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htb south

HIV TREATMENT BULLETIN SOUTH

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EDITORIAL

Welcome to the first HTB South 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.

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.

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.

The Southern African HIV Clinicians Society

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

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

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

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

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TREATMENT ALERT

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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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 year's 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/a5n9mfj>

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.

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 (≥ 350 cells/mm³) 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

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

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

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 known 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.

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

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).

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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 ug.h/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, Cmax was lower in the youngest group than the other two (median 43.65 vs approximately 49 ug/mL), T-max was lower (mean 1.00 vs approximately 1.13 hours) and AUC lower (median 103.85 vs 159.25 ug.h/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 (Cmax 35 – 40 ug/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-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 Cmax in the youngest versus oldest groups (median 9.4 vs 7.16 ug/mL), higher and earlier mean peak in Tmax (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, Cmax, Tmax, AUC2-5 and half-life of 0.13 h⁻¹, 5.64 ug/mL, 2.02 hours, 13.62 ug.h/mL and 5.55 hours, respectively.

All of the infants achieved adult target INH values, which range between 3 and 5 ug/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

- Janssen-Cilag press release. Darunavir (Prezista) oral suspension receives EU approval for young children with HIV-1 infection. 25 October 2012.
- 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/mm³).

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 ³	CD4 <200 cells/mm ³
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 please see the product label. [1]

References

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2. Rilpivirine Summary of Product Characteristics. (EMA website assessed 28 January 2013). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002264/WC500118874.pdf
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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

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.

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.

References

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>
2. Aidspace. More people than ever before on ART; cost of treatment continues to decline. (25 July 2012). http://www.aidspace.org/gfo_article/more-people-ever-art-cost-treatment-continues-decline

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%

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.

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

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.

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 AND COMPLICATIONS

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 loss 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.

Marlous 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-naïve 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 ≥ 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 $52 (\pm 13)$ ug/L; reference range 22–87; $p=0.009$ and higher CTX 288 levels (± 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/mm³, 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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PREGNANCY AND PMTCT

The challenge of adherence during pregnancy and after

Polly Clayden, HIV i-Base

Data on adherence rates during and after pregnancy are limited. These data are important particularly as international guidance moves towards universal ART in pregnancy and during breastfeeding.

A systematic review and meta-analysis published in the 23 October 2012 edition of *AIDS* was conducted to estimate adherence rates in pregnancy and postpartum and found that achieving adequate adherence during this period was a challenge particularly after delivery. [1]

Jean Nachega and an international group of researchers performed a literature search, which included all studies from low-, middle-, and high-income countries reporting adherence rates in HIV positive women as a primary or secondary outcome. From the review, 72 articles were selected of which 51 met the inclusion criteria for the analysis.

The majority (74%) of the studies were observational and the remaining ones were RCTs evaluating PMTCT programmes. Most were conducted in the United States (27%), followed by Kenya (12%), South Africa (10%) and Zambia (10%). Almost half (45%) the studies reported adherence rates in women receiving ART, and 29% and 24% in women receiving AZT and single dose nevirapine (NVP) respectively. One study compared adherence rates between women receiving ART and those AZT. Adherence thresholds differed across studies from >80% to 100% and most used self reported questionnaires followed by pill count and pharmacy refills. Most studies (76%) reported adherence during the antepartum period, 8% post partum, and 16% reported rates during both periods.

A pooled analysis of all studies found an estimate of 73.5% (95% CI 69.3 – 77.5%) of women with adequate ART adherence (>80%). The pooled proportion of women who achieved adequate adherence was significantly higher during the antepartum (75.7%, 95% CI 71.5 – 79.7%) than the postpartum period (53%, 95% CI 32.8 – 72.7%, $p=0.005$).

The pooled adherence of women with good adherence rates was significantly higher in low- and middle-income countries (76.1%, 95% CI 72.2 – 79.7%) than in high-income countries (62%, 95% CI 50.1 – 73.3%, $p=0.021$). When the investigators excluded single dose NVP studies from the analysis, this difference became non-significant (74.3 vs 62%, $p=0.062$). When the analyses were limited to adherence thresholds of >90% (74.8 vs 69.7%, $p=0.071$) and 100% (78.3 vs 74%, $p=0.103$) the differences between low- and middle-income countries and high-income countries were also non-significant.

