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EDITORIAL

Welcome to the first issue of HTB of 2014.

Conference reports kick of with the annual International Workshop on HIV & Women – now in it's fourth year. Giving a thought provoking start to the year, presentations reminded us that two decades into the epidemic, women are still underrepresented in HIV research and disparities in treatment outcomes need to be addressed.

A presentation at the 17th International Conference on AIDS and STIs in Africa showed that rates of discontinuation of efavirenz in African settings might be underestimated.

And, thanks to natap, David Margolis gives a brilliant overview of the complexities facing cure research discussed at the 6th International Workshop on HIV Persistence.

Recent European approvals include dolutegravir for HIV, sofosbuvir for hepatitis C (which was approved in the US a few weeks earlier) and bedaquiline for TB.

The BHIVA guidelines have also been updated, largely to comment on the choice of ARVs for preferred and alternative first-line therapy and to reflect the recommendations from the new hepatitis guidelines.

International news has the addition of atazanavir to the Patent Pool, more donations pledged to the Global Fund (but still falling short of the US$15 billion goal), and the Fund's urgent request to Nigeria to reconsider their unjust and discriminatory new anti-gay law and its consequences.

Next issue will be dominated by reports from CROI 2014 – taking place in Boston this year from 3-6 March.

BHIVA members – print copies of HTB

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Notice of error

The PDF file distributed for the November/December edition of HTB included an error that was corrected for the print and online editions. The roll-over arm in the LATTE study should have referred to maintenance therapy usual the oral formulation rather than injections. We apologise for this error.

CONFERENCE REPORTS

4th International Workshop on HIV & Women

13-14 January 2014, Washington DC

Introduction

Despite cut backs, travel restrictions and horrible weather, attendance at the 4th International Workshop on HIV and Women exceeded expectations – and the past three meetings – with over 50 abstracts and 130 participants.

This years meeting included presentations on treatment, models of care, contraception, prevention, menopause, pregnancy and infant outcomes.

Slide presentations are online at:

http://regist2.virology-education.com/2014/4hivwomen/13jan.html

Abstracts from the workshop are published in the journal Reviews in Antiviral Therapy & Infectious Diseases 1 2014.

http://regist2.virology-education.com/abstractbook/2014_1.pdf

Reports from this workshop are:

- Women, HIV research and antiretrovirals
- Improved virological outcomes for women starting efavirenz-based first-line regimens in South Africa
- High rates of pregnancy in HIV positive women in Zambia and South Africa

- Contraceptive choices among a Canadian cohort of HIV positive women
- Bone disease and older HIV positive women
- Lower immune response to the qHPV vaccine in HIV positive girls
- HIV exposed vs unexposed babies have lower gestational age and birth weight in Danish study
- Outcomes in infants exposed to lopinavir/ritonavir in utero

Women, HIV research and antiretrovirals

Polly Clayden, HIV i-Base

Several presentations at the 4th International Workshop on HIV and Women again highlighted the relative paucity of data to guide treatment decisions in women – particularly with newer drugs.

The inclusion (or exclusion) of women in HIV research

A collaboration between IAS, IAVI and AMFAR reviewing the inclusion of women in HIV research – trials of antiretrovirals, vaccines and cure strategies – exposed the unsurprising finding that women are underrepresented, particularly in antiretroviral trials and cure strategies. [1]

Notably publically funded antiretroviral clinical trials (including US National Institute of Health [NIH] sponsored trials) only included small proportions of women despite existing regulation intended to correct this.

Although the proportion of women in antiretroviral trials remains low, there has been an increase over time. The proportion of women is particularly low in trials conducted in high-income countries. Vaccine trials do better and include a higher proportion of women.

Shirin Heidari presented results from this literature review for which the investigators performed systematic searches in PubMed for antiretroviral, vaccine and cure trials. Antiretroviral included articles describing trials published during three time periods (1994-1997, 2001-2004 and 2008-2011). Vaccine included articles published 2000-2012 that reported results from vaccine trials. Cure included articles describing cure trials published through 2012.

The review excluded trials that only enrolled one sex. The investigators extracted data describing the number of women compared to the total number of participants (enrolled, completed the trial and/or reached an endpoint), date of publication, trial phase, countries in which the trial was conducted and funding sources.

The analysis included 387 antiretroviral, 53 vaccine and 113 cure trials. Women participants made up a median of 19.2%, 38.2% and 11.1% of the total study population in antiretroviral, vaccine and cure trials respectively.

The proportion of women included in antiretroviral trials increased over time, overall p=0.0001. But this was no greater than 28% in any time period.

Antiretroviral trials conducted in high-income countries included the least women, median percentages (excluding eight trials without country classification) were: 50%, 18% and 23.2% in low- and middle-income, high-income, and mixed income countries respectively, p<0.001.

There was a significant variation in the proportion of women in antiretroviral trials according to funding source. Median percentages were: 19%, 29.2%, 16.7%, 19.8% and 17.8% for private (commercial), private (non-commercial), public mixed and trials with no data respectively, p=0.05 (p=0.03 excluding "no data").

NIH supported antiretroviral trials had a lower proportion of women compared to those sponsored by other sources, 15.3% (n=96) vs 22.3% (n=220), p=001.

The inclusion of women in vaccine trials also increased over time, p=0.03. No linear relationship was observed between the inclusion of women and time for cure trials. High-income countries were also associated with a lower proportion of women in cure trials, p=0.003, but a higher proportion in vaccine trials, p=0.02. Funding source did not have an effect on proportion of women in vaccine and cure trials.

The investigators noted that although federal policies have been established to address the gap between the proportion of men and women in trials, their analysis found that publically funded antiretroviral trials have even lower representation of women participants, suggesting that these policies are neither enforced nor monitored.

Sharon Warmsley illustrated the disparity between men and women in an invited lecture: State-of-the-ART new therapy options by showing an analysis of the proportion of women in pivotal clinical trials for more recently approved antiretrovirals. See Table 1.

Two presentations followed Dr Walmsley's lecture with data from subgroup analyses women receiving rilpivirine/emtricitabine/tenofovir DF (RPV/FTC/TDF), and raltegravir (RAL) in the respective pivotal trials. For both analyses the numbers were so few that the confidence intervals around any findings are so wide that there is not much to guide treatment decisions for women from these trials.

Dr Walmsley also showed two examples of ongoing phase 3b trials designed to look at newer treatments in women and help to address this lack of meaningful data. See Table 2.

Table 1: Proportion of women included in pivotal trials

Trial	New drug	Comparator	% women
STARTMRK	raltegravir	efavirenz	19%
Single	dolutegravir	efavirenz	16%
Spring-2	dolutegravir	raltegravir	15%
Flamingo	dolutegravir	darunavir/r	13%
Gilead 102	elvitegravir	efavirenz	22%
Gilead 103	elvitegravir	atazanavir/r	8%
ECHO	rilpivirine	efavirenz	23%
Thrive	rilpivirine	efavirenz	26%
STaR	rilpivirine	efavirenz	7%

Table 2: Ongoing phase 3b trials of antiretrovirals in women

Trial	Drug/regimen	Comparator	Sponsor	Design/status	Primary endpoint	n
WAVES	elvitegravir/cobicistat/ FTC/tenofovir	atazanavir/ritonavir + FTC/tenofovir	Gilead Sciences	RCT, 1:1, blinded, placebo, trial in ART-naïve women NCT01705574 Enroling	<50 copies/mL at 48 weeks	510 255 per arm
ARIA	dolutegravrir/ABC/3TC	atazanavir/ritonavir + FTC/tenofovir	ViiV Healthcare	Randomised 1:1, open label trial in ART-naïve women NCT01910402 Enroling	<50 copies/mL at 48 weeks	474 237 per arm

Single-tablet regimen rilpivirine/emtricitabine/tenofovir DF

STaR compares the safety and efficacy of two once daily fixed dose combination (FDC) regimens: RPV/FTC/TDF vs efavirenz/emtricitabine/ tenofovir DF (EFV/FTC/TDF).

It is an open-label, multicentre, randomised 1:1, 96-week study in treatment-naive participants. The primary endpoint was the proportion of participants with viral load <50 copies/mL at 48-weeks (12% non-inferiority margin; snapshot analysis).

Overall RPV/FTC/TDF (n=394) was non-inferior to EFV/FTC/TDF (n=392): 86% vs 82%, difference 4.1% (95% CI -1.1%, to 9.2%) at week 48; and 78% vs 72%, difference 5.5% (95% CI -0.6%, 11.5%) at week 96.

Beth Elbert presented the subgroup analysis of women in STaR. As the proportion of women in the trial was only 7% this represented 28 women in each arm at 48 weeks and 7 and 8 women had no 96-week data in the RPV and EFV arms respectively.

The proportion of women with viral load <50 copies/mL at 48 weeks was 79% vs 61% in the EFV/FTC/TDF vs RPV/FTC/TDF arms, difference 17.4% (95% CI -8.8% to 43.6%). At 96 weeks, the proportion was 68% vs 57%, difference 12% (95% CI-15.5% to 39.5%).

The rate of all grades treatment-associated adverse events of importance in >5% of women in the RPV/FTC/TDF and EFV/FTC/TDF arms respectively were: dizziness 3 (11%) vs 8 (29%), somnolence 1 (4%) vs 4 (14%), headache 3 (11%) vs 3 (11%), anxiety 2 (7%) vs 0, abnormal dreams 1 (4%) vs 2 (7%), insomnia 2 (7%) vs 5 (18%), depression 0 vs 2 (7%) and rash 1(4%) vs 8, (29%).

There were 2 adverse event-related discontinuations (1 cerebrovascular accident and 1 gout) in the RPV/FTC/TDF arm and 3 (1 depression, 1 pyrexia and 1 toxic skin eruption) in the EFV/FTC/TDF arm. All occurred before 48 weeks.

There were 5 discontinuations due to an adverse event among the women.

Raltegravir

STARTMRK and QDMRK were double blind, randomised, controlled phase 3 trials of RAL in treatment-naive participants.

STARTMRK compared RAL 400mg (twice daily) to EFV (once daily) both given with TDF/FTC for up to 5 years. QDMARK compared RAL 400mg (twice daily) to RAL 800 mg (once daily), both with TDF/FTC for up to 48-weeks.

Kate Squires presented data at 48-weeks from a post hoc, pooled exploratory subgroup analysis by sex in the RAL 400 mg arms of these studies.

The proportion of participants with viral load <50 copies/mL and mean change from baseline in CD4 counts were summarised. Observed failure approach was used for missing data. Cinical and laboratory adverse events and changes in laboratory parameters were recorded.

Of 669 participants who received raltegravir 400 mg, 525 (78%) were men (mean age 38 years) and 144 (22%) were women (mean age 38.5 years).

There were a smaller proportion of white participants (37% vs 64%) and a greater proportion of black participants (29% vs 9%) and Asian participants (20% vs 8%) among women compared to men. Baseline viral load was >100,000 copies/mL in 40% of women vs 47% of men, and

CD4 count was ≤200 cells/mm3 in 33% of women vs 39% of men. Overall, 89% of women and 91% of men completed 48 weeks of treatment.

Other than pregnancy, which occurred in 4 (3%) women, most reasons for discontinuation were similar between cohorts. At week 48, 93% of women (126/135) and 91% of men (458/505) had viral load <50 copies/mL, difference: -3.0, (95% CI (-7.4 to 3.0). The mean change in CD4 cell count from baseline to week 48 was 189 cells/mm3 in women and 194 cells/mm3 in men, difference: 5.3 (95% CI -21 to 31).

Adverse events were reported by 85% of women and 88% and led to treatment discontinuation in 2% of each cohort. Serious adverse events were less common in women (2%) than in men (9%). Laboratory adverse events occurred in 7% of women vs 9% of men and were considered drug-related in 3% of each cohort. Changes in laboratory parameters were similar between cohorts: grade 2/3 increase in LDL-cholesterol in 5% of women vs 6% of men; grade 2/3 increase in total cholesterol, 6% vs 5%; grade 2/3 increase in serum triglycerides, 0% vs 1%.

Gender disparities in treatment outcomes persist

Although data from women in trials frequently suggest that efficacy and safety of antiretrovirals and the occurrence of adverse events is similar in men and women, a presentation by Peter Saunders from the Royal Free Hospital, London reminded us that gender disparities in treatment outcomes persist in the era of modern antiretroviral therapy.

This study looked at all antiretroviral-naive HIV positive people who attended the Royal Free clinic and started ART from 1 January 2006 onwards. To be eligible for analysis they needed to have at least one documented viral load test after starting ART.

The proportion experiencing virological failure (1 of 2 consecutive viral loads >200 copies/mL >6 months post ART) and treatment modification were estimated using standard survival methods.

Of 1131 overall, 29% (327) were women, 58% (563) were men who have sex with men (MSM) and 19% (241) non-MSM men. Women and non-MSM men started ART at a more advanced stage, with a median CD4 at ART initiation of 219 and 218 cells/mm3 respectively compared to 298 in MSM. Women (60%) and non-MSM men (44%) were also more likely to be of black African ethnicity and to have a previous AIDS diagnosis.

Time to achieve virological suppression (viral load<50 copies/ml) was similar in all groups with 88.8% of MSM, 83.4% of non-MSM men and 84.7% of women achieving this by one year, p=0.19.

After 18 months of treatment a greater proportion of women had experienced virological failure: 2.6% MSM, 6.2% non-MSM men and 9.8%, p<0.0001. Non-MSM men had more than three times the rate of virological failure, AHR 3.69 (95% CI 1.76 to 7.74) and women more than 4 times the rate, AHR 4.63 (2.26 to 9.48), compared to MSM, p=0.0001.

After 12 months 42.6% of women had changed a component of their treatment regimen compared to 35.5% of non-MSM men and 26.9% of MSM, p<0.0001; 16.6% women changed their regimen due to adverse events compared 9.6% of MSM and 12.09% non-MSM men.

By 12 months, 5.0% of MSM, 12.0% of non-MSM men and 15.4% of women had completely discontinued ART for at least two weeks, p<0.0001.

The investigators found that non-MSM men had over twice, AHR 2.28 (95% CI 1.35 to 3.83) and women had more than three times the rate, AHR 3.45 (95% CI 2.20 to 5.40) of complete ART discontinuation compared to MSM, p<0.0001.

Dr Saunders concluded that women in this cohort are still more likely than both MSM men and non-MSM men to change or discontinue their ART regimen and also to experience virological failure. Further research is urgently needed to address the reasons for these differences.

C O M M E N T

Underrepresention of women in HIV clinical trials is no big surprise and much of the discussion following the presentations focused on the difficulties of enrollment. Strategies to increase this must continue to be improved.

Generally, data suggests that there are few differences in ARV efficacy between women and men. But because women often present very late, there can be implications for drugs that are not recommended at high viral loads such as rilpivirine. Any differences in toxicities by sex, tend to emerge in post marketing studies and will only be evaluated in a more systematic way if research is designed to look at how drugs perform in women – such as the ARIA and WAVES studies.

Disparities in treatment outcomes in real-life situations persist and need to be addressed.

References

All references from 4th International Workshop on HIV & Women, 13-14 January 2014, Washington DC unless indicated otherwise.

