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EDITORIAL

For the last issue of HTB for 2013, we lead with a report about paediatric TB care from the 44th Lung Conference held in Paris.

And reports from the recent EACS conference in Brussels include promising data on new antiretrovirals, including on dolutegravir, which this month received a positive opinion for EU approval.

As we highlighted in the last issue of HTB when reporting US approval (where dolutegravir is ten times more expensive than gold), the price set in the UK will determine whether this promising new drug becomes a focus for treatment access issues here.

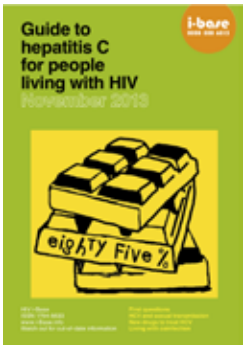
Globally, treatment access news includes optimistic reports that many governments, including the UK and the US, will increase their financial support of the Global Fund for 2014-2016.

It also includes a more sobering snapshot of treatment access in South Africa, where ARV stockouts remain routine in this country with over two million people on treatment.

As is customary at this time of year, we would like to thank our readers, contributors and supporters for your encouragement and help through the year and to close with the best seasonal wishes for happy and peaceful holidays over the New Year.

HTB SUPPLEMENT:

Guide to HIV and HCV coinfection (November 2013)



This major revision has been updated to include:

- The development of new directly acting HCV drugs, recognising the importance of the HCV pipeline and how rapidly this is likely to change treatment options.
- The move to use FibroScan instead of biopsy, especially in the UK.
- The ongoing issue of sexual transmission of HCV in the UK, especially among HIV positive gay men.
- A section on areas of controversy for areas where ongoing research may change management in the near future.

As with all i-Base publications, the guide is free, including in bulk to clinics in the UK. Please order online.

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CONFERENCE REPORTS

44th Union World Conference on Lung Health

30 October - 3 November 2013, Paris

Introduction

The 44th Union Conference on Lung Health was held this year in Paris from 30 October - 3 November 2013.

This is the largest annual meeting focusing on lung health (with a strong emphasis on TB) as this relates to low- and middle-income countries and populations. Although there are only a limited number of presentations relating to HIV, the issue of HIV and TB coinfection is always covered at this meeting and the following report focuses on TB treatment in children.

Abstracts and webcasts from the meeting are available free online.

http://www.worldlunghealth.org/conf2013/

Webcasts

http://slideonline.eu/recordings/2013/union2013/

Abstract book (PDF download)

http://www.worldlunghealth.org/conf2013/images/1_Paris2013/Forms/ABSTRACT_BOOK_2013_Web.pdf (PDF)

Preventing and treating TB in children – more baby steps

Polly Clayden, HIV i-Base

Children with tuberculosis (TB) are usually not infectious, so they are rarely considered to be a public health priority.

Where children's needs are not neglected, prevention and treatment practice is mostly guided by findings extrapolated from adult research, so might not always be appropriate.

Pharmacokinetics (PK) of all drugs can vary hugely between babies, children and adults because of physiological differences, immaturity of enzyme systems and other mechanisms involved in drug metabolism. There is also great variability across age groups.

For example, drugs given to pre- and full-term neonates tend to have considerably longer half-life than that of adults. Between two and six months of age this difference disappears. Conversely, after this period, half-life in children can be shorter than in for specific drugs and pathways.

Children with TB have a wider spectrum of disease than adults. Although a larger proportion of young children below three years old have disseminated TB, primary childhood TB is typically more benign than that of adults. Adult forms of TB only emerge during adolescence. Like adults, children can be infected with or develop multi-drug resistant (MDR)TB.

As with HIV, young children who are unable to swallow tablets need child friendly formulations. Ideally – and where there are sufficient data to guide dosing – these should be in solid fixed dose combination (FDC) forms that are dispersible in liquids and can facilitate dosing across different weight bands.

Currently the only fixed dose formulations available for first-line TB treatment in children use old doses and there are scant data for second-line TB drugs. There is also data very little to guide use of even first-line ones in neonates and infants with low birth weight.

Several abstract and symposium sessions at the 44th Union Conference on Lung Health, and ongoing research first presented at this meeting last year, showed glimmers of progress in prevention and treatment of TB in children.

New first-line formulations

The doses of first-line TB drugs in children have mostly been scaled down from those of adults, using milligram per kilogram (mg/kg) ratios. The current first-line treatment for drug-sensitive TB is a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol.

In 2010 the WHO revised its dosing recommendations for first-line drugs for children, after several PK studies found suboptimal levels with previously recommended doses. [1] See Table 1. Currently there are no quality-assured medicines available in the formulations recommended by WHO to treat children with TB. This means that children are treated with far-from-simple regimens of FDCs formulated with previous ratios, and a mix of divided and single tablets to make up the dosing shortfall.

Table 1. WHO-suggested simplified table for FDCs for TB treatment in children <25kg

Weight bands	Intensive phase		Continuation phase
	75R /50H /150Z	100 E	75R /50H
4.0 – 7.9 kg	1 tablet	1 tablet	1 tablet
8.0 – 11.9 kg	2	2	2
12.0 – 15.9 kg	3	3	3
16.0 – 24.0 kg	4	4	4

Note: Children weighing 4.0-7.9, 8.0-11.9, 12.0-15.9 and 16.0-24.0kg should receive daily doses of 75, 150, 225 and 300mg of rifampicin (R); 150, 300, 450 and 600mg of pyrazinamide (Z); and 50, 100, 150 and 200 mg of isoniazid (H), respectively.

New formulations for first-line treatment are an urgent priority, so news during the conference that TB Alliance – a not for profit development partnership – has entered into collaboration with Svizera Europe to develop and distribute new dispersible FDCs with the recommended doses is welcome. [2] The FDC tablets produced with the old doses by this company are approximately 30% smaller than those from other brands and this is important for children.

A proposed trial – SHINE (SHorter treatment for mINimal TB in children) – sponsored by the UK Medical Research Council (MRC), in collaboration with South African, Zambian, Ugandan and Indian researchers, will use these new FDCs. [3] The principal research question for this trial is whether the standard 6-month regimen can be reduced with similar efficacy to 4 months in HIV positive and negative children with minimal TB, using revised dosing guidelines.

Other key questions are: Do the new doses, given as new FDCs and prescribed according to weight bands, result in appropriate drug exposures compared to historical paediatric and adult PK data and to dosing with single products? For children coinfected with HIV, can currently recommended adjusted strategies and doses of antiretrovirals appropriately overcome the effect of rifampicin at higher doses?

The trial is planned to start in 2014.

PK for second-line dosing

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

At the Union meeting last year Annekke Hessling from the Department of Paediatrics and Child Health, University of Stellenbosch, Cape Town, described a large ongoing study to characterise PK and toxicity of second-line TB drugs for treatment and prevention of drug resistant TB in HIV positive and negative children, by age and HIV status. [4] She presented preliminary data for three second-line TB drugs: ethionamide, amikacin and ofloxacin.

This ambitious study will be running over the next five years with an enrollment target of about 300 children. Age matched HIV positive children not on TB treatment will be enrolled as controls (42 receiving efavirenz and 22 lopinavir/r). The drugs under evaluation are: ethionamide, terizidone, ofloxacin, levofloxacin, moxifloxacin, amikacin, high dose isoniazid (INH), PAS, linezolid and capreomycin (the group will be looking at delamanid and bedaquiline and novel TB drugs as they become available for children).

The study includes intensive PK sampling, clinical follow up until treatment completion for children with active TB, cross sectional PK data from children receiving prophylaxis and toxicity monitoring.

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

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

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

The PK evaluation for ethionamide, revealed HIV negative children with higher C-max in the 0-2 years age group than the other two groups (median 7.66 vs approximately 5 ug/mL) but this was not significant; T-max peaked sooner and achieved higher target levels earlier (mean 1.80 hours vs 3.15 in the oldest age group, p=0.001), although overall exposure (AUC) was similar across age groups. HIV positive children had lower levels than HIV negative ones (median 4.86 vs 6.37 ug.h/mL, p=0.051). Dr Hessling noted that a larger sample size would probably show lower AUC as well. She described the finding that younger children peaked higher and earlier as “quite surprising” as the only other study that has looked at ethionamide PK in children by age group showed the opposite, she suggested that this might be due to crushing the tablets. The lower levels seen with HIV positive children compared to negative is consistent with previous observations. Although adult targets are unclear, the MIC achieved in children was similar or above that of adults.

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

Fluoroquinolone antibiotics are potent anti-TB medications. They are the most important drugs in current treatment regimens for MDR TB and are likely to be key components of future regimens for the treatment and prophylaxis of drug-susceptible and DR-TB in adults and children.

Concerns about arthropathy in juvenile animal studies have historically limited the use of fluoroquinolones in children. Other potential toxicity concerns are QT interval prolongation and CNS toxicity. There are limited data on their PK in children with TB disease and latent TB infection. There is particularly limited paediatric data on fluoroquinolone safety and tolerability for prolonged courses required for DR-TB treatment (especially about QT prolongation).

Levofloxacin MIC is approximately half of that of ofloxacin. Oral bioavailability is good for both drugs: 85-95% ofloxacin and 99% levofloxacin. Elimination is primarily unchanged in urine.

Because the newer fluoroquinalones have improved efficacy, South African guidelines recommend moxifloxicin in children above and levofloxacin in children below 8 years of age for treatment and prevention of MDR-TB.

Target concentrations for fluoroquinalones are: AUC0-24/MIC primary PD index (target 100), Cmax/MIC (target 8-10) and Cmax (target 8-12 ug/mL).

Dr Hessling reported that giving ofloxacin achieved higher Cmax in the youngest versus oldest groups (median 9.4 vs 7.16 ug/mL), higher and earlier mean peak in Tmax (1.42 vs 2.60 hours, p=0.39) and similar overall exposure. This drug is given routinely as prophylaxis for MDR-TB and levels were higher in this group but this might be an age effect as it is given only to younger children. There was no difference by HIV status and adult targets were achieved.

At this years Union meeting, Anthony Garcia-Prats from the same research group showed more data from the study for ofloxacin in a symposium session: MDR TB in children and adolescent issues. [4]

This analysis was in 85 children, of which 55 had MDR-TB disease and 30 were receiving MDR prophylaxis. In the disease group there were approximately 30% of children in each of the 0-2 and 2-5 year old age groups and 40% in the 6-15 years group. Almost 75% of children in the prophylaxis group were 2-5 years and the remainder 0-2. Almost 75% of children in the disease group had pulmonary TB and the rest had extra pulmonary or both; 20% of the TB disease group had HIV. There were a substantial amount of underweight and stunted children in both groups but very little acute malnourishment.

The youngest age groups had a higher mean C-max of 10.4 ug/mL and this occurred earlier at 1.3 hours, these values were 8.5 and 8.1 ug/mL and 1.8 and 2.5 hours in the 2-5 and 5-16 age groups respectively, p<0.001. There were no differences in AUC by age. The median t1/2 was shorter in the youngest age group, 3.2 ug.h/mL vs 3.5 in children 5 years and older, p=0.001.

There were no differences in PK parameters by HIV status or weight for age Z-score (WAZ). There was a trend towards higher Cmax in children who received crushed tablets; it also occurred slightly earlier and this was significant, p=0.03.

The Cmaxs reported in this study compared favourably to those in adults receiving an 800 mg dose, but elimination was twice as rapid and AUC less than half.

The investigators used these PK data to generate pharmacodynamic indices with assumed ofloxacin MIC of 1.0 and 2.0. With an MIC of 1.0 the Cmax/MIC would be within the proposed targets for most children but below with an MIC of 2.0; AUC/MIC was far below proposed targets. See Table 2.