The investigators noted that this meta-analysis showed that adherence during pregnancy is significantly below that recommended for virologic suppression. They wrote: "It is crucial to monitor ART adherence, investigate specific barriers for nonadherence, and develop interventions to assist antepartum and postpartum women in adhering to ART and ensure the long-term efficacy of such an approach for both maternal health and PMTCT."

C O M M E N T

The importance of adherence in pregnancy and post partum is a big consideration in discussions about WHO Option B+, ie all women starting lifelong treatment in pregnancy regardless of CD4.

There are many brilliant community models to support adherence. MSF recently launched a toolkit describing their very successful Adherence Clubs in the Western Cape. [2]

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PAEDIATRIC CARE

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 premasticated 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 ≥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 ≥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 ≥1 year with minimal or no symptoms with the following CD4 values:

- Aged 1 to <3 years with CD4 cell count <1000 cells/mm³ or CD4 percentage <25%.
- Aged 3 to <5 years with CD4 cell count <750 cells/mm³ or CD4 percentage <25%

- Aged ≥ 5 years with CD4 cell count ≤ 500 cells/mm³

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

- Aged 1 to < 3 years with CD4 cell count ≥ 1000 cells/mm³ or CD4 percentage $\geq 25\%$
- Aged 3 to < 5 years with CD4 cell count ≥ 750 cells/mm³ or CD4 percentage $\geq 25\%$
- Aged ≥ 5 years with CD4 cell count > 500 cells/mm³

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 ≥ 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 ≥ 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 ≥ 3 years. Once-daily dosing of boosted darunavir in children aged < 12 years is not recommended.

Raltegravir is now FDA-approved for children aged ≥ 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-naive 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 ≥ 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 ≥ 12 years and who weigh ≥ 35 kg; and Atripla (FTC/TDF/efavirenz) is now FDA-approved for use in adolescents aged ≥ 12 years and who weigh ≥ 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
- **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-naive 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>

Resistance in infants and children receiving ART in South Africa

Polly Clayden, HIV i-Base

Virological outcomes and resistance patterns in children receiving ART in Africa are not well characterised. Two presentations at the Eleventh International Congress on Drug Therapy in HIV Infection showed resistance data from the Children with HIV Early Antiretroviral Therapy (CHER) trial and a cohort in Cape Town respectively.

Avy Violari presented data from CHER. [1] This trial, conducted in South Africa, compared deferred but continuous ART to early limited ART in young infants who were followed for up to six years. Interim data from CHER led to early ART irrespective of CD4 count or disease progression to be recommended in all paediatric guidelines from 2008.

In the trial, all infants received lopinavir/ritonavir (LPV/r) plus AZT and 3TC and were randomised to one of three arms: to start immediately and stop at 40- or 96-weeks and restart when CD4 percent fell below 20% or clinically indicated, or defer ART until clinical progression or CD4 percent drop. Final results were presented at CROI last year and showed early limited ART was safe in children with regular clinical and CD4 monitoring. [2] Only 7 children in switched to second line ART during follow up.

The resistance analysis was conducted to compare rates of virological suppression at last visit on ART and look at resistance at virological failure

Viral load was measured in all children with a stored sample at their last visit, having been on initial or restarted ART, and followed for at least 24 weeks.

At enrollment, infants were a median age of just over 7 weeks, with a CD4 percent of 35% and a viral load of 5.7 log₁₀. Through PMTCT strategies, 63% had been exposed to nevirapine (NVP), 11% were unexposed, 4% had AZT exposure, 20% had AZT plus NVP, and 3% were exposed to maternal ART. The infants receiving deferred ART started at a median age of 26.1 weeks and those in the two immediate arms at 7.5 weeks. The median duration of ART was 240 weeks and similar across all three arms.

Of a total of 377 children, 46 were excluded: 17, 7 and 4 died; and 3, 4 and 5 were lost to follow up in the deferred ART, 40-week ART and 96-week ART arms respectively. In the deferred ART and 40-week ART arms 4 and 2 children never started treatment. The remaining 331 children were included in the resistance analysis.

At the last study visit, viral load was <400 copies/mL in 88/101 (87%), 95/113 (84%) and 97/117 (83%) in the deferred ART, 40- and 96-week arms. Respectively 5/101 (5%), 14 (12%) and 13 (11%) had viral load ≥1000 copies/mL.