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4. Squires K et al. The efficacy and safety of raltegravir in women. Oral abstract_17. http://regist2.virology-education.com/2014/4hivwomen/docs/27_Squires.pdf
5. Saunders P et al. Gender disparities in treatment based outcomes persist in the era of modern ART. Oral Abstract_20. http://regist2.virology-education.com/2014/4hivwomen/docs/30_Saunders.pdf

Improved virological outcomes for women starting efavirenz-based first-line regimens in South Africa

Polly Clayden, HIV i-Base

Women receiving efavirenz (EFV) first-line experienced better virological outcomes than those receiving nevirapine (NVP) in a multicentre cohort in South Africa, according to data presented at the 4th International Workshop on HIV & Women 2014.

Bonaventure Egbujie from Kheth'Impilo – an NGO that provides health system strengthening and technical assistance to the South African Department of health – showed findings from a comparison of virological outcomes in women starting EFV or NVP based ART in a public health setting.

A total of 53,447 women were included in the study, of these 33,946 (63.5%) initiated treatment with EFV and 19,531 (36.5%) with NVP. At baseline, women starting with EFV were older, median 36 vs 30 years; had lower median CD4 count 125 vs 148 cells/mm3 and were more likely to be receiving concomitant TB treatment 12.4% vs 7.8%; but fewer were pregnant 2.2% vs 18.6% (all comparisons p<0.0001).

At 60 months women receiving EFV had a 40% reduced risk of unsuppressed viral load (>400 copies/mL) compared to those receiving NVP: AOR 0.6 (95% CI 0.58 to 0.63), p<0.0001. Pregnant women receiving EFV had a 28% reduced risk AOR 0.72 (95% CI 0.58 to 0.91), p=0.005.

At 48 months, the cumulative probability of confirmed virological failure (two consecutive viral loads >1000 copies/mL) was lower in the EFV cohort: 44% reduced risk AHR 0.56 (95% CI 0.50 to 0.63), p<0.0001. The cumulative probability of virological rebound (>400 copies/mL) after initial viral suppression was reduced in the EFV cohort: 16% reduction AHR 0.84 (95% CI 0.76 to 0.93), p=0.001.

The proportion of women who switched to a second-line regimen was substantially lower in the EFV cohort: 1.3% vs. 4.2%, relative risk 0.31 (95% CI 0.28 to 0.36), p<0.0001.

In this study, virological outcomes of women who received EFV were significantly better than those who received NVP for first-line ART despite having more advanced HIV at baseline. Pregnant women also had improved virological outcomes with EFV. Dr Egbujie noted that these results support the recent WHO recommendations to use EFV in preference to NVP in adults including for pregnant women.

C O M M E N T

It can still be confusing for health workers and HIV positive people in many settings that the efavirenz label does not recommend its use in pregnancy, despite ever increasing reports of favourable outcomes with this WHO recommended regimen.

Ref: Fatti G et al. Improved virological outcomes amongst women starting efavirenz for first-line antiretroviral treatment in South Africa. Oral Abstract_18.

http://regist2.virology-education.com/2014/4hivwomen/docs/28_egbujie.pdf

High rates of pregnancy in HIV positive women in Zambia and South Africa

Polly Clayden, HIV i-Base

Unmet need for family planning is high in sub-Saharan Africa and preventing unintended pregnancies is a priority for maternal health and eliminating vertical transmission.

Two presentations at the 4th International Workshop on HIV & Women showed high rates of pregnancy among HIV positive women in Zambia and South Africa.

Unintended pregnancies and limited contraceptive use in rural Zambia

S Okawa presented findings from a study conducted to assess unintended pregnancies and contraceptive use in HIV positive pregnant women, and to look at the associated factors in rural Zambia.

This was a prospective cohort study from July 2011 to March 2013 of 371 women accessing PMTCT services at 11 health centres in Chongwe district.

Data was collected through face-to-face interviews in which participants were asked about their background characteristics, pregnancy intention, contraceptive use, and reasons for not using contraceptives.

About half of the women already knew their HIV status before the current pregnancy, 51%% were less than 30 years old, 67% had less than 8 years of education, 83.% were married, 38.% had more than 4 children, and 63% were unemployed.

About a third had HIV positive partners and just under half had partners in permanent employment. The majority (88.5%) of women had disclosed their HIV status to their partners, and 19% had experienced domestic violence.

A total of 187/371 (50%) reported unintended pregnancies, of those 101 (54%) did not use any contraceptive. Reasons for not using contraception are listed in Table 1.

Table 1: Reasons for not having used contraception (multiple answer)

Reason	n	%
Did not want to use	45	45.9
Did not ask health worker	42	42.9
Don't know any	31	31.0
Afraid of side effects	26	26.8
Did not know where to get it	24	24.5
Partner did not want to use it	23	23.5
Religion did not allow use	6	6.1
Traditional contraception instead	6	6.1

In multivariate analysis, unintended pregnancy was associated with mother older than 30 years AOR 1.78 (95% CI 1.12 to 2.84), p=0.02; unmarried status AOR: 3.79 (95%CI 1.48 to 9.33), p=0.01; and partner with non-permanent AOR 1.63 (95%CI 1.03 to 2.57), p=0.04.

Only unmarried status was associated with non-contraceptive use AOR 2.01 (95%CI 0.99 to 4.09), p=0.05.

The investigators concluded: "There is an urgent need to increase contraceptive coverage among HIV- positive women and their partners who are not considering further pregnancies." "Provision of family planning services at antiretroviral therapy clinic and PMTCT services could increase contraceptive coverage", they added.

Increasing numbers of young pregnant women in a South African metropolitan district

In a related presentation Bonaventura Egbujie from Kheth'limpilo, Cape Town, showed findings from a cohort study that took place at three facilities in the Nelson Mandela Metropolitan District, Eastern Cape between January 2009 and June 2012. The study investigated the age distribution of HIV pregnant women over time in order to estimate age-specific prevalence trends using individual level electronic clinical data.

A total of 1455 HIV positive women were included of a median: age 26.8 years (IQR 2.9 to 36.6); baseline CD4 count 351 cells/mm3 (IQR 235 to 509) and gestational age 21 weeks (IQR 16 to 26). At presentation 65% were unaware of their HIV status and 12% were on ART. Of the total: 111 (7.5%), 225 (15.3%), 754 (51.2%) and 383 (26%) presented in 2009, 2010, 2011 and 2012, respectively.

The analysis revealed the proportion of women aged 15 to 24 years almost doubled between 2009 and 2012, from 27.9% (95% CI 19.8 to 37.2%) to 41.1% (95% CI 36.0% to 46.2%), p= 0.0003. The proportion of women aged 18 to 21 years more than doubled from 8.1% (95% CI 3.8% to14.8%) in 2009 to 18.1% (95% CI 14.3% to 22.4%) in 2012, p= 0.0015). The proportion of adolescents aged <18 years increased by almost 70% from 3.6% (95% CI: 0.1%-7.1%) to 6.1% (95% CI: 3.7 to 8.6%) during the same period, p= 0.084.

Factors associated with these trends are shown in Table 2.

Table 2. Age-related associations with pregnancy in HIV positive women

Age (years)	<18	18-21	22-24	>24	p-value
HIV status unknown (%)	93	81	69	57	<0.0001
On ART	2	3	5	18	<0.0001
Chooses formula feeding (%)	8	16	31	38	<0.0001
Infant 6 week HIV PCR positive (% n=450	-	4.1	7.1	1.9	0.05

The investigators concluded that increasing proportions of younger women with HIV are presenting at facilities in this district. Although Dr Egbujie expained that neither HIV incidence or prevalence cannot be directly measured from these data, these trends suggest increasing HIV incidence among younger women and/or increasing youth pregnancy.

Very young women were less likely to be aware of their HIV status or be on ART and had higher vertical transmission rates.

"Factors driving these findings should be investigated, and intensified HIV prevention and family planning efforts showed be directed toward youth and younger women in this area" he said.

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1. Okawa S et al. High proportion of unintended pregnancies and limited contraceptive use among HIV- positive women in rural Zambia. 4th International Workshop on HIV & Women, Washington DC. 13-14 January 2014. Oral Abstract_13.
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Contraceptive choices among a Canadian cohort of HIV positive women

Polly Clayden, HIV i-Base

Contraception use is high and barrier contraception use moderately high in a Canadian cohort of HIV positive women.

Malika Sharma presented findings at the 4th International Workshop on HIV & Women 2014, from a substudy conducted to understand associations between demographic and HIV-related data and contraceptive choices among women participating in the CTN236: HPV Vaccine in HIV trial.

For the substudy, data on contraceptive use were abstracted for sexually active, pre-menopausal women. Variables included demographics, use and type of ART, CD4 count, viral load, hepatitis B coinfection, details on substance use and sexual history.

Data were available from 377 girls and women of whom 168 women did not meet the inclusion criteria for the substudy: 24 (6.3%) were pre-menarchal, 36 (9.5%) had never had intercourse, 29 (7.7%) were post- menopausal, and 79 (21.0%) had not been sexually active in the past year. The remaining 209 women aged 15 to 57 were included in the analysis.

Of these women: 87% reported a previous pregnancy: 89% reported at least one method of current contraception; 82% reported barrier protection: and 73% reported condom use (with or without other methods) most or all of the time.

Over half (53%) used barrier contraception; 15% barrier plus other; 15% barrier and hormonal; 8% other; 5% none (personal or partner sterilisation) and 4% hormonal contraception.

The majority (80%) of the 17% of the cohort using hormonal contraception did so in combination with barrier protection and 75% of women reported hormonal contraception use in the past.

The median age of women using hormonal contraception (alone or with barrier protection) was 31, while that of women using no contraception or barrier protection alone was 39 and 37 years, respectively.

Of the 34 women using combination HC and barrier methods, 45% were white, 29% were black, 13%) were Aboriginal and 4 13% belonged to other ethnicities. Almost half (48%) of women using barrier methods alone were black. Almost half (46%) of all hormonal contraception users were currently smoking.

Women using hormonal with or without barrier contraception had higher CD4 counts 515 cells/mm3 and 660 cells/mm3, respectively, than those using no contraception 330 cells/mm3. But 82% of women using no contraception had an undetectable viral load compared to 55% of those using hormonal contraception and 48% of those using combined barrier and hormonal contraception.

The majority of women had received prior ART, but 11% were not on ART at study entry. Thirty-one of the women reporting hormonal contraception had received ART (i 11 currently on a PI and 4 an NNRTI based regime), which Dr Sharma noted raised the potential for drug interactions.

Contraception use was high in this cohort but the investigators highlighted high rates of smoking and inconsistent condom use (31% every time and 34% most of the time) as findings of concern in this analysis.

Ref: Sharma M et al. Understanding current contraceptive choices and patterns among a cohort of HIV- positive women. 4th International Workshop on HIV & Women, Washington DC. 13-14 January 2014. Oral Abstract_11.
http://regist2.virology-education.com/2014/4hivwomen/docs/16_Sharma.pdf

Bone disease and older HIV positive women

Polly Clayden, HIV i-Base

Bone disease and the associated risk of fracture are poorly understood in HIV positive people, particularly older HIV positive women. Savannah Cardew from the Women's College Hospital, Canada, gave an excellent overview of what is known (and unknown) in this patient population at the 4th International Workshop on Women & HIV.

Dr Cardew began with some definitions – these are important as most of the research into bone disease and HIV has been done in young men. T-score is the number of standard deviations below the mean bone mineral density (BMD) for a healthy, young, sex-matched population. For post-menopausal women and men of 50 and over osteoporosis is diagnosed by T-score -2.5 or less or fragility fracture of the hip or spine. She noted that this definition should not be used for other populations.

For young people Z-score of -2.0 or less is below what is expected for their age group.

HIV positive people can have an increased risk for prevalence of traditional risk factors for low BMD including: low body mass index (BMI), glucocordicoids, comorbidities, hepatitis C and liver disease, smoking and early menopause.

Added to his HIV infection causes elevated levels of inflammatory cytokines and in turn bone loss. And antiretroviral treatment (ART) can increase contribute to loss of BMD – particularly tenofovir and efavirenz.

Studies of low BMD in HIV positive people have been inconclusive. One study in HIV positive people aged 20 to 30 years found no difference in BMD compared to HIV negative controls. A meta-analysis of longitudinal studies found that starting ART is associated with accelerated bone loss, lasting about a year, followed by bone stability or increase.

Most research into low BMD in HIV positive people has been done in young men, which can make it hard to interpret for women. Findings from studies vary with regard to HIV-specific risk factors: the effect of antiretrovirals, AIDS defining illnesses and CD4 nadir.

For older HIV positive women, a prospective cohort study of 92 positive and 95 HIV negative post menopausal Latina and African-American women found the women with HIV had lower BMD at the spine and total hip (adjusted), associated with elevated bone turnover markers. Dr Cardew noted that this difference – although significant – was slight and that the control group were patients at the clinic. There was no difference in BMD between HIV positive women receiving and not receiving ART.

In a subset (one site) of women followed longitudinally in this study, HIV positive status was associated with slightly more bone loss in lumbar spine at one year (adjusted). There was no difference at other sites.

There was an association between tenofovir and greater bone loss.

Dr Cardew remarked that these are the only studies that have investigated low BMD specifically in post- menopausal HIV positive women.

She then showed findings from studies looking at whether or not HIV positive people are at increased risk of fracture.

A population-based, retrospective case controlled study in HIV positive people (75% men) over the age of 40 conducted in Spain in 2007 to 2009, showed an age and sex adjusted hazard ratio (AHR) of 6.2 for all hip fractures and 2.7 for all major fractures: hip, clinical spine, pelvis, tibia, multiple rib, proximal humerus and wrist/forearm. Dr Cardew suggested that the latter value might be more meaningful than AHR as patients cannot be separated from confounders. This study was not controlled for ART use.

A Danish study of mostly men over 16 and population-based controls conducted between 1995 and 2010 showed an overall fracture incident rate of 1.3 per 1000 person years in people with HIV alone and 2.9 in HIV/HCV co-infected patients. HCV was known to correspond with injection drug and alcohol use in this cohort.

And a large retrospective case controlled study looking at hip, wrist and spine fractures conducted 1996 to 2008 showed an overall prevalence of 2.87 fractures per 100 HIV positive people and 1.77 per 100 controls – giving a 60% increase in HIV positive people.

There have not been studies in post-menopausal HIV positive women. A prospective case controlled study – 1728 HIV positive women, 66% receiving ART and 663 clinic-based controls – followed non-white women who were mostly premenopausal 2002 to 2008. In this study, the positive women were older (40 vs 36 years), more were post-menopausal and they had lower BMI (28.5 vs 30). But they were more likely to be taking hormone replacement therapy, calcium and/or vitamin D and less likely to smoke. In this study HIV was not associated with an increased risk of fracture in multivariate analysis but traditional risk factors were predictive.

Dr Cardew concluded that more research is needed in this population to define the scope of the problem and to develop treatment options and strategies.