Table 2. Estimated pharmocodynamic parameters for ofloxacin

	Oflox MIC 1.0	Oflox MIC 2.0	Proposed targets
Mean Cmax/MIC (SD)	8.97 (2.33)	4.48 (1.17)	>8-10
Mean AUC/MIC (SD)	44.17 (10.3)	22.1 (5.17)	>100

Dr Garcia-Prats noted that despite low AUCs, 92% of children had successful outcomes with MDR-TB treatment in their cohort with this dose of ofloxacin.

Safety and tolerability analyses from 44 children in the disease group receiving 6 to 8 drug regimens with a median time of 7.2 months follow up revealed no ofloxacin-related grade 3 or 4 events, or discontinuations. There was no arthralgia or arthritis.

Stephanie Thee from the Stellenbosch group showed PK data from a cross over study of ofloxacin and levofloxacin in an oral abstract session: Novel concept in the diagnosis and treatment of tuberculosis and children. [5]

The study aims were to investigate the PK and characterise the cardiac effects of ofloxacin and levofloxacin in HIV positive and negative children aged 0-8 years.

The study is nested in the ongoing larger MDR-PK study with the same inclusion/exclusion criteria as described above. It was a cross over design with intensive PK evaluation (T0, 1, 2, 4, 6, 8) on first flouroquinalone at steady state (2-8 weeks) followed by switch with intensive PK on second flouroquinalone at steady state (1-8 weeks).

Ofloxacin was dosed at 20 mg/kg and levofloxacin at 15 mg/kg, using crushed or whole tablets, given on an empty stomach.

Cardiotoxicity was assessed with 12-lead ECGs, baseline and during PK sampling at 3 hours post dose.

A total of 23 children were included in the analysis; 12 were being treated for MDR disease and 11 were receiving prophylaxis for MDR prevention. A third of the children being treated were in the 0-2, 2-6 and >6 year old age groups and 5 children age 0-2 and 6 children aged 2-6 were receiving flouroquinalones for MDR prevention. Four children in the disease group were HIV positive and all were over 6 years old. Five in the disease group and one in the prevention group were malnourished (WAZ <-2).

Table 3. PK of ofloxacin and levofloxacin in 23 children

Parameter	Ofloxacin	Levofloxacin
Cmax (ug/mL)	9.67 (7.09-10.90)	6.71 (4.69-8.06)
Tmax (h)	1.61 (0.72)	1.44 (0.51)
kel (1/h)	0.22 (0.19-0.25)	0.22 (0.20-0.26)
t1/2	3.2 (2.84-3.57)	3.18 (2.68-3.51)
AUC0-8 (ug*h/mL)	43.34 (36.73-54.46)	28.29 (23.81-36.39)

Note: All parameters median and IQR except Tmax mean and SD.
Results available from 22 patients for ofloxacin kel and T1/2.

Table 4. Ofloxacin by clinical characteristics

	Cmax (ug/mL)			T1/2 (h)			AUC0-8 (ug*h/mL)		
Sub group	n	Median (IQR)	p-value	n	Median (IQR)	p-value	n	Median (IQR)	p-value
MDR disease	11	10.20 (7.51-10.90)		10	3.13 (2.89-3.44)		11	46.53 (38.88-54.98)	
MDR prevention	11	8.88 (7.05-12.70)	0.77	11	3.18 (2.64-3.61)	0.89	11	43.34 (29.75-50.89)	0.53
Age									
0-2 years	9	10.90 (10.20-12.70)		9	2.91 (2.61-3.26)		9	46.53 (43.05-54.46)	
2-6 years	9	8.78 (5.39-9.82)		9	3.21 (3.00-3.61)		9	44.34 (28.99-48.76)	
>6 years	4	7.69 (6.21-9.39)	0.02	3	3.44 (2.89-3.57)	0.29	4	39.01 (33.47-48.06)	0.54
HIV status									
HIV positive	4	7.69 (6.21-9.39)		3	3.44 (2.89-3.57)			39.01 (33.47-48.06)	
HIV negative	18	9.86 (8.09-11.57)	0.25	18	3.16 (2.63-3.34)	0.48		44.67 (36.73-54.46)	0.55
Weight for age Z-score (WAZ)									
≥ -2	18	10.05 (8.78-11.57)		18	3.20 (2.89-3.44)			45.77 (39.12-54.98)	
< -2	4	6.63 (5.15-7.98)	0.04	4	2.64 (2.56-3.57)	0.42		29.37 (28.52-34.45)	0.03

Table 5. Levofloxacin by clinical characteristics

	Cmax (ug/mL)			T1/2 (h)			AUC0-8 (ug*h/mL)		
Sub group	n	Median (IQR)	p-value	n	Median (IQR)	p-value	n	Median (IQR)	p-value
MDR disease	11	7.00 (4.69-8.06)		11	3.24 (3.01-3.99)		11	32.50 (24.41-38.83)	
MDR prevention	11	6.32 (4.63-8.17)	0.53	11	2.98 (2.64-3.51)	0.31	11	29.89 (21.07-32.75)	0.34
Age									
0-2 years	9	7.00 (6.32-8.06)		9	2.79 (2.62-3.14)		9	29.89 (24.05-36.39)	
2-6 years	9	6.86 (4.69-7.51)		9	3.22 (2.98-4.24)		9	31.69 (23.81-33.11)	
>6 years	4	4.98 (4.52-7.48)	0.40	4	3.37 (3.12-4.01)	0.18	4	27.49 (24.73-34.03)	0.91
HIV status									
HIV positive	4	4.98 (4.52-7.48)		4	3.37 (3.12-4.01)		4	27.49 (24.73-34.03)	
HIV negative	18	6.88 (5.36-8.06)	0.39	18	3.09 (2.64-3.51)	0.23	18	31.38 (24.41-36.39)	0.67
Weight for age Z-score (WAZ)									
≥ -2	17	6.86 (4.69-8.06)		17	3.14 (2.78-3.51)		17	45.77 (39.12-54.98)	
< -2	5	6.71 (5.38-7.12)	0.91	5	3.23 (2.68-3.51)	0.97	5	29.24 (25.75-32.50)	0.91

Table 6. Pharmacodynamic parameters using published MICs of M.tb oxofloxacin and levofloxacin in children (n=23)

	Oxofloxacin 20mg/kg		Levofloxacin 15 mg/kg		p-value
MIC for M.tb/published (ug/mL)	2.0	1.0	1.0	0.5	
Mean AUC0-inf/MIC (SD) (target 100)	23.13 (7.2)	46.3 (14.3)	32.6 (9.2)	65.3 (18.4)	p<0.001
Mean Cmax/MIC (SD) (target 8-10)	4.5 (1.5)	9.6 (3.1)	6.5 (2.0)	13.1 (4.0)	p<0.001

Dr Thee showed very detailed analyses of PK parameters by subgroups – see tables 3 to 6. For ofloxacin there was no difference between the disease and prevention groups. Cmax was higher in the older children and AUC similar. There was no difference by HIV status but malnourished children had a much lower Cmax and AUC than those who were not.

None of the comparisons for levofloxacin were statistically significant.

Following a dose of ofloxacin 20 mg/kg and levofloxacin 15 mg/kg drug levels in children are less than half those of adults receiving standard oral doses of 800 mg and 750 mg respectively. PD indices favoured levofloxacin over ofloxacin. In Dr Garcia Prats' presentation he suggested that 15-20 mg levofloxacin might be more appropriate and the group are currently looking at this dose.

No QTc prolongation (defined as QTc >450 ms) was reported in this study; mean QTc was 361 and 369 ms for ofloxacin and levofloxacin respectively.

Dr Thee noted that more data are urgently needed on fluoroquinalones in children in combination with optimised background regimen as well as novel anti tuberculosis drugs. The large PK study of anti-TB drugs for treatment and prevention of MDR-TB is ongoing and will result in a very important data set.

Three drug MDR-TB prevention

In the MDR symposium, James Seddon from Imperial College, London presented data on effectiveness, tolerability and adherence to a 3-drug MDR preventive therapy regimen on behalf of the Stellenbosch group and investigators from the UK. [6]

Once again, there are limited data to guide the management of children exposed to MDR. This study looked at the tolerability and toxicity of a standard preventive therapy regimen, given to children exposed to infectious MDR-TB, and explored the risk factors for poor outcome.

It was a prospective cohort study conducted in the Western Cape. Children <5 years old, or HIV positive children <15, were recruited from May 2010 through April 2011 if they had been exposed to someone with ofloxacin-susceptible MDR-TB.

Children were given a preventive therapy regimen according to local guidance: ofloxacin, ethambutol and high-dose isoniazid for six months. Adherence and adverse events were evaluated; poor outcome was defined as incident TB or death from any cause. The children were followed for 1-2 years.

The study included 186 children with a median age of 34 months (IQR 14–47). Nine children (5.0%) out of 179 tested for HIV, were positive; 73/183 (40%) were TST positive.

The majority (75.8%) of children had good adherence. Only 6 (3.2%) children developed Grade 3 adverse events. Of these, 3 events were associated with inadvertent overdosing of ofloxacin. Very few side effects were associated with muscle, joint or bone pain. No children had their regimen changed or modified. One child (0.5%) died – thought to be sudden infant death syndrome – and 6 (3.2%) developed incident tuberculosis during 219 patient-years of observation.

The investigators observed 31.9 (95% CI 12.8-65.9) per 1000 patient years: poor outcome was associated with: young age <1 year, HIV-positive status, multiple source cases and poor adherence. See Table 7.

Table 7. Outcome of children on 3-drug MDR-TB prevention therapy

	Sub-group	Events	Years of observation	Incidence (95% CI)	Rate ratio	p-value
Age	>12 months	2	175.5	11.4 (1.4-41.1)	1	-
	0-12 months	5	43.5	114.9 (37.3-268.2)	10.1 (1.65-105.8)	0.009
Source cases	Single	2	152.4	13.1 (3.28-52.5)	1	-
	Multiple	5	56.4	88.6 (36.9-213.0)	6.75 (1.11-70.4)	0.036
HIV status	Negative	5	201.5	24.8 (8.4-579.1)	1	-
	Positive	2	7.6	263.8 (31.9-950.6)	10.6 (1.01-64.4)	0.049
Adherence	Good	2	164.3	12.2 (1.5-44.0)	1	-
	Poor	5	54.8	91.3 (29.6-212.9)	7.5 (1.23-78.7)	0.026

This is the largest observational study of children on 3-drug preventive therapy regimens – Dr Seddon noted that an RCT is needed. He concluded that the regimen was well tolerated and few children who were adherent to therapy developed TB or died. He added that the provision of preventive therapy to vulnerable children following exposure to MDR-TB should be considered.

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

A novel approach for accelerating access to new TB drugs and regimens, in infants and young children, was presented at the Union meeting last year; this was discussed again in the MDR-TB symposium.

Researchers from the TB Alliance and the Stellenbosch group have been looking at ways to speed up access to new TB drugs and regimens in infants and young children. Stephen Murray presented the proposed framework for this evaluation.

It will soon be appropriate for the TB Alliance to begin trials in children for some of the drugs that they are currently studying in adults. Their approach is to enrol people who are sensitive to the drugs in the regimens being studied regardless of DS/MDR classification. The proposal would do the same in children.

TB trials with efficacy as the primary endpoint are not required for children as power would be prohibitive and at least similar efficacy to adults is assumed. Matching PK parameters to that in adults has proven to be safe and effective and regulators recognise that it is possible to extrapolate efficacy in children from adult data. But trials in children cannot begin until the adult dose has been established and safety and efficacy demonstrated in this population – the question is when is this?

The traditional approach to collecting PK and then safety data in children is sequentially in de-escalated age bands: 12-16, 6-12, 2-6 and 0-2 years. But experience in older children might not mitigate the risk in younger ones as differences are caused by changes in metabolism at different ages. Drugs to be used mainly by children are not developed in this way.

