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EDITORIAL

Welcome to the last bumper issue of HTB for 2012.

If we include the launch meeting of the British Society of Nanomedicine, and a community debate at the 1st Southern African Clinician's Society meeting, this edition includes reports from seven conferences.

Leading with coverage from the biennial Glasgow meeting, reports cover important aspects of HIV care that still divides expert opinion. This includes when to start ART, HIV and ageing, and the impact of HIV on life expectancy. These are key concerns for HIV positive people and essential to follow. Plus new results on dolutegravir and Quad.

We are also fortunate to be able to include a comprehensive report from the recent US Liver Meeting (AASLD), hinting at the dramatic promise for HCV treatment and eradication, including early data in HIV/HCV coinfection. Tracy Swan's expertise picks through these complex results to separate the hope from the hype.

This issue's treatment access news includes the ongoing concern about continued use of d4T globally. Though further evidence shouldn't be needed we review a South African study, stopped for safety reasons, that reported reporting mitochondrial damage within four week of stating d4T.

More optimisitcally, another paper we review, from the D:A:D group, reports that liver-related mortality (in countries that have dropped d4T) is overwhelmingly linked to confection with hepatitis B and/or C, rather than toxicity of ART.

We also highlight the new BHIVA standards for HIV Care, produced with extensive collaborations, that hope to set the minimum framework for commissioning HIV services and care. The standards were launched to coincide with World AIDS Day, together with latest HPA reports on both HIV and HCV in the UK, and all are available now online.

Over the years i-Base has been lucky to work with a dynamic network of other HIV organisations. i-Base encourages translations and collaborations and at the end of the year it is good to see that HTB is now produced in three similar editions: "HTB South" (in southern Africa), "HIV Tedavi Büleni" (in Turkey) and most recently, "HIV Bilten" (for the West Balkans). These collaborations, lead by HIV organisations in these regions, are in parallel to translations of the i-Base treatment guides (over 25 languages are available online).

With this in mind, we would like to thank all our readers, colleagues, collaborators, contributors and supporters from 2012 and wish everyone best seasonal greetings for a happy, prosperous and successful 2013.

CONFERENCE REPORTS

11th International Congress on Drug Therapy in HIV

11-15 November 2012, Glasgow

Introduction

The International Congress on Drug Therapy in HIV is held in Glasgow every two years and has the advantage of a single-track programme that this year included many excellent overview lectures and more than 300 posters.

The abstracts from the meeting are published as a supplement to the Journal of the International AIDS Society and are also available to download free in PDF format from the conference web site.

Web casts from the oral sessions will be posted on the conference web site in early December.

nttp://www.hiv11.com

Reports in this issue include:

- Issues that divide expert opinion: when to start, HIV and ageing and the impact of HIV on life expectancy
- Dolutegravir: integrase resistance and the impact of the background regimen
- Update on Quad: 96 week data from phase 3 studies
- HIV/HCV coinfection: early glimpses of an interferon-free future and EuroSIDA incidence data
- Resistance in infants and children receiving ART in South Africa

Issues that divide expert opinion: when to start, HIV and ageing and the impact of HIV on life expectancy

Simon Collins, HIV i-Base

The Glasgow programme included overviews of three key aspects of HIV that still divides experts. This included when to begin ART, the overlapping complexity of HIV and ageing and the impact of both these issues on life expectancy.

The range of views held on each subject can make these discussions an unsettling experience for a patient who just wants to do the best thing for their health and who is faced with conflicting expert opinions.

- Should everyone start treatment or is greater caution and additional data warranted, on a population level, and especially for those with highest CD4 counts?
- Does HIV drive earlier and more complex ageing or can the differences previously reported be explained by use of inappropriate control groups and modifiable lifestyle factors?
- Is life expectancy for HIV positive people approaching that of HIV negative people, or are we still falling 10-20 years short because of HIV itself or the complex demographics of HIV cohorts?

If this is confusing for people diagnosed early when their CD4 count is still high and who have good access to treatment, it is more confusing for people with more complex histories. These questions are more than just an academic debate and the overlapping connections between these three subjects made for interesting discussions at the conference.

When to start: asap or not so fast?

A few years ago, when the international START study was being planned, feedback from UK doctors argued for the CD4 threshold for early treatment to be 450 as there was a concern that setting this at 500 would be make the study impossible to enrol. Even 450 was expected to be a challenge given the consensus to defer until treatment was "really needed".

A lot has changed since then. There has been increasing attention given to concerns from unsuppressed viraemia and the associated immune inflammation. There is also greater confidence that ART is protective of serious non-AIDS events including cardiovascular, renal and hepatic disease and some cancers, rather than driving morbidity due to side effects. Finally, the reduced infectiousness demonstrated in HPTN-052 proves the potential of ART to reduce onward transmission.

In Glasgow, one of the first sessions included a debate on the timing of ART on a population level, with the extreme viewpoints of either universal treatment on diagnosis compared to deferring until the CD4 count reaches 350 cells/mm^3.

Michael Saag, from University of Alabama, (and a member of the US DHHS guideline panel) argued that the above benefits are sufficient in themselves to move to a policy of treatment after diagnosis, irrespective of CD4 count. [1]

This is broadly recommended in the US DHHS guidelines but expressed more extremely by the 2012 IAS-USA guidelines. Both panels believe that the complications of current treatment are sufficiently manageable for the difference of an average of 40 rather than 35 lifetime years of treatment to be negligible, and that public health will benefit from reductions in population viral load. While data from randomised studies are not available for people with higher CD4 counts, Saag argued that cohort data suggests that earlier treatment, at the least in the short-term, does not indicate significant harm. Also, for some doctors, the increasing concern of the long-term implications from uncontrolled HIV viral replication prior to starting treatment, and to a lesser extent, even residual viraemia on treatment, has become such a convincing concern that they see withholding treatment, even from people with the highest CD4 counts, as approaching medical negligence.

To counter this interpretation of the current evidence, Jens Lundgren, from the University of Copenhagen, (a member of the EACS guideline panel and co-chair of the START study) argued that a move to universal treatment was a sufficiently important public health policy for this to need to be driven by rigorous evidence that personal benefits outweigh the risks for patients with CD4 counts higher than 350 and especially when higher than 500. [2] The need for this to come from randomised studies is important because so far, large cohort studies have reported contradictory results for these patients. The lack of evidence from studies that were designed to look at the potential harm from earlier treatment (this not a strength of cohort studies) has lead to a reliance for this aspect of the guidelines, on expert opinion, which is universally accepted as the least reliable evidence base for treatment recommendations.

One caution that should temper any rush to universal treatment at higher CD4 counts, comes from data showing that outside the context of clinical studies, 10-30% of patients do not achieve optimal viral suppression on their first combinaton, increasing the likelihood of drug resistance, potentially years before there was a clinical need for treatment. Also, while tolerability with todays treatment has steadily improved, potential toxicity may be reduced further in future treatments.

This raises a reasonable caution against everyone starting treatment at CD4 >350 when the absolute risk of HIV related events is already very low, especially given that historically, earlier treatment based on expert opinion has invariably proven to be wrong. The equipoise supported by the current data is especially important to emphasise for people currently in the START study.

This large international study will enroll the last of its 4000 proposed participants earlier in 2013, all with CD4 counts higher than 500 cells/mm^3 at baseline. Following randomisation to either immediate ART or deferring until CD4 counts reach 350, results are expected by 2016, or earlier if the differences between the two arms are strikingly different.

Participants currently in the deferred arm of the START study, should remain confident and supported by data from large European cohorts showing that the absolute risk for events occurring while their CD4 count is between 350 and 500, is unlikely to very be different from if they started at 500.

Similarly, participants in the immediate arm of START should be reassured that cohort data support the low risk of complications from earlier ART, but that this is dependent on maintaining an undetectable viral load, itself related to careful adherence. Also, that a lower quality of life should not become the price for reducing community viral load, though both are challenging to measure: treatment is easy to modify or switch if the first combination is difficult to tolerate.

Until the START study produces results, individuals with high CD4 counts should be supported if their preference is to start treatment, whether they are doing this for their own or their partner's health. HIV treatment is highly individual though and this decision will be right for some but not for others.

For patients outside the START study, the drive for treatment as prevention is only likely to increase between now and 2016 - irrespective of the clinical impact of earlier treatment - it is important to keep a clear distinction between population level benefits and personal health benefits when individualising the decision to start treatment.

HIV and ageing: a clinical concern or confounded by inappropriate controls?

The impact and association of HIV and ageing was the second topic discussed in Glasgow upon which experts hold diverse opinions. Again, these views impact on clinical decisions, including whether to start earlier treatment. At one extreme, the question of whether HIV directly contributes to significantly faster ageing and increased comorbidities, even in the context of stable treatment – or whether previous reports of early or premature ageing can be explained by the difficulty of identifying appropriate HIV negative control populations?

Several important research groups have contributed to this debate. In July 2012, a supplement to JAIDS, published to coincide with the IAS conference in Washington DC, reviewed four key areas on HIV and ageing. This included the mechanisms for functional decline in innate and adaptive immunity in HIV positive people, the evidence for increases in some biomarkers associated with both HIV and ageing, the role of comorbidities and the diverse behavioural and socio-economic factors that make the HIV positive population such a complex demographic group. While acknowledging that ART increased life expectancy to 70 years, the paper focused on why this hasn't normalised to HIV negative levels. It also proposed key research challenges that need to be prioritised in order to answer these questions. [3]

At CROI 2012, Amy Justice, from the Veterans Affairs Healthcare System (and a co-author of the JAIDS review), emphasised the difference between the potential role of HIV in both "accelerated ageing" (where comorbidities might be occuring at an earlier age) and "accentuated ageing" (where they occur at a higher rate) – and that these effects are not mutually exclusive. This oral presentation also reported the data showing how the lack of adjustment for the younger age of HIV positive compared to general population cohorts, can explain studies that previously suggested HIV positive people might age 20-30 years earlier than HIV negative people. [4]

In Glasgow, Peter Reiss, from the University of Amsterdam, the Netherlands (a co-author of the JAIDS supplement on ageing and a member of both EACS and IAS-USA guideline panels), presented an overview on the potential mechanisms for how HIV might negatively interact with comorbidity and ageing. [5]

As background, many Western epidemics are approaching the time where more than half the HIV positive population will be older than 50 years old, and that the exponential increase in chronic conditions commonly identifies age as the single strongest risk. This includes cardiovascular, renal, pulmonary and hepatic disease, bone health, neurocognitive function, diabetes and frailty.

Concerns about HIV and ageing are especially focused on people who initiated treatment at lower CD4 counts, who are less likely to achieve CD4 counts >500 cells/mm^3 on treatment, often due to late presentation. Adjustment for the younger age of HIV positive cohorts has explained earlier reports that HIV positive people developed non-AIDS cancers at an earlier age. [6] However, several studies have also reported that there is greater use of concomitant medications at an earlier age (polypharmacy) – though this may be driven by the better care and more frequent monitoring that HIV positive people receive. [7]

Prior to treatment, immunologic disruption, HIV and CMV replication, the loss of mucosal gut integrity and microbial translocation, all contribute to a heightened state of immune activation. Although greatly reduced on ART, residual activation may maintain an inflammatory state that continues to increase the risk of fibrotic and coagulant states and these are associated with higher comorbidites. The degree to which this accelerates a healthy ageing process, that by definition involves changes in immune function and tissue and cellular structure, is for research to establish.

So, however compelling and plausible the concerns from inflammation appear, Reiss emphasised that these concepts currently remain a hypothesis that needs to be either proven or refuted – and that this is already the focus of several large studies. Until then, lifestyle choices (including diet, exercise, quitting smoking) may be able to ameliorate many of these additional risks factors that contribute to comorbidity in HIV positive people, just as they do in the general population. And that the issue of HIV and ageing, will become increasingly important globally.

Life expectancy: models for the ultimate outcome

The JAIDS supplement on ageing referred to above, while acknowledging that ART dramatically extends life, also included the following provocative sentence in the opening paragraph of the reports executive summary: "On average, a 20-year old initiating ART may already have lost one-third of the expected remaining years of life compared with demographically similar HIV-uninfected populations" [3], based on a study by the Antiretroviral Therapy Cohort Collaboration (ART-CC) published in 2008. [9]

The conference in Glasgow included a session on HIV and life expectancy. The first of three presentations was an overview by Caroline Sabin from University College London. [8] Given this ultimate outcome is such an important concern, it is notable that this may have been the first time this subject has been given a dedicated session in a conference programme.

Life expectancy, as an important indicator of health, is sometimes referred to from birth, but in the context of HIV is more often presented as additional life years in relation to age at diagnosis/infection. Other measures include:

- years of life lost,
- potential gains in life expectancy,

- excess mortality (per 1000 patient years), and
- standardised mortality ratios (SMR) compared to an age and sex matched general population control group.

With the durability of ART, several research groups have reported increasing levels of life expectancy, that now approach that of a similarly matched HIV negative general population. These include models from cohort studies (including ART CC and UK CHIC) estimating an additional 45-49 years of life expectancy for someone diagnosed at age 20 in a Western country with good access to care. [9, 10]

A more recent model, published in AIDS earlier this year, extended life expectancy to 75 years (95%CI: 68-77) for a gay man diagnosed in 2010 at age 30 with a CD4 count of 430, losing approximately 7 years of life due to HIV. Life expectancy dropped to 71, if the CD4 count was 140 on diagnosis, losing approximately 10 years. [11]

These studies are broadly similar in reporting that the factors associated with longer life expectancy include calendar year, higher CD4 count, suppressed viral load, earlier presentation, fewer coinfections and in non-IDU populations. Adjustment for lifestyle factors may also account for the majority of the differences between HIV positive and general population estimates (approximately 8 out of the 11 year differences in a US study). Gender, race, injecting drug use (IDU), late presentation and stopping treatment were all associated with greater differences. [12]

An analysis from more than 80,000 HIV positive people in the European COHERE cohort collaboration in 2012 reported that IDU (16% of the cohort) and low CD4 count explained most of the differences in life expectancy between HIV positive and HIV negative groups. [13]

Mortality rates became similar to those of the general population once CD4 counts reached >500 on treatment in non-IDU men [SMR 0.9; 95% CI 0.7-1.3], and in women after three years at this level (SMR 1.1, 95% CI 0.7-1.7). Of note, although mortality rates increased with age, excess mortality relating to HIV status significantly reduced with older age, with HIV positive MSM older than 60 years who haven't had a previous AIDS diagnosis achieving reduced SMR mortality compared to the matched general population.

However, mortality rates for the whole cohort remained four times higher than the general population (SMR for men: 3.8, for women: 7.4) at 1.2/100 person-years. Mortality for IDU was 13.1 times higher (95% CI 10.5–16.5) than in the general population, and by gender, results were 11.7 higher (95% CI 9.4–14.7) in men and 22.7 times (95% CI 18.0–28.7) higher in women. Mortality also remained elavated in IDU even with CD4 >500 (SMR 5.7; 95% CI 4.2–7.8). Although duration on treatment helped, even after five years, rates remained significantly increased.

Take as a whole, this returns the focus for ageing and life expectancy studies back to the difficulties of finding appropriate general population control groups. Within the UK, for example, average life expectancy can vary by 20 years depending on geographic region and even within London post codes can vary by greater than 10 years. Modifiable lifestyle factors are important, irrespective of HIV status.

Across all these studies, modelled estimates are dependent on extrapolating relatively short-term data. They may underestimate life expectancy by not accounting for future advances in treatment (think of the cure research) and overestimate it by not accounting for currently unknown future complications (whether from ART toxicity, drug resistance or the role of inflammation). Sabin summarised that life expectancy remains poorly explained for children and that the ageing population will clearly having important implications for the global epidemic.

C O M M E N T

These three issues are closely related, but luckily the middle ground for most people reduces the urgency of each extreme viewpoint, which should be informed by data from well designed studies.