Ref: Cardew S. Osteoporosis in elderly HIV infected women. 4th International Workshop on HIV & Women. 13-14 January, 2014. Washington DC. Invited lecture.

http://regist2.virology-education.com/2014/4hivwomen/docs/22_Cardew.pdf

Lower immune response to the qHPV vaccine in HIV positive girls

Polly Clayden, HIV i-Base

Lower immune response was observed in HIV adolescent girls compared to HIV negative girls given the human papillomavirus quadrivalent (qHPV) vaccine. But the response was comparable to that in older negative women for whom this level of response gives efficacy against HPV.

The qHPV vaccine was approved for use in HIV negative adolescents in 2006. HIV negative girls aged 9 to 13 years have the highest level of antibody response to the vaccine. There is limited information on who well the vaccine will perform in HIV positive adolescents.

Deborah Money presented data from a sub-analysis of 9 to 13 year old girls in a Canadian study to evaluate the safety and immunogenicity of the vaccine, at the 4th International Workshop on HIV & Women.

The study was conducted at 11 Canadian sites between November 2008 and December 2012, and enrolled 407 HIV positive girls and women.

Girls included in the substudy (n=26) were a minimum of 9 years, able to consent, and with a cervix present. The duration of the study for each participant was 27 months during which they received three doses of the qHPV vaccine at months 0, 2 and 6.

Geometric mean antibody titers (GMT) before receiving the vaccine and at months 7, 12, 18 and 24, were evaluated to HPV types 6,11,16 and 18. Results were compared to the 3-dose arm of a previous 2-dose vs 3-dose study in HIV negative girls in the same age group receiving qHPV vaccine (n=252).

There were 32 HIV positive girls enrolled in the 9 to 13 year age group; 1 was seropositive to HPV18 at baseline and all others were seronegative to all four types in the quadrivalent vaccine. All girls completed the vaccine schedule. No adverse events related to the vaccine were reported.

The HIV positive girls were a mean age of 11 years, 4% white, 70% black and 26% Asian. The mean time since HIV diagnosis was 9 (5 to11) years. Median baseline CD4 was 692 mm3 (IQR 557 to 960), 76% were receiving ART and 59% had an undetectable viral load.

The investigators compared GMTs in HIV positive and HIV negative girls (from the previous study) in an age-adjusted analysis at month 7 and found statistically significantly lower peak GMTs against each HPV type in HIV positive girls. See Table 1.

Table 1. Month 7 GMTs (mMu/mL) in HIV positive vs HIV negative girls aged 9 to 13

HPV type	HIV positive	HIV negative	p-value
16	4382	7650	<0.01
18	640	1703	<0.0001
6	830	1856	<0.001
11	977	2096	<0.0001

The investigators noted that the GMTs were in the HIV positive girls were comparable to those in HIV negative 18 to 26 year old women for whom the vaccine efficacy has been demonstrated to be effective.

A subset of HIV positive girls (n=16), with 24 week follow up data showed considerably reduced efficacy against all HPV types – the GMTs for the HIV negative were also reduced but the differences were significant. See Table 2.

Table 2. Month 24 GMTs (mMu/mL) in HIV positive vs HIV negative girls aged 9 to 13

HPV type	HIV positive	HIV negative	p-value
16	628	1739	<0.01
18	55	267	<0.0001
6	101	359	<0.0001
11	105	422	<0.0001

Month 7 GMTs against all four HPV types were significantly higher in HIV positive girls with an undetectable viral load <50 copies/mL (n=19) compared to those whose viral load was detectable (n=13). See Table 3.

Table 3. Month 7 GMTs (mMu/mL) in HIV positive girls aged 9 to 13 with undetectable vs detectable viral load

HPV type	<50 c/mL	>50 c/mL	p-value	Ratio of GMTs
16	5851	1739	0.05	2.02
18	1032	330	0.03	3.11
6	1083	562	0.09	1.9
11	1307	639	0.05	2.01

But in conclusion the investigators noted that: "Until an immune correlate of protection is defined in HIV negative and HIV positive persons, understanding of the meaning of antibody levels remains limited."

C O M M E N T

The role of booster dosing needs to be investigated for girls and women with HIV.

Ref: Money D et al. Lower immune response in HIV positive girls to the qHPV vaccine. 4th International Workshop on HIV & Women, 13-14 January 2014, Washington DC. Oral abstract_15.

http://regist2.virology-education.com/2014/4hivwomen/docs/21_Money.pdf

HIV exposed vs unexposed babies have lower gestational age and birth weight in Danish study

Polly Clayden, HIV i-Base

HIV exposed, uninfected children were more likely to have a lower gestational age and birth weight, and were more likely to be delivered by Caesarean section compared to unexposed controls, according to a Danish nationwide study.

Ellen Larsen presented preliminary results on birth related characteristics from a study conducted to evaluate rates, diagnoses, lengths of hospital admission and use of antibiotics among HIV exposed, uninfected children aged 0 to 4 years of age, compared to a matched control group of children not exposed to HIV. These data were shown at the 4th International Workshop on HIV & Women, 2014.

For this analysis the investigators collected information on all births in Denmark from 1 January 2000 to 31 December 2010 from the national registries at Statistics Denmark. They found a total of 712.428 children were born during the time period and 268 children were born to HIV positive mothers.

HIV positive mothers were less likely than HIV negative ones to be married 80% vs 93% and slightly older, mean 32 years, (95% CI 31.4 to 32.7) vs. 31 years, (95% CI 30.7 to30.8). Both comparisons p<0.001. The HIV exposed infants had a shorter mean gestational age, 267 days (95% CI 264 to 269) vs 278 days (95% CI 277 to 278); were more likely to be delivered by Caesarean section, 64% vs. 21%; and had a lower mean birth weight, 3035g (95% CI 2951 to 3121) vs 3478g (95% CI 3477-3480). All comparisons p<0.001.

Smoking habits during pregnancy, completed pregnancies, multiple births, and Apgar score at 10 minutes were similar in both cohorts.

The study will intends to further investigate whether due to these factors there is an increased morbidity in HIV exposed uninfected children. The investigators noted that there might be a need for a closer follow-up of these children.

Ref: Larsen EM et al. Morbidity among HIV exposed uninfected children compared to children not exposed to HIV – a Danish nationwide study. 4th International Workshop on HIV & Women, Washington DC. 13-14 January 2014. Oral abstract_22.

http://regist2.virology-education.com/2014/4hivwomen/docs/32_Larsen.pdf

Outcomes in infants exposed to lopinavir/ritonavir in utero

Polly Clayden, HIV i-Base

A systematic review of outcomes of infants born to women receiving lopinavir/ritonavir (LPV/r) in pregnancy – performed by investigators from the originator company – suggests that in utero exposure may not increase the risk of preterm birth.

M Martinez presented data from an assessment of the vertical transmission rate and risk of adverse infant outcomes among women treated with LPV/r based regimens in pregnancy at the 4th HIV & Women Workshop, 2014.

The investigators searched PubMed/EMBASE databases and HIV conferences for studies published to the end of January 2013 or March 2013 respectively. They looked for randomised trials or prospective/retrospective cohort studies of outcomes of infants exposed to LPV/r in utero as a primary or secondary endpoint.

The investigators also searched the AbbVie Global Safety Database for the infant outcome of prematurity to the end of December 2011.

They included 27 publications (n=12) and abstract presentations (n=15) describing 17 studies in the review. These studies reported on 4331 women receiving LPV/r in pregnancy, of these 2263 received LPV/r 800/200 mg/day, 101 received >800/200 mg/day, and for 1967 the dose was undocumented. Table 1 shows the results.

Table 1: Infant outcomes from a systematic review of LPV/r in pregnancy

Outcome	Studies reporting outcome (n)	Rate reported (%)
Vertical transmission	10	0 – 2.8
Preterm birth	13	8.7 – 25.0
Very preterm birth	6	0.4 – 5.0
Low birth weight	6	0.4 – 5.0
Very low birth weight	4	0.3 – 3.0
Still birth	5	1.0 – 4.8
Infant mortality	4	0 – 5.8

Post-marketing safety data from the company database showed a preterm rate of 0.66/10,000 patient treatment years for LPV/r.

One study showed similar preterm, low birth weight and vertical transmission rates for women receiving 800/200 mg and >800/200 mg LPV/r.

Three studies reporting birth defects showed a prevalence of 2% to 8.5%, which compared to the Antiretroviral Pregnancy Registry (APR) rate of 2.4%.

In one study the incidence of mortality among preterm infants was similar with LPV/r based treatment to that for women treated with triple NRTIs.

The authors concluded: "Preterm birth rates in the included studies reflected the rate for the geographical area in which the study was conducted; these data and post-marketing safety data suggest that in utero exposure to LPV/r may not increase risk of preterm birth. Infants born to women who received LPV/r 800/200 mg/day and those born to women who received >800/200 mg/day had similar rates of preterm birth, low birth weight, and MTCT."

C O M M E N T

Although analyses (particularly conclusions) performed by the originator company need to be approached with a little caution, these can be useful and results from this one supports the current APR data for LPV/r.

Ref: Martinez M et al. Systematic review of clinical outcomes of infants born to women receiving lopinavir/ritonavir-based antiretroviral therapy (ART) during pregnancy. 4th International Workshop on HIV & Women, Washington DC. 13-14 January 2014. Oral Abstract_21.
http://regist2.virology-education.com/2014/4hivwomen/docs/31_Martinez.pdf

CONFERENCE REPORTS

17th International Conference on AIDS and STIs in Africa (ICASA)

7-11 December 2013, Cape Town

Introduction

ICASA is the biggest HIV/AIDS conference in Africa – attended by about 10,000 people from all over the continent.

The scope of the conference is wide so there are limited scientific presentations.

Slides are online at:

http://www.icasa2013southafrica.org/conference-programme/-programme-outline.html

The report in this issue is:

- Two percent rate of efavirenz discontinuation in an ART programme in Malawi

Two percent rate of efavirenz discontinuation in an ART programme in Malawi

Polly Clayden, HIV i-Base

Two percent rate of intolerance to efavirenz – leading to treatment discontinuation – was observed in an ART programme in Malawi, according to data presented at the 17th ICASA in Cape Town. This rate is double that of previous estimates from the Malawi national programme.

Approximately 450,000 people are receiving ART in Malawi at 675 clinics. Since 2003 the standard first line regimen was a fixed dose combination (FDC) of d4T/3TC/NVP. The phase out of d4T for first-line treatment, due to toxicity concerns, began in July 2013. The new regimen is an FDC of TDF/3TC/EFV. This regimen has been an alternative in Malawi for several years. Since September 2011 it has been standard of care for women receiving ART in pregnancy (Option B+) and people coinfected with TB. Since July 2013 all adults initiating treatment started on TDF/3TC/EFV, and people receiving d4T/3TC/NVP and d4T/3TC/EFV are switched as stocks are used up at facility level. This transition is ongoing.

Local data on efavirenz side effects is limited and before a national regimen switch accurate estimates of intolerance rates are critical for forecasting future drug needs.

Colin Speight presented findings on behalf of colleagues from Lighthouse Trust, Kamazu Central Hospital and University of North Carolina Project, Lilongwe, Malawi. [1] Lighthouse Trust is a tertiary referral clinic and public trust within the Ministry of Health, with a cohort of approximately 25,000 patients of whom about 22,000 are on ART and 700 seen per day. The cohort has a large, robust, electronic patient database.

Before this analysis was conducted the efavirenz intolerance rate leading to discontinuation in Malawi – based on national cohort data – was estimated to be <1%.

The study was a case note review. The case definition of "efavirenz intolerant" was simple: anyone who switched from TDF/3TC/EFV to TDF/3TC + NVP was assumed to be intolerant to efavirenz. The case notes from those switching were reviewed and the reason for switching recorded.

The analysis revealed that by March 2013, 4808 people were receiving TDF/3TC/EFV and 330 TDF/3TC+NVP; 94 had switched from the efavirenz-based regimen giving a 2% rate of intolerance. A clear indication for drug substitution was recorded in 45 of 94 cases.

The most common reasons were persistent or disabling dizziness in 26 (58%), rash in 7 (16%), psychosis in 6 (13%), memory loss in 4 (9%) and confusion in 3 (7%). Less common reasons included insomnia, heavy sleeping, abnormal gait, drooling and gynaecomastia.

The median duration of efavirenz use prior to switching was 47 days (IQR 28 to 105). The investigators looked at weight, age and sex as possible predictors of intolerance in this cohort and none were significant.

Dr Speight noted that the difference between the estimated and observed rates of intolerance in patients likely to be started on efavirenz in the coming months would be: 1 percent of 270,000 patients = 2,700 patients vs 2 percent of 270,000 patients = 5,400 patients, that will require long term TDF/3TC+NVP. The higher percentage is far more likely to be closer to the true risk.

He suggested that the reasons for lower estimated rates nationally were the lack of alternative regimens at lower level facilities and less confidence about switching among health workers. He also noted that stock outs of TDF/3TC+NVP had been avoided at all sites.

According to estimates based on these observed data, 0.6% of patients in Malawi are likely to develop (or have already developed) significant CNS side effects, which equates to about 1,600 people nationally. Dr Speight noted with concern the high risk of people not presenting to the clinic to complain and emphasised that people receiving ART and their families and friends, as well as health workers, need to be aware of the symptoms that might be related to efavirenz.

He recommended that significant psychiatric history should be excluded before starting efavirenz in the national programme.

He explained that because of these side effects there had been bit of a backlash against TDF/3TC/EFV, which had been promoted as the new wonder drug in Malawi. But many patients who had been switched had no d4T side effects at the time and "mild" efavirenz side effects are very common. He asked whether people switching or starting when they feel healthy might be less willing to tolerate efavirenz side effects.

He also noted the possible occurrence of falsely attributed incidental neurological or psychiatric symptoms given the high numbers of people receiving (and who will receive) efavirenz. There had been three recent cases at Kamazu Central Hospital where patients or relatives all blamed the change in ART regimen. On investigation, hygroma, intracerebral bleeding and meningioma caused the respective symptoms in these three cases.

Finally, he suggested that these problems be considered in the context of d4T, where previously approximately 15% of patients required a switch to an alternative first line regimen. In these cases lipoatrophy would be progressive over time without switching and lactic acidosis is almost universally fatal if missed and there is strong evidence that it has been greatly under-diagnosed.

C O M M E N T

As noted in the analysis, the higher 2% estimate for efavirenz discontinuation is likely to be closer to the true risk.

Notably, in rich settings, where there are more options for switching as well as increased monitoring, the proportion of people starting on efavirenz and discontinuing it, is likely to be ten times higher than this.

Reference

Speight C et al. Rates of intolerance to efavirenz, in the context of the national mass switch to TDF/3TC/EFV: the experience at the Lighthouse Clinic, Lilongwe, Malawi. 17th ICASA, Cape Town. 7-11 December 2013. SUADS01 - First Line Treatment in Africa, Sunday 8 December. Oral abstract ADS032.

http://www.icasa2013southafrica.org/images/stories/ICASA_presentations/Sunday/Plenary/10h45/EFV%20Intolerance%20presentation%20for%20ICASA%20-%20final%20[Compatibility%20Mode].pdf

CONFERENCE REPORTS

6th International Workshop on HIV Persistence During Therapy

3-6 December 2013, Miami, USA

Introduction

This workshop has been held every two years since 2003.