Resistance testing was performed on all but one infant in the 40-week ART arm and, of these, 16/31 (52%) had mutations. Testing revealed no infant with thymidine analogue mutations (TAMs); 11 (35%) with mutations conferring resistance to NRTIs: 10 (33%) with M184V and 1 with L74V; 2 (6%) with major PI mutations (V82A), and 6 (19%) infants with major NNRTI mutations (K101, K103, Y181).

Baseline resistance testing results were available for 21/32 of the infants with last time point mutations. Of these, 8/21 had major NNRTI mutations prior to starting first line ART; 3/8 were also detected at last visit, despite no exposure to NNRTI except through PMTCT. There were no PI or NRTI mutations at baseline.

There were no statistical differences in time to virological failure across the three arms.

In a related presentation, Catherine Orrel showed findings from a retrospective analysis of receiving ART at the Hannan Crusaid Treatment Centre, a public sector ART clinic in Cape Town, between 2003 and 2010.

Children in this cohort were treated with either NNRTI- or LPV/r-based regimens first line, except for infants <6 months old who received full-dose ritonavir-based ART from 2004-2007. Those switching to second line received the alternative regimen.

Resistance testing was performed on stored samples from children at first or second line virological failure, defined as viral load >1000 copies/mL.

Out of 472 children starting first line ART in this cohort, 279 (60%) remained in care, 45 (9%) were lost to follow up, 73 (15%) transferred, and 4 (1%) died on first-line treatment. Seventy-one (15%) children had virological failure and 37 of these had samples available for genotype testing. The median age of the children with genotype results was 5.5 years (IQR 1.6 – 7.7). Eight (22%) children had wild-type virus, 7 (19%) had TAMs, 24 (65%) had NNRTI resistance, and two (5.4%) had multiple PI resistance.

Of 78 children who switched, 48 (63%) remained in care, 6 (8%) were

lost, 6 (8%) transferred, and 1 child (1%) died during second-line treatment. Fifteen (20%) had virologic failure and 13 had samples available for testing. The median age of the children with genotype results was 3.6 years (IQR 3.1 – 4.2). Three (23%) had wild-type virus, 8 (62%) had TAMs, nine (69%) had NNRTI resistance, and 5 (38%) had multiple PI resistance (all had received full-dose ritonavir).

Dr Orell noted that a similar proportion of children had wild type virus at first and second-line failure perhaps indicating challenges with adherence. She also noted more TAMs at second-line failure, 19% vs. 62%.

Multiple PI resistance mutations were seen in 50% of those receiving full-dose ritonavir at some time during the analysis but little PI resistance was seen with those receiving LPV/r.

C O M M E N T

The CHER results confirm the rarity of PI resistance using LPV/r in infants and young children and the ability of a PI to protect against development of TAMs. This was also seen in the arm of the PENPACT1 trial where switching ART was deferred until viral load was 30,000 copies/mL.

CHER also showed that virological suppression was just as good after a treatment interruption and that there was no increase in resistance. Concerns still remain about interrupting treatment in children, based on the negative impact this has in adults.

In the Cape Town cohort, children seemed to do better virologically and develop less resistance wise when started on an NNRTI-based combination and then switched to a PI. However, this is likely to be because those switching from PI were the selected non adherers, more than those moving from NNRTI to PI.

Age may well be a confounding issue here as well as the youngest children would have started on a PI. These data also show little PI resistance in children receiving LPV/r.

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ART and adverse birth outcomes in Botswana

Polly Clayden, HIV i-Base

Data describing the association between adverse birth outcomes – preterm delivery (PTD), small for gestational age (SGA) and stillbirth (SB) – and ART are conflicting.

The association between PTD and protease inhibitors has also been observed in some studies but not others. An article in the 1st December 2012 issue of the Journal of Infectious Diseases presents findings from the largest surveillance study of birth outcomes among HIV positive women receiving ART to date. The study was conducted in Botswana during 2009 – 2011.

Women who delivered live births or stillbirths at 20 weeks gestation or more at six public hospitals - chosen to include geographic diversity and primary and tertiary levels of obstetric care – were included in this analysis. Data were obtained from obstetrical records on discharge from maternity wards.