ART clearly increases life expectancy for all groups, and this may be normalised in people without late diagnosis, complicated HIV histories, comorbidities or injecting drug use, especially if CD4 count return to >500 on treatment. Whether any additional health benefit is derived for people starting treatment at much higher CD4 counts is only likely to be adequately answered by START and its critical substudies. [14]

The largest impact on population mortality is more likely to come from reducing modifiable risk factors including earlier diagnosis and access to care and reducing risks associated with IDU.

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Dolutegravir: integrase resistance and the impact of the background regimen

Simon Collins, HIV i-Base

Two oral presentations and a poster provided updated information on the integrase inhibitor dolutegravir.

Results from the VIKING-3 study, in 183 treatment experienced patients with resistance to integrase inhibitors plus at least two other classes and viral load >400 copies/mL on current treatment. The study design continued the background regimens for eight days, switching a current integrase inhibitor to dolutegravir 50 mg twice-daily, and then optimising the background regimen for the next 24 weeks. [1]

This was an advanced group with median baseline CD4 of 140 cells/mm^3 (range 19 - 1110), a median of 13 years previous ART (range 0.3 - 25 years) and 56% CDC Class C. In addition to integrase resistance at screening (n=124) or historical (n=59), at least two major mutations to RTIs and PIs were held by 79% and 70% of participants respectively, with 75% having >1 NNRTI major mutation. Prior ART included darunavir (73%), etravirine (56%), T-20 (49%) and maraviroc (32% - 62% having non-R5 tropic virus detected). Demographics included 23% women, 27% African-American and 21% HBV or HCV positive.

At day 8, mean viral load reduced by 1.4 log copies/mL (95% CI: 1.3, 1.5; p <0.001). At week 24, 63% patients with endpoint data (72/114) had suppressed viral load to <50 copies/mL, with 32% (37/114) non-responders and 5% (5/114) discontinuing due to side effects.

Response rates at both time points was closely related to the prior pattern integrase resistance, with lower responses reported in people with mutations on the Q148 pathway (approximate -1.0 log reductions at day 8 and 48% suppression to <50 copies/mL at week 24, if Q148 + two or more secondary mutations were also present, see Table 1.

Virologic response rates at week 24 were inversely correlated with to presence of Q148 + 2 additional primary mutations, and with fold change in sensitivity to dolutegravir but was not related to overall susceptibility score (OSS) of the drugs in the optimised background regimen, see Table 2. This is very unusual for a new drug used in treatment-experienced patients. As a mechanism for this is difficult to understand these finding will need to be confirmed with larger patient numbers.

Table 1: Virologic responses to dolutegravir by genotype pathway

Primary INI mutations at baseline	N	mean (SD) VL change at day 8	% VL <50 week 24
Total	183	–1.4 (0.61)	82%
T66	1	–1.9	100%
Y143	28	–1.7 (0.42)	96%
N155	33	–1.4 (0.51)	82%
Q148 + ≤ 1 sec. mutations*	32	–1.1 (0.51)	69%
Q148 + ≥ 2 sec. mutations*	20	–1.0 (0.81)	48%
≥ 2 primary mutations	8	–1.4 (0.76)	75%
No primary mutations	60	–1.6 (0.55)	95%

* Secondary mutations: G140A/C/S, L741, E138A/K/T

Table 2: Virologic response rates by OSS score

Derived integrase mutation group	OSS = 0	OSS = 1	OSS ≥2	Total
No Q148 *	100% (2/2)	83% (24/29)	76% (31/41)	79% (57/72)
Q148 + 1 **	100% (2/2)	43% (3/7)	36% (4/11)	45% (9/20)
Q148 + 2+**	50% (1/2)	0 (0/7)	0	11% (1/9)

* 143, 156, 66, 96, historical evidence only ** G140A/C/S, E138A/K/T, L74I

People with only historical integrase resistance are likely to drive viral response at Day 8 higher as selective pressure is likely to take longer than one week to return, so it was significant that this group achieved one of the highest response rates at week 24. The breakdown of resistance patterns by pathway was not presented for these patients.

VIKING-3 also reported that overall drug susceptibility score (OSS) to the background regimen was not associated with week 24 response with 83%, 63%, 59% and 69% achieving <50 copies/mL for OSS 0, 1, 2 and >2, respectively.

Discontinuations due to side effects were uncommon, reported by 3% of participants (6/183). The most common drug-related side effects were diarrhoea, nausea and headache, each reported in 5% of patients.

Secondly, a poster was presented that combined 48 week results from the Phase 3 SPRING-2 and SINGLE studies of dolutegravir in treatment-naive patients was notable for the stratification of responses by baseline viral load and background nucleosides, given that abacavir/3TC is currently not recommended in guidelines at VL >100,000 copies/mL (though contended by GlaxoSmithKline). [2]

SPRING-2 randomised 822 patients to dolutegravir 50 mg once-daily or raltegravir 400 mg twice-daily, plus investigator-selected NRTIs (tenofovir/FTC or abacavir/3TC) finding dolutegravir non-inferior. SINGLE randomised 833 patients to once-daily regimens of either dolutegravir 50 mg + abacavir/3TC or efavirenz/tenofovir/FTC (Atripla) finding the integrase combination superior based on fewer side effects.

While cross study comparisons of different combinations in different populations have only limited value, pulling results from high baseline viral load may be useful in the context of the considerable caution reported in ACTG-5202. These results are detailed in Table 2.

Table 2: Results of SPRING-2 and SINGLE studies stratified by baseline viral load

	SPRING-2		SINGLE	
	Dolutegravir + RTIs	Raltegravir + RTIs	Dolutegravir + abacavir/3TC	Efavirenz/tenofovir/FTC
Baseline viral load <100,000 copies/mL				
ABC/3TC	115/132 (87%)	110/125 (885)	253/280 (90%)	---
TDF/FTC	152/165 (92%)	154/170 (91%)	---	236/288 (83%)
Baseline viral load >100,000 copies/mL				
ABC/3TC	30/37 (81%)	32/39 (82%)	111/134 (83%)	---
TDF/FTC	64/77 (83%)	55/77 (71%)	---	100/131 (76%)

Results were also presented from SPRING-2 on responses by futher stratification at viral load >100k copies/mL. In the <100k group viral suppression to <50 copies/mL at week 48 was achieved by 88% (225/257) vs 91% (306/335) in the abacavir/3TC vs tenofovir/FTC groups respectively. Responses were 86% (36/42) vs 82% (72/88) ar 100k-250k, 81% (13/16) vs 76% (29/38) in the 250k-500k and 72% (13/18) vs 64% (18/28) in the >500k groups respectively. The numbers of patients in these analysis become very low.

Finally, a second oral presentation reported results from in vitro passaging of increasing doses of dolutegravir from 0.05 nM (25% of the EC50) to 50-100 nM over six months, in MT-2 cells and PBMCs. [3]

The most common integrase mutations varied by HIV subtype: R263K followed by H51Y in subtype B and A/G; G118R followed by H51Y in subtype C.

R263K alone resulted in approximately 3 - 6-fold level of resistance in culture, a 30% drop in levels of recombinant integrase strand transfer activity, as well as an approximate 20 - 30% loss in viral replicative capacity.

H51Y had little impact alone, but together with R263K together with H51Y increased dolutegravir resistance to 15-fold, with approximately 50% loss in both viral replication capacity and integrase strand transfer activity.

C O M M E N T

The lack of differences in the high viral load analyses (though these were smaller numbers than ACTG 5202) nevertheless show some support that in a clinical trial setting, when dolutegravir is used as the third drug, abacavir/3TC does not show the same potency issues as with NNRTIs or protease inhibitors.

This is important given the single pill formulation of dolutegravir/abacavir/3TC that is already in Phase 3 studies.

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Updated results on Quad: 96 week data from phase 3 studies

Simon Collins, HIV i-Base

Two oral presentations presented 96 week data from the two phase 3 treatment studies for the recent approval of the single-tablet, four-drug combination of elvitegravir/cobicistat/tenofovir/FTC, developed as Quad, and now approved as Stribild in the US.

Entry criteria for both studies included being treatment-naive and having an eGRF >70 mL/min/1.73m^2.

The first study comparing Quad to Atripla, reported similar rates of virologic suppression to <50 copies/mL of 84% vs 82% (difference 2.7%, 95% CI - 2.9% to 8.3%). This compared to 48-week results of 88% vs 84%, difference (3.6%, 95% CI -1.6% to 8.8%). A sub-group analysis, by baseline viral load below and above 100,000 copies/mL report rates of 81% vs 83%. Mean CD4 cell increases were 295 vs 273 cells/mm^3. [1]

Discontinuation rates due to side effect were similar in each arm (5% vs 7%) with greater reporting of CNS side effects (47% vs 66%) and rash (21% vs 31%) with Atripla but higher rates of renal discontinuations with Quad (2%; n=7 vs 0).

Two patients discontinued Quad after week 48 due to serum creatinine increases but without features of proximal renal tubulopathy. Median changes in serum creatinine (mmol/L [mg/dL]) at week 96 in the Quad vs Atripla arms (11.5 vs 0.9 [0.13 vs 0.01]) were similar to those at week 48 (12.4 vs 0.9 [0.14 vs 0.01]).

Quad had smaller median increases (mmol/L [mg/dL]) in total (0.23 vs 0.47 [9 vs 18], p<0.001) and LDL cholesterol (0.23 vs 0.41 [9 vs16], p=0.011), and similar increase in triglycerides (0.05 vs 0.09 [4 vs 8], p=0.41).

In the second study, 96 weeks results were reported comparing Quad to the boosted PI combination of atazanavir/ritonavir plus tenofovir/FTC, in just over 700 treatment-naive patients.

The proportion of patients with viral load <50 copies/mL at week 96 was 83% vs 82% (difference 1.1%; 95% CI: 4.5%, 6.7%). This compared to 90% vs 87% (difference 3.0%; 95% CI: 1.9% to 7.8%) at week 48, finding Quad to be non-inferior at both timepoints. Results in patients with baseline viral load >100,000 copies/mL were 82% vs 80% (all comparisons, Quad vs ATZ/r respectively).

Mean CD4 cell increases at week 96 were also similar between arms (256 vs 261 cells/mm^3).

Discontinuation rates due to side effects were 4% vs 6%, and caused by renal complications in 3 (0.8%) vs 2 (0.6%) of patients. One person in each arm discontinued between week 48 and 96 due to elevated serum creatinine.

Resistance was reported in 2% vs <1% of patients.

Median increases from baseline in serum creatinine (mmol/L [mg/dL]) at week 96 (10.6 vs 7.1 [0.12 vs 0.08]) were similar to those at week 48 (10.6 vs 7.1 [0.12 vs 0.08]).

Quad had smaller increases (mmol/L [mg/dL]) in triglycerides (0.06 vs 0.18 [5 vs 16], p=0.012) but greater increases in total cholesterol (0.36 vs 0.21 [14 vs 8], p=0.046) with similar changes in LDL and HDL cholesterol. Quad had smaller mean decreases (%) in BMD (hip: 3.16 vs -4.19, p=0.069, spine: 1.96 vs 3.54, p=0.049).

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HIV/HCV coinfection: early glimpses of an interferon-free future and EuroSIDA incidence data

Simon Collins, HIV i-Base

Amongst the most exciting advances in Glasgow related to preliminary results from early studies of interferon (IFN)-free studies that had just been presented at the 63rd AASLD liver disease conference in the US.

For more details, see the detailed report from AASLD by Tracy Swan later in this issue of HTB.

In Glasgow, Jürgen Rockstroh, from the University of Bonn, Bonn, Germany presented an over view of new treatment that started with results from two studies presented at the American meeting from small groups of patients with HCV monoinfection. [1]

In the first, 100% sustained virological responses at 12 weeks (SVR12) were reported for 25 treatment naive patients with HCV genotype 1. Additional, results for 9 prior null responders reported 9/9 achieving an end of treatment response and SVR12 in 3/9 with data available (results pending for the remaining 6/9) using a uridine nucleotide analogue (sofosbuvir, GS-7977) and an NS5A inhibitor (GS-5885), both in development by Gilead. The full study is a multi-arm study (at last count, 11 arms) in 95 patients including genotype 1, 2 and 3. [2]

In the second study, Kowdley and colleagues reported SVR12 rates of 99% in 79 treatment naive and 93% in 45 prior null responders, in a preliminary on-treatment analysis (always a caution), using a combination from Abbott of ABT-450/r (an HCV protease inhibitor boosted with 100 mg ritonavir), ABT-267 (an NS5A inhibitor) and/or ABT-333 (non-nucleoside NS5B inhibitor) ± ribavirin. The full study includes 571 patients (n=438 naive and 133 null responders). [3]

Both studies also included ribavirin in the combination, and importantly, the duration of treatment was only 12 weeks. Although HIV/HCV coinfection can be more difficult to treat (higher baseline HCV viral load, higher resistance) and will involve potentially complex drug interactions and overlapping toxicity with ART, these are very positive indications of future HCV treatment.

It is notable that these advances are being reported in the year when mortality studies have shown that since 2007, HCV has overtaken HIV and the leading cause of death in the USA. [4] This has lead to a US CDC recommendation to move HCV screening from “at risk” groups to universal testing for people born between 1945 and 1965. [5]

Many people with HIV/HCV coinfection have deferred HCV treatment with PEG-IFN and ribavirin due to the low response rates in genotype 1 and toxicity. Even after approval of bocepravir and telaprevir in 2011, which increased cure rates for genotype 1 from about 40% to 65%, treatment is still being deferred, as these directly acting antivirals (DAAs) require three times a daily dosing with food and a difficult side effect profile, plus continue to require PEG-IFN and ribavirin. Response rates in these studies were also dependent on multiple factors including age, gender, race/genetics (IL28B), liver condition (stage, HCV viral load) and comorbidities (obesity, diabetes, alcohol use).

Using either bocepravir and telaprevir with PEG-IFN and ribavirin is now recommended in European treatment guidelines (EACS, 2011) as the standard of care in HIV/HCV coinfection, although optimal duration of treatment has not been establish in coinfection. The talk also included a caution on the complexity of drug-drug interactions with ART that makes some HIV drugs contraindicated. The future is exciting though, with at least eight coinfection studies planned or underway, including new studies from Vertex, Boehringer Ingelheim, Tibotec, BMS, Gilead and Abbott.

The presentation also discussed the increase of sexually acquired HCV in HIV positive gay men (but also in HIV negative gay men, largely potentially undiagnosed). In the absence of spontaneous clearance, treating during acute infection is still often recommended because of the high cure rates even with PED-IFN plus ribavirin. It is a concern that neither spontaneous clearance nor successful treatment provides protection against HCV reinfection and several case reports include examples of successive treatment and reinfection.

Professor Rockstroh highlighted that the lack of evidence explaining the exact mode for sexual HCV transmission is an essential hurdle for effective HCV prevention, especially in the context of men who serosort to limit the chance of HIV transmission. While epidemiology studies report strong associations between sexual HCV transmission and recreational drug use, group sex and fisting, there are many cases of men who have contracted HCV through sexual contact without any of these risk factors.

Biopsy studies looking for the cellular and tissue targets would enable effective interventions that would reduce transmission risks based on the actual route of infection. HCV has a higher viral burden and viral turnover than untreated HIV, is predominantly a blood-blood transmitted infection, and remains infectious outside the body for far longer than HIV (which more rapidly is destroyed on contact with air).

While HCV levels may be detectable in semen at a higher level in HIV positive compared to HIV negative men, it has not been convincingly proven that exposure to semen is the route for sexual transmission. If this is not the case, then advice to use condoms, while popular with health workers for reducing other infections, might not be appropriate or effective at reducing sexual HCV transmission.

Two further oral presentations on HIV/HCV coinfection from the large EuroSIDA cohort were also included in the same conference session.