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

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

This approach could provide faster information for registration and evidently that both the FDA and EMA have indicated that they are open to considering it.

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Unless otherwise stated, references from the 44th Union Conference on Lung Health, 30 October - 3 November 2013, Paris.

See also the HTB report from last years Union meeting: Paediatric TB: glimpses of PK data and a potential new approach to drug development.
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CONFERENCE REPORTS

14th European AIDS Conference (EACS)

16-19 October 2013, Brussels

Introduction

The 14th European AIDS Conference (EACS) was held from 16-19 October 2013 in Brussels.

This marked the 25th anniversary of the European Clinical AIDS Society which organises these biennial meetings.

Access to the programme and abstracts this year uses a new web interface, which helpfully already includes access to PDF files for many of the posters.

http://www.eacsmobile.org/

Abstracts:
http://www.eacsmobile.org/libraryEntry/list

E posters:
http://www.abstractstosubmit.com/eacs2013/eposter

Webcasts (free registration required):
http://www.multiwebcast.com/eacs/2013/14th/listing

Articles in this issue include:

- Dolutegravir superior to darunavir/r at week 48 in open label treatment naïve study
- GSK744: 24-week results with oral integrase inhibitor planned for once-monthly injections
- Cenicriviroc: 48 week results compared to efavirenz
- Approaches to once-daily raltegravir: new formulation likely to require food
- DSMB stops boosted atazanavir monotherapy study due to virological failure

- Recreational drug use is common in HIV positive gay men and is extensive in a significant minority
- Osteoporosis triples risk of later fracture in 1000-person US HIV group
- Bone turnover marker changes early in ART predict bone loss after 96 week
- Low HDL cholesterol Is main lipid abnormality in HIV+/HIV- comparison
- Classic risk factors, but not HIV, linked to arterial stiffness in middle-aged

Dolutegravir superior to darunavir/r at week 48 in open label treatment naïve study

Simon Collins, HIV i-Base

A subgroup analysis from the phase 3 FLAMINGO study was presented by Bonaventura Clotet. [1]

This was a randomised open label study (n=242 in each arm) comparing once-daily dolutegravir to once-daily darunavir/ritonavir (800 mg/100 mg) plus investigator-selected choice of abacavir/3TC or tenofovir/FTC. Patients were stratified by baseline viral load >100,000 copies/mL and choice of background nucleosides. The primary endpoint was viral suppression < 50 copies/mL at week 48 by snapshot algorithm, with follow-up to 96 weeks. this was a non-inferiority study with –12% lower margin. The main analysis from this study was reported a few weeks earlier at the 54th ICAAC in Denver. [2]

Baseline characteristics included approximate median CD4 and viral load of 400 cells/mm^3 (with 10% starting <200 cells/mm^3) and 4.5 log copies/mL (with 25% starting >100,000 copies/mL), respectively. Median age was 34 years, 15% were women and a third used abacavir/3TC. As with previous ViiV presentations, baseline data was not presented for either IQR or range for median values.

At week 48, viral suppression was reported for 90% vs 83% of people in the dolutegravir vs darunavir/r arms respectively, finding doultegravir to be statistically superior [difference: +7.1% (95%CI: 0.9, 13.2) p=0.02].

Only one patient in each arm had virological failure. Fewer patients discontinued dolutegravir for side effects or other reasons (4% vs 10%), though rates were generally low in both groups. Dolutegravir was also superior in patients with high baseline viral load, with no significant difference by background NRTI, CD4 count, sex or race. CD4 increases were +210 cells/mm^3 in each arm.

Two patients in each arm had protocol defined viral failure (to >200 copies/mL), none with drug resistance. Both arms were well tolerated with slightly fewer drug-related discontinuations in the dolutegravir group (2% vs 4%), with similar rates of events across subgroups.

Grade 3/4 laboratory results included elevated creatine kinase (0.10 -0.18 mg/dL) in 7% of dolutegravir vs 4% darunavir patients. Median change in fasting LDL was lower in the dolutegravir compared to darunavir/r arms (+3.1 vs +14.1 mg/dL).

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GSK744: 24-week results with oral integrase inhibitor planned for once-monthly injections

Simon Collins, HIV i-Base

Early results were also presented at EACS 2013 for ViiV Healthcare's follow-up compound to dolutegravir, which currently has the development name GSK-744. [1]

Previous results with this integrase inhibitor have reported a sufficiently long half-life with both IV and SC injectible formulations to support once-monthly dosing both in therapeutic and PrEP prevention studies.

Viral efficacy results from the LATTE study were from using the oral formulation of GSK-744 in combination with tenofovir/FTC. Participants who become undetectable by week 24, roll over to use dual therapy with oral GSK-744 plus oral rilpivirine, out to 96 weeks. [2]

The first part of the study was a randomised open label dose finding study comparing 10 mg, 30 mg and 60 mg of GSK-744 to a control arm of efavirenz plus tenofovir/FTC. Approximately 60 patients were in each arm.

Baseline median CD4 count was approximately 400 cells/mm^3 with mean viral load or 4.2 – 4.4 log copies/mL Again, no data on the range or variance for the baseline data were included in the presentation, limiting the ability to interpret the results, although broadly people were in early HIV infection.

At week 24, viral load reductions in the 10 mg, 30 mg, 60 mg and control arms were –2.53, –2.53, –2.50 and –1.88 log copies/mL, respectively The percentage of patients (95% CI) with viral suppression to <50 copies/mL was 88% (80%, 96%), 85% (76%, 94%), 87% (78%, 95%) and 74% (63%, 85%), respectively.

Future development will go forward using the 30 mg dose.

C O M M E N T

Given the approximate –2.2 log reductions seen following 10 days of monotherapy with GSK-744 and that tenofovir and FTC are included for six months with such a low baseline viral load, it is difficult to understand why a higher percentage of people had an undetectable viral load.

While ART is generally getting better, the target should be for near-100%.

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Cenicriviroc: 48 week results compared to efavirenz

Simon Collins, HIV i-Base

Cenicriviroc is a CCR5 inhibitor (also active against CCR2) that has been in development for many years at Tobira Therapeutics (originally as TBR-652).

At EACS 2013, Judith Feinberg from University of Cincinnati presented 48 week results from a randomised (2:2:1), doubled-blinded, double placebo, dose finding study comparing cenicriviroc 100 mg or 200 mg to a control arm using efavirenz. All patients (n=143) were treatment naïve and used tenofovir/FTC as background NRTIs. This required participants taking six pills twice-daily in a twice-daily regimen, using a 50 mg formulation of CVC taken in the morning with breakfast and efavirenz taken in the evening. [1]

Results from the primary endpoint of virological response at 24 weeks were reported at CROI 2013. [2]

Baseline characteristics included approximate baseline CD4 and viral load of 400 cells/mm^3 (range 77-1090) and 25–40,000 copies/mL (14-25% >100,000), respectively. The study population was 94% male; 62% Caucasian, 32% African American; 24% Hispanic. Mean age was 36 years (range 19–63).

At week 48, viral suppression to <50 copies/mL (snapshot analysis) was reported for 68%, 64% and 50% of the 100 mg, 200 mg and efavirenz groups respectively, which were significantly lower than the week 24 results of 76%, 73% and 71%, especially for the efavirenz arm.

Most of the efavirenz discontinuations were due to side effects, but virological failure occurred more frequently in the cenicriviroc arms: 7% (=4) and 11% (n=6) vs 4% (n=1), although patient numbers were low.

Other than efavirenz discontinuations, there were few other differences between results at week 24 and 48, with no new safety signals, virological failure or further resistance. Drug resistance was detected in 5/10 patients failing with cenicriviroc, mainly M184V/I compared to 0/1 using efavirenz.

Mean reductions from baseline of sCD14 (an immune activation biomarker that is independently associated with mortality) by week 24 (by –0.04 log x 10(6) pg/mL) in the cenicriviroc groups, returned to baseline by week 32. This compared to a steady increase of sCD14 by +0.10 log x 10(6) in the efavirenz group by week 48. The clinical significance of these findings requires further investigation.

Although phase 3 studies use the 200 mg dose (and a new 200 mg formulation), several questions after the presentation focused on the problems of the trial design. A coformulation of cenicriviroc and generic 3TC is also planned.

A presentation at the 15th Workshop on Comorbidities and Adverse Drug Reactions held a few days earlier reported preliminary anti-fibrotic and anti-inflammatory effects from cenicriviroc in a mouse model for Non-Alcoholic Steatohepatitis (NASH). [3]

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Approaches to once-daily raltegravir: new formulation likely to require food

Simon Collins, HIV i-Base

Several raltegravir pharmacokinetic studies were presented at EACS 2013 looking at whether there is potential for once-daily dosing.

New once-daily formulation

Results from a PK study involving a new once-daily formulation of raltegravir were presented as a poster. [1]

However, the new formulation required a higher daily milligram dose, compared to the current formulation.

This was an open-label, single-dose, randomised, 2-cohort, 3-period, crossover, study looking at the impact of food, in 36 HIV negative volunteers. The once daily formulation using 2 x 600 mg tablets was compared to 3 x 400 mg tablets using the current formulation. This is a 50% higher daily dose than currently used.

Interpreting the results from this study is therefore problematic, given that the current formulation is licensed at a dose of 1 x 400 mg tablet twice-daily (to be take with or without food) and this was not included as a control arm.

PK results and geometric mean (CV%) are reported in Table 1.

In summary, the new reformulation reported a divergent relationship with food depending on whether this was a low fat meal. There were decreases in all parameters when coadministered with a low fat meal and increases in AUC and Cmax (and similar C24hr) with a high fat meal.

The current formulation similarly reported reductions in all PK parameters with a low fat meal which with a high fat meal attenuated the reductions in AUC and Cmax and increased C24hr.

Table 1: Effect of food on current and reformulated raltegravir (1200 mg dose) in two PK studies

	AUC (%CV)	Cmax (%CV)	C24hr (%CV)
Reformulated, fasted, multiple dose	34.9 µM-hr (122%)	9.4 µM (203%)	46.3 nM (54%)
Standard, fasted, multiple dose	58.1 µM-hr (67%)	23.1 µM (77%)	59.8 nM (87%)
Reformulated + low fat meal, single dose	40% decrease	52% decrease	16% decrease
Reformulated + high fat meal, single dose	3% increase	28% increase	12% decrease
Standard + low fat meal, single dose	71% decrease	75% decrease	18% decrease
Standard + high fat meal, single dose	26% increase	24% decrease	70% increase

A second raltegravir PK study (with a strange design) compared pharmacokinetic parameters of two doses of 400 mg raltegravir, taken 12 hours about, to a single 800 mg dose which was chewed rather than swallowed.

The missing comparators, given that that is comparing a new method of administration, of either a 400 mg BID chewed group, or an 800 mg QD swallowed group make the higher peak concentrations reported with the QD dose impossible to interpret, as is the reported reduction in interpatient variability for AUC.

The current indication for raltegravir is to swallow tablets and not to chew them.

A third study reported results from using the twice-daily formulation with once-daily dosing in treatment experienced patients who were had been virally suppressed to <50 copies/mL for at least 6 months. This was a single-arm observational study in 71 patients (17/71 were already using raltegravir twice-daily for a median of 8 (range 1–28) months.

Median duration of previous treatment was 14 years (range 1–22) years with a median five previous combinations (range 1–15). Median CD4 count was 588 cells/mm^3 (range 248–1328).

The backbone combinations used with the once-daily switch were: tenofovir/FTC (n=40), abacavir/3TC (n=13), etravirine (n=7), atazanavir (n=7), nevirapine (n=3) and efavirenz (n=1).