Details from the meeting are on the conference website, together with free access to the abstract book and selected presentations from the meeting.

http://www.informedhorizons.com/persistence2013

Abstract book

http://www.informedhorizons.com/persistence2013/PDF/EBook_PW2013_Final.pdf (PDF)

Selected presentations

http://www.informedhorizons.com/persistence2013/presentations.html

This following report was written by David Margolis and posted online to natap.org.

- Report from the 6th workshop

Report from the 6th workshop

David Margolis MD, UNC Chapel Hill and the Collaboratory of AIDS Researchers for Eradication (CARE)

The Sixth International Workshop on HIV Persistence during Therapy took place at the Marriott Marquis in Miami, rather than the sunny, sandy climes of St. Maarten, the site of this workshop every other year since 2003.

Started a decade ago as a boutique meeting of interest to a few, the meeting was larger than ever before, and packed (perhaps overly so) with 67 oral presentations in two and a half days.

Bob Siliciano (Hopkins) opened the meeting with a plenary talk on the first evening outlining "Challenges in HIV eradication research." [1] He outlined some of the many contributions that his group has made to the understanding of latent, persistent HIV infection of resting CD4+ T cells. He highlighted the recent work of Yan Chi Ho et al. in Cell, demonstrating the presence of proviral genomes that are not detected

following a single round of in vitro activation in the gold-standard quantitative viral outgrowth assay (QVOA) that most accurately measures the size of the latent reservoir.

Siliciano made the point that the demanding QVOA represents a definitive but perhaps minimal measurement of the presence of latent infection, as some "non-induced proviruses" can be recovered by PCR amplification and genetic reconstruction, or by additional cell activation and culture in the lab.

Next he showed data from another recent publication showing that in a novel cell culture system, most current studied latency reversing agents contemplated for use in "shock and kill" approaches result in very little virus expression when compared to maximum T cell activation, suggesting that we have a long way to go before we will have potent, safe, and effective anti-latency therapy. He cited older evidence that even after successful induction of HIV gene expression, infected cells do not die from viral cytopathic effects and are not lysed by cytolytic T lymphocytes (CTL) from most patients on antiretroviral therapy. Finally, he suggested that viruses with escape mutations in major CTL epitopes dominate the population of the latent reservoir.

Most of the audience felt that it was a very pessimistic note on which to open the meeting, but perhaps as the cure field exerts a strong selective pressure for glass-half-full researchers, nobody packed up and went home. This optimism was borne out, as for most of the rest of the meeting various presentations showed that labs all over the world are hard at work at all of these challenges.

Mechanisms of HIV latency

Jon Karn (Case Western) opened the first session on the basic mechanisms of HIV latency by discussing the output of his group's effort performing shRNA library screens in Jurkat T-cells models of HIV latency to discover gene products that affected HIV latency. [2] Many of the genes discovered were associated with chromatin silencing mechanisms. A novel target, the estrogen receptor ESR1, was discovered and both this receptor and its downstream signaling target, SRC3, are under study as potential targets of anti-latency therapy. Preliminary studies suggest that gossypol, an inhibitor of SRC3, can disrupt latency both alone and in synergy with the HDAC inhibitor vorinostat (SAHA or VOR).

Melanie Ott from UCSF outlined a flurry of work from her lab, and several others, that suggested that the bromodomain (BRD) family of transcriptional regulator proteins might be targeted to disrupt HIV latency. [3] Like the histone deacetylase inhibitors, the BRD family is large and complex, with multiple factors for multiple function. BRD proteins have the potential to inhibit some steps of HIV expression and activate others. Like HDAC inhibitors, numerous inhibitors of different specificities and selectivities exist. Many are potential clinical tools, and serve as scaffolds for the development of human drugs, such as the molecule JQ1.

Guido Poli (Institute San Raffaele) suggested that Class II histone deacetylases, not thought to have a direct role in HIV latency, might actually be a useful target to disrupt HIV latency as during stress or starvation, the Class II HDAC4 travels to the cell nucleus and affects the Class I HDACs known to be a key anti-latency target. [4] Poli suggested the potentially synergistic use of class I and II HDAC inhibitors for reactivating latent proviral reservoirs.

Carine van Lint (University of Brussels) outlined previous studies on the importance of the cellular cofactor CTIP2 for latency in a microglial cell model, a potential brain reservoir of virus. [5] She suggested that CTIP2 has a double impact on HIV-1 latency, by both recruiting chromatin-modifying enzymes to enforce latency, and by inhibiting P-TEFb function, an activator required to escape latency.

Stephan Emiliani (Paris), pointed to a complex of factors involved in viral integration, LEDGF/p75 associated with the cellular factors Spt6 and Iws1, as involved in the post-integration silencing of HIV the establishment and maintenance of HIV latency. [6] And finally, David Alvarez (from the Karn lab at Case Western) presented evidence that pharmacological inhibitors of the CoREST complex chromatin-modifying enzymes LSD1 and G9a/GLP could be of use in the treatment of HIV-infected microglial cells, but in this case to block activation and HIV expression, and potentially to prevent HIV-induced CNS toxicity. [7]

Warner Greene (Gladstone) took the discussion in a different direction, with new data suggesting that a cell destruction pathway known as pyroptosis ("apoptosis by fire" or cell death with inflammation) is triggered by HIV infection, driving both CD4 T-cell death, and chronic inflammation that may drive cell proliferation and thereby allow latently infected cells to divide without being destroyed or expressing HIV. [8] This very complex model that is sure to attract further study. Greene's lab studied human lymphoid aggregated cultures (HLACs) prepared using tonsil and spleen tissue from consenting HIV-infected volunteers not on ART. Productive HIV infection in activated CD4 T cells from tonsil and spleen promoted caspase-3-mediated apoptosis, but abortive infection of nonpermissive resting CD4 T cells (the majority of cells in this tissue) leads to by caspase-1-mediated pyroptosis, an intensely inflammatory form of programmed cell death. These events combine to create a vicious pathogenic cycle where dying CD4 T-cells release inflammatory signals that attract more cells to become abortively infected and die by pyroptosis causing more inflammation. Greene suggested that inhibitors such as VX-765, a small-molecule inhibitor of caspase-1 shown to be safe in humans, be tested in clinical studies.

Steve Deeks (UCSF) presented an overview highlighting the potential contributory role of persistent inflammation and immune dysfunction. [9] The model suggests that a vicious cycle might exist in which HIV persistence causes inflammation that in turn contributes to HIV persistence.

Remi Fromentin (of the Chomont group at VGTI Florida) showed some data consistent with this model, in which eight different markers were measured on PBMCs from 48 virally suppressed subjects. [10] Three of these eight markers, cellular receptors that transmit negative regulatory signals, PD-1, LAG-3 and TIGIT, were associated with incomplete CD4 T-cell restoration and HIV persistence as measured by HIV DNA. Given the variable association of HIV DNA with true persistence, this is an interesting but not definitive observation.

Robbie Mailliard (of the Rinaldo group at U Pittsburgh) proposed that certain cytotoxic T lymphocyte (CTL) responses to HIV became dysfunctional, in that they provided an inflammatory response to did not kill or clear HIV. Such cells might paradoxically enhance cell-to-cell HIV infection and thereby allow persistence of infection. [11]

Assays to measure HIV persistence

Janet Siliciano opened this discussion with by detailing a recent collaborative study comparing 11 different approaches for quantitating persistent HIV-1. [12] Assays were compared to the gold-standard quantitative viral outgrowth assay (QVOA) that measures the frequency of the recovery of replication-competent HIV from circulating resting CD4+ T cells. Various PCR-based assays of either PBMCs or resting CD4+ T cells for total HIV-1 DNA, or specifically for integrated HIV, circularised proviral episomes, or HIV DNA in rectal cells gave infected cell frequencies at least two logs higher than the viral outgrowth assay, even in subjects who started ART during acute/early infection.

These DNA measures were not even useful on a per-patient basis for anything but a general categorisation (ie "a whole lot" of latent infection or "not so much") as the ratio of infected cell frequencies determined by viral outgrowth to any of the PCR-based assays varied dramatically between patients.

The dramatic differences in infected cell frequencies and the lack of a precise correlation between culture and PCR-based assays means that even if a patient was actually cured of HIV infection, DNA might still be detected, or that if a patient had undergone a procedure that depleted 50% of the latent reservoir, it might not register on a DNA assay.

Certainly, such assays could still be useful as they are so simple, and might give a signal of some very substantial effect (which is what is ultimately needed), but they emphasise the fact known to retrovirologists for decades, that most of the detectable HIV DNA is non-functional. To be provocative but to make a long-ignored point, it is formally incorrect and perhaps even intellectually dishonest at this point to claim that we are "measuring the HIV reservoir" when any PCR measure of HIV DNA is done. The viral rebound in the "Boston patients" who showed huge declines of HIV DNA (more on that later), prove this point yet again.

This is not to say that the QVOA is perfect. There is no free lunch in this business, it seems. Janet Siliciano again discussed the work of Ho et al., reviewing the data that showed that in about half of the handful of patients studied thus far, the QVOA assay appears to represent the "true reservoir" relatively well, but in the other half of patients a large excess of genomes can be detected (5-fold to 60-fold) that express HIV RNAs without major genetic defects and that appear to be able to replicate in culture systems. The glass-half-empty view is that "the barrier to cure may be up to 60-fold greater than previously estimated." The glass half full view is that it is not so in a lot of patients, and in the others the total number of cells is still less than that of a small, removable tumor. The challenge of course, is getting ALL of the tumor out in a reasonable period of time, in a safe and affordable way.

Siliciano did mention that in preliminary studies, about 25% of the viruses that are not recovered from cells after a single round of stimulation in the lab, do emerge in culture after a second round of stimulation. So part of the answer may be serial purging of the reservoir.

Three presentations then followed describing various uses of the emerging "digital droplet" PCR technique to quantitate HIV RNA and DNA forms. Matthew Strain (UCSD), Zixin Hu (Brigham and Women's), and Ward De Spiegelaere (Ghent) discussed this new technique that is based on performing ddPCR in a solution portioned by microdroplets. [13, 14, 15] The instruments generate thousands of picoliter-sized droplets that contain PCR reaction mixtures and (on average due to dilution of the sample) no more than one target DNA or RNA molecule per droplet.

This allows ddPCR to assay millions of cells and to be very more precise at low copy number. Strain showed data measuring unspliced HIV Gag (a late mRNA), multiply spliced Tat-Rev RNA (an early mRNA), and full-length RNAs encoding the poly A tail. Various technical issues are still to be ironed out, including noise signal at the lower limits of the assay (more troublesome when measuring HIV RNA than HIV DNA), variability of RNA extraction depending on the kit used, and viral target sequence variation issues, among others. But the ddPCR technology appears to be a promising new tool for the quantification of HIV-1 cell-associated DNA and RNA.

Sarah Palmer, late of the Karolinska but now at the Westmead Millennium Institute and University of Sydney, studied the genetic makeup of HIV DNA in cells over time. [16] Whereas the frequency of HIV DNA does not give a very good measure of the frequency of true replication-competent infection, the changes of the population of HIV DNA sequences over time does provide definitive proof that HIV was growing in the cell studied in the past, as this is the only way this RNA virus leaves a DNA footprint.

Using single-genome and single-proviral sequencing techniques, Palmer's lab isolated intracellular HIV-1 genomes derived from defined subsets of T cells (naïve, central-, transitional-, and effector-memory) from peripheral blood, marrow, GALT, and lymph node tissue. Samples were collected at two time points (separated by six months) from eight subjects on suppressive therapy (4-12 years): five who initiated therapy during acute infection and three who initiated therapy during chronic infection. Maximum likelihood phylogenetic trees were constructed using the general time reversible model.

Looking at the frequency of specific DNA sequences over time, and the changes seen in DNA sequences over time, the expansion of some HIV genetic populations and the contraction of others with little evidence of viral evolution – that is more cells contained specific sequence population "X" and specific sequence population "Y" disappeared or diminished in proportion. As an example in one patient, a clonal sequence species containing a large 380 base pair deletion was dominant, and increased from 71% to 92% of the sequences found over six months in peripheral blood effector memory T cells. The results were consistent with a model in which the pool of HIV-infected resting memory CD4+ T cells typically does not change dramatically over six months in different tissue compartments. The increase of clonal HIV-1 sequences, especially a large deletion mutant, indicates an expansion of cells with dead, defective proviral DNA rather than active viral replication.

Frank Maldarelli (NIH Frederick) described the case of a single patient with an oral carcinoma who developed persistent low-level viremia 200-300 copies/mL after 11 years of suppressive ART. [17] Single-genome sequencing (SGS) revealed both wild type (WT) and multidrug-resistant HIV. The WT population consisted largely of multiple identical sequences; the drug-resistant population comprised diverse variants encoding K103N and M184V. Switch of ART to raltegravir plus tenofovir/FTC produced a 10-fold reduction of the drug-resistant variants, leaving almost only the WT variants. The emergence of clonal, WT viremia on ART and its insensitivity to cART implies that the source of viraemia was an expanded clone of HIV-infected cells perhaps including increased HIV production from that clone.

The same group investigated the distribution of HIV-infected cells within gut mucosa by analysing endoscopy-derived material. Representative biopsy samples from seven patients were obtained throughout the colon in all patients and from ileum in 4/7 patients. Single genome sequencing showed that HIV proviruses are extensively and uniformly distributed throughout the GALT without clear evidence of sampling variation. Clonally expanded populations present in gut mucosa were not anatomically restricted, and were not divergent from pre-therapy HIV.

Maldarelli and colleagues concluded that detection of the same identical sequences in gut derived DNA and RNA, and in plasma suggests that GALT could be one source of persistent viraemia on ART. But while this conclusion is potentially true, it could equally be true that persistently infected cells, perhaps originating from a proliferating founder population, could traffic through the GALT where they encounter environmental activation signals and produce RNA but not necessarily spreading infection/replicating virus in the face of ART.

Laboratory and animal models of persistent HIV infection

Several presentations focused on laboratory and animal models of latent HIV infection, a critical need as fully validated models are still lacking.

Vicente Planelles (University of Utah) opened with a presentation from the CARE collaboratory (note: the author of this report is a member and a co-author for this presentation) that compared the reactivation of latent HIV in virtually all the primary cell models of latent HIV infection that have been described in the literature. [18] The group sought an answer to a burning question – what is the best cell culture model system for replication latent HIV infection in resting CD4+ T cells in vivo?

Although major advances have been facilitated by the use of latently infected T cell lines, these are usually criticised as artificial, and the newer primary cell models in which primary cells are infected and then forced in to the latent state are felt to be preferred. However, notable differences exist among cell model systems. Furthermore, screening efforts in specific cell models have identified drug candidates for “anti-latency” therapy, which often fail to reactivate HIV uniformly across models. Therefore the group compared the responses of five primary T cell and four J-Lat cell line models to that of the standard viral outgrowth assay using patient-derived infected cells (QVOA) across a panel of thirteen stimuli that are known to reactivate HIV by defined mechanisms of action.