Ole Kirk from the Copenhagen HIV Programme, Copenhagen, Denmark, presented data on the incidence of HCV infection from 2002 to 2010 in EuroSIDA, with reference to different patient groups and identifying risk factors associated with HCV infection. [6]

EuroSIDA reported that 150 HCV acute infections (95 [63.3%] in MSM) occurred in 4295 patients during 18,928 person years of follow-up (PYFU), giving an overall incidence of 0.79 per 100 PYFU (95% CI: 0.67-0.92). Overall incidence by calendar year appeared stable between 2002 and 2007 at approximately median of 0.5 infections per 100 PYFU (varying between 0.36 and 0.82). However, rates were higher at 1.22 in 2008, 1.10 in 2009 and 2.34 (95%CI: 1.24 - 3.44) per 100 PYFU in 2010.

In multivariate analysis, IDU was associated with a higher incidence rate ratio (IRR) than MSM: 4.59 (2.40 - 8.80; $p< 0.0001$), South and East Europe both had higher IRR compared to Western Europe, respectively (1.98 [1.12 - 3.49]; $p = 0.018$ and 2.41 [1.41 - 4.12]; $p = 0.0014$). Calendar year per 2 years was also associated with a higher IRR (1.29 [1.19 - 1.39]; $p <0.0001$).

David Grint, from UCL, Royal Free Campus, London, presented data from EuroSIDA on the uptake of HCV treatment (PEG-IFN +/- ribavirin) over the 1998-2010 period. [7]

Approximately a quarter of almost 2000 people with HIV/HCV coinfection (n=456/1947; 23.4%) received HCV treatment over a median follow-up time of 107 months (IQR: 57 - 156).

The incidence of HCV treatment increased significantly from 0.29 (95% CI: 0.13 - 0.45) per 100 PYFU in 1998 to 5.26 (95% CI: 3.87 - 65) in 2007, but dropped to 3.73 (95% CI: 2.40 - 5.06) in 2009. Treatment incidence increased 11.0% (95% CI: 4.0 - 18.4; p = 0.0016) per 2 calendar years. Although treatment increased in all European regions, there were considerable regional differences.

In a multivariable model, factors associated with use of treatment included: CD4 cell counts greater than 350 cell/mm3 (incidence rate ratio [IRR]: 1.75 [1.37 - 2.23; p < 0.0001]); HIV viral load <500 copies/mL (IRR: 1.58 [1.18 - 2.12; p = 0.0023]); HCV genotype 3 (IRR: 1.55 [1.21 - 1.98; p = 0.0006), compared to genotype 1; and those from south (IRR: 1.99 (1.45 - 2.72; p <0.0001) and east central Europe (IRR: 1.61 [1.11 - 2.34; p=0.011), each compared to west Europe. HCV treatment was not associated with all-cause death (355 deaths, IRR: 0.81 [95% CI: 0.54 - 1.19; p=0.28]) or liver-related death (95 deaths, IRR: 1.0 [95% CI: 0.50 - 2.02; p=0.99]).

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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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CONFERENCE REPORTS

63rd Annual Meeting of the American Association for the Study of Liver Disease (AASLD)

9-13 November 2012, Boston

Introduction

The 2012 "Liver Meeting" was held in the US just prior to the Glasgow conference. This report from Tracy Swan provides and excellent overview of the exciting developments for both HCV monoinfection and HIV/HCV coninfection.

Early front-runners include two in-house combinations, each from Abbott and Gilead, but these are early days and a lot can happen between phase 2 studies and regulatory submission – and there are over 60 pipeline compounds in development.

Abstracts from the meeting can be viewed online using the itinerary planner on the conference website. This requires a free login and is searchable, but uses a format that does not allow including direct URL links to each abstract.

http://aasld.org

Reports in this issue are:

Cure rates with pipeline HCV drugs: reports from AASLD

Tracy Swan, TAG

It is difficult to be anything other than dazzled by astounding cure rates of up to 100% from a multitude of interferon-free hepatitis C virus (HCV) clinical trials presented at the American Association for the Study of Liver Diseases (AASLD) meeting in November of 2012.

Proof-of-concept has been established: hepatitis C, a disease that claims more than 350,000 lives annually, can be cured with three months of oral antiviral drugs.

These incredible advances bear scrutiny, since most of these interferon-free trials enrolled people with minimal liver disease—many of whom were being treated for the first time. Information about safety, efficacy and tolerability of interferon-free regimens is needed in other groups, including people coinfected with HIV, liver transplant candidates and recipients, and people with cirrhosis (especially those who are treatment-experienced). These are also the people with the greatest immediate need of a safe and effective cure.

Cure rates for interferon-containing and interferon-free regimens have skyrocketed in HCV genotype 1, although in treatment-naive people certain factors such as HCV subtype (1a versus 1b), IL-28B genotype (CC versus non-CC), and extent of liver damage (advanced versus mild-to-moderate) may impair response to treatment (see Table 2. Update: Interferon-free regimens in HCV genotype 1, treatment-naïve).

When is a cure really a cure?

The term sustained virologic response (SVR) is used when the hepatitis C viral load (also called HCV RNA) remains undetectable after completing HCV treatment; it indicates that hepatitis C has been cured. SVR has been proven to lower the risk for liver-related illness and death, although people with pre-treatment cirrhosis should be monitored regularly, since they are still at risk for liver cancer.

With pegylated interferon and ribavirin, a person was considered cured when HCV RNA became undetectable during treatment and remained undetectable for 24 weeks after completing therapy (known as SVR-24). Recently, the U.S. Food and Drug Administration (FDA) regulators revised this time point from SVR-24 to SVR-12, since most post-treatment relapses (when HCV RNA becomes detectable after treatment completion) occur within 12 weeks. Thus, SVR-12 became the new primary outcome for clinical trials studying peginterferon-based regimens.

The hunger for information about cure rates from interferon-free regimens has led to earlier reporting of results; SVR-4 (undetectable HCV RNA four weeks after finishing treatment) is now commonly used. But with interferon-free regimens, SVR-4 does not always predict SVR-12, and SVR-12 does not always predict SVR-24. In fact, there have been two late relapses, between 24 and 48 weeks after treatment with an interferon-free regimen: one in Abbott's PILOT trial [1] and one in Boehringer Ingelheim's SOUND-C2 trial [2]. In both cases, treatment consisted of an HCV protease inhibitor, a non-nucleoside polymerase inhibitor and ribavirin. Although SVR-12 and SVR-24 are primary outcomes for interferon-free trials, monitoring for late relapse will continue.

Results from trials in both treatment-naive and treatment experienced people with HCV genotypes 2 and 3 were presented at AASLD (see Table 5. Update: HCV genotypes 2 and 3, treatment-naive and treatment-experienced).

In late November 2012, Gilead Sciences issued the somewhat disappointing top-line results from POSITRON, a 278-person, interferon-free phase III trial in HCV genotypes 2 and 3. POSITRON compared 12 weeks of sofosbuvir (a nucleotide polymerase inhibitor) and ribavirin to placebo in treatment-naive, interferon ineligible, intolerant or unwilling participants. [3] In HCV genotype 2, SVR-12 was close to 100%, but in HCV genotype 3, SVR-12 was only 61% (see Table 1. SVR in genotypes 2 and 3 by population and regimen).

In treatment naive people with HCV genotypes 2 and 3, interferon-free regimens offer the advantage of improved tolerability and ease of administration. But high prices will make these drugs unappealing to payers without a clear demonstration of improved efficacy, and the potential to fill unmet therapeutic needs.

In genotypes 2 and 3, a retreatment regimen—especially for people with HCV genotype 3 who do not have any options—should be prioritised by pharmaceutical companies. Sponsors need to develop safe, effective, tolerable and affordable regimens when no alternatives exist, in addition to improving the existing standard of care.

AASLD also brought good news for treatment-experienced people with HCV genotype 1 (see Table 3. Update: Interferon-free regimens in HCV genotype 1, treatment experienced). Phase 3 trials of DAA combinations, in both treatment-naive and treatment-experienced people, with and without peginterferon and/or ribavirin are ongoing or soon to be launched.

Although people with hepatitis C and their medical providers want to dispense with interferon and ribavirin, some people—especially null responders with HCV genotype 1a and IL28B non-CC genotypes—may require one or both drugs plus a combination of direct-acting antivirals (DAAs) for a cure. Therefore, regimens that shorten duration of pegylated interferon and/or ribavirin or substitute peginterferon lambda (a potentially more tolerable type of interferon) for peginterferon alfa, are moving forward (see Table 4. Update on interferon-based regimens in HCV genotype 1, treatment-naive and treatment-experienced).

AASLD brought good news for treatment-experienced people with HCV genotypes 2 and 3, since there is currently no recommended retreatment option when peginterferon and ribavirin are unsuccessful.

For treatment-naïve people with HCV genotypes 2 and 3, interferon-free regimens combining sofosbuvir (a nucleotide polymerase inhibitor) and ribavirin yielded cure rates similar to those achieved with the current standard of care (which is 24 weeks of peginterferon and ribavirin), but duration was shortened to 8 weeks. When daclatasvir (an NS5a inhibitor) was added, SVR increased but duration doubled from 12 to 24 weeks (see Table 5. Update: HCV Genotypes 2 and 3, Treatment-Naive and Treatment-Experienced).

Table 1. SVR in genotypes 2 and 3 by population and regimen

Regimen	Population	SVR	Comment
Current standard of care: 24 weeks of peginterferon/ ribavirin. *	HCV genotype 2, treatment naive	74% (SVR-24)	
Current standard of care: 24 weeks of peginterferon/ribavirin. *	HCV genotype 3, treatment naïve	69% (SVR-24)	
ELECTRON trial: 12 weeks of sofosbuvir/ribavirin.	HCV genotypes 2 and 3, treatment naïve, (N=10).	100% (SVR-24)	[4] Gane et al.
POSITRON trial: 12 weeks of sofosbuvir/ribavirin.	HCV genotype 2 treatment naive plus interferon ineligible, intolerant and unwilling, (N=120).	93% (SVR-12)	[3] Gilead PR.

* European Society for the Study of Liver Diseases (EASL). EASL Clinical Practice Guidelines: Management of hepatitis C virus infection. June 2011. http://www.easl.eu/assets/application/files/4a7bd873f9cccbf_file.pdf (PDF file)

For people with HCV genotypes 4 and 6, big news came in a small group of treatment naive, non-cirrhotic people in the ATOMIC study, treated with 24 weeks of sofosbuvir, peginterferon and ribavirin. Of the 11 people with HCV genotype 4, 82% had an SVR-12 (two participants, who were responding to treatment, did not return for follow-up visits). In genotype 6, 100% of 5 people had an SVR-12. No relapses were reported between weeks 12 and 24. [19]

Adding an HCV protease inhibitor to peginterferon and ribavirin boosted SVR and shortened treatment duration for 30 non-cirrhotic, treatment-naive people with HCV genotype 4. The DAUPHINE trial studied 50, 100 or 200 mg of danoprevir/r (a boosted protease inhibitor) plus peginterferon and ribavirin for 24 weeks (with the exception of one arm, where treatment was response-guided; early responders stopped treatment at 12 weeks). Regardless of the danoprevir/r dose, or treatment duration, 97% achieved SVR-24 (one person was lost to follow up). In the response-guided arm, all seven participants were eligible for 12 week of treatment, and SVR-24 was 100%. [20]

Peginterferon lambda may be a good option for people with HCV genotype 4, if phase III trials confirm the favourable side effect profile seen in phase 2. The EMERGE trial (which compared safety, efficacy and tolerability of peginterferon alfa and ribavirin versus peginterferon lambda and ribavirin) included a small group of people with HCV genotype 4 (approximately 18; 12 received peginterferon lambda). [21] Although overall efficacy was comparable, lambda was significantly less likely to cause flulike symptoms and laboratory abnormalities such as anemia and neutropenia than peginterferon alfa-2a. [16]

HIV/HCV coinfection

Final results from a Phase 2 trial of telaprevir plus peginterferon and ribavirin in HIV/HCV coinfected people were presented at AASLD.

In this trial, there were no relapses between 12 and 24 weeks post-treatment: 74% of people who received telaprevir-based triple therapy versus 45% of people given peginterferon and ribavirin plus placebo achieved SVR-24.

Telaprevir levels were similar in study participants in the no-ART arm as well as those taking a boosted atazanavir-or efavirenz-based regimen; in turn, antiretroviral concentrations were not significantly altered by telaprevir, confirming results of earlier drug-drug interaction studies. [22]

Sofosbuvir is already being studied in HIV/HCV coinfected people with HCV genotypes 2 and 3; a clinical trial is comparing 12 vs. 24 weeks of sofosbuvir and ribavirin is ongoing.[23]

Results from drug-drug interaction (DDI) studies of sofosbuvir and commonly used antiretroviral agents were presented at AASLD. There were no clinically significant interactions between sofosbuvir and efavirenz, rilpivirine, boosted darunavir, raltegravir, tenofovir and emtricitabine in healthy volunteers. [24]

Pharmacokinetics and DDIs may be different in people with hepatitis C—especially those with advanced liver damage—and HIV-positive people, compared with healthy volunteers. Nonetheless, these results suggest that these drugs can be co-administered with sofosbuvir, though careful monitoring in clinical trials is still warranted.

Hopefully, the near future will bring more interferon-free trials to HIV/HCV coinfected people.