The percentage of patients who remained undetectable at week 24 (the primary endpoint) was 99 % (95%CI: 96-100%) and 96% (95%CI: 91–100 %) at week 96. One patient had virological failure by week 24 with two further cases by week 48.

Resistance to raltegravir was detected at virological failure in 2/3 patients and was also associated with previous resistance drugs used in the backbone combination.

C O M M E N T

Although raltegravir has impressive virological and safety results, and is included as a preferred option for first-line ART in treatment guidelines, this is a twice-daily drug.

In earlier studies, notably in the QDMRK, once daily raltegravir failed to show non-inferiority to twice-daily dosing in treatment naïve patients with rates of 83% vs 89% virological response (difference -5·7%, 95% CI -10·7 to -0·83; p=0·044). [4]

The new formulation reported by Krishna et al requires a higher daily dose than the current dose (1200 mg vs 800 mg daily) and may require to taking with a high fat meal. Although the C24hr levels seem okay, overall bioavailability seems less and it is unclear whether this is compensated for by reduced interpatient variability.

The study by Cattaneo et al by chewing chalky tablets s impossible to interpret.

Finally, the study by Caby et al, although small and without a control group, suggests that QD dosing by doubling the current dose may be a switch option when background drugs are fully active and there is no historical likelihood of drug resistance. Similar results has been reported in other small studies and suggests that switching to QD once suppressed might have been a better study design for the QDMRK study.

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DSMB stops boosted atazanavir monotherapy study due to virological failure

Simon Collins, HIV i-Base

Interim results from a study that switched virally suppressed patients to boosted atazanavir monotherapy, showed a significantly higher rate of failure compared to standard of care triple therapy.

This was a randomised, open label, non-inferiority study in 103 patients (84% males, 13% HCV-infected, median (IQR) age of 42 (36-48) years).

Enrolment criteria included viral suppression to <50 copies/mL for greater than 6 months on a combination that included atazanavir/ritonavir (300/100 mg) plus two NRTIs. Participants were randomised to switch to atazanavir/rintonavir monotherapy or continue with triple therapy.

In the 48-week interim analysis (ITT analysis), viral suppression was maintained by 73% (37/51 patients) in the monotherapy arm compared to 85% (44/52) in the triple-therapy arm (difference: -12.1%, 95% CI: -27.8 to 3.6).

This was sufficient for the Data and Safety Monitoring Board (DSMB) to recommended to stopping the study. Confirmed virological failure occurred in 11 vs 2 patients in the monotherapy vs triple-therapy groups and although this was reported as significantly more common in people with HCV coinfection (56% vs 17%; p=0.024), this was in very small numbers of patients.

Viral load was resuppressed in all patients with virological rebound by reintroducing previous NRTIs. Although drug resistant mutations were not detected, median HIV viral load was only 197 (IQR 134-510) copies/mL at the time of testing.

Although drug-related side effects were more common in the triple therapy group (n=0 vs 6, p=0.027), it is notable that these were mostly associated with atazanavir (5/6) rather than the NRTIs.

C O M M E N T

An earlier study already reported high rates of virological failure when atazanavir is used as boosted monotherapy. [2]

It therefore is unclear why Bristol-Myers Squibb supported this study other than from a marketing-driven interest.

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Recreational drug use is common in HIV positive gay men and is extensive in a significant minority

Simon Collins, HIV i-Base

An analysis from the ASTRA (Antiretrovirals, Sexual Transmission Risk and Attitudes) study was reported as an oral presentation at EACS 2013.

The results are important because of the size of the study and for highlighting different patterns of recreational drug use that have not been well studied and are therefore likely to have been underestimated. Although the study was carried out two years ago, there is little evidence to suggest that drug use has reduced in 2013.

The ASTRA study included 3,258 HIV positive people attending one of eight HIV out-patient clinics in London, Manchester and Brighton, of whom 69% were men who have sex with men (MSM). Participants were enrolled during 2011-2012 and self-completed a confidential study-specific questionnaire, which recorded information on socio-demographics, lifestyle factors, ART, health and wellbeing, HIV transmission beliefs and sexual lifestyle.

Approximate demographics for the gay men in this survey (n=2,248) included mean age 45 years (+/-SD 9.5), 62% were employed, 44% had a university degree or higher and 89% were white. Median time since HIV diagnosis was 10 years (IQR: 5 to 16 years), 76% had an undetectable viral load (85% were on ART) and 84% had a CD4 count >350 cells/mm3.

Half of gay men in the survey (n=1,140) used one or more recreational drugs in the previous three months, with 32% of this group using only one drug and 21% using only two; 15%, 10% and 21% of this group used 3, 4 and 5 or more different recreational drugs, respectively. Injecting recreational drugs was reported by 3% (n=68 men). Patterns of drugs use varied considerably with the types of drug used. Of men reporting drug use, the most commonly used drugs were poppers (54%), with just over 40% reporting use of each of cannabis, Viagra (or similar) and cocaine. Approximately 15-25% of men who used drugs had taken heavier "party" drugs including ketamine (25%), ecstasy (23%), GHB/GBL (19%), crystal meth (15%) and mephedrone (14%). Fewer men used speed (7%), anabolic steroids (5%), LSD (4%) and codeine (4%). Less than 2% used crack cocaine, khat, heroin, morphine or opium.

Further information on the pattern of drug use was also presented based on the number of drugs used. So, for example, of the people reporting using only one drug (n=369), 37% used poppers and 37% used cannabis, with hardly any use of heavier party drugs. Men reporting using >5 drugs (n=241 men), also reported the highest use of ketamine, ecstasy, GHB/GBL, crystal meth and mephedrone (each accounting for about 10% of all drugs used in this group) and the lowest use of cannabis and poppers.

In adjusted multivariate analysis, risk factors most significantly associated with recreational drug use included younger age (adj Odds Ratio: 2.45 [95% CI: 1.52, 3.96] <30 vs >50 years old), alcohol dependency (adj OR: 1.53 [95% CI: 1.26, 1.86] possible vs not), non-adherence to ART (adj OR: 1.78 [95% CI: 1.35, 2.36] missing >2 days in previous 3 months vs adherent on ART); all $p<0.001$. Men not on ART had similar levels of drug use to those who were adherent on ART. No independent association was seen for ethnicity, education, employment, housing, financial hardship, CD4 count, depression and anxiety (all $p>0.05$).

The survey also looked broadly at sexual behaviour in the previous three months using several different measures. These included having more than five partners, not using a condom with a negative partner(s), having group sex, using the internet to find partners, having a previous STI or having more than ten new partners (in the previous year). Recreational drug use was significantly associated with all these measures (all adj OR approximately 2.5-5.0 - compared to not using recreational drugs with narrow 95% CIs, $p<0.001$ for all).

Broadly, each measure was positively associated with increasing number of drugs used. For example, compared to men who had used only one recreational drug, people who had used five or more drugs were more than twice as likely to use the internet to meet partners, more than four times as likely to have more partners, more than three times as likely to have had group sex, and more than twice as likely to have been recently diagnosed with another STI.

In terms of condom use, men using five or more drugs were almost twice as likely to report having sex without a condom with a partner of "negative or unknown status" (a combined option in the survey) compared to those using only one drug (24% vs 13%), and about 3 times as likely compared to the no drug group (9%).

However, the results on drug use and behaviour need to be interpreted carefully in terms of HIV transmission risk, because behaviour was not reported in relation to viral load (when undetectable viral load is likely to dramatically reduce risk). Some of the outcomes will include sex between positive partners (not relevant for HIV transmission, although potentially important for transmission of other STIs including HCV).

C O M M E N T

Recreational drug use is commonly associated with dance and club culture. As this has been well established in the gay scene for at least the last twenty years it should not be unexpected that recreational drug use is common among HIV positive gay men, similar to HIV negative gay men and heterosexuals.

However, the results show that 50% of HIV positive gay men at these urban centres are likely to use at least one recreational drug, even though that for most people this is either poppers or cannabis. They also show that at least 10% use heavier party drugs that are associated with health risks including reduced adherence.

The results help describe a minority of HIV positive men for whom recreational drug use involves many drugs and that higher recreational drug use overlaps with using drugs for sex. This overlaps with the risk factors reported for other health problems including sexually transmitted HCV in HIV positive gay men and the increasing demand of drug counselling services from gay men irrespective of HIV status.

These results are from an HIV outpatient sample and so tell us nothing about whether HIV positive gay men are behaving any differently to HIV negative men. However, as the largest study of its kind, future analyses from the ASTRA results will provide important insight into the complex diversity of the HIV population in the UK, including attitudes and patterns relating to sexual behaviour, serosorting, recreational drug use and clinical health.

The design, methods and patient characteristics were published last month as an open access paper in PLoS ONE. [2] The questionnaire from the study is also available online. [3]

Simon Collins is a community representative on the Steering Group for the ASTRA study.

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Caution against prolonged use of bisphosphonates in patients with mild-moderate fracture risk

Simon Collins, HIV i-Base

A useful overview of advances in the prevention and management of osteoporosis was presented by Todd Brown from Johns Hopkins School of Medicine. [1]

This included focusing on the absolute risk of fracture, the benefits and risks of bisphosphonate therapy and new strategies for fracture risk reduction with reference to both US National Osteoporosis Foundation (NOF) guidelines and those from the International Osteoporosis Foundation (IOF).

A new focus on the absolute risk of fracture has changed the way that osteoporosis is now treated in the US.

In 2003, US (NOF) guidelines recommended screening all women older than 65, younger women with one of more risk factors and postmenopausal women who present with a fracture. Lifelong alendronate treatment was recommended if DEXA T-score was -2.0 in absence of other risk factors, at -1.5 with one or more risk factors and for anyone with a prior vertebral or hip fracture.

By contrast, 2003 IOF guidelines required risk factors and a fracture for screening with treatment only recommended if T-score was -2.5 or lower.

Although osteoporosis is defined as a systemic skeletal disorder characterised by low bone mineral density (BMD) and a microarchitectual deterioration of bone tissue which together increase bone fragility and the risk of fracture, DEXA only identifes BMD.

As both bone quality and risk of falls are as important when assessing risk of fracture, T-score is now interpreted due to these underlying risks. A T-score of -2.5 will present a different risk, for example, for someone who is 80 years old compared to someone who is 50. Guidelines, including EACS and BHIVA, focus on those at highest risk, using the FRAX equation (www.sheff.ac.uk/FRAX).

NOF guidelines revised in 2013 now recommend treatment for patients with T-score between -1.0 and -2.5 when 10 years FRAX score is >3% for hip fracture or when FRAX is >20% for all osteoporosis related fractures.

IOF 2012 guidelines use FRAX slightly differently based on fracture probability prior to DEXA results.

Treatment changes since 2003 include no longer using estrogen/hormone therapy to reduce fracture risk or calcitonin (due to carcinogenic risk and poor efficacy).

In 2003, treatment using oral bisphosphonates (risedronate, alendronate, ibandronate) to inhibit osteoclast activity was generally lifelong. Since then, zolendronic acid injections have been approved as a new option. However, oversuppression of bone turnover is associated with long-term risks that include osteonecrosis of the jaw (ONJ) and spontaneous or minimal trauma atypical femur fractures that are often bilateral. Although the incidence for these complications are not precisely known, both are categorised as rare, although the risk increases with duration of bisphosphonate use.

This has lead to a recommendation (based on very limited data) to stop bisphosphate treatment in some patients based on their fracture risk.

Continuous treatment is still recommended for those at high risk, interrupting treatment (risedronate, alendronate and zolendronic acid) after 3-5 years is recommended for those at moderate risk, and permanently discontinuing treatment is recommended for those now defined as low risk. There is no data on use of ibandronate or on duration of the treatment break and how to monitor. [2]

New treatments include teriparatide (Forteo) which promote bone formation but which is only indicated for patients who have continued bone loss or fracture on bisphosphonates. Teriparatide is given by daily injection for 12-24 months. However, increases in bone density are rapidly lost if antiresorptive drugs are not used.