During the study period women with CD4 counts <250 cells/mm³ were eligible for ART – usually nevirapine (NVP) plus AZT/3TC. Women with CD4 counts >250 cells/mm³ received AZT monotherapy for PMTCT. Starting in late October 2009, a limited number of women received ART with CD4 counts >250 cells/mm³ through a pilot programme. This regimen was lopinavir/ritonavir (LPV/r) plus AZT/3TC.

The investigators reported, of 33,148 women, an impressive 32,113 (97%) were tested for HIV, and 9504 (30%) tested were HIV positive. In multivariate analysis, HIV was significantly associated with SB (AOR 1.5; 95% CI 1.3 – 1.7), PTD (AOR 1.3; 95% CI 1.3 – 1.4), SGA (AOR 1.8; 95% CI 1.7 – 1.9), and neonatal death (NND) (AOR 1.4; 95% CI 1.2 – 1.7) in HIV positive compared to HIV negative women. The majority (96%) of 9504 HIV positive women had a recorded date for initiation of antiretroviral drugs in pregnancy. Of 9149 women, 2189 (24%) continued ART from before pregnancy, 1101 (12%) started ART in pregnancy, 4625 (51%) started AZT in pregnancy, and 1234 (13%) received no antiretrovirals.

Only a small proportion (9%) of all women receiving ART received LPV/r-based regimens, the majority received NVP-based regimens or had no regimen specified (and were assumed to have received NVP).

Women starting ART in pregnancy did so at a median gestational age of 25 weeks and those starting AZT at a median of 29 weeks. The overall rate of PTD in HIV positive women was 24% occurring at a median gestational age of 34 weeks. Compared with all other HIV positive women, continuing ART from before pregnancy was significantly associated with PTD (AOR 1.2; 95% CI 1.1 - 1.4). Compared with AZT monotherapy, starting ART in pregnancy was also significantly associated with PTD (AOR, 1.4; 95% CI, 1.2, 1.8). Maternal hypertension and anaemia in pregnancy were also significant independent risk factors for PTD for all HIV positive women.

The rate of SGA among HIV positive women was 18% at a median gestational age of 39 weeks. Similarly, continued ART from before pregnancy was significantly associated with SGA (AOR 1.8; 95% CI, 1.6 - 2.1) among all HIV positive women. Starting ART in pregnancy compared to AZT was also associated (AOR 1.5; 95% CI, 1.2, 1.9) with higher rates of this adverse outcome. Among women receiving ART, continuing treatment was associated with higher risk of SGA than starting in pregnancy (AOR 1.3; 95% CI 1.0 – 1.5). Maternal hypertension and CD4 count <200 cells/mm³ were also independently

associated with SGA infants for all HIV positive women.

There was a 5% rate of SB in HIV positive women in this cohort at a median gestational age of 32 weeks. Continuing ART from before pregnancy was associated with higher risk of SB (AOR 1.5; 95% CI, 1.2, - 1.8) among all HIV positive pregnant women. Starting ART in pregnancy compared to AZT was also associated with SB (AOR 2.5; 95% CI, 1.6 - 3.9). Maternal hypertension and CD4 count <200 cells/mm³ were also additional risk factors.

Neonatal death (NND) occurred in 2.3% of infants born to HIV positive women. In univariate analysis, the rate was significantly in higher infants born preterm compared to those at term (7% vs 0.8%, $p < 0.0001$) and SGA infants were at higher risk than those with appropriate weights for their gestational age (3.5% versus 1.5, $p < 0.0001$). The investigators did not find higher rates of NND in women who continued ART from before pregnancy compared to other HIV positive women but women who started ART versus AZT in pregnancy had a higher risk (1.9% vs 0.8%). Because of the small numbers of events and the potential for multiple interactions with PTD, SGA and NND, the investigators did not perform multivariate analyses for this outcome.

One of the limitations of this study is that CD4 counts were not recorded for 51% of HIV positive women but when the analyses were limited to those with available data, the investigators observed no differences in their findings. Further sensitivity analyses included an evaluation of the association between PI-based ART and PTD. This analysis found 20 of 45 (42%) women who continued PI-based ART had a PTD compared to 522 of 1998 (26%) women who continued non-PI-based ART (OR 2.0; 95% CI, 1.1 - 3.6). A further 44 of 178 (25%) women starting PI-based ART in pregnancy had a PTD compared to 131 of 654 (20%) initiating non-PI-based ART (OR 1.2; 95% CI, 0.9 - 1.9).

