/hiv/pub/guidelines/sex_worker/en/index.html)

## OTHER NEWS

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### **“AllTrials” campaign for publication of full research results**

#### **AllTrials campaign**

**The AllTrials initiative is campaigning for the publication of the results (that is, full clinical study reports) from all clinical trials – past, present and future – on all treatments currently being used.**

Doctors and regulators need the results of clinical trials to make informed decisions about treatments. But companies and researchers can withhold the results of clinical trials even when asked for them. The best available evidence shows that about half of all clinical trials have never been published, and trials with negative results about a treatment are much more likely to be brushed under the carpet [1].

This is a serious problem for evidence based medicine because we need all the evidence about a treatment to understand its risks and benefits. If you tossed a coin 50 times, but only shared the outcome when it came up heads and you didn't tell people how many times you had tossed it, you could make it look as if your coin always came up heads. This is very similar to the absurd situation that we permit in medicine, a situation that distorts the evidence and exposes patients to unnecessary risk that the wrong treatment may be prescribed.

It also affects some very expensive drugs. Governments around the world have spent billions on a drug called Tamiflu: the UK alone spent £500 million on this one drug in 2009, which is 5% of the total £10bn NHS drugs budget. But Roche, the drug's manufacturer, published fewer than half of the clinical trials conducted on it, and continues to withhold important information about these trials from doctors and researchers. So we don't know if Tamiflu is any better than paracetamol.

Initiatives have been introduced to try to fix this problem, but they have all failed. Since 2008 in the US the FDA has required results of all trials to be posted within a year of completion of the trial. However an audit published in 2012 has shown that 80% of trials failed to comply with this law [2]. Despite this fact, no fines have ever been issued for non-compliance.

We believe that this situation cannot go on. We are calling on governments, regulators and research bodies to implement measure to achieve this. And we are calling for all universities, ethics committees and medical bodies to enact a change of culture, recognise that underreporting of trials is misconduct and police their own members to ensure compliance.

Source: <http://www.alltrials.net>

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## ON THE WEB

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### **Conference abstracts**

**The following conferences and workshops now have webcasts and other conference material available for free access online.**

These are a valuable resource not only to people who are unable to attend these meeting but also as a reference to those who attend.

### **11th International Congress on Drug Therapy in HIV, 11-15 November 2012, Glasgow**

The webcasts from the 11th Glasgow conference are now available.

<http://www.hiv11.com/ContentPageView.aspx?ContentPageId=78>

PDFs of posters presented in Glasgow will be available to view as poster books, sorted by Congress abstract submission category. These are being added to as authors confirm approval to include them.

Scientific Abstracts from the Congress are published by the Journal of the International AIDS Society.

<http://www.jiasociety.org/index.php/jias/issue/view/1461>

## **BHIVA Autumn Conference, 6-7 October 2012, London**

BHIVA consistently provide both webcasts and powerpoint slides for free online viewing from their conferences.

These meetings include an impressive speaker programme.

Abstracts for the conferences are also posted online and the spring meetings increasingly include PDF files of many of the posters.

<http://www.bhiva.org>

## **AIDS vaccine 2012 conference, 9-12 September 2012, Boston**

The AIDS Vaccine 2012 conference is organised by the Global HIV/AIDS Vaccine Enterprise, the Ragon Institute of MGH, MIT & Harvard and the Harvard Center for AIDS Research.

Webcasts of all the conference sessions are now available online.

<http://aidsvac.capitalreach.com/portal>

The abstracts have been posted as a supplement to the open access journal *Retrovirology*.

<http://www.retrovirology.com/supplements/9/S2/all>

### *Resources, newsletter and reports*

## **Poster on the immune response to HIV**

### **Nature magazine**

**This neat (and complex) poster summarises how HIV establishes infection at mucosal surfaces, the ensuing immune response to the virus involving dendritic cells, B cells and T cells, and how HIV subverts this response to establish a chronic infection.**

The poster is available as a free download.

[View this poster as a high-resolution PDF \(2.03 MB\)](#)

[View a PDF of supplementary text and references for this poster \(108.0 KB\)](#)

[http://www.nature.com/nri/posters/hiv/nri1201\\_hiv\\_poster.pdf](http://www.nature.com/nri/posters/hiv/nri1201_hiv_poster.pdf)

## **RITA online: PrEP issue**

**This important edition of Research Initiative, Treatment Action (RITA!) interviews key researchers and features two comprehensive reviews of preexposure prophylaxis (PrEP).**

<http://www.centerforaids.org/pdfs/ritawinter2012.pdf> (PDF)

Robert Grant (UCSF), principal investigator of the iPrEx study argues the importance of considering PrEP for anyone who states they want to find new ways to protect themselves or their partners from HIV, regardless of apparent or perceived risk factors and Raphael Landovitz (UCLA) explains how he and other clinicians have begun integrating PrEP into practice.

Together, the review articles offer a thorough analysis of PrEP research to date, including a practice-oriented synopsis of trials involving Truvada for PrEP. The first analyses the importance of adherence to once-daily Truvada PrEP, the potential for less than once-daily PrEP, resistance risk with Truvada PrEP, and cost. The second provides the first research-based analysis of kidney function and bone density risk with Truvada PrEP in HIV-negative men and women who are most likely to consider PrEP.

## **Reports on cure research**

### **Towards an HIV cure, 20 - 21 July 2012, Washington**

An excellent report of the complex range of research presented at the AIDS2012 pre-conference symposium is expected to be online by the time this issue of HTB is back from press.

<http://www.iasociety.org/Default.aspx?PageId=606>

### **Community HIV Cure Workshop ! 4 March 2012, Seattle**

Useful and very readable summary report from a meeting organised prior to CROI last year by three leading US advocacy organisations, and featuring presentations from leading researchers in cure research.