The monoclonal antibody denosumab (given twice yearly) reduces risk of spine or hip fracture by antiresorptive mechanism on osteoclasts but carry similar safety concerns to bisphosphonates due to oversuppression of bone turnover, with a possibly increased risk of infection that may require further study for use in HIV positive patients. [3, 4]

Anabolic drugs in the pipeline include scelrostin antibodies and antiresorptives including cathepsin K inhibitors that promotes bone formation.

Research that focuses on muscle and physical function is also likely to impact on future fracture risk.

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Osteoporosis triples risk of later fracture in 1000-person US HIV group

Mark Mascolini, for NATAP.org

Only three factors independently predicted a new fracture in a combined analysis of the US HOPS and SUN Study HIV cohorts – older age, smoking, and osteoporosis. Osteopenia did not affect fracture risk in multivariate or univariate analyses.

Several studies confirm a higher fracture rate in people with than without HIV infection. For example, in a 5826-person HIV Outpatient Study (HOPS) analysis, HOPS members 25 to 54 years old had a higher fracture rate and a higher relative proportion of fragility fractures than did a general population comparison group [2]. Low bone mineral density (BMD) is frequent in HIV populations, but a link between low BMD and subsequent fracture had not been demonstrated in people with HIV.

To explore the possible association between low BMD and later fracture – which has been demonstrated in the general population – CDC researchers and collaborators analysed combined data from the SUN Study and HOPS, two prospective US cohorts. They focused on people who had at least one DEXA scan to determine BMD and follow-up to the last patient contact or to June 2012 (SUN) or September 2012 (HOPS). They defined osteopenia and osteoporosis by DEXA-measured T score in the standard way, and they defined incident fracture as all fractures.

Median age of the combined 1008-person groups was 42 (interquartile range [IQR] 35 to 48), 83% were men, 68.5% men who have sex with men (MSM), and 67% non-Hispanic white. Median CD4 count stood at 408 (IQR 254 to 598). More than half of cohort members (54%) were current or former smokers, and 12% had HCV infection.

DEXA scans determined that 366 people (36.3%) had osteopenia and 29 (2.9%) had osteoporosis. Sixty people (6%) had a fracture before follow-up began. People with osteopenia or osteoporosis were significantly older and included significantly higher proportions of men, MSM, and whites. People with osteoporosis had a significantly lower average nadir CD4 count than those without osteoporosis (92 versus 200, $p = 0.008$). HCV infection was more prevalent in people with osteoporosis (27.6%) or osteopenia (14.5%) than in those with neither condition (10.1%) ($p = 0.003$).

Significantly more people with osteoporosis than with osteopenia or neither condition already had a fracture when follow-up began (20.7% versus 6.6% versus 4.9%, $p = 0.009$), and significantly more people with osteoporosis had a new fracture during follow-up (31% versus 10.1% versus 8%, $p = 0.003$).

During a median follow-up of 5 years, 95 people (9.4%) fractured a bone. Fractures were most common in the rib/sternum (18), hand (17), foot (15), and wrist (11). Compared with people who did not break a bone during follow-up, those who did were significantly older (median 43 versus 41, $p = 0.007$) and more likely to be a current or former smoker (65.3% versus 53.1%, $p = 0.031$), to have HCV infection (20.0% versus 11.4%, $p = 0.023$), and to have a previous fracture (12.6% versus 5.3%, $p = 0.008$).

People with a new fracture were less likely to have normal bone density (T score $\geq$ -1) and more likely to have a T score below -2.5, indicating osteoporosis ($p = 0.002$). Median BMD was -1.0 (IQR -2.1 to -0.4) in people who broke a bone during follow-up and -0.7 (IQR -1.4 to -0.1) in those who did not.

Multivariate analysis identified three factors associated with a higher risk of fracture during follow-up.

Osteoporosis tripled the risk (adjusted hazard ratio [aHR] 3.0, 95% confidence interval [CI] 1.5 to 6.3), every additional 10 years of age raised the risk 40% (aHR 1.4, 95% CI 1.1 to 1.7), and current or former smoking upped the risk 50% (aHR 1.5, 95% CI 1.0 to 2.3) ($P \leq 0.05$ for all associations). Factors not independently associated with incident fracture in this analysis were osteopenia, current or nadir CD4 count, gender, injection drug use versus MSM transmission risk, public versus private insurance, and HCV infection.

The HOPS/SUN team noted that this analysis is limited by their inability to distinguish fragility fractures from other fractures. They questioned whether fracture reporting and smoking data were complete in these patients and suspected underreporting of fractures. The investigators suggested that channeling bias my affect their results: people referred for DEXA scanning may be those with more fracture risk factors. They also cautioned that women made up only 17% of the study group. Because the analysis found a strong association between osteoporosis

and subsequent fracture in this relatively young population, the researchers suggested that DEXA screening may be a valuable clinical tool in people with HIV.

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Bone turnover marker changes early in ART predict bone loss after 96 week

Mark Mascolini, for NATAP.org

Changes in markers of bone resorption (destruction) and formation early in the course of antiretroviral therapy (ART) predicted clinically significantly bone loss after 96 weeks of treatment in a trial that randomised people to either raltegravir or tenofovir/emtricitabine (TDF/FTC), both with lopinavir/ritonavir. [1]

Adding to the complexity of bone marker studies, results of this analysis indicated that greater increases in bone formation markers through 16 weeks of treatment were associated with clinically meaningful BMD loss at week 96.

Previous research has reported that bone mineral density (BMD) drops 2% to 6% in the 2 years after antiretroviral therapy begins regardless of the antiretrovirals taken [2]. When treatment starts, bone resorption markers increase faster than bone formation markers, creating what these researchers call a "catabolic window." Because it remains unclear whether early changes in turnover markers predict antiretroviral-associated bone loss, these investigators addressed that question in PROGRESS study participants.

PROGRESS randomised 206 antiretroviral-naive adults to start either raltegravir or TDF/FTC with lopinavir/ritonavir. Seventy-eight people in the raltegravir arm and 82 in the TDF/FTC arm completed the study and had baseline and week-96 DXA scans to measure BMD. At baseline and weeks 4, 16, 48, and 96, researchers measured type 1 C-terminus telopeptide (CTx, a bone resorption marker), osteocalcin, procollagen type 1 propeptide (P1NP), and bone-specific alkaline phosphatase (BSAP) (all bone formation markers). The primary goal was to determine the impact of marker changes on clinically significant bone loss, defined as at least a 5% decrease in total BMD at week 96.

Among people included in the bone turnover analysis, about 90% were men, about 80% were white, and almost half smoked. Age averaged about 40 years in both groups and body mass index about 25 kg/m(2). Two thirds of study participants drank alcohol. Through 96 weeks of treatment, total BMD remained essentially stable in the raltegravir group (+0.68%) while dropping in the TDF/FTC group (-2.48%) ($P < 0.001$).

Levels of CTx, the resorption (destruction) marker, lay in the mid-normal range at baseline and rose significantly in both treatment arms through 96 weeks. Levels of osteocalcin, a bone formation marker, started in the low-normal range and also climbed significantly in both arms. Levels of P1NP and BSAP lay in the normal range at baseline and did not change much through 96 weeks of treatment in either arm. CTx and osteocalcin levels rose significantly more with TDF/FTC than with raltegravir over 96 weeks.

Nineteen of 160 study participants (11.9%) had 5% or greater total BMD loss through 96 weeks, including 3 of 78 in the raltegravir group and 16 of 82 in the TDF/FTC group, a significant difference (3.8% versus 19.5%, $p = 0.003$). In a logistic regression model that did not include the antiretroviral effect, two nonmarker factors were associated with lower odds of at least a 5% loss in total BMD (age under 40 and male gender) and two nonmarker factors were associated with higher odds of more than 5% bone loss (white race and baseline CD4 count below 200).

In this analysis, the impact of baseline bone marker levels and early bone marker changes were complex. For CTx, the bone resorption marker, higher baseline levels and greater change over 4 weeks were both linked to at least 5% total BMD loss at week 96. But greater week-4 increases in the bone formation markers P1NP, osteocalcin, and BSAP generally protected against 96-week bone loss, although only the P1NP change reached statistical significance. After 16 weeks of treatment, however, larger changes in the bone formation markers P1NP and osteocalcin were positively associated with bone loss, a result suggesting to the investigators that these markers reflect overall bone turnover rather than just bone formation.

In the analysis including antiretroviral treatment effect, younger age and male gender remained protective against week-96 bone loss of 5% or more, while white race and baseline CD4 count below 200 again raised the odds of week-96 bone loss. And once again higher baseline CTx and greater absolute change in CTx through treatment week 4 were associated with higher odds of total BMD loss at week 96. Associations between baseline bone formation markers and changes at weeks 4 and 16 were all similar to those associations in the analysis excluding treatment effect and approached or achieved statistical significance. In this analysis treatment with raltegravir versus TDF/FTC did not significantly protect against 96-week bone loss, a result suggesting to the investigators that antiretroviral differences in impact on bone loss can largely be attributed to changes in bone turnover markers.

All told, the PROGRESS investigators proposed, "these data provide evidence supporting the hypothesis that early relative changes in markers of bone resorption and bone formation (i.e., the catabolic window) are important predictors of bone loss in HIV positive persons" starting antiretroviral therapy. They called for further study of the mechanisms behind this effect and the effects of individual antiretrovirals on bone turnover.

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Low HDL cholesterol is main lipid abnormality in HIV+/HIV- comparison

Mark Mascolini, for NATAP.org

Low "good" high-density lipoprotein (HDL) cholesterol rather than high "bad" low-density lipoprotein (LDL) cholesterol proved the principal lipid abnormality in a prospective cohort of HIV positive and negative people in Ireland.

HIV infection independently predicted a higher (worse) total-to-HDL cholesterol ratio, an established cardiovascular risk factor. Despite ongoing study since the dawn of combination antiretroviral therapy (cART), lipid abnormalities in cART-treated people remain incompletely characterised, especially in relation to lipids in a similar cohort of HIV negative people. To address this issue, researchers in Ireland and the United Kingdom analysed lipid levels in 210 HIV positive and 264 HIV negative members of the prospective HIV UPBEAT cohort in Ireland.

They compared fasting lipids between the two groups, including total cholesterol, HDL cholesterol, LDL cholesterol, total-to-HDL cholesterol ratio, and triglycerides.

Recruited between February 2011 and July 2012, HIV positive and negative cohort members differed significantly in median age (39 with HIV versus 42 without HIV, p = 0.03), proportion of men (58.6% versus 43.6%, p = 0.001), proportion of Caucasians (60.5% versus 75.4%, p = 0.001), median body mass index (26 versus 27 kg/m(2), p = 0.05), median systolic blood pressure (127 versus 123 mm Hg, p = 0.05), proportion of current smokers (16.2% versus 36.3%, p = 0.0001), and proportion of statin users (3.1% versus 12.6%, p = 0.0002).

Compared with HIV negative people, those with HIV had significantly lower HDL cholesterol (1.1 versus 1.4 mmol/L, p = 0.0001) and total cholesterol (4.7 versus 4.9 mmol/L, p = 0.01) and significantly higher total-to-HDL ratio (4.0 versus 3.4, p = 0.0001).

While proportions with total cholesterol above 5.18 mmol/L did not differ significantly between groups (33.2% versus 39.4%, p = 0.21), a significantly higher proportion with HIV had a total-to-HDL ratio above 6.0 (13.2% versus 5.0%, p = 0.004). LDL cholesterol was marginally lower in the HIV group (2.9 versus 3.0 mmol/L, p = 0.09), while triglycerides were significantly higher in HIV positive people (1.1 versus 0.9 mmol/L, p = 0.0001; proportion above 1.7 mmol/L, 21.6% versus 11.2%, p = 0.004).