The investigators noted that previous conflicting results from other observational studies might be due to their limited power and differing exposure categories and comparisons.

C O M M E N T

In an accompanying editorial, Heather Watts and Lynne Mofenson note that the increased risks of coinfections such as TB and malaria are also associated with adverse pregnancy outcomes. They also remind us that the pathogenesis of preterm delivery among all women and the potential increased risk among HIV positive women are not well understood.

As ART in pregnancy is rolled out more widely, they stress the importance of monitoring pregnancy outcomes to determine optimal regimens for improving maternal health and maximising HIV-free survival in infants.

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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/>

The case for pre-approval access to bedaquiline

TAC, TAG, i-Base, GTB-CAB, MSF and SAHCS

Bedaquiline is an anti-tuberculosis drug that is still being tested in clinical trials. It has recently been approved in the United States. [1]

Several organisations, including the Treatment Action Campaign, the Treatment Action Group, HIV i-Base, the Global Tuberculosis Community Advisory Board, Medecins Sans Frontieres and the Southern African HIV Clinicians Society have called for the drug to be made available to patients with drug-resistant tuberculosis (TB) before it is approved. This demand was made as far back as the World Lung Conference in Mexico in 2009. Yet little progress towards pre-approval access has been made in South Africa. The South African medicines regulatory authority, the Medicines Control Council (MCC), has responded sceptically.

We make the case for pre-approval access in this article. Although we deal with bedaquiline specifically, the arguments made here can perhaps be applied to other drugs, including another new anti-TB drug, delamanid, which is also at an advanced stage in clinical trials.

Pre-approval access has also been called compassionate care access and expanded access. We think pre-approval access is the most dispassionate and accurate way to describe what we are calling for. By pre-approval access we mean making bedaquiline available, with reasonable conditions, to patients with drug-resistant TB before the drug is approved. In South Africa the obvious mechanism for doing this would be through Section 21 authorisations approved by the MCC. [2] Patients who immediately need life-saving treatment might also access the drug by taking part in a trial that has been proposed to examine the drug's safety.

Pre-approval access has risks. While we have some understanding of bedaquiline's safety and efficacy, there is not yet enough data to say with the utmost confidence that it is safe and effective. Prescribing it to patients with drug-resistant TB is undoubtedly risky.

The MCC is understandably cautious about pre-approval access. No phase III clinical trial of bedaquiline has been completed. Although results of a randomised controlled Phase II trial of bedaquiline have been published, the trial was small.

Also, there is a clamour for the MCC to register thousands of dubious treatments for numerous ailments even though they have not been tested properly. It is understandable that the MCC is worried that giving pre-approval access to one drug will open the door for other drug-manufacturers to demand pre-approval access. [3]

These are legitimate concerns. Making medicines available to patients before they are properly tested, evaluated and approved is not something that the MCC can do at a whim. Nevertheless, we believe the arguments for making bedaquiline available are compelling and outweigh the concerns.

The arguments for pre-approval access

It is reasonable for patients with drug-resistant TB to choose to take experimental medicines

Drug-resistant TB treatment outcomes vary a lot from location to location. Nevertheless, the risk of treatment failure and death is high in all settings. In a recent meta-analysis of over 9,000 patients with multi-drug resistant (MDR) TB from 23 countries, 46% died, relapsed, failed treatment or defaulted. [4] Several studies of drug-resistant TB in South African settings have been published. In a study of a Durban cohort of 60 people with extensively drug resistant (XDR) TB, 25 (42%) died. Only 12 (20%) sputum-converted. [5] A study of the Tugela Ferry TB register for the years 2007 to 2009 found that at one year, mortality with XDR TB was 82% and with MDR TB it was 69%. Over time MDR TB mortality dropped from 87% to 45%, perhaps reflecting improved treatment, but there was no significant decrease in XDR TB mortality. [6]

In Kwazulu-Natal, health workers are at particularly high risk. A study by Max O'Donnell and colleagues found that the incidence of MDR-TB hospitalization was about 65 per 100,000 health care workers versus 12 per 100,000 for non-health care workers (IRR: 5.46, 95%CI: 4.75-6.28). For XDR TB it was 7 per 100,000 health care workers versus 1 per 100,000 non-health care workers (IRR: 6.69, 95%CI: 4.38-10.20). [8] The state has a duty to do everything it can for its employees who have likely become ill because of their work.