[http://www.projectinform.org/pdf/cure\\_report\\_2012.pdf](http://www.projectinform.org/pdf/cure_report_2012.pdf) (PDF)

*Free full text online articles:*

## **PLoS Medicine**

**A selection of recent papers from PLoS Medicine.**

### **Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicentre cohort study -**

Cornell M et al.

Differences in mortality for HIV-positive men and women on antiretroviral therapy in South Africa.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001304>

### **Misrepresentation of randomized controlled trials in press releases and news coverage: a cohort study -**

Yavchitz A et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001308>

In this study, the researchers evaluated the presence of “spin” in press releases and associated media coverage and analyzed whether the interpretation of RCT results based on press releases and associated news items could lead to the misinterpretation of RCT results.

Nearly half the press releases and article abstract conclusions contained “spin” and, importantly, “spin” in the press releases was associated with “spin” in the article abstracts.

### **The potential impact of Pre-Exposure Prophylaxis for HIV prevention among men who have sex with men and transwomen in Lima, Peru: a mathematical modelling study -**

Gomez GB et al.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1001323>

Gabriela Gomez and colleagues developed a mathematical model of the HIV epidemic among men who have sex with men and transwomen in Lima, Peru to explore whether HIV pre-exposure prophylaxis could be a cost-effective addition to existing HIV prevention strategies.

## **FUTURE MEETINGS**

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### **Conference listing 2012/13**

**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.

#### **20th Conference on Retroviruses and OIs (CROI) 2013**

3 – 7 March 2013, Atlanta, USA.

<http://retroconference.org>

#### **19th Annual (BHIVA) 2013**

16th – 19th April 2013, Manchester.

<http://www.bhiva.org>

#### **14th International Workshop on Clinical Pharmacology of HIV Therapy**

22 – 24 April 2013, Liverpool, UK.

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

#### **48th International Liver Congress (EASL 2013)**

24 – 28 April 2013, Amsterdam.

<http://www.easl.eu>

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

4 – 8 June 2013, Toronto

<http://www.informedhorizons.com/resistance2013>

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

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

<http://www.ias2013.org>

### **53rd ICAAC**

10 – 13 September 2013, Denver, USA.

<http://www.icaac.org>

### **14th European AIDS Conference (EACS)**

16 – 19 October 2013, Brussels, Belgium.

<http://www.europeanaidsclinicalsociety.org>

## **PUBLICATIONS & SERVICES FROM i-BASE**

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### **i-Base website: 2012 update for PDA access**

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

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

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

All i-Base publications are available online, including editions of the treatment guides. The site gives details about services including the UK Community Advisory Board (UK-CAB), our phone service and Q&A service, access to our archives and an extensive range of translated resources and links.

Publications and regular subscriptions can be ordered online.

The Q&A web pages enable people to ask questions about their own treatment:

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

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

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

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

### *Non-technical treatment guides*

#### **i-Base treatment guides**

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

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

- Introduction to combination therapy (April 2012)
- HIV testing and risks of sexual transmission (February 2013)
- HIV and quality of life: side effects & complications (July 2012)
- Guide to changing treatment and drug resistance (February 2013)
- Guide to HIV, pregnancy & women's health (September 2011)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)

## *Publications and reports*

### **HIV Treatment Bulletin (HTB)**

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

### **HTB South**

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

### **HTB Turkey**

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

### **HTB West Balkans**

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

### **Why we must provide HIV treatment information**

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

## *Translations of i-Base publications*

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

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

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

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

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

## *Advocacy resources*

### **Online treatment training for advocates**

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

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

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

### **UK CAB: reports and presentations**

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

<http://www.ukcab.net>

## *Phoneline and information services*

### **Treatment information request service - 0808 800 6013**

i-Base runs a specialised treatment information service.

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

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

## Online Q&A service

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

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

## Other resources

### Treatment 'Passports'

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

### Generic clinic forms

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

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

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

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

### Order publications and subscribe by post, fax or online

All publications can be ordered online for individual or bulk copies. All publications are free. Unfortunately bulk orders are only available free in the UK.

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

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

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## *htb(e)*

### HIV TREATMENT BULLETIN (e)

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

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

by sending an email to: [subscriptions@i-Base.org.uk](mailto:subscriptions@i-Base.org.uk)

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

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**<http://www.i-Base.info>**

HIV i-Base is a registered charity no 1081905 and company reg no 3962064. HTB was formally known as DrFax.





## HIV i-Base

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

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• HIV Treatment 'Passports' - Booklets for patients to record their own medical history

1  5  10  25  50  Other \_\_\_\_\_

• Guide To HIV Testing and Risks of Sexual Transmission (February 2012)

1  5  10  25  50  Other \_\_\_\_\_

• Guide To HIV, Pregnancy and Women's Health (September 2011)

1  5  10  25  50  Other \_\_\_\_\_

• Introduction to Combination Therapy (April 2012)

1  5  10  25  50  Other \_\_\_\_\_

• Guide to Changing Treatment and Drug Resistance (February 2011)

1  5  10  25  50  Other \_\_\_\_\_

• HIV and your Quality of Life: Side Effects and other Complications (July 2012)

1  5  10  25  50  Other \_\_\_\_\_

• Guide To HIV and hepatitis C coinfection (March 2009)

1  5  10  25  50  Other \_\_\_\_\_

• Clinical Trials: a community guide to HIV research (March 2009)

1  5  10  25  50  Other \_\_\_\_\_

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

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

1 Sheet  1 pad  5 pads  10 pads  Other \_\_\_\_\_

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