A linear regression model adjusted for age, gender, ethnicity, smoking, and body mass index found no association between HIV and total cholesterol (parameter estimate [PE] -0.15, p = 0.11) or LDL cholesterol (PE -0.05, p = 0.57). But the same analysis linked HIV infection to significantly lower HDL cholesterol (PE -0.20, p = 0.0001), higher total-to-HDL ratio (PE 0.06, p = 0.0001), and higher triglycerides (PE 0.11, p = 0.0001).

Defining abnormal lipid values according to National Cholesterol Education Program cutoffs, the researchers found similar results in a regression model adjusted for the same variables. Odds of abnormal total cholesterol and LDL cholesterol did not differ significantly between the HIV-positive and negative groups. But the HIV group had significantly higher odds of abnormal HDL cholesterol (odds ratio [OR] 3.61, p = 0.0001), total-to-HDL ratio (OR 2.67, p = 0.01), and triglycerides (OR 2.37, p = 0.005). Repeating this analysis after excluding people taking statins or those with a drug-injecting history did not alter the results.

The HIV UPBEAT team concluded that in this contemporary prospective cohort, the principal lipid abnormalities involve HDL cholesterol and triglycerides, not LDL cholesterol. The independent association between HIV infection and a worse total-to-HDL ratio, the researchers noted, is driven by low HDL cholesterol.

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Classic risk factors, but not HIV, linked to arterial stiffness in middle-aged

Mark Mascolini, for NATAP.org

Smoking and hypertension were associated with greater arterial stiffness – a possible signal of impending cardiovascular disease – in a comparison of 45-and-older people with and without HIV infection in Amsterdam. [1]

But HIV infection itself was not associated with greater arterial stiffness in this 1000-person study.

Heightened rates of cardiovascular disease in HIV positive people are an established phenomenon. Arterial stiffness, measured as pulse wave velocity, has emerged as a reliable independent predictor of incident cardiovascular disease in the general population. Meta-analysis determined that every 1 m/s greater pulse wave velocity raises the risk of total cardiovascular events 14%. [2]

Because arterial stiffness studies in people with HIV have been small and yielded inconsistent results, researchers working with Amsterdam's AGEhIV cohort conducted this study.

The AGEhIV cohort includes 597 people with HIV and 551 without HIV, all 45 or older. Researchers made baseline measurements in 2010-2012, and all cohort members have pulse wave velocity and blood pressure measured. This analysis involved 566 people with HIV (89% men) and 507 without HIV (86% men). The HIV-positive and negative groups did not differ significantly in median age (52.8 with HIV, 52.0 without HIV, p = 0.07) or proportion of men who have sex with men (MSM) (76.4% versus 71.4%, p = 0.07).

The HIV group included a higher proportion of current smokers (32.9% versus 24.8%)), who smoked significantly more than people without HIV (22.5 versus 14.7 pack-years, p < 0.001). A higher proportion of people with HIV ever injected drugs (3.2% versus 1.0%, p = 0.02), but the groups did not differ significantly in current heavy drinking (5.1% and 6.6%) or recreational drug use (22.8% versus 21.5%).

People with HIV had a higher (worse) median waist-to-hip ratio (0.97 versus 0.92, p < 0.001), and a higher proportion of HIV positive people had hypertension or were taking antihypertensives (31.3% or 22.4% versus 25.1% or 11.8%, p = 0.02 and p < 0.001). About twice as many HIV-positives already had one or more cardiovascular events (11.3% versus 6.0%, p < 0.003).

People with HIV had significantly higher markers of inflammation or innate immune activation (hsCRP, sCD14, sCD163), while those without HIV had significantly higher levels of D-dimer, a coagulation marker. Total-to-high-density-lipoprotein cholesterol ratio was higher (worse) in the HIV group (4.2 versus 3.9, p = 0.01), as were triglycerides (1.6 versus 1.4 mmol/L) and free fatty acids (0.31 versus 0.28 mmol/L) (p < 0.001 for both).

People with HIV had been infected for a median 12.1 years, median nadir CD4 count stood at 170 and median current CD4 count at 570. Most HIV-positive people (95%) were taking antiretroviral therapy, and 91.3% had an undetectable viral load.

Median pulse wave velocity was slightly but significantly higher in the HIV group (7.9 versus 7.7 m/s, p = 0.004), as were mean arterial pressure (99 versus 97 mm Hg, p = 0.02) and diastolic pressure (83.8 versus 82.3 mm Hg, p = 0.006). Systolic pressure was marginally higher in the HIV group (129.3 versus 126.5 mm Hg, p = 0.09).

Statistical analysis adjusted for age, mean arterial pressure, and gender determined that people with HIV had a 0.19 m/s higher pulse wave velocity, indicating greater arterial stiffness, than did people without HIV (95% confidence interval [CI] 0.01 to 0.36, p = 0.04). But when the analysis included smoking and hypertension, HIV infection was no longer associated with significantly greater pulse wave velocity (0.022 m/s difference, 95% CI -0.16 to 0.20, p = 0.8). Several variables were associated with greater pulse wave velocity in the AGEhIV cohort:

Difference in pulse wave velocity, m/s (95% confidence interval):

- Every 5 years of age: +0.219 (0.15 to 0.28), p < 0.001.
- Every 5 pack-years smoking (current smokers): +0.121 (0.09 to 0.15), p < 0.001.
- Every 5 pack-years smoking (past smokers): +0.051 (0.02 to 0.08), p < 0.001.
- Antihypertensive use: +0.527 (0.28 to 0.77), p < 0.001.
- Born in Netherlands: +0.22 (0.01 to 0.44), p = 0.04.
- Ever mg/L hsCRP: +0.039 (0.02 to 0.06), p = 0.001.
- Every 100 ng/mL sCD163 (men only): +0.056 (0.00 to 0.11) p = 0.04.
- Postmenopausal status: +0.610 (0.09 to 1.12), p = 0.02.
- Every mmol/L HDL cholesterol: -0.304 (-0.51 to -0.10), p = 0.004.
- Every 100-cell higher nadir CD4 count: -0.103 (-0.20 to 0.01), p = 0.04.

The researchers propose that the modestly but significantly greater arterial stiffness in people with than without HIV is clinically relevant. But the study showed that after statistical adjustment for smoking and hypertension, HIV infection is not independently associated with greater arterial stiffness. Smoking, high blood pressure, and markers of inflammation (hsCRP) and immune activation (sCD163) – all significantly higher in the HIV group – were independently associated with greater arterial stiffness.

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ANTIRETROVIRALS

Elvitegravir approved in EU: data on food and drug interactions

Simon Collins, HIV i-Base

On 18th November, the European Commission approved the integrase inhibitor elvitegravir as a separate formulation for use in combinations with a boosted protease inhibitor (PI). [1]

Approval is for use in HIV positive people who do not have genotypic resistance to elvitegravir.

Two formulations are available depending on the concomitant PI.

- The 85 mg tablet is for use in combinations that include atazanavir/ritonavir 300 mg/100 mg or the combined lopinavir/ritonavir 400 mg.
- The 150 mg tablet is for use with the ritonavir-boosted protease inhibitors darunavir 600 mg and fosamprenavir 700 mg.

Elvitegravir needs to be taken with food. The amount of type of food is not included in this recommendation but it may be important to include fat. The food interaction data in the SPC includes that elvitegravir AUC increased by 36% with a light meal (~373 kcal, 20% fat) and by 91% with a high-fat meal (~800 kcal, 50% fat).

- Drug interactions include with antacid medicines which can reduce levels of elvitegravir. Antacids need to be separated by at least four hours.
- Multivitamins also need to be separated from elvitegravir by at least four hours due to a potential interaction.
- Elvitegravir has the trade name Vitekta and is manufactured by Gilead Sciences. Elvitegravir is included in the fixed dose combination tablet Stribild (Quad) where it is boosted by cobicistat.

For further details see the Summary of Product Characteristics (SPC) posted to the EMA website. [2]

C O M M E N T

Although elvitegravir has not yet been approved in the US as a separate drug, a recent appendix added to the US DHHS guidelines included raltegravir, elvitegravir and dolutegravir equally as preferred first line options.

The food interaction data in the SPC was from a single-dose study. This mean C24h (%CV) values for elvitegravir under fasted, light meal or high fat meal conditions were 253 ng/mL (57%), 355 ng/mL (54%) and 488 ng/mL (66%), respectively. [3]

Although C24h values can be used to qualitatively compare concentrations across treatments, this cannot be used as a Ctrough (the most important parameter from the concern of drug resistance). Ctrough can only be determined from a multiple dose study after steady-state concentrations are achieved.

Although it is encouraging that the C24h was above the IC95 for elvitegravir (45 ng/mL) with all doses, the single-dose study is limited any to a conclusion that "expects elvitegravir Ctrough to be higher when administered with a meal compared to fasted".

Source
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ViiV file 572-trii fixed dose combination in the US: positive opinion to approve dolutegravir in the EU

ViiV press statements

On 22 October 2013, ViiV Healthcare submitted a new drug application to the US FDA for a single tablet combination of dolutegravir, abacavir and 3TC. [1]

EU submission for the combination (developed as 572-trii) is expected to follow in the next few months.

ViiV is responsible for producing all three drugs, although US patents for both 3TC and abacavir have now expired for single formulations. In the UK, generic 3TC is already available and abacavir is due to come off patent in 2014. [2]

Dolutegravir was approved in the US in August 2013 (brandname Tivicay). [3] EU approval is expected within the next two months, following a positive opinion recommending authorisations bt the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) on 22 November 2013. [4]

Source
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TREATMENT ACCESS

Obama increases US contribution to Global Fund to $5 billion over three years

Global Fund press statements

In a speech to mark World AIDS Day, US President Barack Obama announced that the US would pledge $5 billion to the next three-year funding cycle for the Global Fund to fight AIDS, TB and Malaria.

This is an increase of $1 billion from the previous round of funding in 2010, although the offer is conditional on other donors committing $10 billion. [1]

The speech was made at the White House and included an announcement that the US National Institute of Health (NIH) would be "redirecting" an additional $100 million for funding research for a cure, although this was later clarify to be coming from within the existing HIV research budget. [2, 3]

The meeting also included an announcement that the Bill and Melinda Gates Foundation would increase support to the Global Fund to $500 million for the 2014-2016 funding cycle.

Several other governments recently increased support to the Global Fund, including the UK (to $1.6 billion) and Canada (to $555 million).

Over the last year, the number of people receiving antiretroviral treatment has increased to 6.1 million people, up from 4.2 million people at the end of 2012, although this increase is partially explained by inclusion of new data from India, South Africa, Tanzania and Uganda. The number of new smear-positive TB cases detected and treated increased to 11.2 million, from 9.7 million by the end of 2012. [4]

In April 2013, the Global Fund announced the target of $15 billion for the next cycle of funding. [5]

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HIV struggle in South Africa undermined by medicine stockouts and mismanagement

Treatment Action Campaign

On World AIDS Day, 1st December 2013, the Treatment Action Campaign (TAC) will not be celebrating.

We recognise that we have made very significant progress in the fight against HIV. But medicines stock-outs, corruption, mismanagement and an apparent lack of political will to deal with these problems are undermining our struggle against HIV.

The official World AIDS day event, hosted by the South African National AIDS Council (SANAC), will take place in Piet Retief in Mpumalanga. At this event, hundreds of TAC members will conduct a silent and respectful protest while government relaunches the HIV Counselling and Testing Campaign (HCT) in the same area. While we support the HIV Counselling and Testing (HCT) campaign, we feel attention must be drawn to the serious problems in the health system in Gert Sibande. It will not help people to know their status if they cannot get access to ARV treatment, counseling or quality health care. We cannot celebrate while clinics do not have stock of essential HIV and TB medicines, while hospitals run out of food and important equipment, and in a district where there is a death causing shortage of health workers.