Maddeningly, no single cell model system was able to perfectly capture the ex vivo response characteristics of latently infected T cells from patients. Specific model systems appear biased in favor or against certain signaling pathways. The data is very complex, and will be published soon in PLoS Pathogens. It should allow investigators to select the best model, or group of models, for future studies and allow them to choose models responsive to certain types of signals, if desired.

Janice Clements (Hopkins) reported progress in the study of the SIV macaque model, reporting the use of a quantitative viral outgrowth assays (QVOA) for SIV, quantitating SIV within monocytes, tissue macrophages and microglia. [19] Plasma viraemia was suppressed to low levels (<10 copies/mL) with two different ART regimens and we have used this model to develop a QVOA assay for monocytes and tissue macrophages.

Within the CD11B+ cell population, the authors found 5.2 cells/million were vRNA positive, despite ART suppression. CD11b is expressed on the surface of many leukocytes including monocytes, neutrophils, natural killer cells, granulocytes and macrophages, as well as on 8% of spleen cells and 44% of bone marrow cells, but not T cells.

Koen von Rompay (University of California) then gave an update on effort in the Luciw laboratory to model the effect of the HDAC inhibitor SAHA (vorinostat) on viral reservoirs in ART-suppressed nonhuman primates infected with the RT-SHIV virus construct. [20] This study could validate the primate model by reproducing results seen in human studies of SAHA. Six weeks after intravenous RT-SHIV inoculation, juvenile macaques are started on a once-daily ARV regimen (efavirenz/tenofovir/FTC) known to rapidly reduce plasma viremia. Once plasma virus levels reached very low or undetectable levels, pulsatile treatment with subcutaneous injections of SAHA was begun. The biological effect of the drug, histone acetylation, has been observed in peripheral blood cells. Measurements of the effect of this treatment on HIV reservoirs and HIV RNA expression in both blood and tissue samples is ongoing, with results expected in early 2014.

J Victor Garcia-Martinez (University North Carolina) then discussed the other animal model of persistent HIV infection, presenting a systemic examination of the latent and residual active HIV reservoirs in bone marrow-liver-thymus (BLT) humanised mice undergoing ART. [21] He and his coworkers found that, as in humans, the latent HIV reservoir is broadly disseminated during ART, and that human tissues examined throughout the mouse exhibited low level vRNA production – indicating that the residual active HIV reservoir is also systemic in nature. The BLT appears capable of providing a quantitative framework for the evaluation of the in vivo efficacy of HIV eradication interventions designed to deplete HIV. Garcia then presented two new modifications of the BLT model, the TOM (T cell only) and the MOM (macrophage only) mouse.

HIV replication, ART suppression, viral rebound after ART interruption, and resting cell latent infection were all seen in the TOM. Studies of the MOM are in earlier stages, but low-level HIV replication after infection has been observed. These exciting new tools may allow the dissection of the role of each of these cell types in HIV persistence in vivo.

Following this, Hans Peter Kiem from the Defeat-HIV collaboration, reported on studies in two monkeys (compared to two controls) in whom ex vivo transduction of their stem cells with the mC46 HIV fusion inhibitor construct appeared to produce gene-protected stem cells. [22] Monkeys given these cells then had CD4 preservation after SIV infection.

Jeff Lifson (NCI Frederick) furthered the discussion of NHP model systems, suggesting that major gaps in our understanding of viral reservoir establishment, maintenance, phenotype and tissue compartmentalisation that are particularly difficult to study in humans can be readily studied in NHP. [23]

He illustrated various techniques for visualising HIV RNA in cells and tissues. He highlighted three techniques to detect SIV RNA.

1. Radiolabelled in-situ hybridisation (ISH), which is slow (5-14 days), and subject to high tissue background.
2. Positive-strand viral RNA ISH with chromogenic detection, quicker (3 days) but with poorer resolution.
3. RNA SCOPE ISH, which is quick (8 hours), of low background, and potentially may be able to distinguish single virions.

Pharmacology of HIV persistence

Two years ago at the last St. Martin meeting, Courtney Fletcher (University of Nebraska) presented high-profile data suggesting widely inadequate ART drug concentrations in the tissues. His presentation of data from a continuation of the same study two years later seemed more muted. [24]

He hypothesised that antiretroviral drug concentrations in lymphoid tissue might be insufficient to fully suppress replication in these sites. Twelve patients were followed since ART initiation, with multiple samplings of lymph node, ileum and rectum, and peripheral blood, to determine intracellular concentrations of the ARVs in these tissues and to measure levels of persistent HIV. He restated some findings from two years ago, that concentrations of some frequently used drugs (tenofovir, FTC, efavirenz, atazanavir) are much lower in lymph nodes than in peripheral blood, but darunavir and raltegravir levels were adequate. However, tenofovir and FTC levels were higher in rectal and ileal tissue than plasma. All drug levels were adequate in the rectum.

These data still require a fuller presentation and publication, with internal standards and controls to insure that drug levels did not drop during sample processing. Fletcher did find that on a per-patient basis, higher drug concentrations correlated with more rapid decline in HIV RNA within the follicular dendritic cell network.

Angela Kashuba (University of North Carolina) discussed similar issues, and agreed that limited data exist to evaluate inter-species similarities or differences in extracellular or intracellular drug distribution in tissue sites. [25] She had similar comments on ARV concentrations in animal models. She outlined new methods to evaluate the relationship between pharmacology and HIV persistence, and noted the challenge of tissue homogenization LC-mass spec) without losing sample.

Jay Grobler from Merck presented arcane-sounding work entitled “Inhibitory slopes show minimal variation within and across mechanistic classes of HIV-1 antiretroviral agents and are not likely to contribute to differential effectiveness of combination therapy and viral persistence.” [26] The analysis stems from work in the Siliciano laboratory, which suggested that the slope of the ART concentration inhibition curve (Hill coefficient) is an important factor in selecting the best ART combinations. Grobler showed that this was true when assays of drug effect were performed in a specific cell line, 293T, as had been done in the Siliciano work, but not when assays were run in peripheral blood mononuclear cells (PBMCs) and lymphoid-derived cell lines. He concluded that consistent with clinical experience, the slopes of dose response curves are not likely to be a significant factor in determining clinical efficacy or contribute to the effectiveness of drug specific combinations.

Drug development and testing curative strategies

Daria Hazuda presented an overview of the Merck programme, describing the most advanced of these approaches, the use of histone deacetylase inhibitors (HDACi), and recent studies suggesting the actions of these inhibitors might be complex and unique. HDACis with similar inhibitory potencies can have widely different enzyme binding kinetics, and the potency of HDAC inhibition might not be the most important measure of a compounds utility against HIV latency. [27] She outlined a high-throughput screen that had discovered many new potential anti-latency compounds, many of which appeared to increase in potency when used with the HDACi SAHA (vorinostat). She introduced the discovery of the activity of farnesyl-transferase inhibitors (FTIs) as anti-latency reagents.

Richard Barnard from Merck went into this work in detail in a subsequent talk, outlining the characteristics of these compounds, previously developed as (unsuccessful) anti-cancer drugs. [28] FTIs result in modest induction of the expression of HIV in model systems and in cells from patients, but substantially increase the magnitude of induction in combination with SAHA, as well as more selective HDACi (against specific HDAC isoforms), and with other reagents such as prostratin. FTIs of two different mechanistic classes are active, and activity correlates with FTI potency, suggesting that mode of induction is directly related to inhibition of FT. Data suggested the potential for increased efficacy in combination and providing proof of concept for identifying synergistic combinations using this novel screening paradigm.

Suzanna Valente of the Scripps Research Institute in Florida discussed her recently published findings on a potent inhibitor of the viral activator Tat, didehydro-Cortistatin A (dCA), an analogue of a natural steroidal alkaloid from a marine sponge. [29] Opposite to most current approaches, this strategy would hope to establish a state of “super latency” of HIV, preventing viral reactivation from latently infected cells if ART was stopped. This has been achieved in cell model systems, and dCA inhibits HIV reactivation upon homeostatic and antigenic stimulation of CD4+ T cells isolated from virally suppressed patients undergoing ART. The next step would be proof-of-concept studies in an animal model or in the clinic.

Stephen Mason outlined the BMS programme, which included screening efforts to identify novel anti-latency compounds, but also emphasised immunomodulatory therapies designed to augment the anti-HIV immune response. [30] As proof of concept, nivolumab (anti-PD-1; BMS-936558) has been tested in the context of chronic HCV in human subjects with modest effect. Alternatively, an alternate ligand of the same pathway, BMS-936559 (anti-PD-L1) has been administered to SIV-infected rhesus macaques that were suppressed on a combination of antiretrovirals, and testing in man through the ACTG is in the planning stages.

The effect of anti-PD-L1 immunotherapy in ARV-suppressed rhesus macaques was reported by James Whitney (Beth Israel Deaconess Medical Center). [31] Thirteen MHC-defined rhesus macaques were confirmed SIVmac251 positive and ARV treatment was initiated, using a four-drug ARV regimen, for a minimum of six months prior to the administration of BMS-936559. All 13 animals received either BMS-936559 (n=8) or isotype control antibody (n=5). Five doses of 10 mg/kg were given over two weeks, and effects measured at days 0-14. The repeated dosing of BMS-936559 was also well tolerated in all animals with no noted untoward effects. Receptor occupancy of BMS-936559 was favorable. ART was then continued for six weeks, and then an analytic treatment interruption was undertaken.

In the BMS-936559-treated animals, viral rebound was lower than setpoint viremia in 7 of 8 animals, and 1.5 logs lower in 4 of 8 animals. Rebound was lower than setpoint in only 1 of 5 control animals.

Romas Geleziunas outlined the Gilead programme, a comprehensive effort testing the HDACi rhomidepsin (ACTG study nearing initiation), other agents such as PKC agonists, and including a high-throughput screening effort. [32] Immunotherapeutics mentioned included therapeutic vaccines, and monoclonal antibody therapeutics designed to clear infected cells. Recent studies have identified a TLR7 agonist as an inducer of CD8 and NK cell response, and a combination approach using rhomidepsin and TLR7 in the rhesus model is planned.

Iart Shytaj reported the findings published by the Savarino group (Rome) of a functional cure-like condition in chronically SIVmac251 infected macaques. [33] A combination of ART, auranofin and buthionine sulfoximine (BSO) induced spontaneous post-therapy control of viral load in

chronically SIVmac251-infected macaques [Shytaj et al., Retrovirology. 2013]. This control was associated with increased and broad anti-Gag immune responses and was dependent on the presence of CD8+ cells.

Lucio Gama and Janice Clements (Hopkins) described the use of Ingenol-B (ingenol-3-hexanoate), a potent PKC activator. [34] A hexanoate derivative of Ingenol (Ing-B), a phorbol ester isolated from the Brazilian shrub Euphorbia tirucalli, Ing-B was given to SIVmac251-infected macaques, 0.4 mg/kg/day for 30 days. In the absence of ART Ing-B increases viraemia. With raltegravir, tenofovir FTC, ingenol increased plasma VL, but then after ART interruption, VL dropped to undetectable in some animals. A deeper tissue analysis of the effects of Ing-B is awaited.

Keith Jerome of the Defeat-HIV collaboration discussed the design and delivery of homing endonucleases designed to inactivate HIV provirus. [35] Using a combination of designer HEs that target multiple essential HIV genes for disruption and subsequent inactivation the aim is to inhibit the process of HIV inactivation from latently infected reservoir cells. The group have tested this hypothesis in latently infected primary central memory T cells, by delivery of designer enzymes using scAAV vectors that can infect more than 90% of primary cultured Tcm.

Several groups are beginning to examine therapeutic vaccination as part of an eradication strategy, and the potential interaction of the host effects of anti-latency therapies on the immune response.

Brad Jones (Ragon Institute) used a model of latency resulting from the infection of primary CD4 T cells in culture, and examined the effect of CTL clones on these target cells. [36] HIV-specific CTL clones were co-cultured with these targets in the presence or absence of latency-reversing agents. Interferon-gamma was quantified as a measure of CTL recognition. Jones found that while HDACi and common gamma-chain cytokines both reversed HIV latency, HDACis suppressed CTL function and thus performed poorly in integrated "flush and kill" assays. In contrast, IL-15 superagonist (IL-15SA) both reversed HIV latency and enhanced CTL function. Treating patient CD4 T-cells with a romidepsin pulse/wash followed by co-culture with HIV-specific CTL and IL-15SA resulted in a 5-fold reduction in levels of provirus and in the elimination of infectious virus as measured by viral outgrowth assays.

Julia Sung (University North Carolina) from the author's laboratory presented the use of ex-vivo expanded CTLs as utilised for viral infections in oncology to clear latent HIV infection. [37] As compared to unexpanded CD8s, expanded CTLs reduced p24 production from autologous targets superinfected with the lab virus JR-CSF (median %p24 produced with expanded CTLs=2.5%, vs 29.2% with unexpanded CD8s, $p < 0.05$) or autologous virus obtained from the patient's own latent reservoir (median 8% vs. 20.6%, $p < 0.05$). We feel that ex-vivo expanded CTLs could prove useful in combination with latency reactivating agents.

Human studies

Widely publicised in the general press, Tim Henrich of the Brigham and Women's Hospital, announced the unhappy news that both of the so-called "Boston patients" had rebounded with symptoms of primary infection. [38] These patients had had marrow transplants for cancer, but had not received HIV-resistant cells.

At 4.3 years after transplantation, one patient was completely transplanted, with only donor cells detected, and no HIV DNA in two pools of 25 million PBMCs that were tested, a reduction of HIV DNA of at least 1500-fold compared to the level of DNA prior to transplant. At 2.6 years after transplantation, the second patient was completely transplanted, with only donor cells detected, and no HIV DNA in one pool of 50 million PBMCs that were tested, and no HIV recovered after the culture of 150 million PBMCs.

Both patients had no detectable HIV-specific cellular immune function by ELISpot IFN-gamma screenings of total PBMCs involving comprehensive HLA-specific peptide panels. But they did have significant chronic graft-vs-host disease (GVHD), that is the patients engrafted immune systems were exhibiting a chronic active immune response against the patient's native cells. After the ART interruption, one patient rebounded within 12 weeks (and just after the patients' cases were described at the summer IAS meeting) and the other 224 days after interruption. Of note, an assay for HIV DNA on day 196 was negative, but viraemia recurred 28 days later. It is very unfortunate that, as far as we know at this point, a comprehensive analysis of a sufficient number of cells was not done to stringently analyse viral persistence prior to rebound.

Katherine Luzuriaga (University of Massachusetts) reviewed the well-known case of the Mississippi baby, and the IMPAACT network's plans to attempt to replicate the case by finding and treating high-risk children within 48 hours of birth. [40]

David Margolis (UNC, the author of this workshop report) presented an update from the ongoing studies of SAHA or vorinostat (VOR). [41] The potent Class I HDACi VOR upregulates HIV RNA expression within the resting CD4+ T cells of ART-treated, aviremic HIV positive patients in vivo. But the ability of VOR to repeatedly disrupt latency is unproven, the optimal dosing schema is unknown, and the effect of VOR on host mechanisms that might clear infected cells is uncertain.