Table 2. Update: Interferon-free regimens in HCV genotype 1,treatment-naïve

Study, sponsor & regimen	Population and size	SVR (at 4,12 or 24 weeks post-treatment)	SVR: HCV Genotype 1a vs. 1b	SVR: IL-28b CC vs. non-CC	Comment
AVIATOR Phase 2b. **Abbott Laboratories** Drugs (3 or 4): ABT-450/r (boosted protease inhibitor) with or without ABT-267 (NS5a inhibitor) with or without ABT-333 (non-nucleoside polymerase inhibitor) with or without ribavirin. Duration: 8, 12 or 24 weeks	Non-cirrhotic (N=438; 358 were treatment-naïve; for null responder data see Table 3. Update: Interferon-Free Regimens in HCV Genotype 1, Treatment Experienced).	SVR-12 87.5% in the 8-week 4-drug arm (N=80) vs. 97.5% in the 12-week, 4 drug arm (N=79).	8-week, 4-drug arm: 86% in G1a versus 96% in G1b. 12-week, 4-drug arm: 98% in G1a vs. 100% for G1b. In all 12-week, 3-drug arms: 82% to 88% for G1a vs. 100% for G1b.	8-week, 4-drug arm: 96% in IL28b-CC vs. 85% in non-CC. 12-week, 4-drug arm: 100% in IL-28B CC vs. 97% in non-CC. In 12-week, 3-drug arms: 86% to 100% in IL-28B CC vs. 85% to 88% in non-CC.	[5] Kowdley et al.
SOUND-C2 Phase 2b. **Boehringer-Ingelheim** Drugs: faldaprevir (protease inhibitor) with BI 207127 (non-nucleoside polymerase inhibitor) with or without ribavirin. Duration: 16, 28 or 40 weeks.	(N=362; 329 non-cirrhotic and 33 with compensated cirrhosis).	SVR-12: 39% to 69% non-cirrhotic (highest SVR-12 in the 28-week, twice- daily 207127 arm; N=78). 33% to 67% (in cirrhotic participants; the highest SVR-12 in the 28-week, twice daily 207127 arm).	In 28-week, twice-daily 207127 arm: 85% for G1b vs. 43% for G1a.	In 28-week, twice-daily 207127 arm: 84% in IL28b CC vs. 64% in non-CC.	[6] Zeuzem et al.
AI444-040 Phase 2a. **Bristol-Myers Squibb/ Gilead Sciences** Drugs: daclatasvir (NS5a inhibitor) with sofosbuvir (nucleotide polymerase inhibitor) with or without ribavirin. Duration: 12 or 24 weeks.	Non-cirrhotic (N=126).	SVR-4: 95% to 98% in 12-week treatment groups (N=82). SVR-12: 93% to 100% in 24-week treatment groups (N=44).	No impact on SVR.	No impact on SVR.	[7] Sulkowski et al. Gilead is now only developing an in-house regimen.
AI443-014 Phase 2 **Bristol-Myers Squibb** Drugs: daclatasvir (NS5a inhibitor) with asunaprevir (protease inhibitor) with BMS-791325 (non-nucleoside polymerase inhibitor). Duration: 12 or 24 weeks.	Non-cirrhotic (N=32)	SVR-4 24-week dosing group (N=16): 94% SVR-24 12-week dosing group (N=16): 94%	No impact on SVR.	No impact on SVR.	[8] Everson et al.
ELECTRON Phase 2 **Gilead Sciences** Sofosbuvir (nucleotide polymerase inhibitor) with ribavirin with or without GS-5884 (NS5a inhibitor) Duration: 12 weeks	Non-cirrhotic (N=50).	SVR-4 100% (25/25) for triple therapy with sofosbuvir plus RBV and GS-5885. SVR-12 84% (21/25) for sofosbuvir plus RBV.	No impact on SVR.	No impact on SVR.	[9] Gane et al.
SPARE Phase 2 **Gilead Sciences/NIH** Drugs: sofosbuvir (nucleotide polymerase inhibitor) with weight-based ribavirin dosing (WBD) or low-dose ribavirin (600 mg). Duration: 24 weeks.	(N=60) Most were African American, IL-28B non-CC and non-cirrhotic (N=43); a small group had advanced fibrosis or compensated cirrhosis (N=13).	SVR-12 Part 1. Non-cirrhotic, WBD ribavirin: 90% (9/10). Part 2. WBD RBV (included 24% with advanced fibrosis): 72% (18/25). Part 2. Low-dose RBV (including 28% with advanced fibrosis): 56% (14/25).	No impact on SVR.	No impact on SVR.	[10] Osinusi et al.
Vertex Pharmaceuticals Drugs: telaprevir (protease inhibitor) with VX-222 (non-nucleoside polymerase inhibitor) with ribavirin. Duration: response guided, either 12 weeks triple (N=11) or 12 weeks triple plus 24 weeks of PEG/RBV if HCV RNA detectable at week 2 or 8 (N=27).	Non-cirrhotic (N=46).	SVR-12 Overall 72% 33/46. 12-week group: 82% (9/11). 36-week group: 89% (24/27).	100% (5/5 for 12 weeks of triple in G1b vs. 67% (4/6) in G1a. 85% (11/13) in 36-week group in G1b vs. 93% (13/14) in G1a.	Data not broken out by IL-28b genotype.	[11] Sulkowski et al.

Table 3. Update: Interferon-free regimens in HCV genotype 1, treatment experienced

Study, sponsor & regimen	Population and size	SVR (at 4,12 or 24 weeks post-treatment)	SVR: HCV Genotype 1a vs. 1b	SVR: IL-28b CC vs. non-CC	Comment
AVIATOR Phase 2b **Abbott** ABT-450/r (boosted protease inhibitor) with ABT-267 (NS5a inhibitor) with ribavirin with or without ABT-333 (non-nucleoside polymerase inhibitor) Duration: 12 or 24 weeks.	Null responders, non-cirrhotic (N=133).	SVR-12 93% (42/45) for 4-drug regimen. 89% (40/45) for ABT 450/r, ABT-267 and ribavirin (12-week treatment group only; follow up of 24-week treatment group is ongoing).	100% in G1b vs. 81% to 89% in G1a.	100% in IL28B CC vs. 89% to 93% in non-CC.	[5] Kowdley et al. Regimen slightly more effective in G1b vs. G1a, and for IL28b CC vs. non-CC.
AI447-011 Phase 2 **Bristol-Myers Squibb** Drugs: daclatasvir (NS5a inhibitor) with asunaprevir (protease inhibitor),once- or twice-daily. Duration: 24 weeks.	Null responders (N=101), HCV genotype 1b only (N=38; 16%, or 8 people had advanced fibrosis).	SVR-12, 65% (13/20) to 78% (14/18) for once- versus twice-daily asunaprevir.	Enrollment in asunaprevir/ daclatasvir arms limited to G1b due to lack of efficacy in G1a.	All but one person was IL28b non-CC.	Lok et al. [12] In this trial, the same combination, plus ribavirin, was given to people with HCV genotypes 1a and 1b. Peginterferon was added in G1a due to high rates of viral, breakthrough; in HCV genotype 1b, SVR-4 was 100%.
ELECTRON Phase 2. **Gilead Sciences** Drugs: GS-5885 (NS5a inhibitor) with sofosbuvir (nucleotide polymerase inhibitor) with ribavirin Duration: 12 weeks	Null responders, (N=9), non-cirrhotic	SVR-4, 100% (3/3).			[9] Gane et al. Only 3/9 null responders have completed treatment; the other 6 are being followed.
MATTERHORN Phase 2. **Hoffman-La Roche** Drugs: danoprevir/r (boosted protease inhibitor) with mericitabine (nucleoside polymerase inhibitor) with ribavirin Duration: 24 weeks	Partial (N=23) and null responders (N=32) HCV genotype 1b, non-cirrhotic.	SVR-12 Partial responders: 39% (9/23) Null responders: 55% (17/31)	All G1a patients added peginterferon due to high rates of virologic breakthrough and are not included.	>90% were IL28b non-CC.	[13] Feld et al. Baseline viral load higher in partial vs. null responder.

Compensated cirrhosis and pre-and post-transplant

Reports of pre-transplant cures are encouraging but severe adverse events and poor tolerability of triple therapy with peginterferon, ribavirin and an HCV protease inhibitor significantly limit use in "real-life" situations in people with compensated cirrhosis, especially those with a platelet count of <100,000/mm^3 or serum albumin level of <35 g/L. [25]

In fact, one study conducted at a transplant center reported discontinuation rates among people with compensated cirrhosis of >60%. [26] Clearly, DAA combination trials are needed in people with cirrhosis, to avert transplantation or treat post-transplant reinfection.

In CRUSH-C, a 103-person trial of protease-inhibitor-based triple therapy in post-transplant, treatment efficacy is promising: 57% of participants had an early response; HCV RNA was undetectable during treatment, at week 4 and week 12. But treatment safety and tolerability, as well as management of drug-drug interactions with immunosuppressants complicate treatment in the post-transplant setting. Only 14% discontinued treatment for adverse events, but most participants required dose reductions of peginterferon, ribavirin or both drugs and/or growth factors, and 48% required blood transfusions. After starting protease inhibitors (90% telaprevir; 10% boceprevir), immunosuppressant dosing was adjusted (cyclosporine was reduced by 75%; tacrolimus by 90%); nonetheless, a third of participants experienced worsening renal function, and graft rejection was noted (during transition off of the protease inhibitor). [27]

There is a single post-transplant case report of successful interferon-and ribavirin-free treatment of severe, recurrent hepatitis C infection, cured with 24 weeks of daclatasvir and sofosbuvir. [28]

Other drugs may be combined to create interferon-and ribavirin-free regimens in the post-transplant setting: drug-drug interaction studies with simeprevir (TMC-435, a protease inhibitor currently in phase III) and sofosbuvir did not report clinically significant interactions with immunosuppressants in healthy volunteers. [19, 20]

These glimmers of hope need to materialise into trials and programs providing access to lifesaving drugs, the sooner the better.

Table 4. Update on interferon-based regimens in HCV genotype 1, treatment-naive and treatment-experienced

Study, sponsor and regimen	Population and size	SVR (at 4,12 or 24 weeks post-treatment)	SVR: HCV Genotype 1a vs. 1b	SVR: IL-28b CC vs. non-CC	Comment
AI447-011 Phase 2. **Bristol-Myers Squibb** Drugs: daclatasvir (NS5a inhibitor) with asunaprevir (protease inhibitor) once-or twice-daily with peginterferon and ribavirin (QUAD).	Null responders (N=101), 41 treated with QUAD.	95% (20/21) for once-daily asunaprevir QUAD vs.90% (18/20) for twice-daily asunaprevir QUAD.	Most participants were G1a: 85% (17/20) in the twice-daily asunaprevir QUAD arm and 91% (19/21) in the once-daily asunaprevir QUAD arm.	All participants were IL28b non-CC.	[12] Lok et al. This trial had a third arm, combining daclatasvir, twice-daily asunaprevir and ribavirin (N=22). Ten of 18 with G1a had viral breakthrough; 8/18 added peginterferon and are being followed (one achieved SVR-4; 100% (4/4) G1b achieved SVR-4).
D-LITE Phase 2b. **Bristol Myers Squibb** Drugs: peginterferon lambda and ribavirin with asunaprevir (HCV protease inhibitor) or daclatasvir (NS5a inhibitor). Duration: 24 weeks or 48 weeks (response-guided).	Treatment-naive, non-cirrhotic, N=119; data from early responders treated for 24 weeks (N=69).	SVR-12 76% (26/37) of the daclatasvir group; 75% (22/32) of the asunaprevir group.	Both regimens more effective in G1b: 93% (13/14) of G1b in the daclatasvir group vs. 65% (15/23 of G1a; 91% (10/11) of G1b in the asunaprevir group vs. 67% (14/21) of G1a.	Daclatasvir group, no difference (between IL28b CC vs. non-CC; asunaprevir group 90% (9/10) IL 28b CC vs. 68% (15/22).	[14] Izumi et al. [15] Vierling et al. Daclatasvir more tolerable than asunaprevir. Additional data from Japanese substudy (N=14) in HCV genotype 1b: SVR-12 100% (8/8) in daclatasvir arm; 5/5 in asunaprevir arm.
EMERGE Phase 2b. **Bristol Myers Squibb** Drugs: peginterferon alfa-2a and ribavirin or peginterferon lambda and ribavirin. Duration: 48 weeks.	Treatment naive, non-cirrhotic, (N=197).	SVR-24, ~39% for both peginterferons.	Not reported.	Not reported.	[16] Muir et al.
Gilead Sciences **Phase 2.** Drugs: GS-5885 (NS5a inhibitor) with GS-9451 (protease inhibitor) with peginterferon and ribavirin. Duration: 6 or 12 weeks.	Treatment-naive, non-cirrhotic, (N=123).	SVR-12 81% (39/48) in 6-week treatment arm; 100% (40/40) in 12-week treatment arm.	More effective in G1b; of the 8 treatment failures reported, 75% (6 of 8) had G1a.	All participants were IL28b CC.	[17] Thompson et al. Interim analysis; some participants are still in post-treatment follow-up and results from people who did not have an early response not yet available.
MATTERHORN Phase 2. **Hoffman-La Roche** Drugs: danoprevir/r (boosted protease inhibitor) with peginterferon and ribavirin (triple therapy) with or without mericitabine (nucleoside polymerase inhibitor) (QUAD) Duration: for partial responders 24 weeks; for null responders 24 or 48 weeks.	Treatment-experienced non-cirrhotic partial (N=99) and null responders (N=151).	SVR-12 56% (27/48) for partial responders triple therapy vs. 86% (43/50) for QUAD. 84% (62/74) in null responders, 24 weeks of quad therapy; 48-week treatment group ongoing.	91% (19/21) for triple therapy in partial responders with G1b vs. 30% with G1a. 96% (25/26) for QUAD in partial responders with G1b vs. 75% (28/24) with G1a. 100% for QUAD in null responders with G1b vs. 73% (32/44) with G1a.	More than 90% were IL28b non-CC.	[13] Feld et al. [18] Jacobson et al. Regimen more effective in genotype 1b versus 1a. Although numbers were small, efficacy of triple and QUAD did not differ between people with mild to moderate liver fibrosis.

Table 5. Update: HCV genotypes 2 and 3, treatment-naive and treatment-experienced

Study, sponsor & regimen	Population and Size	SVR (at 4,12 or 24 weeks post-treatment)	Comment
AI444-040 Phase 2 **Bristol Myers Squibb and Gilead** Drugs: daclatasvir (NS5a inhibitor) with sofosbuvir (nucleotide polymerase inhibitor) with or without ribavirin Duration: 24 weeks	Genotypes 2 and 3, treatment-naive, non-cirrhotic (N=44)	SVR-24 88% (14/16) (sofosbuvir lead-in + daclatasvir) 100% (14/14) (daclatasvir and sofosbuvir) 93% (13/14) daclatasvir, sofosbuvir and ribavirin	[7] Sulkowski et al. Gilead is developing an in-house co-forumlation of sofosbuvir and GS 5885, their NS5a inhibitor rather than continuing co-development with BMS.
ELECTRON Phase 2 **Gilead Sciences** Drugs: sofosbuvir with ribavirin with or without peginterferon Duration: 8 weeks	Genotypes 2 and 3, treatment-naive, non-cirrhotic (N=35)	SVR-24 100% (10/10) in triple-therapy arm (sofosbuvir plus peginterferon and ribavirin) SVR-12 64% (16/25) for sofosbuvir and ribavirin.	[4] Gane et al
ELECTRON Phase 2 **Gilead Sciences** Drugs: sofosbuvir with ribavirin Duration: 12 weeks	Genotypes 2 and 3, treatment-experienced, non-cirrhotic (N=25)	SVR-12 68% (17/25)	[4] Gane et al. Regimen most effective with weight-based ribavirin dosing and 12-week vs. 8-week duration

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Unless stated otherwise, all references are to the 63 Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), 9-13 November 2012, Boston, Massachusetts. Abstract can be viewed online using the itinerary planner on the conference website. Free login required.

http://www.aasld.org

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CONFERENCE REPORTS

3rd International Workshop on HIV and ageing

5-6 November 2012, Baltimore

Introduction

The 3rd International Workshop on HIV and Ageing took place from 5-6 November 2012 in Baltimore.

Highlights of the meeting included the following talks.

- **HIV disease progression is associated with exhaustion of lymphopoiesis driven by immune activation** - Victor Appay, INSERM, Paris, France.
- **An overview of cellular senescence** - Norman Sharpless, UNC School of Medicine, Chapel Hill, USA.
- **Higher veterans aging cohort study (VACS) index scores are associated with concurrent risk of neurocognitive impairment** - David Moore, University of California San Diego, Psychiatry, San Diego, USA.
- **Association of HIV-associated neurocognitive disorder with frailty in HIV-1-seropositive men** - Bryan Smith, Johns Hopkins University Department of Neurology, Baltimore, USA.
- **Effect of aerobic exercise training in older HIV-infected patients** - Kris Oursler, University Of Maryland School of Medicine, Baltimore.
- **General overview of aging as multi-system failure** - Russell Tracy, University of Vermont, Colchester, USA.
- **Multimorbidity, risk assessment, and personalised health care for those aging with HIV** - Amy Justice, Yale School of Medicine,USA.

Abstracts from this meeting are published in Reviews in Antiviral Therapy & Infectious Diseases and a PDF version of the abstract book can be downloaded from the conference website.

Many of the slide sets from the oral presentations are also available.

http://www.virology-education.com

http://regist2.virology-education.com/abstractbook/2012_9.pdf (PDF file of abstract book)

CONFERENCE REPORTS

BHIVA Autumn Conference

6-7 October 2012, London

Introduction

The British HIV Association (BHIVA) organises two conferences eash year, one in the Spring and one in the Autumn. These meetings include both international speakers and high quality research specific to health care in the UK.

For the last two years BHIVA has also supported wider access to the presentations by making the programme available online. This includes comprehensive web casts and the option to download PowerPoint slides from nearly all oral presentations. It is impressive that so many of the posters from the Spring meeting are also online as PDF files.

Broadening access to these meetings is important and to be commended as a move to reduce barriers to medical information.