We acknowledge the positive leadership that continues to be shown by Health Minister, Dr Aaron Motsoaledi. Over two million people are receiving antiretroviral treatment in South Africa and all indications are that the rate of new infections is on the decline – although it remains shockingly high at around 1,000 new infections per day.

However, we cannot turn a blind eye to the crumbling public health systems in most of our provinces.

The following issues are of particular concern across provinces.

1. Medicine stock-outs

Between September and October 2013, the Stop Stock-outs Project (SSP) undertook a national telephone survey to quantify the extent of ARV, TB and vaccine stock-outs.

More than one in five facilities reported a stock out or shortage of ARV and/or TB medicines in the last three months. Six out of the nine South African provinces had more than 17% of their facilities reporting shortages. Mpumalanga, Limpopo and the Free State fared the worst with an unacceptable 25.9%, 40.8% and 53.8% respectively. This report is now published online. [1, 2]

Medicine stock outs and shortages lead to patients taking partial doses of their treatment, interrupting it or defaulting treatment altogether. Medical consequences and costs to the health system and patients can be grave, including drug resistance, decreasing immunity, increased risk of opportunistic infections and transmission of HIV and TB, ultimately leading to more illness and death. In 20% of affected facilities patients were sent home or referred elsewhere without medicines, adding to travel costs for already deprived people.

2. Crumbling health systems

In many provinces, the public health system is plagued by corruption and mismanagement. Doctors and nurses have to work under extremely difficult conditions. Often, essential equipment is not available and buildings are insufficient. Many health workers are paid months late. Many posts remain vacant.

TAC and SECTION27 have recorded the unacceptable state of the Eastern Cape health system in our recently published report 'Death and Dying in the Eastern Cape'. [3]

However, the Eastern Cape is not the only province that is struggling and similarly shocking reports could be written about Limpopo, Mpumalanga and Gauteng.

3. Civil society sidelined in NHI discussions

The introduction of National Health Insurance has the potential to be a massive step forward for the provision of quality healthcare for all in South Africa. However, we are deeply concerned with the many delays in publishing further policy documents that would explain how NHI is to be funded.

We are also deeply concerned with the lack of consultation with civil society – in general, but more particularly in the areas where NHI is being piloted. Meaningful community engagement will be essential to the success of NHI.

4. TB prevention and integration still not addressed

The purchase of Gene Xpert machines to speed up the diagnosis of TB has been a significant step forward in our struggle to bring the TB epidemic under control. Alone, however, it will not be enough. More than two years after a policy document on the decentralisation of MDR-TB was published, provinces are struggling to implement this policy. This means that many MDR-TB patients are not diagnosed, and not optimally treated once diagnosed. The laxness from provinces in implementing this policy is unacceptable.

Furthermore, very little progress has been made on the health emergency that is TB in prisons. It is almost exactly one year since the Constitutional Court stated categorically that the government has a duty to take concrete measures to prevent TB in our prisons. But while new TB guidelines for diagnosing and treating TB in prisons have been published, these guidelines do not go nearly far enough. Our prisons are overcrowded and therefor an ideal setting for the spread of TB. We need aggressive measures to ensure that overcrowding in prisons is reduced and that sufficient infection control measures are implemented in all correctional facilities.

For all these reasons TAC says that World AIDS day 2013 does not give us reason to celebrate. It is a time to step up our commitment, not pat our backs. If we do not address urgent measures to solve these problems, then the success of South Africa's precious National Strategic Plan on HIV, STIs and TB will be threatened.

Source: This article was edited from the Treatment Action Campaign electronic newsletter. (29 November 2013).

References

1. Treatment Action Campaign. Independent national survey reveals extents of ARV and TB medicine stock outs. (28 November 2013). http://www.tac.org.za/news/independent-national-survey-reveals-extent-arv-tb-medicine-stock-outs
2. SSP Stockouts National Survey. November 2013. http://stockouts.org/uploads/3/3/1/1/3311088/stock_outs_a_national_crisis.pdf (PDF)
3. Death and dying in the Eastern Cape: an investigation into the collapse of a health system. http://echealthcrisis.org

TREATMENT GUIDELINES

European guidelines launched at EACS

The European AIDS Clinical Society (EACS) published the October 2013 update for their HIV clinical guidelines for treatment and management of HIV positive people.

The guidelines are a practical guide, formatted largely using summary tables with appropriate notes.

The guidelines are organised into five sections:

1. Assessment at initial & subsequent Visits
2. Antiretroviral treatment (ART)
3. Prevention and management of comorbidities
4. Chronic HBV and HCV coinfection
5. Opportunistic infections

Additional material is also available online for sections that were not included in the combined booklet.

http://www.eacsociety.org

Download link (PDF file):

http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf (PDF)

Paediatric guidelines on the prevention and treatment of opportunistic infections

US DHHS

In November 2013, the US DHHS paediatric guidelines for prevention and treatment of HIV related opportunistic infectsions (OIs) were published.

Major changes from the previous version in 2009 include:

- Greater emphasis on the importance of antiretroviral therapy (ART) for prevention and treatment of OIs, especially those OIs for which no specific therapy exists.
- Increased information about diagnosis and management of IRIS.
- Information about managing ART in children with OIs, including potential drug-drug interactions.
- Updated immunisation recommendations for children who have either been exposed to or infected with HIV, including pneumococcal, human papillomavirus, meningococcal, and rotavirus vaccines.
- Addition of sections on influenza, giardiasis, and isosporiasis.
- Elimination of sections on aspergillosis, bartonellosis, and HHV-6 and HHV-7 infections.
- Updated recommendations on discontinuation of OI prophylaxis after immune reconstitution in children.

The most important recommendations are highlighted in boxed major recommendations preceding each section, and a table of dosing recommendations appears at the end of each section.

The guidelines conclude with summary tables that display dosing recommendations for all of the conditions, drug toxicities and drug interactions, and 2 figures describing immunisation recommendations for children aged 0 to 6 years and 7 to 18 years.

Ref: Panel on Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children. Department of Health and Human Services.

http://aidsinfo.nih.gov/guidelines

http://aidsinfo.nih.gov/contentfiles/lvguidelines/ oi_guidelines_pediatrics.pdf (PDF)

US HIV guidelines update information on integrase inhibitors

On 30 October 2013, the US DHHS treatment guidelines were updated to include new recommendations on the use of integrase inhibitors.

The guidelines recognise advantages and disadvantages for each of the three approved integrase inhibitors (dolutegravir is approval is expected shortly in Europe). Previously, raltegravir was a preferred option and elvitegravir was only included as an alternative.

The guidelines now recommend the following four integrase inhibitor-based regimens as preferred regimens for ART-naive patients (all rated AI, arranged in order of drug approval).

- Raltegravir 400 mg twice daily plus tenofovir 300 mg/emtricitabine 200 mg once daily
- Elvitegravir 150 mg/cobicistat 150 mg/tenofovir 300 mg/emtricitabine 200 mg once daily in patients with estimated CrCl ≥70 mL/min
- Dolutegravir 50 mg once daily plus abacavir 600 mg/lamivudine 300 mg once daily in patients who are HLA B*5701 negative
- Dolutegravir 50 mg once daily plus tenofovir 300 mg/emtricitabine 200 mg once daily

Ref: Panel Statement on Integrase Inhibitor Use in Antiretroviral Treatment-Naive HIV Infected Individuals. 30 October 2013.

http://aidsinfo.nih.gov/guidelines

http://aidsinfo.nih.gov/contentfiles/AdultARV_INSTIRecommendations.pdf (PDF)

SIDE EFFECTS

Efavirenz is associated with higher suicide risk in meta-analysis of four ACTG studies

Matt Sharp, HIV i-Base

Efavirenz is one of the most widely used antiretroviral drugs despite a side effect profile that includes anxiety, mood changes, sleep disturbance, depression and serious psychiatric adverse events including suicide ideation and suicide. A new analysis supports these concerns.

In a presentation at IDWeek, Katie Mollan and colleagues analysed retrospective data from four independent investigator-led ACTG trials (A5095, A5142, A5175, A5202) to look for reports of suicidal thinking or behavior from 2001–2007. Each ACTG trial was randomised to either efavirenz or a non-efavirenz containing arm (three were PI-based and one was triple nucleoside) in antiretroviral naïve subjects. Three out of four of the trials efavirenz were open label.

This analysis included 5332 participants (3241 efavirenz, 2091 efavirenz-free) with a median follow-up of 150 weeks. Approximately 74% of participants were enrolled in US sites and 73% were men. The median age was 37 years (IQR 30, 43) and 32% reported a pre-psychiatric diagnosis or were prescribed a psychoactive medication 30 days prior to study entry. Less than 10% had injected drugs.

In the primary analysis, there were 47 suicide events in the efavirenz arm compared to 15 in the no efavirenz group (8.08 vs 3.66 per 1000 person-years) with a hazard ratio (HR) of 2.28 (95% CI 1.27 to 4.10, p=0.006). Completed or attempted suicide was also higher in the efavirenz group with 17 vs 5 events (2.90 versus 1.22 per 1000 person-years; HR 2.58; 95% CI 0.94 to 7.06, p=0.065), but this was not statistically significant. An intent-to treat analysis showed stronger significance finding 27 vs 7 attempted suicides (HR 2.61; 95% CI:1.1 to 5.9, p=0.03). Similar results were seen in ITT and as treated analyses.

In multivariate analysis, four risks found to be associated with suicide were use of efavirenz (HR 2.15; 95% CI: 1.20 to 3.87, p=0.01), under 30 years of age versus 45 or older (HR 2.82, 95% CI 1.25 to 6.34, p=0.04), injection drug use history (HR 2.18; 95% CI 1.11 to 4.30, p=0.02) and having a psychiatric history or psychoactive drug use: HR 3.90 (95% CI 2.23 to 6.82, p< 0.001). When assessing for risk in the countries studied, the US was higher (HR 2.32, 95% CI 1.23 to 4.38) compared to other countries (HR 2.02, 95% CI 0.43 to 9.53).

These results showed that use of efavirenz approximately doubled the risk of suicide with a number needed to harm (NNH) risk over one year of 217 for suicidal thought or behaviour and of 538 for attempted or completed suicide.

Despite concluding that the overall risk of suicide was low in this analysis, the authors urge that people treated with efavirenz be monitored for suicide risk.

C O M M E N T

This is an important analysis given that relatively rare events are unlikely to have statistical significance in smaller studies. This was a large study with three years follow up. The results should prompt a larger analysis from other randomised ACTG studies.

Although suicidal ideation is unlikely to be reported and confounding only allows reporting an association, analyses of suicides and efavirenz use in cohort studies, including D:A:D, might be important given their large patient numbers and length of follow up.

References

Mollan K et al. Hazard of suicidality in patients randomly assigned to efavirenz for initial treatment of HIV-1: a cross-study analysis conducted by the AIDS Clinical Trials Group (ACTG). IDWeek 2013. 2-6 October 2013, San Francisco. Abstract 670.

https://idsa.confex.com/idsa/2013/webprogram/Paper40032.html

BASIC SCIENCE

Dual HIV infection in long term nonprogressor elite controllers

Matt Sharp HIV i-Base

Researchers from Spain led by Maria Pernas analysed the prevalence, host genetic polymorphisms and the clinical consequences of HIV-1 dual infection (DI) in a cohort of 20 HIV long-term nonprogressor elite contollers (LTNP-EC).

The analysis included median of 15.5 samples per patient over a median follow-up of 10.2 years (range 2.5-17.2 years) . All participants had maintained undetectable HIV viral load (<50 copies/mL) without treatment since their diagnosis. During follow up, they remained clinically asymptomatic. Phylogenetic analysis was performed used 1-5 samples per patient, with follow up in 13-21 samples.