In a Phase I-II single-center study, HIV positive participants maintained suppressive ART, and resting CD4+ T cells were obtained by leukapheresis. If an increase in resting CD4+ T cell-associated HIV RNA (RC-RNA) was measured following a single VOR 400 mg dose, patients received VOR 400 mg daily M-W for 4 weekly cycles, followed after a 4 week rest period by another 4 weekly cycles. Sparse VOR PK, biomarker measurements of histone acetylation within PBMCs, HIV RNA single-copy assays, RC-RNA, total cellular HIV DNA, and quantitative viral outgrowth assays (QVOA) from resting CD4+ T cells were obtained.

In five patients VOR was well tolerated with no adverse events greater than Grade I; mild declines in platelet counts < Grade I were seen commonly. VOR exposures were within expected parameters. However, when measured after dose 11 (second dose of cycle 4) and dose 22 (second dose of cycle 8) cellular histone acetylation was little increased from baseline levels, and measures of RC-RNA only modestly increased in some patients. QVOA and other assays were also generally stable. We believe that complex feedback host mechanism blunt the response to repeated VOR doses if the dosing interval is too frequent.

Sharon Lewin (Melbourne) presented follow-up data from her study of daily VOR. [41] She evaluated differential gene expression in blood from 20 HIV positive patients on ART who received vorinostat (400 mg/day) for 14 days. Gene expression was analysed at baseline and two time points on vorinostat (day 1 and day 14) and post-cessation of vorinostat (day 84). We found that the effect of vorinostat on chromatin largely occurred within the first day after the first dose of drug and that after 14 days of continuous dosing, there were compensatory mechanisms associated with transcriptional repression and cell survival. These results demonstrate significant effects of vorinostat on viral proteins and host genes that may have a significant impact on the potency of activation of latent virus.

Thomas Rasmussen also presented further data on the Aarhus Hospital's ongoing panobinostat studies. [42]

In a phase I/II clinical trial, 16 HIV positive adults on suppressive ART received treatment with oral panobinostat (20 mg, three times per week MWF, every other week) over the course of 8 weeks. There were 16 grade-1 adverse events, with 10 thought to be drug related, mostly fatigue or GI upset. Although CD4 cells were stable, there was a mild drop in neutrophils and platelets, which reversed and did not achieve a gradable toxicity. An increase of histone acetylation was seen post-dosing but never seemed to return all the way to baseline. HIV cell-associated RNA increased variably, with a clear 2-fold increase on dose 1, but a variable increase of 1.5-2.5 fold after that.

Joumana Zeidan reported the results of the Sangamo trials of the zinc finger nuclease SB-728-T that edits the human CCR5 gene and confers HIV resistance to cells (as I believe had been reported at ICAAC). [43]

In seven SB-728-T treated CCR5 delta-32 HIV positive subjects, viral load decreased by >1 log from peak in three subjects after ART interruption. Two subjects achieved unmeasurable viral load, in one subject from 11 through 19 weeks of treatment interruption, and ongoing. Viral load reduction from peak correlated with the level of circulating bi-allelically CCR5 modified cells during the interruption ($r=-0.81$, $p=0.015$). As high levels of CCR5 modification, along with poly-functional CD8 anti-GAG responses, and low HIV-DNA levels in PBMCs appear to play an important role in functional control of HIV with SB-728-T treatment, the group seeks to pursue cytoxan chemotherapy pre-conditioning to "make room" in the marrow and enhance SB-728-T engraftment.

Bernard Macatangay (University Pittsburgh) reported the results of a dendritic cell-based HIV therapeutic vaccination study. [44]

Autologous dendritic cell (DC) vaccine pulsed with autologous, inactivated HIV-1-infected apoptotic cells were given to 10 ART-treated subjects. After at least eight weeks of virologic suppression, 6/9 subjects had residual viraemia detected by a new single-copy assay (iSCA) ranging from 2.0-49.5 copies/mL. In 6/10 subjects, increasing levels of residual viraemia were observed after vaccination despite continuous ART.

Increased residual viraemia was measured by iSCA in 40% of subjects despite continuous ART. This increase was not associated with increased T cell activation. iSCA is a more sensitive tool for detecting rebound viraemia than the FDA-cleared Roche Amplicor assay v1.5. Therapeutic vaccination may increase HIV-1 replication or expression from latent reservoirs.

Finally, some evidence suggests the Wnt cellular signaling pathway plays a role in maintaining latency. Lithium, an inhibitor of Wnt signaling pathway, might synergise with HDAC inhibitors in inducing the reactivation of the latent HIV-1 LTR.

Maria Puertas (IrsiCaixa, Badalona) and colleagues nested an examination in to an ongoing clinical study designed to assess the effect of lithium on HIV-associated neurocognitive impairment, and explored lithium's potential effect on HIV-1 reactivation and viral reservoirs. [45] Nine ART-suppressed subjects received treatment with lithium carbonate, beginning a twice-daily 400 mg dose, and further adjusting the dose according to drug levels in serum. Changes in total cell-associated HIV-1 DNA and RNA in circulating primary CD4+ T cells were estimated by droplet digital PCR at weeks 0, 2, 4 and 12 during treatment with lithium. The frequency of latently infected cells was also quantified by the viral outgrowth assay (IUPM) at weeks 0 and 12.

The therapeutic administration of lithium in ART-suppressed subjects did not show any sign of viral reactivation or had a significant effect on the size of the HIV-1 reservoir. However, the Wnt pathway is complex, and the effect of lithium on the pathway may be bimodal. Alternative inhibitors or inducers that affect Wnt signaling might have a larger impact.

Overall, the workshop was exciting and packed with information. The HIV Cure research field is moving ahead, although the road is still a long one. Surely there will be more news at CROI this spring, and IAS this summer.

David Margolis is on the Steering Committee for the 6th International Workshop. This article is a slightly amended version of a report first published on natap.org. Full references added by i-Base.

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ANTIRETROVIRALS

Dolutegravir approved in Europe

ViiV Healthcare press statement

On 21 January 2014, ViiV Healthcare announced that the European Commission has approved dolutegravir for use in combination with other antiretroviral medicinal drugs for the treatment of HIV infected adults and adolescents above 12 years of age.

Approval was based on results from four Phase 3 adult studies in treatment-naïve and treatment-experienced patients, including people with resistance to other integrase inhibitors. The submission supporting today's approval included data from four pivotal Phase III clinical trials in which 2,557 adults received treatment with dolutegravir or a comparator. The submission also included data from a fifth study in children aged 12 years and older5.

The efficacy of dolutegravir – as a 'third agent' – was statistically superior to its comparator in two pivotal Phase III studies1,2 and non-inferior in a third comparator study. In clinical trials, Tivicay had low rates of discontinuation due to adverse events (1-3%) in both treatment-naive and treatment-experienced patients.

The safety profile is based on pooled data from Phase IIb and Phase III clinical studies in 980 previously untreated patients, 357 previously treated patients unexposed to integrase inhibitors and 234 patients with prior treatment failure that included an integrase inhibitor (including integrase class resistance). The most commonly seen treatment emergent adverse reactions were nausea (15%), diarrhoea (16%) and headache (14%). The most severe adverse reaction, seen in an individual patient, was a hypersensitivity reaction that included rash and severe liver effects.

The recommended dose of dolutegravir for most patients is one 50 mg tablet once daily. For patients with documented or clinically suspected resistance to the integrase class, or when co-administered with certain medicines, the recommended dose of dolutegravir is 50 mg twice daily.

Please refer to the full European Summary of Product Characteristics for full prescribing information, including contraindications, special warnings and precautions for use. [2]

Dolutegravir is manufactured by ViiV Healthcare and has the trade name Tivicay.

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TREATMENT ACCESS

BMS to add atazanavir to Patent Pool

On 12 December, the Medicines Patent Pool (MPP) announced that Bristol-Myers Squibb (BMS) have agreed to let atazanavir be produced by generic companies for use in developing countries. [1]

This is the first MPP agreement for a drug that is currently a WHO-preferred option for second-line therapy.

The agreement from BMS allows for a technology transfer package to sub-licensed generic companies help manufacture atazanavir for use in 100 countries. The press statement notes that: "While royalties are not applicable in the vast majority of the countries and are waived for all paediatric products, any royalties that are collected under this license agreement will be reinvested in local HIV/AIDS groups in those countries."

The MPP works by creating a pool of relevant patents for licensing to generic manufacturers and other producers. This facilitating generic competition to brings down prices and can help stimulate innovation, especially for simplified fixed-dose combinations and better formulations for children.

Other companies who have joined this collaborative programme include Gilead Sciences, ViiV Healthcare and Roche (for valganciclovir). Notable companies that so far withheld their drugs include Abbvie (Abbott), Janssen (J&J) and Merck (MSD). [2]

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Donors pledge $12 billion to Global Fund for 2014–2016: increase still short of $15 billion goal

Global Fund Observer

Donors pledged an historic $12.007 billion to the Global Fund to Fight AIDS, Tuberculosis and Malaria for implementation of its new approach that will see more resources targeting key affected populations in the countries least able to pay.

The pledges were made before and during the Fourth Replenishment conference in Washington, DC on 2–3 December.

While a considerable improvement over the $9.2 billion in pledges made at the last replenishment conference in 2010 for the 2011–2013 period, the pledges fell short of the hoped-for $15 billion the Global Fund has estimated is required to meet the needs in the 150 countries where prevention and treatment programmes are currently supported.

A needs assessment, jointly conducted by the Fund with the World Health Organization, UNAIDS, Roll Back Malaria and the Stop TB Partnership, determined in April 2013 that $87 billion from both domestic and external sources was needed to completely vanquish the three diseases.

The commitments to the 2014–2016 cycle from countries included a promise by the US government to match every $2 raised with $1, subject to approval from the US Congress, up to $5 billion. "Don't leave our money on the table," US President Barack Obama said on 2 December at an event to open the pledging conference.

The UK government also conditioned its pledge of up to £1 billion ($1.64 billion) to match 10% of the global contribution to the Fund. "What is needed more than ever is political commitment" to the global fight against three of the biggest killers and inhibitors of economic development in low-income countries, UK Prime Minister David Cameron said in a video message.

Twenty-three other countries and the European Commission joined the US and UK in pledging to support the next cycle of programming under a soon-to-be inaugurated new funding model (NFM) that will require a deeper commitment to responding to the needs of vulnerable populations, including men who have sex with men, commercial sex workers, injection drug users and prisoners.

France, which has traditionally been the second-largest contributor to the Fund after the US, was slightly edged out in this round by the UK promise, offering €1.08 billion ($1.4 billion), which includes some €20 million in technical assistance to Francophone countries, mostly in West and Central Africa, for proposal development under the NFM and for grant implementation. Germany and Japan tied as the Fund's fourth largest contributors, each offering $800 million over the next three years.

Italy proudly returned to the ranks of contributing nations after five years of absence with a pledge of €100 million. Other countries that upped their contributions significantly included The Netherlands, from $210 million to $250 million, and Sweden, which attributed a more than 30% increase in its pledge to $382 million to the strength of its economy and its currency, the kroner.

But if there were countries whose largesse to the financing mechanism befitted the strength of their economies, so too were there others whose modest national coffers were also tapped to contribute to the financing mechanism.

Malawi, which has benefitted from some $834 million in Global Fund grants since 2002, committed "in [their] own small way" $500,000 to show support. Namibia vowed to make good on its commitment in the previous funding cycle before the end of the year and pay its balance of $250,000 on a $750,000 pledge. Meanwhile Nigeria, a billion-dollar recipient of Global Fund aid, announced its intention to spend more

than $450 million domestically on its fight against the epidemics and offered another $30 million back to the Fund's coffers.

Other implementing countries making contributions included India, at $16.5 million, China, at $15 million, and Mexico, which committed to redirecting $30.5 million in assistance back to the global coffers.

Private sector contributions were assessed at $108 million for the next funding cycle. But Aidspan understands from sources within the private sector delegation that more could be forthcoming as the Fund implements its new approach and generates impact and results data that show better value for money.

The United Methodist Church became the first faith-based organisation to pledge support for the Fund, offering $19.9 million. The Bill and Melinda Gates Foundation remained the single largest foundation supporter of the mechanism, offering $200 million in matching grants for private sector contributions in addition to $300 million in promissory notes already extended.

"The Global Fund is one of the smartest investments that the world can make toward a better future," Bill Gates told assembled delegates on 2 December. "The Global Fund helps provide treatment and prevention so communities and countries get the chance to be healthy and productive."

Despite the not-insignificant boost in contributions over the last funding cycle, there were some disappointments. Neither Japan nor Australia increased their contributions from the previous replenishment. Both Spain and Brazil cited their current financial crises as the justification for their inability to commit funds, despite their continued support for the Fund. And Switzerland and Russia were unable to announce their commitments due to ongoing budgetary negotiations at the legislative level.

Aidspan will publish a complete table of contributions shortly.

Source:

Global Fund Observer, issue 233. Donors Pledge $12 Billion for 2014–2016. (09 December 2013).

http://www.aidspan.org/gfo_article/donors-pledge-12-billion-2014–2016

Global Fund and UNAIDS urge Nigeria to reconsider new anti-gay law

Global Fund Observer

The law restricts gay and lesbian people from associating in public and imposes jail time of up to 14 years for same-sex unions.

The law was passed by the Nigerian national assembly in May 2013 but President Goodluck Jonathan resisted signing it until early January, doing so with little fanfare as he knew the likely firestorm it would provoke among Nigeria's development partners.

Governments including the US and the UK released strongly worded statements that matched the urgent request by the Global Fund and UNAIDS for Nigeria to review the constitutionality of the law, which will impose jail sentences of up to 14 years for those entering into same-sex unions and restricts public association by gay and lesbian Nigerians.

In a 14 January statement, the two organisations said the new law "could prevent access to essential HIV services for LGBT people who may be at high risk of HIV infection, undermining the success of the 'Presidential Comprehensive Response Plan for HIV/AIDS' which was launched by President Goodluck Jonathan less than a year ago".

Nigeria should put comprehensive measures in place to protect the ongoing delivery of HIV services to LGBT people without fear of arrest or other reprisals, the Global Fund/UNAIDS statement added.

Estimates from 2012 suggest there are some 3.4 million people in Nigeria living with HIV, a national prevalence rate of around 4%. Prevalence among men who have sex with men is estimated at 17%.

"The provisions of the law could lead to increased homophobia, discrimination, denial of HIV services and violence based on real or perceived sexual orientation and gender identity. It could also be used against organisations working to provide HIV prevention and treatment services to LGBT people," they said.

The law may have serious public health and human rights implications for Nigeria and could be a bellwether for similar repressive legislation across West Africa.

There are already more than 30 countries in sub-Saharan Africa that have criminalised homosexual activity: most of which are recipients of Global Fund support. The implications of the new law are already evoking concerns among civil society groups that work specifically with men who have sex with men. The Global Fund Secretariat told Aidspan that it did not know yet what the law meant for the programmes it supports in Nigeria, but that contact with government was continuing.