Highlights from the Autumn conference, already online, include:

- **Viral latency and eradication strategies** - Sharon Lewin, Alfred Hospital and Monash University, Melbourne, Australia.
- **Do cancer patients with HIV die sooner?** - Mark Bower, Chelsea and Westminster Hospital, London.
- **Does ageing really matter in HIV?** - Paddy Mallon, Mater Misericordiae University Hospital, Dublin, Ireland.
- **Antiretrovirals and the kidneys** -Ian Williams, University College London Medical School.
- **Antiretrovirals and the heart** - Duncan Churchill, Royal Sussex County Hospital, Brighton.
- **Patient-centred outcomes in HIV** - Brian Gazzard, Chelsea and Westminster Hospital, London.

BHIVA Autumn conference web casts and presentations:

http://www.bhiva.org/Autumn2012Presentations.aspx

ANTIRETROVIRALS

Darunavir 800 mg tablet approved in the US

On 9 November 2012, the FDA approved an 800 mg tablet of darunavir (Prezista).

The Dosage and Administration section of the product label has been changed to:

Treatment-naïve adult patients and treatment-experienced adult patients with no darunavir resistance associated substitutions: 800 mg (one 800 mg tablet or two 400 mg tablets) taken with ritonavir 100 mg once daily and with food.

Source: FDA announcement (9 November 2012)

http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm328097.htm

TREATMENT ACCESS

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
Nevirapine/3TC/AZT zidovudine FDC scored tablets for Oral Suspension, 30 mg/50 mg/60 mg, for children weighing 5 to 25 kg.	Cipla, India	16 October 2012
Tenofovir/3TC tablets, 300 mg/300 mg for adults and pediatric patients 12 years of age and older and weighing at least 35 kg.	Macleods Pharmaceuticals Limited, India	8 November 2012
Efavirenz/tenofovir/3TC FDC tablets tablets, 600 mg/300 mg/300 mg, for adults and pediatric patients weighing at least 40 kg.	Hetero Labs, India	8 November 2012

* full approval; FDC: Fixed Dose Combination

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

Fixed Dose Combinations are reviewed for PEPFAR under the FDA guidance titled "Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously approved Antiretrovirals for the Treatment of HIV".

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

Effective patent dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:

http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

An updated list of generic tentative approvals (now at 140) is available on the FDA website:

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

Source: FDA list serve:

http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm

d4T – time to move on

Polly Clayden, HIV i-Base

The first conference of the Southern African Clinician's Society [1] burst into life with a demonstration by the Treatment Action Campaign (TAC).

TAC were unequivocal that repurposing d4T at any dose is not an acceptable way to conquer cost concerns with treatment scale up in South Africa. TAC then joined a packed auditorium to hear the pros and cons of a proposed non-inferiority trial of 20 mg d4T vs tenofovir, presented by Francois Venter, the trial's principle investigator, and MSF's Eric Goemaere, who agrees with the community that the trial is not a good idea.

On numerous occasions, activists from the south and north have made it clear that we want to say goodbye to d4T [2]. Goemaere included many of our previous objections – at 96 weeks the trial is too short to answer its own safety question; the 1990s d4T parallel track programme of over 10, 000 people showed 15% with neuropathy in those receiving 20/15 mg (although better than 21% with 40/30 mg); and research showing people receiving concurrent TB treatment are at increased risk of toxicity (regardless of d4T dose). He then added a few related to newer data, including a study showing early mitochondrial depletion among South African patients receiving low and standard doses of d4T [3].

The debate did not start well, with the moderator quoting a description of patients as people who, "cannot help themselves" (two brilliant documentaries, TAC: Taking HAART [4] and How to Survive a Plague [5], the story of ACT UP, might correct this perception), but livened up during the presentations and discussions from the panellists and audience. Venter's arguments focused mainly on cost saving, which, although remains an advantage of d4T, the more optimistic among us expect ongoing research into treatment optimisation plus alternatives in the pipeline to address this in the not too distant future [6]. Recent stock outs of tenofovir in South Africa, causing substitution with d4T, were universally agreed to be a problem, both there and in many other settings. Opinions varied as to whether potential issues with supply provided any justification for the trial.

TAC's Vuyiseka Dubula who has been an outspoken opponent of the trial and the use of d4T in poor countries reminded us why she would not take the drug herself, nor recommend the trial to her family or her community [7]. Graeme Meintjes of GF Jooste Hospital and University of Cape Town argued eloquently for evidence that a threshold exists between 20 mg and 30 mg, below which unacceptable d4T-associated toxicities can reasonably be expected not to occur, to justify conducting the trial.

Eric Goemaere's closing remarks, in which he stated that HIV must not go the way of TB treatment, which hash't changed since the 1960s, resonated. Indeed, we should remember that for HIV, innovation has been nimble and we have seen big demands and bold aspirations. Seeking a comeback for a drug virtually abandoned in rich countries does not fit with this history, nor does it serve the community well.

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Global Fund provides ART for 4.2 million people: 2012 update

Global Fund press release

On 29 November 2012, the Global Fund to Fight AIDS, Tuberculosis and Malaria announced a substantial increase in the number of people being treated for HIV and in the prevention of mother-to-child transmission.

The increase of 900,000 in the number of people receiving ART since the end of 2011, takes the total number of people supported by the Global Fund to 4.2 million.

The increase has been driven to a great extent by a steady scale-up of access to life-saving antiretroviral medication in sub-Saharan countries, such as Zimbabwe and Zambia. It reflects rising investment in treatment by countries with support from the Global Fund, which is narrowing the gap in coverage.

In 2011, Zambia reached universal access, defined as more than 80% antiretroviral coverage. Between 2009 and 2011, Zimbabwe increased the coverage of people receiving treatment by more than 50%. Cambodia, Namibia, Rwanda and Swaziland also reached universal coverage in 2011.

A steady fall in the cost of drugs has been another factor contributing to the rapid scale-up of treatment. A year's supply of first-line antiretroviral drugs costs today less than $100 for the least expensive regimen recommended by the WHO, down from more than $10,000 in 2000.

The new results show a rise in all HIV-related interventions financed by Global Fund grants.

The number of pregnant women receiving antiretroviral medicines to prevent the transmission of HIV to their unborn children grew from 1.3 million to 1.7 million from the end of 2011. The number of HIV counselling and testing sessions also increased from 190 million to 250 million in the same period (please see table below).

The total number of condoms distributed jumped from 3.5 billion to 4.2 billion between the end of 2011 and 2012. Interventions related to behaviour change communications almost doubled, from 160 million to 300 million.

Care and support services provided to patients increased from 13 million to 19 million, and services delivered to Most-at-Risk Populations, including female sex workers, injecting drug users and men who have sex with men, rose from 23 million to 30 million.

The results also show significant progress in the fight against tuberculosis and malaria. The number of new smear-positive TB cases detected and treated increased from 8.6 million, by the end of 2011, to 9.7 million, by the end of 2012. Over the same period, 80 million new insecticide-treated nets were distributed, taking the total number of nets handed out by the Global Fund to date to 310 million.

Source:

Global Fund Press Release. Global Fund support extends ART to 4.2 millions people. (29 November 2012).

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

$84 million grant to Zimbabwe to reach universal access in 2012

Global Fund Observer

The Global Fund has disbursed $84 million originally scheduled for 2014 to help Zimbabwe to achieve universal coverage of antiretrovirals (ARVs) by the end of 2012.

The $84 million is part of an HIV grant worth $204 million that began in 2010, and was renewed in June 2012. The grant focuses on prevention and treatment for young people, people living with HIV, women and children. The $84 million, however, will be used specifically for treatment.

The Global Fund said in a statement that Zimbabwe is expected to reach 85% of adults in need of treatment by the end of the year. Many countries have defined "universal coverage" as at least 80% of people in need of treatment.

The statement, released on 2 October 2012, said that the money will cover the cost of ARVs for an additional 10,000 new patients, and will bring the total number of people on treatment in Global Fund–supported programmes in Zimbabwe to 203,440 by the end of 2012.

The Global Fund added that part of the money will also pay for the creation of a buffer stock of six months of ARVs for the approximately 480,000 people on treatment in Zimbabwe. The buffer stock will provide security of supplies of ARVs to patients.

The Global Fund said it has agreed to raise treatment coverage together with the US President's Emergency Plan for Aids Relief (PEPFAR). PEPFAR is funding an increase in the number of people on treatment it supports in Zimbabwe from 80,000 to 140,000 this year and to 160,000 in 2013. The UK's Department for International Development (DFID) is also funding treatment for 35,900 patients.

The statement said that the Global Fund is coordinating its efforts with the Government of Zimbabwe, which is supporting 124,000 patients on ARV through its innovative AIDS levy initiative through which it collected $26 million in 2011. The AIDS levy is charged on individuals, companies and trusts at a rate of 3% of the amount of income tax assessed. Of the total funds collected, 50% goes towards the ARV programme.

Source: GFO, Issue 204: 30 November 2012.

Ref: Global Fund. Zimbabwe to attain universal coverage of AIDS treatment by the end of the year. (02 October 2012).

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

Mark Dybul to be the next executive director of the Global Fund

Bernard Rivers, Global Fund Observer

The Global Fund Board has selected Dr Mark Dybul to serve as the Fund's next Executive Director. He previously served as head of the US President's Emergency Program for AIDS Relief (PEPFAR).

The decision was made by the Board on 15 November at its 28th meeting in Geneva, and the appointment will take effect in early February. Gabriel Jaramillo will step down as General Manager on 31 January, as was always intended. Dr Dybul is expected to take office in early February,

The selection of Dr Dybul was the final step in a lengthy and carefully-planned recruitment process. The Board's Ad-Hoc Nominating Committee – whose work was praised by many Board members – carried out the search and the shortlisting process, eventually delivering four names to the Board. Those names were Monique Barbut, the French outgoing chief of the UN's Global Environment Facility; Mark Dybul; Robert Greenhill, the Canadian Managing Director of the World Economic Forum and former President of the Canadian International Development Agency (CIDA); and Barbara Stocking, the British outgoing head of Oxfam.

Dr Dybul helped create, and later led, PEPFAR, the bilateral US AIDS programme that is comparable in size to the Global Fund, and is the largest global health initiative ever undertaken to address a single disease. Trained as a medical doctor with a specialty in immunology, he became an expert on AIDS as a clinician, scientist and administrator. Dr Dybul, born in 1963, is openly gay.

Dr Dybul has considerable understanding of programmes to treat and prevent AIDS, TB and malaria in developing countries, and has experience working with health administrators at many levels, especially in Africa. During his years with PEPFAR, he worked closely with the Global Fund, and in 2007–2008 served as Chair of the Fund's Finance and Audit Committee.

This news item is edited from a longer article in GFO Issue 202 (16 November 2012).
http://www.aidspan.org

Global Fund press release. Global Fund picks Mark Dybul as the next executive director. (15 November 2012).
http://www.theglobalfund.org/en/mediacenter/newsreleases/

US NIH to enforce open access to clincal trial results

The US National Institutes of Health (NIH) has a public-access policy for research that it funds.

This requires investigators to submit papers arising from NIH-funded research to the PubMed Central repository as soon as they are accepted for publication. [1]

The papers must then be freely accessible to the public within 12 months of publication. However, this currently only has a compliance rate of 75%.

On 16 November 2012, the NIH announced next year (beginning as soon as spring 2013), it would withhold the future grant instalments from recipients who have not complied. [2]

C O M M E N T

Ensuring that publically funded research is freely accessible is a major step towards the democratisation of medical literature. This should parrallel the broader involvement of patients at all stages of their care.

The UK Research Council has a similar policy – sometimes requiring open access within six months – but it is unclear how well this is currently implemented. [3]

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SIDE EFFECTS

Low incidence of liver-related deaths in HIV positive people without HBV and/or HCV co-infection

Muirgen Stack, HIV i-Base

This anlaysis from the D:A:D study highlights that the risk of liver failure in HIV positive patients is almost entirely driven by coinfection with HBV and/or HCV rather than ART toxicity in HIV monoinfection.

Kovari and colleagues from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study reported a low incidence ART-related toxicity and that mortality was rare in this large prospective cohort study, published as an advance access paper in the 22 October 2012 edition of CID. [1]

Previously, the group have reported that approximately 16% of deaths in D:A:D are related to liver failure. [2] The effect from ART without HBV/HCV co-infection or alcohol use is less well characterised. However, some ARVs have specific liver concerns including didanosine with non-cirrhotic portal hypertension and nevirapine with liver-relarted hypersensitivity reactions. [3]

All D:A:D study participants with negative HCV and HBV status were included in this analysis. Chronic and previous HCV infection and chronic, active and previous HBV infections were exclusion criteria, as well as unknown HBV or HCV status. Severe alcohol use was defined according to the WHO definition as alcohol consumption of >60 grams/day for men and >40 grams/day for women. When any form of liver failure was cited as the cause of death and HCV or HBV status was negative, clinical charts were obtained and retrospectively reviewed by local investigators. This provided more information on the aetiology of the disease along with laboratory and histology samples if they were available.

Of 49,737 participants followed between 1 December 1999 and 1 February 2010, approxmiately 40% (n=19,618) were HCV or HBV positive either at baseline, or during follow-up and 2506 (5%) had unknown HCV or HBV status. About 9% (n= 4703) participants were excluded because they belonged to cohorts not responding to the requested information for the study. Thus, 22,910 (46%) HCV and HBV negative participants were followed for 114,478 patient-years and included in the analyses.

In the final study group, median age was 38 (IQR 32-46 years), and 73.1% were male. Ethnicity was: white 47%, black 7%, other 2% and unknown 43%. Median year of first HIV diagnosis was 1999 (IQR 1994-2004), median duration of cohort follow-up was 4.9 (IQR 2.2-8.3 years) and cumulative ART exposure was 0.9 (IQR 0-3.5 years). Median CD4 cell count was 410 cells/mm^3 (IQR 250-595), percentage with previous AIDS diagnosis was 23% and treatment status was; naïve 38%, on ART 57% and undergoing interruption 5%. BMI, smoking status and diabetes mellitus diagnosis was also recorded.

From a total of 1059 (4.6%) of deaths, only 12 (0.05%) were liver-related. Thus the incidence of liver-related deaths in people without HCV or HBV coinfection was 0.1 per 1000 person-years (95% CI: 0.05 to 0.18). Seven of the 12 patients that died had severe alcohol use of the cause of death, along with one with an additional diagnosis of haemochromatosis. Five of the 12 patients died due to ART toxicity, meaning

the rate of ART-related death in treatment-experienced individuals was 0.04 (95% CI: 0.01 to 0.1) with 5 events over 1000 person-years. Two of the five patients experienced acute liver failure with lactic acidosis on regimens including didanosine and stavudine. Two others died of non-cirrhotic portal hypertension - both had been exposed to didanosine. The other patient died from fatal liver failure from a hypersensitivity reaction to nevirapine.

1047 patients died from other causes, with 376 (35.9%) from AIDS, 116 (11.1%) from CVD, 149 (14.2%) from non-AIDS malignancies, 315 (30.1%) from other causes and 91 (8.7%) from unknown causes. The only significant difference between patients with liver-related death and patients who died of other causes was median longer exposure to ART at baseline: 5.5 (IQR 4.1-6.6 years) vs 2.8 (IQR 0.1-5.2 years), p = 0.008. The authors speculated that the longer exposure to ART may have included older drugs such as didanosine and stavudine.

C O M M E N T

Although the small number of endpoints in the study made multivariate analyses unfeasible, e.g. the role of patient characteristics on risk of liver-related and other cause mortality, it is still important to clarify incidence rates.

In this case, it should reassure HIV positive people that, apart from didanosine and stavudine, now both rarely used in richer countries, or the hypersensitivity reaction to nevirapine, ART is not associated with liver-related mortality when HCV and HBV negative.