The current standard of care is a great burden for patients. The World Health Organisation (WHO) guidelines recommend a 20-month treatment regimen. Five recommendations are given for composing the regimen. All the recommendations are graded very low quality evidence which is WHO's lowest level of evidence. This grading means, "Any estimate of effect is very uncertain". [7]

The side effects of the standard drugs used to compose MDR TB regimens are awful. In one South African MDR TB cohort, more than half the patients taking aminoglycosides became hearing impaired. [8] In another, 28% had severe adverse events. [9] In a Turkish cohort, side effects were severe enough to cause drug changes in more than half the patients. [11] This is how an MDR TB patient, Colisile Lushaba, who kept a blog of her progress, described taking her regimen: "I take 10 pills in the morning, together with the injection. In the evenings I only take antiretrovirals. Although I am slightly better than I was at the start of my treatment, I am not yet feeling very well. I am still coughing, though not as much as I used to. I still vomit a lot, especially after taking the pills. I have to say that this treatment is very difficult and, right now, I am still feeling very weak and unsure of where I will be in the next few months."

In a nutshell, patients on MDR TB regimens typically take a side effect ridden regimen with a poor evidence base for more than a year and a half and still only have a slightly better than half chance of a successful treatment outcome. Mortality and morbidity are extremely high.

Given this situation, it is reasonable for patients with drug-resistant TB to consider taking experimental medicines that have some good quality safety and efficacy evidence. Below, we explain that bedaquiline is such a medicine.

The MCC should be more open to considering pre-approval access for people facing high morbidity or mortality on current best-approved treatments. This is not a frequent situation. It no longer applies to diseases like HIV or diabetes for example. But it does apply to drug-resistant TB.

The evidence shows bedaquiline is promising

The evidence showing that bedaquiline's benefits outweigh its risks needs to be developed, but so far it is promising.

Bedaquiline is a diarylquinoline and is the first drug in this class for the treatment of drug-resistant TB, so there is unlikely to be any existing resistance to it. Bedaquiline inhibits mycobacteria ATP synthase. It is patented by Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson. [12]

In a phase II randomised controlled trial bedaquiline was given to 23 patients and placebo to 24 patients, for eight weeks. All patients received standard MDR TB regimens as well. Bedaquiline significantly reduced the time to culture conversion over 24 weeks (HR 2.3; 95% CI: 1.1-4.7; $p=0.03$). Nearly half the patients on bedaquiline became sputum-negative versus less than 10% of patients on placebo. The number of colony forming units was much lower in the bedaquiline arm too. Nausea was the only adverse event reported to occur significantly more often in the bedaquiline group (26% vs. 4%, $p=0.04$). [13] A study with two year follow up data of this trial has been published and confirms the initial promising outcomes. [14]

An open-label safety trial of bedaquiline with about 200 patients has also been conducted. Janssen has presented 24-week data from this trial. The 2012 Pipeline Report explains: "The data indicated that adding bedaquiline to an individualized MDR-TB regimen was safe and well tolerated and resulted in an overall 81% culture conversion rate at week 24, with median times to culture conversion of 8 weeks for patients with MDR-TB, 12 weeks for patients with pre-XDR-TB, and 24 weeks for patients with XDR-TB." [15]

As far as interactions with antiretrovirals go, which is obviously an important concern in South Africa where many drug-resistant patients are co-infected with HIV, a small Phase I study found that bedaquiline is well-tolerated with efavirenz and that the effect of efavirenz on bedaquiline concentrations is unlikely to be clinically significant. Bedaquiline was associated with QT prolongation. [15]

The 2012 Pipeline Report further explains: "Janssen now plans to start a phase III trial of 600 subjects with sputum smear-positive pulmonary MDR- or pre-XDR-TB (confirmed by rapid diagnostic test). Participants in the first arm will receive 9 months of bedaquiline and a background regimen. Those in the control arm will receive placebo and the background regimen. Participants in a third rollover arm, which will capture the failures from the first two arms, will receive an individualized salvage regimen. The primary endpoint will be relapse-free cure at 15 months for those in the first two arms. The final analysis will look at relapse-free cure at 21 months." [18]

Janssen is also taking into consideration TB/HIV-coinfection and pediatric drug-resistant TB in its development plans.