However, the adverse implications for outreach programmes to the MSM community could be considerable. In the administrative capital Abuja, the International Center for Advocacy on Right to Health (ICARH) established a clinic in 2011, providing condoms and ARVs to slow the spread of HIV in this population.

"This law will be very harmful to our work," Ifeanyi Kelly Orazulike, ICARH's Head of Programmes told Aidspan. "The primary beneficiaries of our programmes are men who have sex with men. Over 600 people are benefitting from our services, and 200 of them are receiving ARVs. What will happen to these people who are on ARVs? There is a real possibility that they will drop out of the programme as MSM will henceforth fear coming out in public to receive the services."

Mr Orazulike said that anecdotally, he has heard from many men preparing to flee the country once the law is fully implemented because due to

the way it is written, it creates an atmosphere that encourages targeting of people on the basis of their sexual orientation. As part of an intensive year-long campaign to keep the bill from being passed, ICARH delivered a paper to the Nigerian senate about the potential implications for public health. The paper, he said, was ignored.

"The international community should put pressure on the Nigerian government to understand the negative impact of this law in terms of financing for programmes targeting key populations," he said, noting that the support by the Global Fund and other donors is crucial.

The Global Fund has disbursed about $1 billion to Nigeria since 2002, some two-thirds of which supports HIV programming including the provision of anti-retroviral therapy for more than 520,000 people.

Speaking by telephone to Aidspan, Ibrahim Umoru, coordinator of Nigeria's Network of People Living with HIV/AIDS, which has been a sub-recipient (SR) of Global Fund grants since 2006, called the law inconsistent with the country's need to slow the spread of HIV transmission and infection. Tackling AIDS is not just about providing anti-retroviral treatment; it's about sensitising people about prevention and changing behaviours to avoid infection. So the grey areas not yet clarified in the application of the new law could make his job decidedly more complicated.

"For instance, in my work, I come across situations where I may need to offer counselling to MSM people who are HIV positive. Since the new law criminalises the public display of same-sex activities, will such counselling be prevented?" he asked. "As a person living with HIV, my concern is not about people's sexual orientation but rather about sexual health. Treatment must be given to all people without discrimination."

Discouragement with the passage of the bill that they spent a year fighting will not make AIDS activists in Africa's most populous nation complacent, Mr Umoru vowed; instead, they will continue to agitate for government to ensure a conducive environment for the implementation of HIV/AIDS programmes for all people, including those engaged in same-sex activities.

Yakasai Umar Tanko, the national coordinator of Network of Youth on HIV/AIDS in Nigeria (Nynetha), a sub-recipient of Global Fund grants for Round 9, said the government should be prepared to fill the void if donors who have been funding LGBT programmes are unable to operate because of the new law.

"The government must have been aware of the implications of coming up with that law and should be ready for the consequences that the law will have on donor funding for HIV/AIDS programmes," he said.

Source

Global Fund Observer, issue 235. (21 January 2014).

http://www.aidspan.org/gfo_article/global-fund-and-unaids-urge-nigeria-reconsider-new-anti-gay-law

See also an article in the same GFO issue: "Funding Côte d'Ivoire programmes for men who have sex with men meets with resistance. Global Fund Observer 235. (21 January 2014).

http://www.aidspan.org

TREATMENT GUIDELINES

BHIVA update adult ARV guidelines

Simon Collins, HIV i-Base

In November 2013, BHIVA updated the 2012 adult antiretroviral guidelines, largely to reflect the recommendations from the new hepatitis guidelines that were also published in the same month. [1, 2]

Changes, highlighted in yellow in the new PDF file, include:

- Elvitegravir/cobicistat is included as a preferred third drug for first-line treatment. This is based on non-inferiority results in studies compared to efavirenz and atazanavir/ritonavir.
- Rilpivirine is included as an alternative option for first-line treatment. This is largely because of the limitation for baseline viral load to be <100,000 copies/mL and concern over food requirements and potential interactions with antacids.
- New recommendations on ARV choice were based on a new analysis of comparative studies, and this is included in appendices 3 and 4.
- Recommendations for coinfection with HBV and/or HCV, and related auditable outcomes, have been updated to reflect the November 2013 coinfection guidelines.
- The discussion on when to start ART is expanded to explain why the CD4 threshold remains at 350 rather than increasing to 500. This includes referring to the importance of the START study in assessing both the benefits and risks of earlier treatment and that other factors could results in different recommendations outside the UK.
- The guidelines reaffirm that irrespective of CD4 count, ART should be available to all HIV positive people for whom the reduced potential for transmission is a factor in starting treatment.

- The timing of ART in patients starting treatment with a serious bacterial infection low CD4 is discussed to reflect recent research suggesting a caution to immediate ART, even though these were in a different health setting to the UK.
- Of note, a discussion of use of fixed dose combinations (FDC) compared to prescribing individual components separately, supported the benefits of FDCs, and noted the lack of evidence supporting separate dosing.

The full guidelines are available free online and are also published as a supplement to the 2014 edition of HIV Medicine. [1]

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PREGNANCY and PMTCT

Data from two cases of rilpivirine use in pregnancy

Polly Clayden, HIV i-Base

There are currently no safety or pharmacokinetic (PK) data available to guide the use of rilpivirine in pregnancy.

The PANNA study was established to collect data on PK and transplacental passage of new antiretrovirals during pregnancy. [1] It is a non-randomised, open-label, multicentre phase IV study.

Angela Colbers and colleagues from the PANNA group described two cases of rilpivirine use in pregnancy from PANNA in a letter to the 14 January 2014 edition of AIDS. [2]

Rilpivirine is an NNRTI, given once daily and available as a single 25 mg tablet and coformulated with tenofovir and FTC in a fixed dose combination (FDC). Rilpivirine is indicated for treatment-naïve adults with a viral load of 100,000 copies/mL or less.

The first case presented was a 19-year-old black woman, diagnosed with HIV in 2011, when she started antiretroviral treatment with the rilpivirine/tenofovir/FTC FDC (Eviplera). She conceived after approximately 14 weeks on this regimen.

The regimen was stopped after pregnancy was confirmed, then restarted at week 25 (viral load 3500 copies/mL) and continued for the rest of the pregnancy and after delivery.

At week 32, the investigators performed a full PK analysis, which gave the following values: AUC-24 1.25 mg*h/L; Cmax 0.07; C0h 0.04mg/L and T1/2, 30 hr.

At 38 weeks of pregnancy, the mother was admitted to the hospital due to irregular contractions. This was reported as a serious adverse event not considered associated with Eviplera

The infant was delivered vaginally at 39 weeks and 5 days gestational age; the mother's viral load was undetectable <50 copies/mL. The infant was a girl, had no congenital abnormalities and weighed 3620 g. The infant's HIV DNA PCR test at two weeks after delivery was negative.

The cord blood/maternal blood ratio was 0.74 at delivery.

At 45 days after delivery, maternal postpartum PK values were: AUC0-24 1.79 mg*h/L; Cmax 0.11 mg/L; C0h 0.07 mg/L and T1/2 43 hr.

The second case was a 24-year-old white woman, who was diagnosed with HIV in 2010. She began ART in September 2011 with a regimen of atazanavir/ritonavir 300/100 mg once daily and AZT/3TC. She switched to Eviplera in August 2012 and had been taking it for 10 weeks when she conceived.

The PK analysis was performed at 32 weeks of pregnancy, with the following values: AUC0-24 1.42 mg*h/L; Cmax 0.14mg/L, C0h 0.04mg/L and T1/2 33hr.

The infant was delivered by emergency Caesarean at 38 weeks and five days gestational age. The mother's viral load was 77 copies/mL two weeks before delivery but was undetectable again four weeks post partum. The infant was also a healthy girl, she weighed 2945 g and tested negative for HIV at one day and 18 days of age.

Postpartum maternal PK values were: AUC0-24 2.49 mg*h/L; Cmax 0.15 mg/L; C0h 0.07mg/L and T1/2, 48 hr.

The investigators noted that exposure was 30–43% lower during pregnancy. This compares to the decrease seen for protease inhibitors. Postpartum AUC0-24 in these two cases is in line with the mean steady-state AUC0-24 in adults previously described in the literature. They suggested that the lower exposure during pregnancy might be driven by a shorter rilpivirine half-life – but accurate measurement of this under steady-state conditions is difficult.

They explained that target rilpivirine trough concentration, derived from phase III studies is 0.04 mg/L. In both cases, the Ctrough concentrations in the third trimester and the maternal sample at delivery were 0.04mg/L or less, indicating subtherapeutic levels during pregnancy.

Despite the low concentration, no vertical transmission of HIV was reported, but this needs to be confirmed with longer follow up of the infants.

The investigators noted that a limitation with these case studies is that no unbound rilpivirine concentrations were determined. Lower protein binding during pregnancy can compensate for lower total concentrations. They did not report any major safety issues in these two cases.

They recommended therapeutic drug monitoring for rilpivirine during pregnancy.

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BASIC SCIENCE AND CURE RESEARCH

HIV rebounds in Boston stem cell transplant recipients

Richard Jefferys, TAG

On 5th December 213, at a scientific conference in Miami, Timothy Henrich from Brigham and Women's Hospital in Massachusetts, shared the disappointing news that HIV viral load had rebounded to detectable levels in two individuals who had previously undergone stem cell transplantation and later discontinued HIV treatment. [1]

This lead to restarting of antiretroviral therapy (ART)—in one case in August of this year, in the other more recently after eight months off treatment.

In July 2012, Henrich first reported on two HIV positive individuals in the Boston area who had undergone stem cell transplants to treat cancers, and subsequently lost all detectable traces of virus reservoirs. [2] These case reports were later published in the Journal of Infectious Diseases. [3]

Both individuals were maintained on ART throughout the transplantation procedures and afterwards, so initially it was uncertain if the results represented a profound depletion of HIV reservoir levels or a cure of the infection.

Earlier this year Henrich presented short-term results after ART interruptions, drawing widespread attention because HIV levels remained undetectable (for seven and 15 weeks of follow up, respectively), prompting hope that a cure may have been achieved. [4]

The first response to these findings is concern for the two individuals involved. In the scientific context of the search for an HIV cure, the outcomes are sobering, but also have the potential to make a massive contribution to the research effort.

One immediate implication is that the use of stem cells from a donor lacking the CCR5 co-receptor may have been crucial to the case of Timothy Brown, who for now is the lone adult considered cured of HIV (he remains off ART with no viral rebound for over six years and counting).

Henrich's patients received stem cell transplants from donors with normal levels of CCR5, and there was speculation that perhaps other elements of the procedure could contribute to eliminating HIV (such as the immune-depleting conditioning regimens that are used, and/or the transient graft-versus-host disease that developed afterward).

The results also emphasise that a short-term absence of HIV rebound after stopping ART must be viewed cautiously and cannot be interpreted as evidence of a cure (Henrich was careful to stress this point when he described the initial lack of rebound earlier this year), and highlight the challenge of identifying trace amounts of HIV in the body that can fly beneath the radar of current technologies.

Further discussion of the cases and their implications for cure research can be expected at the Conference on Retroviruses and Opportunistic Infections (CROI), which takes place in Boston from 3-6 March, 2014. [5]

Source

TAG Basic Science Blog. HIV rebounds in Boston stem cell transplant recipients (06 Dec 2013).

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HEPATITIS

EASL update guidelines for treatment of hepatitis C

In December 2013, the European Association for the Study of the Liver issued revised clinical guidelines for management of hepatitis C. [1]

These Clinical Practice Guidelines (CPGs) are intended to assist physicians and other healthcare providers, as well as patients and other interested individuals, and replace the previous edition in 2011.

C O M M E N T

The guidelines note that the document only relates to use of treatment that were approved in Europe in November 2013.

A significant limitation is that the only two direct acting antivirals (DAAs) mentioned in the context of treatment are boceprevir and telaprevir.

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Sofosbuvir approved in the US and Europe for HCV genotypes 1-6

EMA and FDA press releases

On 17 January 2014, the EU approved sofosbuvir, a new oral treatment for chronic hepatitis C (CHC) in adults. This indication specifically includes use by people with HCV and HIV coinfection. [1]

Sofosbuvir is a once-daily (400 mg) oral nucleotide analogue polymerase inhibitor that needs to be used in combination with other antiviral drugs (ribavirin (RBV) and pegylated interferon alpha (peg-IFN) depending on hepatitis C (HCV) genotype.

This will allow shorter treatment durations and interferon-free combinations for some patients (see Table 1 and 2.

- Sofosbuvir monotherapy is not recommended.
- Treatment regimen and duration are dependent on both viral genotype and patient population
- Treatment response varies based on baseline host and viral factors.

Sofosbuvir was approved in the US on 6 December 2013.

Sofosbuvir is manufactured by Gilead Sciences and is marketed under the trade name Sovaldi.

For full details, see the EU and US Summary of Product Characteristics. [3, 4]

Table 1: EU recommended regimens in chronic HCV monoinfection and HCV/HIV-1 co-infection

Population	Treatment	Duration
Genotype 1, 4, 5 or 6	(i) sofosbuvir + PEG-IFN alfa + ribavirin (ii) sofosbuvir + ribavirin Only for use in patients ineligible or intolerant to peg-IFN	(i) 12 weeks (ii) 24 weeks
Genotype 2	sofosbuvir + ribavirin	12 weeks
Genotype 3	(i) sofosbuvir + PEG-IFN alfa + ribavirin (ii) sofosbuvir + ribavirin	12 weeks 24 weeks
Awaiting transplant	(i) sofosbuvir + peginterferon alfa + ribavirin	Until transplant

Table 2: FDA recommended regimens in HCV monoinfection and HCV/HIV-1 co-infection

Population	Treatment	Duration
Genotype 1 or 4	sofosbuvir + PEG-IFN alfa + ribavirin	12 weeks
Genotype 2	sofosbuvir + ribavirin	12 weeks
Genotype 3	sofosbuvir + ribavirin	24 weeks

Notes: See prescribing information for dosing recommendation for PEG-IFN for patients with genotype 1 or 4 CHC. Dose of ribavirin is weight-based (<75 kg = 1000 mg and ≥75 kg = 1200 mg). The daily dose of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤ 50 mL/min) require ribavirin dose reduction; refer to ribavirin prescribing information.

C O M M E N T

Better and more effective treatments could make hepatitis C curable for most people with just three months of oral medication. Whether this impacts the global burden of disease – and an estimated 185 million people have hepatitis C – will depend on access to treatment and this will be determined by the price.

Sofosbuvir in the US will cost $84,000 for a three-month course or roughly $1000 a day - and some people need six months. This has been the focus of much of the news coverage in the US, both from treatment activists and in mainstream reports. [5, 6, 7]

The price was apparently calculated, not based on research and development costs - or even acquisition costs (Gilead paid paid $11 billion to purchase Pharmasset in November 2011). [8] Instead, it is being justified on the potential savings to the healthcare system for future years of therapy, hospitalisations, transplants and other healthcare costs that will be avoided. This model is based on the assumption that everyone enters the healthcare system, but people also have the option to be excluded from care or to die beforehand. The model also depends on paying these estimated lifetime costs up-front now.