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Rapid drop in mitochondria in fat biopsies within four weeks of d4T use

Muirgen Stack, HIV i-Base

A study by Menezes and colleagues from the University of the Witwatersrand, Johannesburg, published in HIV Medicine, was stopped by the DSMB due to the negative impact of d4T (stavudine) on mitochondria after only four weeks of use. [1]

This was a prospective, open-label, randomised, controlled trial comparing standard and low-dose d4T with tenofovir, designed to assess early differences in adipocyte mitochondrial DNA (mtDNA) copy number, gene expression and metabolic parameters in HIV positive, black South African patients.

Recruitment to the trial was stopped early after a data safety and monitoring board (DSMB) analysis of the first 60 patients demonstrated the group given d4T at both standard and low doses showed a greater fall in the mean mtDNA copies/cell than those in the arm receiving tenofovir.

A total of 60 HIV positive, treatment naive adults were enrolled between September 2008 and December 2009. They were randomly assigned 1:1:1 to receive 3TC (lamivudine) and efavirenz, plus: standard weight-based dose of d4T (30 mg if < 60 kg or 40 mg if > 60 kg) according to the then South African guidelines [2], or a low dose of d4T (20 mg if < 60 kg or 30 mg if > 60 kg), or tenofovir (300 mg).

Inclusion criteria included an absolute neutrophil count (ANC) $\geq$750 cells/mm3, haemoglobin $\geq$7.0 g/dL (70 mg/mL) and a platelet count $\geq$50,000 platelets/mm^3. Patients also needed an alanine and aspartate aminotransferase measurement and an alkaline phosphatase measurement < 2.5 x the upper limit of normal (ULN) and a total bilirubin measurement < 2.5 x ULN. Patients were excluded if they were pregnant or breastfeeding and if they had received any antiretroviral drugs (including post exposure prophylaxis) other than single-dose nevirapine within the past six months.

Baseline characteristics including age and BMI were well matched between the three arms, although this was a cohort that was largely female (85%) and black (98%). All patients had a CD4 count below 200 cells/mm^3, with 78% being at WHO stage 1 and 3% at stage 4.There was no statistically significant difference in the markers of inflammation (leptin, adiponectin) and lipid (HDL, LDL and triglycerides) and glucose metabolism between the arms at baseline.

At weeks 0 and 4, subcutaneous fat biopsies from the supra-ilac region were performed under local anaesthetic on fasted subjects. Total DNA was extracted at the same time points from adipose tissue. This allowed for determination of mitochondrial and nuclear gene copy numbers. The nuclear genes assayed included the peroxisome proliferator-activated receptor (PPAR)-gamma coactivator 1-alpha (PGC1), nuclear respiratory factor-1 (NRF1) and mitochondrial transcription factor-A (TFAM). Other genes measured included those involved in mitochondrial energy metabolism: cytochrome c oxidase subunit III (COX3), cytochrome c oxidase subunit IV (COX4) and mitochondrial cytochrome B (MTCYB). Two nuclear genes involved in lipid metabolism, leptin (LEP) and lipoprotein lipase (LPL), were also assayed.

The authors found a 29% decrease in the mean mtDNA copies/cell from baseline to four weeks in the standard-dose (30-40 mg) d4T arm (P < 0.05), and a 32% decrease in the low-dose (20-30 mg) d4T arm (P < 0.005), when compared with the tenofovir arm, which only had a 4% decrease in the mean mtDNA copies/cell.

For each individual dose of d4T (20, 30 and 40 mg), there was also a drop in mean mtDNA copy number (22, 35 and 31% respectively) vs. tenofovir (300 mg) (4%) at 4 weeks of HAART. The decrease in mtDNA copy number for both d4T 30 and 40 mg doses was significantly higher than for tenofovir 300 mg (P < 0.005 and P < 0.05, respectively). The drop in mtDNA copy number with the d4T 20 mg dose was not significant when compared with tenofovir (P = 0.40).

Only two of the genes assayed had their expression levels significantly altered by stavudine. NRF1 and MTCYB had a greater fall in expression (mean±SD) with the standard (-0.21±0.32 and -0.2±0.43) but not the low dose (0.0±0.51 and -0.11±0.5) of d4T dose when compared with the tenofovir 300 mg arm (0.11±0.26 and 0.16±0.42), ($P < 0.05$). There were no statistically significant changes in the markers of inflammation and lipid and glucose metabolism with any of the drug doses.

C O M M E N T

These findings supporting the policy to switch from d4T to tenofovir in first line public sector HAART made by the South African government in 2010. [3]

Despite the advance of newer ARVs with better side effect profiles, the issue of cost is used by some countries to continue d4T use. Although d4T is being phased out, it is estimated to still be used by approximately 50% of people on treatment globally. Dose reduction (from the standard 40 mg twice daily to 30 mg or 20 mg twice daily) has been proposed as an interim measure that may have similar efficacy, but reduced toxicity. [4] However, other studies have shown that serious side effects continue at significant levels even with a lower dose, and that routine management often fails to detect and switch patients early, leading to peripheral neuropathy and lipoatrophy that is irreversible. [5]

Despite the study stopping enrolment early, limiting its statistical power, it still produced clear findings. There is an early association between mitochondrial depletion and stavudine therapy in this black South African population compared to minimal effect on copy number and related gene expression in patients using tenofovir. The rapid onset of these changes (four weeks) after starting stavudine supports the recent changes in South African guidelines to preferentially use tenofovir.

Combined with the reduced expression of NRF1 and MTCTYB, the authors speculate a role for these changes in the pathology of NRTI toxicity and an associated pre-requisite for lipodystrophy. However, whether these changes were transient or remained throughout the course therapy is less clear due to the lack of measurements past four weeks.

Finally, whilst the lowest dose of d4T (20 mg) was associated with non-significant alterations in mtDNA and gene expression levels compared to tenofovir 300 mg, this may be related to the study size. This should not be seen as supporting the safety of the reduced dose.

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High dose multivitamin use in advanced HIV has no benefit to CD4 and viral load and may cause liver toxicity

Nathan Geffen, CSSR, University of Cape Town

Whether daily micronutrient supplements improve health has for decades been a hotly debated question. In recent years several large studies have been published and received wide publicity. Results, whether in trials for HIV positive or HIV negative participants, have been inconsistent.

In the 17 October 2012 edition of JAMA, Fawzi and colleagues report results from a randomised double-blind trial that examined high dose vitamin supplements versus standard dose supplements in people with HIV on antiretroviral treatment. This is the first major study published considering high-dose micronutrient supplementation for people on antiretroviral treatment. [1]

The primary outcome measure was disease progression or death. Over 3,400 patients were randomised, just over 1,700 to each arm, to receive daily oral supplements of vitamin B complex, vitamin C, and vitamin E at either high or standard levels. The standard dose was based on recommended daily allowance (RDA) with high-dose supplements providing 2 to 21 times the RDA for the B vitamins, 2 times the RDA for vitamin E, and 6 times the RDA for vitamin C, see Table 1. Both supplements were matched in appearance and taste.

Over 65% of participants were women. Approximate mean (SD) baseline demographics included age 38 (± 8.6) years, CD4 count 130 (± 100) cells/mm3 and BMI 21 (± 4.1), with no significant differences found between the arms at baseline. Only 20% of patients had a CD4 count > 200 cells/mm3 and 40% had a count <100 cells/mm^3 and viral load was 5.2 log (± 0.7) log copies/mL. All patients were initiated on 3TC plus either nevirapine or efavirenz, with 70% patients using d4T (stavudine) and 30% using AZT.

Recruitment began in November 2006 and was planned to run for two years. An interim analysis in 2007 showed an increase in deaths in the high-dose arm, so the DSMB recommended all patients receive standard-dose supplements between November 2007 and March 2008. However, a further analysis showed that increased risk from high dose supplementation was restricted to patients affected were severely malnourished. This allowed the study to continue, but excluded patients with BMI less than 16 from enrolment.

The study was halted a second time by the DSMB early in March 2009, this time permanently, due to increased levels of alanine transaminase (ALT) in the high-dose arm. Median follow-up at this time was 15 months (IQR 6-19 months).

The absolute risk of HIV progression or death was 72% in the high-dose group vs 72% in the standard-dose group (risk ratio [RR], 1.00; 95% CI, 0.96-1.04). Approximately 1,230 patients experienced HIV progression in each arm with about 450 deaths divided almost evenly between the arms.

High-dose supplementation had no effect on CD4 count, plasma viral load, body mass index, or hemoglobin level concentration, but increased the risk of ALT elevations (1239 events per 1215 person-years vs 879 events per 1236 person-years; RR, 1.44; 95% CI, 1.11-1.87, p = 0.006) vs standard-dose supplementation. However, this was for increases above the upper limit of normal (ULN >40 IU/L). For the more rigorous and clinically relevant cut-off of 5xULN (>200 IU/L) was reported in only 2% of participants with a non significant RR 1.12 (0.50 to 2.50), p = 0.79, NS.

However, the high-dose arm reported a significantly reduced risk of peripheral neuropathy which was extensively reported and still very common in the high dose arm (1213 events per 1503 person years vs 1365 events per 1450 person years). Nevertheless, this difference was significant (RR 0.81 (0.70 to 0.94), p=0.004).

Table 1: Supplement content for standard and high dose

Vitamin	Standard Dose	High Dose
Thiamin	1.2 mg	20 mg
Riboflavin	1.2 mg	20 mg
Vitamin B_6	1.3 mg	25 mg
Niacin	15 mg	100 mg
Vitamin B_{12}	2.4 µg	50 µg
Folic acid	0.4 mg	0.8 mg
Vitamin C	80 mg	500 mg
Vitamin E	15 mg	30 mg

C O M M E N T

This trial is a setback for proponents of high-dose supplementation. At best there was no benefit (or perhaps a reduced rate of neuropathy, though the prevalence of neuropathy in both arms remained alarmingly high) and at worst a potentially negative impact on liver enzymes (though non-significant at a clinically relevant level).

A more compelling study for the benefits of micronutrient supplementation was published in 2004 in the New England Journal of Medicine by Wafaie Fawzi of Harvard Medical School and his colleagues. [2] In this randomised placebo-controlled trial, 67 of 271 pregnant women who received a supplement containing vitamins B, C and E progressed to WHO stage 4 or died compared to 83 of 267 women who received placebo (24.7% vs. 31.1%; RR:0.71; 95%CI: 0.51-0.98; p=0.04).

The multivitamin arm participants also had significantly higher CD4 and CD8 cell counts and significantly lower viral loads. Interestingly, the study found that adding vitamin A to the regimen reduced its benefit. The quality of this study was high but the targeted population was very specific, i.e. pregnant women in a very poor country. Recommending micronutrient supplementation to people with HIV or even only pregnant women with HIV cannot be generalised on the basis of this study alone.

However, a Cochrane Review published in March 2012 considered 78 clinical trials of antioxidants that included nearly 300,000 patients. [3] The authors concluded that the "current evidence does not support the use of antioxidant supplements in the general population or in patients with various diseases." They also wrote, "Beta-carotene and vitamin E seem to increase mortality, and so may higher doses of vitamin A. Antioxidant supplements need to be considered as medicinal products and should undergo sufficient evaluation before marketing."

Four relevant Cochrane Reviews have been conducted on vitamins and HIV:

- **Sinclair and colleagues (November 2011) considered 23 trials with over 6,800 patients that examined nutritional supplements for people with TB. They concluded that there was not enough evidence to judge whether multivitamins reduced mortality in HIV negative people with TB, but found moderate quality evidence that they had little or no effect in people co-infected with HIV. [4]**

- **Van den Broek and colleagues considered vitamin A supplementation during pregnancy and examined 31 trials, of which 14 were included in their analysis. They published in March 2011. Overall, vitamin A supplementation did not reduce maternal mortality, perinatal and newborn mortality, stillbirth, preterm birth, low birthweight or newborn anaemia. They did however find good evidence that vitamin A deficiency is common. The evidence also suggested a reduction in maternal infection, but the authors wrote that these data were not of a high quality. [5]**
- **Siegfried and colleagues published a review earlier this year that considered four trials in pregnant women and their infants. They concluded that micronutrient supplements improved the health of pregnant women and their infants. They also wrote that no significant adverse effects were reported. However, zinc supplementation did not show any significant benefits. They found that selenium did not benefit mothers HIV progression or their pregnancy but may increase the likelihood of a child surviving and may reduce diarrhoea in mothers. They found insufficient evidence about the effects of supplements on pregnant women living with HIV who were on antiretroviral medicines. [6]**
- **The same authors published another review in January 2012 that updated an earlier review they did in 2005 titled, "Micronutrient supplementation for children and adults with HIV infection". Their findings are quite nuanced. They reviewed 30 trials involving over 22,000 participants. Of these, 20 trials examined single supplements (vitamin A, vitamin D, zinc, selenium) and 10 examined multiple micronutrients. Eight trials were in children. [7]**

  Vitamin A had no benefit in adults, but halved all-cause mortality in a meta-analysis of three trials in African children.

  Zinc supplements reduced diarrhoea in one trial of South African children, but showed no benefits to adults in a trial of Tanzanian women or Peruvian adults with persistent diarrhoea.

  The authors found that selenium reduced diarrhoea in pregnant women in Tanzania, and reduced viral load in two separate small trials in American adults.

  Vitamin D showed no benefits when taken alone. They cited the Tanzanian trial described above as evidence for benefit to pregnant women and their children. They also found another Tanzanian trial in which supplements reduced the recurrence of pulmonary TB and increased weight gain in co-infected patients.

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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 N E 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

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/mm^3 were eligible for ART – usually nevirapine (NVP) plus AZT/3TC. Women with CD4 counts >250 cells/mm^3 received AZT monotherapy for PMTCT. Starting in late October 2009, a limited number of women received ART with CD4 counts >250 cells/mm^3 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/mm^3 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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GUIDELINES

UK Standards for HIV Care launched by BHIVA

On 29 November 2012, the British HIV Association (BHIVA) launched "Standards of Care for People Living with HIV" at the Royal College of Physicians in London to an audience of over 150 people.

It is hoped that this document will help with the planning of both national and local services to ensure that HIV positive people receive access to the appropriate levels of treatment and care.

The Standards were compiled by a wide range of stakeholders, including doctors, nurses, pharmacist, community advocates and HIV positive people and revised after consultation for comments.

Further information on process of producing the standards, together with links to download PDF versions are on the BHIVA website.

http://www.bhiva.org/standards-of-care-2012.aspx

The recommendations cover 12 major areas of care.

1. Diagnostic Testing for HIV

2. Access to, and retention in, HIV treatment and care

3. Provision of outpatient treatment and care for HIV, and access to care for complex co-morbidity

4. Safe ARV prescribing: Effective Medicines Management
5. Inpatient care for people living with HIV
6. Psychological care
7. Sexual health and secondary HIV prevention
8. Reproductive Health
9. Self management
10. Service user engagement / involvement
11. Competencies
12. Data, Audit and Research

HIV TRANSMISSION

Quantifying HIV-1 exposure to illuminate resistance to infection

Richard Jefferys, TAG

In the early 1990s, the research group of Frank Plummer at the University of Manitoba drew considerable attention—and some controversy—when they reported that, among a large cohort of female sex workers in Nairobi, a subset showed evidence of resistance to HIV infection. [1]

The evidence emerged over the course of a long-term study that found that women starting sex work faced a very high risk of seroconverting in the first two years. However, for a subset of women who remained HIV negative, the risk of becoming infected subsequently declined significantly over time, which Plummer and colleagues interpreted as evidence of resistance to acquisition. Despite initial skepticism, the findings prompted efforts to identify individuals with possible resistance to HIV in other settings, such as among serodiscordant couples (in which one partner is HIV positive and the other negative). There is now a substantial amount of literature on the topic and ongoing workshops and research collaborations, but one of the challenges in the field is that there are no widely accepted criteria for defining high exposure to HIV (an important part of assessing whether an individual may be resistant as opposed to simply unexposed).