The evidence base for bedaquiline is better than most other MDR TB drugs

The South African MDR TB treatment guidelines recommend a regimen that includes kanamycin, ethionamide, pyrazinamide, levofloxacin and terizidone. [19] Other drugs like linezolid are also often used for MDR TB. The efficacy of pyrazinamide has been well established, but there is likely much resistance to it amongst MDR TB patients because it is also part of the standard first-line regimen. We searched for controlled clinical trials of the remaining drugs to treat TB, i.e. kanamycin, ethionamide, levofloxacin, terizidone and linezolid.

Kanamycin We can find one clinical trial of kanamycin in people with TB, though it is more accurate to describe it as a prospective case-controlled study. It was published in 1958 and compared kanamycin to streptomycin in 162 patients. It does not appear to have been randomised and the two groups of patients appear not to have been matched at baseline. The data showing the effectiveness of kanamycin is no better, and perhaps worse, than the data on bedaquiline. [22] The available data shows that the side effect profile of kanamycin is much worse than bedaquiline. Kanamycin causes hearing problems in 3 to 10% of patients and it also causes kidney problems. [23, 16]

Ethionamide A tiny clinical trial of 27 people compared ethionamide against thiacetazone in 1963. Cycloserine was given to patients in both arms. Nine out of 14 versus three out of nine patients on the ethionamide and thiacetazone arms respectively had what the authors call "bacteriologically quiescent disease" after one year. The authors state that the ethionamide arm performed statistically significantly better than the thiacetazone one. [17] A Japanese controlled clinical trial that compared ethionamide against prothionamide was published in 1968. However, since all patients also received isoniazid and streptomycin and nearly all patients sputum-converted in all arms of the trial, it is impossible to calculate the effectiveness, if any, of ethionamide in this trial. [24] There are other clinical trials of drug-resistant TB patients that use ethionamide as part of a treatment regimen, but we can find no other clinical trial evidence in people with TB in which ethionamide is tested against a control. Ethionamide is associated with serious side effects. Liver toxicity in particular is common and may continue even after patients stop taking the drug. [23] It is also associated with peripheral neuropathy.

Levofloxacin Besides a seven day early bactericidal activity trial, we can find no clinical trials of levofloxacin that have considered the drug for the treatment of MDR TB. It also has several side effects, including phototoxicity, glucose disturbances, QT prolongation and others. [23]

Terizidone We can find one reference to possible clinical trials of terizidone in a 1972 paper written in Croatia, but we are unable to get the paper. [25] The evidence base for terizidone is poor. [16]

Linezolid Linezolid has been used in South Africa for drug-resistant TB for some time. Yet the first randomized controlled trial of linezolid in patients with drug-resistant TB was only published in October 2012 and it was a smaller trial ($n=41$) than the Phase II bedaquiline trial described above. The results are promising and significantly more patients taking linezolid sputum-converted compared to the controls, but the drug was also associated with more serious adverse events than bedaquiline. [20]

This is not a comprehensive literature review or comparison, but except for pyrazinamide the controlled clinical trial evidence supporting the use of bedaquiline for the treatment of MDR TB is better than any other medicine recommended for this indication in the South African treatment guidelines. For XDR and pre-XDR TB patients, the additional drugs that are often used have even less compelling evidence supporting their use than the ones discussed here. Surely, it is reasonable for people to request and receive bedaquiline to try and treat their drug-resistant TB infection.

Precedents

In Europe and North America there are several pre-approval access precedents, particularly with antiretrovirals. For example, more than 35,000 people received didanosine before the FDA approved it in 1991. [21] This was controversial but likely prolonged many lives.

Other antiretrovirals were also available before approval.

There are of course risks with pre-approval access. There were cases of didanosine-associated pancreatitis during the drug's pre-approval phase. Thousands of people took adefovir as an antiretroviral but it ended up not being approved for HIV treatment.

In South Africa, lopinavir/ritonavir (branded as Kaletra) was made available to patients on Section 21 authorisation before the drug was registered.

Pre-approving access to bedaquiline would therefore not be an unprecedented step by the MCC.