Premium pricing is no longer an acceptable model for bringing new drugs to market. Just as in HIV care, new HCV drugs should be matched to current treatment costs. The premium should come from greater use due to their better efficacy and tolerability. If the actual costs are cheaper then treatment costs should come down. The estimated manufacturing costs for sofosbuvir may be as little as a few hundred dollars. [9]

If the new direct acting antivirals (DAAs) in Europe are set at similar prices to sofosbuvir in the US this will result in treatment rationing and limit access in the UK to use as a salvage therapy for people who have to first fail pegylated interferon and ribavirin. Currently in the UK, only 3% of the estimated 230,000 people living with HCV are treated each year.

In the US, even if only one third of the 3-4 million people with HCV have health insurance, Gilead could largely recoup the acquisition costs if the price was $10,000.

This is an area where patient demand should drive the solution. At least for people with genotype 1, oral only treatment should rapidly become the standard of care. Profits need to be calculated from the broadest distribution and access.

Globally, access is just as urgently needed in lower and middle-income countries, accounting for 90% of people with living with HCV. Similar strategies to those that enabled global access to ARVs need to be developed, including working with generic manufacturers and collaborations such as UNITAID and the Patent Pool.

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Simeprevir approved in the US

FDA news release

On 22 November 2013, the US FDA approved simeprevir 150 mg capsules for the treatment of chronic hepatitis C (CHC) infection.

Approval is based on use as a component of a combination antiviral treatment regimen with peginterferon alfa and ribavirin.

Simeprevir is a hepatitis C virus (HCV) NS3/4A protease inhibitor.

- Simeprevir must not be used as monotherapy.
- Simeprevir efficacy in combination with peginterferon alfa and ribavirin is influenced by baseline host and viral factors.
- Simeprevir efficacy in combination with peginterferon alfa and ribavirin is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with hepatitis C virus (HCV) genotype 1a without the Q80K polymorphism. Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.

Simeprevir is manufactured by Janssen Pharmaceuticals and is marketed under the trade name Olysio.

For full details, see the US Summary of Product Characteristics. [2]

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1. FDA press release. Olysio (simeprevir) for the treatment of chronic hepatitis C in combination antiviral treatment. (22 November 2013). (Includes Reduced version of the simeprevir SPC).
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2. Simeprevir Summary of Product Characteristics (US).
   http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s000lbledt.pdf

Fair Pricing Coalition criticises cost of new HCV drugs

The FPC issued this press statement following the announcement of the price of sofosfuvir in the US.

Press statement

The Fair Pricing Coalition (FPC) today condemned Gilead Sciences for the price set for its direct acting antiviral (DAA) sofosbuvir (Sovaldi), a once-daily, first-in-class nucleotide polymerase inhibitor approved by the U.S. Food and Drug Administration on December 6, 2013, for the treatment of chronic hepatitis C, including those co-infected with HIV.

While FPC believes that all hepatitis C virus (HCV) drugs are priced too high, the coalition of HIV and viral hepatitis treatment activists is especially dismayed by the wholesale acquisition cost (WAC) of $84,000 for a 12-week course of sofosbuvir. For comparison purposes, the FPC notes the 12-week WAC for the recently approved NS3/4A protease inhibitor simeprevir (Olysio) is $66,360.

“Sofosbuvir is a very safe and highly effective drug that will significantly shorten HCV therapy and either reduce or eliminate the need for injected pegylated interferon,” explained FPC Co-Chair Lynda Dee. “However, this does not give Gilead unconscionable pricing carte blanche, particularly when considering that sofosbuvir still needs to be combined with ribavirin for the treatment of HCV genotype 2 for 12 weeks or genotype 3 for 24 weeks. Twelve weeks of therapy with sofosbuvir plus both pegylated interferon and ribavirin is required for the treatment of HCV genotype 1, the most common genotype in the US, and HCV genotype 4.”

The WAC for 12 weeks of HCV treatment with pegylated interferon and ribavirin is approximately $9,000, resulting in a combined WAC of $93,000 for a sofosbuvir -inclusive regimen to effectively treat a single person living with HCV genotypes 1 or 4. To treat HCV genotype 3, 24 weeks of sofosbuvir plus ribavirin is required, resulting in a sofosbuvir WAC of $168,000.

Price Portends an Ominous Future

“Gilead has set the bar dangerously high as other companies determine prices for similar hepatitis C drugs as they enter the market,” Dee said. The effectiveness of sofosbuvir as a component of future pegylated interferon-free regimens for the treatment of HCV will ultimately depend on co-administration with other DAAs currently in development, and are anticipated to come with their own high price tags.

“Sofosbuvir is expected to transform the curative landscape for hundreds of thousands of people living with hepatitis C in the U.S. who require therapy or responded poorly to previous treatment,” said Lorren Sandt, FPC Co-Chair. “Yet the high price will result in significant barriers to treatment access, particularly in limited and fixed-budget programmes, such as Medicare and state Medicaid programmes, AIDS Drug Assistance Programmes, the Veterans Administration, and in correctional systems.”

The high price may also lead to access challenges imposed by private insurance plans and Qualified Health Plans in the new Affordable Care Act (ACA) Marketplaces, notably those with high co-payment and other out-of-pocket requirements.

“There may be reluctance to add sofosbuvir to formularies quickly and payers may force people living with HCV to engage in step therapy in which they are first required to try less expensive options that are less effective,” Sandt added. “These options take longer to complete and are associated with serious side effects, which present a serious impediment to adherence and, ultimately, to being cured of hepatitis C.”

Concessions where they count

Although Gilead refused FPC's demand for fair pricing of sofosbuvir, the company has agreed to all FPC requests for concessions regarding sofosbuvir access programmes. These include:

- The SupportPath (www.mysupportpath.com) patient assistance programme (PAP), with a $100,000 maximum income allowance for a household of three and 500% of the federal poverty level (FPL) eligibility criteria for larger households.
- The SupportPath sofosbuvir co-pay coupon programme will provide co-pay assistance for eligible patients with private insurance, including ACA Marketplace exchange patients, who need assistance paying for out-of-pocket medication costs. Most patients will pay no more than $5 per co-pay. Co-pay assistance of up to 20% ($16,000) of the WAC price for sofosbuvir can also be applied toward prescription deductibles and co-insurance obligations.
- Gilead has made a contribution to the Patient Access Network (PAN) for co-pay assistance for Medicare Part D clients and has initiated an emergency sofosbuvir supply programme for patients that may lose their prescriptions.
- Gilead has agreed to ensure access to its PAP and co-pay assistance programs for AIDS Drug Assistance Programme (ADAP) patients who are co-infected with HIV, even in states with ADAP programmes that will not include sofosbuvir on their formularies.

The FPC urges Gilead to widely disseminate the details of its SupportPath PAP and co-pay coupon programme, which must include providing written SupportPath information for prescribers, prominently featured SupportPath information in its professional and direct-to-consumer advertisements, and clear links to www.mysupportpath.com via the Gilead and sofosbuvir websites.

Source

FPC press statement. Fair Pricing Coalition condemns Gilead Sciences on the high price of new hepatitis C drug Sovaldi, and urges rapid and wide dissemination of support programme details for uninsured and underinsured people living with hepatitis C. (11 December 2013).

http://fairpricingcoalition.org/2013/12/11/fair-pricing-coalition-condemns-gilead-sciences

Boehringer Ingelheim stops development of deleobuvir for HCV

On 23 January 2014, the community website HIVandhepatitis.com reported that Boehringer Ingelheim will stop development its non-nucleoside hepatitis C virus polymerase inhibitor deleobuvir (formerly BI 207127). [1]

The decision was made based on blinded results from the Phase 3 HCVerso 1 and 2 trials, which evaluated a regimen consisting of deleobuvir, the HCV protease inhibitor faldaprevir (formerly BI 201335), and ribavirin.

The company statement reported "a higher rate of premature discontinuations suggesting a lower efficacy rate compared to other interferon-free therapies in development. [...] Boehringer Ingelheim has therefore concluded that the expected therapeutic value of the deleobuvir-containing regimen would not justify further development."

The company will move forward with the submission process for faldaprevir, which has shown promising results in combination with pegylated interferon and ribavirin in the STARTVerso trials.

Sources: HIV and Hepatitis.com. Boehringer Ingelheim halts testing of deleobuvir Hepatitis C regimens. (23 January 2014).
http://www.hivandhepatitis.com/hcv-treatment/experimental-hcv-drugs/4491

Boehringer Ingelheim announcement. January 17, 2013.

TUBERCULOSIS

EMA recommends conditional approval of bedaquiline for drug resistant TB with orphan drug status

EMA press statement

On 20 December 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended granting a conditional marketing authorisation for bedaquiline (Sirturo) for use as part of a combination therapy for pulmonary multidrug-resistant tuberculosis in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

In the European Union, tuberculosis is an orphan indication and was estimated in 2011 to occur in 2.3 out of 10,000 people. Multidrug-resistant tuberculosis is defined as tuberculosis that is resistant to at least isoniazid and rifampicin, which are two major anti-tuberculosis medicines used in standard treatment. Approximately 450,000 cases of multidrug-resistant tuberculosis occur globally every year, which corresponds to approximately 5% of the world's annual burden of tuberculosis.

In recent years, the burden of tuberculosis resistant to first-line therapy has increased rapidly in the absence of new treatment options. Multidrug-resistant tuberculosis is associated with a high mortality rate and poses a significant public-health threat as individuals infected with drug-resistant strains are unable to receive adequate treatment and can potentially spread their infection.

Sirturo is the first representative of a new class of medicines against mycobacteria. The Committee considered that Sirturo could contribute to responding to the high unmet medical need for new treatment options for pulmonary multidrug-resistant tuberculosis. It recommended granting conditional marketing authorisation because, although the data supplied by the applicant show that the medicine's benefits outweigh its risks, the data are not yet comprehensive. Therefore, additional studies on the use of Sirturo should be conducted.

Sirturo is the third positive opinion recently granted by the CHMP for a medicine to be used in the treatment of multidrug-resistant tuberculosis, after the November 2013 recommendations for delaminid (Deltyba), also for a conditional approval, and Para-aminosalicylic acid Lucane.

Bedaquiline is manufactured by Janssen-Cilag and was designated as an orphan medicinal product.

Conditional approval allows the marketing authorisation of medicines that target areas of unmet medical need before comprehensive data sets are available, in order to speed up access to much needed new medicines.

Source: EMA press statement. European Medicines Agency recommends approval of a new medicine for multidrug-resistant tuberculosis. (20 December 2013). http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/12/news_detail_001999.jsp&mid=WC0b01ac058004d5c1

ON THE WEB

Online journals

Comparative efficacy of lamivudine and emtricitabine: a systematic review and meta-analysis of randomised trials

Nathan Ford et al. November 11, 2013DOI: 10.1371/journal.pone.0079981

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0079981

This review of 12 randomised studies in 2251 patients concluded that from the perspective of treatment guidelines, 3TC and FTC are clinically equivalent, although this included limited data on drug resistance and excluded studies where baseline viral load was >100,000 copies/mL.

Antiretroviral treatment French guidelines 2013: economics influencing science

Raffi F and Reynes J. J. Antimicrob. Chemother. (2014) doi: 10.1093/jac/dkt533 First published online: January 16, 2014.

http://jac.oxfordjournals.org/content/early/2014/01/16/jac.dkt533.full.pdf+html

Community publications and reports:

Anal cancer in people with HIV

Mark, Mascoloni, RITA, Winter 2013

In this edition of the community publication Research Initiative, Treatment Action (RITA) Mark Mascolini comprehensively reviews the issue of anal cancer in people with HIV and includes an interview with leading researcher Joel Palefsky.

- Soaring anal cancer incidence in the combination ART era
- Risk factors for anal lesions and anal cancer in people with HIV
- Anal cancer screening approach awaits more data and clinical expertise
- HPV vaccination for people with HIV—who, when, why?
- Tackling tough questions on anal cancer incidence, screening, and HPV vaccination - an interview with Joel Palefsky, MD.

http://www.centerforaids.org/pdfs/rita1213.pdf

Epidemiology data sets for US epidemic

Updated slidesets now available online.

http://www.cdc.gov/hiv/library/slideSets/index.html

FUTURE MEETINGS

Conference listing 2014

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.

Conference on Retroviruses and Opportunistic Infections (CROI) 2014

3-6 March 2014, Boston

http://www.croi2014.org

12th European Meeting on HIV & Hepatitis - Treatment Strategies & Drug Resistance

26 - 28 March 2014, Barcelona, Spain

http://www.virology-education.com

Third Joint Conference of BHIVA with BASHH (2014)

1-4 April 2014, Liverpool

http://www.bhiva.org/AnnualConference2014.aspx

2nd International Workshop on the Optimal Use of DAA's in Advanced Liver Disease and Transplantation

8 April 2014, London, UK

http://www.virology-education.com

15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy

19 May 2014 - 21 May 2014, Washington DC, USA

http://www.virology-education.com

International Workshop on Antiviral Drug Resistance

3-7June 2014, Berlin, Germany

http://www.informedhorizons.com/resistance2014

10th HIV and Hepatitis Coinfection Workshop

12 - 13 June 2014, Paris, France

http://www.virology-education.com

20th IAS World AIDS Conference

20-25 July 2014, Melbourne, Australia

http://www.aids2014.org

12th International Congress on Drug Therapy in HIV Infection

2-6 November 2014, Glasgow

http://hivglasgow.org

JOB VACANCIES

i-Base currently has two vacancies.

Treatment advocate

i-Base currently have a vacancy for a treatment advocate (full-time or part-time) to help with the treatment information services.

Specifications include:

- A good knowledge and experience of HIV treatment issues.
- Confidence in researching treatment questions from medical publications and treatment guidelines.
- Good written and spoken English – including being able to explain and discuss medical issues using everyday language.
- The ability to work carefully with an attention to detail.
- The ability to problem-solve.
- Being computer and web literate, including standard programmes.
- Motivation and ability to work without direct supervision.
- A committment to understanding current treatment issues.

Some training will also be provided, but the successful applicant will already have a good working knowledge of HIV treatment issues.

This is an excellent opportunity for someone who already has a good understanding and who wants to develop their skills further to help other people.

Applications are particularly welcomed from HIV positive people but HIV positive status is not a requirement.

If you are interested in this position, please email an introductory letter and examples of written work to: jobs@i-base.org.uk

i-Base is in able to pay a competative salary for the right person. Salary is by negotiation depending on experience.

For further details and an application please see online:

http://i-base.info/about-us/volunteering-and-staff-vacancies

Medical writer

We are currently looking for a treatment advocate/writer to work on a freelance basis writing for HIV Treatment Bulletin.

If you are interested in this position, please email an introductory letter and examples of written work to: jobs@i-base.org.uk

Equal opportunities

HIV i-Base is an equal opportunities employer. We welcome applications from people living with HIV.

For further details on both positions please see the addtional information on the i-Base website:

http://i-base.info/about-us/volunteering-and-staff-vacancies/

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website: updates for PDA access

The i-Base website is designed 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.

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

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.

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.

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

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

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 580 members from over 120 organisations.

http://www.ukcab.net

Phoneline and information services

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

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

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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http://www.i-Base.info

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From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

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