In a new paper in the Journal of Infectious Diseases, Romel Mackelprang and colleagues from the Partners in Prevention HSV/HIV Transmission Study describe a method for quantifying HIV exposure among serodiscordant couples, with the goal of enhancing efforts to identify individuals with potential resistance to infection. [2]

The study draws on data from a trial involving 3,408 serodiscordant heterosexual African couples. Risk factors that were associated with HIV transmission—such as unprotected sex, viral load in the HIV positive partner, and genital ulcer disease—were used to create "exposure scores" for the study participants. Unsurprisingly, high exposure was associated with a 6.9-fold increased risk of infection compared to low exposure. But these scores also identified a subset of 475 individuals with persistently high exposure who remained seronegative. Echoing Frank Plummer's findings, the risk of HIV infection appeared to decline over the time in the high exposure group, while remaining constant among participants with lower exposure.

To further validate these findings, the researchers applied a simplified version of the exposure score model to an independent cohort of 485 serodiscordant couples from Kampala, Uganda, and Soweto, South Africa. Again, the analysis identified a group (comprising 48 individuals) with high exposure but a decreasing risk of acquiring HIV infection over time. The study authors conclude: "our approach to estimating HIV-1 exposure using longitudinal data from both partners in HIV-1–serodiscordant couples provides an objective tool to identify subsets of HESN [HIV-1–exposed seronegative] individuals to target for identification of host factors protecting against HIV-1." Additional details on the exposure scoring system are provided as supplementary data on the journal website. [3]

Source: TAG basic science web log. (12 September 2012).

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Immune activation, inflammation and HIV acquisition risk

Richard Jefferys, TAG

The geographic variation in the risk of HIV acquisition among heterosexuals has prompted extensive speculation and debate as to the underlying causes.

The lack of a clear explanation has even fueled conspiracy theories, playing a prominent role in Thabo Mbeki's disastrous embrace of AIDS denialism in South Africa and driving a campaign that—in the face of a mountain of evidence to the contrary—insists that non-sexual transmission is the answer.

It has not helped that much of the research on the subject has focused on behavior, with hypotheses such those based on concurrent sexual partnerships being aggressively promoted by certain individuals even though many view the evidence supporting them as slim to non-existent (for a recent critique, see "HIV, logic and sex in Africa" by Lucy Allais and Francois Venter [1]).

Relatively speaking, biological explanations have received less attention, despite the fact that it is well known that the immunological environment in which HIV finds itself has a huge impact on its ability to replicate and thrive. Only a handful of published studies have looked at how geographic location can impact levels of immune activation, finding that background levels are significantly higher in locations on the African continent compared to Europe and the US. The first such study to specifically analyse immune activation in the genital tract (comparing women in Kisumu, Kenya and San Francisco, USA) was published only two years ago. [2]

Several new papers report data potentially relevant to this topic. Researchers involved in the CAPRISA 004 trial, an evaluation of the preventive efficacy of a gel form of the antiretroviral tenofovir, describe results from an analysis of immune activation and HIV acquisition risk among trial participants (44 who acquired HIV infection and 37 who remained HIV negative). Elevated systemic innate immune activation was a significant risk factor for HIV infection (odds ratio 11.27, 95% CI 1.84-69.09, p=0.009) while a quiescent innate immunity profile was associated with reduced risk (odds ratio 0.06, 95%CI 0.013-0.33, p=0.001). [3]

The data echo similar findings from a study of genital tract inflammation among CAPRISA 004 participants, which were presented at CROI in 2011 [4] and further discussed at CROI this year by Quarraisha Abdool Karim. In those analyses, women with genital track inflammation were 14 times more likely to acquire HIV infection than those without. The researchers argue that strategies for dampening immune activation and inflammation should be considered in the context of biomedical HIV prevention research.

Among the potential causes of genital tract inflammation and immune activation, sexually transmitted diseases obviously stand out, and many STDs have been reported to significantly increase HIV acquisition risk (including HSV-2, gonorrhoea, chlamydial infection, trichomoniasis, and bacterial vaginosis). A more recent addition to this list is Mycoplasma genitalium [5], and a study just published online by the journal Infection and Immunity suggests that, unsurprisingly, this effect is likely mediated by increased inflammation. [6]

The question of whether human papilloma virus (HPV) has a role in enhancing HIV acquisition has not been clearly answered, but a review and meta-analysis in the journal AIDS finds that the available evidence is consistent with a doubling in risk (although no associations with specific genotypes were detectable). The authors stress that the findings require validation, but note that three of the studies they reviewed contained sufficient data to estimate the proportion of HIV infections that may have been attributable to the presence of HPV infection at baseline: in women in Zimbabwe and South Africa, the figures were 21% and 37%, respectively, and in heterosexual men in Kenya the estimate was 28%. A recommendation that emerges from these analyses is that the effect of HPV vaccination programs on HIV incidence should be evaluated, particularly as vaccine coverage of HPV genotypes improves. [7]

Unfortunately, unlike HPV, no vaccine exists for other STDs. At one time it was hoped that treatment of STDs could significantly reduce HIV acquisition risk but promising results from an initial randomised controlled trial were not confirmed by subsequent studies. [8] More recently, compelling evidence has emerged that inflammation and immune activation are critical factors underlying this apparent disconnect. In the case of HSV-2, a detailed study revealed that numbers of CCR5-expressing CD4 T cells and DC-SIGN-expressing dendritic cells are elevated in the genital tract of infected individuals, and that acyclovir treatment does not significantly alter this environment. [9]

In the 01 July 2012 issue of the Journal of Infectious Diseases, researchers in South Africa report that symptomatic vaginal discharge, a criteria for syndromic STD diagnosis, is in fact a poor predictor of inflammation and the presence of laboratory-diagnosed STDs. [10] Furthermore, levels of inflammation were significantly elevated among women with laboratory-diagnosed STDs regardless of whether they were symptomatic or asymptomatic. The latter paper prompted a commentary from Myron Cohen that concludes: "the 'hidden epidemic' of classical STDs is squarely blocking optimal prevention of HIV-1 transmission. These STDs—symptomatic or asymptomatic—simply cannot be ignored. As we commit to combination HIV-1 prevention, we must redouble our efforts to think of every possible way to recognise and treat classical STDs. Surely this problem is no more impossible to attack or less important than any other part of the HIV-1 pandemic." [11]

Source: TAG basic science web log. (21 Aug 2012).

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BASIC SCIENCE

Hopes raised by HDAC inhibitor, but uncertainties remain

Richard Jefferys, TAG

In the 26 July 2012 issue of the journal Nature, Nancy Archin and colleagues from the laboratory of David Margolis published results from a trial investigating whether the approved cancer drug vorinostat can reverse HIV latency. [1]

Vorinostat (also known as SAHA, trade name Zolinza) belongs to a group of compounds called histone deacetlyase (HDAC) inhibitors. Histone deacetylases are a class of cellular enzymes involved in condensing DNA and repressing gene expression. In laboratory experiments, inhibiting histone deacetylases appears to free latent HIV from lockdown, causing viral RNA to be produced. HDAC inhibitors have therefore emerged as lead candidates for depleting latent HIV reservoirs, a task that is widely believed to be an important step along the path to a cure.

Margolis has previously presented preliminary results from the trial, first at a meeting in St. Maarten in December 2011, then at CROI and Keystone in March of this year. Each time the number of participants with available data increased, from four initially to six at CROI and seven at Keystone. The published Nature paper brings the final count to eight. I wrote about the data when it was initially presented, and below is an updated version of that report.

The first step of the protocol involved screening potential participants to assess whether vorinostat could reactivate latent HIV from their CD4 T cells ex vivo. Sixteen individuals had lymphocytes extracted by leukopheresis, then sorted into discrete pools of 1 million purified resting CD4 cells each (ending up with 12-48 pools per participant). These pools were exposed to either vorinostat or no drug, and a mean level of HIV RNA per million cells (and a standard deviation) was calculated for each person (the assay used can measure down to 10 copies per million cells). Margolis noted in St. Maarten that the statistical approach used to calculate the mean RNA levels is robust but complicated, and a paper explaining it is currently in press at a statistics journal. Eleven of the sixteen people screened showed an upregulation of HIV RNA expression in this analysis and eight agreed to participate in the next step of the trial.

A 200 mg dose of vorinostat was given first for safety, followed by a 400 mg dose to study pharmacokinetics and for analyses of histone acetylation and acetylation of the p21 gene (in other words, analyses of the effects of the drug on cellular genetic machinery and not HIV). The pharmacokinetic data mirrored reports from cancer studies, with peak levels occurring a mean two hours after dosing. A significant increase in the acetylation of cellular histone H3 was observed, along with a trend towards increased acetylation of histones at the p21 gene in five participants who had sufficient cells available for this analysis.

A final 400 mg dose of vorinostat was then administered with leukopheresis performed 4-6 hours afterward based on the pharmacokinetic data indicating this would be around the time of maximum activity. No grade 1 or greater toxicities were seen, and cell-associated unspliced HIV gag RNA expression increased significantly compared to baseline in all eight individuals by a mean of 4.8-fold (range: 1.5-10-fold). HIV RNA in peripheral blood was assessed using a single copy assay but no change was detected. The researchers also state that "a limited evaluation did not reveal a substantial reduction in the frequency of replication-competent HIV within resting CD4 T cells" but the data is not included in the paper, and they note that this would not be unexpected given that only a single dose was administered. The primary import of the results, they conclude, is the proof-of-concept: "these findings demonstrate that therapy targeted at persistent, latent infection within resting CD4 T cells is feasible, and open the way for the development of HDAC inhibitors with improved specificity, potency and safety profiles for the selective targeting of latent proviral genomes."

When he presented the early results in December 2011, Margolis offered a list of questions that remain to be answered.

- Is there an equal effect from multiple doses or does it become attenuated?
- How much drug exposure is needed?

- Should drug be administered continuously or pulsed?
- Will toxicities emerge?
- What number of cells is needed to measure relatively rare reactivation events?
- Are additional inducers needed?
- Does RNA expression lead to virion production or clearance of the infected cell?
- Are additional interventions needed to clear the latently cells that have been induced to express HIV RNA?

Since that time, data addressing some of these questions has been presented and published. Tae-Wook Chun's laboratory at NIAID has shown that the induction of RNA expression by vorinostat does not lead to significant virion production or clearance of the infected cell. Robert Siliciano's group also documented a lack of clearance of infected cells, and furthermore demonstrated that functional HIV-specific CD8 T cells are needed to perform this task.

More recently, at the AIDS 2012 conference that took place in July in Washington DC, Jeff Lifson presented data indicating that multiple doses of vorinostat do not have consistent effects on the viral reservoir in the SIV/macaque model. The relevance of these findings to humans should be revealed when results become available from a clinical trial involving a 10-day course of vorinostat, which is currently being conducted by Sharon Lewin in Australia.

In addition to the caveat that HDAC inhibitors alone appear unlikely to be sufficient to achieve a cure of HIV infection, there is also a question that wasn't on Margolis's list: are there latently infected cells that cannot be reactivated by these drugs? At a symposium on cure research that took place immediately prior to AIDS 2012, Robert Siliciano presented evidence that, while the majority of resting CD4 T cells containing HIV DNA harbor viral genomes that are compromised by various genetic alterations (such as deletions) some—16.8% in his study (range: 6-36%)—contain replication-competent HIV that is not induced by normal methods. It is as yet unclear if this virus can be induced to replicate in vivo.

In a commentary accompanying the Archin paper, Steve Deeks highlights the work that remains and the likely need for combination approaches, but also emphasises that these results represent an important first step beyond antiretroviral therapy and into new territory, with a cure for HIV infection the ultimate destination. [2]

Source: TAG Basic Science Blog (27 July 2012).

http://tagbasicscienceproject.typepad.com

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Post-treatment control of HIV replication and prospects for a functional cure

Richard Jefferys, TAG

In a review article in the open-access journal Retrovirology, Guido Vanham and Ellen Van Gulck provide a detailed accounting of the multitude of immune-based therapy (IBT) studies that have been conducted over the years (both in people with HIV and the SIV/macaque model). [1]

The authors were prompted by the recent resurgence in interest in attempting to induce immune control of HIV in the absence of ongoing antiretroviral therapy (ART), a goal that is now described as achieving a "functional cure." While the term is new, the goal itself is not: in the late 1990s, it was described more circumspectly as "remission." Unfortunately, the best results to date from IBT studies involve small and transient diminutions in viral load associated with receipt of some therapeutic vaccine candidates. Despite the disappointments, attempts to achieve more robust control of HIV continue; Vanham and Van Gulck are pursuing a therapeutic vaccine approach involving delivery of HIV antigens to dendritic cells using messenger RNA (mRNA).

The review also highlights the potential value of studying—and trying to learn from—rare individuals who maintain undetectable viral loads after ART interruption, a group now dubbed "post-treatment controllers" or "secondary controllers." As Vanham and Van Gulck note, a number of cases of post-treatment control have been reported. Most involve individuals treated during acute HIV infection, such as the members of the VISCONTI cohort in France that were described recently at the AIDS 2012 conference and the oft-forgotten original "Berlin Patient" (who featured as a case report in the New England Journal of Medicine in May of 1999). The latter individual was treated intermittently with ART during acute HIV infection and has maintained viral load below 50 copies for many years after stopping treatment entirely (although this case has since been eclipsed by the second Berlin Patient, Timothy Brown, a new book is in the works by author and researcher Nathalia Holt that promises to tell both stories).

Although far less common, there have also been occasional anecdotes regarding possible post-treatment control in individuals with chronic HIV infection, but there is little in the way of published documentation. Vanham and Van Gulck have themselves recently reported on a total of four cases that have been identified in the HIV cohort of the Institute of Tropical Medicine of Antwerp. [2, 3]

In exploratory analyses, these individuals showed low levels of intracellular viral RNA, lower viral fitness and high proliferative T cell responses towards Gag and Pol.

Given the potential importance of this type of research to the broader effort to cure HIV, there appears to be a need for a more coordinated global effort to identify and study possible cases of post-treatment control in chronic infection. The International HIV Controllers Study, led by Bruce Walker from the Ragon Institute, is primarily focused on elite controllers (individuals who control viral load to undetectable levels without requiring ART) but, according to the website, also accepts samples from individuals who have maintained viral load <2,000 copies/mL for at least one year after interrupting ART. The researchers have not yet reported whether any such individuals have joined the study.

Source: TAG Basic Science Blog (17 October 2012).

http://tagbasicscienceproject.typepad.com

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OTHER NEWS

HIV in the United Kingdom: 2012 report

Health Protection Agency

The 2012 HPA report on HIV in the UK was released at the end of November to coincide with World AIDS Day in 2012.

HIV infection has been transformed from a fatal to chronic life-long infection due to the introduction of effective antiretroviral therapy (ART) in the mid-1990s. Consequently, the number of people living with diagnosed HIV has risen year on year, with an increase in number of new diagnoses among men who have sex with men (MSM) and people born in high prevalence countries.

By the end of 2011, an estimated 96,000 (95% credible interval 90,800 – 102,500) people were living with HIV in the UK; approximately one quarter (22,600, 24% [19%- 28%]) of whom were undiagnosed and unaware of their infection. This is an increase from the 91,500 people estimated to have been living with HIV by the end of 2010. The estimated prevalence of HIV in 2011 was 1.5 per 1,000 (1.5-1.6) population of all ages, 2.1 per 1,000 (1.9 – 2.3) men and 1.0 per 1,000 (1.0 – 1.1) women.

Reference:

Health Protection Agency (HPA). HIV in the United Kingdom: 2012 Report. November 2012.

http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317137200016 (PDF download)

Hepatitis C in the UK: 2012 report

Health Protection Agency

In July 2012 the Health Protection Agency (HPA) released its most recent report on incidence of hepatitis C in the UK.