Maximum likelihood (ML) analysis of multiple envelope sequences was performed and showed that all patients had subtype-B. Monophyletic groups were detected above 80% significance except for nine patients, yet four of those patients were clustered in monophyletic groups less than 80%. Five patients had nucleotide sequences that were segregated in 2 or 3 different clusters with greater than 80% significance. The investigators looking at longer gene fragment in these five participants to ensure these five did not generate viral evolution. Four of the 20 LTNP-EC patients were identified as having dual HIV-1 infection.

During the follow-up, there was no statistical difference in epidemiological and clinical markers between those who were single and dual infected. The predominant route of transmission was IV drug use (which is also associated with a higher number of transmitted founder viruses). During follow-up, LTNP-EC status was maintained over 20 years by three out of the four people with dual infection.

There was no difference in median CD4 count between people with single and dual infection (~990 cells/mm^3; range 597-1355) However, in the dual infected group the mean difference in CD8 count was significantly higher [median 1213 (range 882-2438) vs 808 (range 234-1227), $p < 0.02$] and the CD4/CD8 ratio was lower [median 0.8 (range 0.2-1) vs 1.3 (range 0.6-3.0), $p < 0.01$].

Other host factors such as MHC class I group B and HLA alleles were associated with viral control in this cohort. Dual infections was also associated with several host genetic polymorphisms that are indicated in viral control in single infected LTNP-EC, including the HLA-B*35 allele.

Ref: Pernas M et al. Prevalence of HIV-1 dual Infection in long term nonprogressor-elite controllers. JAIDS 2013;64:225–231.

http://journals.lww.com/jaids/Abstract/2013/11010/Prevalence_of_HIV_1_Dual_Infection_in_Long_Term.1.aspx

HEPATITIS C

EU recommends approval of sofosbuvir for HCV

EMA press statement

On 21 November 2013, the Committee for Medicinal Products for Human Use (CHMP) recommended approval for sofosbuvir (400 mg film-coated tablets) as a treatment for chronic hepatitis C.

Sofosbuvir is a direct acting antiviral (DAA, ATC code not yet assigned) and is the first NS5B polymerase inhibitor.

Sofosbuvir provides the first interferon-free treatment option for chronic hepatitis C. In patients where interferon is still needed for efficacy, sofosbuvir enables a shortened treatment duration compared to current standard-of-care. Furthermore, when used before liver transplantation, sofosbuvir can prevent graft reinfection with HCV.

The most common side effects were fatigue, headache, nausea and insomnia. The safety profile of sofosbuvir in combination with ribavirin, with or without peginterferon was consistent with the expected safety profile of ribavirin and peginterferon alfa treatment, without increasing the frequency or severity of the expected adverse drug reactions.

A pharmacovigilance plan for sofosbuvir will be implemented as part of the marketing authorisation.

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued 67 days from adoption of the opinion.

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

Source:

EMA press statement. European Medicines Agency recommends approval of sofosbuvir for the treatment of chronic hepatitis C. (22 November 2013).

www.ema.europa.eu

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/11/news_detail_001970.jsp&mid=WC0b01ac058004d5c1

Compassionate use of declatasvir with sofosbuvir for people in urgent need of HCV treatment

EMA press statement

On 22 November 2013, the European Medicines Agency (EMA) issued advice on compassionate use of daclatasvir in combination with sofosbuvir in patients with chronic hepatitis C in urgent need of therapy to prevent progression of liver disease.

Compassionate-use programmes are set up at the level of individual Member States. They are intended to give patients with a life-threatening, long-lasting or seriously disabling disease with no available treatment options access to treatments that are still under development and that have not yet received a marketing authorisation. In this specific case, Sweden has requested an opinion from the CHMP on the conditions under which early access through compassionate use could be given to daclatasvir, for the use in combination with sofosbuvir, with or without ribavirin, for a specific patient population.

Compassionate use is intended for adult patients at a high risk of their liver being no longer able to function normally (decompensation) or death within 12 months if left untreated, and who have a genotype 1 infection. Further, it is recognised that the potential benefit of such combination therapy may extend to patients infected with other HCV genotypes.

Daclatasvir and sofosbuvir are both first-in-class antiviral medicines against HCV. These medicines have been studied in combination, with or without ribavirin, in a clinical trial which included treatment- naive (previously untreated) with HCV genotype 1, 2 and 3, as well as patients with genotype 1 who have previously failed telaprevir or boceprevir treatment.

Results from the trial indicate high efficacy, also in those who have failed treatment with these protease inhibitors. Many such patients have very advanced liver disease and are in urgent need of effective therapy in order to cease the progression of liver injury.

The assessment report and conditions of use of daclatasvir in combination with sofosbuvir with or without ribavirin in this setting will be published shortly on the Agency's website.

Daclatasvir is developed by Bristol-Myers Squibb and sofosbuvir is developed by Gilead.

Source

EMA press statement. European Medicines Agency advises on compassionate use of daclatasvir, 2013. 21 November 2013.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/11/news_detail_001971.jsp&mid=WC0b01ac058004d5c1

PREVENTION AND TRANSMISSION

The little blue pill that can stop HIV: PROUD study enrolling gay men in the UK

Simon Collins, HIV i-Base

The PROUD study using tenofovir/FTC as PrEP to reduce the risk of HIV transmission enrolling well but may only have a limited window for new participants. Continued enrollment is essential in order to generate UK data to enable PrEP to become an option for men who continue to be at high risk.

This study offers gay men in the UK one of the few chances to be able to use PrEP and as such should receive a high profile in GUM clinics.

The iPrEX study rpeorted the potential to reduce the risk of transmission by more than 95% with good adherence. Given the high levels of new HIV transmissions among gay men in the UK (3500 new diagoses in 2012), this is a compelling opportunity to use a new approach.

This is a two year study and participants are randomised to either immediate PrEP or deferred access in the second year. This is a much better than using a placebo design (as in France), as all participants are guaranteed access to PrEP.

Although some people may be disappointed to be randomised to the delayed group, the study still provides PrEP long before the NHS is likely to decide on broader access. The study include good care, support and monitoring, but otherwise just involves keeping an adherence diary, plus potential sexual risks.

PrEP is likely to have the greatest protection for people who have the greatest risks. So it is not targeted at people who currently use condoms every time.

For people who don't always use condoms, or don't regularly use condoms, this study could prevent their next HIV test coming back positive. A recent survey reported that about 50% of gay men in London were interested in PrEP as an option to prevent HIV.

This largest study in gay men (iPrEX) was particularly important because it enrolled men who had a high risk of catching HIV.

This profile would broadly overlap with factors that are relevant to gay men in the UK who have a high risk for HIV.

- Half were 18-25 and most of the rest were under 40.
- Men were sexually active (average 18 partners in the previous 3 months).
- Alcohol use was common (half had more than 4 drinks on days they were drinking).

- Condom use was inconsistent (80% had had sex without a condom in the previous 6 months).
- HIV was rarely discussed before sex (only 2% had knowingly had recently sex with a positive partner).
- At least 10% of men had also had a recent STI.

The iPrEX study showed that PrEP had a greater protection against HIV than condoms, but this was dependent on good adherence.

This is because consistent condom use is low and they can tear or fall off. In the context of good adherence, the protection from PrEP is continuous – 24 hours a day, 7 days a week.

Protect is likely to be systematic and include against oral transmission.

Just as condoms sometimes get missed, pill can be forgotton. Luckily, the level of protection is still likely to be high with occasional missed dose. Unlike HIV treatment, missed doses for PrEP is not associated with a risk of developing drug resistance in HIV negative people.

The researchers caution that PrEP does not protect against other sexually transmitted infections (STIs) and the study emphasises the importance of condoms and includes other information to support better sexual health.

The PROUD study is being run at nine of the largest sexual health clinics in London. It is also running in Birmingham, Brighton, Manchester, Sheffield and York.

The study is sponsored by Public Health England (PHE) and the Medical Research Council (MRC).

C O M M E N T

i-Base supports this study as a potentially important and exciting option for gay men to be able to use if they are at a high risk of catching HIV.

i-Base has no financial relationship with the study or the clinic sites.

Further information and links:

PROUD study website
http://www.proud.mrc.ac.uk/

PROUD trial sites
http://www.proud.mrc.ac.uk/where_are_we_recruiting.aspx

iPrEX study modeling close to 100% protection with good adherence
http://i-base.info/htb/16327

First report of iPrEX results in December 2010
http://i-base.info/htb/14191

Survey result showing half of gay men in London would be interested in using PrEP
http://i-base.info/htb/16694

ON THE WEB

Online journals

National Survey of Sexual Attitudes and Lifestyles (Natsal-3)

The third NATSAL results on sexual attitudes and lifestyles in Britain through the life course and over time were published in the 30 November 2013 edition of Lancet as a series of six open access reports. Free online registration is required.

http://www.thelancet.com/journals/lancet/issue/vol382no9907/PIIS0140-6736(13)X6059-3

Antiretrovirals Sexual Transmission Risk and Attitudes' (ASTRA) Study. Design methods and participant characteristics.

Speakman A et al. PLoS ONE 8(10): e77230. doi:10.1371/journal.pone.0077230.

http://dx.plos.org/10.1371/journal.pone.0077230

Life expectancy living with HIV: recent estimates and future implications

Nakagawa F et al. Current Opinion in Infectious Diseases: February 2013 - Volume 26 - Issue 1 - p 17–25 doi: 10.1097/QCO.0b013e32835ba6b1.

http://journals.lww.com/co-infectiousdiseases/Fulltext/2013/02000/

HIV and pregnancy: how to manage conflicting recommendations from evidence-based guidelines

Giles ML. AIDS: 27 March 2013 - Volume 27 - Issue 6 - p 857–862 doi: 10.1097/QAD.0b013e32835ce308

http://journals.lww.com/aidsonline/toc/2013/03270

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.

4th International Workshop on HIV & Women - From Adolescence through Menopause

13 - 14 January 2014, Washington, DC.

http://www.virology-education.com

Conference on Retroviruses and Opportunistic Infections (CROI) 2014

3-6 March 2014, Boston, USA

http://www.croi2014.org

Third Joint Conference of BHIVA with BASHH (2014)

1-4 April 2014, Liverpool

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

1st International workshop on the Optimal Use of DAAs in Liver Transplanted Patients

23 April 2014, Amsterdam

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://www.hiv11.com

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 the 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: 2012 update 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 (October 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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- **HIV Treatment Bulletin (HTB) every two months** ☐ **by e-mail (PDF file)** ☐ **by post**
- **HIV Treatment 'Passports' - Booklets for patients to record their own medical history**
  1 ☐ **5** ☐ **10** ☐ **25** ☐ **50** ☐ **Other** _____
- **Guide To HIV Testing and Risks of Sexual Transmission** *(February 2013)*
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- **Guide To HIV, Pregnancy and Women's Health** *(March 2013)*
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- **Introduction to Combination Therapy** *(April 2013)*
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- **Guide to Changing Treatment and Drug Resistance** *(February 2013)*
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- **HIV and your Quality of Life: Side Effects and other Complications** *(July 2012)*
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- **Guide To HIV and hepatitis C coinfection** *(November 2013)*
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- **Clinical Trials: a community guide to HIV research** *(March 2009)*
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Treatment guides in other languages are available as PDF files on the website

- **Phoneline support material** *(please specify quantity of each)*

  A3 posters _____ ***A5 leaflets*** _____ ***A6 postcards*** _____ ***Small cards*** _____

Please fax this form back, post to the above address, or email a request to HIV i-Base:

020 7407 8489 (fax) subscriptions@i-Base.org.uk