Responsibility for serious adverse events or treatment failure

A concern with pre-approving drugs is who should bear responsibility for the risk of patients experiencing severe adverse events. It is our view that until a drug is registered, if it is used outside of a clinical trial setting as part of pre-approval access, then the pharmaceutical company that manufactures, tests or holds the patent on the drug should not be responsible for the risk. This means that it is very important that doctors tell patients of the risk of taking an experimental drug. Patients have to be aware that the experimental drug they are taking has not yet been fully tested, that it might not work, that it might cause severe adverse events and that it might be worse than not taking it at all although this is unlikely.

The one exception is if the pharmaceutical company held back important safety and efficacy data that might have influenced a patient's decision to take the experimental drug or a doctor's decisions to prescribe it. In that case, the pharmaceutical company must be held responsible.

Because of the risk of taking an experimental drug and the need for patients to be properly informed of the risks, as well as the public interest to limit resistance to bedaquiline, the drug should only be made available to institutions which are likely to have the capacity to monitor patient adherence and inform them of the risk. In our view, health units run by or partnered with academic institutions and proven medical delivery organisations, for example Medecins Sans Frontieres, meet these criteria.

The benefits of pre-approval access outweighs the risks

There are benefits and risks of pre-approval access to bedaquiline. On the current evidence, the benefits of pre-approval access outweigh the risks. Pre-approval access is likely to give patients hope, increase their chances of being cured, reduce the time that they are infectious and possibly reduce their risk of death. The MCC should acknowledge the risks but give drug-resistant TB patients who attend well-run health facilities and who have been properly informed, the opportunity to add bedaquiline to their treatment regimen.

The original document was published on 24 November 2012. The following amendment was published on 21 December 2012.

Following the publication of the Case for Bedaquiline we became aware of a further phase II clinical trial of bedaquiline that we did not include. Information on this trial was made available in November in a report to the US Food and Drug Administration. [26]

In this trial 79 people were randomised to take bedaquiline and 81 to take placebo. All participants had MDR TB and were on a standard background regimen. Participants in the bedaquiline arm had significantly faster time to sputum conversion at 24 weeks ($p < 0.0001$). This benefit was still present at 72-week follow-up. At

week 24, 79% vs. 58% of people had sputum-converted on the bedaquiline and placebo arms respectively ($p = 0.008$). However, a significant safety issue was reported. Ten people died on the bedaquiline arm and two died in the placebo arm ($p = 0.02$, Fisher's exact test). This result is possibly a statistical anomaly but it is concerning and emphasises the need for a phase III study with adverse events as an endpoint.

All but one of the deaths on the bedaquiline arm occurred after the drug was stopped and the time range over which the deaths occurred was wide, but bedaquiline has a long half-life and a causal effect cannot be ruled out. The only cause of death that was reported more than once was TB, which supports the possibility of the mortality result being a fluke.

C O M M E N T

Since the last issue of HTB South, the FDA has approved bedaquiline for the treatment of MDR-TB. This is however conditional on Janssen conducting a phase III trial of the drug. The South African Medicines Control Council has granted Section 21 authorisation for the use of bedaquiline in a safety trial on pre-XDR and XDR TB patients at three sites: Khayelitsha sub-district in the Western Cape, King George V Hospital in Kwazulu-Natal and Sizwe Tropical Disease Hospital in Gauteng. This trial will facilitate access to bedaquiline for very ill patients with few or no other options while Janssen tests continues testing the drug in a phase III trial.

Bedaquiline's safety issues are a concern. The probability of the higher mortality rate in the C208 stage II trial being a statistical fluke is nearly one in 80. However, given that all but one of the patients on the bedaquiline arm died after bedaquiline use ended, that the only repeated cause of death was TB, that bedaquiline reduced time to sputum conversion and that there are few drugs in the TB pipeline, it is worth testing this drug further. Offset against this is that bedaquiline has a long half-life and determining causes of death due to it would therefore be difficult. Close monitoring of patients on the drug is crucial as is the phase III trial.

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US fund additional \$11 million 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

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).
<http://tagbasicscienceproject.typepad.com>

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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).

<http://tagbasicscienceproject.typepad.com>

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<http://jvi.asm.org/content/early/2012/11/08/JVI.01928-12>

TRANSMISSION AND PREVENTION

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

OTHER NEWS

“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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FUTURE MEETINGS

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.europeanaidscinicalsociety.org>

HIV i-BASE

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

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

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

All i-Base publications are available online.

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

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

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

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

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

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

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

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



HIV i-Base

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