- An estimated 216,000 individuals are chronically infected with hepatitis C (HCV) in the UK; most of this infection (~90%) is genotype 1 and genotype 3.
- Injecting drug use continues to be the most important risk factor. Data from the Unlinked Anonymous Monitoring (UAM) survey of injecting drug users (IDU) suggest that levels of infection in this group remain high in 2011 (45% in England, 29% in Northern Ireland and 39% in Wales); levels of infection among IDU surveyed in Scotland in 2010 are higher still (55%).
- Both hospital admissions and deaths from HCV-related end stage liver disease (ESLD) and hepatocellular carcinoma (HCC) are continuing to rise. Hospital admissions have risen from 612 in 1998 to 1,979 in 2010, while deaths have risen from 98 in 1996 to 323 in 2010. An overall increase in registrations for liver transplants with a code of post-hepatitis C cirrhosis has been observed from 45 in 1996 to 101 in 2011.
- In England, statistical modelling predicts that 15,840 individuals will be living with HCV-related cirrhosis or HCC in England in 2020 if left untreated.
- Action plans and work programmes are in place across the UK to help tackle the infection, and public health action is focused in four main areas prevention of new infections, increasing awareness of infection, increasing testing and diagnosis and getting diagnosed individuals into treatment and care.
- In England, enhanced surveillance of newly acquired HCV infection in men who have sex with men (MSM) provides evidence of ongoing, but declining sexual transmission of HCV among HIV positive MSM. In this population, the estimated incidence of infection declined significantly over time from 7.38 per 1,000 person years in 2008 to 1.46 in 2011($p<0.001$).

C O M M E N T

Although this report continues to include very little information about HIV/HCV coinfection except for the reported reduction in sexual transmission of HCV in HIV positive gay men. This should be welcomed cautiously, as annecdotally diagnosis is still common in London clinics.

Ref: Hepatitis C in the UK. HPA 2012.

http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317135237219

New Frontiers: Inaugural meeting of the British Society for Nanomedicine

Muirgen Stack, HIV i-Base

Introduction

The inaugural meeting of the British Society for Nanomedicine (BSNM) was held in Liverpool from 15-16 October 2012. It was the formal launch of the society, and acted as forum for exchange on the latest advances in nanomedicine as well as future prospects and challenges.

Presentation summaries

By involving researchers, clinicians and members of industry and community from the beginning, the BSNM will hopefully establish itself as a leading nanomedicine organisation. In this regard, the UK plans to catch up, as equivalent European and American societies for nanomedicine are already established. Nevertheless, presentations given by Lajos Balogh (one of the five founders of the American Society for Nanomedicine – ASNM) and Beat Loffler (co-founder of the European Foundation for Clinical Nanomedicine – CLINAM) shows that the BSNM is already working as part of an international network.

The programme for the day covered a wide range of topics, including:

- Novel drug delivery systems (using virus-like particles or synthetic polymers),
- Nanotechnology for viral diagnostics
- Cell/tissue targeting and understanding the hydraulics of a cell's cytoplasm

Three other presentations were of particularly interest, the first of which was given by Andrew Owen from the University of Liverpool and the current Chair of the BSNM. He spoke about the application of solid drug nanoparticles to treat HIV. The talk focused on oral nanoformulations of efavirenz and lopinavir, which off the back of promising in vitro work are now on the verge of entering clinical trials. Although produced in a solid state, the formulations are also water-soluble. This increases the possible modes of drug delivery, as well as giving more storage and transportation options – something of particular importance in resource limited settings.

Vicki Stone from Herriot Watt University, Edinburgh then presented on the safety of nanomaterials. She cited the current confusion surrounding the toxicities as a result of the differences in the methods used to study them. Her group has focused on research into gold, silver, titanium dioxide and multi-walled carbon nanotube (MWCN) particles, all of which have connections to nanomedicine. Various tissue types were exposed to the particles and then any subsequent changes in gene expression, inflammation markers and oxidative stress were recorded. Supplementary in vivo work using rats looked at any further effect on the markers of cytotoxicity from the route of exposure (intravenous or inhalation) with the nanoparticles.

The results showed large differences in cytotoxicity between different types of tissue, with the liver being the most consistent tissue type to predict overall cytotoxicity. Cytotoxicity was greatest when the animals were exposed intravenously. However, and worryingly, distal organ inflammation was also seen after exposure via inhalation even when no local inflammation of the lung was detected. This supported other research that tracked had previously found up to 95% of inhaled nanoparticles end up in the liver, where it could potentially lead to inflammation and/or cause cytotoxicity.

Clearly, as with conventional drugs, nanoformulations must be be supported by both safety and efficacy data. The work suggests a previous underestimation of potential toxicities, in part through a lack of a suitable model to test for them, but also from not checking for toxicities in distal tissues. Standardisation and expansion of these testing systems are therefore essential if nanoformulations of drugs using materials such as gold and silver are to become viable.

A cautionary note then came in a presentation by Henry Stemplewski from the Medicines and Healthcare products Regulatory Agency (MHRA), London. He outlined the difficulties in regulating nanodevices and nanomedicines for the UK market. The primary problem appears to be a lack of specific nanomedicine guidelines. However, even in the U.S. where the FDA has specific guidelines, much of the data used to decide approval drug candidates are actually based on the non-nano formulations.

This led to a discussion of whether separate toxicity, immunotoxicity and other "nano-specific" tests were warranted as part of any nanomedicine guidelines. The consensus amongst the audience was mixed and with no real clarity emerging, this appears to remain unresolved at present.

However, the concerns over future regulation strategies are actually in contrast to the many nanomedicine products that already in use in U.S. and to a lesser extent the UK. These include a liposome type carrier system for the anti-cancer drug, doxorubicin (caelyx), a reduced scale nanoformulation of the drug sirolimus, (given to prevent organ transplantation rejection) and pegylated interferon for the treatment of chronic HCV infection. They have all been proved safe and efficacious and show that nanomedicine is not just a future prospect.

Panel discussion and perspectives

The conference culminated in a panel discussion, which allowed topics brought up during the meeting to be expanded upon in detail. The main talking point was on increasing public awareness of nanomedicine and improved communication. This would encourage an openness to research and hopefully create realistic expectations of what nanomedicine can offer. Fortunately, this push for greater communication (to the public and between researchers and clinicians) was deemed to be vital to the society's success.

The opening conference for the BSNM covered a variety of topics on nanomedicine and acted as an excellent opportunity to understand the current state of the science in the UK. The cautionary presentations given on the potential toxicities of nanomedicines and related regulatory challenges were then balanced out by the encouraging research into antiretroviral nanoformulations. Overall, the inaugural meeting portrayed an honest view of nanomedicine in the UK: full of innovative research and slowly making its way into medical care.

Ref: Inaugural Meeting of the British Society for Nanomedicine, 15-16 October 2012, Liverpool, UK.

See the BSNM website for information on nanomedicine (from background to current research abstracts, including educational resources and video links). Different levels of memberships are available, free to all.

http://www.britishsocietynanomedicine.org/

An HTB report on potential nano medicines for HIV and TB treatment (2011).

http://i-base.info/htb/14934

Anti-homosexuality laws back in African parliaments

Rebecca McDowall, HIV i-Base

The Ugandan Parliament is poised once more to pass a bill which would see any person alleged to be homosexual at risk of life imprisonment

Other clauses within the bill mean that the reputation and safety of anyone working with the gay or lesbian community could be severely compromised.

If the bill is passed it could lead to even more HIV infections in marginalised populations, especially among men who have sex with men. They will be prevented from having access to essential public health information, such as how to protect themselves from HIV and how to access life saving treatment and support services that are stigma-free [1].

And it's not just in Uganda. Further West parliament in Nigeria are considering new anti-gay laws which could lead to:

- 10 years in prison for living with someone of the same sex
- 10 years in prison for supporting the idea of a pride march
- 14 years in prison for trying to have a same-sex wedding [2]

All Out have launched online campaigns to gain international support to prevent the bills being passed.

To sign the petitions visit:

http://www.allout.org/

References:

1. International HIV/AIDS Alliance. Uganda's 'Anti-homosexuality bill' would be disastrous for HIV response. 23 Nov 2012. http://www.aidsalliance.org/NewsDetails.aspx?Id=291463
2. All Out. Stop Nigeria's 'Jail the gays' bill. http://www.allout.org/en/actions/nigeria-veto

REVIEWS

Bad Pharma: How drug companies mislead doctors and harm patients: by Ben Goldacre

Review by Marcus Low, TAC and Quackdown

Dr Ben Goldacre is perhaps best know for writing a long-standing popular quack-busting column called "Bad Science" for the Guardian newspaper, and a collected review of articles published as a book with the same name.

Along with Nathan Geffen's "Debunking Delusions", Bad Science has become my standard book recommendation for new interns at the Treatment Action Campaign, young health journalists, and just about anyone with an interest in how quackery and pseudo-science actually works.

In his new book "Bad Pharma: How drug companies mislead doctors and harm patients", Goldacre turns his attention to what is probably a more serious problem: the large scale distortion of our knowledge of medicines. Do not be fooled by the title though. Even though the accumulation of evidence presented here reflects very poorly on the pharmaceutical industry, the focus is as much on the insufficient regulatory framework that allows the industry to get away with the things it does. If you are looking for overly-simplistic pharma-bashing, this is not the book for you. Of course, the book does cover the already well-documented ways in which drug companies over-market their drugs. However, the most interesting chapters of the book are not those dealing with the depressing details of pharma-sponsored speaking tours or the cynical ways in which drug reps cultivate relationships with and then manipulate doctors, it is the way in which important evidence is hidden away from scrutiny.

One of the examples cited in the book is the way in which GlaxoSmithKline neglected to publish studies showing that their antidepressant paroxetine does not work in children. This was despite the fact that they knew paroxetine was being prescribed to thousands of children. Not only were these children prescribed a drug that did not work, they were exposed to the side effects of paroxetine. It would also emerge over time that paroxetine increased the risk of suicide in some depressed children.

But paroxetine is only the tip of the iceberg. Rather disturbingly, it is not at all uncommon for studies with negative findings to be buried in this way. Industry-funded studies are much more likely to report positive results than publically funded studies. This runs deep: from the decision on whether or not to publish, down to rigging studies by using to high doses of competing drugs as a comparitor or by changing the criteria by which you measure your treatment once you have access to all the results.

On the other side of the coin, the regulators who are supposed to police this kind of thing have often shown what is either naivety, or a disregard for the public interest. So, for example, the European Medicines Agency (EMA) for years refused to release details of studies done on the weight loss drug rimonabant.

The EMA made the ridiculous argument that the research data on rimonabant was confidential commercial information, without explaining what required such secrecy. It eventually emerged that people taking rimonabant are at an increased risk of serious psychiatric side effects and the drug was withdrawn. In short, the EMA's refusal to share information meant that this increased risk remained hidden for no good reason whatsoever.

Many readers will have heard about many of these cases before, but Goldacre brings them all together in one place and maps out the relationships between them. Indeed, an extract from the book has been a hit online. The book has already been positively reviewed in the Economist and The New Statesman.

But reading summaries or book reviews, like this one, about Bad Pharma is not enough. Precisely because the machinery of medical evidence is so extensive and its imperfections are so widely distributed within this system, no summery or extract can get you close to the whole, rather awe-inspiring picture.

In an interview on the Nature magazine podcast, Goldacre was asked about the complexity of the subject matter. His reply was that the issues are not complex, but rather that they are big. I agree. And the best way to get your head around a big topic like this is to have it all mapped out in a book – which is what Goldacre has done.

Whereas some science writers may have a few relatively simple ideas that they tease out into best-sellers, Bad Pharma is remarkably stripped down for a book of over 300 pages. There are none of the digressions or indulgences that are often used to pad out popular science writing. There is also no need here to overplay or cherry-pick evidence to fit a narrative because the subject matter speaks for itself.

It would have been easy for Goldacre to make more of the intrusion of economic interests into healthcare and to describe what is happening against a broader social-political context. But he wisely chooses to steer clear of politics and instead to deliver an argument that is focused, evidence-based, and to the point.

Goldacre himself applies the same rigorous standards of evidence that he would like to see others apply. Wherever possible he cites systematic reviews of the questions he is discussing. Where evidence is lacking, he is open about that. In this, and in his attempt to avoid cherry-picking the subtext of this book, even more than his previous one, is that being serious about evidence is not only a matter of nit-picking geekiness, but essential to what it means to be moral in the information age.

As we know very well in South Africa, a poor understanding of how scientific evidence works can cost hundreds of thousands of lives. AIDS denialism was an obvious and clear case of policy not supported by evidence. What Goldacre exposes in Bad Pharma is something almost as monstrous. It is less obviously immediate and the players are less obviously misguided, but after reading Bad Pharma I am convinced that drug companies failing to publish negative findings, or regulators refusing to release detailed information about side effects can be and often are as harmful as AIDS denialists or anti-vaccination quacks.

And in case you think this sounds implausible, the book provides a number of disturbing examples of real harm done and lives damaged and lost.

Much of the lethargy about getting researchers, regulators and industry to clean up their act seems to be because the harm done by suppressing data or cherry-picking study outcomes is not as obvious as, for example, quack-based health policy. After all, poor an excuse as it is, we intuitively understand that people would be more excited about publishing positive findings than negative ones. Goldacre is correct to compare this conspiracy of mediocrity to the UK's phone hacking scandal and MPs expenses scandal. As in those cases, the fact that the practice is widespread will only shroud its moral indefensibility for so long.

Incidentally, the book is released at a time when South Africa's Medicines Control Council (MCC) is being replaced by the new SA Health Products Regulatory Authority (SAHPRA). This change over offers useful opportunities to make our medicines regulator more transparent and efficient than the slow and opaque beast that the MCC has become over the last 14 years. One hopes that those involved in the switch-over will read this book and think seriously about the issues raised on openness and accountability.

Which is not to say that Bad Pharma is an essential read for only regulators, doctors and researchers. It is a clearly written and accessible diagnosis of a problem that impacts all of us, since the distortion of medical evidence misleads all doctors and thereby harms all patients. This is everyone's business.

When scientific medicine is abused and distorted like it currently is, it undermines public confidence in medicine. As a first step toward getting more people to recognise the extent of the problem, Bad Pharma is a uniquely important book.

Marcus Low is an activist in South Africa who is the editor of the Treatment Action Campaign's Equal Treatment newsletter. This review was originally published on Quackdown.info (19 October 2012)

http://www.quackdown.info/article/goldacre-shows-us-how-be-moral-information-age/

An excellent interview with Ben Goldacre is online on the Guardian website:

http://www.guardian.co.uk/science/audio/2012/oct/22/science-weekly-podcast-ben-goldacre-bad-pharma

FUTURE MEETINGS

Conference listing 2012

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

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

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: 2012 update for PDA access

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

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

http://www.i-Base.info

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

Publications and regular subscriptions can be ordered online.

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

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

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

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

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

Non-technical treatment guides

i-Base treatment guides

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

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

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

Publications and reports

HIV Treatment Bulletin (HTB)

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

HTB South

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

HTB Turkey

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

HTB West Balkans

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

Why we must provide HIV treatment information

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

Translations of i-Base publications

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

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

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

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

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

Advocacy resources

Online treatment training for advocates

http://i-base.info/ttfa

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

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

UK CAB: reports and presentations

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

http://www.ukcab.net

Phoneline and information services

Treatment information request service - 0808 800 6013

i-Base runs a specialised treatment information service.

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

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

Online Q&A service

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

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

Other resources

Treatment 'Passports'

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

Generic clinic forms

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

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

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

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

Order publications and subscribe by post, fax or online

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

http://i-base.info/order

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

htb(e)

HIV TREATMENT BULLETIN (e)

HTB(e) is the electronic version of HTB, which is published six times a year by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered by fax or post using the form on the back page or directly from the i-Base website:
http://www.i-Base.info
by sending an email to: subscriptions@i-Base.org.uk
Editor: Simon Collins
Contributing Editor: Polly Clayden

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

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

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